Energy balance-related factors: epidemiologic evidence for deriving recommendations for breast cancer prevention and survival

A thesis submitted for the degree of Doctor of Philosophy

by

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Declaration of Originality

I declare that the work described in this thesis is my own work and that where any material could be understood as the work of others; it is appropriately referenced, and /or acknowledged.

The present thesis is based on the work for the World Cancer Research Fund International Continuous Update Project that was established to undertake the work from the Second Expert Report. I started working in the project in August 2007.

The methods for the systematic literature review on food, nutrition, physical activity and the risk of breast cancer were modified by the Principal Investigator of the Continuous Update Project, Dr. Teresa Norat, in respect to the Second Expert Report. I contributed to this modification. I also contributed to the development of the protocol for reviewing breast cancer survival studies with the advice of the Expert Panel. I prepared the search strategy with the librarian at Imperial College London; for which, I did a pilot test. With the advice of the Expert Panel, I did a second pilot test on the protocol to decide on the search strategy and on how to analyse the data in relation to the exposure factors timeframe and breast cancer outcomes. I modified the data extraction interface with the database manager, Mr. Rui Vieira. I worked on maintaining the quality of the data, with the assistance of the database managers, Mr. Rui Vieira and Mr. Christophe Stevens.

I conducted the literature search, study selection and data extraction with the Continuous Update Project team. I checked and reviewed the data together with the data collected by the Systematic Literature Review Centre at the National Cancer Institute, Milan for the Second Expert Report. I conducted all data analyses and interpreted the results in the present thesis. I interacted with the statistical adviser of the project, Dr. Darren Greenwood at the University of Leeds. I used the STATA codes from the statistical adviser and wrote the STATA programmes for the statistical analysis.

I was responsible for leading the production of the breast cancer reports for the Continuous Update Project. I contributed to writing the reports and presenting the results to the World Cancer Research Fund International Secretariats and the Expert Panel.

I worked with Dr. Dora Romaguera at Imperial College London and Dr Panagiota Mitrou at the World Cancer Research Fund International to review the literature on World Cancer Research Fund Cancer Prevention Recommendations adherence and breast cancer risk. I was responsible for the statistical analysis and results interpretation.

The views expressed in this thesis are my own opinions.

Copyright Declaration

Abstract

Background

There is evidence that diets and active lifestyle that allows adequate body weight contribute to breast cancer prevention. It is important to keep the evidence base updated to inform lifestyle recommendations and provide useful guidance.

Methods

As part of the work for the World Cancer Research Fund (WCRF) International Continuous Update Project, the accumulated evidence from cohort studies and randomised controlled trials on energy balance-related factors (total energy intake, physical activity and adiposity) and risk of female breast cancer development and mortality after breast cancer, was systematically reviewed and meta-analysed. The evidence was graded (convincing, probable, limited) and compared with the conclusions published in the 2007 WCRF Second Expert Report.

Results

Overall, 230 publications were meta-analysed.

Higher body fatness, as indicated by body mass index (BMI), and adult weight gain, convincingly increased (12% per 5 kg/m^2 and 7% per 5 kg, respectively); and recreational and vigorous physical activity probably reduced (12% and 10% for high vs low levels) postmenopausal breast cancer risk. Evidence on abdominal and gluteofemoral fatness (waist and hip circumferences, waist-hip-ratio) supports these findings. As reported previously, BMI was inversely associated with premenopausal breast cancer risk. Physical activity remains graded limited suggestive, but new findings on vigorous physical activity suggested probable protection (21% for high vs low levels) against breast cancer in premenopausal women. Evidence from studies on breast cancer survivors was limited, but suggested that women with normal body weight and with higher levels of physical activity may have the most favourable survival after breast cancer.

Conclusion

The new accumulated evidence is consistent with the previous WCRF conclusions, and supports the recommendations for women to aim to have normal body weight (BMI 18.5-24.9 kg/m^2) and be physically active (≥ 30 minutes/day moderate-vigorous activity), and to prevent gain in weight and waist circumference. Breast cancer survivors may potentially benefit by following these recommendations after cancer treatment.

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List of Abbreviations

5-FU	5-fluorouracil
AJCC	American Joint Committee on Cancer
BC	Breast cancer
BMI	Body mass index
BRCA	Breast cancer susceptibility protein
CI	Confidence interval
CMF	Cyclophosphamide, methotrexate, fluorouracil
CUP	Continuous Update Project
ER	Oestrogen receptor
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
hs-CRP	high-sensitivity C-reactive protein
HT/HRT	Hormone therapy/hormone replacement therapy
IGF-1	Insulin-like growth factor-1
IL-6	Interleukin 6
IL-1beta	Interleukin 1 beta
LCI	Lower limit confidence interval
MET-hour	Metabolic Equivalent of Task-hour
MHT/PHT	Menopausal hormone therapy/postmenopausal hormone therapy
NOS	Newcastle and Ottawa Scale
OC/OCP	Oral contraceptive/oral contraceptive pill
PostBC	Postmenopausal breast cancer
PreBC	Premenopausal breast cancer
PA	Physical activity
Phet	P-value for heterogeneity
Pmet	P-value for meta-regression
PR	Progesterone receptor
Ref	Reference
RR	Relative risk
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SES	Socioeconomic status
SHBG	Sex hormone-binding globulin
SIR	Standardised incidence ratio
SLR	Systematic literature review
TNBC	Triple-negative breast cancer
TNF-alpha	Tumour necrosis factor-alpha
UCI	Upper limit confidence interval
UICC	Union for International Cancer Control
WC	Waist circumference
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
WHR	Waist-hip-ratio
WHO	World Health Organisation

List of Abbreviations of Study Names

40-y	Age 40-programme
ABCPP	After Breast Cancer Pooling Project
ABCFR	Australian Breast Cancer Family Registry
ABCSG	Adjuvant Denosumab in Breast Cancer Trial
ACCFR	Australasian Colorectal Cancer Family Registry
ACLS	Aerobic Center Longitudinal Study
AICHI	Three-Prefecture Cohort Study in Aichi
AHS	Agricultural Health Study
AHS, 1974	Adventist Health Study
ANZDCC	Australian and New Zealand Diabetes and Cancer Collaboration
APCSC	Asia-Pacific Cohort Studies Collaboration
ARIC	Atherosclerosis Risk in Communities Study
ATAC	The Arimidex, Tamoxifen Alone or in Combination study
BCAC	Breast Cancer Association Consortium Studies
BCDDP	Breast Cancer Detection Demonstration Project Follow-up Study
BCSC	Breast Cancer Surveillance Consortium
BIG 02-08	The Breast International Group 02-08 Randomised Trial
BWEL	Breast Cancer WEight Loss Study
BWHS	Black Women's Health Study
CAHS	College Alumni Health Study
CASH	Cancer and Steroid Hormone Study
CARE	Women's Contraceptive and Reproductive Experiences Study
CCHS	Copenhagen City Heart Study
CCPPS	Copenhagen Center for Prospective Population Studies
CDBCPT	Canadian Diet and Breast Cancer Prevention Study
CGHFBC	Collaborative Group on Hormonal Factors in Breast Cancer
CGPS	Copenhagen General Population Study
CHANCES	Consortium of Health and Aging: Network of Cohorts in Europe and the United States
CLUE I/II	Campaign Against Cancer and Heart Disease I/II
CNBSS	Canadian National Breast Screening Study
Columbia, MO cohort	Columbia Missouri Breast Cancer Serum Bank
CONOR	Cohort of Norway
CPRD	Clinical Practice Research Datalink
CPS I/II	American Cancer Society - Cancer Prevention Study I/II
CPS II-Nutrition Cohort	Cancer Prevention Study II- Nutrition Cohort
CSDLH	Canadian Study of Diet, Lifestyle and Health
CSECK	Cancer Screening Examination Cohort of Korea
CTS	California Teachers Study
CWLS	Collaborative Women's Longevity Study
DBCG	Danish Breast Cancer Cooperative Group
DCH	Danish Diet Cancer and Health Study
DOM-project Utrecht	DOM Project for the Early Detection of Breast Cancer
E3N	Etude Epidémiologique de Femmes de la Mutuelle Générale de

	l'Education Nationale
EBCTCG	Early Breast Cancer Trialist' Collaborative Group
EPIC	European Prospective Investigation into Cancer and Nutrition
EPIC-PANACEA	European Prospective Investigation into Cancer and Nutrition–Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity
FAHBS	Finnish Adult Health Behaviour Survey
FFTC	Finnish Female Teachers Cohort
FHS	Framingham Study
FHS-Offspring Cohort	Framingham Heart Study - Offspring Cohort
GACS	Glasgow Alumni Cohort study
GPRDC	General Practitioners Research Database Cohort
HAHS	Harvard Alumni Cohort
HBCCS	Hereditary Breast Cancer Clinical Study
HEAL	Health, Eating, Activity, and Lifestyle Study
HEBON	Hereditary Breast and Ovarian Cancer Study (HBOCS)
HeCOG	Hellenic Cooperative Oncology Group
HSDH	Hawaii State Department of Health, 1975
HUNT	HUNT (North-Trondelag Health Study), Norway
IBCCS	International BRCA1/2 Carrier Cohort Study
IBCSG	International Breast Cancer Study Group
Iowa 65 and RHS	Iowa 65+ Rural Health Study
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort study
JPHC I/II	Japan Public Health Center-based Prospective Study
KBCR	Korean Breast Cancer Registry
kConFab	Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer
KNHIC	Korean National Health Insurance Corporation Study
KPMCP	Kaiser Permanent Medical Care Program
KWC	Korean Women's Cohort
LACE	Life After Cancer Epidemiology
LIBCS	Long Island Breast Cancer Study
LSOA	Longitudinal Study on Aging
MCCS	Melbourne Collaborative Cohort Study
MCHES	Mobile Clinic Health Examination Survey
MCS	Miyagi cohort study (MIYAGI-I)
MDCS	Malmö Diet and Cancer Study
MEC	Multiethnic Cohort Study
Me-Can	Metabolic Syndrome and Cancer Project
MIYAGI-II	Three-Prefecture Cohort Study in Miyagi
MPP	Malmö Preventive Project
MSP	Mammography Screening Program
MSP, Modena	Modena Screening Program, Modena
MWS	Million Women Study
NCS	Norwegian Counties Study
NHANES I/III	National Health and Nutrition Examination Survey I/III

NHEFS	National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study
NHIS	National Health Interview Survey
NHS and NHS II	Nurses' Health Study and Nurses' Health Study II
NIH-AARP	National Institute of Health (NIH)-AARP(formerly the American Association for Retired Persons) Diet and Health Study
NBCSS	Norwegian Breast Cancer Screening Study
NLCS	The Netherlands Cohort Study on Diet and Cancer
NNHSS	Norwegian National Health Screening Service study
NNTHS	Norwegian Nord-Trøndelag Health Study
NOWAC	Norwegian Women and Cancer Study
NSABP – P1	National Surgical Adjuvant Breast and Bowel Project - Breast Cancer Prevention Trial
NSPT	Norwegian Screening Programme for Tuberculosis
NYSC	New York State Cohort
NYUWHS	New York University Women's Health Study
NSMSC	Northern Sweden Mammary Screening Study
ORDET	Hormones and Diet in the Etiology of Breast Cancer Study
P-1	Breast Cancer Prevention Trial
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening trial
Pooling Project	The Pooling Project of Diet and Cancer of Prospective Studies of Diet and Cancer
PSC	Prospective Studies Consortium
SBCS	Shanghai Breast Cancer Study
SBCSS	Shanghai Breast Cancer Survival Study
SCCS	Southern Community Cohort Study
SCHS	Singapore Chinese Health Study
SEARCH	Studies of Epidemiology and Risk Factors in Cancer Heredity
SFCTW	Sweden, Finland Co-twin Study
SIMS	Swedish Intergenerational Mortality Study
SISTER	The Sister Study
SMC	Swedish Mammography Cohort
SNMC	Swedish National March Cohort
SNUHBCC	Seoul National University Hospital Breast Care Center
SOF	Study of Osteoporotic Fractures
SSGPS	Southern Sweden General Population Study
SSOS	Southern Swedish Occupational Study
STAR	Study of Tamoxifen and Raloxifene
STC	Swedish Twin Cohort
SNDRCS	Swedish National Diabetes Register Cohort Study
SU.VI.MAX	Supplémentation en Vitamines et Minéraux Antioxydants Study
SWHS	Shanghai Women's Health Study
TBCSS	Taiwanese Breast Cancer Screening Study
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening
USRT	U.S. Radiologic Technologists cohort
VCS	Vlaardingen cohort study
VHM&PP	Vorarlberg Health Monitoring and Prevention Programme

VIP	Västerbotten Intervention Project
VITAL	Vitamins And Lifestyle Study
VMC	Vermont Mammography Cohort
WHEL	Women's Healthy Eating and Living Study
WHI	Women's Health Initiative
WHI-CT	Women's Health Initiative Clinical Trials
WHI-DM	Women's Health Initiative Dietary Modification Trial
WHI-OS	Women's Health Initiative Observational Study
WHS	Women's Health Study
WINS	Women's Intervention Nutrition Study
WLHS	Swedish Women Lifestyle Health Cohort Study
WLHS, Sweden and Norway	Women Lifestyle Health Cohort Study, Sweden and Norway

1 Introduction

Breast cancer (BC) is a major public health burden, with 1.67 million new cases and about half a million deaths estimated in 2012 worldwide[1].

In economically developed countries such as the UK, there were approximately 620,000 women diagnosed with breast cancer during 1995-2009, and net 74-81% were estimated to have survived for the next five years[2]. The figure is growing due to the aging populations, mammography screening programmes, advancement of medical facilities and treatment and changes in lifestyle, reproductive and hormonal factors, such as, higher obesity rates, lower parity and earlier menarche.

Breast cancer incident and mortality rates vary with time and economic development, between geographic regions and in migrants or generations of migrants moving across these regions[3-6]. These signify the role of environmental and lifestyle factors in the aetiology of breast cancer.

Previous evidence has shown that obesity increases and physical activity may decrease the risk of breast cancer development in postmenopausal women[7]. There is less evidence in premenopausal women, in which breast cancer risk is probably reduced and suggestively reduced with these factors, respectively[7]. Lifestyle factors may also have a role in survival after breast cancer diagnosis[8-10].

Hence, one potential prevention strategy is the modification of unhealthy lifestyles, particularly chronic positive energy balance (excess energy intake and insufficient physical energy expenditure) that leads to weight gain, overweight and obesity, a phenomenon that is prevalent in Western countries and is increasing among economically developing countries[11;12]. About 10.2% of postmenopausal breast cancer was attributable to high body mass index (BMI) ($\geq$25 kg/m^2) in 2012 globally[13], thus avoiding excess adiposity may reduce the burden of breast cancer.

In 2007, World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) issued ten evidence-based Cancer Prevention Recommendations on diet, physical activity, body fatness and weight gain, alcohol consumption, dietary supplement use and breastfeeding, which are applicable to people with or without cancer[7]. Adherence to the WCRF/AICR recommendations has been shown to prevent cancer development[14], improve cancer survival[15], and reduce mortality[16].

Because breast cancer is largely a hormone dependent cancer, lifestyle factors such as alcohol consumption, postmenopausal hormone use and excess body weight affect its risk primarily through the hormonal pathway, and other inter-related pathways (insulin-IGF axis, inflammation, and adipocytokines metabolism)[17]. Although breast cancer is increasingly recognised as a heterogeneous disease[18-21], it is still unclear whether the influence of lifestyle factors on breast cancer development varies across the different breast cancer types. Other areas that need clarifications include lifestyle factors during early adulthood, as this may be one susceptible critical period to breast cancer development[22].

Therefore, more effort is needed to disentangle the relationships, which will help identify targets for public health prevention strategies that are urgently needed to prevent the development of new breast cancer cases and improve the survival of breast cancer patients.

1.1 Aims of the PhD study

The aim of the present PhD study was to provide evidence base for the update of the WCRF/AICR recommendations for cancer prevention[7]; and more specifically, to provide the scientific evidence from epidemiologic findings on energy balance-related factors and the risk of breast cancer development and mortality after breast cancer. We also aimed to examine its consistency with the 2007 WCRF/AICR Cancer Prevention Recommendations[7] and whether adherence to these recommendations protects against breast cancer development.

To fulfil this aim, relevant evidence was systematically reviewed and meta-analysed. The findings were graded for their strength in terms of causality, and compared with the grading made in the WCRF/AICR Second Expert Report[7] to enable its update.

1.2 Structure of the thesis

The next two chapters cover the background information of the present PhD study. Chapter two introduces the context of the disease, in terms of the pathogenesis, detection and diagnosis, and treatments of female breast cancer. Chapter three covers the risk factors for breast cancer development and the prognostic factors for breast cancer survival in women; in particular, factors related to energy balance (total energy intake, physical activity, weight change and adiposity) and the proposed underlying biological mechanisms that link physical activity and excess adiposity to breast cancer. The evidence-based WCRF/AICR Cancer Prevention Recommendations published in 2007[7] are also introduced here.

Chapter four is the materials and methods of the updated systematic reviews and meta-analyses conducted in the present PhD study, as part of the work for the WCRF Continuous Update Project. The method used by the WCRF to grade the evidence for its strength to infer causality is illustrated.

This is followed by the results of the systematic reviews and grading of the evidence, on the associations of energy balance-related factors and breast cancer risk (Chapter five) and mortality risks after breast cancer (Chapter six). The chapters are concluded with the judgements on the new accumulated evidence and whether these judgements were consistent with those made for the WCRF Second Expert Report. Chapter seven is a systematic review of studies on adherence to WCRF/AICR Cancer Prevention Recommendations[7] and breast cancer risk.

Finally, chapter eight is the discussion of the findings of the present PhD study and whether they supported the 2007 WCRF/AICR Cancer Prevention Recommendations[7], along with the discussion of

the strengths and limitations of the present study, possible future work, and implications of the findings.

2 Anatomopathology of breast cancer

2.1 Female breast anatomy and physiology

The breast is made of connective tissue, fat and glandular tissue and ducts. The latter comprise lobules, which are glands that produce milk; and ducts, which are tubes that carry milk from the lobules to the nipple during lactation (Figure 2.1).

There are 15 to 20 lobes that are divided further into 20 to 40 lobules per lobe in each breast[23]. Lobules or terminal duct lobular units (TDLUs) are thought to be the primary anatomical source of most breast cancer precursors and cancers[24]. Lining the lobules and terminal ducts are epithelial cells. The breast is supplied by many blood and lymph vessels and more than 75% of the lymphatic drainage is through the lymph nodes in the axillary region (20 to 30 nodes).

The main lactiferous ducts are formed at birth and the mammary glands remain under-developed until puberty[25]. During puberty, the production of ovarian oestrogen and progesterone induces the growth of the breasts. Terminal differentiation of the breasts takes place during pregnancy and lactation.

The breasts undergo cyclical changes in response to the changing levels of the ovarian hormones during the menstrual cycle. After menopause, the cessation of ovarian activity leads to a fall in oestrogen and progesterone levels and the glandular tissues in the breasts involute. The size and shape of the breast is determined by the amount of connective tissue and fat tissue. The density of the breast is measured by the proportion of non-fat tissue to fat tissue. Denser breasts have more non-fat tissue and less fat tissue.

2.2 Pathogenesis of breast cancer

Breast cancer is characterised by uncontrolled cellular proliferation and aberrant programmed cell death, as a result of changes in the genetic information of cells and the accumulation of unrepaired DNA mutations. Along with accompanying alterations in surrounding tissues, the affected cells and tissues progress through multiple stages that can take over decades[26].

About 5-10% of all breast cancer cases are attributable to the inheritance of a mutated gene, of which up to 30% is due to germline mutations in the high penetration genes *BRCA1* and *BRCA2*[27]. Most breast cancer cases are sporadic, occur spontaneously during cell replication or as a result triggered by exposure to environmental carcinogens or factors.

Breast cancer is a hormone dependent cancer. The growth of breast cancers, as does the breast *per se*, is driven by oestrogen and progesterone[28;29]. The underlying biological mechanisms that link circulating oestrogen and progesterone to breast cancer risk in women is not well understood, but is thought to involve the turnover of epithelial tissue, stem cells and the extracellular matrix, in addition to the regulation of the phenotype and function of stromal and immune cells, including macrophages and regulatory T cells in the breasts; which lead to genome instability, increased likelihood of random

genetic mutations, dampen immune surveillance and promote tolerance of pre-cancerous cells in the mammary gland, and thus increase the risk of breast cancer initiation[30].

The majority of breast cancers are adenocarcinomas that arise from the epithelial lining of the TDLUs. Sarcomas, account for <1% of primary breast cancers, arise from the connective (stromal) components of the breast[31].

Metastatic breast cancer is spread primarily through lymphatic drainage of the epithelial and mesenchymal components of the breast[23]. Cells from a primary breast cancer may break away and form a secondary cancer in other organs. About 5% of breast cancer survivors will get a second primary breast cancer within 8 years of their initial diagnosis and 14% after 25 years[32].

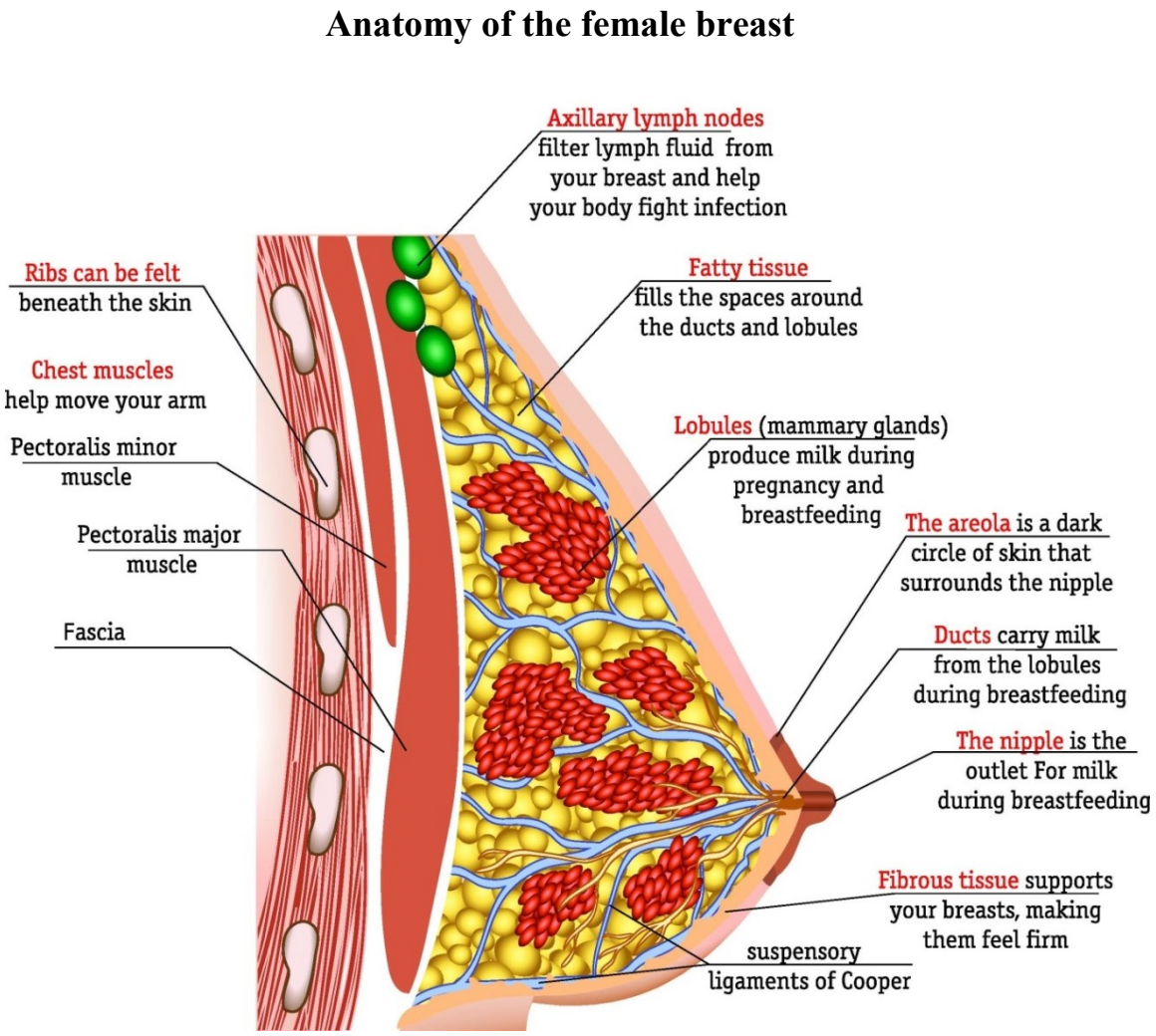

Figure 2.1 Anatomy of the female breast.

Source: Elen Bushe/Shutterstock.com

2.3 Breast cancer classification

Breast cancer is a heterogeneous disease. Breast cancer can be classified into histological and molecular subtypes[20;33].

Histological subtypes of breast cancer

Ductal carcinoma in situ (*DCIS*) and Lobular carcinoma in situ (*LCIS*) are tumour cells confined to the basement membrane in the breast. *DCIS*, the most common form of non-invasive breast cancer (stage 0) (83% of all CIS), is considered a precursor of invasive breast cancer; although the natural history of progression is not clear[34]. The widespread use of screening mammography has led to an increase in incidence of DCIS in recent decades[35;36]. *LCIS*, also known as lobular neoplasia (13% of all CIS), is generally not thought to be a precursor of invasive breast cancer, although *LCIS* is a risk factor for invasive breast cancer[37] (see section 3.1.1).

About 70-80% of all invasive breast cancer (International Classification of Diseases [ICD]-9 code 174 or ICD-10 code C50) are ductal carcinomas, follows by lobular carcinomas at about 10%, and the rest are rare specific subtypes (mucinous [colloid], medullary, papillary and tubular carcinomas)[33].

Invasive carcinoma is graded according to the tubule formation, nuclei grade and mitotic rate, into well-differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3) breast cancer. Malignancy or aggressiveness of the tumour increases from low to high grade. Low grade tumours have a better prognosis because of slower growth and less likely to spread than high grade tumours.

Obese breast cancer patients are likely to have more biologically aggressive tumours because a number of cellular proliferation pathways are upregulated in the obese state and lead to increased tumour cell proliferation and metastasis[38].

Molecular subtypes of breast cancer

The molecular subtypes are classified basing on the surface receptors expression of the breast cancer cell determined by diagnostic tests such as immunohistochemistry (IHC) test and in-situ hybridization (ISH) test, specifically according to oestrogen (ER), progesterone (PR) and human epidermal growth factor receptor-2 (HER2 or c-erbB-2 or HER2/neu) tumour status[39]. The presence of hormone receptors (HR+) means that these breast cancers are sensitive to hormones.

There are at least four different breast cancer molecular subtypes: luminal A (ER+ and/or PR+, HER2−) (71% of all breast cancers) is low grade and have the best prognosis, follows by luminal B (ER+ and/or PR+, HER2+) (12%) that tends to be of higher grade with a poorer prognosis than luminal A breast cancer. Triple-negative (TNBCs) (ER−, PR− and HER2−) (12%) are larger and of higher grade, although less likely to have lymph node metastases, is associated with the worst

outcome[40]. HER2-enriched (ER−, PR− and HER2+) (5%) tend to grow and spread more aggressively than other HR+ breast cancers[39].

Molecular classification of breast cancer allows better personalised treatment and prediction of prognosis[33;41].

2.4 Staging of breast cancer

Breast cancer stage refers to the extent of breast cancer at diagnosis. One internationally accepted classification for staging cancer is the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM Classification of Malignant Tumours. This classification system uses the information regarding the size of the tumour (T), whether the tumour has spread to the lymph nodes (N) – regional extension – , and whether the tumour has metastasised (M)[42]. There may be other breast cancer staging systems, but TNM staging is used commonly by the National Cancer Institute Surveillance, Epidemiology, and End Results Program registries in the US and other cancer registries worldwide.

Numeric or roman numerals staging of breast cancer uses the combined information on the T, N, and M of the tumour. Stage 0 breast cancer (*DCIS*) is a non-invasive cancer, where abnormal cells are confined in the ducts and lobules of the breast tissue. Stage I-IIA breast cancers are early invasive breast cancers, where the tumours are smaller (no larger than 50 mm) and may or may not have spread to the lymph nodes. Stage IIB-IIIC breast cancers are locally advanced invasive breast cancers, where the tumours are larger and/or have spread to more number of lymph nodes. Stage IV metastatic breast cancer is tumour of any size and has spread to other organs or chest wall.

The systems have been updated throughout the years. The latest 8th edition of the UICC/AJCC TNM staging classification includes both clinical staging and pathological staging, and an overall stage is assigned with the ER, PR, HER2 status and grade of the cancer.

TNM staging is important for predicting the prognosis of a cancer patient and helps clinicians to decide on the treatment plans. Tumours with higher T and N stages are more advanced and often have poorer prognosis. Higher breast cancer stages in obese women may reflect tumour biology (obesity drives the development of more aggressive breast cancers) or delated diagnosis, which is linked to higher risk of recurrence and mortality [43]. Hence, epidemiological studies of cancer survivors should take into account cancer staging.

2.5 Breast cancer detection and diagnosis

Breast cancer screening in asymptomatic women aims to reduce breast cancer mortality and morbidity associated with advanced stages of the disease via early detection. The single most effective method is mammography[39]. However, there has been considerable controversy over the potential benefits and harms in mammography screening.

Studies have shown mortality reductions of 23% in women (aged 50-69 years) invited and 40% in women attended mammography screening compared with women not screening[44]. Screened versus non-screened women were reported to have smaller tumours and lower risk of multiple tumours[45], and higher proportions of localised cancer and well-differentiated tumour[45].

The review conducted by a specially convened independent panel in the UK has reported supporting evidence[46]. The meta-analysis of randomised controlled trials (RCTs) of mammography screening showed a 20% (95% CI: 11–27%) reduction in breast cancer mortality in women invited for screening. However, there was also evidence of overdiagnosis of breast cancer. It was estimated that 19% (95% CI: 15–23%) of *in situ* or invasive breast cancers diagnosed in women invited for screening would not have caused any problem if left undiagnosed and untreated. This approximately translates to the prevention of 43 breast cancer deaths and 129 cases of overdiagnosed breast cancer for every 10,000 UK women aged 50 years invited to screening for the next 20 years[46]. Other harms in relation to mammography screening include false positive results and radiation-induced cancer.

Uptake of routine invitations to the National Health Service Breast Screening Programme in England among women aged 50-70 years has fallen from 72.1% in 2015-2016 to 71.1% in 2016-2017[47]. It is important to provide clear information on the benefits and harms of mammography screening for women invited to screening to make informed decisions.

Magnetic resonance imaging has been proposed as an adjunctive screening to mammography in those with extremely dense breasts[48], and in those of increased lifetime breast cancer risk[39]; while the use of breast ultrasound and other imaging techniques for diagnosis are still under investigation. Physical examinations, such as clinical breast examination and breast self-examination are no longer recommended because of unclear benefits[39].

2.6 Breast cancer treatment

The standard treatments include surgery, radiotherapy, chemotherapy and hormonal therapy that are personalised taking into account the tumour characteristics, age and menopausal status of the patient, among other factors[39].

Primary treatment in most women with early stage breast cancer is local surgery (breast-conserving surgery or mastectomy). Neoadjuvant therapy that is given before surgery aims to shrink larger breast tumours to aid and allow for less extensive surgical removal. After surgery, adjuvant therapy (radiotherapy, chemotherapy, hormonal therapy, and targeted therapy) is used to eliminate any undetected micro-metastases in other parts of the body and prevent recurrence. Metastatic breast cancer patients are mostly treated with systemic therapies. Hormonal therapy is given to hormone-sensitive breast cancer patients to lower oestrogen levels (aromatase inhibitors, such as letrozole, anastrozole and exemestane) or to block the effects of oestrogen on tumour growth (selective

oestrogen receptor modulators, such as tamoxifen and raloxifene). Premenopausal patients with active production of ovarian oestrogens require ovarian ablation before the use of aromatase inhibitors. Because of effective hormone therapy, luminal A breast cancer patients in Western countries have higher survival rates and lower recurrence rates compared to breast cancer patients with other molecular subtypes[39]. Targeted therapy (such as trastuzumab) is available to HER2-positive breast cancer patients; however, currently there are no targeted therapies for patients with TNBC, which partly explains the worse prognosis in these patients[39].

Weight gain[49], physical pain and fatigue[50], joint pain, boss loss and osteoporosis[51], cardiac toxicity[52], and endometrial cancer[53] are among the common side-effects of breast cancer treatment, and would further affect lifestyles, quality of life and prognosis of the breast cancer patients.

In addition to cancer staging, epidemiological studies of cancer survivors should take into account information on treatment and comorbidity conditions of the patients; as medical complications, sub-optimal treatment, and comorbidity may lead to poorer prognosis in overweight and/or obese breast cancer patients (see below for effect modification of hormone therapy and breast cancer outcomes by obesity).

BMI and surgery

Obese women have more surgical site complications, such as infections and wound dehiscence; and systemic medical complications, such as venous thromboembolism and pneumonia, after surgery[54-56]. Obese women have higher risk of developing lymphedema after surgery (RR = 5.5)[57].

BMI and chemotherapy

Concerns about cardiotoxicity in obese breast cancer patients receiving chemotherapy have led to the usual practice of dose reduction in the past, and insufficient treatment has affected prognosis in these patients[58;59]. However, a recent review has demonstrated that there is no indication of increased hematologic or non-hematologic toxicity among these patients, and recommended the use of full weight-based chemotherapy doses for treating obese patients[60;61].

BMI and targeted therapy

A recent meta-analysis has estimated that in HER2-positive breast cancer patients, trastuzumab-related cardiotoxicity occurred in 6.5% (95% CI: 2.3–12.5%) of the patients with a BMI ≥25 kg/m^2, as opposed to 3.0% (95% CI: 2.4–3.6) in all patients[62].

BMI and hormonal therapy

Obesity in breast cancer patients may reduce the efficacy of aromatase inhibitors as a result of inadequate suppression of the increased aromatase activity and serum oestrogen levels in these

women[63]. At least three clinical trials of aromatase inhibitors found differential drug response by obesity status.

In the Arimidex, Tamoxifen, Alone or in Combination trial, obese postmenopausal breast cancer patients using anastrozole compared with tamoxifen had higher risk of total recurrence (RR = 1.39) and distant recurrence (RR = 1.46) than their normal weight counterparts[64]. In the Austrian Breast and Colorectal Cancer Study Group 6a trial, extended use of adjuvant anastrozole versus no further use conferred better disease-free survival and overall survival in normal weight but not overweight and obese postmenopausal breast cancer patients[65]. In the Austrian Breast and Colorectal Cancer Study Group 12 trial, premenopausal breast cancer patients using anastrozole plus goserelin compared with tamoxifen plus goserelin and were overweight or obese had worse disease-free survival (RR = 1.49) and overall survival (RR = 3.03) than normal weight patients[66]. However, the Breast International Group 1-98 trial found that survival benefit from letrozole compared with tamoxifen was the same for normal weight and obese postmenopausal women[67]. Letrozole may be more effective than anastrozole in obese patients.

BMI and comorbidity

Comorbid health conditions, such as diabetes, hypertension, myocardial infarction and stroke are more prevalent in obese compared with normal weight breast cancer patients[68;69], and breast cancer patients with comorbidity are less likely to receive optimal treatment, which impact on survival[70].

3 Epidemiology and prevention of breast cancer

There were 1.67 million new breast cancer diagnosis (age-standardised rate [ASR] per 100,000, 43.1) and 521,907 deaths from breast cancer (ASR 12.9) in women worldwide in 2012[1]. Breast cancer is the most frequently diagnosed cancer (25.1% of all incident cancers) and the leading cause of cancer death (14.7% of all cancer deaths) in women[1]. Lifetime risk of developing breast cancer is about 12% (1 in 8)[71].

Across the continents, the incidence rates vary by about three-fold, with the lowest rate in Asia (ASR 29.1) and the highest rate in North America (ASR 91.6). The variation in mortality rate is smaller, with the lowest rate in Asia (ASR 10.2) and the highest rate in Africa (ASR 17.3) (Figures 3.1-3.3). Age-standardised 5-year net survival from breast cancer diagnosed between 2005 and 2009 ranged from 53-60% in countries such as South Africa, Mongolia and India to ≥80% in most Western countries and countries such as Brazil, China, Japan and Australia[2]. In the UK, there were about 550,000-570,000 breast cancer survivors in 2008[72]; and as of 2014, US alone had 3.1 million female breast cancer survivors[39].

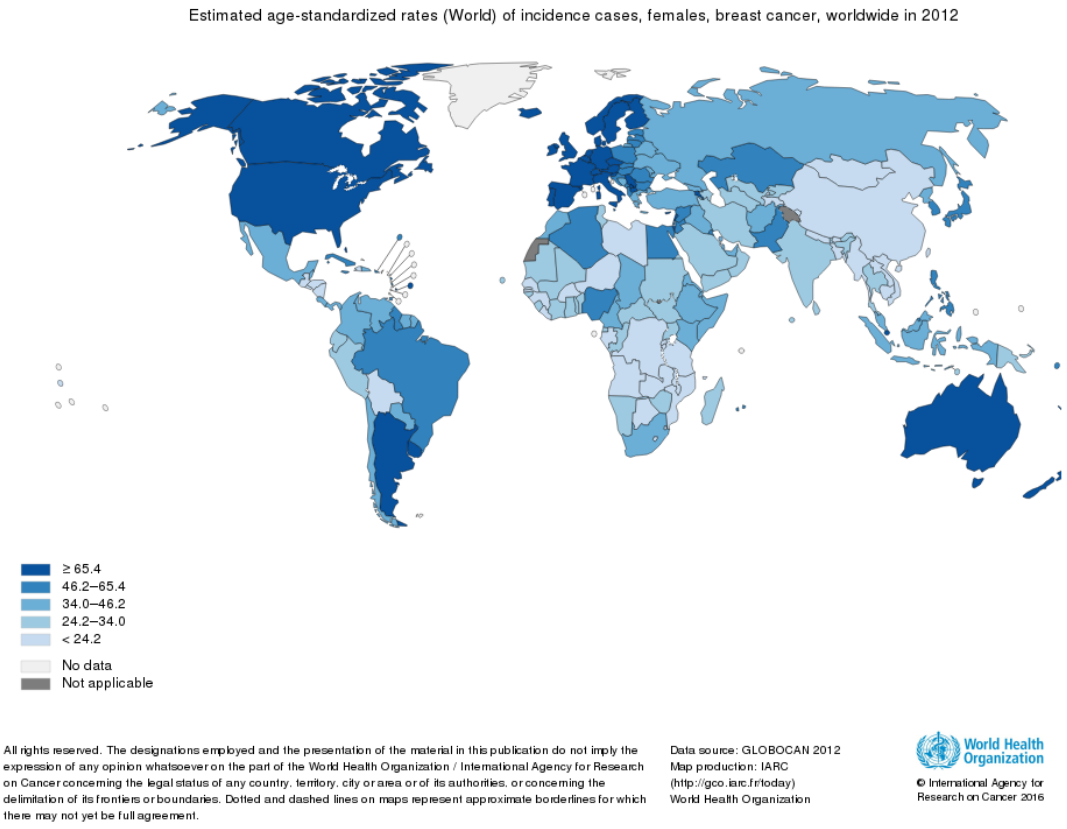

Figure 3.1 Estimated global age-standardised incidence rates of female breast cancer, GLOBOCAN 2012

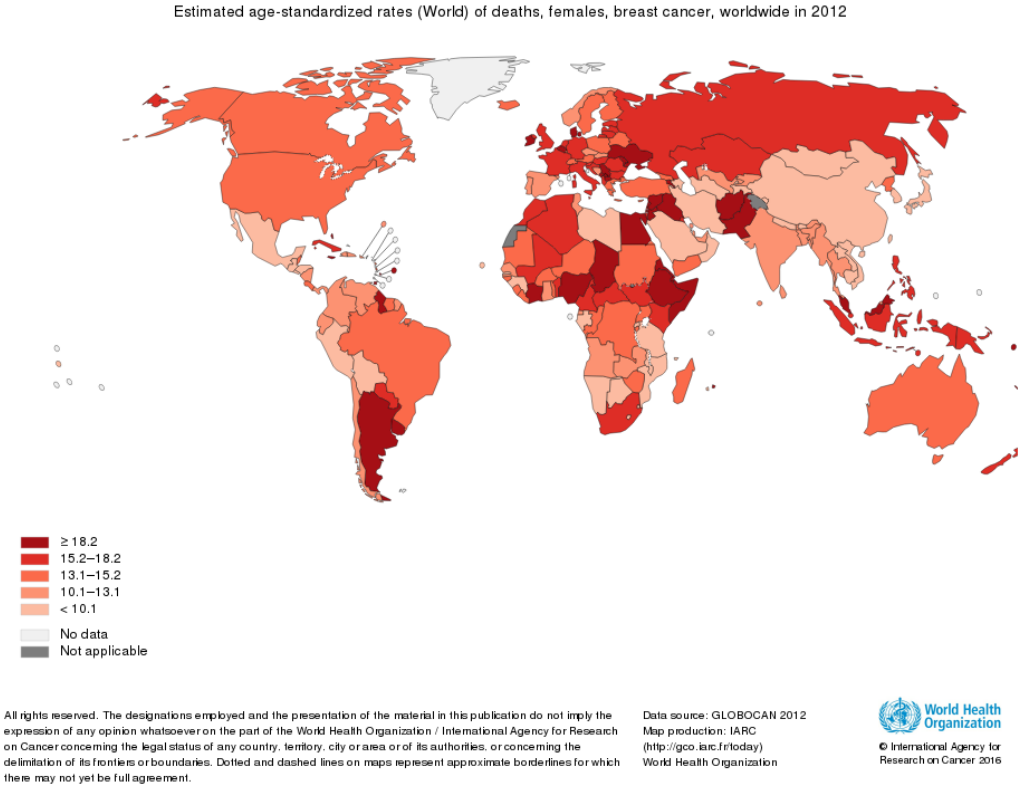

Figure 3.2 Estimated age-standardised mortality rates of female breast cancer, GLOBOCAN 2012

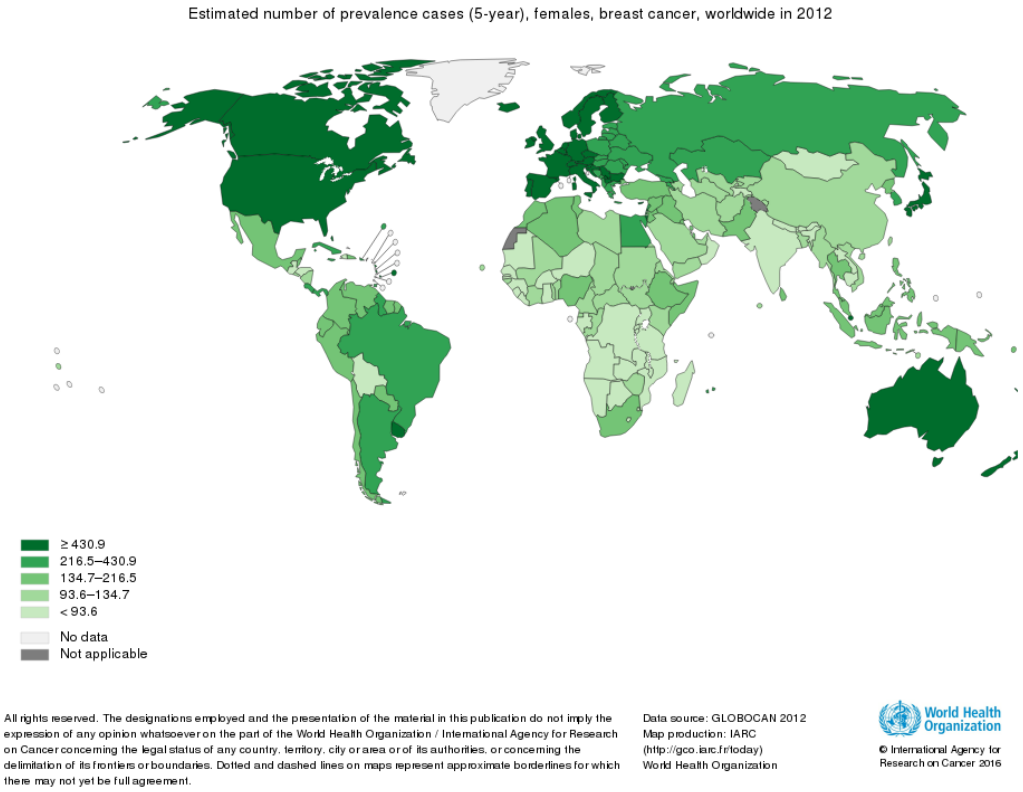

Figure 3.3 Estimated number of 5-year prevalence cases of female breast cancer, GLOBOCAN 2012

Breast cancer incidence is expected to increase in developing countries that are going through socioeconomic and nutritional transition that leads to the so-called Westernisation of lifestyle (excessive energy intake, decreased physical output, weight gain and obesity, nulliparity, fewer children, and late pregnancy)[4]. Such changes in lifestyle pattern and cancer rates are parallel to those observed in migrant studies, in which the risk of breast cancer rose over several generations of migrants from traditionally low-risk countries and approached that in the host country[5;6]. These signify the importance of lifestyle factors in cancer development.

The pool of breast cancer survivors is also growing in economically developed countries because of the aging populations, longer life expectancy, mammography screening programmes and advancement of medical facilities and treatment[73].

Based on the age-specific cancer rates in 2008, 2.2 million new breast cancer diagnosis and 0.74 million breast cancer deaths are projected by 2030[74]. The annual cost of breast cancer to the UK economy was £1.5 billion, with £0.6 billion from healthcare alone[75]. Therefore, breast cancer is a major public health burden.

3.1 Risk factors in breast cancer development

Many factors have been shown to increase the risk of breast cancer development[39]. Factors, such as age, genetic factors, family history and reproductive factors, are not modifiable; while lifestyle factors, for example factors related to energy balance can be intervened. Chronic positive energy balance, as a result of excess energy intake, inadequate energy expenditure through physical activity and increase sedentary behaviour, manifests into excess adiposity over time[76]. This phenomenon is prevalent in modern societies and has increasingly become a global burden[11;12] . In 2012, about 10.2% of postmenopausal breast cancer was attributable to high body mass index (BMI $\geq$25 kg/m^2) globally[13]. Hence, targeting energy balance-related factors are potentially useful for breast cancer prevention. Some lifestyle factors, not only implicate breast cancer risk, but also may affect disease outcomes[8;60;77].

One endures exposure to these risk factors throughout life, although there may be susceptible critical periods to breast cancer development[22]. Exposures during adolescence or early adulthood may be particularly relevant for breast cancer development because this period is characterised by increases in sex hormone levels and rapid proliferation of incompletely differentiated breast tissue[22]. Research has focused primarily on exposure to risk factors during adulthood because of the difficulty of collecting exposure data for other life periods.

3.1.1 Personal characteristics and family history

Age

Breast cancer incidence rate generally increases with age. Age-specific incidence rates (ASR per 100,000) in women rise sharply from aged 30-34 years (ASR 31.7) and peak at aged 85-89 years in the UK (ASR 476)[78]. The decrease thereafter may reflect lower rates of screening and/or incomplete detection. About 1 in 4 breast cancers happen before age 50 years[79].

Younger women have lower net five-year survival (85% in aged 35-39 years) compared with slightly older women (92% in aged 60-69 years)[78], possibly due to adverse pathological factors including tumours that are late stage, high grade, triple negative and HER2-positive[80]. However, women in the oldest age group have the lowest survival rate (70% in aged 80-99 years)[78].

Race/ethnicity

Breast cancer incidence and mortality rates are higher among non-Hispanic white and non-Hispanic black compared with American Indian/Alaska Native, Hispanic/Latina and Asian/Pacific Islander women[39].

Specifically, African-American women have been shown to have lower risk of developing breast cancer (hazard ratio [HR] = 0.75, 95% CI: 0.61-0.92) but higher risk of dying after breast cancer (1.79, 95% CI: 1.05-3.05) than white women[81]. Higher frequency of high grade and ER-negative tumours in African-American women may contribute to their poorer prognosis.

Hispanic/Latina, American Indian/Alaskan Native and Asian/Pacific Islander women also have lower risks of developing breast cancer compared with white women, but the associations were largely explained by breast cancer risk factors such as family history, reproductive factors, exogenous hormone use, mammography and other lifestyle factors (HRs = 0.89 to 0.98, all P-values $\geq$0.62)[81].

Women of Ashkenazi Jewish descent were reported to have higher risk of developing breast cancer compared with other racial or ethnic groups (RRs = 1.10, 95% CI: 0.84-1.44 overall; 3.78, 95% CI: 1.74-8.16 with family history of breast cancer)[82]. The increase in risk is likely due to higher prevalence of *BRCA1/2* gene mutations, which are genetic risk factors of breast cancer (see below, genetic factors), in Ashkenazi Jews (1 in 40 individuals) than in the general population (1 in 400)[83].

A higher proportion of ER-positive breast cancers is found with women of Western populations and ER-negative breast cancers with Asian women[84]. Early onset breast cancer (<50 years of age) is also more frequent among Asian women. When diagnosed, the cancer is of high grade and advanced stage because of the lack of early detection by screening programmes in some countries, apart from China, Taiwan, Singapore, Japan and South Korean. Hence, survival after breast cancer is affected [84].

Family history

Women with a family history of breast cancer are at increased risk of breast cancer because of genetic factors and common lifestyle and behaviour[85;86]. As shown in a large collaborative study of 58,209 women with breast cancer and 101,986 women without the disease, the risk ratios for breast cancer in

women with one, two and ≥ three affected first-degree relatives were 1.80 (99% CI: 1.70-1.91), 2.93 (99% CI: 2.37-3.63) and 3.90 (99% CI: 2.03-7.49) compared with women with no family history[85]. Having an affected second-degree relative also increased the risk (RR = 1.50, 95% CI: 1.40-1.60)[86]. Family history was not associated with breast cancer mortality in the collaborative study[85].

Genetic factors

In the past decades, we have gained increasing knowledge on the link between genetic risk factors and breast cancer[87].

Women with a high penetrance cancer-predisposing gene, such as *BRCA1* and *BRCA2*, have increased risk of breast cancer compared with those without. Cumulative breast cancer risks at age 70 years are 57% (95% CI: 47-66%) for *BRCA1* mutation carriers and 49% (40-57%) for *BRCA2* mutation carriers[88]. Whether *BRCA1* and *BRCA2* mutation carriers have poorer overall and breast cancer-specific survival[89], or not[90], is not clear.

Other high penetrance genes include *PTEN, TP53, CDH1, STK11* and *MMR*, which confer a RR of >5. Moderate penetrance genes include *CHEK2, ATM, PALB2 and BRIP1*, which confer a RR of 1.5 to 5[27].

In addition, large-scale genome-wide association studies have identified 77 common low-risk single-nucleotide polymorphisms (SNPs) that are individually associated with breast cancer risk, and together with the moderate and high penetrance genes explained about 50% of the heritability of breast cancer[91].

Breast cancer risk may influence by the interplay of genetic and lifestyle risk factors, but such data are still scarce. One early example is that being physically active or having a normal weight in adolescence may prevent or delay the onset of breast cancer in *BRAC1/2* carriers[92].

Advances in genomic knowledge are useful in predicting disease susceptibility, drug response and drug-induced toxicity. In terms of risk stratification, multiple genetic variations modestly improved breast cancer risk prediction when genetic profile was included with family history, benign breast disease, age at menarche and age at first live birth in the risk assessment models (see section 3.2 on Gail model)[93].

Personal history of breast disease

Breast cancer risk is influenced by proliferative breast diseases. A recent meta-analysis of 32 observational studies reported that the associations were modest in diseases without atypia (RR = 1.76, 95% CI: 1.58-1.95), strong in diseases with atypia (atypical lobular hyperplasia, atypical ductal hyperplasia) (3.93, 95% CI: 3.24-4.76), and non-significant in non-proliferative breast diseases (1.17, 95% CI: 0.94-1.47)[94].

Women with *LCIS*/lobular neoplasia are 7-12 times more likely, and women with *DCIS* are 8-10 times more likely to develop invasive breast cancer than women without these conditions[39].

Breast density

Dense breast is a risk factor of breast cancer. In a meta-analysis of 13 case-control studies, significant positive associations between breast density (see section 2.1 for definition) and breast cancer risk were observed in both premenopausal (odd ratio [OR] per 1 standard deviation [SD] = 1.52, 95% CI: 1.39-1.66) and postmenopausal women (OR per 1 SD = 1.53, 95% CI: 1.44-1.64)[95] .

The increase in risk was progressive with increasing density[96], and was stronger among postmenopausal hormone therapy (MHT) users than non-users[97]. On the other hand, higher breast density was not associated with breast cancer mortality[98]. Higher breast density decreases with age, parity and body weight, and is higher in women with postmenopausal hormone use[99], which are all important risk factors for breast cancer. Sensitivity of mammography in women with BMI ≥25 versus <25 kg/m^2 had been reported to be higher[100], likely because tumours in dense breasts are more difficult to detect on a mammogram as tumours often appear white, unlike fatty tissue of the breast that appears dark (masking)[99]. Detection inaccuracy could lead to an overestimation of the association between obesity and breast cancer risk in postmenopausal women, but one breast cancer surveillance study has shown that the increased rates of breast cancer overall and advanced-stage disease associated with increased BMI were not primarily due to mammography use and accuracy[101].

Socioeconomic factors

In economically developed countries, such as in Europe and North America, women with higher versus lower socioeconomic status (SES) have higher breast cancer incidence risk (RR = 1.25)[102], likely ascribed to being nulliparous or having delayed child birth, alcohol use, higher uptake of mammography screening and MHT use.

On the other hand, women of higher SES have more favourable survival than women of lower SES (RR = 0.72)[102]. Mammography screening and early detection, having better tumour-related prognostic factors, health insurance, treatment and lifestyle and less comorbidity may partly explain the socioeconomic disparity in breast cancer survival[102;103].

Height

Being taller compared with shorter is associated with increased breast cancer risk. For each 5 cm increase, the associated increase risk of postmenopausal breast cancer was 7%[104]. The relationship is complex and is likely to be a marker of genetic predisposition, early nutrition and growth, and SES. Several studies, mostly from an earlier period, evaluated whether height affects breast cancer survival. The findings in general suggested a null association[105-115].

3.1.2 Reproductive factors

Menstrual cycles and pregnancy

Early menarche (< age 12 years) and late menopause (> age 55 years) prolong the lifetime exposure of endogenous hormones, thus increase the risk of breast cancer[116]. Women who are nulliparous or have delayed first full-term pregnancy (> age 30 years) have an increased risk of breast cancer compared with those who have higher parity or a first child earlier in life.

Lactation

Breastfeeding for a longer duration is associated with reduced risk of breast cancer (RR per 5 months = 0.98, 95% CI: 0.97-0.99)[117]. Structural changes of the breast or reduced lifetime number of menstrual cycles following breastfeeding and weaning may be the underpinning reasons.

Oral Contraceptive use

The Collaborative Group on Hormonal Factors in Breast Cancer reported in a pooled analysis of 50 epidemiologic studies that current or recent oral contraceptive (OC) users had a slightly higher breast cancer risk than never users. The risk was the highest when the use was started during teenage years and declined after cessation for ≥10 years to the level comparable to never users. In addition, for those who stopped using OC pills for ≥10 years had less advanced breast cancers than the never users[118].

Postmenopausal hormone therapy use

MHT use, in particular in long-term combined oestrogen and progesterone users, is related to a higher risk of breast cancer compared with the non-use; and the risk drops after the cessation of use[119].

A study with over a million women showed that compared with never users, current MHT users had a higher risk of developing and dying from breast cancer (RRs = 1.66, 95% CI: 1.58-1.75 and 1.22, 95% CI: 1.00-1.48, respectively); and no significant association was observed with past users (1.01, 95% CI: 0.94-1.09 and 1.05, 95% CI: 0.82-1.34, respectively), which suggested the increased risk is reverted with the cessation of MHT use[120].

3.1.3 Energy balance-related factors

The associations between total energy intake, physical activity and body fatness and the risk of breast cancer development were systematically reviewed and meta-analysed in the WCRF/AICR Second Expert Report published in 2007[7].

Below are the results summarised from cohort studies in the Second Expert Report[7]:

In the meta-analysis of five cohort studies, total energy intake was not associated with postmenopausal breast cancer risk (summary RR per 300kcal/day = 0.98, 95% CI: 0.96-1.01). There were no cohort data on premenopausal breast cancer[7].

For physical activity, it was shown in the meta-analysis of three cohort studies that recreational physical activity statistically significantly reduced the risk of postmenopausal breast cancer by 3% (summary RR per 7 MET-hours/week = 0.97, 95% CI: 0.95-0.99). The systematic review on premenopausal breast cancer risk found that the evidence from prospective studies was inconsistent[7].

For body fatness, the meta-analyses of cohort data showed a decreased risk of breast cancer in premenopausal women (summary RR per 2 kg/m^2 BMI = 0.94, 95% CI: 0.92-0.95, 14 studies) (or 15% per 5 kg/m^2) and an increased risk in postmenopausal women (1.03, 95% CI: 1.01-1.04, 17 studies) (or 8% per 5 kg/m^2), with higher BMI[7]. As reported, one additional pooled analysis found that each 5 kg/m^2 increase of BMI was associated with a 14% decreased risk of premenopausal breast cancer and a 9% increased risk of postmenopausal breast cancer[104]. BMI was used as a measure of total adiposity.

Higher abdominal adiposity, as measured by waist circumference and waist-to-hip ratio, was reported to consistently and significantly increase the risk of postmenopausal breast cancer, but not premenopausal breast cancer risk. The summary RRs were 1.05 (95% CI: 1.00-1.10) (4 cohort studies) and 1.00 (95% CI: 0.98-1.03) (2 cohort studies) per 8 cm of waist circumference; and 1.19 (95% CI: 1.10-1.28) (5 cohort studies) and 1.20 (95% CI: 1.01-1.44) (3 cohort studies) per 0.1 unit of waist-hip-ratio; respectively[7].

In addition, seven cohort studies were identified and four were included in a meta-analysis of adult weight gain and postmenopausal breast cancer risk in the Second Expert Report[7]. All showed increased risk with increasing amounts of adult weight gain (summary RR per 5 kg = 1.03, 95% CI: 1.02-1.04). Studies of weight gain and premenopausal breast cancer risk showed no significant association (0.99, 95% CI: 0.95-1.03) (2 studies)[7]. There was no conclusion on how intentional weight loss modifies the risk of breast cancer at the time of the Second Expert Report[7] because of limited data.

In addition, only small number of studies had reported results on breast cancer risk by HR status of the tumour[7]. Below are the few studies that have reported results:

It was reported that recreational physical activity was not related to ER-positive and PR-positive breast cancers in postmenopausal women, the same was observed for vigorous recreational physical activity and postmenopausal HR-positive breast cancers[121].

The Nurses' Health Study (NHS) showed significant positive associations between BMI (long-term or after menopause) and both ER-positive and ER-negative tumours in MHT never users; whereas the association of life-long BMI and ER-positive tumours was significantly inverse in MHT users[122].

The results were not clear in the Iowa Women's Health Study (IWHS), with RRs for waist-hip-ratio and postmenopausal breast cancer risk ranging from 0.81 to 1.05 according to HR status[123].

There are increasing number of studies that examine the associations by the molecular subtypes of the tumour[18;19], but it is still unclear whether the influence of lifestyle factors on breast cancer development varies across these subtypes.

Back in 2007, the Panel of the Second Expert Report concluded that evidence on the relationship of energy-related factors and cancer progression and survival were variable in quality and difficult to interpret[7]; however, several intervention and observational studies reported improvement of quality of life with practice of physical activity after breast cancer. RCTs of different types of supervised or home-based exercise programmes on quality of life outcomes reported a benefit from the intervention on at least one of the measures of physical, functional and emotional well-being, as well as measures of physical fitness[7]. As noted, other reviews of observational studies also showed enhanced quality of life in cancer survivors[124-126].

It was also reported that the only physical activity intervention identified on breast cancer recurrence did not find a significant association[127], while evidence from observational studies found a reduction of breast cancer mortality risk in women who were physically active compared with sedentary women[128], and a reduction of total mortality risk overall or among women who were overweight or obese at the time of diagnosis[129].

The Panel concluded an overall increased risk of mortality with increasing BMI, although the results were inconsistent[7]. As reported in the three reviews identified at the time, 12 out of 21 observational studies showed statistically significant associations between higher BMI and worse outcome, one study found inverse association between higher BMI and mortality risk and others showed non-significant results[124-126;129].

There is very little data on the effect of weight lost on cancer events and survival after breast cancer. The Women's Intervention Nutrition Study (WINS) suggested that intentional weight loss may improve relapse-free survival in breast cancer patients[130]. WINS was a dietary intervention trial that aimed to reduce dietary fat intake with no specific guidance on weight loss. However, during the trial, there was a 19 g, 167 kcal, as well as 2.7 kg difference in fat intake, total energy intake, and body weight between intervention and control groups at median 60 months follow-up, respectively; so it is difficult to determine whether the observed benefits are due to change in diet, in energy balance, or both.

The associations between energy balance-related factors and the risk of breast cancer development and mortality after breast cancer were updated in the present PhD study (see Chapters 5 and 6).

3.1.3.1 Biological mechanisms underpinning energy balance-related factors and breast cancer development and progression

Animal studies have consistently shown that energy intake is positively related to breast cancer development[131], and restriction of the intake reduces breast cancer risk[132]; however, such evidence in humans remains elusive[133;134].

It is increasingly realised that adipose tissue is an active endocrine organ instead of simple energy storage. Adipose tissue produces mediators that affect physiological functions and control processes such as growth, metabolism and reproductive cycles. These inter-related pathways are proposed to underpin the link between obesity (chronic positive energy balance) and cancer development and progression, and may further implicate breast cancer prognosis. The four widely studied biological mechanisms involve the dysfunctional hormonal systems, insulin resistance, inflammation, and altered adipocytokines metabolisms[17;135;136] (Figure 3.4):

Hormonal pathway

Breast cancer is a hormone-sensitive cancer[137]. Obesity implicates breast cancer development and progression primarily through the hormonal pathway.

Bioavailable oestrogen induces cancer cell proliferation and inhibits apoptosis[29]. Oestrogens and testosterone have been shown to significantly associate with breast cancer risk[136].

In obese postmenopausal women, the increased expression of aromatase in adipose tissue increases peripheral conversion of androgens to oestrogens, increasing breast cancer risk[138]. In obese premenopausal women, obesity is linked to higher frequency of irregular menstrual cycles and anovulation, which lowers serum progesterone level and its proliferative activity in breast epithelial cells[139]. This could explain why obese women are at lower risk of premenopausal breast cancer compared to non-obese women.

Insulin-IGF-1 Axis

Obesity is linked to insulin resistance, a condition where glucose and insulin levels are elevated (hyperinsulinemia)[136]. Increased systemic glucose levels (hyperglycemia) provide tumour cells with the required energy to maintain their rapid rates of cell division. Cancer cells can also alter glucose metabolism (Warburg effect) to facilitate the uptake of glucose

Insulin stimulates cancer cell growth and proliferation by binding to their respective cell surface receptors and activates the intracellular signalling pathways phosphatidylinositol 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) and Ras signalling networks[140]. Insulin and IGF-1 interact with oestrogen signalling pathways, leading to increased level of free oestradiol and the promotion of hormone-dependent breast cancer. In adipose stromal cells, IGF-1 up-regulate aromatase activity. Insulin inhibits hepatic synthesis of steroid-hormone binding globulin (SHBG).

Elevated insulin or C-peptide levels (a biomarker of insulin secretion) increases breast cancer risk[136]. Type 2 diabetes is a modest positive risk factor for postmenopausal breast cancer[141]. Fasting glucose and fasting insulin have been shown to associate positively with distant disease-free survival in breast cancer patients. Elevated insulin levels increased the risk of overall survival[136].

High waist circumference is associated with hyperinsulinemia[142] and type II diabetes[143]. Hyperinsulinemia could promote breast cancer development indirectly through IGF-1 (increased) and its binding proteins (decreased) via the insulin receptor[144], leading to higher levels of circulating free IGF-1, which is more potent than insulin in terms of mitogenic and anti-apoptotic activities[145]. Pre- and postmenopausal breast cancer risks have been shown to increase with high circulating concentrations of IGF-1[146], although not all obese patients have elevated IGF-1 levels[147].

Inflammation

Tumour necrosis factor-α (TNF-α) and interleukin-6 (IL6) induces aromatase activity and thus oestrogen biosynthesis. Visceral adiposity is associated with higher production of IL6 and may affect breast tumour cells through systemic inflammation[148].

Obesity causes both in-breast and systemic inflammation that contribute to breast cancer pathogenesis and progression[149]. The inflammatory biomarkers, high-sensitivity C-reactive protein (hs-CRP) and IL-6, increase with higher BMI and decrease with weight loss[150].

Circulating levels of hs-CRP have been shown to associate with postmenopausal breast cancer risk[151], but further studies are needed to evaluate possible residual confounding of lifestyle factors, such as alcohol and smoking and effect modification by BMI.

Adipokines metabolism

Two widely studied adipokines are leptin, which is mutagenic, pro-inflammatory, anti-apoptotic, and pro-angiogenic; and adiponectin, which is anti-inflammatory, and insulin-sensitising. Obese patients often develop leptin resistant, whereas adiponectin is inversely associated with general and abdominal adiposity[136].

Most cancer cells express receptors for leptin and adiponectin. The PI3K and JAK/STAT pathways are activated through the stimulation of leptin receptor, while the adenosine monophosphate–activated protein kinase (AMPK) signalling network is activated through the binding of adiponectin receptor. AMPK inhibits the intracellular pathways of PI3K/Akt/mTOR, JAK/STAT and ERK1/2 and negatively regulate proliferation. These opposing effects may not operate optimally in an obese state.

Lohmann *et al.* found that adiponectin was inversely but not statistically significantly associated with premenopausal and postmenopausal breast cancer risk, while leptin was significantly positively associated with breast cancer risk[136].

Physical activity is thought to influence breast cancer through modulating oestrogens and other factors that influence hormone receptor function and improving insulin sensitisation, either directly or through body fatness regulation[152;153]. Independent effect of physical activity involves enhanced immune functions. The increased number and activity of macrophages, natural killer cells, lymphokine-activated killer cells and regulating cytokines enhances immune surveillance and abnormal cells apoptosis[154].

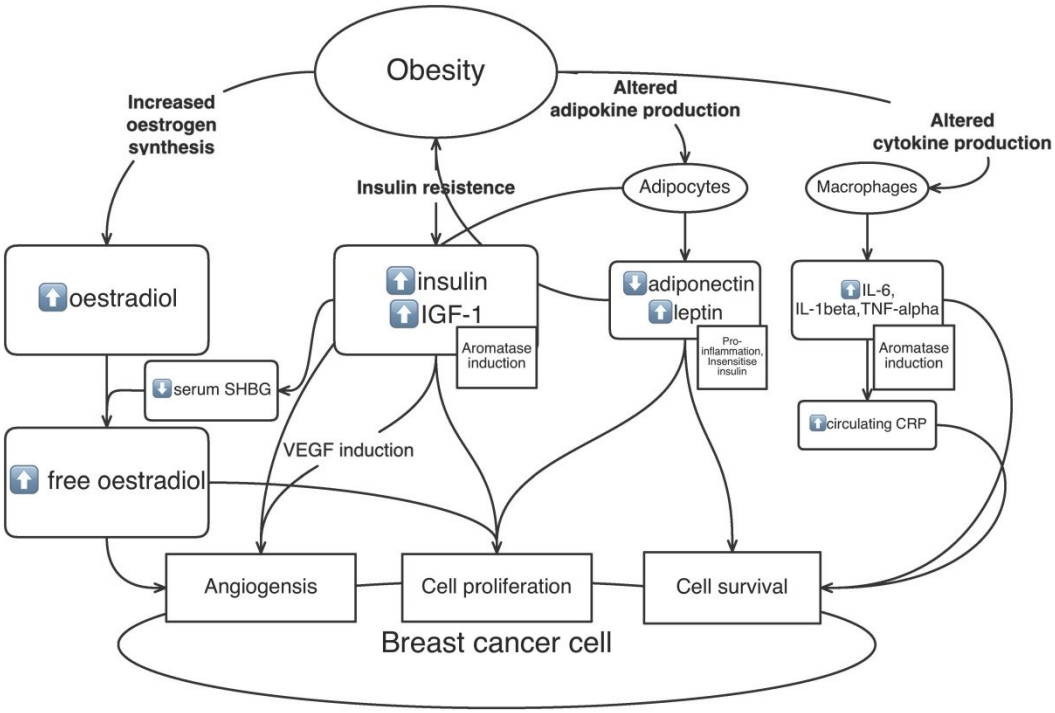

Figure 3.4 Metabolic pathways linking obesity and breast cancer risk.

Figure modified from Sinicrope *et al.,* 2011. Ref.155

3.1.4 Other dietary and lifestyle factors

Dietary fat

A few early observational studies have shown increased risk of postmenopausal breast cancer with total fat intake[7]. However, dietary fat reduction did not significantly lower the risk of postmenopausal breast cancer[156]. The RR estimate for intervention of low-fat dietary pattern versus comparison with no dietary advice was 0.91 (95% CI: 0.83-1.01) in the Women's Health Initiative Randomised Controlled Dietary Modification Trial (WHI-DM) after an average of 8.1 years follow-up[156].

A recent systematic review concluded from 18 studies including two RCTs (reviewed below) that dietary fat intake is possibly associated with survival after breast cancer[157].

Women's Intervention Nutrition Study (WINS), the low fat intervention study of breast cancer survivors, reported significant improvement in relapse-free survival (HR for reduce dietary fat [15% of energy] vs conventional treatment = 0.76, 95% CI: 0.60-0.98) but not in total survival (0.89, 95% CI: 0.65-1.21) at 60 months[130]. Women's Healthy Eating and Living (WHEL) observed no significant association of dietary pattern that was high in vegetables, fruit and fibre, and low in fat with disease-free survival (0.96, 95% CI: 0.80-1.14) and total survival (0.91, 95% CI:0.72-1.15) compared with the 5-a-day dietary advice group[158].

Plant-based foods

Dietary fibre[159], fruit, and total fruit and vegetables[160] showed a weak reduction in breast cancer risk, as reported in the published meta-analyses based on the work in the WCRF Continuous Update Project (CUP)[161]. The summary RRs were 0.95 (95% CI: 0.91-0.98) per 10 g/day dietary fibre intake, 0.96 (95% CI: 0.93-1.00) per 200 g/day total fruit and vegetables intake and 0.94 (95% CI: 0.89-1.00) per 200g/day fruit intake. No association was observed for vegetable intake (summary RR per 200g/day = 1.00, 95% CI: 0.95-1.06).

A pooled analysis of 20 cohort studies published in 2013 observed an inverse association between vegetable intake and ER-negative breast cancers, but not ER-positive breast cancers (P for common-effects by ER status <0.001)[162]. No different associations were observed for fruit intake and the risks of ER subtypes of the tumour (P<0.36).

Another published meta-analysis, based on the work in the CUP, showed that higher level of blood concentrations of carotenoids, but not dietary carotenoids, was related to a 22% reduced risk of breast cancer (summary RR per 100 μg/dL = 0.78 95% CI: 0.61-0.99)[163]. Statistical significant inverse associations were also observed with beta-carotene, alpha-carotene and lutein. The use of valid biomarkers may elucidate the inconsistent findings from dietary intake assessed by dietary questionnaires.

Alcohol

Alcohol consumption is a strong risk factor of any breast cancer. The association has been reviewed in several pooled analyses and meta-analyses. Each 10 g/day increase of alcohol intake was associated with a 7% increased risk of breast cancer[164]. When compared high consumption (30-<60 g/day intake) to no consumption, the increased risk was 41%[165]. The relationship was linear, with no threshold effect reported[164;165]. Alcohol consumption was positively associated with the risk of both ER-positive (RR for ≥30 vs 0 g/day = 1.35, 95% CI: 1.23-1.48) and ER-negative tumours (1.28, 95% CI: 1.10-1.49)[166].

Alcohol consumption before or after diagnosis was not significantly associated with total mortality risk in breast cancer survivors, as shown in the meta-analyses conducted in the CUP[167]. The summary RRs per 1 drink/week consumed pre-diagnosis was 1.00 (95% CI: 0.99-1.00) and per 10g/day consumed post-diagnosis was 0.98 (95% CI: 0.93-1.03). Results were similar for the risk of breast cancer mortality.

Smoking

The relationship between smoking and breast cancer risk is not clear. Earlier reviews concluded no suggestion of a causal relationship in 2001[168] and limited evidence of carcinogenicity in 2009[169], while recent evidence suggested a link. A recent meta-analysis reported moderate increased risks of 12% in current smokers and 9% in former smokers compared with never smokers; and 21% increased risk among those who smoked before first birth[170]. Passive smoking may increase the risk of breast cancer[164;171;172]. Findings on smoking and breast cancer prognosis were not consistent[173].

3.1.5 Other factors

Exposure to ionizing radiation, especially during puberty or young adulthood, increases the risk of breast cancer[174].

Radiation therapy versus no radiation therapy after breast conserving surgery has been shown to reduce first recurrence (locoregional or distant recurrence) and improve long-term survival (risk of breast cancer mortality ≥15 years)[175].

3.2 Breast cancer prevention

A potentially useful and cost-effective strategy to reduce the burden of breast cancer is through lifestyle modifications[176;177]. The preventability estimates for breast cancer through reduced alcohol consumption and body fatness, and increased physical activity were 20% for China, 28% for Brazil, 38% for USA and 42% for UK (low to high-income countries)[178].

Other preventive options include chemoprevention and prophylactic surgery, which require prior breast cancer risk assessment conducted by the medical providers of the women considering these options. Risk of breast cancer is estimated using the Breast Cancer Risk Assessment Tool or the Gail

Model[179], based on risk factors such as age, reproductive factors, history of breast biopsies, medical and family history and *BRCA*1/2 gene mutation of the women.

Selective oestrogen receptor modulators (tamoxifen, raloxifene, arzoxifene, and lasofoxifene) have shown overall breast cancer risk reduction by 38% and ER+ breast cancer risk reduction by 51% for up to 10 years after starting a 5-year treatment in a pooled analysis of prevention trials[180]. The National Institute for Health and Care Excellence (NICE) in the UK and Food and Drug Administration (FDA) in the US approved the use of tamoxifen and raloxifene for breast cancer chemoprevention.

In recent years, the diabetic medication – metformin – has received attentions because of its anti-cancer properties and potential use in primary prevention of breast cancer[181]. Potential benefits of metformin use compared with other diabetic therapies have been demonstrated in two meta-analyses of observational studies or RCTs, which showed breast cancer risk reduction by 17% in women with diabetes[182], and reduced risks of overall mortality (36%) and breast cancer mortality (24%) in breast cancer patients with concurrent type 2 diabetes[183]. A recent randomised, placebo-controlled adjuvant trial (NCIC Clinical Trials Group MA.32 Trial) reported improved circulating levels of obesity-related mediators (insulin, glucose, homeostasis model assessment, leptin, hs-CRP) and weight loss in breast cancer patients[184].

Prophylactic surgery (mastectomy and oophorectomy) is not an option for women of average risk but for women at high risk of developing breast cancer. These approaches, unlike lifestyle modifications, have side effects and risks and could affect one's quality of life. Adverse effects of tamoxifen include thromboembolic events and increased risk of endometrial cancer[185]; and of metformin, congestive heart failure, hypoxic states and advanced liver disease[186].

3.2.1 Cancer prevention recommendations

Evidence-based cancer prevention recommendations, such as those issued by the WCRF International, are useful in guiding women to make healthful lifestyle choices[7;187].

The recommendations were developed by experts after rigorous evaluation and interpretation of all related epidemiological evidence to ensure that the conclusions are accurate, reliable and consistent[7;187].

The First Expert Report was published in 1997[188]. Evidence available at the time was systematically reviewed. Breast cancer was judged as one cancer overall, unless specified. Findings on energy balance-related factors included:

- Higher body mass is a probable risk factor of breast cancer
- Adult weight gain probably increases the risk of breast cancer

- Physical activity possibly decreases the risk of breast cancer, particularly postmenopausal breast cancer

The Second Expert Report was published in 2007[7]. Evidence was systematically reviewed and meta-analysed. Separate conclusions were made on pre- and postmenopausal breast cancer (Figure 3.5):

- Greater body fatness convincingly increases the risk of postmenopausal breast cancer, and it probably decreases the risk of premenopausal breast cancer
- Greater abdominal fatness probably increases the risk of postmenopausal breast cancer
- Adult weight gain probably increases postmenopausal breast cancer risk, while the evidence for premenopausal breast cancer risk was limited and no judgement was possible
- Physical activity of all types probably decreases postmenopausal breast cancer risk, while there was limited suggestion that physical activity may decrease the risk of premenopausal breast cancer

In 2007, the three personal recommendations that target energy balance are (Table 3.1)[7;187]:

1) Body fatness - be as lean as possible within the normal range of body weight
2) Physical activity - be physically active as part of everyday life
3) Foods and drinks that promote weight gain - limit consumption of energy-dense foods and avoid sugary drinks.

The other seven recommendations (10 in total) relate to alcohol consumption, red and processed meat intake, salt intake, breastfeeding and supplement use (see Appendix 7)[7;187]. Avoiding/limiting alcohol consumption is another important recommendation in the perspective of breast cancer prevention, because alcohol consumption is a strong risk factor of any breast cancer[164-166].

In addition, cancer survivors are advised to follow the Cancer Prevention Recommendations, as evidence on lifestyle factors and cancer survival were inconsistent and limited in 2007 and recommendations specific to cancer survivors were not formulated.

Such changes in research findings through time emphasise the need to and the significance of keeping the evidence base updated, which allows for timely re-analysis or new analysis of research data and subsequent recommendations development and revision, if in need. Clearly, there were limitations to the previous reviews. In the past, research data mostly came from case-control studies; and case-control studies rank lower in the hierarchy of study design for casual inference, because of possible recall and selection biases and problem with reverse causation that may distort the observed associations. Prospective cohort studies are better in design, but there were fewer of them and studies from outside the US and Europe were scarce. The exploration of between-study heterogeneity was not always possible, because of the low number of studies; also, few studies reported results by molecular subtypes of the tumour, which may associate differently with cancer risk factors. In addition, the

urgently needed recommendations for cancer survivors were lacking. Updating the evidence base not only will fill in the knowledge gaps, but also will help with identifying research priorities, and move the science forward.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BREAST (PREMENOPAUSE)

In the judgement of the Panel, the factors listed below modify the risk of cancer of the breast (premenopause). Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks**
Probable	**Body fatness**	**Adult attained height[1]** **Greater birth weight**
Limited — suggestive	Physical activity[2]	
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; vegetables; fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; milk and dairy products; fats and oils; total fat; vegetable fat; fatty acid composition, *trans*-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium; iron; selenium; carotenoids; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; *trans*-nonachlor; polychlorinated biphenyls; dietary patterns; culturally defined diets; adult weight gain; energy intake; being breastfed	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
2 Physical activity of all types: occupational, household, transport, and recreational.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

World Cancer Research Fund | American Institute for Cancer Research

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BREAST (POSTMENOPAUSE)

In the judgement of the Panel, the factors listed below modify the risk of cancer of the breast (postmenopause). Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks** **Body fatness** **Adult attained height[1]**
Probable	**Physical activity[2]**	**Abdominal fatness** **Adult weight gain**
Limited — suggestive		Total fat
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; vegetables and fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; milk and dairy products; fats and oils; vegetable fat; fatty acid composition; cholesterol; sugar (sucrose); sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium; iron; selenium; carotenoids; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; *trans*-nonachlor; polychlorinated biphenyls; dietary patterns; culturally defined diets; birth weight; birth length; energy intake; being breastfed	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
2 Physical activity of all types: occupational, household, transport, and recreational.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

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Figure 3.5 Summary of judgements of the 2007 WCRF/AICR Second Expert Report[7]

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Table 3.1 2007 World Cancer Research Fund/American Institute of Cancer Research Cancer Prevention Recommendations 1, 2, and 3

Recommendation 1	Recommendation 2	Recommendation 3
BODY FATNESS	**PHYSICAL ACTIVITY**	**FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN**
Be as lean as possible within the normal range[1] of body weight	Be physically active as part of everyday life	Limit consumption of energy-dense foods[1] Avoid sugary drinks[2]
PUBLIC HEALTH GOALS	**PUBLIC HEALTH GOALS**	**PUBLIC HEALTH GOALS**
Median adult body mass index (BMI) to be between 21 and 23, depending on the normal range for different populations[2]	The proportion of the population that is sedentary[1] to be halved every 10 years	Average energy density of diets[3] to be lowered towards 125 kcal per 100 g
The proportion of the population that is overweight or obese to be no more than the current level, or preferably lower, in 10 years	Average physical activity levels (PALs)[1] to be above 1.6	Population average consumption of sugary drinks[2] to be halved every 10 years
PERSONAL RECOMMENDATIONS	**PERSONAL RECOMMENDATIONS**	**PERSONAL RECOMMENDATIONS**
Ensure that body weight through childhood and adolescent growth projects[3] towards the lower end of the normal BMI range at age 21	Be moderately physically active, equivalent to brisk walking,[2] for at least 30 minutes every day	Consume energy-dense foods[1 4] sparingly
Maintain body weight within the normal range from age 21	As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day[2 3]	Avoid sugary drinks[2]
Avoid weight gain and increases in waist circumference throughout adulthood	Limit sedentary habits such as watching television	Consume 'fast foods'[5] sparingly, if at all
[1] 'Normal range' refers to appropriate ranges issued by national governments or the World Health Organization [2] To minimise the proportion of the population outside the normal range [3] 'Projects' in this context means following a pattern of growth (weight and height) throughout childhood that leads to adult BMI at the lower end of the normal range. Such patterns of growth are specified in International Obesity Task Force and WHO growth reference charts	[1] The term 'sedentary' refers to a PAL of 1.4 or less. PAL is a way of representing the average intensity of daily physical activity. PAL is calculated as total energy expenditure as a multiple of basal metabolic rate [2] Can be incorporated in occupational, transport, household, or leisure activities [3] This is because physical activity of longer duration or greater intensity is more beneficial	[1] Energy-dense foods are here defined as those with an energy content of more than about 225–275 kcal per 100 g [2] This principally refers to drinks with added sugars. Fruit juices should also be limited [3] This does not include drinks [4] Limit processed energy-dense foods (also see recommendation 4). Relatively unprocessed energy-dense foods, such as nuts and seeds, have not been shown to contribute to weight gain when consumed as part of typical diets, and these and many vegetable oils are valuable sources of nutrients [5] The term 'fast foods' refers to readily available convenience foods that tend to be energy-dense and consumed frequently and in large portions

4 Methods

The present PhD study formed part of the work for the Continuous Update Project (CUP)[161], a programme established by the WCRF International in 2007 to undertake the work following the Second Expert Report[7]. The aim is to analyse global research on how diet, nutrition, physical activity and weight affect cancer risk and survival in an on-going manner. The accumulated evidence summarised in the systematic reviews and meta-analyses are used to update the Cancer Prevention Recommendations[7;187]. The present PhD study focused on energy balance-related factors and risk of breast cancer development and mortality after breast cancer in pre- and postmenopausal women.

4.1 Systematic reviews of energy balance-related factors and pre- and postmenopausal breast cancer risk

The research topic is: the associations between energy balance-related factors and pre- and postmenopausal breast cancer risk.

Relevant research findings on the topic were systematically reviewed and meta-analysed. The work followed the procedures and methods listed in the standard protocol, developed by the Principal Investigator of the CUP, Dr. Teresa Norat, based on the same rigorous methods set forth by the special Methodology Task Force of experts for the WCRF/AICR Second Expert Report[7]. I assisted in modifying this protocol.

A copy of the protocol is available at:
http://wcrf.org/sites/default/files/Breast_cancer_protocol_170510.pdf

4.1.1 Literature search

The literature was searched in two steps:

1) For Second Expert Report, the systematic literature review (SLR) team at the National Cancer Institute, Milan searched in the various electronic databases (MEDLINE, Embase, ISI Web of Science, BIOSIS, SciSearch, Pascal, Meta-register, LILACS, CAB abstracts, Cochrane Library, CINAHL, IMSEAR, IMEMR, AIM, AMI, Amed and ExtraMed) for relevant articles published from database inception to 10th January, 2006 – the end date of search for the Second Expert Report[7]. The search strategy included a combination of medical subject headings (MeSH terms) and text words for breast cancer and a board range of lifestyle factors that encompass energy balance-related factors, which was decided by the Methodology Task Force and validated by information technologists. In addition, reference lists of related articles were searched for potential relevant publications.

2) For CUP, because data provided from the SLR team indicated that 95% of the articles included in the review have been retrieved from the Medline database, it was decided and approved in the protocol that the search was only to perform in PubMed, which comprises MEDLINE and Non-

MEDLINE citations. The team at Imperial College London used the same search strategy to continue with the search, in PubMed, for relevant articles published from 1st January 2006 to 30th April 2017. This was supplemented by searching through the reference lists of related articles (reviews, meta-analyses and pooled analyses).

There was no language restriction in the search.

4.1.2 Study selection

Potential relevant publications identified by the CUP team were reviewed together with those identified previously by the SLR team.

Inclusion criteria were:

1) Studies with a cohort, nested case-control and case-cohort design, as well as randomised controlled trials (RCT).

2) Investigated energy balance-related factors (total energy intake, physical activity of any kinds, sedentary lifestyle, BMI, waist circumference, hip circumference, waist-to-hip ratio and weight change) for any period in adult life course (≥age 18 years) and the risk of pre- and postmenopausal breast cancer incidence or mortality, overall or by HR status and MHT use.

3) Reported relative risk estimates (relative risk [RR], hazard ratio [HR] or odds ratio [OR]) and the corresponding 95% confidence intervals (CIs) or P-value for the associations.

Studies were excluded if the outcome was breast cancer of unspecified menopausal status. This is because the aetiology of pre- and postmenopausal breast cancers in relation to the exposures of interest appears different. RCT and cohort studies were included because these studies are less prone to confounding and biases than case-control studies.

In the case of multiple publications from the same study, the publication with more number of cases and longer follow-up was selected. When pooled studies of individual data were identified, these were included and the superseded publications from the component studies were excluded. The limitation of including pooled studies in a meta-analysis is that the between-study heterogeneity would be lower than the actual value; but on the other hand it allows the inclusion of a larger number of studies, as not all studies published results separately.

4.1.3 Data extraction

For the Second Expert Report[7], the SLR team extracted relevant data from the identified publications into an Access database. The data were then transferred to a MySQL database (WCRF database) developed by the data manager at Imperial College London. The WCRF database has a new interface to facilitate data extraction, but contains the same fields included in the Access database, including study and quality characteristics and results as follows:

First author's last name, year of publication, geographic location of the study, study characteristics (design, study name, size, length of follow-up), characteristics of the participants (mean age or age range, special characteristic, ethnicity, menopausal status), information on exposure (timing, quantity, assessment method) and outcome (breast cancer stage, histologic subtype, HR subtype), numbers of cases, non-cases, or population at-risk in the analysis, RR estimates with the 95% CI or P-values, and confounder adjustments.

Relevant data from the publications identified after the Second Expert Report were extracted by the CUP team directly into the WCRF database.

Authors of the publications were not contacted for any missing or additional information for the reviews in the CUP due to constraints in time and resources. For the same reason, data extraction was not performed in duplicate. Ten percent of the extracted data from the cohort studies and RCTs were checked by a second reviewer in the CUP team.

4.1.4 Statistical methods

Primary analyses were dose-response meta-analyses, conducted when three or more studies had provided sufficient data required to permit its inclusion in the meta-analysis of premenopausal breast cancer or the analysis of postmenopausal breast cancer. Meta-analyses were also conducted by subgroups defined by *a priori* factors to explore possible heterogeneity sources. In these meta-analyses, two or more studies were included.

Categorical meta-analyses were also conducted for physical activity (highest vs lowest level) and weight loss (highest or overall weight loss vs the reference weight group), as the estimation of a dose-response trend was not possible in most cases. Physical activity was defined and assessed differently in the studies. Most studies on weight loss only reported RR estimates for women who lost weight compared with those did not.

The DerSimonian and Laird's random-effects model, which allows for possible variations of associations across the studies, was used to calculate a weighted average of the RR estimates of the individual studies[189]. This method pools the natural log-transformed RR estimates, weighted by inverse of the within-study variance and the between-study variance (*Tau*). The weighted log-RR estimate was then back transformed. The term RR estimate was used throughout the present PhD study, even though the measure of association reported in most studies was hazard ratio. This was done under the assumption that when events are rare and absolute cancer risks are small, these measures will be approximately equal in studies of diet, physical activity and adiposity and cancer[190].

For the dose-response meta-analysis, study-specific dose-response trend was estimated, when not reported by the study, from the categorical results of at least three levels using the generalised weighted least-squares regression model[191;192], developed based on the Greenland and Longnecker's

method[193]. This method takes into account the covariance between the categorical estimates of association in a study due to the use of the same reference category.

To estimate the dose-response trend, numbers of cases, non-cases or person-at-risk, and point estimate of the exposure range are needed for each exposure category. Mean or median per exposure category was used if known; otherwise, midpoint of the exposure range was estimated. Open-ended categories were assumed to have the same width as the adjacent category. Zero was set as the midpoint to denote a stable weight when the reference weight change category was within ±3 kg, as per the method used in a published meta-analysis[194]; otherwise, zero was used as the lowest boundary and midpoint was estimated accordingly. If the required information were not available and could not be estimated using previously described standard methods[195;196], the study could not be included in the meta-analysis and was excluded as 'study of insufficient data'.

For the studies that reported results for more than one weight loss category, results for the different categories were first combined into one category using the Hamling's method[197], before pooling with the other studies in the meta-analysis that compared overall weight loss versus reference weight. The method also takes into account the non-independence of the RR estimates for the categorical comparison in a study because of a common reference group. The estimates of association in studies that reported by MHT use or other subgroups, but not for all pre- and postmenopausal breast cancer, were first combined using a fixed-effect model before pooling with other studies in a meta-analysis.

Results that were adjusted for the most number of confounding factors were selected. For studies on waist circumference or waist-to-hip ratio, results without BMI adjustment was selected, and further meta-analyses were conducted, including only the results additionally adjusted for BMI, to examine the association independent of BMI.

RR estimates from individual studies and the weighted average of these results from the meta-analysis (the summary RR estimate) are graphically presented in a forest plot. Each line represents a unique study. The size of the box is proportional to the size of the study. The whiskers through the box are the 95% CI. The diamond is the summary RR estimate. The horizontal line is the line of null association. To the left of this line are the studies showing an inverse association, and to the right are the studies showing a positive association.

Between-study heterogeneity was assessed by the Cochran Q test and I^2 statistic (%)[198]. The cut-points of 30% and 50% were chosen to represent low, intermediate, and high proportion of heterogeneity between studies. These values are believed to be tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the magnitude and direction of the association.

Sources of heterogeneity were examined in subgroup meta-analyses by geographic region (Asia, Australia [and New Zealand], Europe, North America or other areas), exposure assessment methods (methods validated or not, and self-reported anthropometric measurements by the participants or

measured by study personnel), main confounding factors adjustment (adjusted or not adjusted for age, alcohol consumption, reproductive factors and MHT use, and physical activity or BMI when appropriate), length of follow-up (< or ≥ 10 years), and study quality score (≤ or > median score) (see section 4.1.5). These pre-defined factors were examined as they are judged as potential factors that could differentiate, or causes of errors and biases that could distort, the measure of association. Meta-regression analyses were also conducted to test the variation in RR estimates by these potential factors[199]. As the subgroups often comprised low number of studies, only univariate meta-regression analysis was possible.

Further meta-analyses restricting to mammography or cancer screening cohorts or cohorts recruited from cancer clinics, and studies only of invasive breast cancer were conducted. Participants in the mammography cohorts may be healthier. The screen-detected cancers may be smaller and are more likely to be *in situ* breast cancers. Specific analyses including only studies adjusted for adult adiposity in the association of early adult BMI, adjusted for initial weight status in the association of adult weight gain, and adjusted for BMI in the association of physical activity were also conducted, in addition to the subgroup analysis of physical activity by BMI categories.

Reverse causation was explored in meta-analysis restricted to studies that excluded early years of follow-up when possible. Publication bias or small study bias was assessed by visual inspection of the funnel plots for asymmetry, and with Egger's test[200]. Each dot in the funnel plot represents the logarithm of RR estimate against standard error as measure of study size. Solid line is the logarithm of summary RR from the meta-analysis. Dashed lines are its 95% CI. The orange line is the fitted line corresponding to the regression test for funnel-plot asymmetry. Study influence on the summary RR was examined by omitting each study in turn.

To explore possible threshold effect in an association, which may be useful in informing cut-points for the recommendations, non-linear meta-analysis using the method of restricted cubic spline regression with three knots placed at the 10th, 50th, and 90th percentile was conducted. The choice of three knots was a trade-off between adequate modelling and levels of data (4 exposure categories are needed in this case) required in the modelling[191;201]. To test for non-linearity, a likelihood ratio test was used to assess the difference between the linear and non-linear models[202]. To allow full exploration of the shape of the relationship, all data points were included. When the reference category was not the lowest category in the study, the RR estimates were recalculated using the method of Hamling *et al.* [197].

4.1.5 Study quality evaluation

As defined in the protocol (http://wcrf.org/sites/default/files/Breast_cancer_protocol_170510.pdf), formal quality grading is not performed on an individual study basis; instead, aspects of study quality, such as methods of exposure assessment and confounding factors adjustment are used in subgroup

meta-analyses to explore their potential sources of bias and possible impact on the summary findings (see section 4.1.4). In the present PhD study, formal quality grading was also performed to compute an overall quality score for each individual study.

To do this, a specially devised tool was developed. There are many tools for accessing quality of observational studies, but most tools are not validated[203]. We based our tool on the Newcastle and Ottawa Scale (NOS)[204], an instrument identified by the Cochrane Collaboration group as a useful tool for assessing risk of bias in non-randomised studies[205].

In order to better evaluate the internal and external validity of the cohort studies on breast cancer, we customised the original 8 items in the NOS[204], on selection and comparability of the cohort, and exposure and outcome assessment; and added new breast cancer-related questions, regarding the number of breast cancer cases (with arbitrary cut-points), and whether the molecular subtypes and invasiveness of the breast cancer are ascertained in the studies.

We formulated some possible scenarios for each item and assigned scores according to their likelihood to be influenced by biases and limitations, for instance, the use of a validated diet questionnaire with some correction for measurement error to assess an usual diet would score 2 points, while the same but without measurement error adjustment would score 1.5 points, and so on:

A modified Newcastle and Ottawa Scale for the evaluation of study qualities in cohort studies

Selection

1) Representativeness of the exposed cohort
   a) the source is the general population – 2 points
   b) selected group of users e.g. nurses, medical insurance subscribers, or health screening programme participants – 1 point
   c) no description – 0 point
2) Selection of the non-exposed cohort
   a) drawn from the same source as the exposed cohort – 2 points
   b) drawn from a different source – 0 point
   c) no description – 0 point
3) Ascertainment of exposure

   Anthropometry:

   a) measured – 2 points
   b) self-reported body measurements validated against other assessment instrument – 1.5 points
   c) self-reported prospectively – 1 point
   d) self-reported retrospectively – 0 point
   e) no description – 0 point

   Diet:

   a) validated diet questionnaire assessing usual diet with some correction for measurement error – 2 points

b) validated diet questionnaire (≥100 items) assessing usual diet with no correction for measurement error – 1.5 points

c) validated diet questionnaire (<100 items) assessing usual diet with no correction for measurement error – 1 point

d) non-validated diet questionnaires or other data source – 0 point

e) no description – 0 point

Physical activity:

a) validated instrument assessing types of activity and frequency – 2 points

b) non-validated instrument assessing types of activity and frequency – 1 point

c) non-validated instrument with only one-two questions – 0 point

d) no description – 0 point

4) Demonstration that outcome of interest was not present at start of study

a) exclusion of prevalent cases at baseline – 1 point

b) exclusion not indicated or prevalent cases included – 0 point

Comparability

5) Comparability of cohorts on the basis of the design or analysis

a) study controls at least for age, alcohol intake, reproductive factors (age at menarche, age at menopause, and/or parity) and hormonal factors (postmenopausal hormone and/or oral contraceptive use) – 2 points

b) study controls at least for age and reproductive or hormonal factors (but not all variables listed in a) – 1 point

c) any other – 0 point

Outcome

6) Assessment of outcome

a) post- and premenopausal breast cancer identified by linkage to cancer/pathology registry or active follow-up with medical verification – 1 point

b) post- and premenopausal breast cancer without documented verification – 0 point

c) no description – 0 point

7) Adequacy of follow up of cohorts

a) virtually complete follow up – (<5% loss) – 2 points

b) authors reported almost complete follow up but percentage is not given – 1.5 point

c) loss to follow-up is 5–10% – 1 point

d) loss to follow-up >10% – 0 point

e) no statement – 0 point

8) Number of cases

Postmenopausal:

a) more than 1000 postmenopausal breast cancer cases – 2 points

b) 500 to 1000 postmenopausal breast cancer cases – 1 point

c) less than 500 postmenopausal breast cancer cases – 0 point

Premenopausal:

a) more than 500 postmenopausal breast cancer cases – 2 points
b) 200 to 500 postmenopausal breast cancer cases – 1 point
c) less than 200 postmenopausal breast cancer cases – 0 point

9) Classification of pre- and postmenopausal breast cancer

Postmenopausal:

a) participants were postmenopausal at baseline (self-report, based on other data) – 2 points
b) participants were postmenopausal at cancer diagnosis (menopausal status assigned through algorithm) – 1 point
c) menopausal status at diagnosis not known – 0 point
d) overall breast cancer only – 0 point

Premenopausal:

a) participants were premenopausal at cancer diagnosis (self-report, based on other data) – 2 points
b) studies of premenopausal women defined at study baseline – 1 point
c) unclear definition of menopausal status – 0 point
d) overall breast cancer only – 0 point

10) Ascertained breast cancer by receptor subtypes, e.g. ER, PR, HER2, etc
a) classified – 1 point
b) not classified – 0 point

11) Breast cancer stage
a) only invasive breast cancers included – 1 point
b) in situ and invasive breast cancers included – 0 point

The scores were then summed up to form an overall quality score for each individual study included in a meta-analysis. The same study may have different overall scores, depending on the exposure factor and the study outcome. The studies were classified into lower or higher quality studies for subgroup meta-analysis (see section 4.1.4). The median scores of all studies on pre- or postmenopausal breast cancer were used as the cut-points, because of the general low number of studies in the subgroups.

To evaluate possible main aspects that affected the study quality, the proportion of lower and higher quality studies not achieving a full score for each item was calculated and compared. This was not tested formally in a statistical analysis.

4.1.6 Grading of the evidence

The accumulated findings from observational studies were graded for their strength to confidently infer causality in the relationship. The WCRF grading criteria was used, as was used by the Panel in the First and Second Expert Reports[7;188]. The grading criteria follow the criteria for causality first set out by Bradford Hill[206], that associations can be judged to be causal in nature when exposures precede outcomes and when associations are consistent, unbiased, strong, graded, coherent, repeated and

plausible[7;188]. This method is consistent to the criteria used by other authoritative organisations, such as the International Agency for Research On Cancer (IARC)[207]. As decided by the Second Expert Report Panel, convincing causal relationship is supported by at least two independent cohort studies, no substantial unexplained heterogeneity between studies, good quality studies that are not affected by confounding, measurement error and selection bias, presence of a dose-response relationship and strong and plausible experimental evidence from human or animal studies. A convincing causal relationship should be robust enough to be highly unlikely to be modified by future evidence. The same criteria are generally required for establishing a probable relationship, except the criterion on strong experimental evidence. A judgement of 'convincing' or 'probable' evidence is considered strong evidence of causality and would normally justify a recommendation; unlike 'limited-suggestive' or 'limited-no conclusion', where further research findings are needed. 'Substantial effect on risk unlikely' is also considered strong evidence (see Appendix 1).

The principle of the WCRF grading criteria is similar to GRADE, another commonly used approach for grading the quality of evidence and strength of recommendations based on systematic reviews[208]. As GRADE is used primarily for formulating clinical guidelines, it has a higher scoring for systematic reviews of RCTs and a lower scoring for systematic reviews of cohort studies; therefore, is not useful in grading the current reviews.

For the present PhD study, judgements were made after checking each factor against the grading criteria; as well as for the presence of publication bias, a potential limitation in a meta-analysis. The judgements were then compared with those made for the Second Expert Report to examine if the accumulated evidence supports the 2007 WCRF/AICR Cancer Prevention Recommendations[7].

4.2 Systematic reviews of energy balance-related factors and survival after breast cancer

The research topic is: the associations between energy balance-related factors and risk of mortality in breast cancer survivors.

For the Second Expert Report[7], a SLR was conducted by the team at the University of Bristol to assess the efficacy of nutritional and physical activity interventions in cancer survivors in relation to various health outcomes (mortality, recurrence or other cancer events, quality of life and adverse effects of treatment regimens). Since then, more epidemiological studies of different designs have published findings, and many of which were focused on breast cancer survivors. In view of the growing numbers in cancer survivors, there is a need to summarise the research findings for the development of evidence-based recommendations specific to cancer survivors.

Therefore a new SLR on breast cancer survival was undertaken and a new protocol was developed by the Principal Investigator of the CUP, Dr. Teresa Norat, with the advice of the cancer survivors protocol development committee. I assisted in the process.

The present systematic reviews and meta-analyses were conducted by following this protocol, and formed part of the work for the WCRF International CUP. Because mortality is considered a hard outcome, unlike breast cancer recurrence and other breast cancer events, for which ascertainment could be incomplete or inaccurate; under the advice of the protocol committee, the work was focused on mortality outcomes.

A copy of the protocol is available here:

http://www.wcrf.org/sites/default/files/protocol_breast_cancer_survivors_protocol.pdf

4.2.1 Literature search

A literature search in MEDLINE and EMBASE and a search in the reference lists of relevant publications were conducted up to 30th June 2013. The platform of OVID was used instead of PubMed because we based our search on a previous search strategy that was constructed by the Bristol team for the Second Expert Report[7]. We modified the search strategy, with the assistant of a librarian at Imperial College London, to include a combination of medical subject headings (MeSH terms for MEDLINE and Emtree terms for EMBASE) and text words for a broad range of lifestyle factors and breast cancer outcomes. The Cochrane Library CENTRAL was also used but did not identify more relevant publications. Only English publications were included because of time constraint.

4.2.2 Study selection

Inclusion criteria were:

1) Follow-up studies of pre- and postmenopausal women with a diagnosis of *in situ* and/or invasive breast cancer (enrolled in prospective population-based cohorts and case-control studies, cohorts of cancer survivors, or RCTs)

2) Reported estimates of the associations of interests

3) Exposure factors were energy balance-related factors for the periods before breast cancer diagnosis (usually one year pre-diagnosis) or after breast cancer diagnosis (one year or more post-diagnosis)

4) Event outcomes were total mortality, breast cancer mortality, death from cardiovascular disease, and death from causes other than breast cancer.

In the case of multiple publications from the same or overlapping study, the publication with more number of cases was selected.

Pooled studies (e.g. After Breast Cancer Pooling Project) were not included in the present meta-analysis and were reviewed separately; as its inclusion may pose a considerable influence on the summary risk estimate when not many other studies of similar size have reported results. The decision was approved by the protocol committee.

4.2.3 Data extraction

We developed a new data extraction form to allow the input of data specific to cancer survival into the WCRF database. The new fields included time of recruitment and exposure factor timeframe (pre-, at or post-diagnosis), and tumour characteristics, treatment and compliance, and comorbidities. These were extracted along with the study and quality characteristics and results as described above (see section 4.1.3).

4.2.4 Statistical methods

Since there was generally less number of breast cancer survival studies, meta-analysis was conducted when at least two studies have provided sufficient data for such analysis. Categorical and dose-response random-effects meta-analyses were conducted (see section 4.14).

Because factors related to energy-balance may change close to diagnosis and during primary treatment of breast cancer[209], the analyses were conducted for three periods: before breast cancer diagnosis, <12 months after diagnosis, and ≥12 months after diagnosis.

Unlike for BMI and the risk of incident breast cancer, where meta-analyses were only conducted to model the linear and non-linear dose-response relationships, categorical meta-analyses were also conducted to evaluate the relative mortality risk in breast cancer survivors of different BMI categories, for the reasons that the association between BMI and mortality risk after breast cancer was likely J-shaped, which suggests an increased risk in underweight women, and also the relative mortality risk for the comparison of obese, overweight, or underweight versus normal weight may be of clinical significance. The categorical meta-analyses were conducted, by pooling results for the relevant category as reported in the studies. The studies used different BMI categories, based on WHO international classification, study-specific quantiles, or author's defined categories. In some studies, underweight ([WHO] BMI <18 kg/m^2) and normal weight women (BMI 18.5-<25.0 kg/m^2) were classified together but, in some studies, they were classified separately. Similarly, most studies classified overweight (BMI 25.0-<30.0 kg/m^2) and obese (BMI ≥30.0 kg/m^2) women separately but, in some studies, overweight and obese women were combined. The reference category was normal weight or underweight together with normal weight, depending on the studies. For convenience, the BMI categories were referred to as underweight, normal weight, overweight, and obese in the present review. In the linear dose-response meta-analyses of BMI and mortality risk, the category underweight was excluded when reported separately in the studies, to minimise the influence of this mostly uncharacterised group in the trend estimation.

Results from maximally adjusted models were selected. For RCTs that only reported unadjusted results, such results were also included in the meta-analysis, as these studies mostly involved a more homogeneous study population. RR estimates by subgroups of age, menopausal status, stage or subtypes of breast cancer, or others in the studies were first pooled for an overall estimate before including in a meta-analysis, as described before (see section 4.1.4).

Cochrane Q test, I^2 statistics, Egger's tests, funnel plots and influence analyses were conducted. Sources of heterogeneity were explored in univariate meta-regression and subgroup analyses by menopausal status, HR status, and geographical location of the studies; as well as indicators of study quality (number of events, length of follow-up, study design, BMI assessment and adjustment for confounders). The statistical methods involved were as reported above (see section 4.1.4).

Second-order fractional polynomial regression model was used to explore non-linear dose-response relationship (between BMI and mortality), with the lowest deviance model defined as the best-fitting model[210]. Non-linearity was tested using the likelihood ratio test[202]. The method was used because studies with only three categorical levels can be used instead of four categorical levels as in the restricted cubic spline with three knots method; as such, more studies could be included in the analysis.

4.2.5 Study quality evaluation

Study quality was not evaluated using an overall quality score for each individual study. Individual aspects of study quality, such as number of events, length of follow-up, study design, BMI assessment and adjustment for confounders were examined in subgroup analysis as mentioned (see section 4.2.4). This allows the evaluation of each specific quality aspect.

4.2.6 Grading of the evidence

The accumulated evidence was graded using the same WCRF grading criteria as described (see section 4.1.6)

4.3 Systematic reviews of WCRF/AICR recommendations adherence and breast cancer risk and survival

The research topic is: the associations between WCRF/AICR Cancer Prevention Recommendations adherence and breast cancer risk and survival

One of the research focuses of WCRF International CUP is to evaluate the associations between *A priori* dietary patterns, including adherence to the WCRF/AICR Cancer Prevention Recommendations, and cancer risk and survival. For the present PhD study, in addition to summarising the relevant findings in a systematic review and meta-analysis, operationalisation of the adherence score in the included studies and the pattern of adherence (overall and for individual

recommendations including those related to energy balance) within the study populations were further described. The former was to understand the use of the recommendations in research and the latter was to identify potential target for intervention.

The work for the systematic review and meta-analysis was conducted by following the protocol for the reviews on breast cancer incidence.
http://www.wcrf.org/sites/default/files/Breast_cancer_protocol_170510.pdf.

The work on the adherence scores formed part of the review conducted in collaboration with Dr. Dora Romaguera at Imperial College London and Dr Panagiota Mitrou at WCRF International.

4.3.1 Literature search

As described in section 4.1.1, the team at Imperial College London searched in PubMed up to 30th April 2017 and in the reference lists of related articles for relevant articles. To ensure that the search was complete, Dr. Dora Romaguera conducted a more specific search, using text words 'adherence', 'concordance' and 'World Cancer Research Fund' or 'WCRF' combined with 'mortality', 'cancer' or 'neoplasm' in PubMed (up to 30th April 2017); in addition, I checked the publications stored in the WCRF database. The last step aimed to identify studies reporting results on multiple cancer outcomes, and may have come through the literature searches for other cancers in the CUP.

4.3.2 Study selection

The study populations to include were women of any age, menopausal status, racial group or ethnicity, from any country, and with and without breast cancer.

The exposure factor of interest was adherence or concordance to the 2007 WCRF/AICR Cancer Prevention Recommendations and the disease outcomes to include were breast cancer incidence in women at risk of the cancer or any health outcomes in breast cancer survivors. The relation between the adherence and breast cancer risk is not thought to be different by menopausal status of the women; therefore, breast cancer of unspecified menopausal status was included and further subgroup analysis by the status was conducted.

Observational cohort studies were selected if the study reported results (relative risk estimates) on a scoring system that measured in women adherence or concordance to the 2007 WCRF/AICR Cancer Prevention Recommendations in relation to breast cancer risk and survival. Case-control studies were excluded.

The review of the adherence scores were only conducted in the studies included in the meta-analysis and hence, studies that only described the construction and distribution of the WCRF/AICR adherence score within the study population were excluded. Studies with overlapping populations were excluded.

4.3.3 Data extraction

Information on study and quality characteristics and results were extracted as described before (see section 4.1.3). In addition, information on the construction/operationalisation of the WCRF/AICR adherence score and related descriptive statistics, such as range of scores and percentage adherence of the participants in the studies were collected and presented in tables.

4.3.4 Qualitative analysis of the adherence score operationalised in the studies

The recommendations and sub-recommendations included in each study, operationalisation of the adherence scores, range and distribution of scores in the study populations, proportion of women meeting the recommendations, and most likely and least likely met recommendations were described qualitatively in text and/or presented in summary tables in the present thesis.

4.3.5 Statistical analysis

A meta-analysis of the association between adherence to the WCRF/AICR Cancer Prevention Recommendations and the risk of breast cancer incidence was conducted, as a sufficient number of studies (≥ 3 studies) had reported results.

Specifically, the results on the associations of overall adherence score and individual components of the score, including those related to energy balance, with breast cancer risk in women of either pre- or postmenopausal status were pooled in random-effects mete-analyses. Meta-analyses for the highest versus the lowest adherence were also conducted to quantify the association for this comparison. A low score would indicate poor adherence and a high score, greater adherence to the recommendations. Potential threshold effect of score adherence in breast cancer risk was explored using restricted cubic spline method with three knots. Cochrane Q test, I^2 statistics, Egger's tests, funnel plots and influence analyses were conducted. The statistical methods involved were as described above (see section 4.1.4).

Sources of heterogeneity were explored in subgroups by geographical region (Europe or North America), menopausal status of the women (pre- or postmenopausal), and HR status of the tumour (HR-positive or HR-negative), and meta-regression was not conducted because of the low numbers of studies.

For all the statistical analyses in the present PhD study, a two-tailed p-value of <0.05 was considered as statistical significant; apart from Egger's test[200], where P <0.10 was considered as statistical significant, as the test is generally low power. RR estimate ≤0.5 or ≥2.0 was considered strong, >0.5 to ≤0.9 or ≥1.10 to <2.0 was moderate, and >0.90 to <1.10 was a null association.

The statistical software, Stata 13.0 (StataCorp, College Station, TX, USA) was used.

5 Systematic reviews of energy balance-related factors and breast cancer risk

5.1 Results of the literature search

Figure 5.1 shows the flowchart of the literature search.

Among the 347 potentially relevant publications identified on energy balance-related factors and breast cancer risk, 100 publications were on breast cancer of unspecified menopausal status and were excluded from the present systematic review. A further 61 publications were excluded because they were either superseded by more recent publications of the same studies or overlapped with other studies included in the meta-analyses. Thirty-six publications were not in any meta-analyses because either the information presented in the publications did not allow their inclusion (n = 14) or were on associations that were examined by ≤3 studies in total (n = 22). Overall, 150 publications were meta-analysed.

Appendix 2 is the list of the publications identified, included in and excluded from each specific meta-analysis. Main study characteristics and findings, as well as the exclusion reason for the studies not included in the meta-analysis were also provided. Appendix 3 shows the main characteristics of the studies included in the meta-analyses.

5.2 Characteristics of the studies

Study design

All studies were observational cohort studies. A few studies were originally a RCT. All participants were being followed-up prospectively, as opposed to being recruited retrospectively as in the case-control studies.

Geographic location and ethnicity/race

The majority of the studies were based in White/Caucasian women from North America and/or Europe. A lesser number of studies were on African American, Native Hawaiian and Latina women residing in the US (multi-ethnic study) and on women from Asia-Pacific countries (Australia and New Zealand, China, Japan, Korea).

Studies of special characteristics/mammography screening studies

Most studies comprised women recruited from the general populations, although some through professional bodies or health screening programmes. There was one historical cohort of *BRCA1/2* carriers[211], one pooled analysis of familial cancer studies[212] and a cohort of sisters of women with breast cancer[213].

Eleven studies were of women from either breast or other cancer screening programmes[101;121;214-222]. Two pooled studies included cancer or mammography screening studies as components[104;223]. In addition, was a chemoprevention (tamoxifen) trial that followed the participants, all at high risk of developing breast cancer, with annual bilateral mammograms[224].

Study size and number of cases and length of follow-up

Most studies had ≥10 years of average follow-up and accrued ≥200 premenopausal and ≥500 postmenopausal cases. Among the included studies, average follow-up ranged from 2[225] to 49 years[226]. The study with the lowest number of premenopausal breast cancer cases was Sesso *et al.*, with just 28 cases from 1,566 women[227]. The smallest study had only 15 postmenopausal breast cancer cases from 590 women[228].

Case ascertainment and loss to follow-up

Case ascertainment was mostly through active follow-up and confirmed by medical records (histology/pathology records) or by record linkage to cancer registries and death registries.

Loss to follow-up was not indicated in most studies. When reported, the proportion was generally low (≤10%), with a few exceptions[216;227;229-231].

Study quality

Median study quality scores were 11 and 12 points in the publications on pre- and postmenopausal breast cancer, respectively. The maximum possible points were 17 points. For the studies on premenopausal breast cancer, study quality ranged from 5[232] to 15.5 points[233]; similar to the scores in the studies on postmenopausal breast cancer, that ranged from 5[211] to 16 points[234-236].

Lower quality studies (< median score) scored poorly in the aspects of loss to follow-up, number of cases and confounding factors adjustment. Across the meta-analyses, the proportions of studies that achieved full score in these aspects were only 0 – 20%, 0 – 15% and 0 – 25% among low quality studies, as oppose to 17 – 80%, 33 – 75% and 60 – 92% among higher quality studies (≥ median score), respectively. In addition, lower quality studies were less likely to analyse the associations for HR subtypes of the tumour or separate invasive from *in situ* breast cancers.

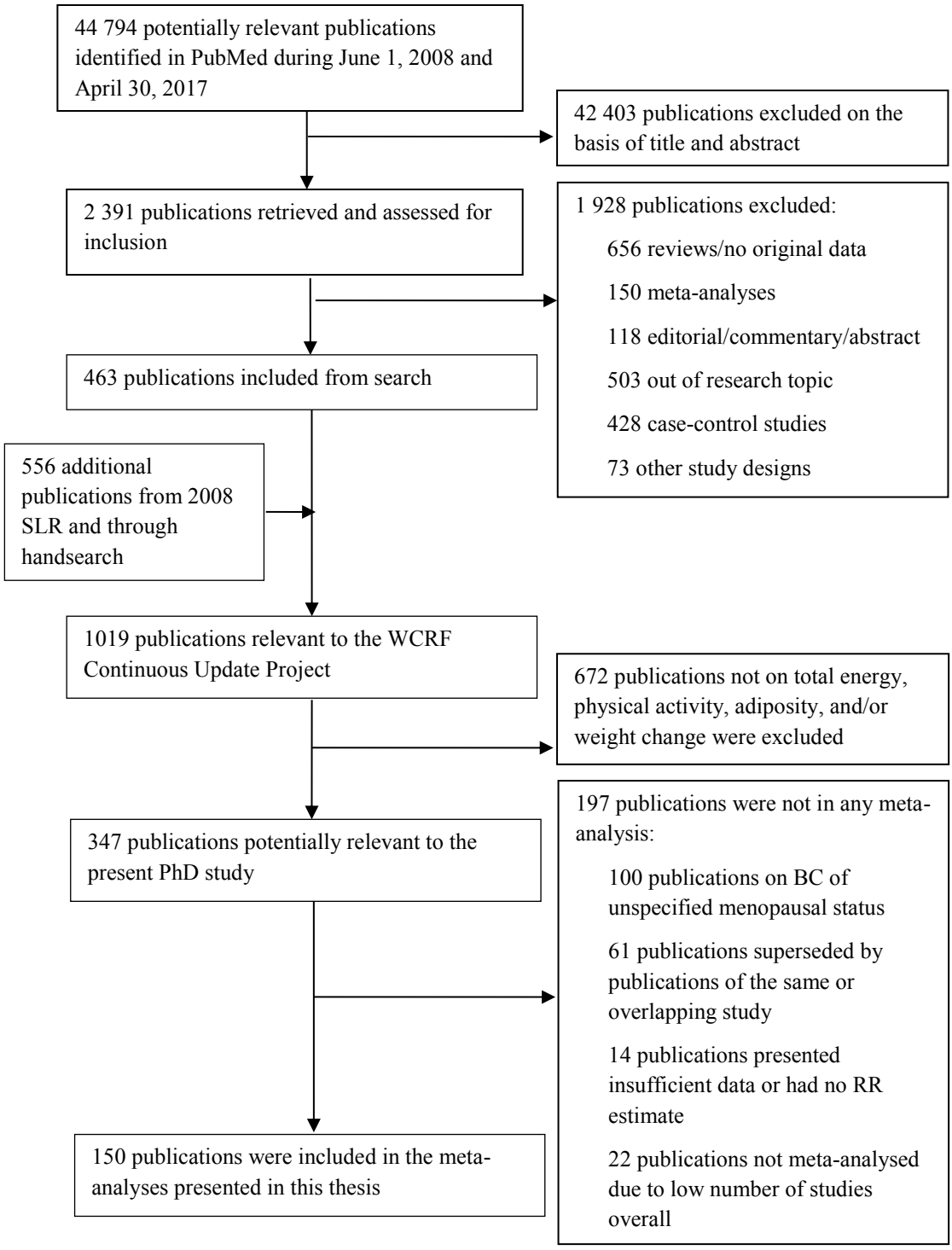


Figure 5.1 Flowchart of search for studies of energy balance-related factors and breast cancer risk

5.3 Results of the studies

Results of the meta-analyses and other individual studies are reported here. The summary of all main meta-analyses are shown in Table 5.1 and the results of the subgroup meta-analyses are provided in Tables 5.2 through 5.11.

5.3.1 Total energy intake and risk of pre- and postmenopausal breast cancer

Three studies on premenopausal breast cancer [237-239] (1,633 cases) and nine studies on postmenopausal breast cancer[214;228;237;238;240-244] (7,803 cases) could be included in the meta-analyses, respectively.

All but one study used food frequency questionnaire (FFQ), with 61[239] to 150 items[238;243], to collect dietary information from the study participants. Total energy intake was estimated by summing the frequency multiplied by the portion size and energy content of the food items.

There were no statistically significant associations between total energy intake and premenopausal breast cancer risk (summary RR per 500 kcal/day = 0.98, 95% CI: 0.92-1.04) (I^2 = 21%, P heterogeneity = 0.28) and postmenopausal breast cancer risk (1.02, 95% CI: 0.97-1.06) (I^2 = 45%, P heterogeneity = 0.07) (Figure 5.2).

Further analyses were not conducted for premenopausal breast cancer because of low number of studies. For postmenopausal breast cancer, there were no evidence of significant publication bias (P for Egger's test = 0.36), non-linear relationship (P for non-linearity = 0.11) and strong influence from any individual study on the summary RR estimate. Meta-analysis by geographic location of the studies showed null associations that were similar across the subgroups; the same for the analyses that concern study quality, including main confounding factors adjustment (age, alcohol, reproductive factors and MHT use) and length of follow-up, as well as for overall study quality (Table 5.2) (all P-values for meta-regression ≥0.66).

Although some studies were able to validate the FFQ against other dietary instruments[237;238;242-244], these studies on average did not find very different results to the studies that used a non-validated FFQ[214;228;240;241] (P for meta-regression = 0.54). The studies with[214;237] and without[228;238;240-244] adjustment for BMI and physical activity, on average, found null associations (P for meta-regression = 0.35) (Table 5.2).

The only study that reported results by subgroups of breast cancer defined by HR status in postmenopausal women found no significant associations[242]

Table 5.1 Summary of meta-analyses of energy balance-related factors and breast cancer risk

Energy balance -related factors	Premenopausal breast cancer			Postmenopausal breast cancer		
	Studies/ cases	RR (95% CI)	I^2 /P	Studies/ cases	RR (95% CI)	I^2 /P
Total energy intake						
Per 500 kcal/day	3/ 1,633	0.98 (0.92-1.04)	21%, 0.28	9/ 7,803	1.02 (0.97-1.06)	45%, 0.07
Total physical activity						
Highest vs lowest	5/ 1,834	0.93 (0.79-1.08)	0%, 0.95	6/ 9,755	**0.86 (0.78-0.94)**	9%, 0.35
Per 20 MET-hour/week	1/ 440	0.96 (0.92-1.01)	-	3/ 2,539	0.98 (0.96-1.00)	61/ 0.08
Recreational physical activity						
Highest vs lowest	12/ >3,937	0.89 (0.75-1.04)	40%, 0.08	21/ >27,224	**0.88 (0.82-0.94)**	35%, 0.06
Per 10 MET-hour/week	3/ 2,331	0.96 (0.90-1.03)	69%, 0.04	6/ 19,816	**0.98 (0.97-0.99)**	0%, 0.61
Vigorous physical activity						
Highest vs lowest	5/ 3,353	**0.79 (0.69-0.91)**	6%, 0.37	11/ 20,171	**0.90 (0.85-0.95)**	0%, 0.96
Per 30 min/day	3/ 1,473	0.91 (0.83-1.01)	0%, 0.63	3/ 2,853	0.94 (0.86-1.02)	0%, 0.95
Occupational physical activity						
Highest vs lowest	8/ 5,339	0.83 (0.65-1.05)	76%, <0.001	9/ 21,932	**0.90 (0.85-0.96)**	0%, 0.89
Walking						
Highest vs lowest	2/ 1,289	0.97 (0.76-1.25)	17%, 0.27	4/ 7,300	0.95 (0.86-1.04)	0%, 0.98
Sitting						
Highest vs lowest	2/ 1,290	1.04 (0.83-1.32)	0%, 0.72	4/ 4,704	1.20 (1.00-1.44)	46%, 0.13
Per 5 hours/day	-	-	-	3/ 4,333	**1.07 (1.01-1.14)**	0%, 0.55
Early adult BMI						
Per 5 kg/m^2	13/ >4,498	**0.86 (0.78-0.96)**	47%, 0.05	18/ >9,271	**0.81 (0.75-0.87)**	50%, 0.01
Adult weight gain						
Per 5 kg gain	9/ 3,990	1.00 (0.97-1.03)	21%, 0.27	16/ 17,150	**1.07 (1.05-1.09)**	64%, <0.001
Per 5 kg/m^2 gain	6/ >900	0.97 (0.77-1.22)	75%, 0.02	9/ >2,575	**1.17 (1.11-1.23)**	0%, 0.81
Adult weight loss						
Weight loss vs reference weight	8/ 1,373	**0.85 (0.74-0.99)**	0%, 0.93	14/ 8,282	**0.90 (0.81-0.99)**	24%, 0.20
Per 5 kg loss	-	-	-	4/ 952	0.96 (0.88-1.04)	0%, 0.46
BMI						
Per 5 kg/m^2	41/ >17,222	**0.94 (0.91-0.98)**	57%, <0.001	65/ >90,388	**1.12 (1.10-1.15)**	76%, <0.001
Waist circumference						
BMI unadjusted Per 10 cm	7/ 2,836	0.99 (0.94-1.03)	0%, 0.88	14/ 16,384	**1.12 (1.10-1.14)**	14%, 0.30
BMI adjusted Per 10 cm	4/ 1,704	**1.15 (1.05-1.26)**	0%, 0.94	7/ 13,668	**1.07 (1.01-1.13)**	71%, 0.002
Hip circumference						
BMI unadjusted Per 10 cm	4/ 1,438	**0.92 (0.87-0.98)**	0%, 0.50	7/ 4,425	**1.07 (1.04-1.11)**	25%, 0.24
BMI adjusted Per 10 cm	3/1,291	1.05 (0.80-1.36)	80%, 0.006	3/ 2,309	1.12 (0.95-1.32)	62%, 0.08
Waist-hip-ratio						
BMI unadjusted Per 0.1 unit	10/ 3,645	1.05 (0.98-1.13)	14%, 0.31	20/ 16,775	**1.11 (1.06-1.17)**	57%,0.001
BMI adjusted Per 0.1 unit	7/ 2,523	1.14 (1.00-1.29)	55%, 0.04	8/ 6,277	1.05 (0.98-1.13)	46%, 0.07

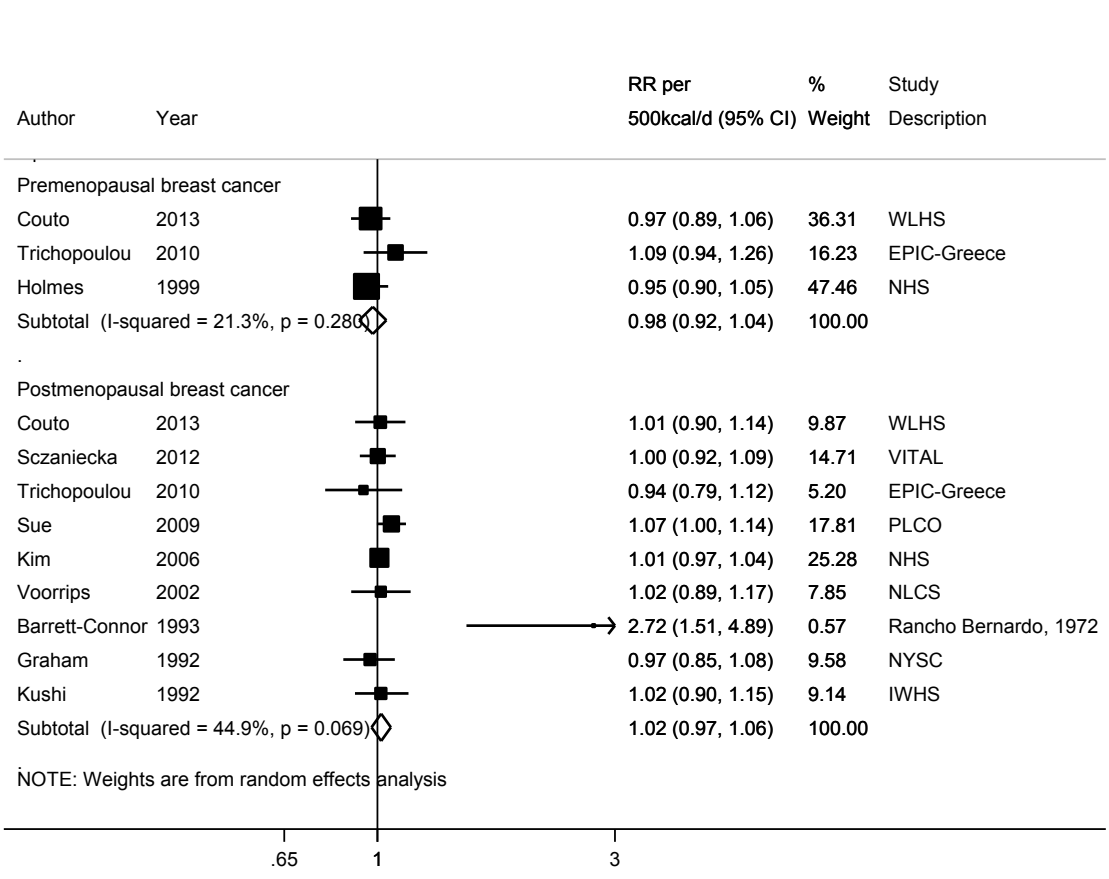


Figure 5.2 Relative risk and 95% CI of pre- and postmenopausal breast cancer for 500 kcal/day increase of total energy intake

Table 5.2 Summary of subgroup dose-response meta-analyses of total energy intake and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Per 500 kcal/day	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	3 1,633	0.98 (0.92-1.04)	21% 0.28	-	9 7,803	1.02 (0.97-1.06)	45% 0.07	-
Geographic location								
Asia	-	-	-	-	-	-	-	-
Europe	-	-	-	-	3 1,358	1.00 (0.92-1.08)	0% 0.74	0.76
North America	-	-	-	-	6 6,445	1.03 (0.97-1.09)	64% 0.02	
Exposure assessment								
Validated	-	-	-	-	4 2,449	1.05 (0.93-1.19)	77% 0.005	0.54
Not validated	-	-	-	-	5 5,354	1.01 (0.98-1.04)	0% 0.95	-
Main confounding factors adjustment								
Adjusted	-	-	-	-	4 6,087	1.02 (0.99-1.05)	0% 0.56	0.66
Not adjusted	-	-	-	-	5 1,716	1.02 (0.91-1.14)	67% 0.02	
BMI and physical activity adjustment								
Adjusted	-	-	-	-	2 1,767	1.05 (0.99-1.12)	0% 0.45	0.35
Not adjusted	-	-	-	-	7 6,036	1.01 (0.95-1.07)	51% 0.06	
Study type								
Screening	-	-	-	-	1 1,319	1.07 (1.00-1.14)	-	0.28
Non-screening	-	-	-	-	8 6,484	1.01 (0.96-1.06)	42% 0.10	-
Length of follow-up								
<10 years	-	-	-	-	6 3,803	1.02 (0.98-1.06)	0% 0.62	0.85
≥10 years	-	-	-	-	3 4,000	1.09 (0.91-1.31)	82% 0.004	
Study quality								
Low	-	-	-	-	4 1,266	1.06 (0.91-1.23)	74% 0.01	0.93
High	-	-	-	-	5 6,537	1.02 (0.99-1.05)	0% 0.55	
Invasive breast cancer	-	-	-	-	5 5,677	1.01 (0.98-1.04)	0% 0.95	-

5.3.2 Physical activity and risk of pre- and postmenopausal breast cancer

Different domains of physical activity were examined, including recreational, occupational and household physical activity; which were combined into total physical activity (all three types of activity), non-occupational (recreational and household activities) and non-recreational physical activity (occupational and household activities) in the studies.

Energy expended through physical activity was accounted for in some studies that examined the intensity levels of the activities. The metabolic equivalent of task (MET) values, as defined in the Compendium of Physical Activities[245;246], were used in some studies to assign the energy cost to each specific activity. One MET is the energy an individual expends at a resting state. According to the Compendium, the MET-values are 1.0-1.5 METs for sedentary behaviour, and 1.6-2.9 METs for light-, 3-5.9 METs for moderate- and ≥6 METs for vigorous-intensity activities.

Specific types of physical activity for example walking, cycling and gardening; and the lack of physical activity, as indicated by sedentary behaviour such as sitting and television watching, were also investigated in some studies.

Studies used questionnaires to subjectively assess physical activity performed by the participants, at study baseline and at specific times in adult life. The information collected varied hugely in terms of the types, dose (frequency, duration and intensity) and timing of physical activity. The difference in measurements had largely reduced the number of studies that could be pooled in a dose-response meta-analysis; hence meta-analyses that compared the highest with the lowest physical activity level were also conducted, as reported below.

5.3.2.1 Total physical activity

Five studies on premenopausal breast cancer [233;247-249] (1,834 cases) could be included in the highest versus the lowest meta-analysis. Only one of these studies reported sufficient information to estimate a dose-response trend[248]. Of the studies on postmenopausal breast cancer, six could be included in the highest versus the lowest meta-analysis[215;233;247;248;250](9,755 cases), and three in the dose-response meta-analysis[215;248;250] (2,539 cases).

Total physical activity was not associated with the risk of premenopausal breast cancer (summary RR for highest vs lowest level = 0.93, 95% CI: 0.79-1.08) (I^2 = 0%, P heterogeneity = 0.95) (Figure 5.3). Influence analysis, in which each study was omitted in turn, showed non-significant results similar to the original analysis. While the highest level of total physical activity significantly decreased postmenopausal breast cancer risk when compared with the lowest level of the activity (summary RR for highest vs lowest level = 0.86, 95% CI: 0.78-0.94) (I^2 = 9%, P heterogeneity = 0.35) (Figure 5.3); the same was not observed in the dose-response meta-analysis (summary RR per 20 MET-hour/week = 0.98, 95% CI:0.96-1.00) (I^2 = 61%, P heterogeneity = 0.08) (graph not shown). The study of

Steindorf *et al.*[247] that found a significant reduced risk and showed influence in the highest versus the lowest meta-analysis (summary RR for highest vs lowest level = 0.86, 95% CI: 0.74-1.00 when the study was omitted) did not provide sufficient data to be included in the dose-response meta-analysis, could have contributed to the null association.

Lower quality studies (two ≤11 points in the premenopausal breast cancer analysis[248;249] and one ≤12 points in postmenopausal breast cancer analysis[248] scored less well in the general representativeness of the cohort, exposure assessment methods, confounding adjustment and loss of follow-up. Subgroup meta-analysis and test of publication bias were not conducted because the numbers of studies were too low to produce meaningful results.

The overall null association with postmenopausal breast cancer risk in the USRT study could be a result of the opposite associations observed in MHT never and ever users (RRs for highest vs lowest level = 0.71, 95% CI: 0.43-1.17 among never users and 1.15, 95% CI: 0.78-1.70 among ever users) (139 and 285 cases, respectively) (P for interaction = 0.44)[248]. Another French study investigated the association among MHT ever users only found a null association (1.01, 95% CI: 0.85-1.21) (1,095 cases)[251].

For subtypes of breast cancer defined by HR status, both the small Japanese study (110 pre- and 118 postmenopausal breast cancer cases)[233] and another larger-sized Norwegian study (1,767 postmenopausal cases) [252] found non-significant results that showed no clear pattern of different associations between the breast cancer subtypes.

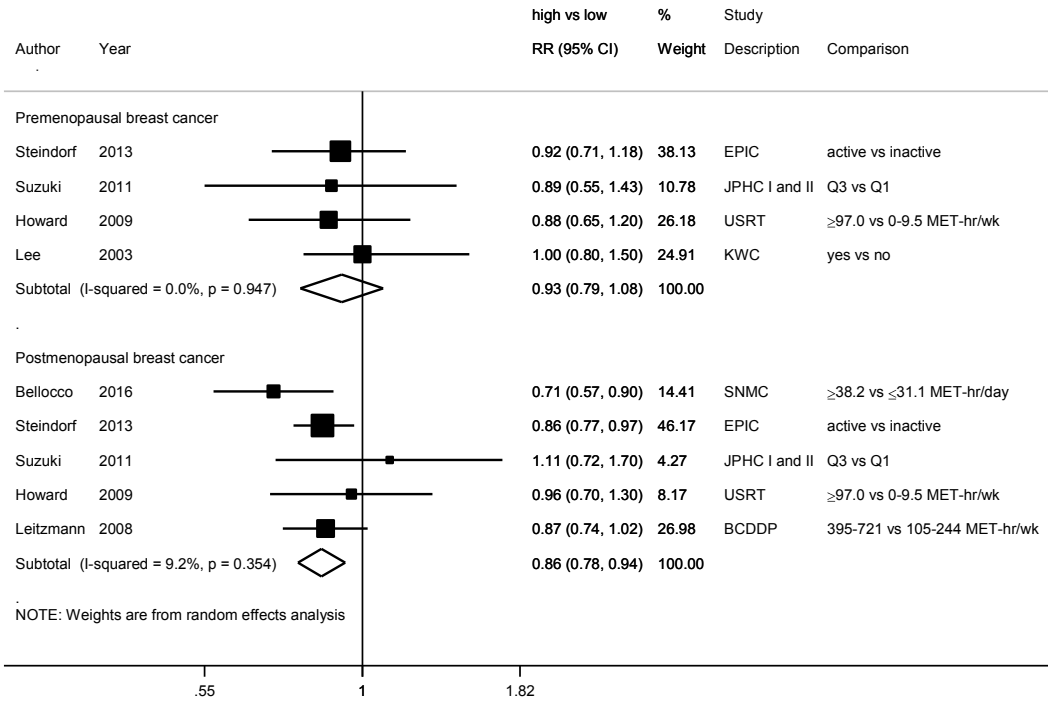


Figure 5.3 Relative risk and 95% CI of pre- and postmenopausal breast cancer for the highest compared with the lowest level of total physical activity

5.3.2.2 Total physical activity across adult life course

One large Norwegian study was identified, which reported non-significant associations with postmenopausal breast cancer risk when comparing very high level (RR = 0.91, 95% CI: 0.78-1.08) and very low level (1.16, 95% CI: 0.82-1.64) to moderate level of physical activity performed at age 30 years (P trend = 0.23) (1,723 cases in total)[252].

5.3.2.3 Change in total physical activity

The abovementioned study also did not detect any significant associations of changes in total physical activity level between age 30 years and study baseline with postmenopausal breast cancer risk[252]. RR estimates were 1.06 (95% CI: 0.89-1.27), 1.04 (95% CI: 0.92-1.18) and 1.01 (95% CI: 0.82-1.25) for women who were consistently inactive, active to inactive and inactive to active compared with women who remained active, respectively[252].

5.3.2.4 Recreational physical activity

Twelve studies on premenopausal breast cancer[227;233;247;253-260] (>3,937 cases) and 21 studies on postmenopausal breast cancer could be included in the highest versus the lowest meta-analyses[121;218;227;233;235;247;253-256;258-267] (>27,224 cases), respectively.

Recreational physical activity was defined as leisure-time physical activity or exercise/sports in the studies. Three studies on premenopausal breast cancer and six studies on postmenopausal breast cancer presented results in MET-hour/week, which could be pooled in the dose-response meta-analyses, respectively. The increment unit was 10 MET-hour/week, which is about 30 minutes of cycling (<10 miles/hour) for 5 days a week or 150 minutes of weekly moderate-intensity activity (4 METs) such as brisk walking.

Recreational physical activity was not statistically significantly associated with premenopausal breast cancer risk (summary RR for highest vs lowest level = 0.89, 95% CI: 0.75-1.04) (I^2 = 40%, P heterogeneity = 0.08) (Figure 5.4). The summary RR remained non-significant in influence analysis and no significant publication bias was detected (P for Egger's test = 0.89). However, in the subgroup meta-analyses, higher quality studies[233;247;255-257], which were among the studies that used validated questionnaire to assess physical activity[227;233;247;254-257;259] and adjusted for the main confounding factors[233;247;255-257], found a significant 17% decreased risk (summary RR for highest vs lowest level = 0.83, 95% CI: 0.70-0.99) (Table 5.3). Nevertheless, in the dose-response meta-analysis, which included three studies, all of high quality[247;256;257], found an average null association (summary RR per 10 MET-hour/week = 0.96, 95% CI: 0.90-1.03) (I^2 = 69%, P heterogeneity = 0.04) (2,331 cases) (Figure 5.5).

For postmenopausal breast cancer risk, statistically significant inverse associations were observed in both the highest versus the lowest and dose-response meta-analyses (Figures 5.4 and 5.5). The

respective summary RRs were 0.88 (95% CI: 0.82-0.94) and 0.98 (95% CI: 0.97-0.99) (6 studies[235;247;256;261;262;267](19,816 cases), with no significant between-study heterogeneity (I^2 = 35% and 0%, P heterogeneity = 0.06 and 0.61, respectively). Significant publication bias was observed (P for Egger's test = 0.01). Visual inspection of the funnel plot shows asymmetry, possibly driven by smaller studies[227;254;260;268], three of which of lower quality[227;254;260], that reported a stronger than the average inverse association (Figure 5.6). In influence analyses, the summary RR for the highest versus the lowest meta-analysis remained materially unchanged, but became borderline significant when three studies[235;262;267] were excluded in turn from the dose-response meta-analysis.

Recreational physical activity remained inversely associated with postmenopausal breast cancer risk in the subgroup meta-analyses by geographic location, exposure assessment method, main confounding factors adjustment, adjustment for BMI and length of follow-up (all P-values for meta-regression ≥0.09) (Table 5.3). Although 12 studies were of lower quality[121;218;227;253;254;258-261;263-265] and only nine studies were of higher quality[233;235;247;255;256;262;266;267]; both groups of studies observed significant inverse associations that were not significantly different (P for meta-regression = 0.77) (Table 5.3).

By MHT use, a significant inverse association was observed among MHT never users (summary RR for highest vs lowest level = 0.80, 95% CI: 0.66-0.96) (I^2 = 26%, P heterogeneity = 0.26) (3 studies[256;269;270], and not among ever users (0.92, 95% CI: 0.81-1.04) (I^2 = 0%, P heterogeneity = 0.81) (4 studies[251;256;269;270]) (results not shown).

Five studies investigated the associations across normal weight, overweight and obese postmenopausal women, with study-specific BMI categories[247;266;267;269;270]. Although there may be a slight tendency of a decreased risk among leaner women, the difference between the groups was not clear (summary RRs for highest vs lowest level = 0.85 (95% CI: 0.72-1.01) in normal weight, 0.95 (95% CI: 0.85-1.06) in overweight and 1.00 (95% CI: 0.86-1.15) in obese women) (P for meta-regression = 0.53) (Figure 5.7).

A restricted cubic-spline analysis could be conducted to evaluate potential threshold effect using the six studies that were included in the linear dose-response meta-analysis of postmenopausal breast cancer risk[235;247;256;261;262;267]. The curve shows a linear decreased risk with increasing levels of recreational physical activity that was statistically significant for the level ≥ 23 MET-hour/week, although data were sparse, especially at and above this level (summary RR for 31 vs 0 MET-hour/week = 0.94, 95% CI: 0.90-0.99) (P for non-linearity = 0.68) (Figure 5.8).

One Japanese study[233] and one American study[271], both with limited number of HR-defined breast cancers (105[233] and 466 cases[271]), examined the associations in premenopausal women, and reported non-significant inverse associations that were similar between ER+PR+ breast cancer (RRs for

highest vs lowest level = 0.80 (95% CI: 0.56-1.15)[271] and 0.64 (95% CI: 0.23-1.78)[233]) and ER-PR- breast cancer (RRs = 0.86 (95% CI: 0.46-1.61)[271] and 0.55 (95% CI: 0.16-1.86)[233]).

Similarly, meta-analyses of an overall six studies (7 publications) of postmenopausal women[121;233;262;263;272-274] showed inverse associations that were comparable across the HR-defined breast cancers. Although the results were only statistically significant for ER-positive (summary RR for highest vs lowest level = 0.87, 95% CI: 0.81-0.94) (3 studies[263;272;273]) (5,741 cases in total) or ER+PR+ (0.89, 95% CI: 0.82-0.96) (5 studies[121;233;262;263;272]) (5,117 cases) and not for ER-negative (0.88, 95% CI: 0.74-1.04) (3 studies[263;272;274]) (1,053 cases) or ER-PR- (0.89, 95% CI: 0.76-1.04) (4 studies[233;262;263;272]) (1,236 cases) breast cancers, this could partly due to the smaller number of cases in the latter breast cancer subtypes (Figure 5.9).

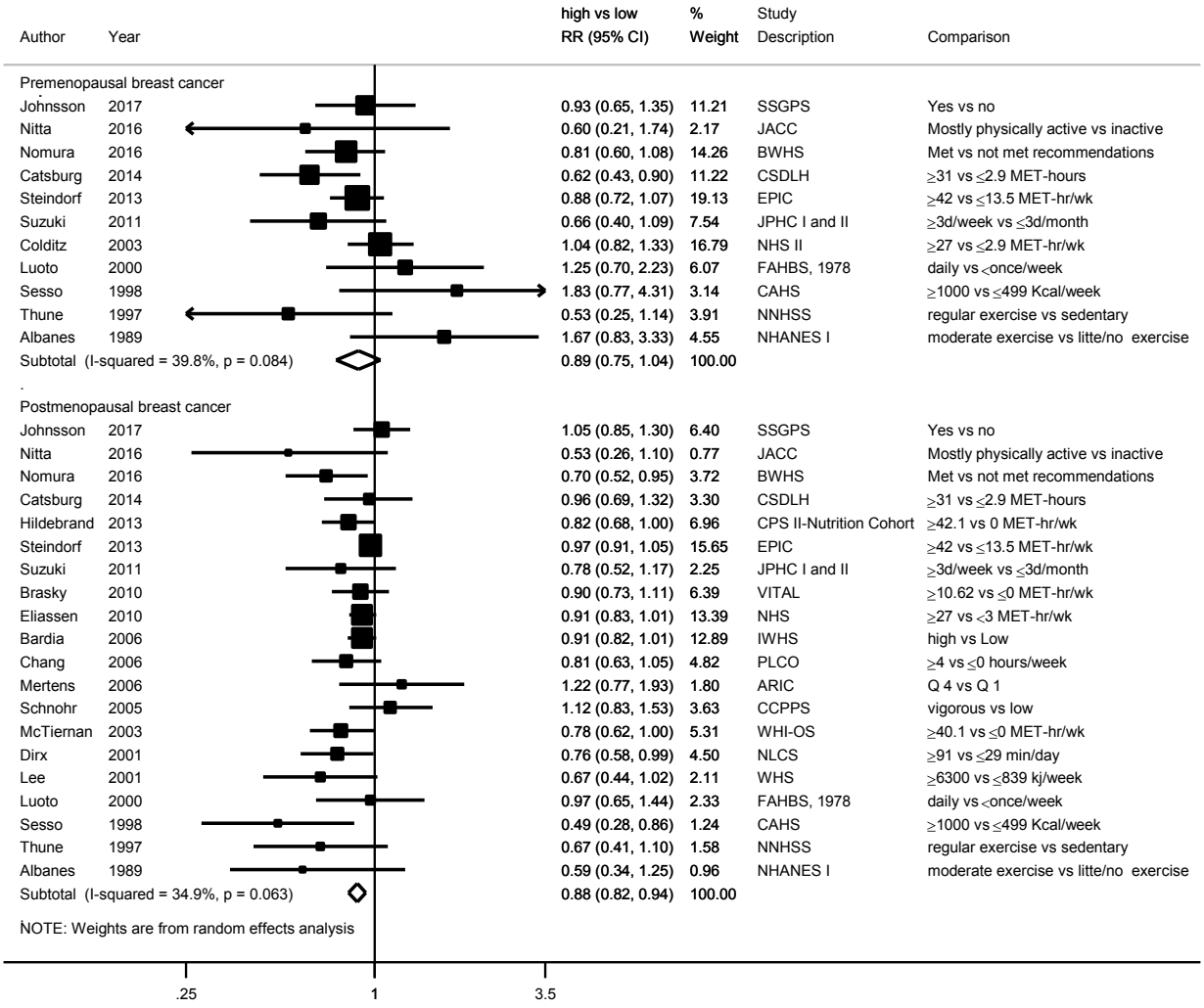


Figure 5.4 Relative risk and 95% CI of pre- and postmenopausal breast cancer for the highest compared with the lowest level of recreational physical activity

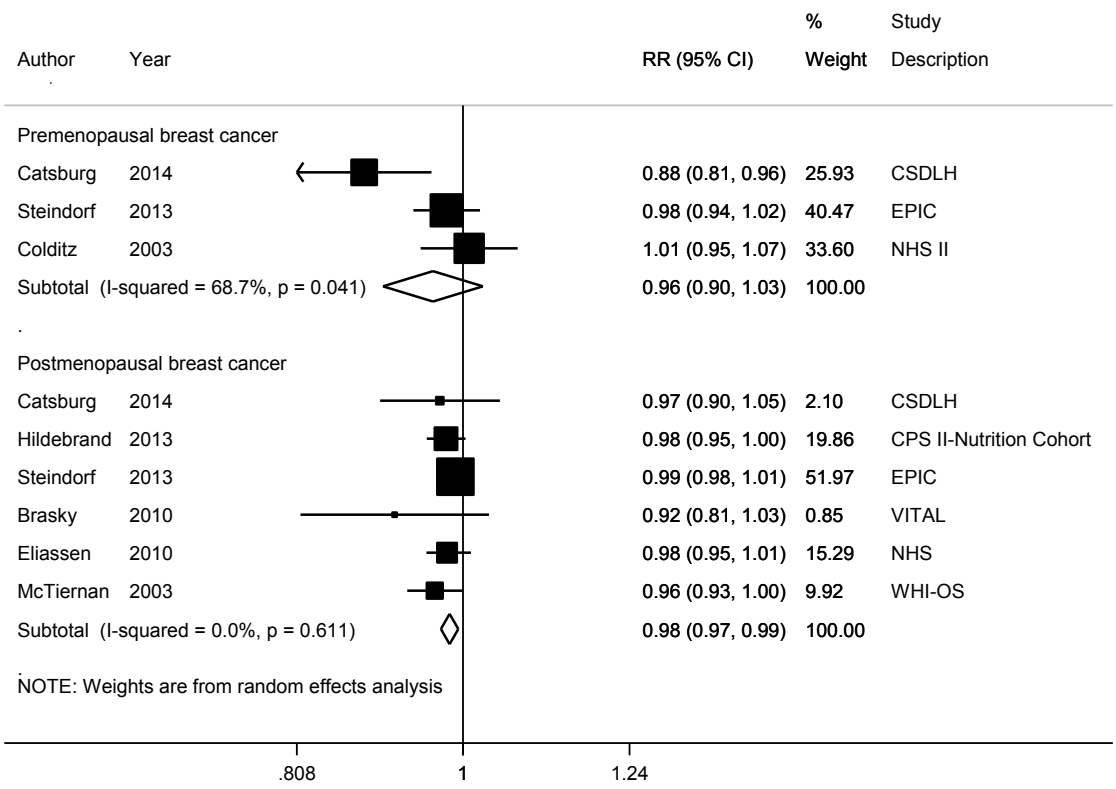


Figure 5.5 Relative risk and 95% CI of pre- and postmenopausal breast cancer for 10 MHT-hour/week of recreational physical activity

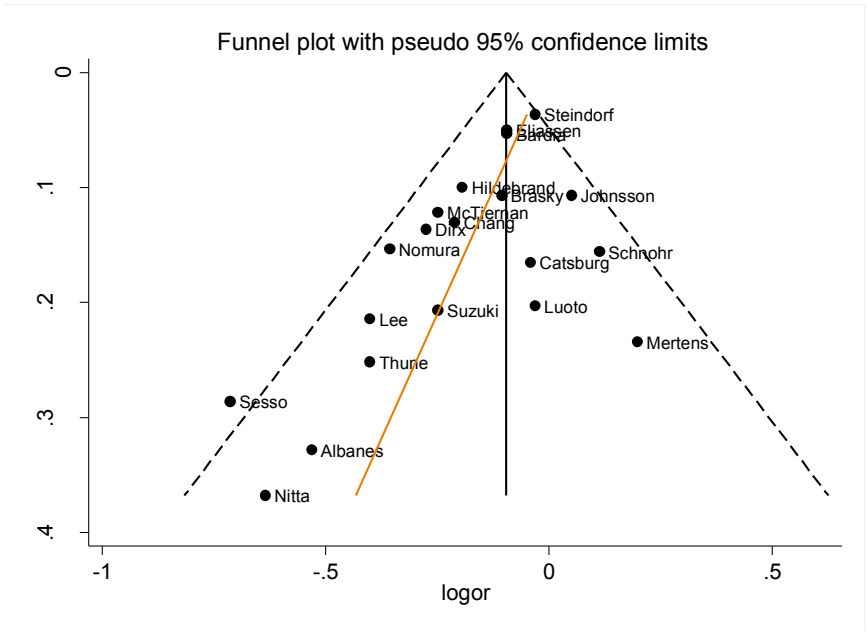


Figure 5.6 Funnel plot of studies included in the highest versus the lowest meta-analysis of recreational physical activity and postmenopausal breast cancer

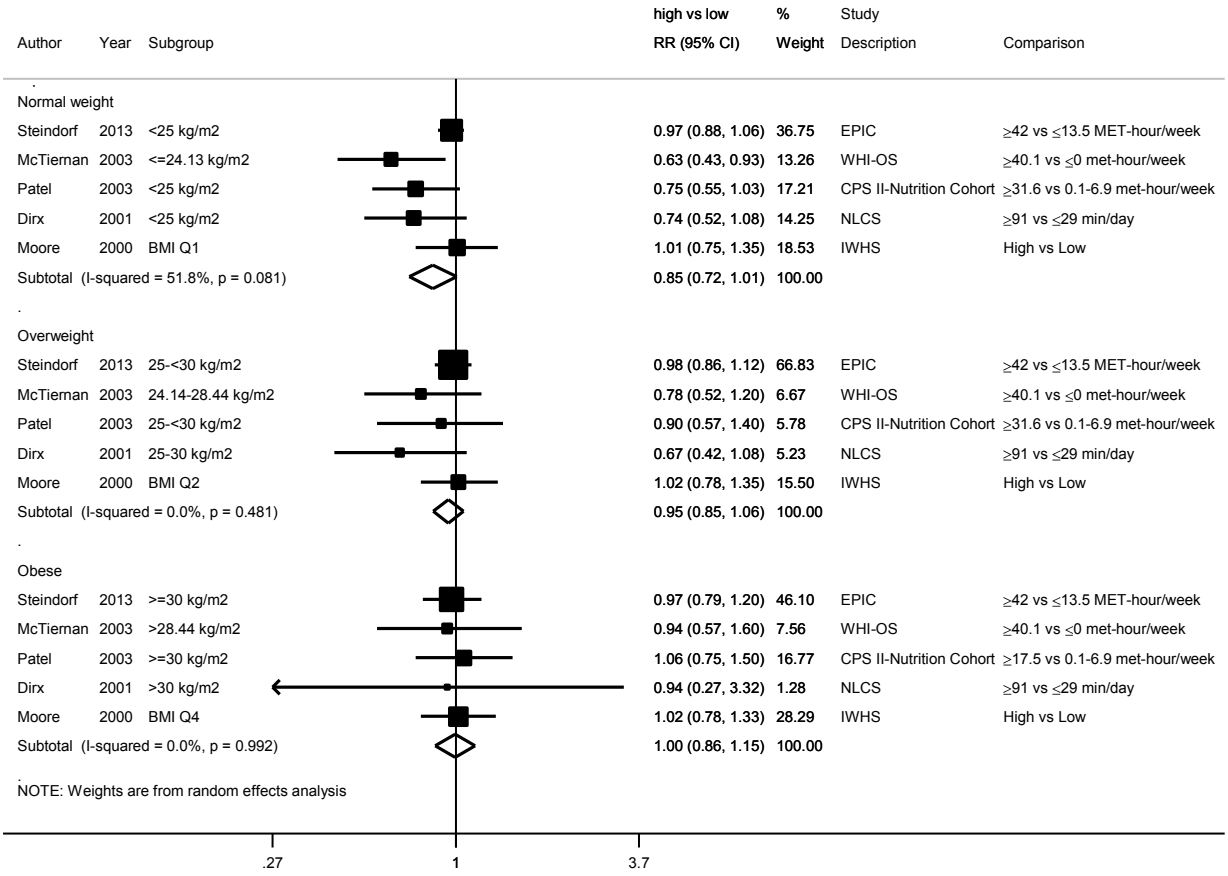


Figure 5.7 Relative risk and 95% CI of postmenopausal breast cancer for the highest compared with the lowest level of recreational physical activity, by BMI categories

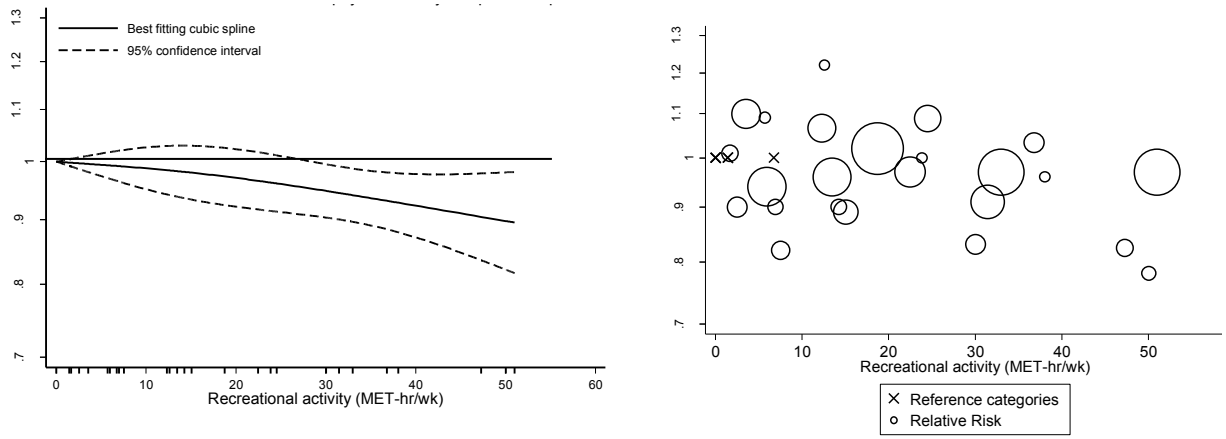


Figure 5.8 Non-linear analysis of recreational physical activity and postmenopausal breast cancer

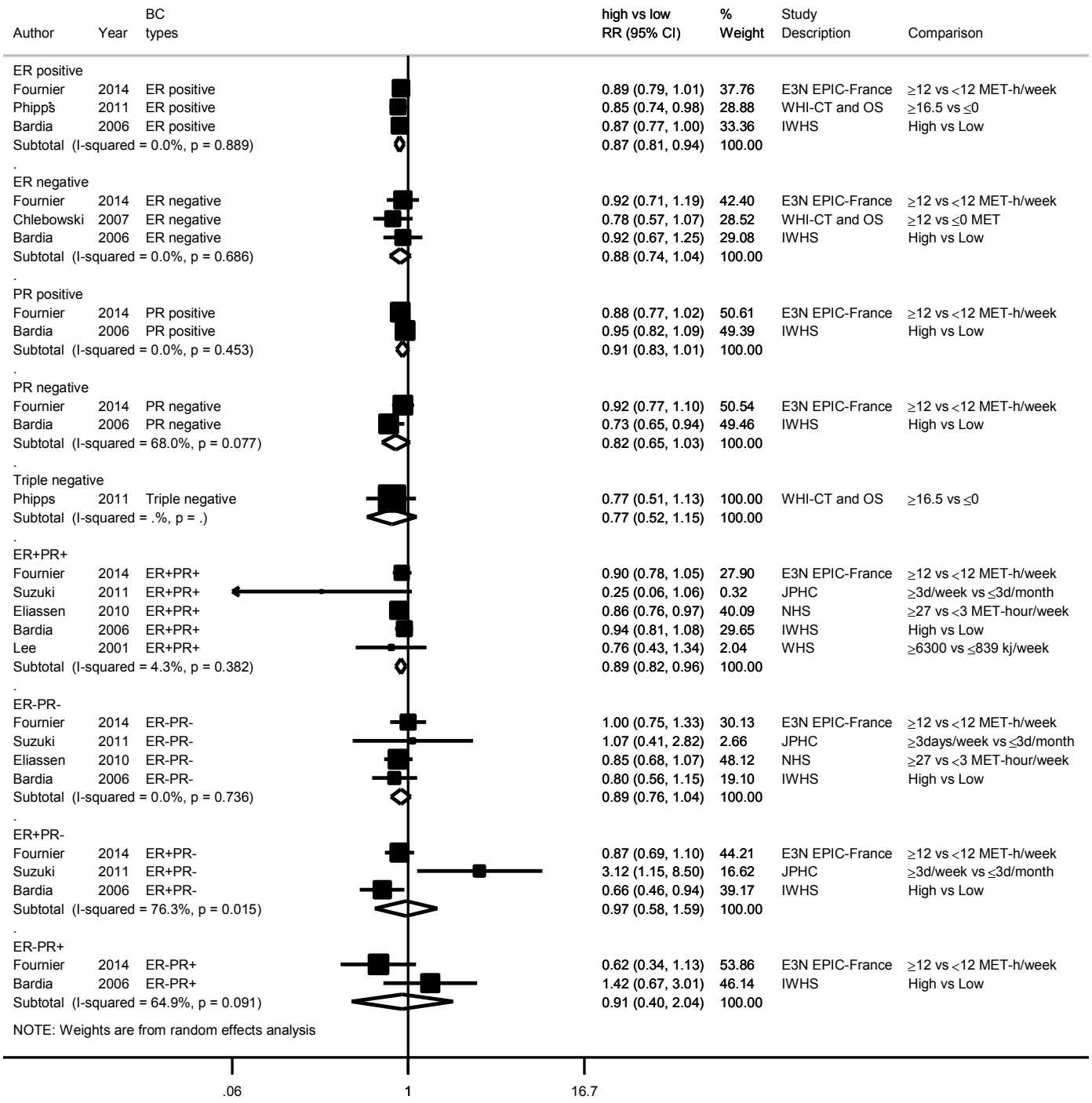


Figure 5.9 Relative risk and 95% CI of hormone receptor-defined postmenopausal breast cancer subtypes for the highest compared with the lowest level of recreational physical activity

Table 5.3 Summary of subgroup meta-analyses of recreational physical activity and pre- and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Highest vs lowest	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	12 >3,937	0.89 (0.75-1.04)	40% 0.08	-	21 >27,224	**0.88 (0.82-0.94)**	35% 0.06	-
Geographic location								
Asia	3 313	0.65 (0.41-1.02)	0% 0.87	0.55	3 386	0.71 (0.50-1.01)	0% 0.36	0.09
Europe	4 >1,457	0.90 (0.75-1.07)	6% 0.36		6 >9,787	0.95 (0.86-1.06)	26% 0.24	
North America	5 2,167	0.97 (0.71-1.31)	65% 0.02		12 17,051	**0.86 (0.79-0.92)**	23% 0.21	
Exposure assessment								
Validated	9 3,468	**0.83 (0.69-0.99)**	40% 0.11	0.16	11 15,494	**0.85 (0.77-0.95)**	50% 0.04	0.82
Not validated	3 >469	1.13 (0.82-1.54)	14% 0.32		10 >11,730	**0.89 (0.82-0.96)**	17% 0.29	
Main confounding factors adjustment								
Adjusted	6 3,269	**0.83 (0.70-0.99)**	40% 0.16	0.27	11 22,812	**0.90 (0.84-0.96)**	30% 0.17	0.58
Not adjusted	6 >668	1.04 (0.74-1.48)	39% 0.15		10 >4,412	**0.84 (0.72-0.97)**	41% 0.08	
BMI adjustment								
Adjusted	11 >3,514	0.88 (0.73-1.06)	46% 0.06	0.85	18 >25,211	**0.88 (0.82-0.94)**	38% 0.06	0.99
Not adjusted	1 423	0.93 (0.65-1.35)	-		3 2,013	0.89 (0.72-1.10)	36% 0.21	
Study type								
Screening	0	-	-	-	0	-	-	
Non-screening	12 >3,937	0.89 (0.75-1.04)	40% 0.08		21 >27,224	**0.88 (0.82-0.94)**	35% 0.06	-
Length of follow-up								
<10 years	0	-	-	-	5 4,614	**0.81 (0.72-0.91)**	0% 0.72	0.09
≥10 years	12 >3,937	0.89 (0.75-1.04)	40% 0.08		16 >22,610	**0.90 (0.84-0.97)**	38% 0.07	
Study quality								
Low	6 >668	1.04 (0.74-1.48)	39% 0.15	0.27	12 >6,697	**0.88 (0.78-0.99)**	39% 0.08	0.77
High	6 3,269	**0.83 (0.70-0.99)**	40% 0.16		9 20,527	**0.88 (0.81-0.95)**	36% 0.14	
Invasive breast cancer	6 3,269	**0.83 (0.70-0.99)**	40% 0.16	-	9 19,639	**0.90 (0.84-0.96)**	24% 0.24	

5.3.2.5 Recreational physical activity across adult life course

Three studies on recreational physical activity/sports assessed for specific times in adult life were identified. One study was on premenopausal breast cancer risk[275] and three on postmenopausal breast cancer risk[266;269;275]. No clear consistent pattern was observed.

The highest levels of recreational physical activity performed during age 18-22 and 23-29 years were non-significantly associated with pre- and postmenopausal breast cancer risk in the Nurses' Health Study II (NHS II) [275]. RRs for ≥72 versus <21 and ≥ 57 versus <15 MET-hours/week respectively for the two time periods were 0.89 (95% CI: 0.72-1.10) and 1.05 (95% CI: 0.87-1.27) for premenopausal breast cancer (1,351 cases) and 0.89 (95% CI: 0.72-1.10) and 1.04 (95% CI: 0.84-1.28) for postmenopausal breast cancer risk (965 cases) (all P for trend values >0.17)[275]. Further analyses by this American study showed that recreational physical activity during age 18-22 years was inversely associated with premenopausal breast cancer risk, in those diagnosed < age 46.9 years (RR for ≥72 vs <21 MET-hour/week = 0.77, 95% CI: 0.60-0.99) (P for trend = 0.05) and not ≥ age 46.9 years (1.02, 95% CI: 0.79-1.32) (P for trend = 0.94)[275]. Although early adult recreational physical activity did not impact on postmenopausal breast cancer risk in NHS II[275] and in other Dutch study that investigated the periods before and after the birth of first child and at age 20 years (RRs for participation vs non-participation ranged from 1.03, 95% CI: 0.76-1.40 to 1.22, 95% CI: 0.89-1.67) (1,208 cases)[266], a non-significant inverse association with the risk of postmenopausal breast cancer was reported in another American study (Cancer Prevention Study-II (CPS-II) Nutrition Cohort) that examined the activity performed slightly later in life, at age 40 years (RR for >42 vs 0-7 MET-hour/week = 0.79, 95% CI: 0.61-1.03) (P for trend = 0.31)[269].

5.3.2.6 Recent, long-term and change in recreational physical activity

No studies were identified on recent recreational physical activity and premenopausal breast cancer risk. The only study reported results on postmenopausal breast cancer found a statistically significant decreased risk in women who performed high level of recreational physical activity in recent four years (RR for ≥12 vs <12 MET-hour/week = 0.90, 95% CI: 0.82-0.99) (2,097 cases), although without a dose-response relationship (P trend = 0.69)[272].

Overall three American studies were found to have reported results on long-term recreational physical activity and the risk of pre- and postmenopausal breast cancer. One study on premenopausal breast cancer reported a possible threshold effect in risk reduction with increasing levels of total lifetime physical activity (RRs = 0.98 (95% CI: 0.77-1.25); 0.93 (95% CI: 0.72-1.20); 0.74 (95% CI: 0.56-0.97) and 0.77 (95% CI: 0.59-1.01) for 21.0-29.9, 30.0-38.9, 39-53.9 and ≥54 vs <21 MET-hour/week, respectively) (P trend = 0.04) (550 cases)[271]. The other study observed non-significant results (RR for consistently high vs consistently low long-term levels = 1.19, 95% CI: 0.43-3.30) (P trend = 0.73), with only 42 premenopausal breast cancer cases in the study[232]. The findings on postmenopausal women in this study demonstrated a decreased risk (RR for the same comparison = 0.33, 95% CI: 0.14-0.82) (P trend = 0.03) (96 cases)[232]; as did the other study that estimated a cumulative average measure from all recreational physical activity assessments (RR for ≥27 vs <3 MET-hour/week = 0.88, 95% CI: 0.79-0.98) (P trend = 0.003)[262].

For change in recreational physical activity, no studies were identified on premenopausal breast cancer risk and two studies were identified on postmenopausal breast cancer risk. Compared with women who consistently performed high levels of recreational physical activity, those who used to have high activity level (≥12 MET-hour/week 5-9 years earlier) then changed to low level recently (<12 MET-hour/week 4 years earlier) had significantly greater risk of postmenopausal breast cancer (RR = 1.16, 95% CI: 1.01-1.35) (1,228 cases)[272]. In concordance, compared with women who always had low levels of activity, those who increased their level from low (<12 MET-hour/week in previous 5-9 years) to high (≥ 12 MET-hour/week in recent four years) showed an inverse association, that was not statistically significant (0.88, 95% CI: 0.72-1.09), possible due to low number of cases (357 cases)[272]. The favourable findings were supported by another study that also found a decreased risk in women who increased their level from <9 to ≥9 MET-hour/week since menopause (0.90, 95% CI: 0.82-0.98) (1,663 cases)[262].

5.3.2.7 Light physical activity

Light-intensity physical activity, for example bowling, golf (riding in a cart), table tennis, slow walking/dancing and light housework as defined in one American study (National Institute of Health (NIH)-AARP), was not statistically significantly associated with postmenopausal breast cancer risk; regardless of when the activity was performed (past 10 years, and between age 19-29 or 35-39 years) and whether or not other moderate to vigorous physical activity and BMI were accounted for (RRs for >7 hours/week vs never or rarely ranged from 1.01, 95% CI: 0.87-1.18 to 1.09, 95% CI: 0.92-1.28)[276]. No other studies were identified to have investigated the topic, apart from some that combined light- with moderate-intensity physical activity, as reviewed below.

5.3.2.8 Moderate or light to moderate physical activity

Moderate-intensity physical activity, such as walking for exercise, casual cycling and aerobics (4-6 METs) as investigated by NHS II, was inversely but not statistically significantly associated with premenopausal breast cancer risk (RR for ≥4 vs <1 hours/week = 0.81, 95% CI: 0.59-1.10) (P trend = 0.08) (550 cases in total)[271].

Three other American studies reported results on the association with postmenopausal breast cancer risk. Moderate[270] or light to moderate-intensity physical activities[215;273] included bowling, golf, light sports or physical exercise, bicycling on a level ground, light jogging, walking and gardening or light housework (3-4 MET). Because one study only reported results by molecular subtypes of breast cancer[273], meta-analysis was not conducted.

Two studies reported null associations. The RR estimates were 0.92 (95% CI: 0.77-1.10) for >4 times/week versus never or rarely in one study (1,371 cases)[270] and 1.02 (95% CI: 0.87-1.19) (P trend = 0.86) for 59.7 versus 14.8 hours/week in another study (1,506 cases)[215]. However, the third study found a significant decrease in risk of ER+ breast cancers (RR for ≥5.75 MET-hours/week vs no

activity = 0.88, 95% CI: 0.79-0.98) (P for trend = 0.01) (2,491 cases) that was not very different to the 0.75 (95% CI: 0.54–1.04) (P for trend = 0.07) (296 cases) observed for TNBC (P for interaction = 0.53)[273]. Two studies were adjusted for strenuous-intensity physical activity[215;273].

5.3.2.9 Vigorous physical activity

Five on premenopausal breast cancer[220;231;248;271;277](3,353 cases) and 11 studies on postmenopausal breast cancer[121;215;220;231;248;262;266;267;270;277;278](20,171 cases) could be included in the highest versus the lowest meta-analyses, respectively. Of these, three studies each (premenopausal breast cancer[231;248;271] (1,473 cases), postmenopausal breast cancer[231;248;267](2,853 cases)) reported results in minutes/day, which could be pooled in the dose-response meta-analyses, respectively.

Most studies assessed vigorous physical activity performed during recreation or leisure times. In some studies, moderate to vigorous physical activity were examined[262;267;279]. Examples of vigorous physical activity given in the questionnaires included physical activity that increases heart and breathing rates[278], running, swimming and tennis[231;262;270;271;273;277], as well as heavy housework and gardening among other activities[215;220;279]. The assigned MET-values were as classified in the Compendium of Physical Activities[262;266], 6 MET[121] or 7 MET[248;267;273].

The highest level of vigorous physical activity was significantly inversely associated with both pre- and postmenopausal breast cancer risk when compared with the lowest level of the activity. The summary RR estimates were 0.79 (95% CI: 0.69-0.91) (I^2 = 6%, P heterogeneity = 0.37) and 0.90 (95% CI: 0.85-0.95) (I^2 = 0%, P heterogeneity = 0.96), respectively (Figure 5.10). There were no evidence of publication bias (P-values for Egger's test = 0.93 and 0.63, respectively). However, dose-response trends were not observed when the limited numbers of studies with sufficient data were included in the dose-response meta-analyses. For each 30 minutes/day increase of vigorous physical activity, the summary RR estimates were 0.91 (95% CI: 0.83-1.01) (I^2 = 0%, P heterogeneity = 0.63) for premenopausal breast cancer and 0.94 (95% CI: 0.86-1.02) (I^2 = 0%, P heterogeneity = 0.95) for postmenopausal breast cancer risk (graph not shown). Non-linear analysis was not conducted due to low number of studies.

The results on premenopausal breast cancer risk were impacted by individual studies. Influence analyses showed that the summary RR estimates became non-significant when the study of Dallal *et al.*[277] was omitted from the highest versus the lowest meta-analysis (summary RR = 0.85, 95% CI: 0.72-1.00); and ranged from 0.88 (95% CI: 0.77-1.00) when Howard *et al.* (USRT)[248] was omitted to 0.94 (95% CI: 0.83-1.06) when Rosenberg *et al.* [231] were omitted in turn from the dose-response meta-analysis. Results on postmenopausal breast cancer risk remained materially unchanged.

Subgroup meta-analyses were not conducted with the relatively low number of studies (5 RR estimates) on premenopausal breast cancer. Four out of the five studies included in the highest versus the lowest meta-analysis of premenopausal breast cancer risk were of higher study quality[220;231;271;277].

The lower quality study (USRT)[248] found a null association, but only contributed 3% in the highest versus the lowest meta-analysis, and showed little influence in the meta-analysis.

Meta-analyses by the pre-defined subgroups showed inverse associations with postmenopausal breast cancer risk (all P-values for meta-regression ≥0.60) (Table 5.4). Higher quality studies (6 studies[231;262;266;267;277;278], all adjusted for main confounding factors, on average observed a significant inverse association (summary RRs for highest vs lowest level = 0.90, 95% CI: 0.85-0.96); but was not significantly different to the non-significant inverse association observed among the studies of lower quality (0.91, 95% CI: 0.80-1.02) (5 studies[121;215;220;248;270]) (P-values for meta-regression = 0.91). Only three studies used validated questionnaire to assess physical activity[231;262;267], the result was also not significantly different to the studies that used non-validated questionnaire[121;215;220;248;266;270;277;278] (P for meta-regression = 0.68). BMI was adjusted in all but one study[266].

For the associations by HR status of the tumour, no studies on premenopausal women were identified, and five studies on postmenopausal women were identified, and included in the meta-analysis[121;215;273;279;280]. Vigorous physical activity appeared to associate inversely and more strongly with the risks of ER-negative breast cancers (summary RR for highest vs lowest level = 0.75, 95% CI: 0.57-0.99) (572 cases in total), ER-PR- breast cancer (0.77, 95% CI: 0.58-1.04) (485 cases) and TNBC (0.76, 95% CI: 0.46-1.26) (503 cases) than with ER-positive breast cancers (0.95, 95% CI: 0.87-1.04) (5,280 cases) and ER+PR+ breast cancer (0.94, 95% CI: 0.82-1.08) (2,361 cases) (Figure 5.11).

5.3.2.10 Vigorous physical activity across adult life course

Two large American studies on postmenopausal breast cancer risk were identified (4,287 cases[276] and 1,780 cases[267]).

Vigorous or moderate to vigorous physical activity did not significantly reduce the risk of postmenopausal breast cancer in women who performed the activity at age 18 years (RR for participation vs non-participation of vigorous activity = 0.94, 95% CI: 0.85-1.04[267] or age 19-29 years (RR for >7 hours/week moderate to vigorous activity vs never or rarely = 1.01, 95% CI: 0.90-1.13)[276]. For the activity performed before age 40 years, the results were inconsistent. One study observed a significant decreased risk (RR for participation vs non-participation at age 35 years = 0.86, 95% CI: 0.78-0.95)[267], while the other study found a null association (RR for >7 hours/week vs never or rarely for age 35-39 years = 0.98, 95% CI: 0.88-1.10)[276].

One of the studies reported results on vigorous activity around menopause and found no significant association (RR for participation vs non-participation at age 50 years = 0.92, 95% CI: 0.83-1.01)[267].

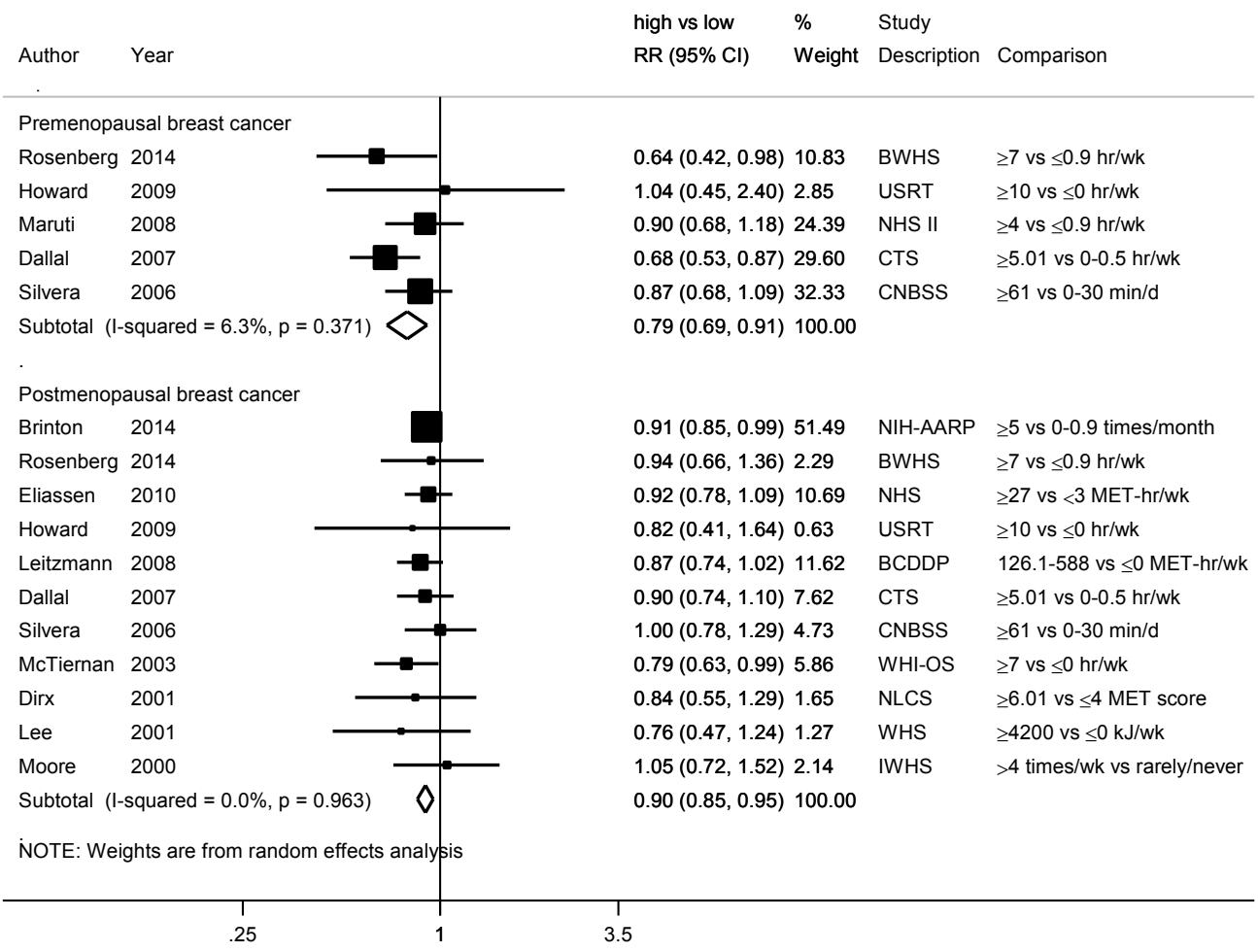


Figure 5.10 Relative risk and 95% CI of pre- and postmenopausal breast cancer for the highest compared with the lowest level of vigorous physical activity

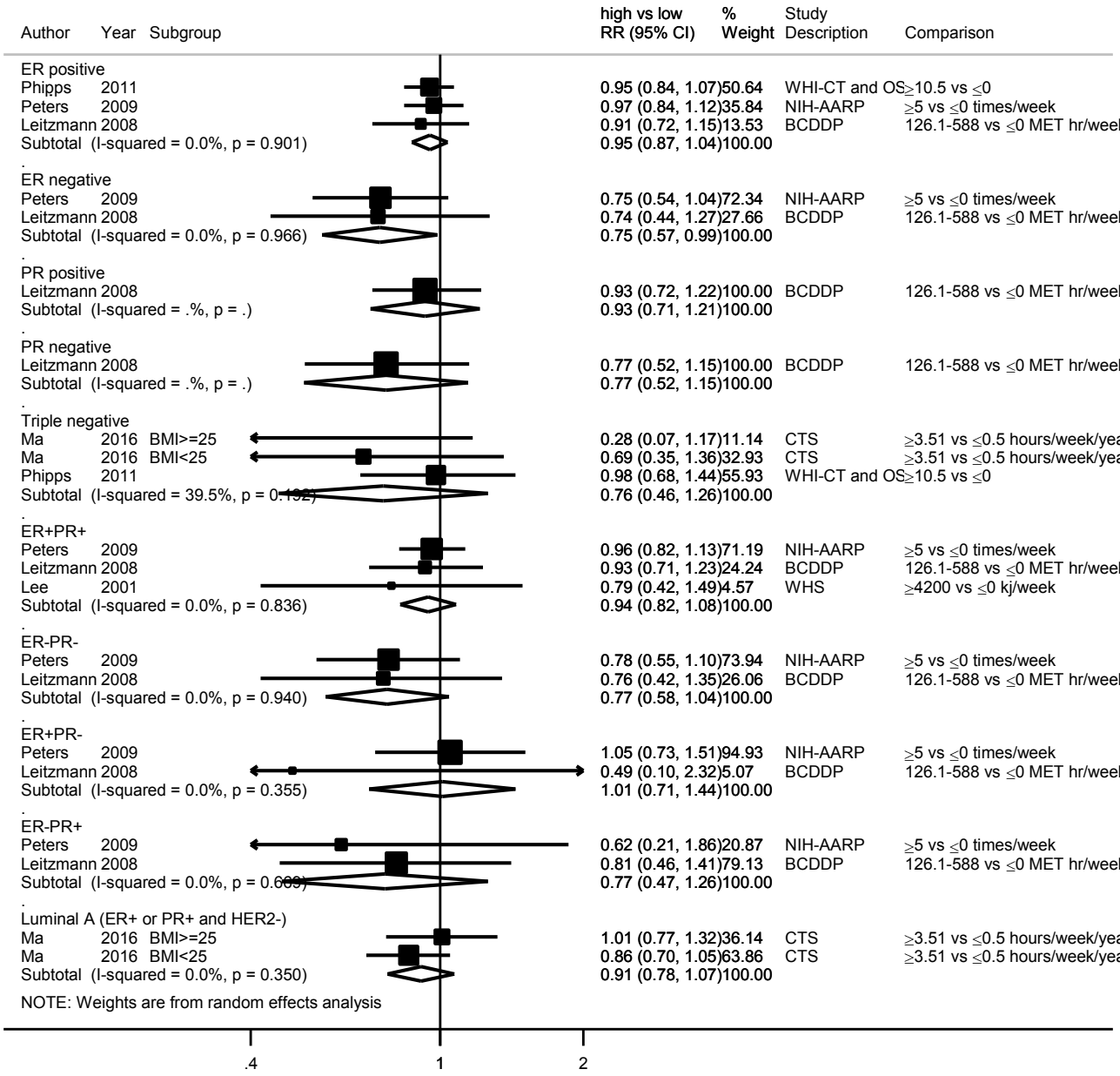


Figure 5.11 Relative risk and 95% CI of hormone receptor-defined postmenopausal breast cancer subtypes for the highest compared with the lowest level of vigorous physical activity

Table 5.4 Summary of subgroup meta-analyses of vigorous physical activity and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Highest vs lowest	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	5 3,353	**0.79 (0.69-0.91)**	6% 0.37	-	11 20,171	**0.90 (0.85-0.95)**	0% 0.96	-
Geographic location								
Asia	-	-	-	-	0	-	-	
Europe	-	-	-	-	1 306	0.84 (0.55-1.29)	-	0.75
North America	-	-	-	-	10 19,865	**0.90 (0.85-0.95)**	0% 0.94	
Exposure assessment								
Validated	-	-	-	-	3 6,761	0.88 (0.78-1.00)	0% 0.53	0.68
Not validated	-	-	-	-	8 13,410	**0.91 (0.85-0.96)**	0% 0.95	
Main confounding factors adjustment								
Adjusted	-	-	-	-	10 19,865	**0.90 (0.85-0.95)**	0% 0.94	0.75
Not adjusted	-	-	-	-	1 306	0.84 (0.55-1.29)	-	
BMI adjustment								
Adjusted	-	-	-	-	10 19,865	**0.90 (0.85-0.95)**	0% 0.94	0.75
Not adjusted	-	-	-	-	1 306	0.84 (0.55-1.29)	-	
Study type								
Screening	-	-	-	-	0	-	-	-
Non-screening	-	-	-	-	11 20,171	**0.90 (0.85-0.95)**	0% 0.96	-
Length of follow-up								
<10 years	-	-	-	-	6 11,645	**0.89 (0.84-0.95)**	0% 0.86	0.60
≥10 years	-	-	-	-	5 8,526	0.92 (0.84-1.02)	0% 0.85	
Study quality								
Low	-	-	-	-	5 4,218	0.91 (0.80-1.02)	0% 0.73	0.91
High	-	-	-	-	6 15,953	**0.90 (0.85-0.96)**	0 0.90	
Invasive breast cancer	-	-	-	-	6 14,609	**0.91 (0.85-0.97)**	0% 0.998	-

5.3.2.11 Recent, long-term and change of vigorous physical activity

Moderate to vigorous physical activity performed in the past 10 years significantly reduced the risk of postmenopausal breast cancer. When women who conducted the activity >7 hours/week were compared with those who never or rarely performed the activity, the RR estimate was 0.87 (95% CI: 0.78-0.96)[276].

Two studies each (3 publications) on long-term vigorous or moderate to vigorous physical activity and pre- and postmenopausal breast cancer risk were identified. No studies investigated change in levels between any time points.

For premenopausal breast cancer, non-significant result was observed in one study (RR for ≥4 vs <1 hours/week lifetime vigorous physical activity = 0.90, 95% CI: 0.68-1.18) (P for trend = 0.14) (550 cases)[271]; while the other study found a significant 32% reduced risk (RR for >5 vs ≤0.5 hours/week of long-term vigorous physical activity = 0.68, 95% CI: 0.53-0.87) (P for trend = 0.02) (1,062 cases)[277].

For postmenopausal breast cancer, protection from vigorous or moderate to vigorous physical activity performed for a long period is possible. The RR estimate for >5 vs ≤0.5 hours/week of long-term vigorous physical activity was 0.90 (95% CI: 0.74-1.10) (P for trend = 0.27) (1,587 cases)[277]. Such results were confirmed by a recent publication of the same study (RR for >7 vs ≤0.5 hours/week/year of long-term moderate and vigorous physical activity = 0.90, 95% CI: 0.81-0.99) (P for trend = 0.01) (5,882 cases); which further demonstrated a significant trend of decreased risk of luminal A-like breast cancers with increasing levels of long-term physical activity (0.87, 95% CI: 0.75-1.00) (P for trend = 0.05) and a non-significant inverse association with TNBC (0.73, 95% CI: 0.49-1.09) (P for trend = 0.11) (348 cases) (P for interaction = 0.38)[280]. Supporting these findings was one study that estimated a cumulative average measure from all moderate/vigorous physical activity assessments (RR for ≥27 vs <3 MET-hour/week = 0.85, 95%CI: 0.69-1.05) (P for trend = 0.009)[262] (4,782 cases).

5.3.2.12 Occupational physical activity

Eight studies on premenopausal breast cancer[247;253;259;260;281-284] (5,339 cases) and nine studies on postmenopausal breast cancer[247;253;259;260;264;266;281-283] (21,932 cases) could be included in the highest versus the lowest meta-analyses, respectively.

The assessment and categorisation of occupational physical activity were very different between the studies, for example, breast cancer risks between non-sedentary women or women in heavy manual work and sedentary women; physical education teachers and language teachers; and moderate active and inactive women were compared. Most studies obtained the information on current and past occupations or long-term jobs directly from the participants[253;260;264;266;281]; one study assessed current

occupation only[247] and one evaluated occupation in the previous year[259]. Two studies used data from the censuses[283;284] and one used employment records[282].

For premenopausal breast cancer, the risk associated with the highest versus the lowest occupational physical activity was inverse but not statistically significant (summary RR = 0.83, 95% CI: 0.65-1.05), and high proportion of between-study heterogeneity was evident (I^2 = 76%, P heterogeneity <0.001). For postmenopausal breast cancer risk, a significant inverse association was observed (0.90, 95% CI: 0.85-0.96) (I^2 = 0%, P heterogeneity = 0.89) (Figure 5.12). There was evidence of significant publication bias with the studies of postmenopausal breast cancer (P for Egger's test = 0.70 and 0.05, respectively) (Figure 5.13).

Because of the diversity in how occupational physical activities were assessed in the studies, it was not possible to conduct subgroup meta-analysis based on this parameter. When each individual study was omitted in turn in influence analyses, the findings remained similar to the original analyses. This included the removal of Steindorf *et al.* (European Prospective Investigation into Cancer and Nutrition (EPIC))[247], where information regarding the duration and frequency of the current job and other long-term jobs were not collected.

Subgroup meta-analyses showed that significant inverse associations were only obtained among studies not adjusted for all main confounding factors (Table 5.5). When considered together with other aspects of study quality, only three studies on premenopausal breast cancer[247;281;284](2,955 cases) and two studies on postmenopausal breast cancer[247;266](7,853 cases) had an overall quality score of more than or equal to the median quality score, and were therefore classified as higher quality studies. On average, higher quality studies found a null association, for premenopausal breast cancer risk (summary RR for highest vs lowest level = 1.06, 95% CI: 0.91-1.23) and for postmenopausal breast cancer risk (0.94, 95% CI: 0.86-1.04). The associations for premenopausal breast cancer risk were on average statistically significantly different between higher and lower quality studies (0.64, 95% CI: 0.52-0.78) (5 studies[253;259;260;282;283]) (2,384 cases) (P for meta-regression = 0.003), and may explain partly the high between-study heterogeneity as mentioned above (I^2 = 76%, P heterogeneity <0.001) (Table 5.5).

The studies did not examine the associations by HR status of the tumour.

5.3.2.13 Occupational physical activity across adult life-course

One study was identified. NHS II investigated the risk of premenopausal breast cancer and early adult occupational physical activity performed during age 23-34 years, and found a non-statistically significant inverse association (RR for >171 vs <114 MET-hour/week = 0.83, 95% CI: 0.63-1.09) (P for trend = 0.42) (550 cases in total)[271].

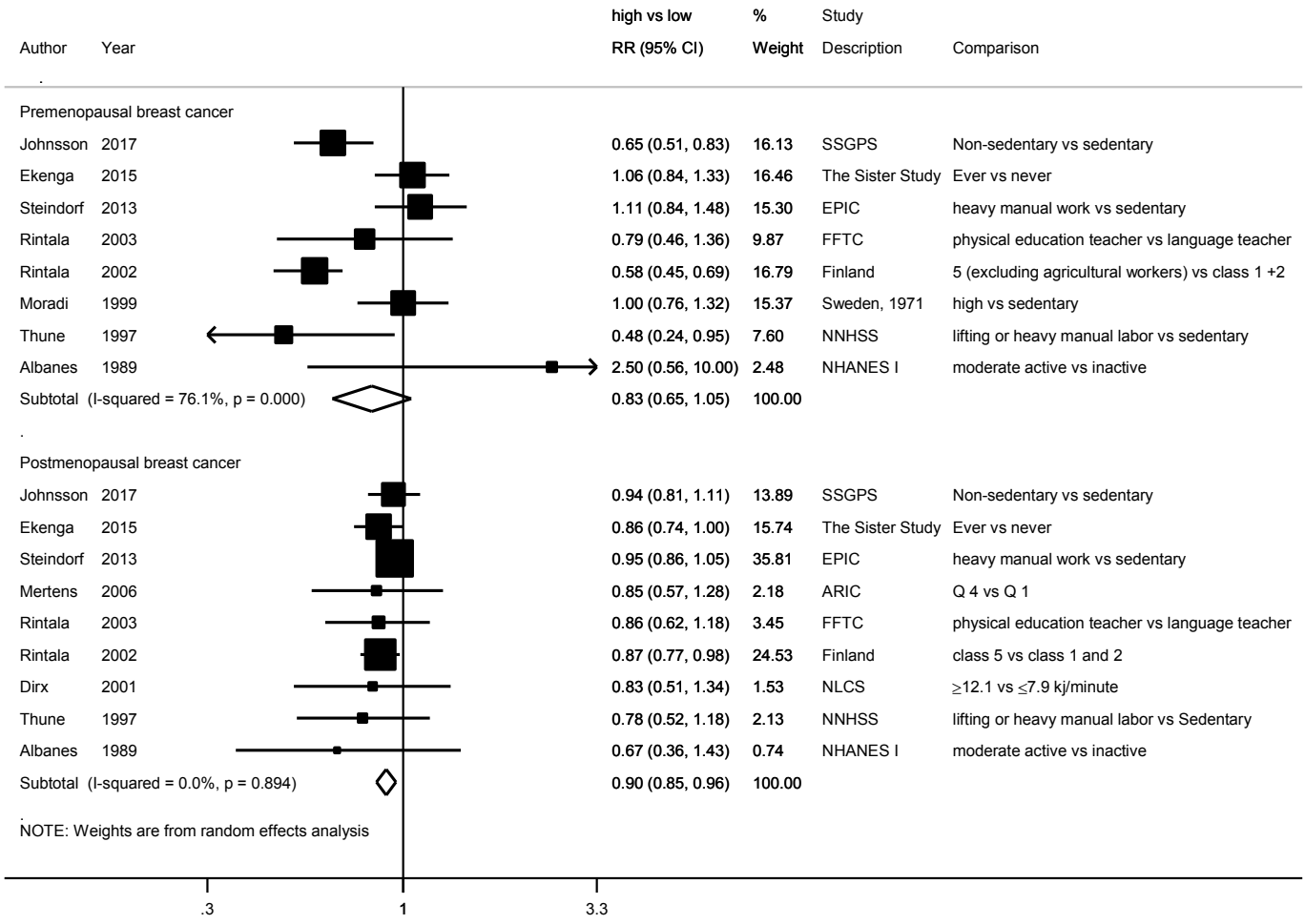


Figure 5.12 Relative risk and 95% CI of pre- and postmenopausal breast cancer for the highest compared with the lowest level of occupational physical activity

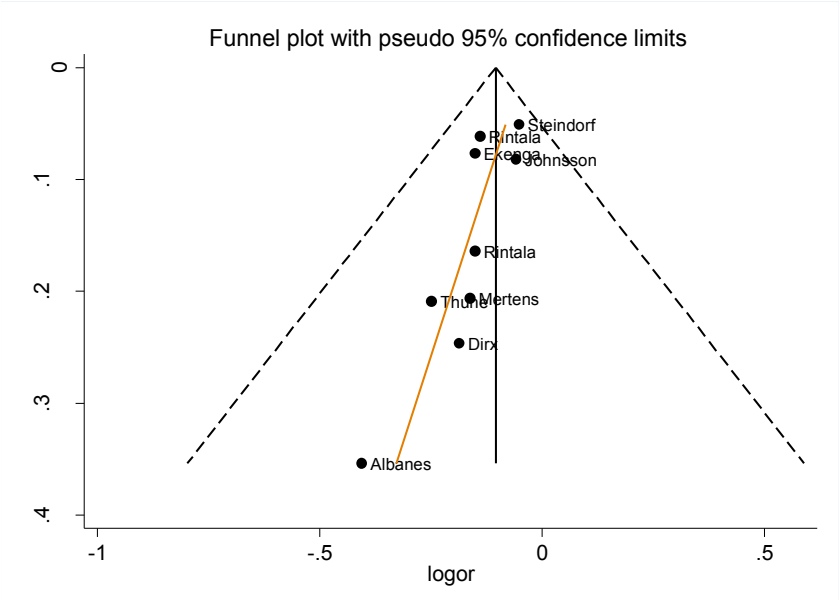


Figure 5.13 Funnel plot of studies included in the highest versus the lowest meta-analysis of occupational physical activity and postmenopausal breast cancer

Table 5.5 Summary of subgroup meta-analyses of occupational physical activity and pre- and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Highest vs lowest	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	8 5,339	0.83 (0.65-1.05)	76% <0.001	-	9 21,932	**0.90 (0.85-0.96)**	0% 0.89	-
Geographic location								
Asia	-	-	-		-	-	-	
Europe	6 4,871	**0.76 (0.56-0.99)**	75% 0.001	0.29	6 20,326	**0.91 (0.85-0.98)**	0% 0.82	0.64
North America	1 46	2.50 (0.56-10.00)	-		2 243	0.80 (0.56-1.13)	0% 0.55	
United States and Puerto Rico	1 422	1.06 (0.84-1.33)	-		1 1,363	0.86 (0.74-1.00)	-	
Exposure assessment methods								
Validated	-	-	-	-	-	-	-	-
Not validated	-	-	-		-	-	-	
Main confounding factors adjustment								
Adjusted	2 1,358	1.08 (0.90-1.29)	0% 0.80	0.10	2 8,461	0.92 (0.84-1.01)	14% 0.28	0.47
Not adjusted	6 3,981	**0.72 (0.56-0.94)**	64% 0.02		7 13,471	**0.88 (0.81-0.96)**	0% 0.94	
BMI adjustment								
Adjusted	3 1,080	0.95 (0.46-1.95)	69% 0.04	0.61	3 7,421	0.93 (0.85-1.03)	0% 0.41	0.39
Not adjusted	5 4,259	0.79 (0.60-1.04)	79% 0.001		6 14,511	**0.88 (0.82-0.95)**	0% 0.97	
Study type								
Screening	0	-	-		0	-	-	-
Non-screening	8 5,339	0.83 (0.65-1.05)	76% <0.001	-	9 21,932	**0.90 (0.85-0.96)**	0% 0.89	-
Length of follow-up								
<10 years	1 422	1.06 (0.84-1.33)	-	0.41	2 2,118	**0.86 (0.74-0.99)**	0% 0.89	0.48
≥10 years	7 4,917	0.79 (0.60-1.03)	74% 0.001		7 19,814	**0.91 (0.85-0.97)**	0% 0.81	
Study quality								
Low	5 2,384	**0.64 (0.52-0.78)**	26% 0.25	0.003	7 14,079	**0.88 (0.81-0.94)**	0% 0.94	0.27
High	3 2,955	1.06 (0.91-1.23)	0% 0.88		2 7,853	0.94 (0.86-1.04)	0% 0.59	
Invasive breast cancer	2 2,533	1.05 (0.86-1.28)	0% 0.61	-	2 7,853	0.94 (0.86-1.04)	0% 0.59	-

5.3.2.14 Household physical activity

Only EPIC, the large multi-centred European study (3 publications), was identified[247;285;286]. Two of its component centres also reported results in three separate publications[287-289].

Household physical activity was significantly inversely associated with the risk of invasive breast cancers that were diagnosed ≤ age 50 years (RR for ≥84 vs ≤24.6 MET-hours/week = 0.77, 95% CI: 0.61-0.97) (P for trend = 0.12) (936 cases) and > age 50 years (0.89, 95% CI: 0.82-0.97) (P for trend = 0.002) (7,098 cases)[247].

5.3.2.15 Non-recreational physical activity

One study was identified. The NIH-AARP study investigated the association between non-recreational (occupational and household) physical activity that involved sitting, standing, walking, stair-climbing and lifting/carrying light or heavy loads and postmenopausal breast cancer risk. Inverse associations, with a significant dose-response trend, were observed across the increasing levels of activeness of the activities (RR for heavy lifting/carrying vs sitting all day = 0.62, 95% CI: 0.42-0.91) (P trend = 0.024)[290].

5.3.2.16 Non-occupational physical activity

One study on premenopausal breast cancer and two studies on postmenopausal breast cancer reported results. The findings appeared to be consistent with those for other physical activity domains, in that the protective effect was more evident in postmenopausal women (RR for ≥123 vs ≤50.5 MET-hours/week = 0.88, 95% CI: 0.81-0.95) (P trend = 0.001) (7,098 cases) than in premenopausal women (0.84, 95% CI: 0.68-1.04) (P trend = 0.19) (936 cases)[247]. Two additional elderly cohorts (mean age 75 years) reported that highly active women had a reduced postmenopausal breast cancer risk relative to inactive and not disabled women (RRs = 0.43, 95 CI: 0.19-0.96[291] and 0.20, 95% CI: 0.05-1.00, P trend = 0.008[292]) (77 cases and 43 cases, respectively).

5.3.2.17 Walking

Only two studies on premenopausal breast cancer[248;257] (1,289 cases) and four studies on postmenopausal breast cancer[235;248;272;293] (7,300 cases) could be included in the highest versus the lowest meta-analyses, respectively.

The studies collected information on walking[235;248;257;272;293] from the study participants via questionnaires. WHI measured walking speed for 10 meters for physical fitness[293]. The Netherlands Cohort Study (NLCS) combined cycling with walking and therefore was not pooled with the other studies in the analysis[266].

The studies showed null associations on average. The summary RRs for the highest compared with the lowest walking level were 0.97 (95% CI: 0.76-1.25) (I^2 = 17%, P heterogeneity = 0.27) for

premenopausal breast cancer risk and 0.95 (95% CI: 0.86-1.04) (I^2 = 0%, P heterogeneity = 0.98) for postmenopausal breast cancer risk (Figure 5.14). No further analyses were conducted because of the low numbers of studies.

The USRT study, as mentioned in the other sections on physical activity, was of lower quality[248]. The non-significant results were no different to those observed in higher quality studies[235;257;272;293].

The NHS study was excluded from the analysis of postmenopausal breast cancer risk because only a dose-response result was reported. In this study, each increase of 20 MET-hour/week (equivalent to 5 hours/week) of walking was associated with a statistically significant 9% decreased risk of postmenopausal breast cancer, regardless of the performance of other types of activity (RR = 0.91, 95% CI: 0.84-0.98) (P for trend =0.01) (4,782 cases)[262]. Other studies did not find an apparent dose-response trend (all P-values for trend >0.09).

No studies reported results on breast cancers defined by HR status. One study described the associations did not differ significantly for ER-positive and ER-negative breast cancers (P for heterogeneity = 0.99) (2,806 ER+ and 498 ER- breast cancers)[235].

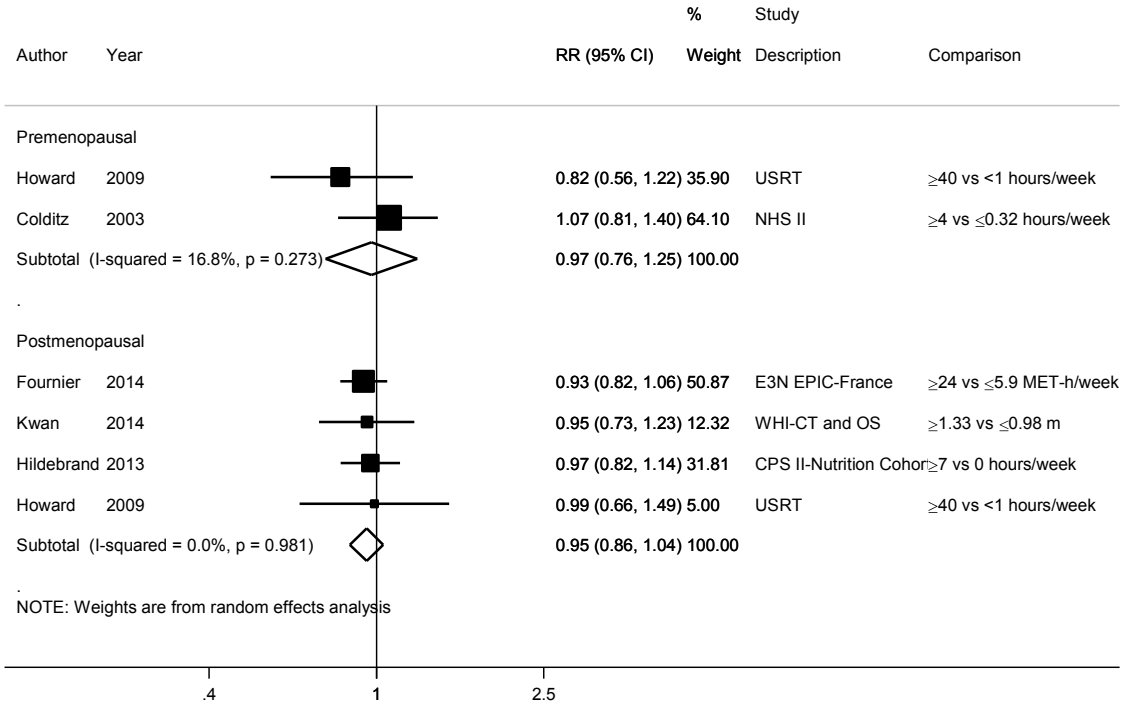


Figure 5.14 Relative risk and 95% CI of pre- and postmenopausal breast cancer for the highest compared with the lowest level of walking

5.3.2.18 Other specific types of physical activity

Overall six studies were identified. Meta-analysis was not conducted for these different activities. It appeared that specific activities of higher intensity, from a distant past at study baseline or for a longer-term were more likely to associate inversely with breast cancer risk. The results were not statistically significant, but supported the inverse associations observed generally with other physical activities.

Inverse associations with breast cancer risks was reported for stairs climbing (RRs highest vs lowest = 0.89, 95% CI: 0.60-1.31, P trend = 0.52, 540 cases for premenopausal breast cancer and 0.83, 95% CI: 0.54-1.29, P trend = 0.24, 518 cases for postmenopausal breast cancer[256]), jogging/running (0.71, 95% CI: 0.45-1.12, P trend = 0.10, 849 cases for premenopausal breast cancer[257] and walking or cycling to work, either over the years of follow-up (RR for ≥ 10 vs <1 years = 0.86, 95% CI: 0.67-1.11, P trend = 0.08, 2,866 cases for postmenopausal breast cancer)[290] or at study baseline (RRs for ≥30 minutes/day vs unemployed/at home = 0.72, 95% CI: 0.38-1.36 for premenopausal breast cancer, although not for postmenopausal breast cancer: 1.01, 95% CI: 0.69-1.50)[258].

While lighter activities such as gardening (RR for highest vs lowest level = 0.93, 95% CI: 0.73-1.17, P trend = 0.23, 943 cases)[266], or recent activities for example cycling and other sports performed in the past four years (0.99, 95% CI: 0.87-1.12, P trend = 0.66, 2,097 cases)[272] did not clearly show an association with postmenopausal breast cancer risk.

5.3.3 Physical inactivity and risk of pre- and postmenopausal breast cancer

Sedentary behaviour, such as sitting was examined in two publications on premenopausal breast cancer and six publications on postmenopausal breast cancer. All two studies on premenopausal breast cancer risk (2 sitting, 2 sitting while watching TV, 1 sitting for work) and all six studies on postmenopausal breast cancer (4 sitting, 4 sitting while watching TV, 2 sitting while working) could be included in the highest versus the lowest meta-analyses. Further, five of the six studies on postmenopausal breast cancer could be included in the dose-response meta-analyses.

The associations with premenopausal breast cancer risk were not clear, but only two studies could be included in the meta-analyses (graph not shown). The summary RRs for the highest versus the lowest level were 1.04 (95% CI: 0.83-1.32) (I^2 = 0%, P heterogeneity = 0.72) for sitting in general and 0.92 (95% CI: 0.71-1.18) (I^2 = 0%, P heterogeneity 0.47) for sitting while watching TV (2 studies each[256;294] (1,295 cases). The only study reported result on sitting for work (adjusted for recreational physical activity) found a possible increased risk of 14% (RR = 1.14, 95% CI: 0.91-1.42) (P for trend = 0.26) (752 cases)[294]. BMI was adjusted for in both studies[256;294] and physical activity in one[294].

For postmenopausal breast cancer, sitting in general increased the risk. The summary RR for the highest compared with the highest level was 1.20 (95% CI: 1.00-1.44) (I^2 = 46%, P heterogeneity =

0.13) (4 studies[256;290;294;295]) (4,704 cases) (Figure 5.15), and was supported by a statistically significant positive dose-response relationship (summary RR per 5 hours/day = 1.07, 95% CI: 1.01-1.14) (I^2 = 0%, P heterogeneity = 0.55) (3 studies[256;290;294]) (4,333 cases) (Figure 5.16). It is possible that sitting in total is an important factor, as no significant results were found for sitting while watching TV (summary RRs for highest vs lowest level = 1.06, 95% CI: 0.98-1.15 and for each 2 hours/day increase = 1.01, 95% CI: 0.99-1.04) (4 studies each[235;256;290;294]) (9,038 cases) or for sitting while working (summary RRs for the same comparison/increment = 0.98, 95% CI: 0.72-1.35 and 1.00, 95% CI: 0.90-1.10, respectively) (2 studies each[266;294]) (1,720 cases) (Figures 5.15 and 5.16).

All[235;256;266;290;294] but one[295] study were of high quality. The study of Cohen *et al.*[295] included mainly low income and uninsured persons from institutions that provided basic health and preventive services and thus not representative of the general populations. As poor lifestyles are highly correlated, uncontrolled or residual confounding may explain the significant increased risk of postmenopausal breast cancer with sitting in this study[295]. Influence analyses showed non-significant results when the study[295] and most other studies were excluded in turn. Catsburg, *et al*[256] did not adjust for physical activity and Dirx *et al.*[266] did not adjust for BMI and physical activity, while all other studies adjusted for both factors, therefore the observed positive associations were mostly independent of these factors. No further analyses were conducted due to low numbers of studies.

The Black Women's Health Study (BWHS) further reported results on the associations of sitting (total and types) with the risks of breast cancer subtypes in pre- and postmenopausal women, and found statistically non-significant results (RRs for highest vs lowest level ranged from 0.76 to 1.85) (all P-values for trend >0.09) (196 to 514 cases); with the exception of an apparent increased risk of premenopausal ER-PR- breast cancer with total sitting time (2.10, 95% CI: 1.12-3.91) (P trend = 0.04), despite small number of cases (173 ER-PR- breast cancer cases)[294]. One additional study reported no statistically significant heterogeneity between sitting and risk of postmenopausal breast cancer by ER status (P = 0.08) (2,806 ER-positive and 498 ER-negative breast cancer cases)[235].

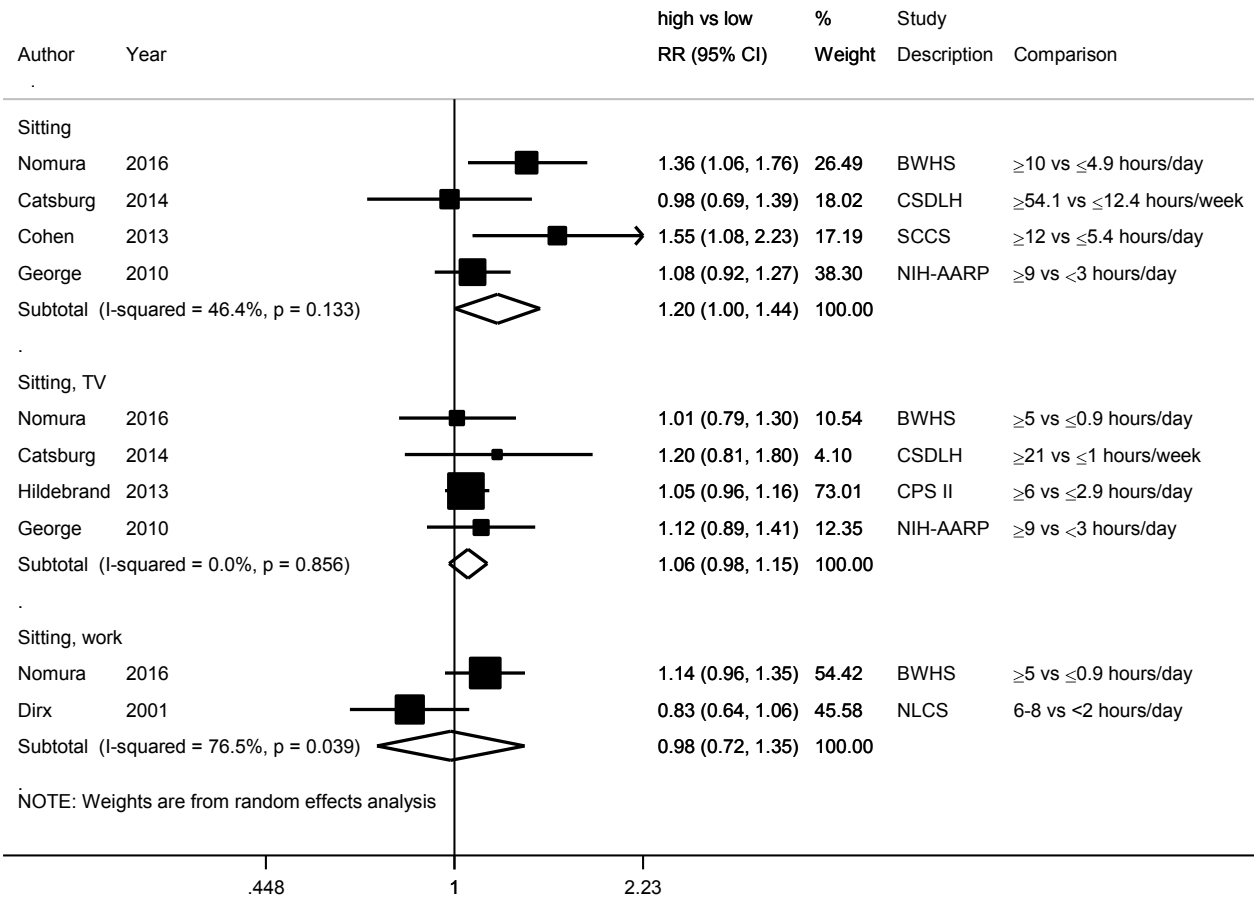


Figure 5.15 Relative risk and 95% CI of postmenopausal breast cancer for the highest compared with the lowest level of sitting

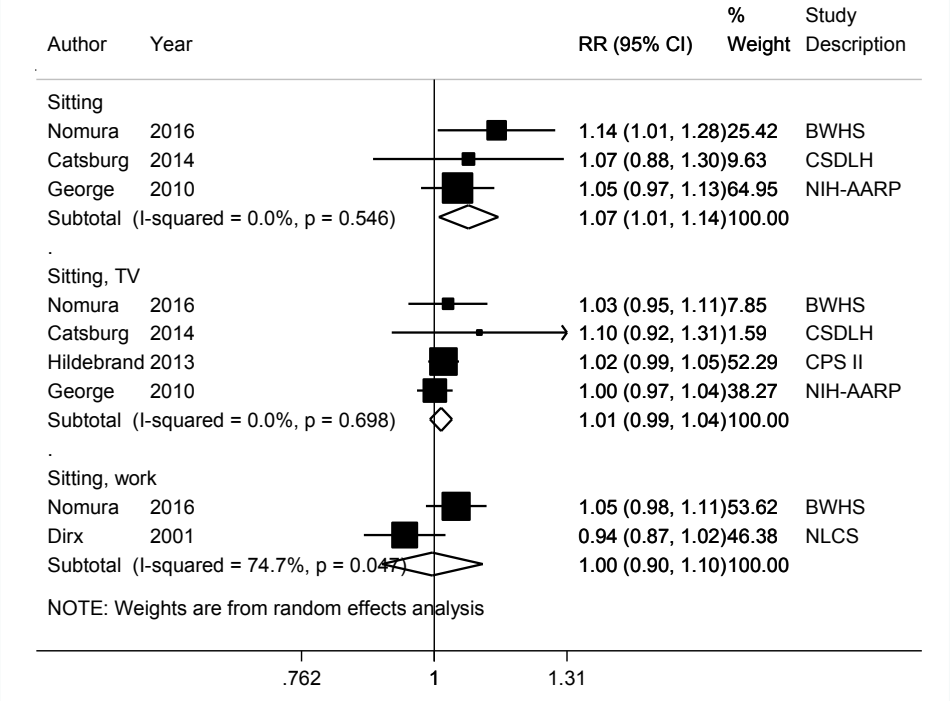


Figure 5.16 Relative risk and 95% CI of postmenopausal breast cancer for 5 hours/day of sitting in total, and 2 hours/day of sitting while watching TV and work

5.3.4 Body fatness and weight change and risk of pre- and postmenopausal breast cancer

Chronic excess in energy intake results to accumulation of body fat and weight gain. To study how these factors relate to breast cancer risk, the studies measured or took body measurements as reported directly from the participants at study baseline or during follow-up. In some cases, participants were asked to recall past measurements.

BMI, an indicator of total body fatness, was calculated using data on weight and height (weight (kg)/height $(m)^2$); while waist circumference, hip circumference and the ratio of these measurements were used to represent regional fat that was deposited around the abdominal (waist) and glutealfumoral (hip) areas, respectively. The studies derived change in body weight or BMI using relevant data between two time points that spanned adult life or parts of adult life.

Dose-response meta-analyses could be conducted to pool the results on pre- and postmenopausal breast cancer risk in relation to these commonly studied anthropometric factors, as reported below.

5.3.4.1 Early adult BMI

Thirteen studies on premenopausal breast cancer[211;212;226;230;256;296-300](>4,498 cases) and 18 studies on postmenopausal breast cancer[123;212;226;230;236;256;297;298;300-306](>9,271 cases) could be included in the respective dose-response meta-analysis of BMI at early adulthood (age 18-30 years).

Early adult BMI was inversely associated with the risk of premenopausal and postmenopausal breast cancer. The summary RRs were 0.86 (95% CI: 0.78-0.96) and 0.81 (95% CI: 0.75-0.87) per 5 kg/m^2 increase of BMI, respectively (Figure 5.17). There were no significant evidence of publication bias (P-values for Egger's test = 0.81 and 0.13, respectively). The statistically significant results were robust and remained unchanged in influence analyses.

Heterogeneity (I^2) between the studies of premenopausal breast cancer dropped from 47% to 24% (P heterogeneity from 0.05 to 0.23) when Dite *et al.,* the familial cancer study was excluded[212]. Because of the non-representativeness of the study population and less confounding factors adjustment, on top of not achieving in other aspects of study quality, this cohort only scored six points overall. This may explain the non-significant positive result observed in the study[212]; however, the study of BRCA1/2 carriers, which also scored six points in study quality, observed a non-significant inverse association[211]. Another study that found a positive association with premenopausal breast cancer risk was also of lower quality (9 points), although early body weight was measured, there were only 30 women with premenopausal breast cancer in this study[226]. When pooled with the other lower quality studies, the summary RR estimate was 0.96 (95% CI: 0.83-1.12) (7 studies[211;212;226;230;298]) (>888 cases), which was not significantly different to higher quality studies (0.81, 95% CI: 0.73-0.91) (6 studies[256;296;297;299;300]) (3,610 cases) (P for meta-regression = 0.14) (Table 5.6).

Moderate-high proportion of heterogeneity was also observed between the studies of postmenopausal breast cancer, despite the consistent inverse associations across the studies (I^2 = 50%, P heterogeneity = 0.01). Unlike for premenopausal breast cancer, a significant inverse association was found in both lower quality (summary RR per 5 kg/m^2 = 0.80, 95% CI: 0.71-0.89) (12 studies[123;212;226;230;298;301;303-306]) (>6,454 cases) and higher quality studies (0.83, 95% CI: 0.76-0.91) (6 studies[236;256;297;300;302]) (2,817 cases) (P for meta-regression = 0.76) (Table 5.6).

Stratified analysis showed that postmenopausal breast cancer studies with weight gain or adult BMI adjustment on average found an inverse association (0.74, 95% CI: 0.65-0.83) (9 studies[123;212;230;297;301;304]) (>2,804 cases) that was slightly stronger than studies without such adjustment (0.88, 95% CI:0.83-0.92) (9 studies[226;236;256;298;300;302;303;305;306]) (6,467 cases). Hence, differential adjustment for weight gain or adult BMI had largely explained the observed between-study heterogeneity (P for meta-regression = 0.009). For the same analysis on premenopausal breast cancer, the inverse associations were not very different between adjusted (0.91, 95% CI: 0.83-0.99) (8 studies[212;230;296;297;299]) (>2,958 cases) and unadjusted studies (0.77, 95% CI: 0.64-0.92) (5 studies[211;226;256;298;300]) (1,540 case) (Table 5.6).

Restricted cubic spline analyses showed linear relationships (P-values for non-linearity = 0.58 for premenopausal breast cancer and 0.29 for postmenopausal breast cancer). Both curves show a gradual decrease in risk that was statistically significant after BMI of 21-22 kg/m^2 (Figure 5.18).

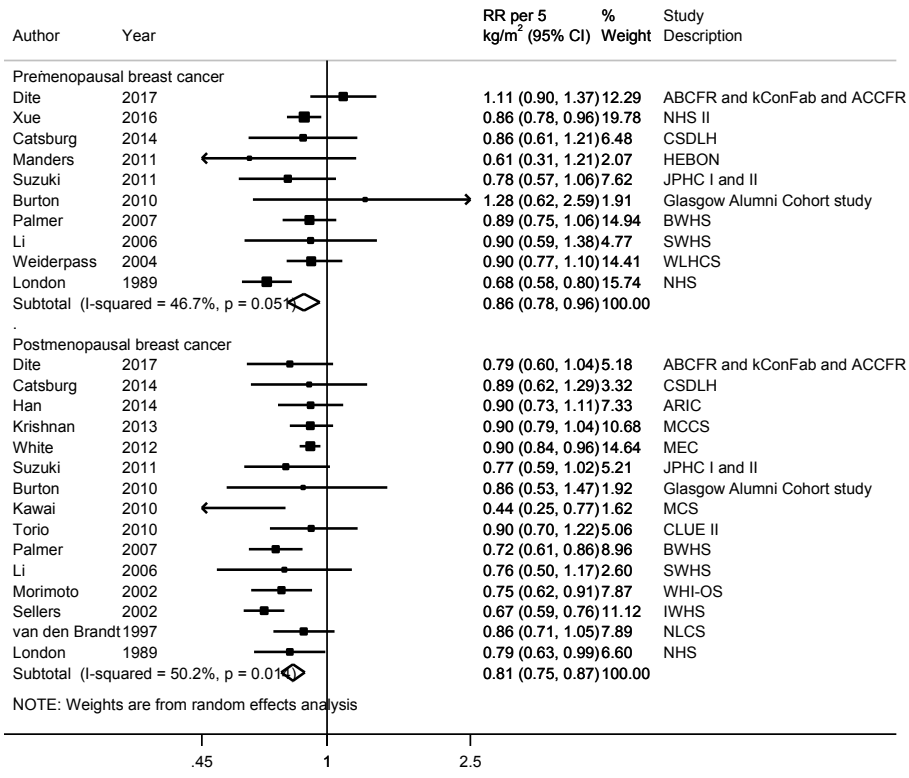
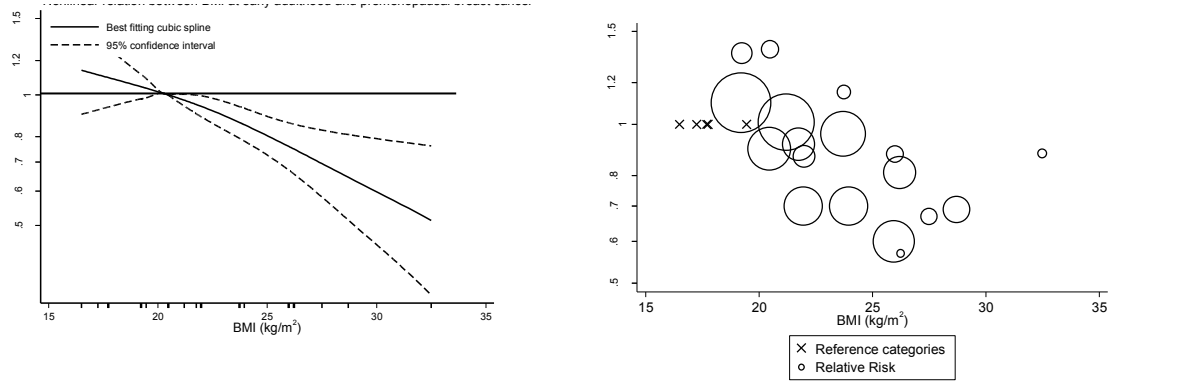


Figure 5.17 Relative risk and 95% CI of pre- and postmenopausal breast cancer for 5 kg/m^2 increase of early adult BM

Premenopausal breast cancer



Postmenopausal breast cancer

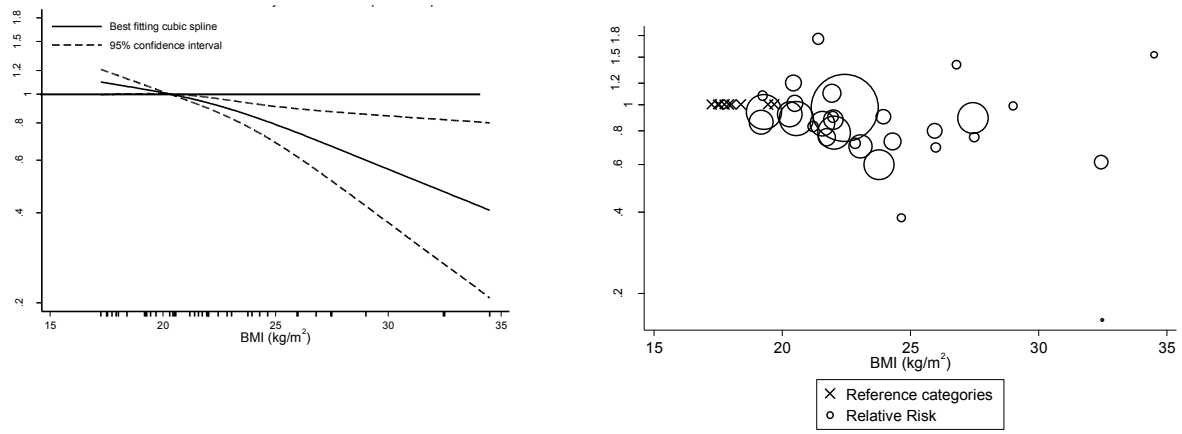


Figure 5.18 Non-linear analysis of early adult BMI and pre- and postmenopausal breast cancer

Table 5.6 Summary of subgroup meta-analyses of early adult BMI and pre- and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Per 5 kg/m^2	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	13 >4,498	**0.86 (0.78-0.96)**	47% 0.05	-	18 >9,271	**0.81 (0.75-0.87)**	50% 0.01	-
Geographic location								
Asia	3 432	0.82 (0.64-1.05)	0% 0.59	0.34	4 509	**0.68 (0.51-0.92)**	39% 0.19	0.56
Australia and New Zealand	3 -	1.11 (0.90-1.37)	-		4 >668	**0.88 (0.77-0.99)**	0% 0.41	
Europe	3 874	0.90 (0.73-1.11)	8% 0.34		2 569	0.86 (0.72-1.03)	0% 0.99	
North America	4 3,192	**0.82 (0.72-0.93)**	58% 0.07		8 7,525	**0.80 (0.72-0.89)**	67% 0.004	
Exposure assessment								
Measured	1 30	1.28 (0.62-2.59)	-	0.33	1 69	0.86 (0.53-1.47)	-	0.82
Self-reported	12 >4,468	**0.86 (0.77-0.95)**	49% 0.05		17 >9,202	**0.80 (0.74-0.87)**	54% 0.009	
Main confounding factors adjustment								
Adjusted	5 2,921	**0.79 (0.69-0.91)**	50% 0.11	0.09	9 7,447	**0.79 (0.70-0.89)**	71% 0.001	0.66
Not adjusted	8 >1,577	0.94 (0.85-1.05)	4% 0.39		9 >1,824	**0.82 (0.75-0.90)**	0% 0.69	
Current body size/weight change adjustment								
Adjusted	8 >2,958	**0.91 (0.83-0.99)**	23% 0.27	0.08	9 >2,804	**0.74 (0.65-0.83)**	46% 0.10	0.009
Not adjusted	5 1,540	**0.77 (0.64-0.92)**	22% 0.28		9 6,467	**0.88 (0.83-0.92)**	0% 0.80	
Study type								
Screening	0	-	-	-	0	-	-	
Non-screening	13 >4,498	**0.86 (0.78-0.96)**	47% 0.05	-	18 >9,271	**0.81 (0.75-0.87)**	50% 0.01	-
Length of follow-up								
<10 years	3 1,499	0.80 (0.64-1.00)	66% 0.06	0.28	5 4,939	**0.86 (0.81-0.93)**	8% 0.36	0.45
≥10 years	10 >2,999	**0.90 (0.82-0.99)**	19% 0.29		13 >4,332	**0.79 (0.71-0.88)**	50% 0.04	
Study quality								
Low	7 >888	0.96 (0.83-1.12)	18% 0.30	0.14	12 >6,454	**0.80 (0.71-0.89)**	64% 0.003	0.76
High	6 3,610	**0.81 (0.73-0.91)**	46% 0.12		6 2,817	**0.83 (0.76-0.91)**	0% 0.55	
Invasive breast cancer	9 >3,610	**0.86 (0.75-0.98)**	65% 0.01	-	12 >6,297	**0.84 (0.78-0.91)**	28% 0.19	-

5.3.4.2 Adult weight gain

Nine studies (8 publications, 3,990 cases)[211;230;232;254;256;307-309] on adult weight gain in kg and six studies (3 publications, >900 cases)[212;297;299] on weight gain in BMI could be included in separate dose-response meta-analyses of premenopausal breast cancer risk. Respectively, 16 studies (16 publications, 17,150 cases)[225;230;232;254;256;302-304;306;307;309-314] and nine studies (6 publications, >2575 cases)[212;236;297;302;305;306] could be included in the dose-response meta-analyses of postmenopausal breast cancer risk.

Adult weight gain (age 18-<30 years to study baseline) was not significantly associated with premenopausal breast cancer risk (summary RRs per 5 kg gain = 1.00 (95% CI: 0.97-1.03) and per 5 kg/m^2 gain = 0.97 (95% CI: 0.77-1.22), but was significantly positively associated with postmenopausal breast cancer risk (per 5 kg gain = 1.07 (95% CI: 1.05-1.09) and per 5 kg/m^2 gain = 1.17 (95% CI: 1.11-1.23) (Figures 5.19 and 5.20). Between-study heterogeneity (I^2) was 21% (P = 0.27), 75% (P = 0.01), 64% (P <0.001) and 0% (P = 0.81), respectively. These results remained materially unchanged in influence analyses. Evidence of significant publication bias was detected in the studies of weight gain (kg) and postmenopausal breast cancer risk (P for Egger's test = 0.04) (Figure 5.21). Asymmetry in the funnel plot was driven by small studies of lower quality[225;232;254;311;314] and Asian studies[304;307] that reported a stronger than the average positive association (Figure 5.21). The same was not identified in other Egger's tests and visual inspection of the funnel plots of studies with premenopausal women (P-values for Egger's test ≥ 0.12) (graphs not shown).

Meta-analyses by the pre-defined subgroups showed null associations between adult weight gain and premenopausal breast cancer risk (Table 5.7). For postmenopausal breast cancer, the increase in risk was stronger among Asian studies (summary RR per 5 kg gain = 1.35, 95% CI: 1.07-1.70) (3 studies[254;304;307]) (871 cases) compared with European studies (1.06, 95% CI: 1.03-1.10) (3 studies[306;309;311]) (2,053 cases), North American studies (1.06, 95% CI: 1.05-1.07) (9 studies[225;230;232;256;303;310;312-314]) (13,558 cases) and the Australia study (1.06, 95% CI: 1.03-1.10) (668 cases)[302]. Although the associations were not significantly different (P for meta-regression = 0.06), geographic location of the studies may contribute toward the observed between-study heterogeneity (I^2 = 64%, P heterogeneity <0.001) (Table 5.7).

Another potential source of heterogeneity was the proportion of MHT users in the studies. Subgroup analyses showed that significant positive associations were only observed among MHT never users (1.06, 95% CI: 1.03-1.09) (4 studies[230;256;302;314]) and never/former users (1.09, 95% CI: 1.07-1.12) (3 studies[309;312;313]), and not current (1.00, 95% CI: 0.98-1.03) (3 studies[309;312;313]) and ever users (1.08, 95% CI: 1.00-1.16) (3 studies[256;302;314]) (P for meta-regression = 0.01) (Figure 5.22). Other subgroup analyses mostly showed significant positive associations.

Restricted cubic spline analyses showed that the relationship with premenopausal breast cancer was non-linear, with a statistically non-significant increase risk with increasing weight gain to about 12 kg and dropped thereafter (P for non-linearity = 0.03); while the increase in risk of postmenopausal breast cancer with increasing adult weight gain was monotonic (P for non-linearity = 0.75) (Figures 5.23).

One Japanese study with limited numbers of premenopausal breast cancer cases reported non-significant positive associations between adult weight gain and risks of ER+PR+ (RR per 5 kg/m^2 = 1.31, 95% CI: 0.82-2.09) (49 cases), and ER+PR- breast cancers (1.25, 95% CI: 0.61-2.58) (22 cases), and non-significant inverse association for ER-PR- breast cancer (0.72, 95% CI: 0.36-1.47) (24 cases)[297].

Meta-analyses could be conducted for HR subtypes of postmenopausal breast cancer, which showed significant positive association for ER+PR+ breast cancer (summary RR per 5 kg gain = 1.11, 95% CI: 1.06-1.17) (6 studies[230;302;312;315-317]) (4,336 cases), but not for ER-PR- (1.02, 95% CI: 1.00-1.05) (same studies, 1,093 cases) and ER+PR- breast cancers (0.99, 95% CI: 0.97-1.02) (4 studies[302;312;315;316]) (958 cases) (P for meta-regression = 0.01) (Figure 5.24).

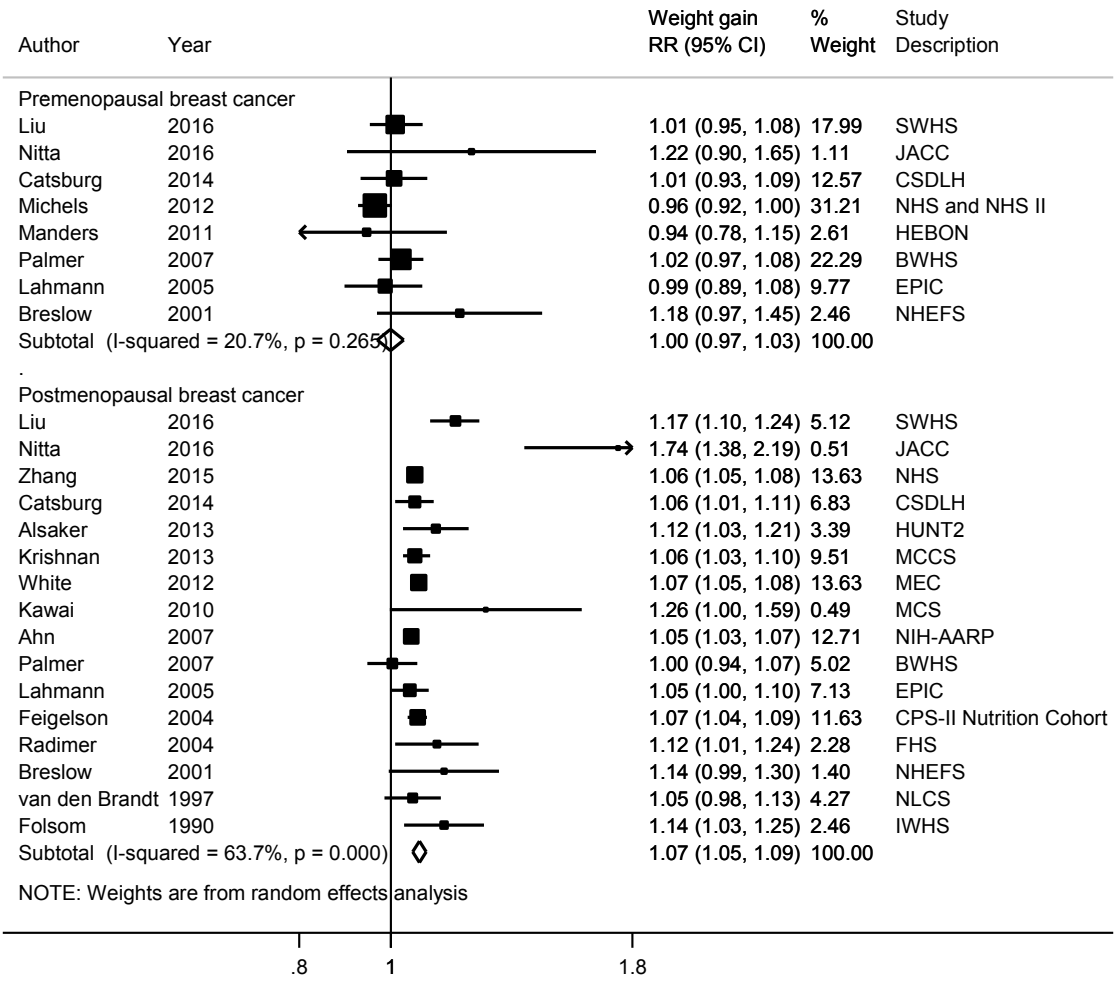


Figure 5.19 Relative risk and 95% CI of pre- and postmenopausal breast cancer for 5 kg increase of adult weight gain

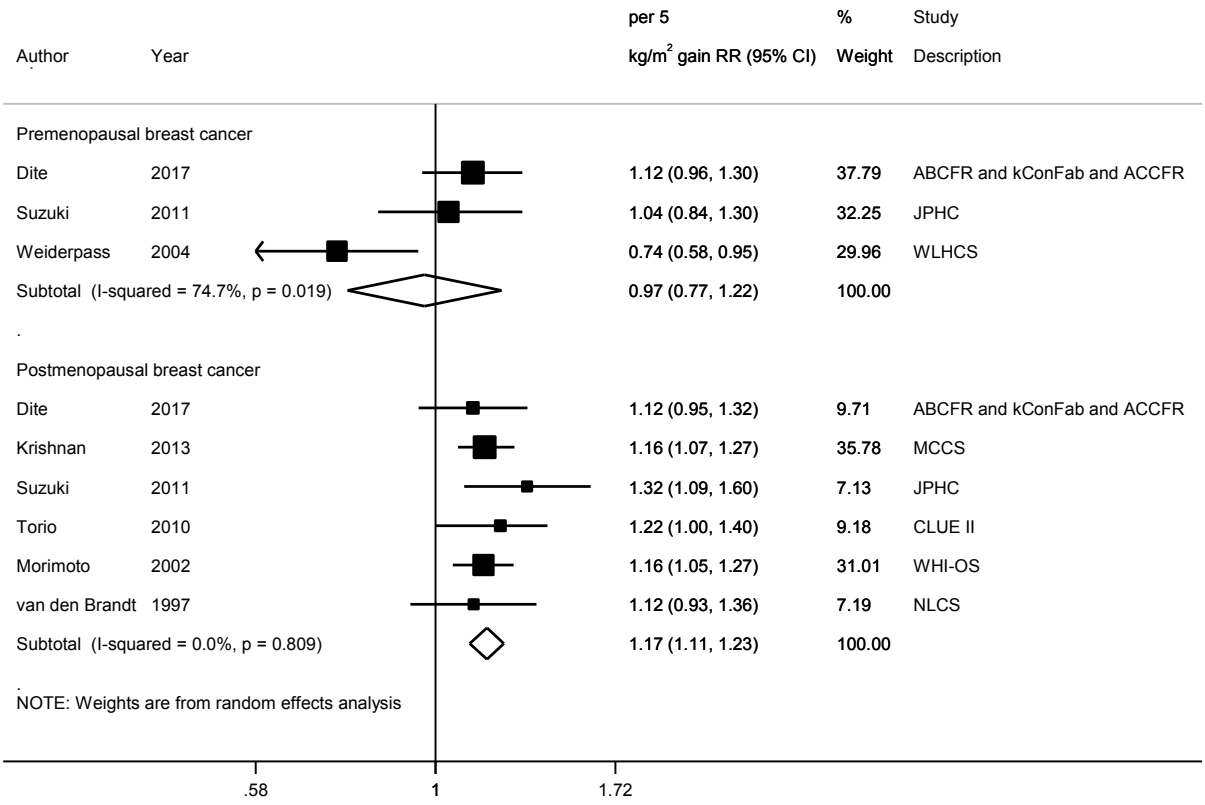


Figure 5.20 Relative risk and 95% CI of pre- and postmenopausal breast cancer for 5 kg/m^2 gain of BMI during adulthood

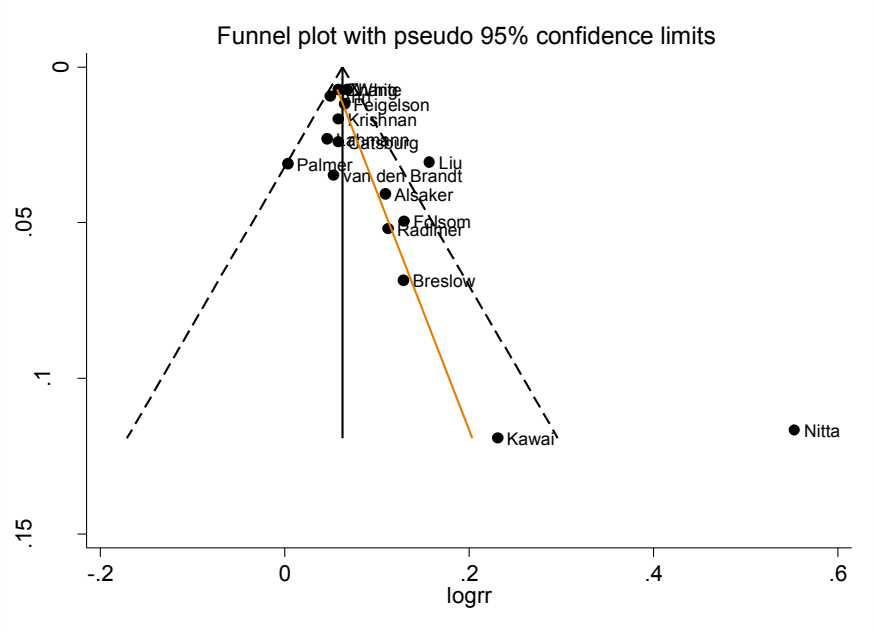


Figure 5.21 Funnel plot of studies included in the dose response meta-analysis of adult weight gain and postmenopausal breast cancer

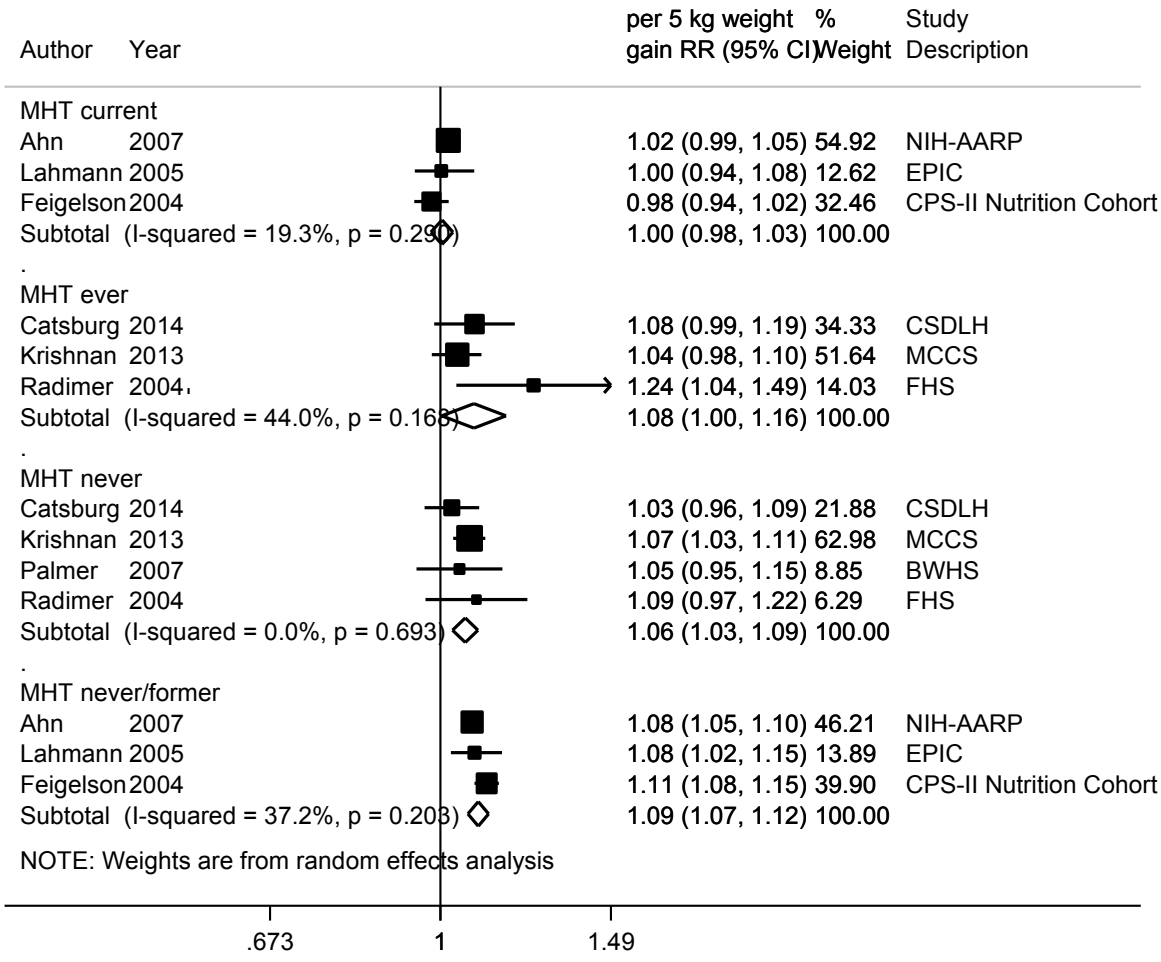
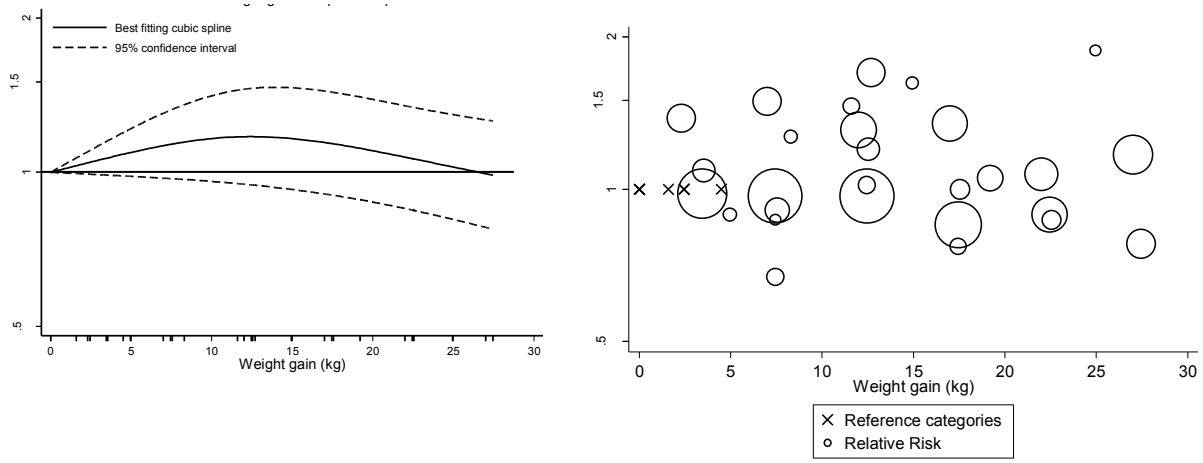


Figure 5.22 Relative risk and 95% CI of postmenopausal breast cancer for 5 kg increase of adult weight gain, by postmenopausal hormone use

Premenopausal breast cancer



Postmenopausal breast cancer

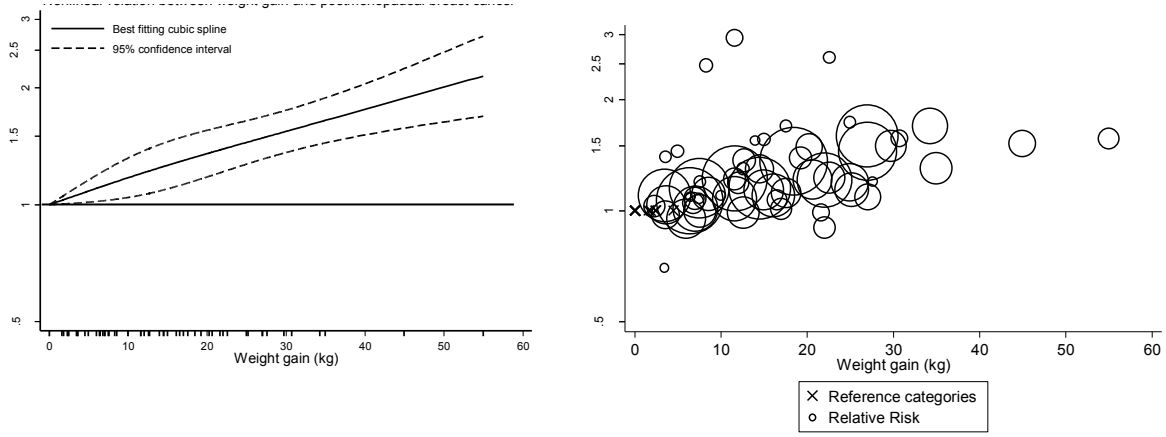


Figure 5.23 Non-linear analysis of adult weight gain and pre- and postmenopausal breast cancer

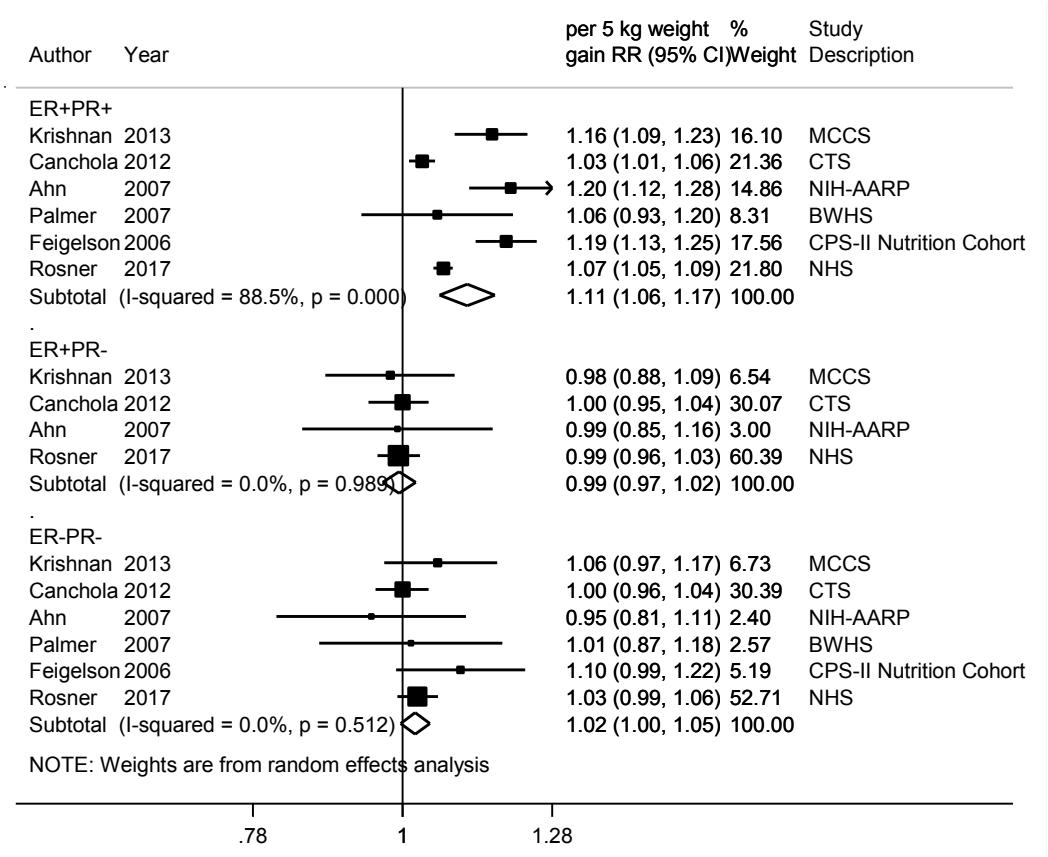


Figure 5.24 Relative risks and 95% CI of hormone receptor-defined postmenopausal breast cancer subtypes for 5 kg increase of adult weight gain

Table 5.7 Summary of subgroup meta-analyses of adult weight gain and pre- and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Per 5 kg gain	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	9 3,990	1.00 (0.97-1.03)	21% 0.27	-	16 17,150	**1.07 (1.05-1.09)**	64% <0.001	-
Geographic location								
Asia	2 691	1.04 (0.91-1.20)	28% 0.24	0.79	3 871	**1.35 (1.07-1.70)**	82% 0.004	0.06
Australia	0	-	-		1 668	**1.06 (1.03-1.10)**	-	
Europe	2 409	0.98 (0.90-1.06)	0% 0.69		3 2,053	**1.06 (1.03-1.10)**	0% 0.39	
North America	5 2,890	1.01 (0.95-1.06)	54% 0.09		9 13,558	**1.06 (1.05-1.07)**	19% 0.28	
Exposure assessment								
Both Measured	3 905	1.02 (0.95-1.08)	23% 0.27	0.57	2 636	**1.12 (1.05-1.19)**	0% 0.97	0.59
Both self-reported	6 3,085	0.99 (0.95-1.04)	28% 0.24		10 14,060	**1.06 (1.05-1.08)**	68% 0.001	
Self-reported then measured	0	-	-		4 2,454	**1.09 (1.04-1.15)**	71% 0.02	
Main confounding factors adjustment								
Adjusted	6 3,304	0.98 (0.95-1.01)	0% 0.40	0.24	13 16,460	**1.07 (1.06-1.08)**	37% 0.09	0.86
Not adjusted	3 686	1.03 (0.95-1.12)	24% 0.27		3 690	1.23 (0.96-1.57)	91% <0.001	
Initial body weight adjustment								
Adjusted	6 3,206	1.00 (0.96-1.04)	40% 0.15	0.81	11 13,814	**1.07 (1.05-1.08)**	54% 0.02	0.70
Not adjusted	3 784	1.01 (0.94-1.09)	0% 0.38		5 3,336	**1.11 (1.04-1.18)**	79% 0.001	
Study type								
Screening	0	-	-	-	0	-	-	-
Non-screening	9 3,990	1.00 (0.97-1.03)	21% 0.27	-	16 17,150	**1.07 (1.05-1.09)**	64% <0.001	-
Length of follow-up								
<10 years	2 295	1.06 (0.89-1.25)	61% 0.11	0.62	7 8,817	**1.06 (1.05-1.07)**	0% 0.46	0.61
≥10 years	7 3,695	1.00 (0.96-1.03)	16% 0.31		9 8,333	**1.09 (1.05-1.14)**	78% <0.001	
Study quality								
Low	5 1,021	1.02 (0.97-1.08)	11% 0.34	0.22	7 2,633	**1.12 (1.04-1.20)**	78% <0.001	0.78
High	4 2,969	0.98 (0.95-1.01)	4% 0.35		9 14,517	**1.07 (1.05-1.08)**	45% 0.07	
Invasive breast cancer	5 3,103	0.99 (0.96-1.02)	15% 0.32	-	9 13,322	**1.06 (1.05-1.07)**	0% 0.52	-

5.3.4.3 Weight gain across adult life course

Six studies (7 publications) on weight gain across adult life course were identified. The periods of change, as defined in the studies, could be broadly classified into periods before (early and middle adulthood) and after menopause (late adulthood), but the diverse measurements had hindered pooling of the results in a meta-analysis.

While adult weight gain was not associated with premenopausal breast cancer risk (see section 5.3.4.2); weight gain around midlife (during 40-50 years) significantly increased the risk of premenopausal breast cancer (RR for 0.83–4.98 vs (-)0.44 to 0.36 kg/year = 1.37, 95% CI: 1.02-1.85) (P trend 0.02) (283 cases)[234].

Several studies reported results on postmenopausal breast cancer risk observed strong positive associations, with long-term weight gain from age 18 years to menopause[315], <45 years and between 45-<55 years[311]. The positive association was evident among MHT non-users and not MHT users[236;312].

5.3.4.4 Adult weight loss

Eight studies (6 publications)[211;297;299;308;309;318] and 14 studies (13 publications)[297;301;302;304;306;309;311;312;314;318-321] on adult weight loss could be included in the categorical meta-analyses of pre- and postmenopausal breast cancer risk, respectively. Further, four postmenopausal breast cancer studies (4 publications, 952 cases)[304;312;314;320] with more than one weight loss categories could be included in the dose-response and the highest weight loss versus reference weight meta-analyses. No studies included in the analyses evaluated intentionality of weight loss.

Overall adult weight loss versus reference weight was significantly inversely associated with premenopausal breast cancer risk (summary RR = 0.85, 95% CI: 0.74-0.99) (I^2 = 0%, P heterogeneity = 0.93) and postmenopausal breast cancer risk (0.90, 95% CI: 0.81-0.99) (I^2 = 24%, P heterogeneity = 0.20) (Figure 5.25). There was no evidence of publication bias (P-values for Egger's test = 0.82 and 0.26, respectively). The findings became non-significant in influence analyses and subgroup analyses (results not tabulated), as well as in the other meta-analyses of postmenopausal breast cancer risk (summary RRs = 0.86 (95% CI: 0.69-1.08) for the highest weight loss vs reference weight and 0.96 (95% CI: 0.88-1.04) per 5 kg weight loss) (graphs not shown).

One study on premenopausal breast cancer reported results before and after the exclusion of first year of follow-up[309]. RR estimates for weight loss versus reference weight were 1.56 (95% CI: 0.96-2.54) and 1.01 (95% CI: 0.59-1.76), respectively. Six studies on postmenopausal breast cancer reported no appreciable change to the RR estimates when potential reverse causation was evaluated (results not shown in the studies)[302;304;306;311;312;320].

Three postmenopausal breast cancer studies reported results by HR status of the tumour[310;312;316]. Findings were mostly inconsistent and statistically non-significant.

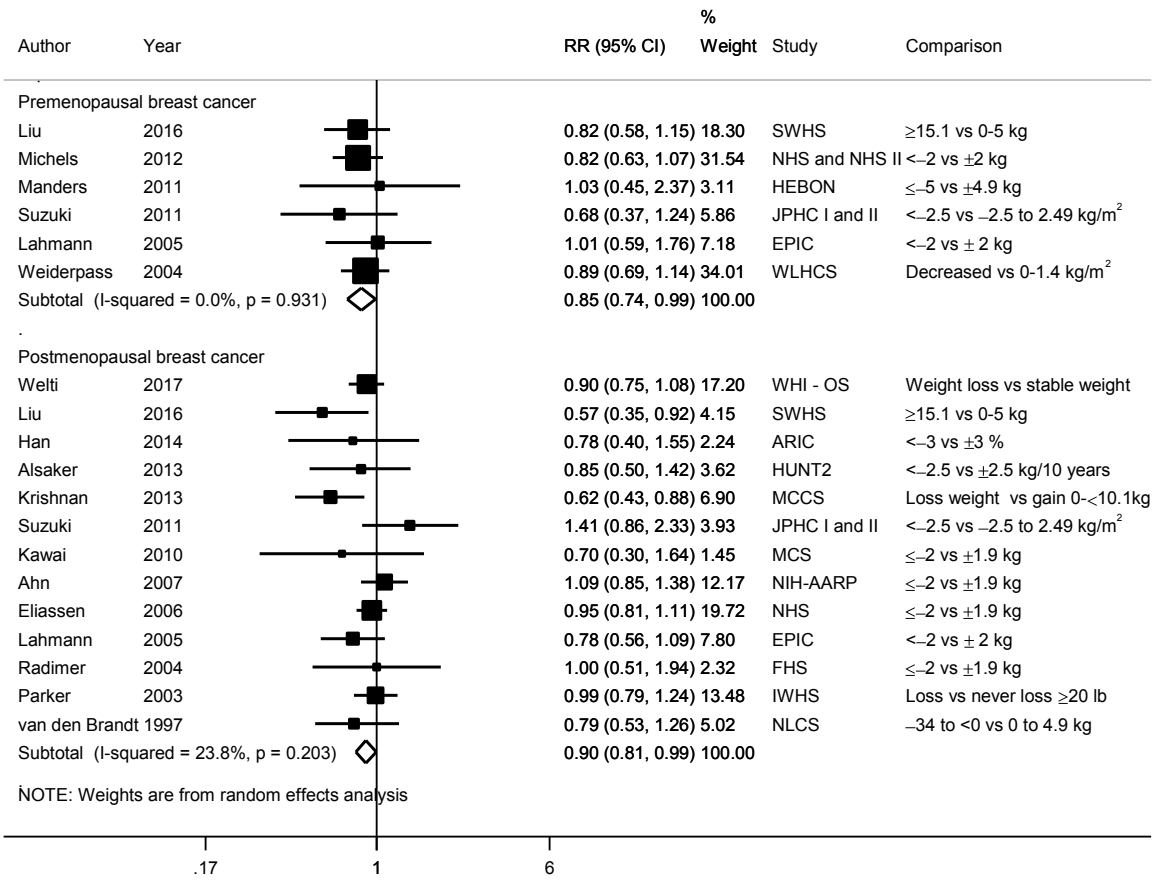


Figure 5.25 Relative risk and 95% CI of pre- and postmenopausal breast cancer for adult weight loss compare with reference weight

5.3.4.5 Weight loss across adult life course

For weight loss during different periods across adult life, one study on premenopausal breast cancer[234] and eight studies (9 publications) on postmenopausal breast cancer[234;311;312;314;315;319;320;322;323] were identified.

Women who lost weight around age 45-50 years were non-significantly inversely associated with premenopausal breast cancer risk (RR = 0.87, 95% CI: 0.61-1.23) when compared with women of stable weight[234]. The results on postmenopausal breast cancer risk were also mostly non-significant (RRs ranged from 0.40 to 1.22). No clear pattern was observed.

Four American studies were able to evaluate sustainable or intentional weight loss in relation to postmenopausal breast cancer risk. The findings were again not consistent, although one study found strong risk reductions, in women who maintained or lost weight from age 18 to 30 years that was followed by weight lost from age 30 years to menopause (RR = 0.36, 95% CI: 0.22-0.60), and in women who maintained or lost weight from age 30 years to menopause and subsequently lost weight

after menopause (RR = 0.48, 95% CI: 0.22-0.65), compared with women who gained weight in these periods[323]. However, compared with women of stable weight, women who intentionally lost ≥ 10 pounds and kept it off did not show a significant reduced risk (RR [baseline BMI adjusted] = 0.90, 95% CI: 0.75-1.08)[319]; and so were the women with the greatest stable weight loss since menopause (RR = 0.70, 95% CI: 0.47-1.04)[320] or between age 50 and 74 years (0.74, 95% CI: 0.46-1.19)[322].

5.3.4.6 BMI and premenopausal breast cancer risk

BMI was assessed at study baseline or during follow-up, which could be for anytime during adulthood.

Dose-response meta-analyses were conducted for the risks of premenopausal breast cancer: incidence (41 studies, 27 publications)[104;111;211-213;216;217;221;222;224;230;237;256;296;299;318;324-334], ER subtypes (5 studies, 4 publications)[224;335-337] and mortality (36 studies, 2 publications)[217;338]. These included >17,222 incident cases overall, 1,499 ER-positive breast cancers, 823 ER-negative breast cancers, and 545 breast cancer deaths.

BMI was significantly inversely associated with premenopausal breast cancer risk (summary RR per 5 kg/m^2 = 0.94, 95% CI: 0.91-0.98) (Figure 5.26). There was evidence of significant between-study heterogeneity (I^2 = 57%, P heterogeneity < 0.001) and publication bias (P for Egger's test=0.05) (Figure 5.27). Inspection of the funnel plot shows asymmetry that could be driven by the large study that reported a stronger than the average inverse association[325]. The summary RR estimate did not change materially in influence analysis.

Meta-analyses by the pre-defined subgroups showed inverse associations (Table 5.8). Geographic location of the cohorts may explain partly the between-study heterogeneity (I^2 = 57%, P heterogeneity < 0.001). The associations were inverse among European studies (summary RR per 5 kg/m^2 = 0.90, 95% CI: 0.87-0.92) (19 studies[104;211;217;222;237;299;324;325;327-334]) (12,056 cases), North American studies (0.97, 95% CI: 0.91-1.04) (9 studies[104;111;216;221;224;230;256;296]) (3,812 cases) and in the United States and Puerto Rico study that involved sisters of women with breast cancer (the Sister Study) (0.90, 95% CI: 0.82-1.00) (413 cases)[213]; but were positive among Asian studies (1.10, 95% CI: 0.93-1.30) (9 studies[318;326]) (941 cases) and in the Australia and New Zealand study that pooled data from three familial cancer studies (1.11, 95% CI: 0.97-1.27)[212] (P for meta-regression = 0.004) (Table 5.8).

Studies that did not represent the general populations scored less towards study quality. When considered together with other aspects of study quality such as confounding factors adjustment, number of cases and loss to follow-up, the abovementioned pooled study of familial cancer studies[212], the NSABP P-1 breast cancer prevention trial that involved women at high breast cancer risk[224], and the cohort of BRCA1/2 mutation carriers[211] scored ≤11 points and were classified as lower quality studies; however, the Sister study that scored 13 points was an exception[213]. Collectively, lower

quality studies showed a null association (summary RR per 5 kg/m^2 = 0.98, 95% CI: 0.90-1.06), although not significantly different to higher quality studies (0.92, 95% CI: 0.89-0.95) (P for meta-regression = 0.23). The associations were similar between studies that involved cancer/mammography screening or not, or other subgroups (all P-values for meta-regression ≥ 0.29).

There was no evidence of non-linear relationship (P for non-linearity = 0.31). The curve from the restricted cubic spline analysis shows a significant inverse association after BMI of 28 kg/m^2, which could be driven by the few data points at the very high levels of BMI (Figure 5.28).

Non-significant associations were observed in the meta-analyses by ER status of the tumour. The summary RR estimates per 5 kg/m^2 were 1.02 (95% CI: 0.83-1.25) (I^2 = 73%, P heterogeneity = 0.01) for ER-positive breast cancers and 1.06 (95% CI: 0.95-1.18) (I^2 = 0%, P heterogeneity = 0.66) for ER-negative breast cancers (Figure 5.29).

No significant association was observed in the meta-analysis of breast cancer mortality (summary RR per 5 kg/m^2 = 1.00, 95% CI: 0.73-1.38). The Million Women Study (MWS)[217] was the only study that could be pooled with the Prospective Studies Collaboration (PSC), a collaboration that was established chiefly to assess the relevance of blood pressure and blood cholesterol to cause-specific mortality (35 studies in analysis)[338] and inconsistent results were reported in these two studies (I^2 = 75%, P heterogeneity = 0.05) (graph not shown).

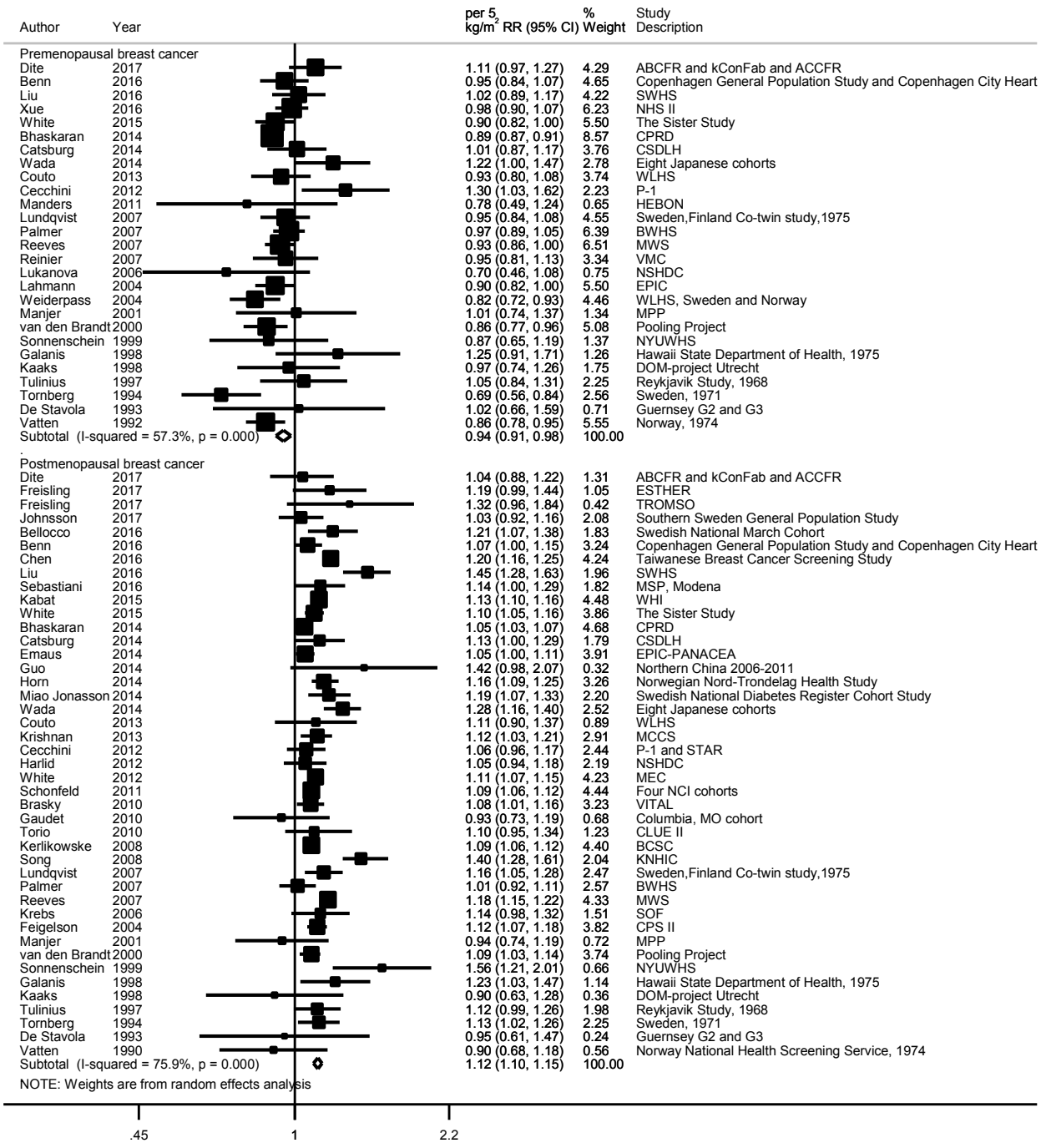


Figure 5.26 Relative risk and 95% CI of pre- and postmenopausal breast cancer for 5 kg/m^{2}increase of BMI

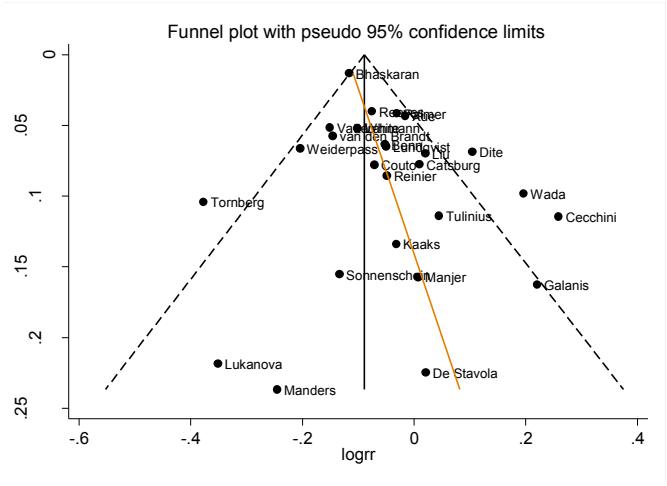


Figure 5.27 Funnel plot of studies included in the dose response meta-analysis of BMI and premenopausal breast cancer

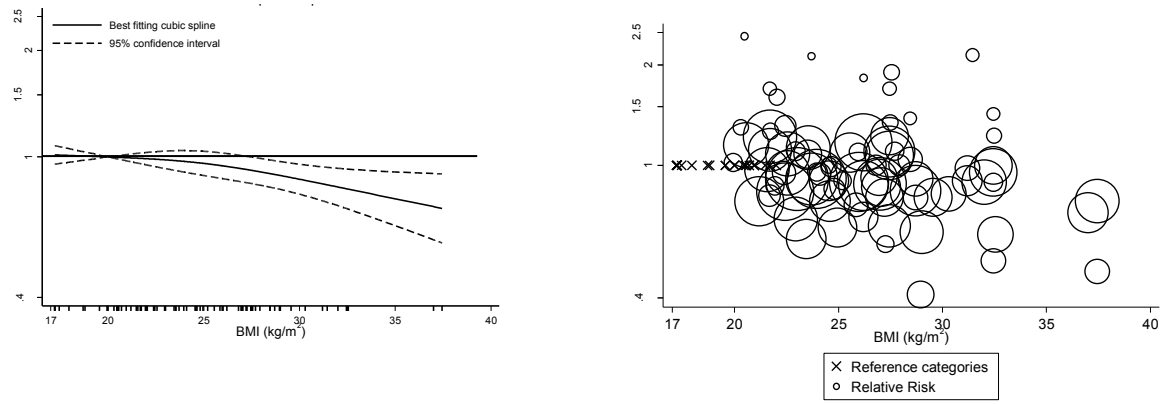


Figure 5.28 Non-linear analysis of BMI and premenopausal breast cancer

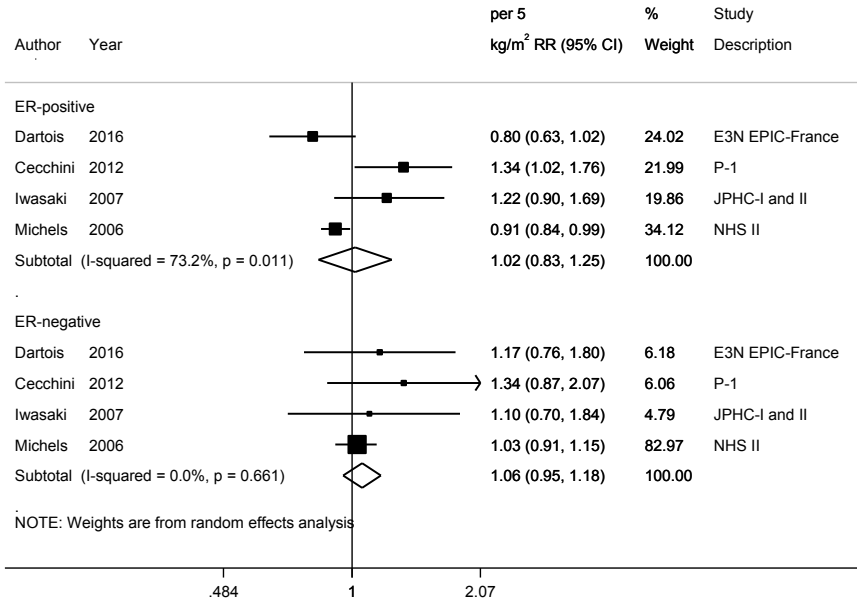


Figure 5.29 Relative risk and 95% CI of hormone receptor-defined premenopausal breast cancer subtype for 5 kg/m^2 increase of BMI

Table 5.8 Summary of subgroup meta-analyses of BMI and premenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Per 5 kg/m^2	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	41 >17,222	**0.94 (0.91-0.98)**	57% <0.001	-	65 >90,388	**1.12 (1.10-1.15)**	76% <0.001	-
Geographic location[1]								
Asia	9 941	1.10 (0.93-1.30)	53% 0.14	0.004	12 8,696	**1.32 (1.21-1.44)**	73% 0.006	<0.001
Australia and New Zealand	3 -	1.11 (0.97-1.27)	-		4 >668	**1.10 (1.03-1.19)**	0% 0.43	
Europe	19 12,056	**0.90 (0.87-0.92)**	10% 0.34		25 47,211	**1.11 (1.07-1.15)**	70% <0.001	
North America	9 3,812	0.97 (0.91-1.04)	41% 0.09		23 32,231	**1.10 (1.08-1.12)**	28% 0.12	
United States and Puerto Rico	1 413	0.90 (0.82-1.00)	-		1 1,582	**1.10 (1.05-1.16)**	-	
Exposure assessment								
Measured	16 9,500	**0.92 (0.87-0.98)**	55% 0.009	0.38	22 49,881	**1.14 (1.09-1.19)**	84% <0.001	0.64
Self-reported	25 >7,722	0.96 (0.91-1.01)	48% 0.02		41 >36,223	**1.12 (1.09-1.15)**	57% 0.001	
Self-reported or measured	0	-	-		1 4,021	**1.05 (1.01-1.11)**	-	
From records	0	-	-		1 263	**1.19 (1.07-1.33)**	-	
Main confounding factors adjustment								
Adjusted	18 6,576	0.95 (0.90-1.00)	41% 0.09	0.68	31 49,742	**1.13 (1.10-1.17)**	72% <0.001	0.39
Not adjusted	23 >10,646	**0.94 (0.89-0.99)**	61% <0.001		34 >40,646	**1.11 (1.08-1.15)**	74% <0.001	
Study type[1]								
Screening	7 1,982	0.97 (0.88-1.07)	29% 0.21	0.56	10 17,856	**1.15 (1.09-1.21)**	76% <0.001	0.32
Non-screening	34 >15,240	**0.94 (0.90-0.98)**	58% <0.001		55 >72,532	**1.11 (1.09-1.14)**	67% <0.001	
Length of follow-up								
<10 years	15 4,687	**0.92 (0.87-0.97)**	36% 0.11	0.29	28 37,427	**1.12 (1.09-1.15)**	71% <0.001	0.77
≥10 years	26 >12,535	0.97 (0.91-1.02)	67% <0.001		37 >52,961	**1.13 (1.09-1.17)**	79% <0.001	
Study quality								
Low	27 >3,436	0.98 (0.90-1.06)	61% 0.001	0.23	43 >58,338	**1.12 (1.08-1.16)**	76% <0.001	0.75
High	14 13,786	**0.92 (0.89-0.95)**	31% 0.15		22 32,050	**1.13 (1.10-1.16)**	67% <0.001	
Invasive breast cancer	29 13,358	0.96 (0.91-1.01)	66% <0.001	-	43 64,432	**1.12 (1.09-1.15)**	78% <0.001	-

5.3.4.7 BMI and postmenopausal breast cancer risk

Dose-response meta-analyses were conducted for the risks of postmenopausal breast cancer: incidence (65 studies, 42 publications)[101;104;111;212;213;217;221-224;230;234;237;250;253;256;261;302;303;305;313;318;324-327;330-333;339-350], HR subtypes (12 studies, 11 publications jointly[213;219;230;302;312;316;335;351-354] and 12 studies, 11 publications individually[101;123;224;229;273;274;302;335;337;355;356]), by MHT use (20 studies, 14 publications)[104;213;217;230;234;236;256;297;302;303;312;313;329;357], and mortality (39 studies, 5 publications)[217;338;351;358;359]. These included >90,388 incident cases overall; 9,587 ER-positive, 2,180 ER-negative, 1,314 PR-positive and 654 PR-negative breast cancers; 3,940 MHT current users and >10,487 MHT never users; and 4,131 breast cancer deaths.

BMI was significantly positively associated with postmenopausal breast cancer risk. For each 5 kg/m^2 increase of BMI, there was a 12% increase in risk (summary RR = 1.12, 95% CI: 1.10-1.15) (Figure 5.26, above). Substantial between-study heterogeneity was detected (I^2 = 76%, P heterogeneity <0.001) and there was evidence of significant publication bias (P for Egger's test = 0.04). Visual inspection of the funnel plot shows asymmetry (Figure 5.30); which could be driven by a weaker than the average positive association reported in one large study, the very same study that showed an impact in the funnel plot of premenopausal breast cancer[325] (see section 5.3.4.6). The significant positive association was robust and materially unchanged in influence analysis.

Restricted cubic spline analysis showed a linear dose-response trend, with risk increased monotonically across increasing levels of BMI (P for non-linearity = 0.31) (38 studies, 29 publications) (Figure 5.31). As estimated, postmenopausal breast cancer risk increased by 15% for being overweight, 29% for being obese and 48% for being severely obese compared with normal weight.

Asian studies on average reported a stronger positive association (summary RR per 5 kg/m^2 = 1.32 95% CI: 1.21-1.44) (12 studies[318;326;340;343;348]) (8,696 cases) compared with studies from Australia and New Zealand (1.10, 95% CI: 1.03-1.19) (4 studies[212;302]) (>668 cases), European studies (1.11, 95% CI: 1.07-1.15) (25 studies[104;217;222;234;237;250;253;324;325;327;330-333;339;341;344-346;350]) (47,211 cases), North American studies (1.10, 95% CI: 1.08-1.12) (23 studies[101;104;111;221;223;224;230;256;261;303;305;313;342;347;349]) (32,231 cases) and one study from United States and Puerto Rico (1.10, 95% CI: 1.05-1.16) (1,582 cases)[213] (P for meta-regression <0.001) (Table 5.8, above).

Significant positive associations were observed among MHT never users (1.16, 95% CI: 1.10-1.23), former users (1.27, 95% CI: 1.13-1.42) and never/former users (1.20, 95% CI: 1.15-1.25), but not among current users (0.98, 95% CI: 0.92-1.05) and ever users (1.01, 95% CI: 0.96-1.06) (P for meta-regression = 0.002) (Figure 5.32). Hence, geographic location and proportion of MHT users in the studies may explain partly the observed between-study heterogeneity (I^2 = 76%, P heterogeneity <0.001), although different associations remained within some subgroups (I^2 ranged from 0 to 75%

and P heterogeneity ranged from <0.01 to 0.66). Other subgroup meta-analyses, for instance of studies that involved cancer/mammography screening, lower quality or higher quality, showed positive associations, that were consistent and comparable in magnitude (P-values for meta-regression ≥0.32) (Table 5.8, above).

Different associations by HR status of the tumour were also observed, which were positive and statistically significant for ER-positive (summary RR per 5 kg/m^2 = 1.18, 95% CI: 1.10-1.27) (10, 224 cases), PR-positive (1.47, 95% CI: 1.36-1.60) (1,314 cases) and ER+PR+ breast cancers (1.25, 95% CI: 1.19-1.31) (>7,312 cases); but not for ER-negative (1.02, 95% CI: 0.96-1.08) (2,034 cases), PR-negative breast cancers (1.05, 95% CI: 0.93-1.18) (654 cases) and other HR-defined subtypes (1.00 (95% CI: 0.93-1.07) for ER-PR- (>1,703 cases); 0.97 (95% CI: 0.92-1.03) for ER+PR- (1,658 cases); and 0.86 (95% CI: 0.58-1.28) for ER-PR+ breast cancers (52 cases)) (Figures 5.33 and 5.34).

Meta-analysis of breast cancer mortality showed that each 5 kg/m^2 increase of BMI increased the risk of dying from breast cancer by 21% in postmenopausal women (summary RR = 1.21, 95% CI: 1.15-1.28) (I^2 = 42%, P heterogeneity = 0.14) (graph not shown).

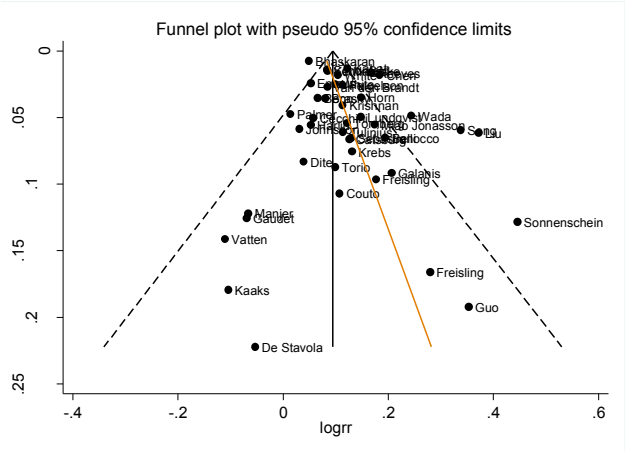


Figure 5.30 Funnel plot of studies included in the dose response meta-analysis of BMI and postmenopausal breast cancer

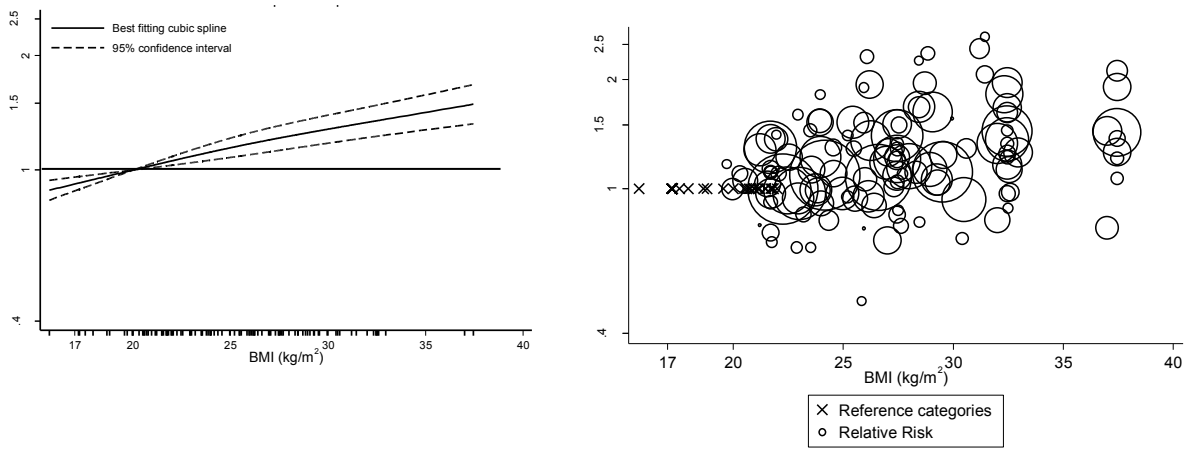


Figure 5.31 Non-linear analysis of BMI and postmenopausal breast cancer

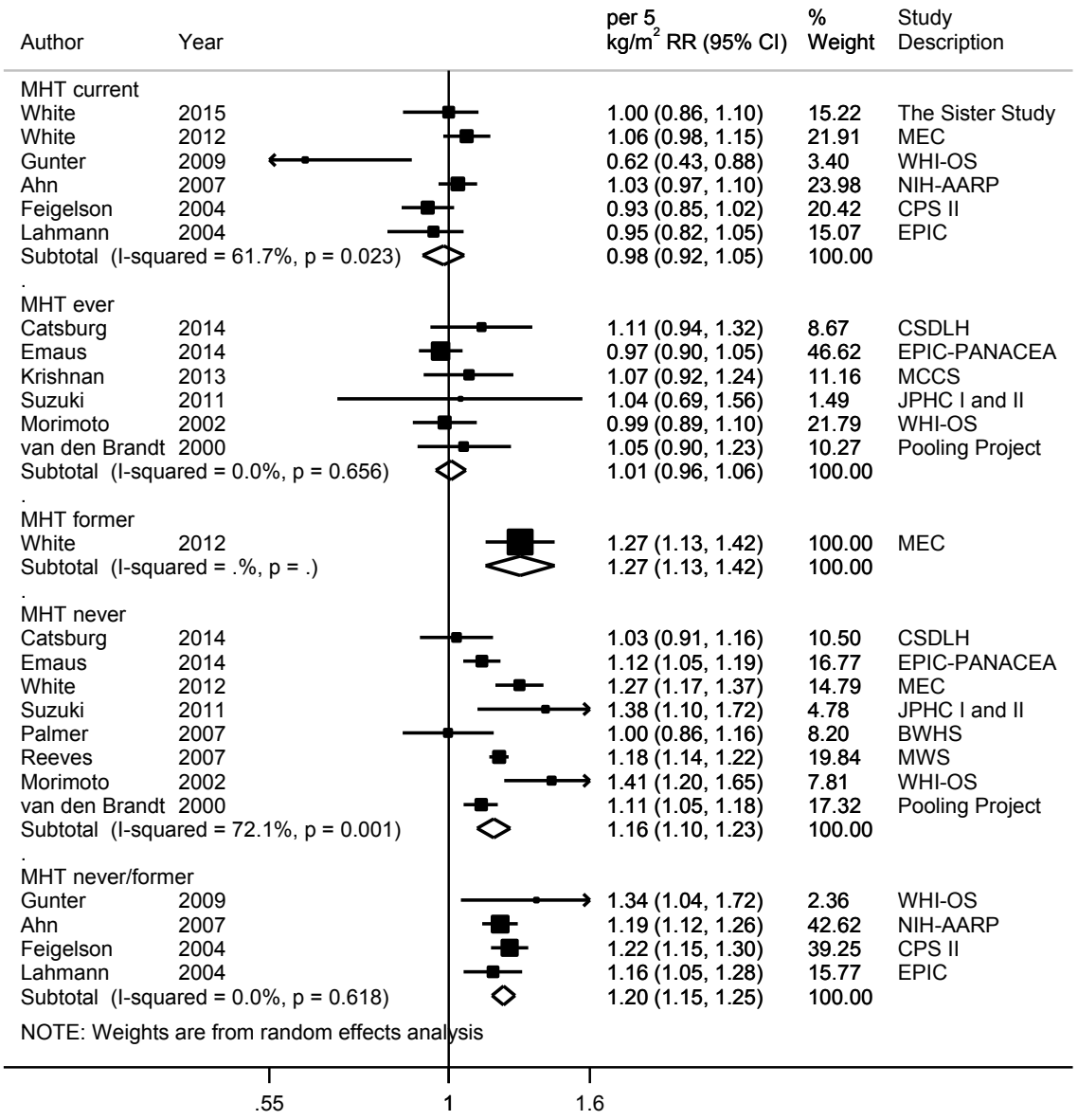


Figure 5.32 Relative risk and 95% CI of postmenopausal breast cancer for 5 kg/m^2 increase of BMI, by postmenopausal hormone use

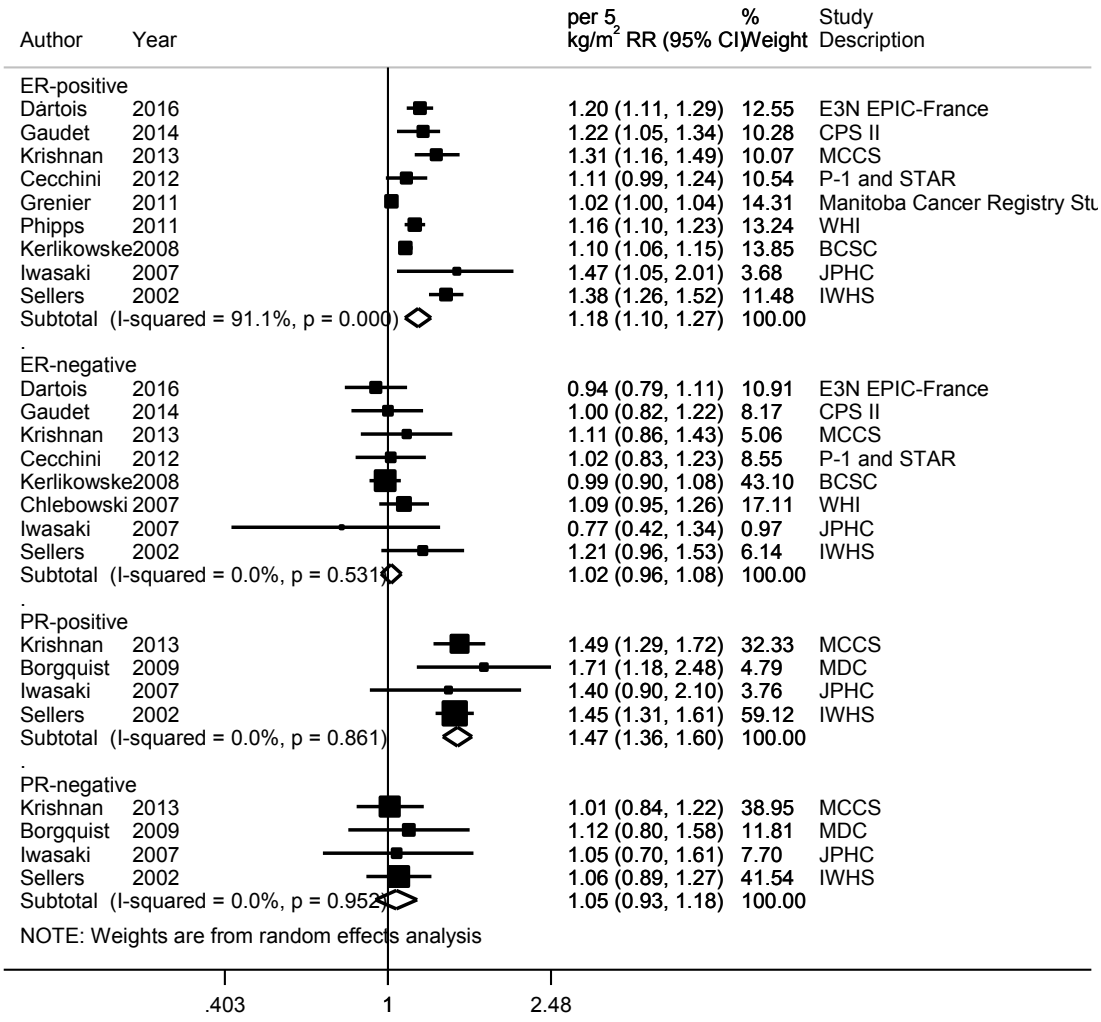


Figure 5.33 Relative risk and 95% CI of hormone receptor-defined postmenopausal breast cancer subtypes for 5 kg/m^2 increase of BMI

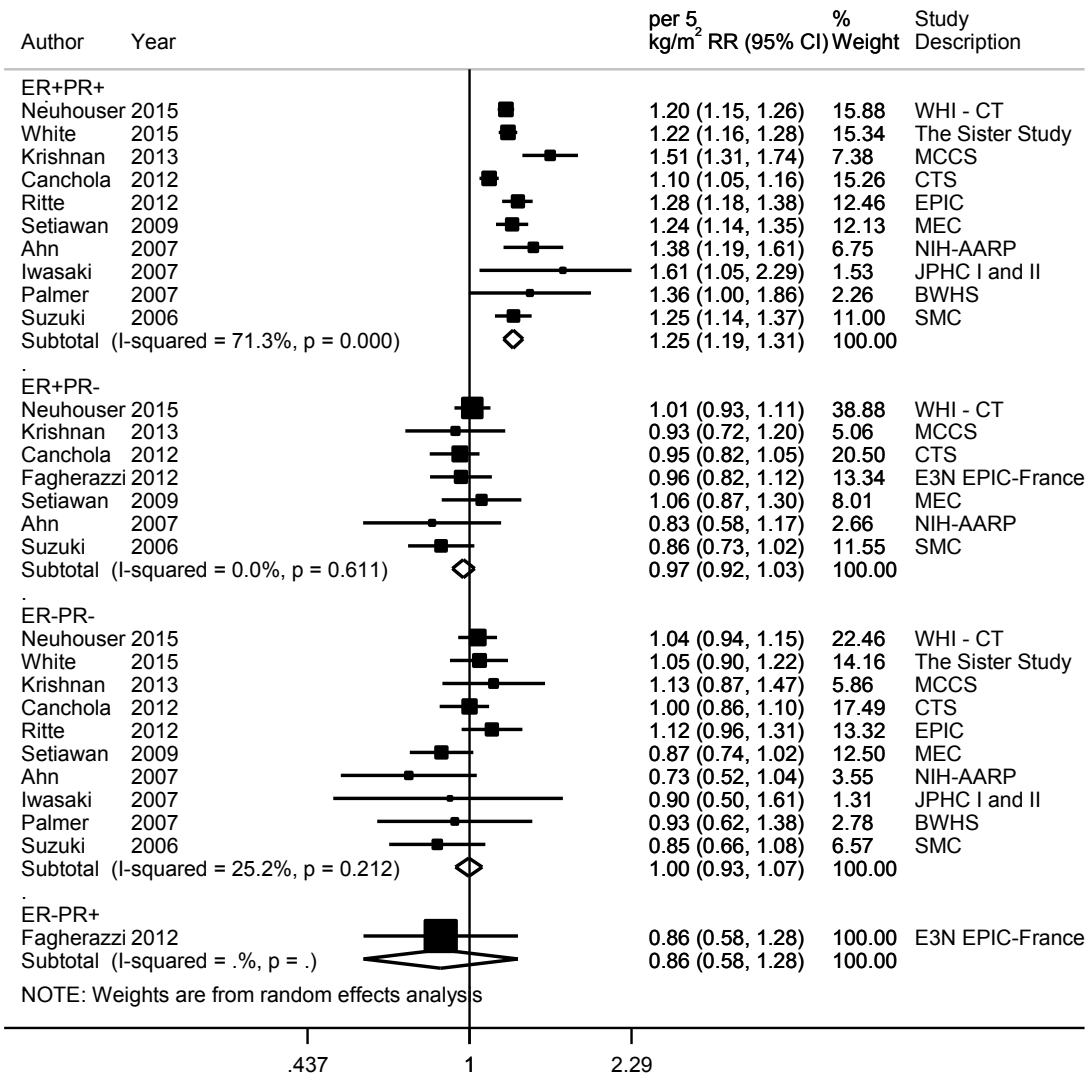


Figure 5.34 Relative risk and 95% CI of joint types of hormone receptor-defined postmenopausal breast cancer for 5 kg/m^2 increase of BMI

5.3.4.8 BMI across adult life course

Two studies (3 publications)[236;273;312] examined BMI at specific times in adult life, other than age 18-<30 years reviewed in section 5.3.4.1.

NIH-AARP reported an increased risk of postmenopausal breast cancer with higher versus lower BMI at age 35 years, among MHT non-users (RR [BMI at 18 years adjusted] for 30-34.9 vs 18.5-22.4 kg/m^2 = 1.17, 95% CI: 0.82-1.67) (P trend = 0.06) (948 cases) but not among MHT current users (0.75, 95% CI: 0.47-1.20) (P trend = 0.38) (1162 cases)[312]. When the same association was evaluated by molecular subtypes of breast cancer, the WHI study found an inverse association with ER-positive breast cancers (RR [baseline BMI adjusted] for ≥24.15 vs <20.83 kg/m^2 = 0.79, 95% CI: 0.64-0.97) (P trend = 0.01) (1,427 cases) and a null association with TNBC (1.03, 95% CI: 0.57-1.87) (P trend = 0.77) (177 cases); but the associations were not significantly different (P heterogeneity = 0.39)[273].

For BMI at age 50 years, both NIH-AARP[312] and WHI[236] found a statistically significant increased risk of postmenopausal breast cancer among MHT non-users (RR [BMI at 18 years adjusted] for ≥40 vs 18.5-22.4 kg/m^2 = 2.00 (95% CI: 1.23-3.26) and RR for ≥31.11 vs ≤22.6 kg/m^2 = 2.07 (95% CI: 1.32-3.25) respectively) (both P values for trend ≤0.001) (948 and 316 cases, respectively); the results were not significant for MHT users (0.92 (95% CI: 0.40-2.10) and 0.90 (95% CI: 0.62-1.31); P trend = 0.02 and 0.34; 1,162 and 702 cases, respectively), which are in line with the findings for adult/baseline BMI. There associations for ER-positive breast cancers (RR ≥26.85 vs <22.07 kg/m^2 = 0.95, 95% CI: 0.74-1.22) (P trend = 0.48) and TNBC (1.93, 95% CI: 0.91-4.08) (P trend = 0.10) were not significantly different (P heterogeneity = 0.28)[273].

5.3.4.9 Waist circumference and premenopausal breast cancer risk

Seven studies on premenopausal breast cancer could be included in the dose-response meta-analysis using BMI unadjusted RR estimates reported by all studies[213;222;230;256;329;360;361] (2,836 cases) . Four studies further reported BMI adjusted RR estimates[213;329;360;361] (1,704 cases), which were pooled in a separate meta-analysis.

Waist circumference was moderately correlated with BMI in premenopausal women (correlation coefficient = 0.52)[362].

The association between waist circumference and premenopausal breast cancer risk was different by BMI adjustment. Waist circumference was significantly positively associated with breast cancer risk in premenopausal women when BMI was included in the models as covariate. Summary RRs per 10 cm were 1.15 (95% CI: 1.05-1.26) (I^2 = 0%, P heterogeneity = 0.94) in studies with BMI adjustment and 0.99 (95% CI: 0.94-1.03) (I^2 = 0%, P heterogeneity = 0.88) in studies without BMI adjustment (Figure 5.35). The associations remained materially unchanged in influence analyses. The null association in studies without BMI adjustment persisted across the subgroup meta-analyses, including

those of lower quality[222;230] and higher quality studies[213;256;329;360;361] (all P-values for meta-regression ≥0.33) (Table 5.9). Because of the low number, further analyses of BMI adjusted studies were not conducted.

There was evidence of significant publication bias (P for Egger's test = 0.04). Asymmetry in the funnel plot (of studies not adjusted for BMI) could be driven by two small studies[213;222] that reported a slightly stronger inverse association than the average; but all studies found a non-significant result (Figure 5.36).

Restricted cubic spline analysis (of studies not adjusted for BMI) showed an increase in risk of premenopausal breast cancer with waist circumference up to 80 cm and dropped after, but the 95% CI was very wide (P for non-linearity = 0.07) (6 studies[222;230;256;329;360;361]) (Figure 5.37).

Results by HR status of the tumour in premenopausal women were reported in three studies (two American studies[213;360] and one French study[354]. Positive associations that were significant for ER-negative breast cancers[360] and non-significant for ER-PR- breast cancer[354]were reported.

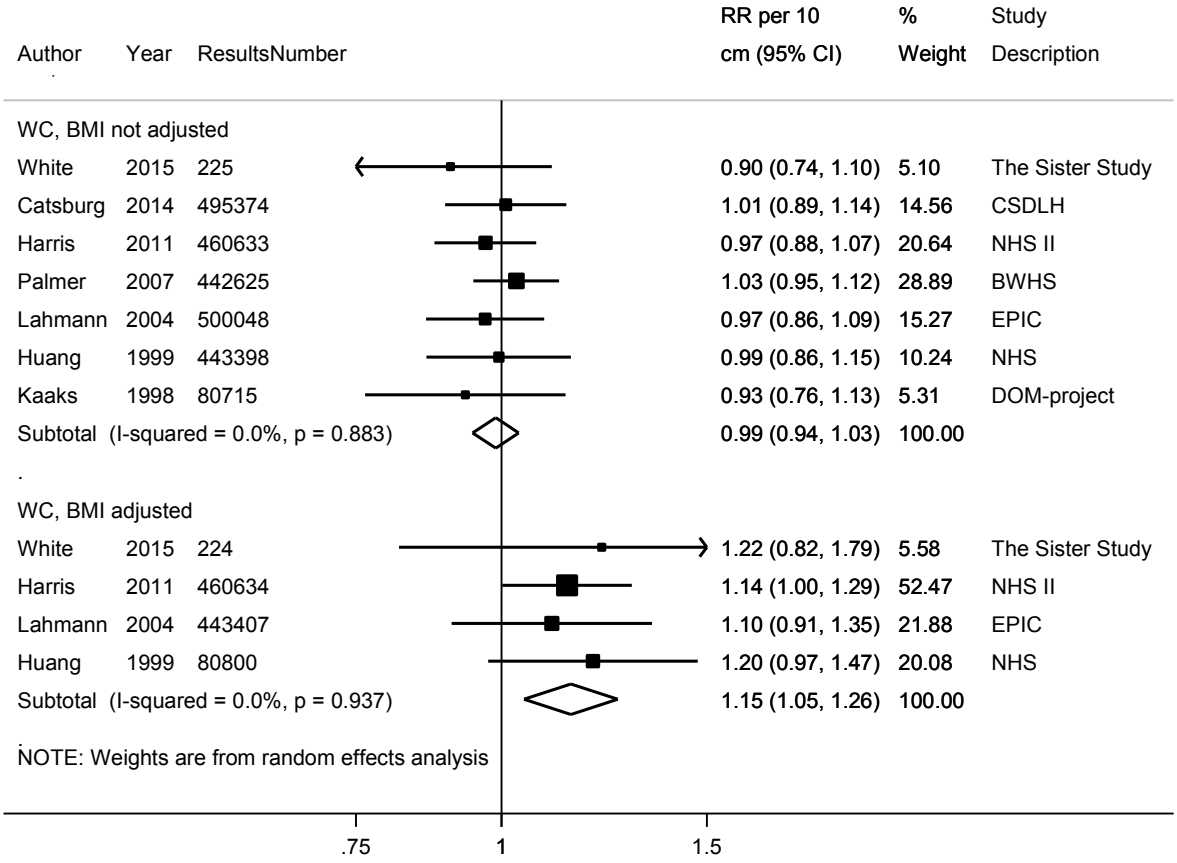


Figure 5.35 Relative risk and 95% CI of premenopausal breast cancer for 10 cm increase of waist circumference

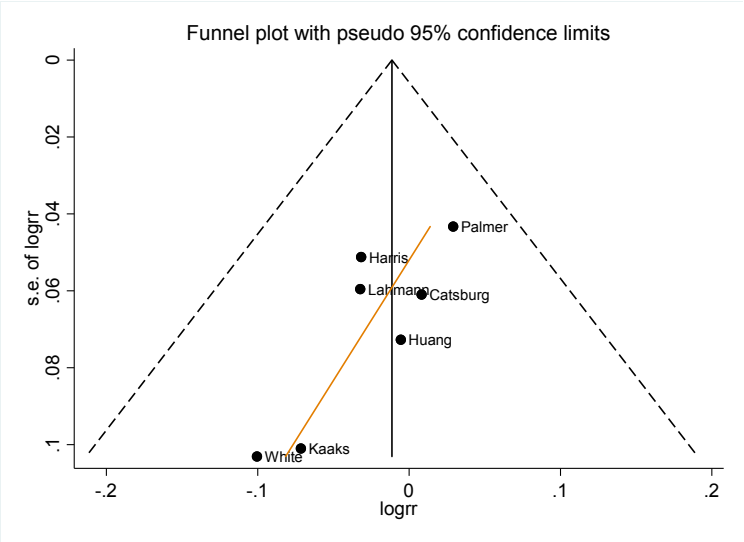


Figure 5.36 Funnel plot of studies included in the dose response meta-analysis of waist circumference and premenopausal breast cancer

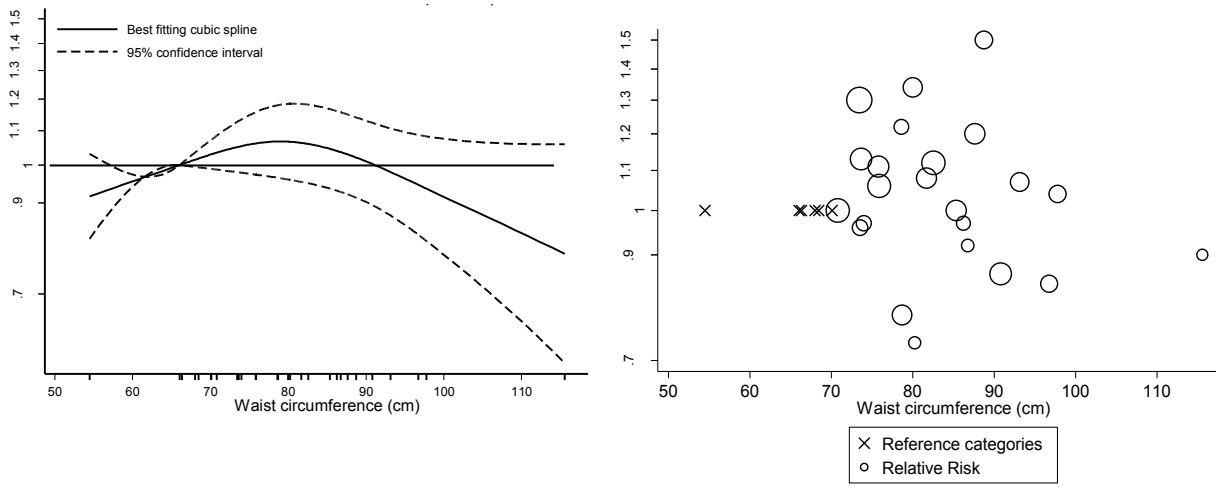


Figure 5.37 Non-linear analysis of waist circumference and premenopausal breast cancer

Table 5.9 Summary of subgroup meta-analyses of (BMI unadjusted) waist circumference and pre- and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Per 10 cm	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	7 2,836	0.99 (0.94-1.03)	0% 0.88	-	14 16,384	**1.12 (1.10-1.14)**	14% 0.30	-
Geographic location								
Asia	0	-	-	-	0	-	-	-
Australia	0	-	-	-	1 357	**1.13 (1.03-1.24)**	-	0.30
Europe	2 621	0.96 (0.87-1.06)	0% 0.74	0.55	4 1,458	**1.16 (1.07-1.25)**	0% 0.40	
North America	4 1,802	1.00 (0.95-1.06)	0% 0.84		8 12,987	**1.10 (1.09-1.13)**	9% 0.36	
United States and Puerto Rico	1 413	0.90 (0.74-1.11)	-		1 1,582	**1.22 (1.10-1.34)**	-	
Exposure assessment								
Measured	3 1,034	0.95 (0.87-1.04)	0% 0.83	0.33	6 9,468	**1.14 (1.09-1.19)**	31% 0.21	0.64
Self-reported	4 1,802	1.00 (0.95-1.06)	0% 0.84		7 6,303	**1.11 (1.08-1.14)**	23% 0.26	
Self-reported or measured	0	-	-		1 613	**1.12 (1.02-1.24)**	-	
Main confounding factors adjustment								
Adjusted	5 2,252	0.98 (0.92-1.03)	0% 0.92	0.48	10 15,238	**1.12 (1.10-1.14)**	0% 0.59	0.43
Not adjusted	2 584	1.01 (0.94-1.10)	0% 0.36		4 1,146	1.13 (1.00-1.27)	56% 0.08	
Study type								
Screening	1 147	0.93 (0.76-1.13)	-	0.57	1 76	1.25 (0.90-1.73)	-	0.55
Non-screening	6 2,689	0.99 (0.95-1.04)	0% 0.85		13 16,308	**1.12 (1.09-1.14)**	18% 0.26	
Length of follow-up								
<10 years	4 1,231	0.96 (0.89-1.04)	0% 0.88	0.40	6 4,916	**1.12 (1.08-1.15)**	0% 0.46	0.99
≥10 years	3 1,605	1.00 (0.95-1.06)	0% 0.66		8 11,468	**1.12 (1.09-1.15)**	33% 0.17	
Study quality								
Low	2 584	1.01 (0.94-1.10)	0% 0.36	0.48	4 1,146	1.13 (1.00-1.27)	56% 0.08	0.43
High	5 2,252	0.98 (0.92-1.03)	0% 0.92		10 15,238	**1.12 (1.10-1.14)**	0% 0.59	
Invasive breast cancer	5 2,252	0.98 (0.92-1.03)	0% 0.92		9 12,555	**1.12 (1.10-1.14)**	0% 0.46	

5.3.4.10 Waist circumference and postmenopausal breast cancer risk

Fourteen studies on postmenopausal breast cancer could be included in a dose-response meta-analysis using BMI unadjusted RR estimates reported by all studies[213;222;229;230;250;256;312;339;342;349;361;363-365] (16,384 cases). Seven studies further reported BMI adjusted RR estimates, which were pooled in a separate meta-analysis[123;213;229;329;339;342;361] (13,668 cases).

Waist circumference and BMI was highly correlated in postmenopausal women (correlation coefficients ranged from 0.79[312] to 0.86[363]); therefore, it represents abdominal body fatness as well as total body fatness.

For postmenopausal breast cancer risk, the summary RRs of studies with and without the adjustment of BMI were comparable. For each 10 cm increase in waist circumference, the summary RRs were 1.12 (95% CI: 1.10-1.14) (I^2 = 14%, P heterogeneity = 0.30) in studies not adjusted for BMI and 1.07 (95% CI: 1.01-1.13) (I^2 = 71%, P heterogeneity = 0.002) in studies adjusted for BMI (Figure 5.38).

There were no evidence of significant publication bias (P-values for Egger's test = 0.21 and 0.46, respectively). The findings did not change materially in influence analysis of BMI unadjusted studies, while the positive association became statistically non-significant when Kabat *et al.*[342] was omitted from other BMI adjusted studies (summary RR = 1.06, 95% CI: 0.99-1.13).

Meta-analyses by pre-defined subgroups in BMI unadjusted studies mostly showed statistically significant positive associations (Table 5.9, above). This included the ten studies of higher quality (summary RR per 10 cm = 1.12, 95% CI: 1.10-1.14)[213;229;250;256;312;342;349;361;364;365]. The associations were not significantly different among the subgroups (all P-values for meta-regression ≥0.30). The same was observed in the subgroup meta-analyses of BMI adjusted studies; with one exception that showed a significant increased risk among studies that measured waist circumference (1.12, 95% CI: 1.04-1.21) (4 studies[213;329;339;342]) (10,090 cases), and an average null association among studies that used measurements that were reported by the participants (1.02, 95% CI: 0.98-1.07) (3 studies[123;229;361]) (3,578 cases) (P for meta-regression = 0.04) (results not tabulated). This may explain part of the high proportion of heterogeneity observed between the BMI adjusted studies in the overall analysis (I^2 = 71%, P heterogeneity = 0.002).

Postmenopausal breast cancer risk was significantly increased among MHT never/former users (summary RR per 10 cm = 1.15, 95% CI: 1.10-1.21), although the analysis only included two studies[229;312]. The positive association among MHT never users was not statistically significant (summary RR = 1.10, 95% CI: 0.98-1.23) (8 studies[230;236;256;339]). The associations among MHT current and ever users were null (Figure 5.39).

There was no evidence of non-linear relationship (P for non-linearity = 0.38). The curve shows a linear increase in risk with increasing (BMI unadjusted) waist circumference (Figure 5.40). Restricted cubic spline analysis was not conducted for studies adjusted for BMI because of low numbers.

Overall, nine studies reported results by HR subtypes of breast cancer in postmenopausal women. Meta-analysis was not conducted because of the low number of studies within each specific subtype. The increase in risks associated with the highest versus the lowest waist circumference (unadjusted for BMI) were statistically significant for ER-positive[366] PR-positive[356;366], PR-negative[356] and ER+PR+[213;316;354] breast cancers. The associations were less clear for other breast cancer subtypes. Hence, there was some difference in associations across the breast cancer subtypes, although the 95% CIs of the RR estimates overlapped. Supporting the findings was one Australian study that only reported dose-response results (RRs per 10 cm = 1.24 (95% CI: 1.06-1.46) for ER-positive breast cancers and 0.79 (95% CI: 0.58-1.07) for ER-negative breast cancers) (P for heterogeneity = 0.008)[364]. When BMI was accounted for in the studies, the associations were weaker and statistically non-significant, with the exception of a strong increased risk of ER-positive breast cancers in one American study[273].

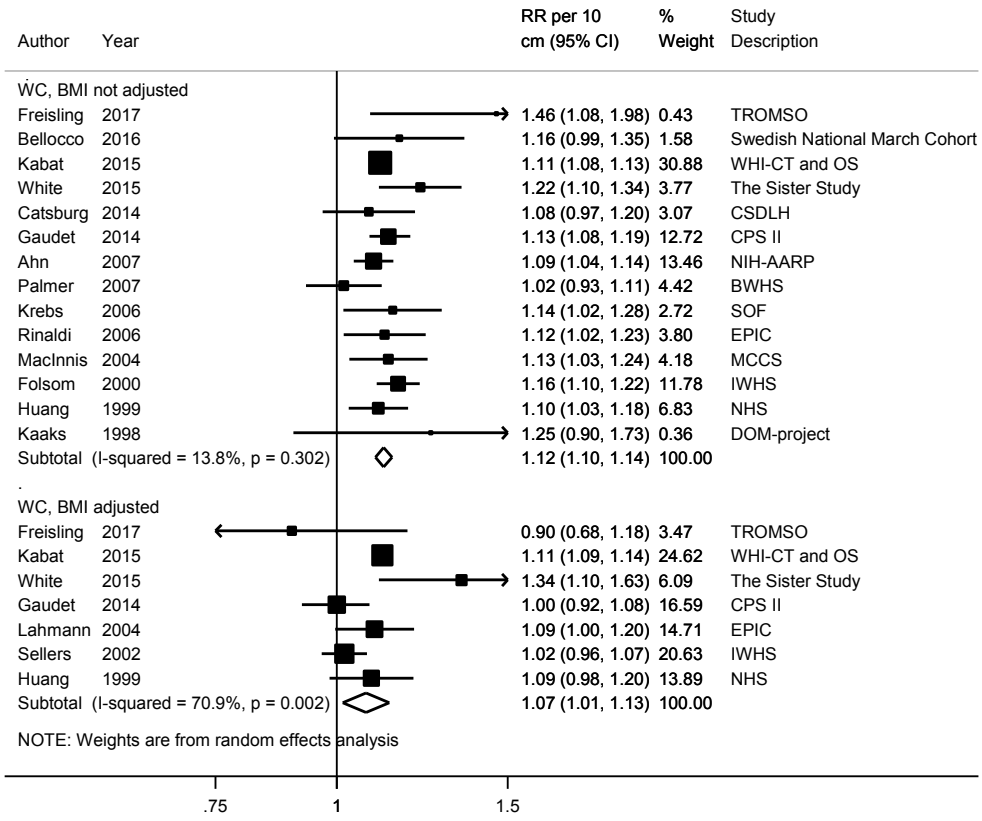


Figure 5.38 Relative risk and 95% CI of postmenopausal breast cancer for 10 cm increase of waist circumference

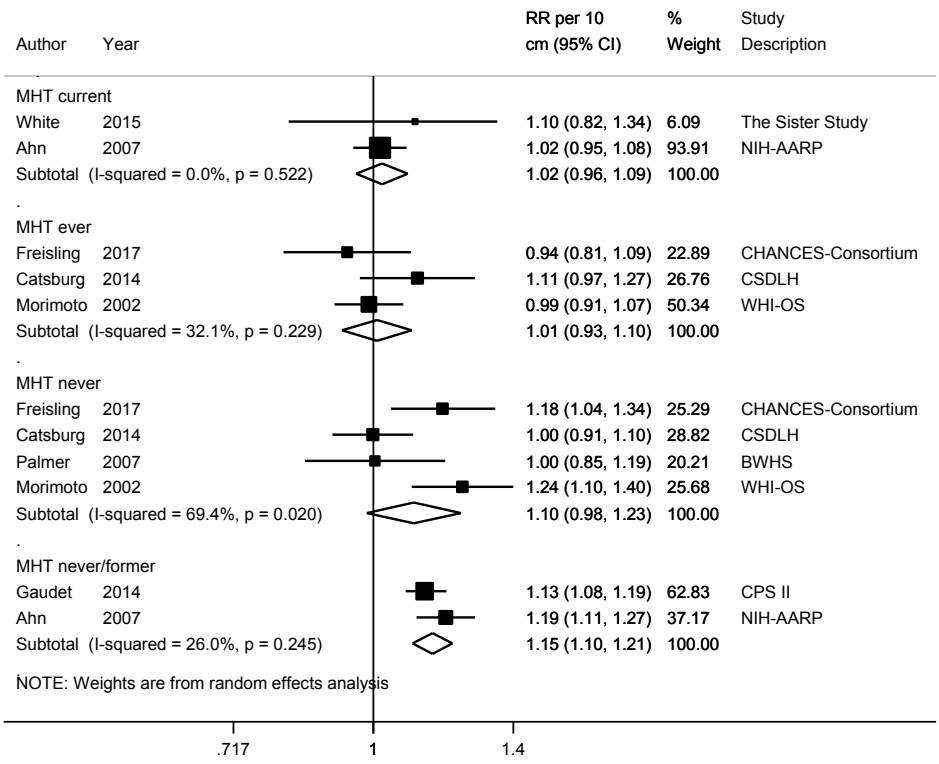


Figure 5.39 Relative risk and 95% CI of postmenopausal breast cancer for 10 cm increase of waist circumference, by postmenopausal hormone use

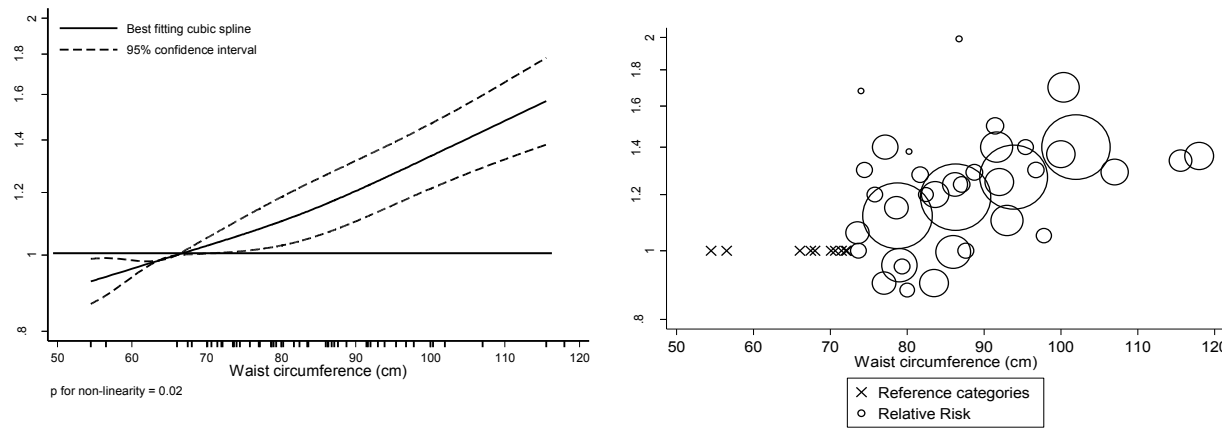


Figure 5.40 Non-linear analysis of waist circumference and postmenopausal breast cancer

5.3.4.11 Hip circumference

Four studies on premenopausal breast cancer (1,438 cases)[222;329;360;361] and seven studies on postmenopausal breast cancer (4,425 cases)[222;236;312;339;361;363;364] could be included in the dose-response meta-analyses, respectively. All studies reported BMI unadjusted results. Three studies each further reported BMI adjusted results (premenopausal breast cancer (1,291 cases)[329;360;361], postmenopausal breast cancer (2,309 cases)[329;339;361]), and were pooled in separate meta-analyses.

Hip circumference reflects the amount of body fat accumulated in the lower part of the body. It was moderately to strongly correlated with BMI (correlation coefficients = 0.42 in premenopausal women[362] and 0.31[363], 0.36[362] and 0.80[312] in postmenopausal women).

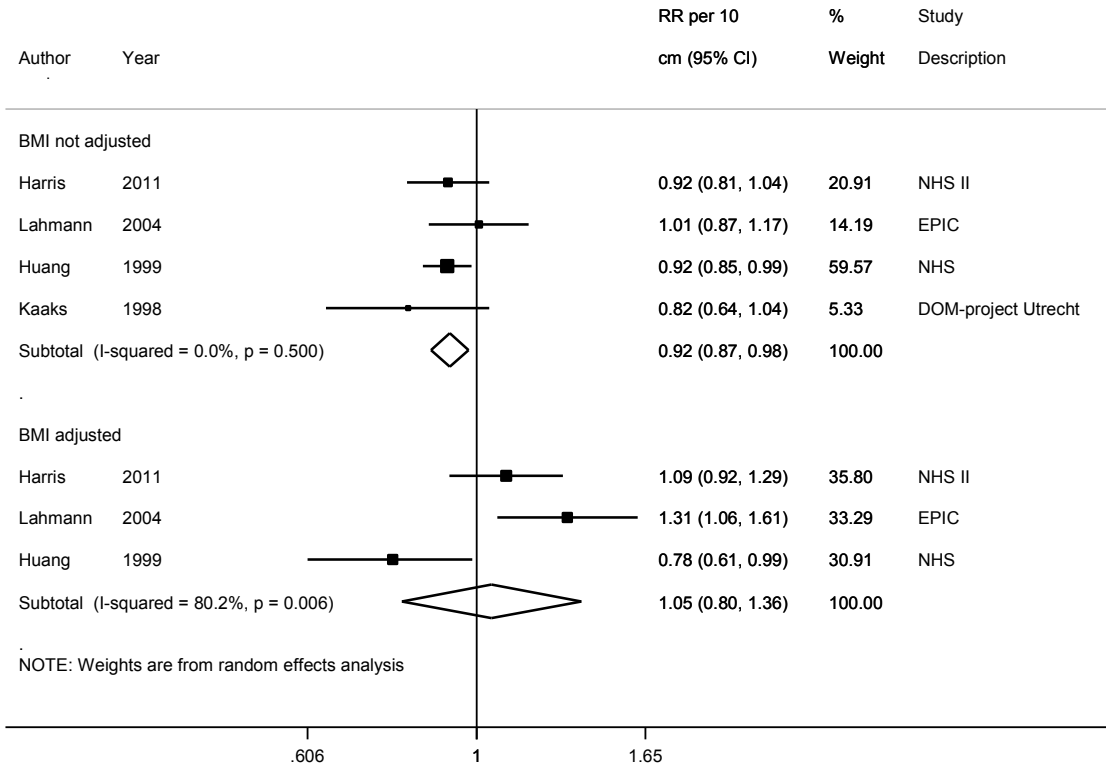
Hip circumference associated statistically significantly with breast cancer risk; specifically, inversely with premenopausal breast cancer risk (summary RR per 10 cm = 0.92, 95% CI: 0.87-0.98) (I^2 = 0%, P heterogeneity = 0.50) and positively with postmenopausal breast cancer risk (1.07, 95% CI: 1.04-1.11) (I^2 = 25%, P heterogeneity = 0.24) (Figure 5.41). The different in associations by menopausal status of the women is akin to those observed for BMI as reported above (see sections 5.3.4.6 and 5.3.4.7). Another similarity is the results by MHT use, in which positive associations were observed for MHT never users (1.32, 95% CI: 1.19-1.47) (2 studies[236;339]) and never/former users (1.13, 95% CI: 1.06-1.21) (1 study[312]); but not for MHT ever users (0.95, 95% CI: 0.87-1.04) (2 studies[236;339]), and current users (1.02, 95% CI: 0.96-1.10) (1 study[312]) (graph not shown).

The association was not as clear when BMI was accounted for in the studies, for which the summary RR estimates were 1.05 (95% CI: 0.80-1.36) and 1.12 (95% CI: 0.95-1.32) for pre- and postmenopausal breast cancer risk, respectively; and the associations were substantially different across the studies (I^2 = 80% and 62%; P heterogeneity = 0.006 and 0.075, respectively) (Figure 5.41).

In influence analysis, the association with premenopausal breast cancer risk became non-significant when Harris, 2011 and Huang, 1999 were omitted in turn. The association with postmenopausal breast cancer risk was robust, with the significant positive association persisted in the sensitivity, and subgroup meta-analyses (Table 5.10). This included lower (3 studies[222;339;363]) and higher quality studies[236;312;361;364]). There was evidence of significant publication bias in the postmenopausal breast cancer studies (P for Egger's test = 0.06), although the low number did not allow full investigation (Figure 5.42).

Restricted cubic spline analysis of BMI unadjusted studies showed a linear relationship between hip circumference and postmenopausal breast cancer risk (P for non-linearity = 0.89). The low number of studies precluded the evaluation of non-linearity for premenopausal breast cancer (Figure 5.43).

Premenopausal breast cancer



Postmenopausal breast cancer

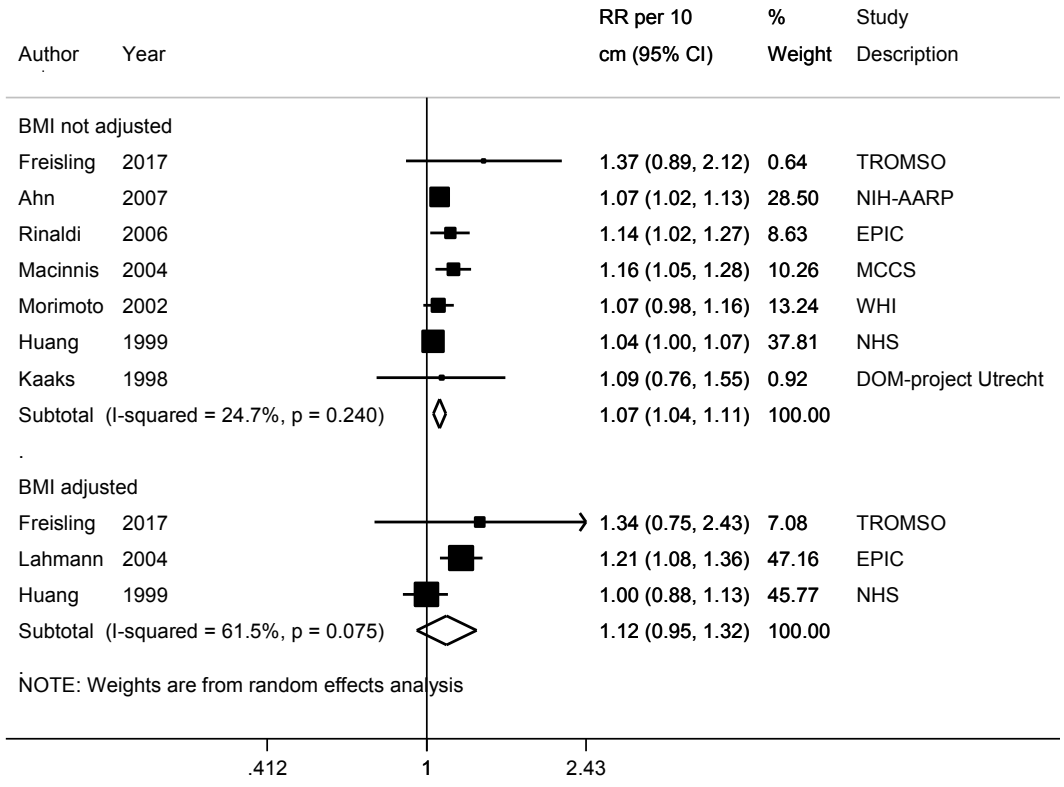


Figure 5.41 Relative risk and 95% CI of pre- and postmenopausal breast cancer for 10 cm increase of hip circumference

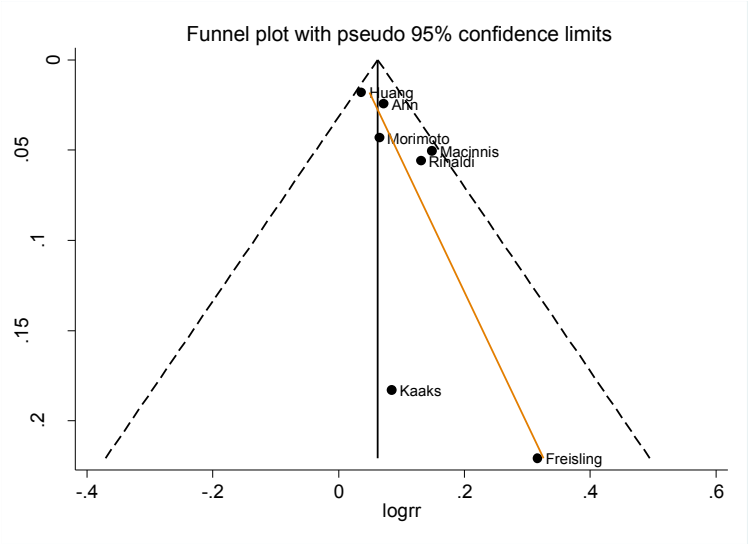


Figure 5.42 Funnel plot of studies included in the dose response meta-analysis of hip circumference and postmenopausal breast cancer

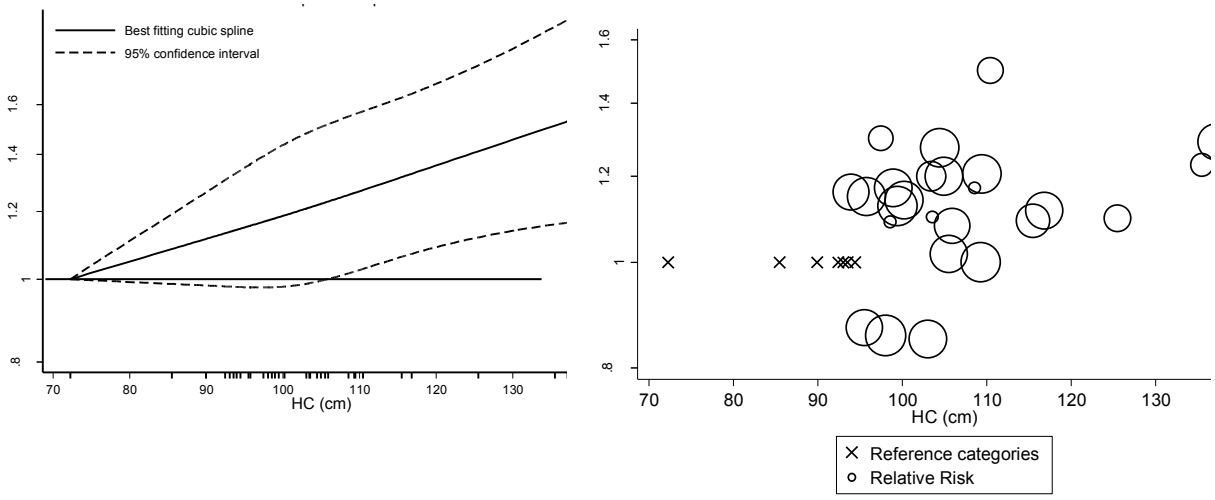


Figure 5.43 Non-linear analysis of hip circumference and postmenopausal breast cancer

Table 5.10 Summary of subgroup meta-analyses of hip circumference and postmenopausal breast cancer risk

	Premenopausal breast cancer				Postmenopausal breast cancer			
Per 10 cm	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	4 1,438	**0.92 (0.87-0.98)**	0 0.50	-	7 4,425	**1.07 (1.04-1.11)**	25% 0.24	-
Geographic location								
Asia	-	-	-	-	-	-	-	-
Australia and New Zealand	-	-	-	-	1 357	**1.16 (1.05-1.28)**	-	0.17
Europe	-	-	-	-	3 753	**1.15 (1.04-1.27)**	0% 0.69	
North America	-	-	-	-	3 3,315	**1.05 (1.02-1.08)**	0% 0.48	
Exposure assessment								
Measured	-	-	-	-	5 2,137	**1.12 (1.06-1.18)**	0% 0.61	0.12
Self-reported	-	-	-	-	2 2,288	**1.05 (1.02-1.09)**	25% 0.25	
Main confounding factors adjustment								
Adjusted	-	-	-	-	4 3,672	**1.07 (1.03-1.11)**	40% 0.17	0.26
Not adjusted	-	-	-	-	3 753	**1.15 (1.04-1.27)**	0% 0.69	
Study type								
Screening	-	-	-	-	1 76	1.09 (0.76-1.55)	-	-
Non-screening	-	-	-	-	6 4,349	**1.08 (1.04-1.12)**	37% 0.16	-
Length of follow-up								
<10 years	-	-	-	-	5 1,091	**1.08 (1.03-1.12)**	40% 0.16	0.99
≥10 years	-	-	-	-	2 3,334	1.10 (0.93-1.30)	20% 0.26	
Study quality								
Low	-	-	-	-	3 735	**1.15 (1.04-1.27)**	0% 0.69	0.26
High	-	-	-	-	4 3,672	**1.07 (1.03-1.11)**	40% 0.17	
Invasive breast cancer	-	-	-	-	4 2,288	**1.08 (1.01-1.15)**	49% 0.12	-

5.3.4.12 Waist-hip-ratio and premenopausal breast cancer risk

Ten studies on premenopausal breast cancer risk[213;221;222;230;256;318;329;360;361;367] (3,645 cases) could be included in the dose-response meta-analysis, using BMI unadjusted RR estimates that were reported in all studies.

To explore whether the risk associated with WHR was independent of BMI, seven studies further reporting BMI adjusted results were pooled in a separate meta-analysis[213;221;318;329;360;361;367] (2,523 cases), as reported below.

Waist-hip-ratio was weakly to moderately correlated with BMI in premenopausal women (correlation coefficients = 0.04[362] and 0.41[221]).

The association of waist-hip-ratio with premenopausal breast cancer risk was, as in for waist circumference (see section 5.3.4.9), different by whether studies were adjusted or not adjusted for BMI. Waist-hip-ratio was borderline significantly positively associated with premenopausal breast cancer risk when BMI was included in the models as covariate by the studies. The summary RR estimates per 0.1 unit were 1.14 (95% CI: 1.00-1.29) (I^2 = 55%, P heterogeneity = 0.04) in studies with BMI adjustment and 1.05 (95% CI: 0.98-1.13) (I^2 = 14%, P heterogeneity = 0.31) in studies without the adjustment (Figure 5.44).

There was evidence of significant publication bias with BMI adjusted studies (P for Egger's test = 0.03) and not with BMI unadjusted studies (P for Egger's test = 0.25). Asymmetry in the funnel plots was possibly driven by small studies that reported a stronger than the average positive association[221;367] (graph not shown). The summary RR estimates mostly remained non-significant in influence analyses, with the exception of excluding Catsburg *et al.*[256] from the BMI unadjusted studies and Lahmann *et al.*[329] from the BMI adjusted studies, for which the summary RR estimates were significant (summary RRs per 0.1 unit = 1.07 (95% CI: 1.01-1.15) and 1.17 (95% CI: 1.07-1.28), respectively). Subgroup meta-analyses of BMI unadjusted studies showed non-significant results across the subgroups (all P-values for meta-regression ≥0.34) (Table 5.11).

For BMI adjusted studies, significant positive associations were observed among North American studies (summary RR per 0.1 unit = 1.21, 95% CI: 1.06-1.38) (3 studies[221;360;361]) (926 cases), studies that used self-reported data (1.17, 95% CI: 1.02-1.34) (2 studies[360;361]) (817 cases) and studies not adjusted for the main confounding factors (1.64, 95% CI: 1.18-2.28); which were also studies of lower quality (1.64, 95% CI: 1.18-2.28) (2 studies[221;367]) (179 cases). Other subgroups showed non-significant positive associations (all P-values for meta-regression ≥ 0.07) (results not tabulated).

No statistically significant departure from linearity was detected in the restricted cubic spline analyses. The curve was flat when BMI unadjusted studies was analysed (P for non-linearity = 0.30). When BMI adjusted studies were used, a positive trend was evident, even though the CI was very wide (P for non-linearity = 0.81) (Figure 5.45).

Three studies reported results by HR-defined status of the tumour[213;354;360]. The findings were not very consistent; although one French study reported a statistically significant inverse association with ER+PR+ breast cancer[354] and one American study observed a statistically significant positive association with ER-negative breast cancers[360].

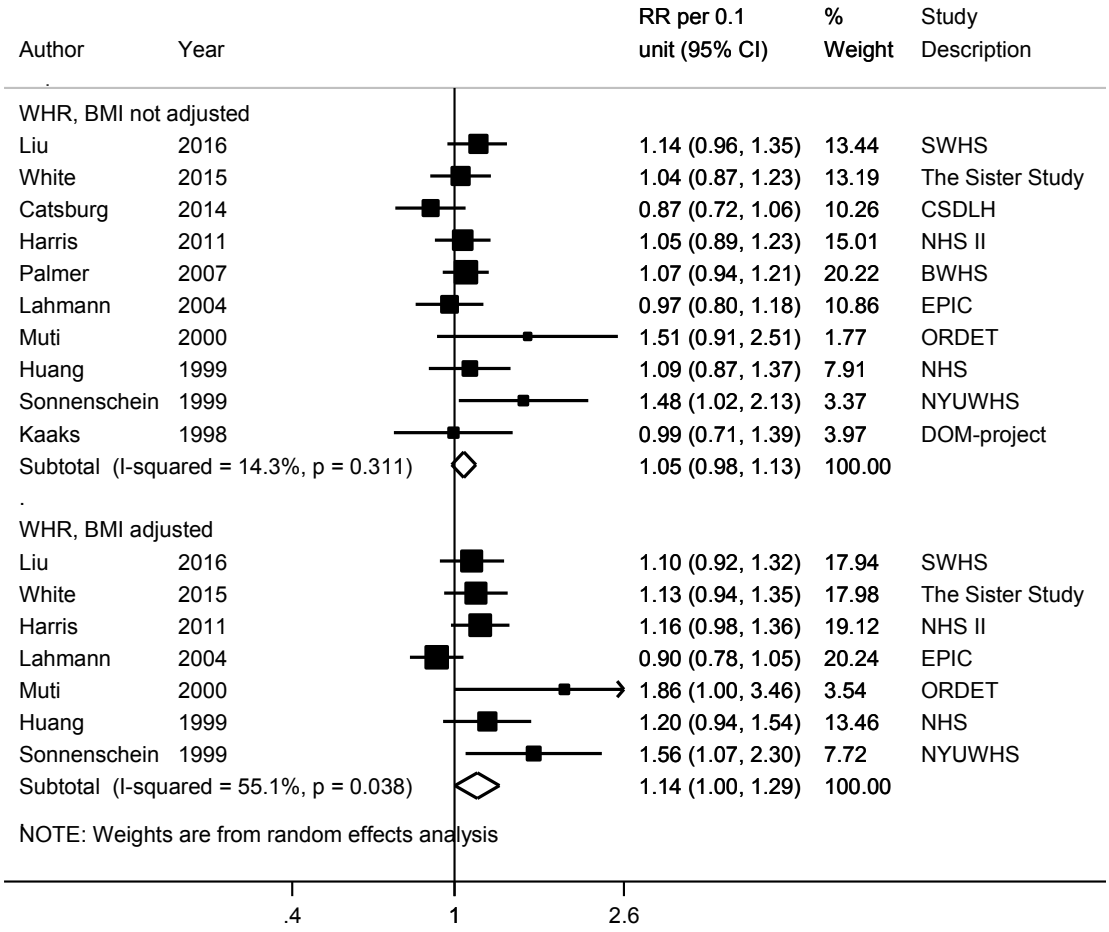
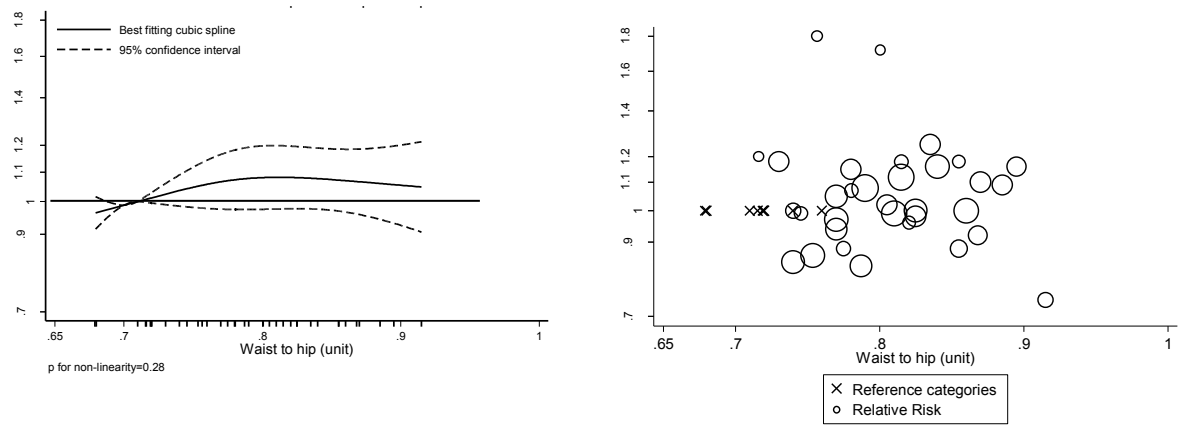


Figure 5.44 Relative risk and 95% CI and 95% CI of premenopausal breast cancer for 0.1 unit increase of waist-hip-ratio

BMI unadjusted studies



BMI adjusted studies

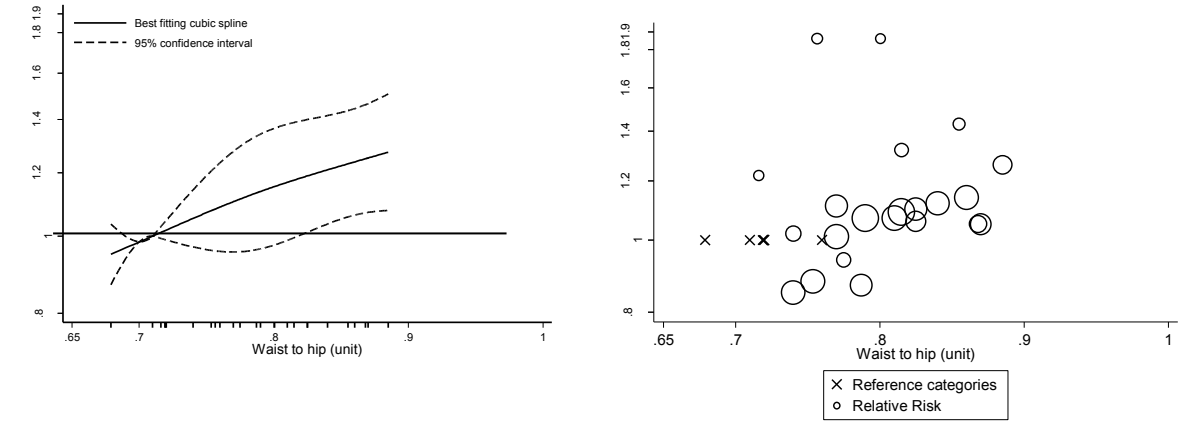


Figure 5.45 Non-linear analysis of waist-hip-ratio and premenopausal breast cancer

Table 5.11 Summary of subgroup meta-analyses of (BMI unadjusted) waist-hip-ratio and pre- and postmenopausal breast cancer

	Premenopausal breast cancer				Postmenopausal breast cancer			
Per 0.1 unit	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**	**N/n**	**RR (95% CI)**	**I^2 Phet**	**Pmet**
Overall	10 3,645	1.05 (0.98-1.13)	14% 0.31	-	20 16,775	**1.11 (1.06-1.17)**	57% 0.001	-
Geographic location								
Asia	1 640	1.15 (0.96-1.35)	-	0.86	1 522	**1.21 (1.02-1.44)**	-	0.48
Australia	0	-	-	-	1 357	1.10 (0.94-1.29)	-	
Europe	3 691	1.04 (0.85-1.26)	21% 0.28	-	9 2,317	1.11 (0.93-1.32)	66% 0.003	
North America	5 1,901	1.05 (0.94-1.18)	41% 0.15	-	7 11,997	**1.11 (1.08-1.14)**	0% 0.52	
United States and Puerto Rico	1 413	1.04 (0.87-1.23)	-		1 1,582	**1.22 (1.10-1.34)**	-	
Exposure assessment								
Measured	6 1,853	1.09 (0.98-1.22)	24% 0.26	0.45	14 11,246	**1.13 (1.04-1.23)**	66% <0.001	0.75
Self-reported	4 1,792	1.03 (0.94-1.12)	7% 0.36	-	6 5,529	**1.11 (1.05-1.16)**	22% 0.27	
Main confounding factors adjustment								
Adjusted	6 2,890	1.03 (0.96-1.11)	0% 0.44	0.34	12 15,866	**1.11 (1.05-1.16)**	64% 0.001	0.56
Not adjusted	4 755	1.16 (0.97-1.38)	34% 0.21	-	8 909	1.18 (0.99-1.42)	47% 0.07	
Study type								
Screening	2 256	1.20 (0.82-1.77)	59% 0.12	0.38	2 226	1.49 (0.89-2.50)	64% 0.097	0.18
Non-screening	8 3,389	1.04 (0.98-1.11)	1% 0.43		18 16,549	**1.10 (1.05-1.16)**	57% 0.002	
Length of follow-up								
<10 years	6 1,410	1.08 (0.96-1.21)	17% 0.30	0.78	10 6,417	1.10 (1.00-1.20)	72% <0.001	0.53
≥10 years	4 2,235	1.04 (0.94-1.15)	31% 0.23	-	10 10,358	**1.13 (1.07-1.18)**	22% 0.24	
Study quality								
Low	4 755	1.16 (0.97-1.38)	34% 0.21	0.34	9 1,542	1.12 (0.94-1.33)	67% 0.002	0.19
High	6 2,890	1.03 (0.96-1.11)	0% 0.44	-	11 15,233	**1.13 (1.09-1.16)**	20% 0.25	
Invasive breast cancer	6 2,320	1.01 (0.93-1.10)	6% 0.38	-	12 12,069	**1.13 (1.07-1.19)**	29% 0.16	-

5.3.4.13 Waist-hip-ratio and postmenopausal breast cancer risk

Twenty studies[213;221;222;230;256;312;318;339;342;349;361;362;364;365;367-369] (16,775 cases) on postmenopausal breast cancer risk could be included in the dose-response meta-analysis, using BMI unadjusted RR estimates that were reported in all, but one study[329].

When these studies were pooled (1 BMI adjusted study[329] and 14 non-overlapping BMI unadjusted studies[213;221;222;230;256;312;318;339;342;349;361;364;365;367]), the summary RR was 1.12 (95% CI: 1.07-1.18) (I^2 = 51%, P heterogeneity = 0.01) for each 0.1 unit increase of waist-to-hip ratio. Eight studies[123;213;221;318;339;361;367;369] (6,277 cases) further reported results adjusted for BMI. To explore whether the risk associated with waist-hip-ratio was independent of BMI, separate meta-analyses restricted to BMI unadjusted and BMI adjusted studies were conducted, as reported below.

As in premenopausal women, waist-to-hip ratio was only weakly to moderately correlated with BMI in postmenopausal women (correlation coefficients = 0.04[362], 0.38[221] and 0.42[363]).

The summary RRs per 0.1 unit of waist-to-hip ratio were 1.11 (95% CI: 1.06-1.17) (I^2 = 57%, P heterogeneity = 0.001) for BMI unadjusted studies and 1.05 (95% CI: 0.98-1.13) (I^2 = 46%, P heterogeneity = 0.07) for BMI adjusted studies (Figure 5.46). No significant publication bias was detected (P-values for Egger's test = 0.56 and 0.46, respectively). The summary RR estimate remained materially unchanged when each BMI unadjusted study was omitted in turn in influence analysis. For BMI adjusted studies, the association became statistically significant when Lahmann *et al.*[369] was omitted (summary RR per 0.1 unit = 1.08, 95% CI: 1.01-1.15).

Subgroup meta-analyses of BMI unadjusted studies showed positive associations that were not always statistically significant, but the associations were similar between the subgroups (all P-values for meta-regression ≥0.18). This included the higher quality studies (summary RR per 0.1 unit = 1.13, 95% CI; 1.09-1.16) (11 studies[213;256;312;318;342;349;361;362;364;365;369]) (15,233 cases), as well as the lower quality studies (1.12, 95% CI: 0.94-1.33) (9 studies[221;222;230;339;367;368]) (1,542 cases) (P for meta-regression = 0.19) (Table 5.11, above).

Associations by MHT use were also not significantly different (P for meta-regression = 0.06); although there was a tendency of positive associations among MHT never users (summary RR per 0.1 unit = 1.12, 95% CI: 0.98-1.27) (7 studies[230;236;339]) (660 cases) and MHT never/former users (1.25, 95% CI: 1.13-1.38) (1 study[312]) (618 cases), and null associations among MHT current users (0.97, 95% CI: 0.88-1.07) (2 studies[213;312]) (1,071 cases) and MHT ever users (0.98, 95% CI: 0.86-1.11) (6 studies[236;339]) (875 cases) (Figure 5.47). The proportion of MHT users in the studies may explain part of the heterogeneity observed between the BMI unadjusted studies (I^2 = 57%, P heterogeneity = 0.001).

Null associations were observed across the subgroups of BMI adjusted studies, apart from the strong positive association (1.17, 95% CI: 1.07-1.27) that was reported in one United States and Puerto Rico study (the Sister Study)[213] (results not tabulated).

Restricted cubic spline analysis of BMI unadjusted studies showed a more or less gradual increase in risk of postmenopausal breast cancer with increasing waist-to-hip ratio (P for non-linearity = 0.06). The J-shaped curve was more pronounced with BMI adjusted studies, but the CI was very wide (P for non-linearity = 0.15) (Figure 5.48).

Five studies (6 publications) reported results by HR status of the tumour. Meta-analysis was not conducted. No clear difference in associations were observed, although strong positive associations, one of BMI unadjusted waist-to-hip ratio (RR for highest vs lowest level = 1.43, 95% CI: 1.15-1.79)[213] and another of BMI adjusted waist-to-hip ratio (1.33, 95% CI: 1.05-1.70)[370] were reported with ER+PR+ breast cancer and not with other HR-defined breast cancers [123;273;354;370]. One additional study that only reported dose-response results found a non-significant positive association for ER-positive breast cancers (RR per 0.1 unit = 1.19, 95% CI: 0.88-1.61) and an inverse association for ER-negative breast cancers (0.69, 95% CI: 0.41-1.16) (P heterogeneity = 0.07)[364].

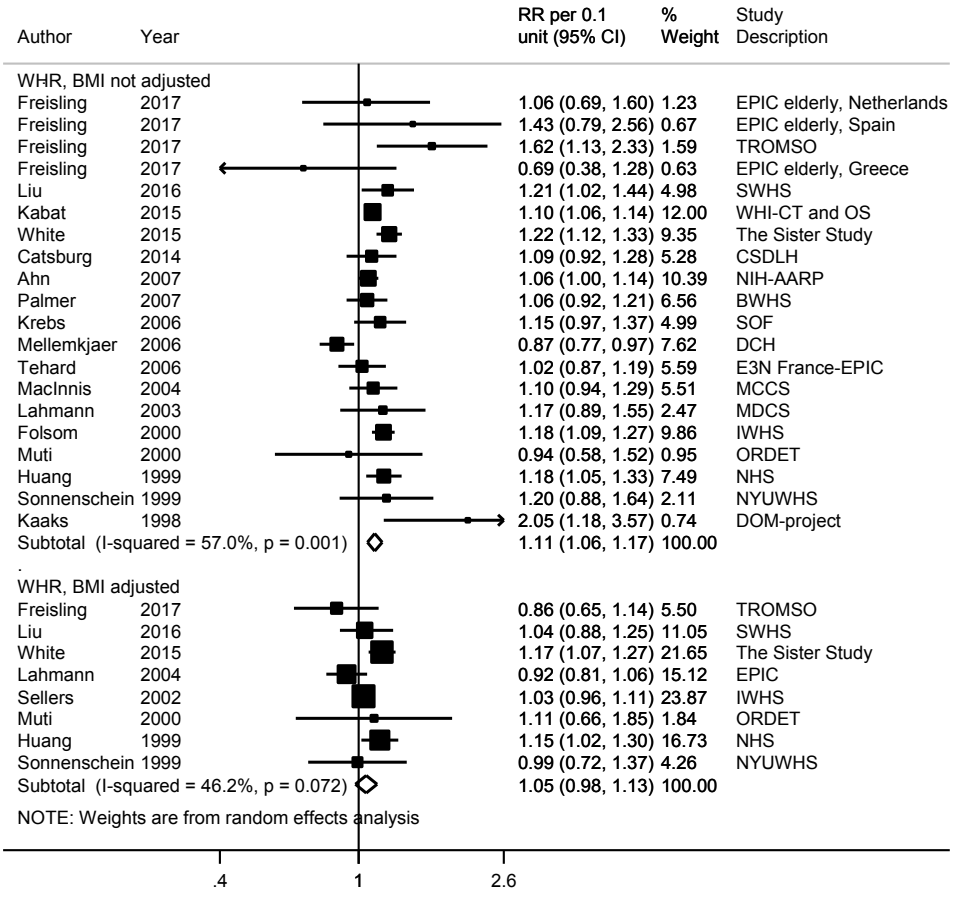


Figure 5.46 Relative risk and 95% CI of postmenopausal breast cancer for 0.1 unit increase of waist-hip-ratio

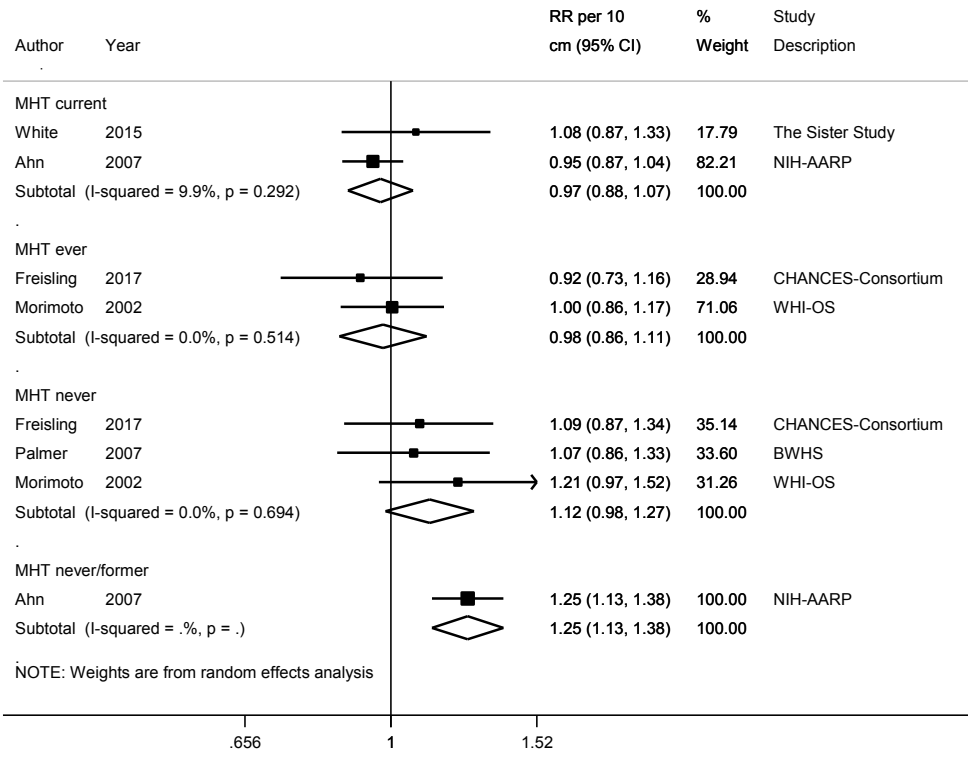
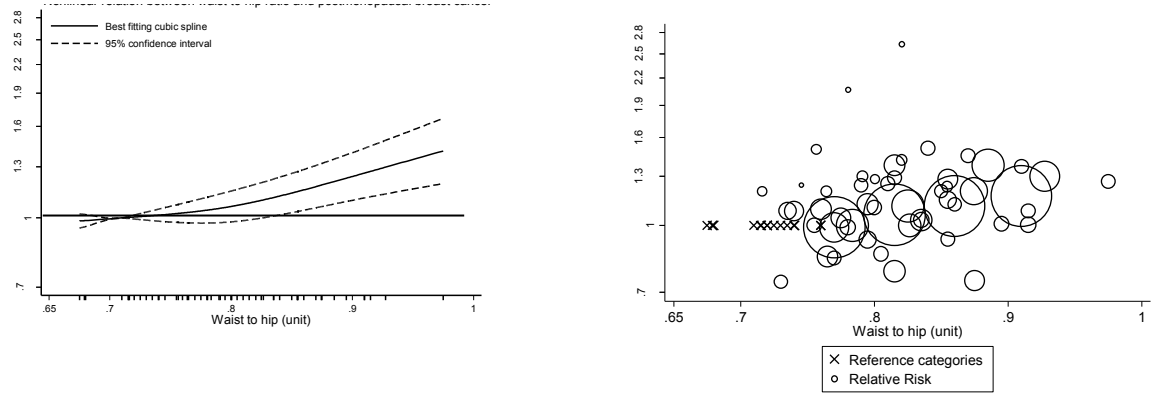


Figure 5.47 Relative risk and 95% CI of postmenopausal breast cancer for 0.1 unit increase of waist-hip-ratio, by postmenopausal hormone use

BMI unadjusted studies



BMI adjusted studies

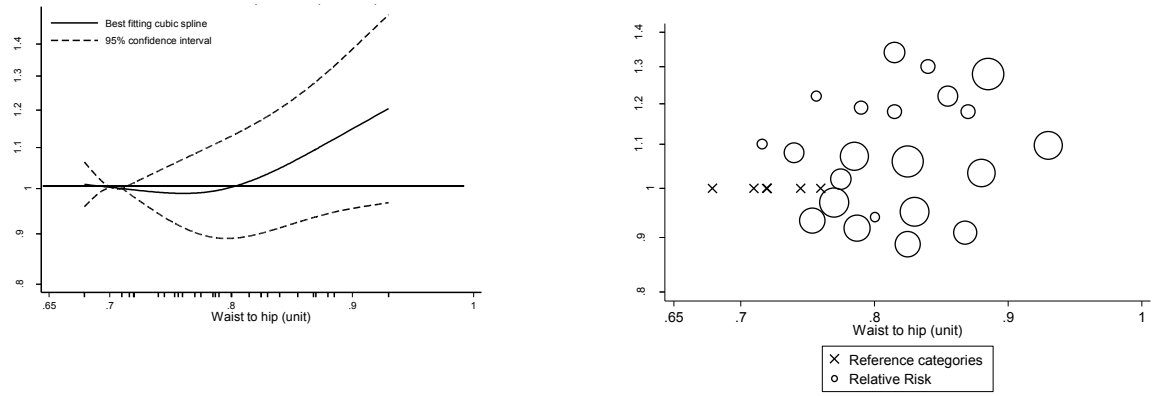


Figure 5.48 Non-linear analysis of waist-hip-ratio and postmenopausal breast cancer

5.4 Summary of the meta-analyses

To summarise, premenopausal breast cancer risk was statistically significantly inversely associated with higher levels of vigorous physical activity, BMI at early age and adulthood that indicates total body fatness, and hip circumference that indicates gluteofemoral fatness. The risk increased with abdominal fatness, indicated by waist circumference and waist-hip-ratio, when total body fatness was accounted for.

Similarly but more consistently, breast cancer risk in women after menopause decreased with higher levels of physical activity, particularly recreational and vigorous physical activities. Higher BMI at early age also statistically significantly inversely associated with postmenopausal breast cancer risk; while higher body fatness, manifested from chronic positive energy balance, as indicated by higher BMI, waist circumference, hip circumference, waist-to-hip ratio, and adult weight gain consistently increased the risk.

Evidence also suggested that longer sitting time, which indicates sedentary behaviour, associated positively with postmenopausal breast cancer risk. Adult weight loss was inversely associated with pre- and postmenopausal breast cancer risk, but the findings were not robust. Total energy intake was not associated with the risk of pre- and postmenopausal breast cancer, possibly because of measurement error and generally being a poorer indicator of energy balance.

5.5 Grading of the evidence

To ascertain whether causality can be inferred confidently in the observed associations, the robustness and quality of the evidence was considered in details and the strength of the evidence was graded according to the WCRF grading criteria (see section 4.1.6), as reported below.

Number and size of studies

There were a large number of cohort studies or cohort studies that were originally a RCT (127 publications). All meta-analyses had at least three studies, with at least 900 breast cancer cases in total; apart from the meta-analyses of walking, and sitting and premenopausal breast cancer risk.

Dose-response relationship

With the accumulated findings, it was possible to conduct meta-analysis to evaluate the relationships between energy balance-related factors and pre- and postmenopausal breast cancer risk in a dose-response manner, except for the associations of occupational physical activity and walking with both pre- and postmenopausal breast cancers, and between sitting and adult weight loss and premenopausal breast cancer; for which only results for the highest versus the lowest levels could be pooled.

For postmenopausal breast cancer, statistically significant dose-response relationships were observed for most factors investigated, except total energy intake, total physical activity, vigorous physical

activity and weight loss. For premenopausal breast cancer, the relationships with energy balance-related factors were less clear, with statistically significant results only observed for BMI at early age and adulthood, waist circumference (in BMI adjusted studies) and hip circumference.

The associations were modest. The summary RR estimates ranged from 0.81 to 1.17, with narrow 95% CIs. The results became non-significant in influence analyses of recreational physical activity and sitting and postmenopausal breast cancer, and hip circumference and premenopausal breast cancer.

Heterogeneity

Statistically significant between-study heterogeneity was detected, and partially explained, in several primary meta-analyses. These included the analyses of occupational physical activity and premenopausal breast cancer; BMI at early ages and adulthood and pre- and postmenopausal breast cancer; weight gain and pre- and postmenopausal breast cancer; and waist-to-hip ratio and postmenopausal breast cancer.

Exploration of potential sources of heterogeneity was not possible in the dose-response meta-analysis of recreational physical activity and premenopausal breast cancer, and in the subgroup meta-analyses because of low numbers of studies.

Publication bias

Evidence of significant publication bias was detected for recreational and occupational physical activities and postmenopausal breast cancer; adult weight gain and postmenopausal breast cancer; BMI and pre- and postmenopausal breast cancer; waist circumference and premenopausal breast cancer; hip circumference and postmenopausal breast cancer.

Asymmetry in the funnel plots show that certain small studies/studies of lower precision reported a stronger than the average association for recreational physical activity (inverse) and adult weight gain (positive) and postmenopausal breast cancer. Since these studies were of lower quality, the findings were mainly supported by higher quality studies of a larger size. In addition, for adult weight gain and postmenopausal breast cancer risk, Asian women may incur a greater risk with greater adult weight gain, which added to the asymmetry in the funnel plot. For BMI and pre- and postmenopausal breast cancer, asymmetries were driven by one particularly large study[325]. For waist circumference and premenopausal breast cancer, all studies reported results observed a null association; therefore, publication bias was unlikely.

Potential publication bias could not be tested in the studies on total energy intake and premenopausal breast cancer; and total physical activity and pre- and postmenopausal breast cancer because of the low numbers. For the same reason, possible explanations to the asymmetry observed in the funnel plot of hip circumference and postmenopausal breast cancer could not be fully explored.

Study quality

Overall, the findings were supported by studies of higher quality, in which the significant results persisted in the subgroup meta-analyses. The few exceptions were for occupational physical activity and postmenopausal breast cancer risk, and adult weight loss and pre- and postmenopausal breast cancer risk. There were caveats with regard to particular aspects of study quality, as illustrated below.

Generalisation of study population and selection bias

The studies, mostly from Europe and North America, involve mostly Caucasian participants, it may not be suitable to generalise to populations with different cultural or sociodemographic backgrounds.

Majority of the studies comprised the general populations, apart from the few studies of *BRCA1/2* mutation carriers[211], family members of women with breast cancer[212;213], breast cancer prevention trial (NSABP P-1) participants[224] and type 2 diabetics[345].

The familial cancer studies[212] and the breast cancer prevention trial[224] observed a positive instead of an inverse association between BMI and premenopausal breast cancer risk, suggesting premenopausal women in these studies may be different. Overall, these studies had little influence in the findings.

Selection bias, in particular for the prospective cohort studies, is unlikely. Healthy cohort effect was possible but there was no indication that the associations were different between studies that involved a screening programme (women attending the programme were possibly healthier) and non-screening studies.

Exposure assessment/measurement error

Energy balance-related factors were assessed before breast cancer diagnosis in the cohort studies, therefore was not subjected to report bias as in the case-control studies.

The null association between total energy intake and breast cancer risk could relate to the insufficiency of FFQ to quantify absolute energy intake in the participants[371]. In addition, the estimated intake is subjected to strong systematic biases[372]. Overweight and obese women and younger postmenopausal women have been found to underestimate energy intake in greater extent than normal weight women and older postmenopausal women[372;373] . The WHI study reported supporting findings in a publication that could not be included in the current meta-analysis, that biomarker calibrated energy intake significantly positively associated with postmenopausal breast cancer risk[374]. The association was attenuated after BMI adjustment, suggesting the effect was not above and beyond that of BMI, or that BMI may a better indicator of chronic excess in energy intake.

Different types of physical activity, such as lighter and household activities were often not (fully) captured in the questionnaires, thereby hindering the ability of the studies to assess total physical activity. Occupational physical activity assessment was mostly based on indictors such as nature of

the job and the actual physical level was not assessed. Many studies did not collect information regarding the frequency, duration and intensity of physical activity. Further, the assessment of intensity was mostly done by prompting participants using examples and absolute values were not measured; and only one MET score was associated to a particular activity, without accounting for the age and fitness level of the participants. Such measurement errors from self-report data could have biased the association between physical activity and breast cancer risk towards null[375]. Over-reporting because of social desirability and differential reporting by weight status (overweight or obese women may over-estimate their physical activity[376] could have caused a downward bias to the association. On the other hand, it was possible that study participants remembered recreational and vigorous physical activity better, as such activities are often more structured and memorable[377], leading to detecting an association if there is one[378;379]. Nevertheless, in the present meta-analyses, there was no significant difference in findings between studies that used validated and non-validated questionnaires to assess physical activity. Further evaluation of any potential bias could not be tested, as no studies used objective methods, such as accelerometer or actigraph to assess physical activity[380].

It was possible that self-reporting of past weight is not reliable, and may be biased by current weight status (overweight and obese women could under-report their weight and over-report their height[381]). For baseline BMI, such a report bias would lead to a weaker inverse association with premenopausal breast cancer risk and a weaker positive association with postmenopausal breast cancer risk. However, good correlations between self-reported and measured data have been reported[382]. Moreover, results in the subgroup meta-analyses by studies that used self-reported or measured anthropometric data were mostly similar, suggesting no relevant impact of report bias in the associations. The inverse associations observed between early adult BMI and pre- and postmenopausal breast cancer risk are also unlikely affected by report bias. First, previous studies have shown good correlations between self-reported weight at age 18 years and college physical examination records[383]. Second, NHS and NHS II validated the measurement of young adulthood body weight, and reported inverse associations not dissimilar to other studies included in the meta-analyses[336;384]. As for the non-significant positive association with premenopausal breast cancer risk and the inverse association with postmenopausal breast cancer risk reported in the only study that measured the height and weight of students at college entry, such findings could be influence by the small numbers of cases (30 and 69 cases, respectively)[226].

As most studies measured the energy balance-related factors only once at study baseline and changes were not accounted for throughout the follow-up. Possible regression dilution effect would bias the association towards null[385].

Confounding

Most studies adjusted for main confounding factors such as age, reproductive factors, MHT use and alcohol intake. As lifestyle factors are closely correlated, residual or unmeasured confounding was possible. Nevertheless, in the present meta-analyses, studies with and without such adjustments on average did not find significantly different results; with one exception, for occupational physical activity and postmenopausal breast cancer risk, only two (out of nine) studies were adjusted and found a null association when pooled.

Participants attended cancer/mammography screening programmes may have healthier lifestyles or better access to medical facilities[386], while obese women may be of lower SES[387] and less likely to attend mammography screening or seek medical help[388]. Such a selection bias would cause a downward bias to the association of BMI and postmenopausal breast cancer risk. On the other hand, an overestimation of the association was possible; due to detection bias by weight status or breast density (overweight or obese women have less dense breasts, which allow more accurate detection of the cancer on a mammogram than leaner women with denser breasts) (see section 3.1.1, breast density). In the present meta-analyses, cancer/mammography screening studies and other non-screening studies on average found similar summary RRs, suggesting little influence from these biases.

Reverse causation

Reverse causation bias from women with occult cancers was possible. This may affect the evaluation of (recent) occupational physical activity and weight change because people with an undiagnosed cancer may be off sick/not work or loss weight unintentionally. However, some studies evaluated the issue by excluding cases from early years of follow-up and found no appreciably changed of results[217;218;227;232;234;238;243;248;262;265;266;268;292;301-304;306;311;312;326;327;329;345;348;356;357;364].

The EPIC study reported that the RR estimate for weight loss and premenopausal breast cancer risk approached unity after excluding breast cancer cases diagnosed during the first year of follow-up, while RR estimates in the weight gain categories were not materially changed[309].

Follow-up

Most studies had record linkages to national cancer incidence and mortality databases or active follow-up with medical confirmation. Detection bias is unlikely because of the largely complete data on case ascertainment. Many studies did not report on loss to follow-up, nevertheless no important losses to follow-up were identified and studies were not likely to be affected by differential follow-up.

Studies of relatively short follow-up may not have sufficient time to attained large number of women with breast cancer; in addition these studies may be under stronger influence by reverse causation. Nevertheless, studies <10 and ≥10 years follow-up mostly found similar results in the present meta-analyses.

Outcome definitions

Misclassification of breast cancer by menopausal status was possible in the studies, especially when age of diagnosis or menopausal status at study baseline was used as a proxy for menopausal status at diagnosis. However, it is unlikely the reason for the positive associations observed between BMI and premenopausal breast cancer risk in the Asian studies. The study that pooled data from eight Japanese cohorts used both baseline and menopausal status at diagnosis to classify the cancer and found positive associations in both analyses[326].

Not all studies separated *in situ* from invasive breast cancer. More *in situ* breast cancer cases are detected through mammography screening, which attendants may have better SES and healthier lifestyle. Analyses restricted to invasive breast cancer showed similar results to the original analyses.

Biological mechanisms

As described in section 3.1.3.1, physical activity may operate through biological pathways both related to and independent of energy balance and adiposity. Plausible obesity-induced mechanisms include changes in menstrual characteristics, reduction of lifetime exposure to circulating sex hormones, enhanced sensitivity to insulin, reduced hyperinsulinaemia and risk for diabetes, and decreased chronic inflammation and reduced inflammatory cytokines in adipose tissue; whereas other hypothesized mechanisms include changes in breast morphology, and improved immune response and antioxidative defense[154;389;390]. Strenuous physical activity before menarche is believed to delay the onset of menstruation and to increase the number of anovulatory cycles, thereby reducing lifetime exposure to circulating sex-hormones[391]; giving support to the observed inverse association between vigorous physical activity and premenopausal breast cancer risk.

The biological mechanisms that influence the inverse associations of early adult BMI and pre- and postmenopausal breast cancer, and BMI with premenopausal breast cancer risk were not entirely clear. Early complete differentiation of the breast[297], and slower physical maturation of breast tissue in obese adolescence that allows more time to repair damaged DNA and render the breast less susceptible to carcinogenic stimuli may be the reasons of the lifelong protective effect of early adiposity[389;392;393]. Disrupted menstrual cycles, in that anovulation reduces oestrogen and progesterone exposures and subsequent mammary cell mitosis in obese young women may also explain the association[394], although inverse associations have been observed in women with and without such menstrual characteristics[336], and in the study that accounted for menstrual characteristics and infertility[299].

Positive associations between excess adiposity, and weight gain and postmenopausal breast cancer risk are influenced by the abovementioned obesity-related biological pathways[17;135]. Specifically for visceral fat, it is linked to hyperinsulinemia and type II diabetes, which are risk factors of breast cancer. Visceral fat releases IGF, inflammatory markers, free fatty acids, locally produced oestrogen,

and adipokines, which are circulated to the breasts[229]. The different associations of abdominal adiposity with breast cancer risk in pre- and postmenopausal women may be explained by the different biological pathways at play in these women. In premenopausal women, abdominal obesity is not associated with elevated oestradiol levels[395], suggesting any effect may be driven through other pathways, such as the insulin-IGF-axis, and explains the increased risk after accounting for total adiposity. In postmenopausal women, abdominal obesity is closely related to general obesity and visceral fat that produce oestrogens[38].

Elevated (local and systemic) oestrogen levels, resulted from increased aromatase expression in the adipose tissue and reduced circulating SHBG, induce PR expression and stimulation of ER+PR+ breast cancer.

Therefore, the findings fulfilled the criteria of temporal relationship, dose-response relationship, consistency, and plausible biological mechanism for establishing causality.

5.6 Judging the evidence

Taken together, the judgements were that there was convincing evidence that the following associations on the risk of breast cancer development are likely causal (Table 5.12):

- Body fatness (BMI, waist and hip circumferences and waist-hip ratio) and adult weight gain increases the risk of postmenopausal breast cancer

The evidence was probable that:

- Physical activity, particularly of vigorous intensity decreases the risk of postmenopausal breast cancer
- Vigorous intensity decreases the risk of premenopausal breast cancer
- Body fatness decreases the risk of premenopausal breast cancer
- Early adult BMI decreases the risk of pre- and postmenopausal breast cancer

There is limited/suggestive evidence that:

- Physical activity decreases the risk of premenopausal breast cancer

No conclusion could be drawn on:

- Other associations, including adult weight gain and premenopausal breast cancer risk

These judgements were consistent to those made in the WCRF/AICR Second Expert Report[7] (see section 3.2.1).

Table 5.12 Summary of judgements on energy balance-related factors and risk of breast cancer development

Premenopausal breast cancer		
	Decreases risk	**Increases risk**
Convincing		
Probable	Early adult adiposity, body fatness (total adiposity*), vigorous physical activity	
Limited – suggestive	Physical activity	
Limited – no conclusion	Total energy intake, sitting, adult weight gain, adult weight loss	
Substantial effect on risk unlikely	None identified	
Postmenopausal breast cancer		
	Decreases risk	**Increases risk**
Convincing		Adult weight gain, body fatness (total adiposity, abdominal fatness, gluteofemoral fatness)
Probable	Early adult adiposity, physical activity, vigorous physical activity	
Limited – suggestive		
Limited – no conclusion	Total energy intake, sitting, adult weight loss	
Substantial effect on risk unlikely	None identified	

***** Further research is needed to elucidate the associations between abdominal fatness and gluteal fatness

6 Systematic reviews of energy balance-related factors and risk of mortality after breast cancer

6.1 Results of the literature search

Figure 6.1 shows the flowchart of the literature search.

Among the 149 potentially relevant publications identified on energy balance-related factors and risk of mortality after breast cancer, 14 publications were excluded because they were either superseded by more recent publications of the same studies or overlapped with other studies included in the meta-analyses. Fifty-five publications were not in any meta-analyses because the information presented in the publications did not allow their inclusion (n = 18), did not have a measure of association (n = 16), reported only unadjusted results (n = 7), were on associations that were examined by ≤3 studies in total (n = 13), or was a pooled analysis (n = 1). Overall, 80 publications were meta-analysed.

Appendix 4 is the list of the publications identified, included in and excluded from each specific meta-analysis, along with the main study characteristics and findings and the exclusion reason for the studies not included in the meta-analysis. Appendix 5 shows the main characteristics of the studies included in the meta-analyses.

6.2 Characteristics of the studies

Studies were follow-up of women with breast cancer identified in prospective cohort studies (women cancer-free at recruitment), or cohorts of breast cancer survivors whose participants were identified in hospitals or through cancer registries, or follow-up of breast cancer patients enrolled in case-control studies or RCTs. Most of the studies were based in North America or Europe. A small number of studies were from Australia, Asian and Tunisia, or were international.

Studies could include premenopausal women only or postmenopausal women only, but most studies included both. Menopausal status was usually determined at time of diagnosis. Patient tumour characteristics and stage of disease at diagnosis varied across studies, but most studies included women with early stage breast cancers. Some studies included breast cancer *in situ*. Not all studies provided clinical information on the tumour, treatment types and co-morbidities of the patients. Compliance, treatment effect and possible changes of regimen were not reported by majority of the studies. Some but not all clinical factors, such as tumour stage, tumour size, ER-status of the tumour, nodal status, treatment and comorbidities were adjusted for in the studies.

Study size ranged from 96[396] to 24 698 patients[397]. Total number of deaths ranged from 26[398] to 7397[399]. The proportion of breast cancer deaths ranged from 22%[400] to 98%[401] when reported. Most studies had on average ≥5 years of follow-up.

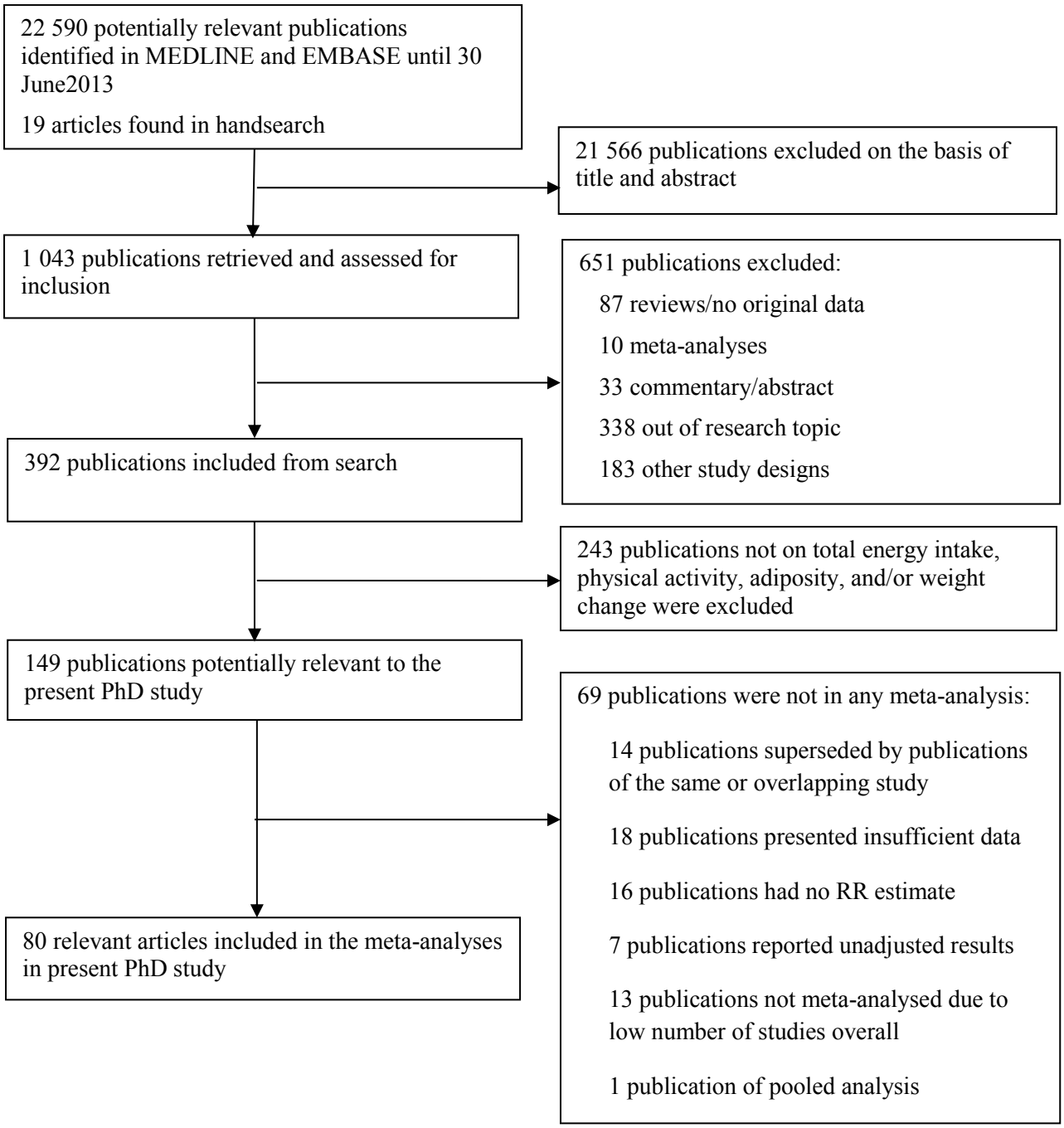


Figure 6.1 Flowchart of search for studies of energy balance-related factors and risk of mortality after breast cancer

6.3 Results of the studies

Below are the results from the meta-analyses. Tables 6.1 to 6.4 show the summary of meta-analyses of pre- and post-diagnosis energy balance-related factors and the risk of total mortality and breast cancer mortality in breast cancer survivors.

In most cases, the limited number of included studies did not allow statistical analyses to evaluate potential sources of heterogeneity, publication bias and non-linear relationship. Study quality was not evaluated using an overall score; any issues detected were discussed in details.

6.3.1 Total energy intake and risk of mortality in breast cancer survivors

6.3.1.1 Total energy intake and total mortality

Three studies on pre-diagnosis total energy intake could be included in the dose-response meta-analysis. No studies on <12 months post-diagnosis total energy intake were identified. Meta-analysis of ≥ 12 months post-diagnosis total energy intake was not conducted because of insufficient data in the three identified studies.

As in the studies of breast cancer incidence, follow-up studies of breast cancer survivors also used FFQ (≥100 items) to estimate total energy intake.

Total energy intake before breast cancer diagnosis was not significantly associated with the risk of total mortality in breast cancer survivors (summary RR per 500 kcal/day = 1.07, 95% CI: 0.80-1.42). There was evidence of high proportion of between-study heterogeneity (I^2 = 82%, P heterogeneity = 0.004) (3 studies[115;398;402]) (542 deaths) (Figure 6.2).

Two of the included studies were of short follow-up and/or low number of deaths[115;398]. The clinical series study conducted by Saxe *et al.* accrued only 26 deaths among 149 breast cancer survivors after an average follow-up of 5 years[398]. Diet a year before was assessed close to cancer diagnosis in this study. The population-based cohort of postmenopausal women, had 56 deaths after following 698 breast cancer survivors for an average 2.9 years [115]. The Canadian survivors study (52 deaths, 477 breast cancer survivors, average 6.1 years follow-up) that could not be included in the meta-analysis also reported a null association (P trend = 0.35)[403]. BMI and physical activity were not adjusted in one study[115]. The other studies accounted for both[402] or just BMI[398;403].

Non-significant results were observed for ≥ 12 months post-diagnosis total energy intake[404-406]. For the highest versus the lowest energy intake, the Women's Healthy Eating and Living (WHEL) Study, a RCT of dietary intervention that recruited breast cancer survivors within 48 months of diagnosis (average 24 months), reported an undjusted RR estimate of 0.74 (no 95% CI) (P trend = 0.24) (135 deaths)[404]. The NHS reported a RR estimate of 0.89 (95% CI: 0.64-1.23) (P trend = 0.97) (378 deaths)[405], and the Collaborative Women's Longevity Study (CWLS), recruited breast cancer

survivors 1-16 years (average 5 years) post-diagnosis, found the same (RR = 0.89, 95% CI: 0.68-1.15) (P trend = 0.33) (525deaths)[406].

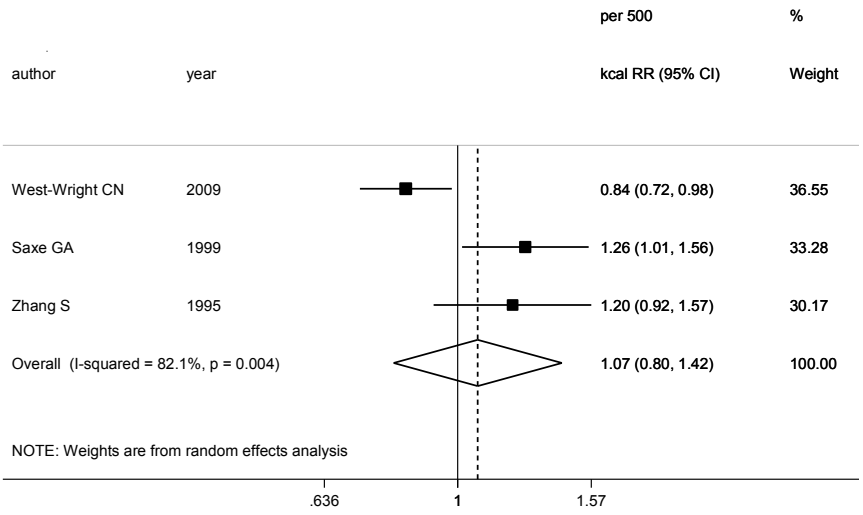


Figure 6.2 Relative risk and 95% CI of total mortality after breast cancer for the highest compared with the lowest level of pre-diagnosis total energy intake

Table 6.1 Summary of meta-analyses of pre-diagnosis energy balance-related factors and risk of total mortality after breast cancer

		Total mortality		
		Pre-diagnosis factor		
Energy balance -related factors (increment/comparison)	**Studies/deaths**	**RR (95% CI)**	**I^2 (%)**	**$P_{heterogeneity}$**
Total energy intake (per 500 kcal/d)	3 542	1.07 (0.80-1.42)	82	0.004
Total physical activity (highest vs lowest)	2 505	0.83 (0.62-1.12)	23	0.25
Recreational physical activity (highest vs lowest)	8 2,892	**0.74 (0.67-0.83)**	5	0.39
Moderate physical activity (highest vs lowest)	3 887	**0.72 (0.57-0.91)**	49	0.14
Moderate-vigorous physical activity (highest vs lowest)	-	-	-	-
Vigorous physical activity (highest vs lowest)	2 537	**0.75 (0.57-0.99)**	0	0.80
Adult weight gain (highest vs lowest)	4 1,664	**1.27 (1.10-1.46)**	0	0.39
Weight loss during adulthood (highest vs lowest)	-	-	-	-
BMI (per 5 kg/m^2)	15 6,358	**1.17 (1.13–1.21)**	7	0.38
Obese vs normal weight	21	**1.41 (1.29-1.53)**	38	0.04
Overweight vs normal weight	19	**1.07 (1.02-1.12)**	0	0.88
Underweight vs normal weight	10	1.10 (0.92-1.31)	48	0.04
Waist circumference BMI unadjusted (per 10 cm)	3 664	1.21 (0.97-1.49)	75	0.017
Waist to hip ratio	-	-	-	-

Table 6.2 Summary of meta-analyses of (</≥12 months) post-diagnosis energy balance-related factors and risk of total mortality after breast cancer

	Total mortality							
	<12 months post-diagnosis factor				≥12 months post-diagnosis factor			
Energy balance -related factors (increment/ comparison)	**Studies/ deaths**	**RR (95% CI)**	**I^2 (%)**	**P heterogeneity**	**Studies/ deaths**	**RR (95% CI)**	**I^2 (%)**	**P heterogeneity**
Total energy intake (per 500 kcal/d)	-	-	-	-	-	-	-	-
Total physical activity (highest vs lowest)	-	-	-	-	3 514	**0.63** **(0.41-0.97)**	44	0.16
(per 10 MET-hr/wk)					3 514	0.90 (0.79-1.03)	78	<0.01
Recreational physical activity (highest vs lowest)	-	-	-	-	5 2,337	**0.61** **(0.50-0.74)**	46	0.12
(per 10 MET-hr/wk)					5 2,337	**0.81** **(0.73-0.90)**	64	0.03
Moderate physical activity (highest vs lowest)	-	-	-	-	1 412	**0.47** **(0.34-0.65)**	-	-
Moderate-vigorous physical activity (highest vs lowest)	-	-	-	-	3 700	**0.57** **(0.41-0.78)**	34	0.22
Vigorous physical activity (highest vs lowest)	-	-	-	-	1 412	0.85 (0.59-1.22)	-	-
Weight gain from before to after diagnosis/treatment (highest vs lowest)	6 2,467	**1.43** **(1.10-1.87)**	61%	0.03	-	-	-	-
Weight gain during treatment (highest vs lowest)	3 347	1.38 (0.79-2.44)	80%	0.007	-	-	-	-
Weight loss from before to after diagnosis/treatment (highest vs lowest)	6	**2.33** **(1.42-3.83)**	90%	<0.001	-	-	-	-
BMI (per 5 kg/m^2)	12 6,020	**1.11** **(1.06-1.16)**	55	0.01	4 1,703	**1.08** **(1.01-1.15)**	0	0.52
Obese vs normal weight	24	**1.23** **(1.12-1.33)**	69	<0.01	5	**1.21** **(1.06-1.38)**	0	0.70
Overweight vs normal weight	22	**1.07** **(1.02-1.12)**	21	0.18	4	0.98 (0.86-1.11)	0	0.72
Underweight vs normal weight	11	1.25 (0.99-1.57)	63	<0.01	3	**1.29** **(1.02-1.63)**	0	0.39
Waist circumference BMI unadjusted (per 10 cm)	3 664	1.21 (0.97-1.49)	75	0.02	0	-	-	-
Waist to hip ratio BMI unadjusted (per 0.1 unit)	4 1,475	**1.31** **(1.17-1.48)**	0	0.73	0	-	-	-

Table 6.3 Summary of meta-analyses of pre-diagnosis energy balance-related factors and risk of breast cancer mortality

		Breast cancer mortality		
		Pre-diagnosis factor		
Energy balance -related factors (increment/ comparison)	**Studies**	**RR (95% CI)**	**I^2 (%)**	**$P_{heterogeneity}$**
Total energy intake (per 500 kcal/d)	-	-	-	-
Total physical activity (highest vs lowest)	2 338	0.80 (0.59-1.10)	0	0.88
Recreational physical activity (highest vs lowest)	7 1,750	**0.76 (0.61-0.95)**	49	0.06
Moderate physical activity (highest vs lowest)	-	-	-	-
Moderate-vigorous physical activity (highest vs lowest)	-	-	-	-
Vigorous physical activity (highest vs lowest)	-	-	-	-
Adult weight gain (per 5 kg in weight)	3 1,725	1.05 (0.95-1.16)	65	0.06
Weight loss during adulthood (highest vs lowest)	-	-	-	-
BMI (per 5 kg/m^2)	18 5,262	**1.18 (1.12-1.25)**	47	0.01
Obese vs normal weight	22	**1.35 (1.24-1.47)**	36	0.05
Overweight vs normal weight	21	**1.11 (1.06-1.17)**	0	0.66
Underweight vs normal weight	8	1.02 (0.85-1.21)	31	0.18
Waist circumference BMI unadjusted (per 10 cm)	-	-	-	-
Waist to hip ratio BMI unadjusted (per 0.1 unit)	-	-	-	-

Table 6.4 Summary of meta-analyses of (</≥12 months) post-diagnosis energy balance-related factors and risk of breast cancer mortality

	Breast cancer mortality							
	<12 months post-diagnosis factor				≥12 months post-diagnosis factor			
Energy balance -related factors (increment/ comparison)	**Studies**	**RR (95% CI)**	**I^2 (%)**	**P heterogeneity**	**Studies**	**RR (95% CI)**	**I^2 (%)**	**P heterogeneity**
Total energy intake (per 500 kcal/d)	-	-	-	-	-	-	-	-
Total physical activity (highest vs lowest)	-	-	-	-	2 217	0.81 (0.48-1.36)	0	0.63
Recreational physical activity (highest vs lowest)	-	-	-	-	2 392	0.71 (0.45-1.12)	33	0.22
Moderate physical activity (highest vs lowest)	-	-	-	-	-	-	-	-
Moderate-vigorous physical activity (highest vs lowest)	-	-	-	-	-	-	-	-
Vigorous physical activity (highest vs lowest)	-	-	-	-	-	-	-	-
Weight gain from before to after diagnosis/treatment (highest vs lowest)	3 810	**1.59 (1.05-2.41)**	47	0.15	-	-	-	-
Weight gain during treatment (highest vs lowest)	-	-	-	-	-	-	-	-
Weight loss from before to after diagnosis/treatment (highest vs lowest)	3	1.86 (0.43-7.98)	94	<0.001	-	-	-	-
BMI (per 5 kg/m^2)	8 3,857	**1.14 (1.05-1.24)**	66	0.01	2 220	1.29 (0.97-1.72)	64	0.10
Obese vs normal weight	12	**1.25 (1.10-1.42)**	53	0.02	2	1.68 (0.90-3.15)	67	0.08
Overweight vs normal weight	12	**1.11 (1.03-1.20)**	14	0.31	2	1.37 (0.96-1.95)	0	0.90
Underweight vs normal weight	5	**1.53 (1.27-1.83)**	0	0.59	1	1.10 (0.15-8.08)	-	-
Waist circumference BMI unadjusted (per 10 cm)	-	-	-	-	-	-	-	-
Waist to hip ratio BMI unadjusted (per 0.1 unit)	-	-	-	-	-	-	-	-

6.3.1.2 Total energy intake and breast cancer mortality

Two studies on pre-diagnosis total energy intake, and three studies on post-diagnosis total energy intake (1 study <12 months post-diagnosis, and 2 studies ≥12 months post-diagnosis) were identified. Meta-analysis was not conducted due to the limited number of studies.

All studies reported statistically non-significant results. For pre-diagnosis total energy intake, the Canadian National Breast Screening Study (CNBSS), a prospective study that originated from a RCT of mammography screening trial, found a null association (RR per 500 kcal/day = 1.00, 95% CI: 0.84-1.19) (76 breast cancer deaths)[112]. The California Teachers Study (CTS), a population-based prospective cohort, reported a non-significant inverse association (RR for >1682 vs <1271 kcal/day before diagnosis = 0.79, 95% CI: 0.56-1.11) (221 breast cancer deaths)[402]; which was similar to the association observed in the Canadian study that recruited breast cancer survivors 2 months after surgery but before adjuvant treatment (RR for ≥1890 vs ≤1262 kcal/day <12 months post-diagnosis = 0.8, 95% CI: 0.5-1.3)[407]. For ≥12 months post-diagnosis total energy intake, the RR estimates for the highest versus the lowest intake were 1.02 (95% CI: 0.61-1.71) (137 breast cancer deaths) in the CWLS[406] and 0.65 (95% CI: 0.37-1.14) (112 breast cancer deaths) in the Australian study that followed women with breast cancer from a population-based case-control study[408].

6.3.2 Physical activity and risk of mortality in breast cancer survivors

Different domains of physical activity performed before or (≥12 months) after breast cancer diagnosis were investigated in the studies, including total physical activity (recreational, occupational and household activities), recreational (non-occupational) physical activity and moderate- and/or vigorous-intensity physical activity. None of the studies investigated physical activity at or shortly (<12 months) after the diagnosis of breast cancer. The information was collected subjectively via self-reported questionnaire, which was validated in some studies[128;409-412]. Similar to the studies of breast cancer incidence, the diverse measurements had hindered the pooling of results in a dose-response meta-analysis; alternatively, the highest versus the lowest meta-analysis was conducted.

6.3.2.1 Total physical activity and total mortality

All two studies on pre-diagnosis total physical activity could be included in the highest versus the lowest meta-analysis, and all three studies on ≥12 months post-diagnosis were in the dose-response and the highest versus the lowest meta-analyses.

Total physical activity, both before and (≥12 months) after breast cancer diagnosis, was inversely associated with the risk of total mortality in breast cancer survivors.

For pre-diagnosis total physical activity, the inverse association was not statistically significant (summary RR for highest vs lowest level = 0.83, 95% CI: 0.62-1.12) (I^2 = 23%, P heterogeneity = 0.25) (2 studies[410;413]) (505 deaths) (Figure 6.3).

For (≥12 months) post-diagnosis total physical activity, the inverse association was statistically significant when comparing the highest with the lowest activity level (summary RR = 0.63, 95% CI: 0.41-0.97) (I^2 = 44%, P heterogeneity = 0.16) (3 studies[409-411]) (514 deaths) (Figure 6.3). When the same studies were included in the dose-response meta-analysis, the summary RR was 0.90 (95% CI: 0.79-1.03) for each 10 MET-hour/week increase in total physical activity (Figure 6.4). There was evidence of high proportion of between-study heterogeneity (I^2 = 79%, P heterogeneity < 0.01).

The Health Eating Activity and Lifestyle (HEAL) Study, a cancer survivor cohort that recruited the participants on average 6 months post-diagnosis, further reported that the RR estimates for >0 versus 0 MET-hour/week total physical activity 2 years post-diagnosis were 0.20 (95% CI: 0.09-0.46) in women with ER-positive breast cancers (34 deaths) and 1.26 (95% CI: 0.15-11.00) in women with ER-negative breast cancers (11 deaths) (P for interaction = 0.27)[410]. The study did not have information on treatment but adjusted for tumour stage along with other confounding factors as in the other studies. Women with severe comorbidities were excluded[410]. Another study that was able to adjust for comorbidity conditions was the study of Friedenreich *et al.* that followed women with breast cancer from a population-based case-control study. No issues relevant to study quality were identified in this study[413].

Participants in the Life After Cancer Epidemiology (LACE) study were diagnosed within 39 months of enrolment[409]. The numbers of recurrence and deaths after following 1,970 long-term breast cancer survivors for an average 87 months were relatively small (225 events, 187 total deaths), suggesting some degree of selection bias. Potential reverse causation was examined in this study and there was no appreciate change to the results[409]. The WHEL Study may also be a healthier cohort, in which post-treatment stage I (≥1 cm) to IIIA breast cancer survivors, diagnosed within past 48 months (average 24 months), were recruited[411].

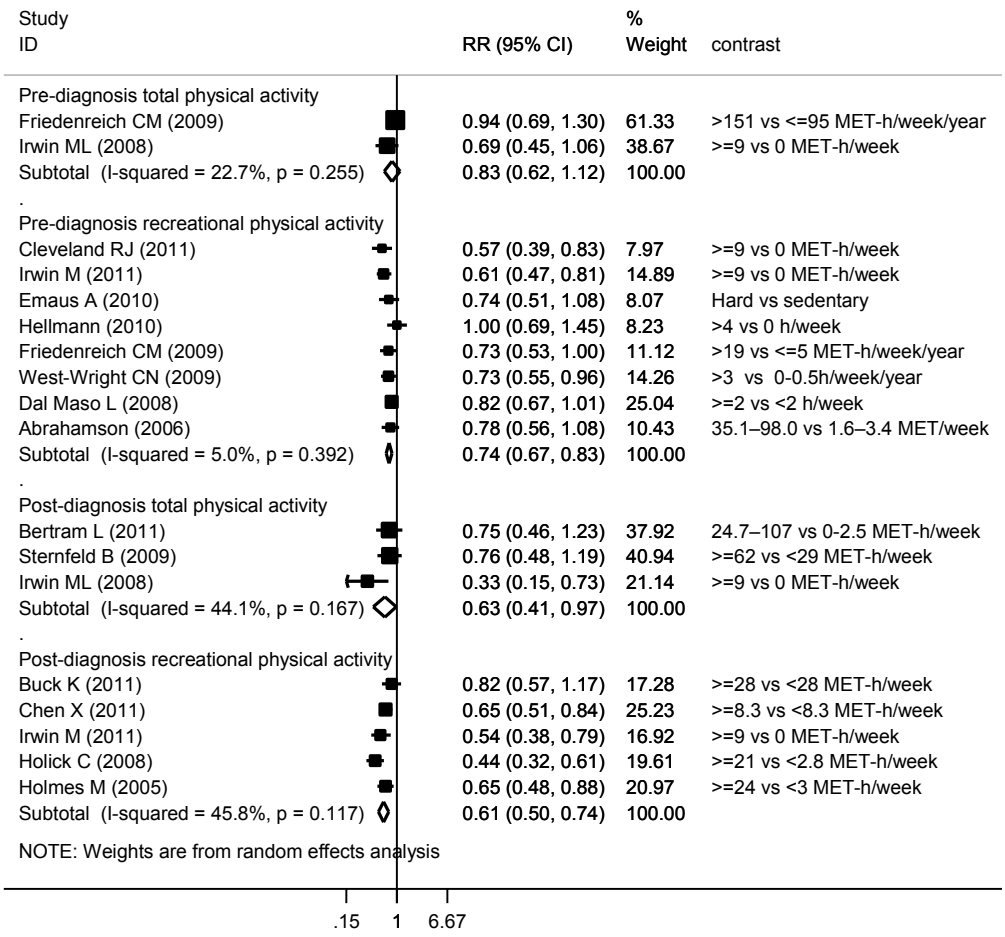


Figure 6.3 Relative risk and 95% CI of total mortality after breast cancer for the highest compared with the lowest level of physical activity (total physical activity, and recreational physical activity, pre- and post-diagnosis)

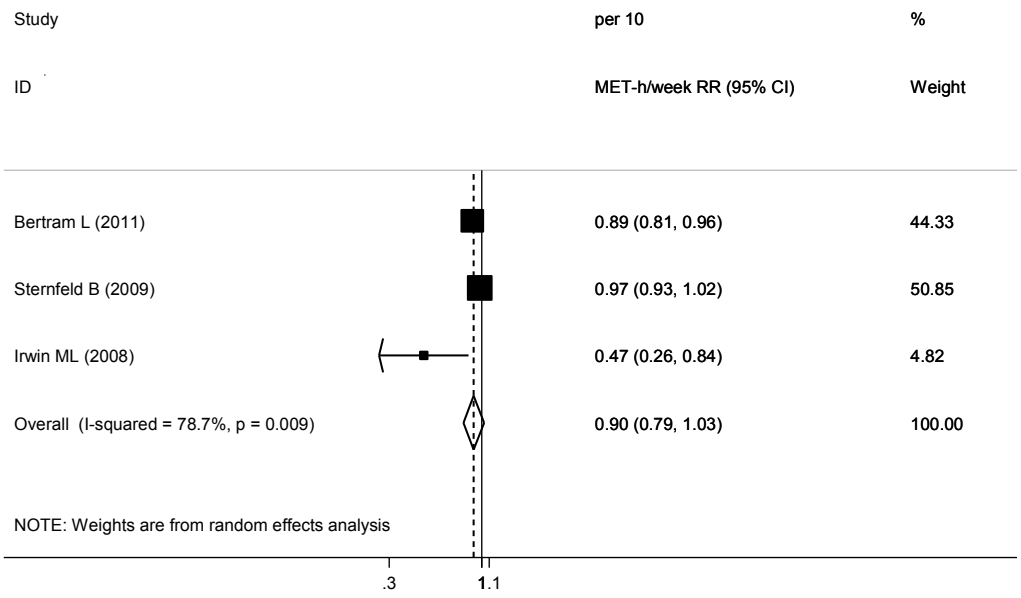


Figure 6.4 Relative risk and 95% CI of total mortality after breast cancer for 10 MET-hour/week increase of post-diagnosis total physical activity

6.3.2.2 Total physical activity and breast cancer mortality

Two studies each on pre-diagnosis and ≥12 months post-diagnosis total physical activity could be included in the highest versus the lowest meta-analyses, respectively.

Total physical activity, both before and after breast cancer diagnosis, was non-significantly inversely associated with the risk of breast cancer mortality. The summary RR estimates for the highest versus the lowest activity level were 0.80 (95% CI: 0.59-1.10) (I^2 = 0%, P heterogeneity = 0.88) (2 studies[410;413]) (338 breast cancer deaths) and 0.81 (95% CI: 0.48-1.36) (I^2 = 0%, P heterogeneity = 0.63) (2 studies[409;410]) (217 breast cancer deaths), respectively (Figure 6.5).

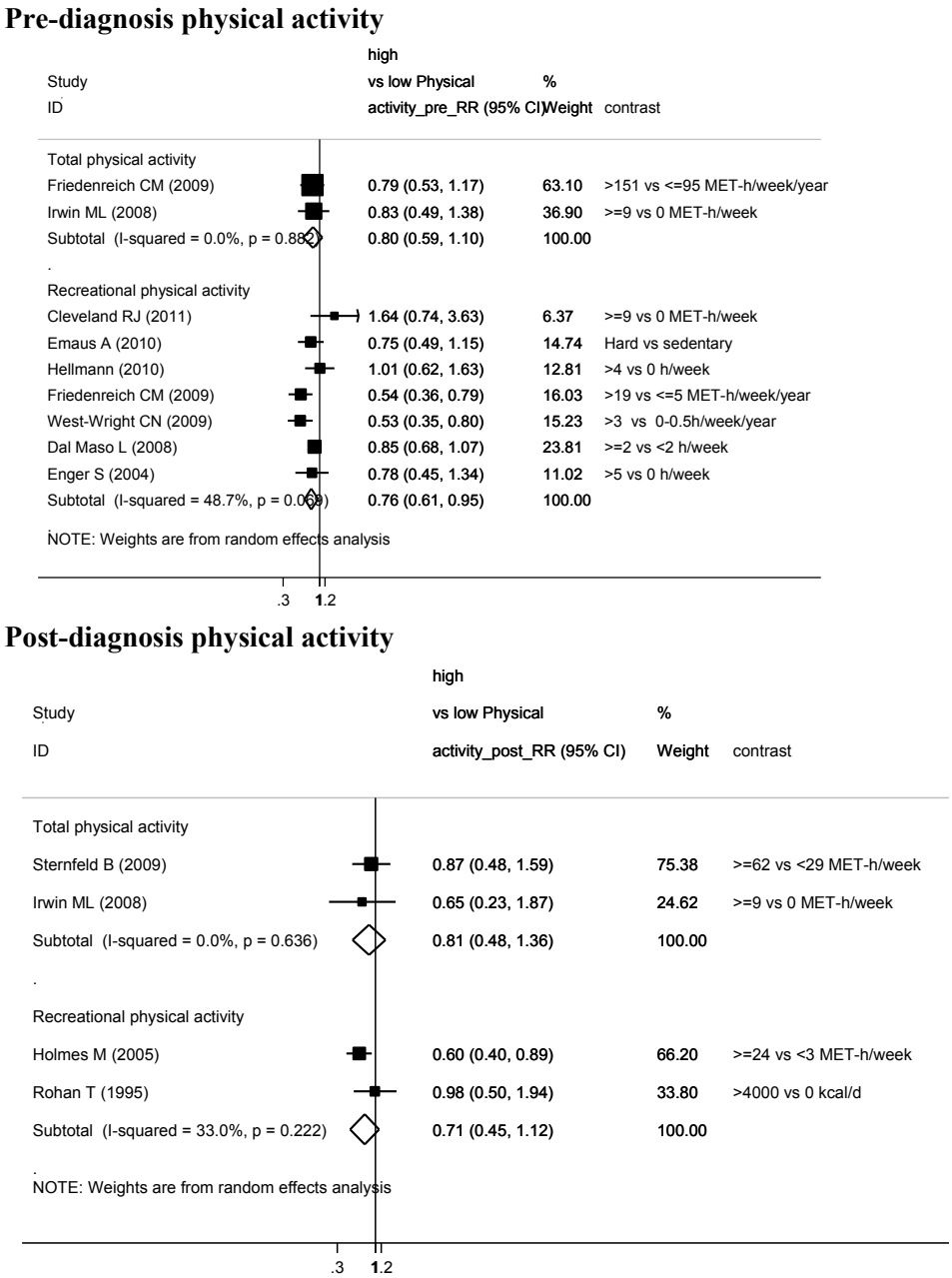


Figure 6.5 Relative risk and 95% CI of breast cancer mortality for the highest compared with the lowest level of physical activity (total physical activity, and recreational physical activity, pre- and post-diagnosis)

6.3.2.3 Recreational physical activity and total mortality

All eight studies on pre-diagnosis recreational physical activity could be included in the highest versus the lowest meta-analysis, and all five studies on ≥12 months post-diagnosis were in the dose-response and the highest versus the lowest meta-analyses.

Recreational physical activity was also defined as leisure-time physical activity in the studies.

Pre-diagnosis and post-diagnosis recreational physical activity was significantly inversely associated with the risk of total mortality in breast cancer survivors. The summary RR estimates for the highest versus the lowest level were 0.74 (95% CI: 0.67-0.83), with low between-study heterogeneity (I^2 = 5%, P heterogeneity = 0.39) (8 studies[129;402;413-418]) (2,892 deaths); and 0.61 (95% CI: 0.50-0.74), with moderate between-study heterogeneity (I^2 = 46%, P heterogeneity = 0.12) (5 studies[128;412;415;419;420]) (2,337 deaths), respectively (Figure 6.3, above).

For recreational physical activity performed ≥12 months after breast cancer diagnosis, the dose-response meta-analysis showed a significant 19% reduced risk of total mortality in breast cancer survivors (summary RR per 10 MET-hour/week = 0.81, 95% CI: 0.73-0.90) (5 studies[128;412;415;419;420]) (2,337 deaths) (Figure 6.6). There was evidence of significant heterogeneity (I^2 = 64%, P heterogeneity = 0.03).

There was no significant publication bias in the studies of pre-diagnosis recreational physical activity (P for Egger's test = 0.72). Other studies were too low in numbers, which precluded the exploration of potential publication bias. In subgroup meta-analysis by menopausal status of the women, the summary RR estimates per 10 MET-hour/week were 0.76 (95% CI: 0.49-1.19) (I^2 = 42%, P heterogeneity = 0.18) in premenopausal women (2 studies[128;420]) (225 deaths) and 0.74 (95% CI: 0.59-0.93) (I^2 = 74%, P heterogeneity = 0.01) in postmenopausal women (4 studies[128;415;419;420]) (902 deaths) (graph not shown).

The WHI study evaluated the association by molecular breast cancer subtypes of the survivors, and found inverse associations[415]. The RR estimates for >0 vs 0 MET-hour/week post-diagnosis ranged from 0.37 (95% CI: 0.19-0.75) (40 deaths) in women with HER2-negative breast cancer to 0.78 (95% CI: 0.35-1.73) (37 deaths) in women with ER-negative breast cancers.

These were population-based cohorts[128;402;415-417]; follow-up studies of women with breast cancer (originated from case-control studies)[129;412;414;418;419] and breast cancer survivor cohorts[413;420]. Several studies had shorter follow-up, around 5 years, and number of deaths around 100[412;414;419;420]. Some studies included *in situ* breast cancer cases[414]. Studies adjusted for multiple confounding factors, including age and tumour stage.

No serious issues relevant to study quality were detected; apart from the low response rate (32%) in the Collaborative Women's Longevity Study (CWLS), in which women with breast cancer were only

recruited from several years after diagnosis[412]. Selective non-response may explain partly the strong inverse association reported in this study.

WHI[415] excluded seriously ill women; and the studies of Emaus *et al.*[416] and Chen *et al.*[420] excluded the first year of follow-up. Reverse causation was also examined in NHS[128], which reported no materially change in results.

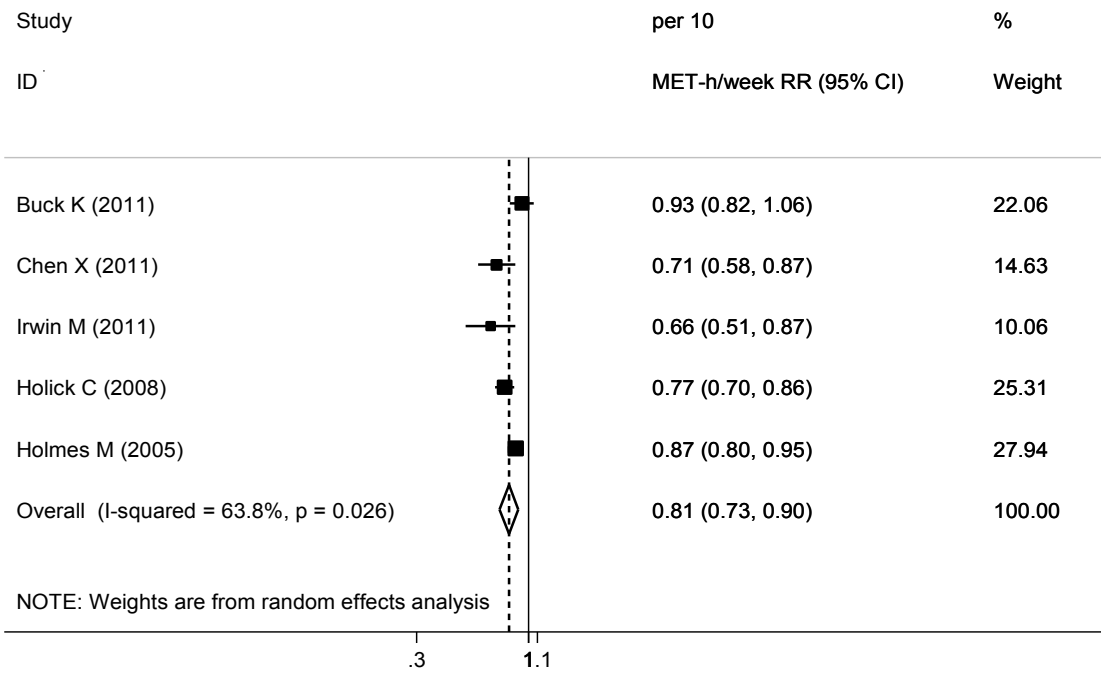


Figure 6.6 Relative risk and 95% CI of total mortality for 10 MET-hour/week increase of post-diagnosis recreational physical activity

6.3.2.4 Recreational physical activity and breast cancer mortality

All seven studies on pre-diagnosis recreational physical activity, and all two studies on ≥12 months post-diagnosis recreational physical activity could be included in the highest versus the lowest meta-analyses, respectively.

Pre-diagnosis and (≥12 months) post-diagnosis recreational physical activity was inversely associated with the risk of breast cancer mortality. The summary RR estimates for the highest versus the lowest level were 0.76 (95% CI: 0.61-0.95) (I^2 = 49%, P heterogeneity = 0.06) (7 studies[110;402;413;414;416-418]) (1,750 breast cancer deaths) and 0.71 (95% CI: 0.45-1.12) (I^2 = 33%, P heterogeneity = 0.22) (2 studies[128;421]) (392 breast cancer deaths), respectively (Figure 6.5, above). There was no significant publication bias in the studies of pre-diagnosis recreational physical activity (P for Egger's test = 0.78).

In addition, non-statistically significant associations that ranged from 0.8 (95% CI: 0.5-1.4) for gardening to 1.8 for jogging (>once a week versus none <12 months post-diagnosis) were reported in a breast cancer survivors cohort[407].

Because of the way physical activity was assessed in the study of Enger *et al.,* participants who performed some exercises might be classified as non-exercisers[110]; which may lead to attenuation of the association, although the inverse associations in this study were similar to other included studies. Both the study of Borugian *et al*.[407] and Rohan *et al*.[421] had limited breast cancer deaths (both 112 breast cancer deaths). All three studies did not adjust for treatment but tumour stage. Quality of the other studies was reviewed above (see sections 6.3.2.1 and 6.3.2.2).

6.3.2.5 Moderate physical activity and total mortality

Some studies further examined recreational physical activity of moderate intensity. As defined, these activities expend energy in MET values of ≥3.0 to <6.0 METs[414], ≥3.0 to ≤6.0 METs[413], about 4 METs[415] and <6 METs[412]. Moderate intensity and vigorous intensity physical activity were mutually adjusted in the studies.

All three studies on pre-diagnosis moderate physical activity could be included in the highest versus the lowest meta-analysis. In addition, one study on ≥12 months post-diagnosis moderate physical activity was identified[412].

Pre-diagnosis moderate physical activity was statistically significantly inversely associated with total mortality risk (summary RR for highest vs lowest level = 0.72, 95% CI: 0.57-0.91) (I^2 = 49%, P heterogeneity = 0.14) (3 studies[413-415]) (887 deaths) (Figure 6.7).

The only study that examined post-diagnosis moderate physical activity found a significant inverse association (RR for ≥10.3 vs <2.0 MET-hour/week = 0.47, 95% CI: 0.34-0.65) (412 deaths). The strong inverse association could partly be a result of selective non-response[412] (Figure 6.7).

6.3.2.6 Moderate physical activity and breast cancer mortality

No studies were identified.

6.3.2.7 Moderate to vigorous physical activity and total mortality

Three studies combined moderate with vigorous intensity physical activity. The following MET-values were assigned to the activities in the studies: 4 to 7 METs[415], 5 to 8 METs[411], and 3 to ≥6 METs[409].

As shown in the highest versus the lowest meta-analysis, moderate-vigorous physical activity performed (≥12 months) post-diagnosis was statistically significantly inversely associated with total mortality risk (summary RR = 0.57, 95% CI: 0.41-0.78) (I^2 = 34%, P heterogeneity = 0.22) (3 studies[409;411;415]) (700 deaths) (Figure 6.7).

6.3.2.8 Moderate to vigorous physical activity and breast cancer mortality

No studies were identified.

6.3.2.9 Vigorous physical activity and total mortality

Two studies on pre-diagnosis vigorous physical activity could be included in the highest versus the lowest meta-analysis. In addition, one study on (≥12 months) post-diagnosis vigorous physical activity was identified.

As defined in the studies, vigorous intensity physical activity was either recreational or non-recreational physical activity of ≥6.0 MET[413;414]. Moderate intensity and vigorous intensity physical activity were mutually adjusted.

Pre-diagnosis vigorous physical activity was statistically significantly inversely associated with total mortality risk (summary RR for highest vs lowest level = 0.75, 95% CI: 0.57-0.99) (I^2 = 0%, P heterogeneity = 0.80) (2 studies[413;414]) (537 deaths) (Figure 6.7). One study[413] contributed 87% weight in the analysis.

CWLS reported a non-significant inverse association. The RR estimate for ≥15.1 versus 0 MET-hour/week vigorous physical activity performed after diagnosis was 0.85 (95% CI: 0.59-1.22) (412 deaths)[412] (Figure 6.7).

6.3.2.10 Vigorous physical activity and breast cancer mortality

No studies were identified.

6.3.2.11 Change of physical activity and risk of mortality in breast cancer survivors

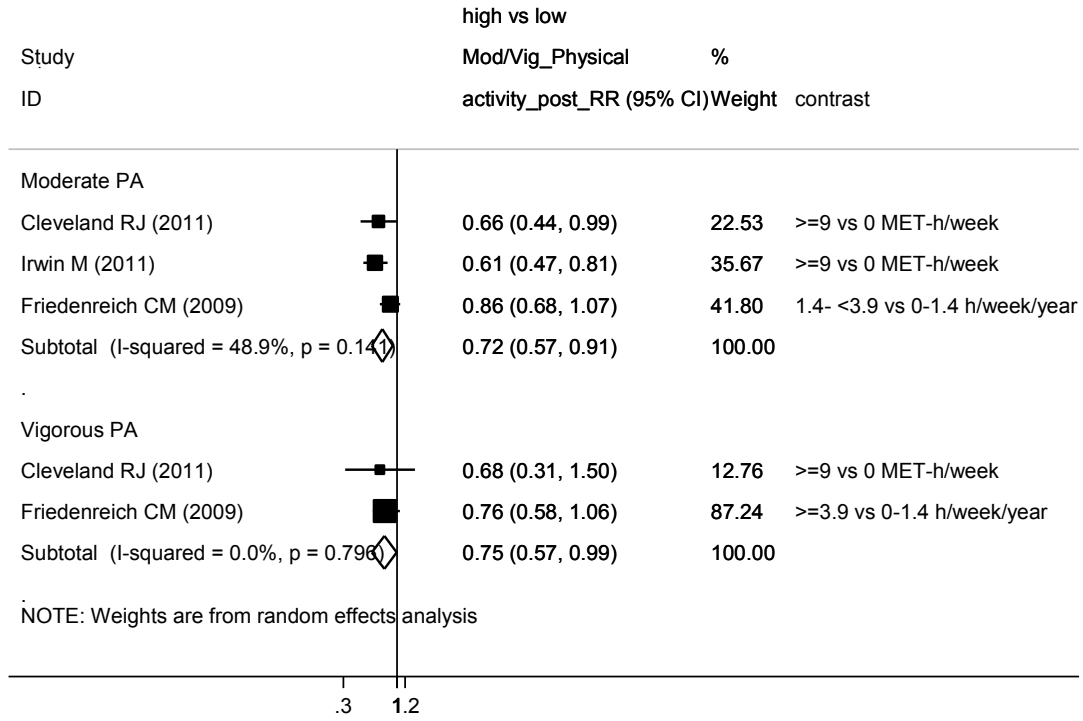
Three studies reported results comparing women who changed their physical activity level during various periods along survival to women who remained inactive[410;411;415].

The HEAL study found that women who increased physical activity level from one year before to two years after diagnosis had reduced risks of total mortality (RR = 0.55, 95% CI: 0.22-1.38) and breast cancer mortality (0.82, 95%CI: 0.29-2.34)[410].

The WHI study reported supporting results. Women who increased their moderate to vigorous intensity physical activity level from pre-diagnosis (4.1±2.3 years) to post-diagnosis (1.8±1 years) had reduced risk of total mortality (RR = 0.67, 95% CI: 0.46-0.96) (115 deaths), although the association with breast cancer mortality was not clear (0.91, 95%CI: 0.51-1.64) (57 deaths)[415].

The WHEL study examined change in levels from study baseline (post-treatment) to 1 year after, and observed total mortality risk reduction among women who remained active (meeting guidelines of 10 MET-hour/week), a null association among women who used to be active but not after (1.04, 95% CI: 0.61-1.77) and non-significant increased risk among women who became more active (1.21 95% CI: 0.77 1.90)[411].

Pre-diagnosis physical activity



Post-diagnosis physical activity

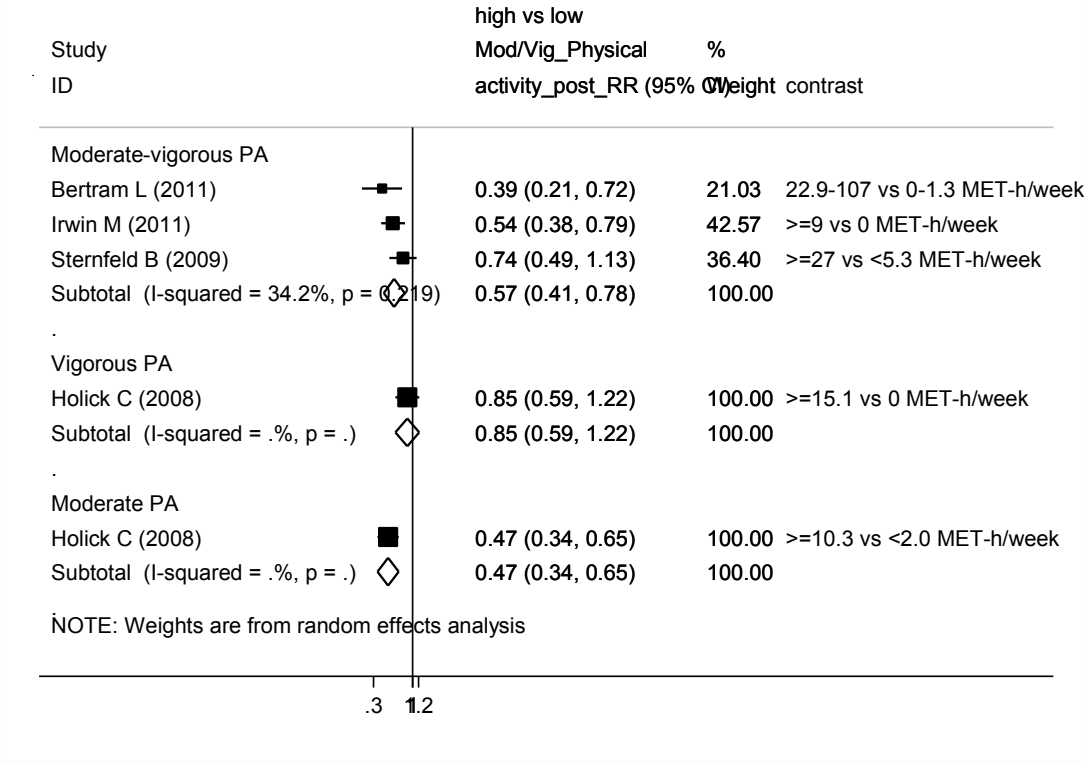


Figure 6.7 Relative risk and 95% CI of total mortality after breast cancer for the highest compared with the lowest level of physical activity (moderate or vigorous physical activity, pre- and post-diagnosis)

6.3.2.12 Physical activity, obesity and risk of mortality in breast cancer survivors

Pre-diagnosis recreational physical activity by BMI status was evaluated in three studies in relation to total mortality risk, and in two studies in relation to breast cancer mortality risk. The results were inconsistent.

One study observed a significant reduced risk of total mortality with pre-diagnosis recreational physical activity among women of BMI <25 kg/m^2, and not among women of BMI ≥ 25 kg/m^2 (RRs for high vs low level = 0.59 (95% CI: 0.36-0.98) and 1.07 (95% CI: 0.60-1.90), respectively) (P for interaction = 0.34)[416]; one study found opposite results, with significant decreased risk among heavier women (1.08 (95% CI: 0.77-1.52) and 0.70 (95% CI: 0.49-0.99), respectively) (P for interaction = 0.05)[129]; and one study observed significant reduced risks in both groups of women (0.44 (95% CI: 0.27-0.70) and 0.66 (95% CI: 0.46-0.96), respectively) (P for interaction = 0.08)[414]. For breast cancer mortality, one study reported a non-significant increased risk among women of BMI <25 kg/m^2 (1.15, 95% CI: 0.58-2.29) and a significant decreased risk among women of BMI ≥25 kg/m^2 (0.41, 95% CI: 0.23-0.74)[402]; while the other study did not observed any significant trends in both normal weight and overweight/obese breast cancer survivors[414].

Three studies examined moderate[409], recreational[415] or total physical activity[410] performed (≥12 months) after breast cancer diagnosis and the risk of total mortality by BMI status of the survivors. Inverse associations were observed across the BMI categories in the studies.

The RRs for the highest versus the lowest levels were: among women of BMI <25 kg/m^2, 0.47 (95% CI: 0.19-1.14)[410], 0.38 (95% CI: 0.17-0.85)[409], and 0.49 (95% CI: 0.27-0.91)[415]; among women of BMI ≥25 kg/m^2, 0.31 (95% CI: 0.13-0.74)[410]; among women of BMI 25-<30 kg/m^2, 0.95 (95% CI: 0.47-1.94)[409], and 0.43 (95% CI: 0.24-0.76)[415]; and among women of BMI >30 kg/m^2, 0.90 (95% CI: 0.38-2.16)[409], and 0.80 (95% CI: 0.45-1.41)[415].

6.3.3 Body fatness and weight change and risk of mortality in breast cancer survivors

6.3.3.1 Early adult BMI and risk of mortality in breast cancer survivors

Two studies were identified.

One study reported a significant increased risk of total mortality (RR for ≥30 vs <18.5 kg/m^2 at age 20 years = 2.93, 95% CI: 1.37-6.29) (P trend = 0.0004), that persisted after adjusting for adult BMI (2.49, 95% CI: 1.15-5.37) (P trend = 0.001) (280 deaths in total)[422]. The other study found a null association with breast cancer mortality risk (RR [adult BMI adjusted] for ≥25.50 vs <21.59 kg/m^2 at age 18 years = 1.00, 95% CI: 0.77-1.30) (P trend = 0.9) (1,347 breast cancer deaths in total)[423].

6.3.3.2 Weight gain and total mortality

Four studies on pre-diagnosis adult weight gain, seven studies (8 publications) on weight gain after cancer diagnosis or treatment, and six studies on weight gain specifically during cancer treatment

were identified. Dose-response meta-analysis was not possible because of the diversity of weight gain assessment in the studies. Alternatively, meta-analyses that compared the highest weight gain with the reference weight group (stable weight or the lowest category of weight change) were conducted. Only four, six and three studies had sufficient information for the analysis, respectively.

All four studies on pre-diagnosis weight gain reported a positive association. Pooling the studies in the highest versus the lowest meta-analysis showed a statistically significant increased risk of total mortality in breast cancer survivors (summary RR = 1.27, 95% CI: 1.10-1.46) (I^2 = 0%, P heterogeneity = 0.39) (4 studies[418;424-426]) (1,664 deaths) (Figure 6.8). All were originally a case-control study. Treatment information was adjusted for in the studies, Cleveland et *al.*[426] further adjusted for initial weight. All women in Bernstein *et al.* had a second primary breast cancer[425].

Weight gain post-diagnosis was also significantly positively associated with total mortality risk. The summary RR estimate for the highest weight gain post-diagnosis versus the reference weight group was 1.43 (95% CI: 1.10-1.87), with high between-study heterogeneity (I^2 = 61%, P heterogeneity = 0.03) (6 studies[422;427-431]) (2,467 deaths) (Figure 6.9). All studies included pre- and postmenopausal women. The Chinese study was of short follow-up (46 months) and only recruited the participants six months after diagnosis[427]. LACE only had 152 deaths in the analysis[429]. No all studies had treatment information[422]. Initial weight status was adjusted for in four studies[422;427;428;430].

For weight gain during treatment, the highest versus the lowest meta-analysis showed a non-significant positive association (summary RR = 1.38, 95% CI: 0.79-2.44) (I^2 = 80%, P heterogeneity = 0.01) (3 studies[422;432;433]) (347 deaths) (Figure 6.10). Camoriano et *al.* included only lymph-node positive premenopausal breast cancer[432]. Thivat *et al.* had only 57 deaths, 111 participants in average 20.4 years[433]. Period of weight change was short for Abrahamson *et al.* (4.2 months)[422].

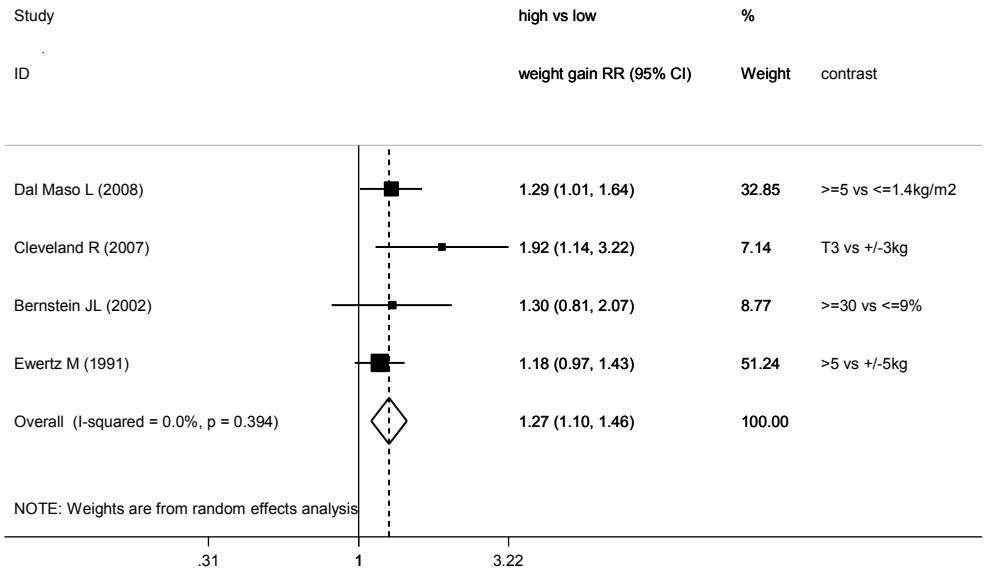


Figure 6.8 Relative risk and 95% CI of total mortality after breast cancer for the highest weight gain pre-diagnosis compared with the reference weight

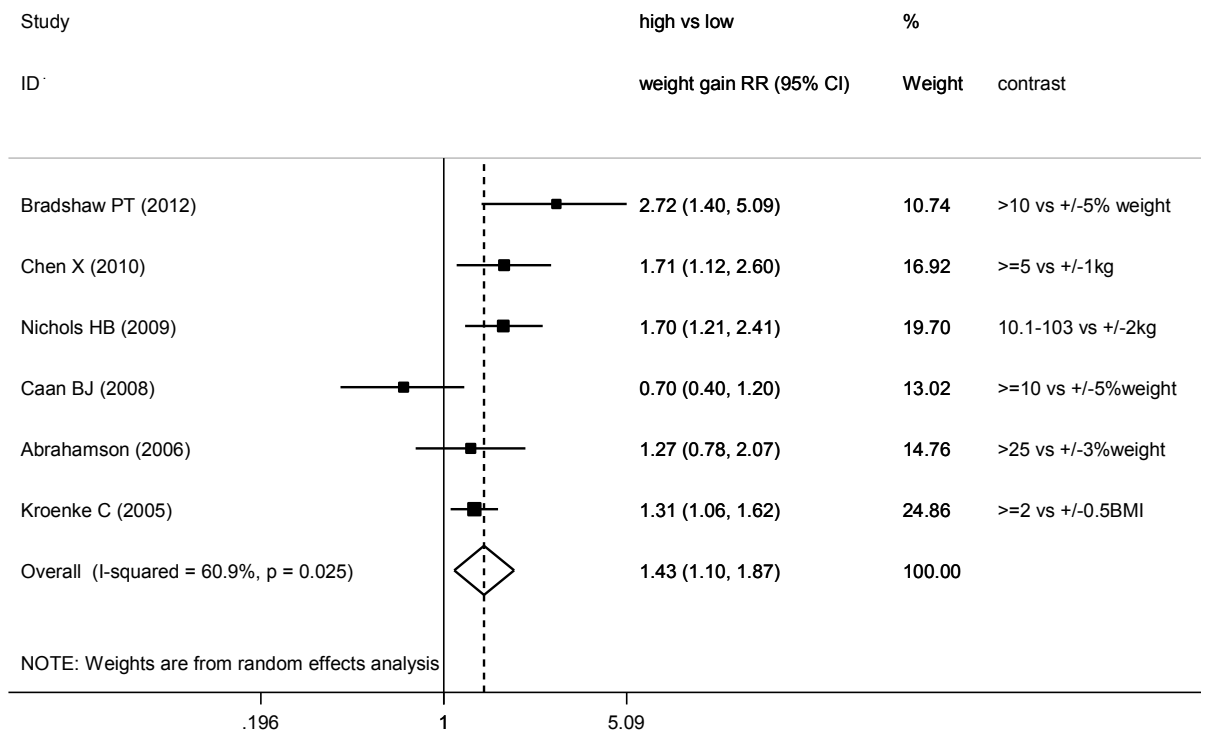


Figure 6.9 Relative risk and 95% CI of total mortality after breast cancer for the highest weight gain post-diagnosis* compared with the reference weight (*from before to after diagnosis/treatment)

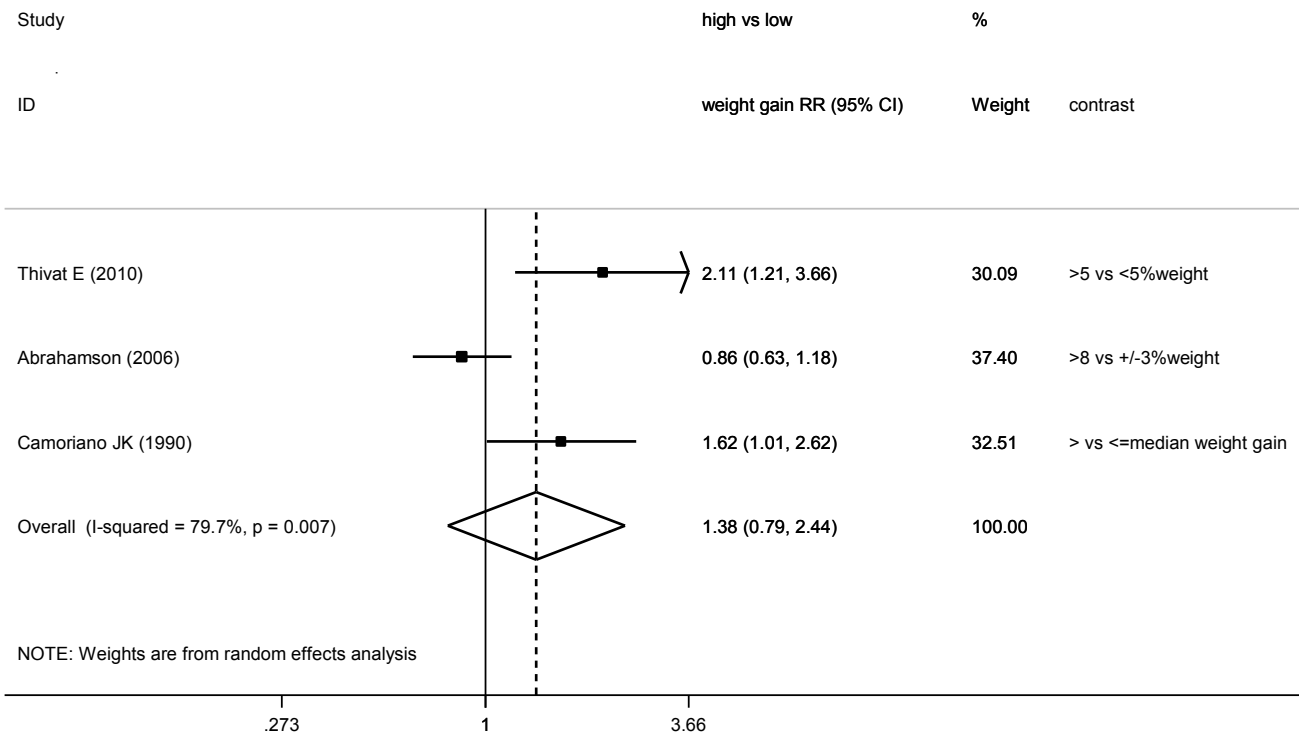


Figure 6.10 Relative risk and 95 % CI of total mortality after breast cancer for the highest weight gain during treatment compared with the reference weight

6.3.3.3 Weight gain and breast cancer mortality

Three studies on pre-diagnosis adult weight gain and three studies on weight gain after cancer diagnosis or treatment could be included in a dose-response meta-analysis, and a highest versus the lowest meta-analysis, respectively. Adult weight gain prior to cancer diagnosis was not significantly associated with the risk of breast cancer mortality (summary RR per 5 kg increase = 1.05, 95% CI: 0.95-1.16) (3 studies[110;423;426]) (1,725 breast cancer deaths) (I^2 = 65%, P heterogeneity = 0.06) (Figure 6.11). The study of Enger *et al.* included only premenopausal breast cancer survivors[110]. Cleveland *et al.* only had 127 breast cancer deaths[426].

Statistically significant increased risk was observed for post-diagnosis weight gain and breast cancer mortality risk. The summary RR was 1.59 (95% CI: 1.05-2.41) (I^2 = 47%, P heterogeneity = 0.15) (3 studies[428;430;431]) (810 breast cancer deaths) (Figure 6.12).

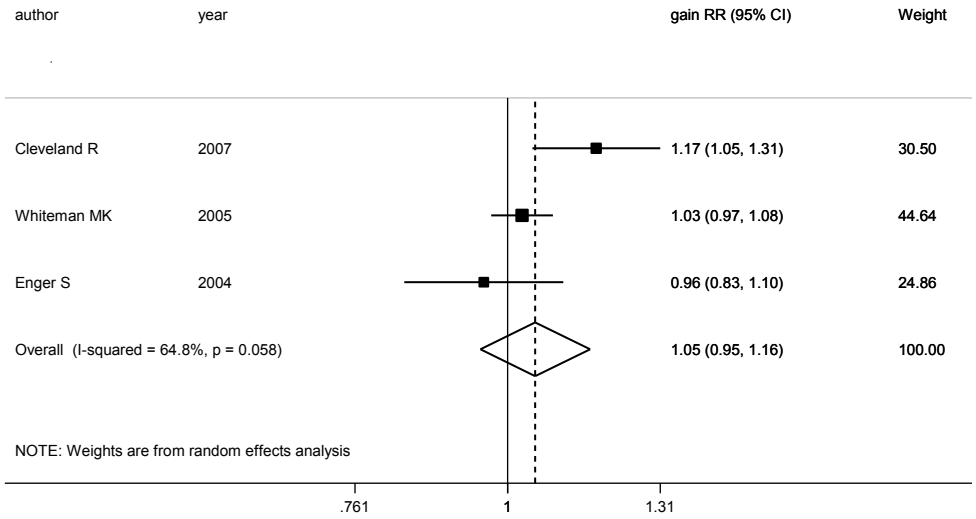


Figure 6.11 Relative risk and 95% CI of breast cancer mortality for 5 kg increase of pre-diagnosis weight gain

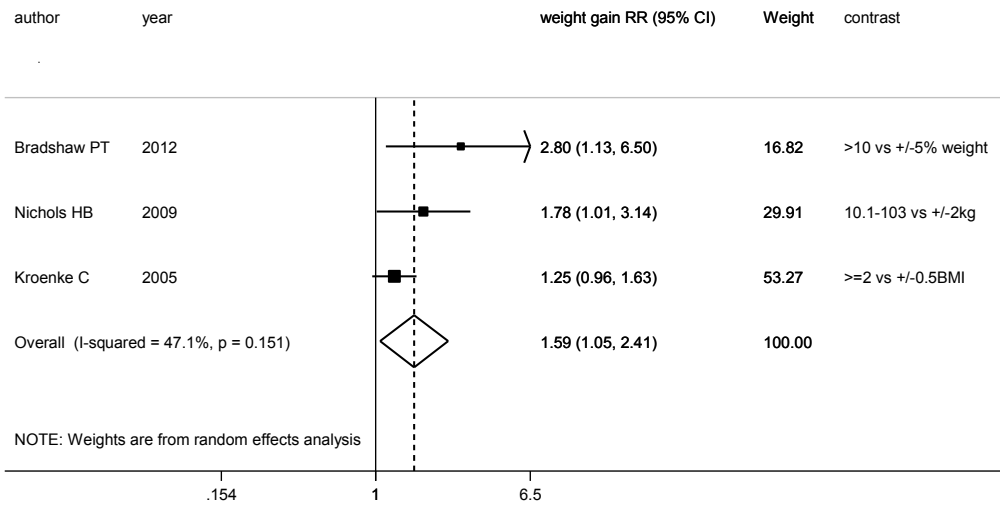


Figure 6.12 Relative risk and 95% CI of breast cancer mortality for the highest weight gain post-diagnosis* compared with the reference weight(*from before to after diagnosis/treatment)

6.3.3.4 Weight loss and total mortality

Three studies on pre-diagnosis adult weight loss, six studies (7 publications) on weight loss after cancer diagnosis or treatment, and two studies on weight loss specifically during cancer treatment were identified. A meta-analysis could be conducted for any weight loss from before to after diagnosis or treatment versus reference/stable weight, but not for weight loss during other time periods.

The results on pre-diagnosis weight loss were not consistent across the studies. In one study, the RR estimates for >3 vs ± 3kg ranged from 1.07 (95% CI: 0.26-4.50) to 3.04 (95% CI: 1.70-5.46) for the different periods of weight loss in premenopausal and postmenopausal women[426]. One study reported a statistically significant increased risk for weight loss ten years before diagnosis (HR >5 vs ±5kg = 1.59, 95% CI: 1.23-2.05)[424]. But one study found moderate pre-treatment weight loss (<5%) had the longest survival compared with 5-10%, and >10% loss (P <0.01)[434].

The studies that examined weight loss after cancer diagnosis or treatment found a strong positive association on average (summary RR for any weight loss vs reference weight group = 2.33, 95% CI: 1.42-3.83), with substantial between-study heterogeneity (I^2 = 89.7%, p<0.0001) (6 studies[422;427-431]) (Figure 6.13). For weight loss during treatment, one study reported a statistically non-significant increased risk (HR >3 vs ±3% weight loss = 1.27, 95% CI: 0.93-1.74)[422], while the other study found no association (P for log-rank test = 0.12 when comparing ≥0% to <0% weight loss)[435].

CWLS excluded women with unintentional weight loss of >5% body weight[428]. Intent of weight loss was not assessed in other studies. The LACE study excluded women who had a breast cancer recurrence, new breast primary or death within the time between diagnosis and three months after enrolment[429].

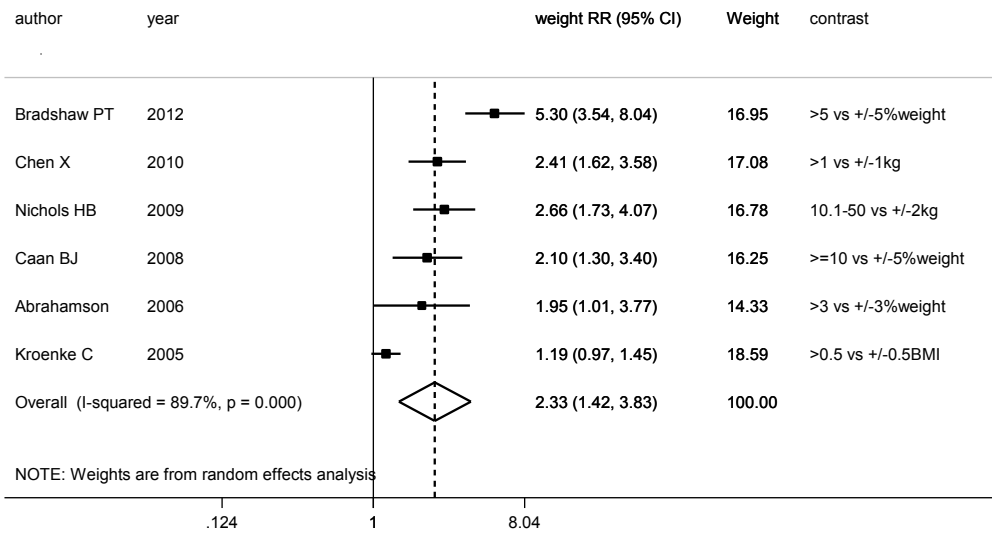


Figure 6.13 Relative risk and 95% CI of total mortality after breast cancer for post-diagnosis* weight loss compared with reference weight (*from before to after diagnosis/treatment)

6.3.3.5 Weight loss and breast cancer mortality

One study on pre-diagnosis adult weight loss, and three studies (4 publications) on weight loss after cancer diagnosis or treatment were identified. No study reported results on weight loss during cancer treatment. A meta-analysis could be conducted for any weight loss from before to after diagnosis or treatment versus reference/stable weight.

Weight loss at various periods during adulthood was not consistently associated with breast cancer mortality risk in premenopausal and postmenopausal women. The RR estimates for >3 vs ± 3kg lost ranged from 0.72 (95% CI: 0.14-3.73) to 4.55 (95% CI: 1.98-10.5)[426].

Inconsistent results were also reported in the three studies on weight loss after cancer diagnosis or treatment. The summary RR estimate for any weight loss compared with stable weight was 1.86 (95% CI: 0.43-7.98) (I^2 = 93.9%, P<0.0001) (3 studies[428;430;431]) (Figure 6.14).

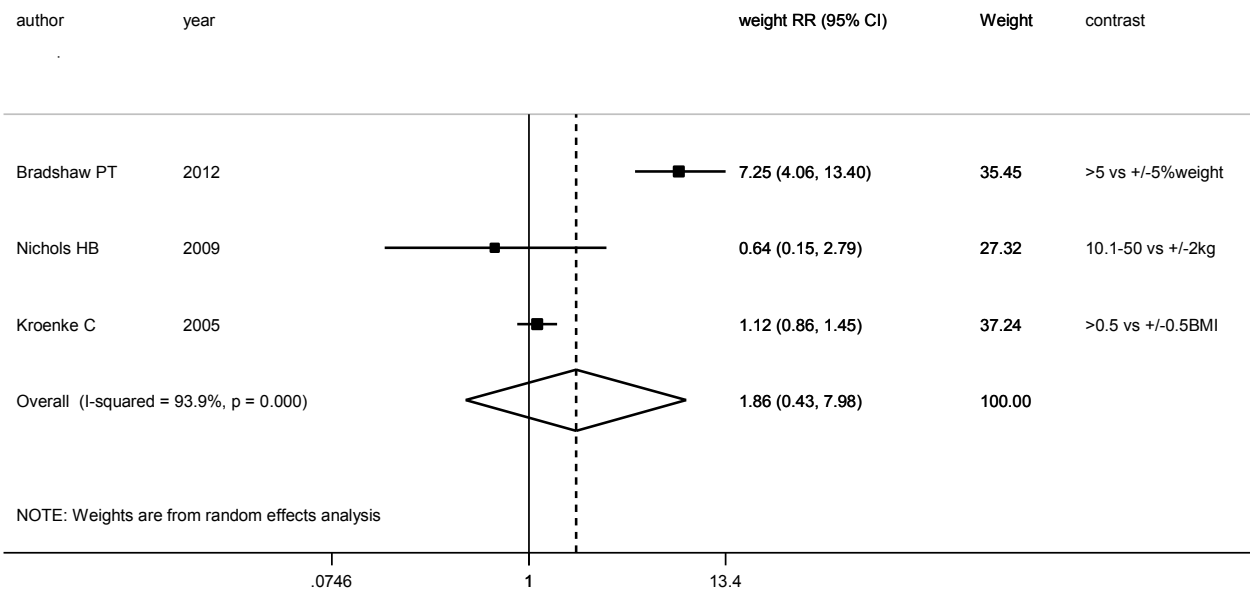


Figure 6.14 Relative risk and 95% CI of breast cancer mortality for post-diagnosis* weight loss compared with reference weight (*from before to after diagnosis/treatment)

6.3.3.6 Pre-diagnosis body mass index and total mortality

A total of 124 publications were potentially relevant in the review of BMI and risk of mortality in breast cancer survivors. Thirty-one publications (4 on obesity index, 12 without a measure of association, and 15 superseded publications or publications of overlapping studies) were subsequently excluded, leaving 79 publications to be included in the meta-analyses.

Fifteen studies on pre-diagnosis BMI and total mortality risk in breast cancer survivors could be included in the dose-response meta-analysis (6,358 deaths)[115;401;402;416-418;422;427-430;436-439]. Of the studies reported results by BMI categories, 21 on obese women[106;115;400-402;416-419;422;425-430;436-440], 19 on overweight women[106;115;400-402;416-419;422;427-430;436-440], and 10 on underweight women[416;417;419;422;425;427;428;430;437;438] could be included in the categorical meta-analyses, with normal weight women as reference group.

Pre-diagnosis BMI significantly increased the risk of total mortality (summary RR per 5 kg/m^2 = 1.17, 95% CI: 1.13-1.21) (Figure 6.15). Low proportion of heterogeneity was detected (I^2 = 7%, P heterogeneity = 0.38). The summary RR remained significant in influence analysis.

Increased risks were also observed in the categorical meta-analyses. Compared with normal weight women, the summary RR estimates were 1.41 (95% CI: 1.29-1.53) (I^2 = 38%, P heterogeneity = 0.04) for obese women, 1.07 (95% CI: 1.02-1.12) (I^2 = 0%, P heterogeneity = 0.88) for overweight women, and 1.10 (95% CI: 0.92-1.31) (I^2 = 48%, P heterogeneity = 0.04) for underweight women (Figure 6.16). The J-shaped relationship was confirmed in second-order fractional polynomial regression analysis (P for non-linearity < 0.01) (Figure 6.17).

Positive associations were observed in both pre- and postmenopausal women and in women of either HR-positive or HR-negative breast cancer. The summary RR estimates for obese versus normal weight were 1.75 (95% CI: 1.26-2.41) (I^2 = 70%, P heterogeneity < 0.01) in women with premenopausal breast cancer and 1.34 (95% CI: 1.18-1.53) (I^2 = 27%, P heterogeneity = 0.20) in women with postmenopausal breast cancer (P meta-regression = 0.28). For the same comparison, the summary RR estimates were 1.43 (95% CI: 1.16-1.78) (I^2 = 0%, P heterogeneity = 0.32) in women with HR-positive breast cancer and 1.18 (95% CI: 0.92-1.52) (I^2 = 0%, P heterogeneity = 0.72) in women with HR-negative breast cancer (P meta-regression = 0.37). Consistent positive associations of similar magnitude were observed across the other subgroups, including number of deaths, length of follow-up, study design and confounding factors adjustments (Table 6.5).

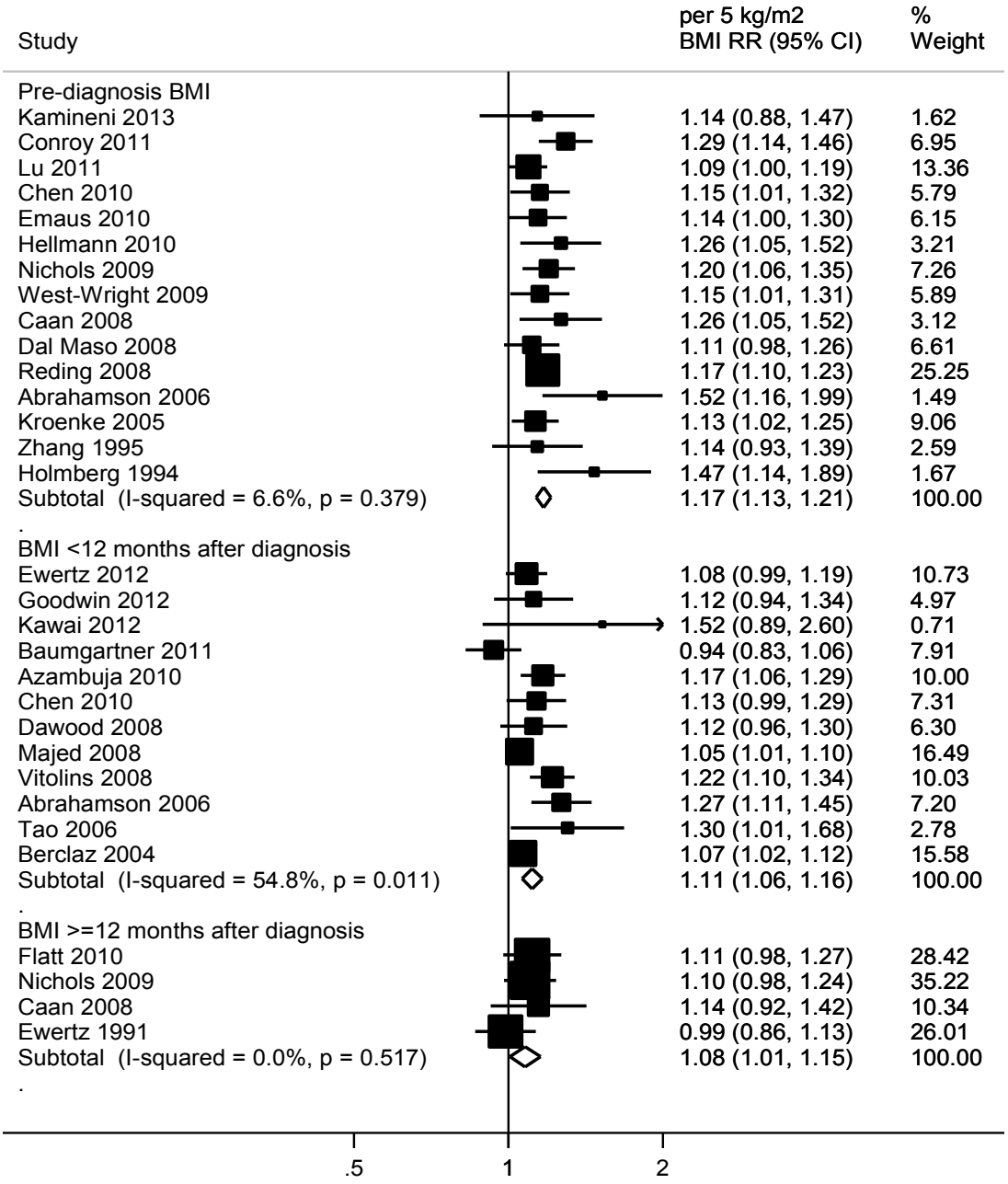


Figure 6.15 Relative risk of total mortality after breast cancer for 5 kg/m^2 increase of BMI ascertained before, a year or more post-diagnosis

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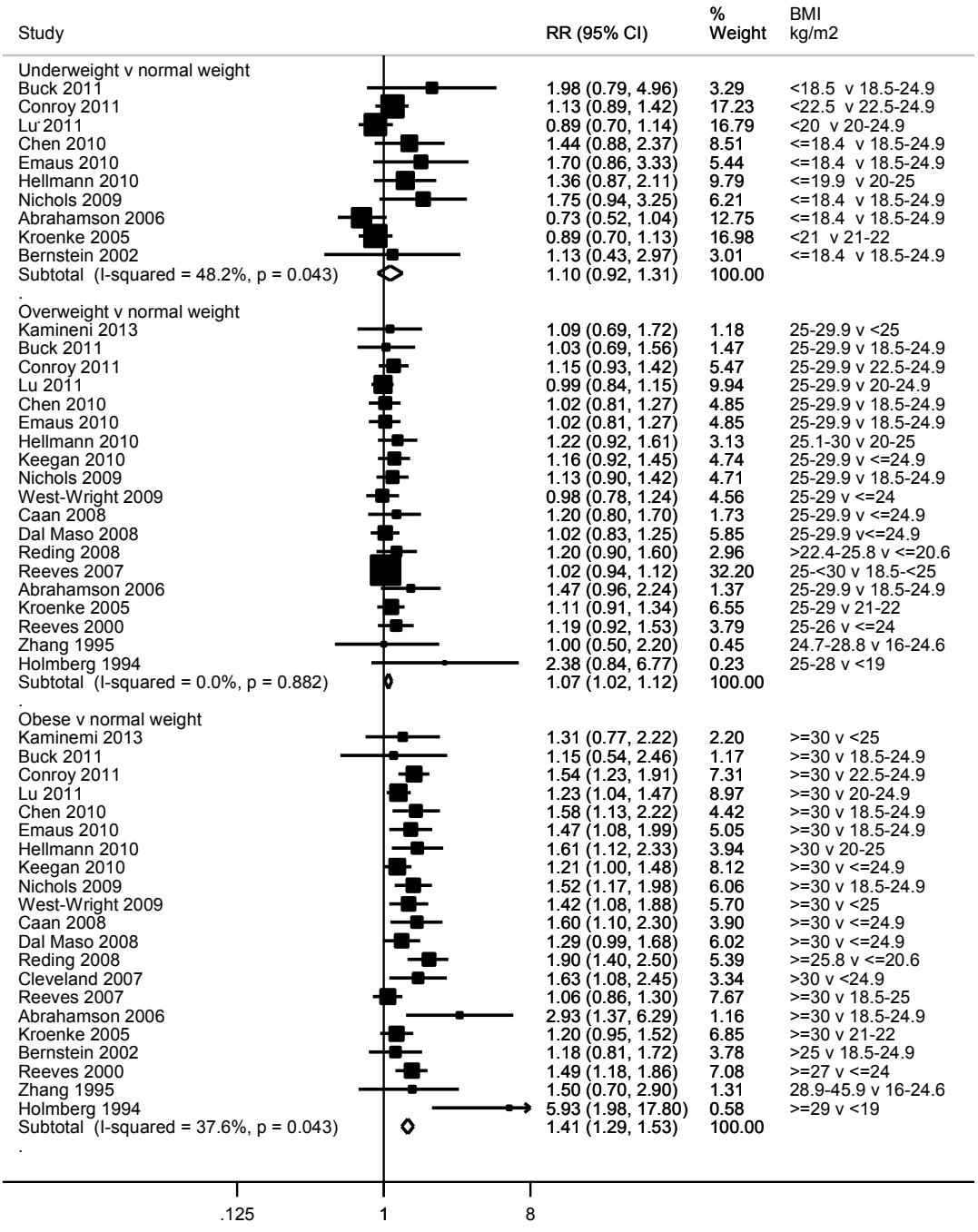

Figure 6.16 Relative risk of total mortality after breast cancer for obese, overweight, and underweight women compared with normal weight women ascertained before diagnosis

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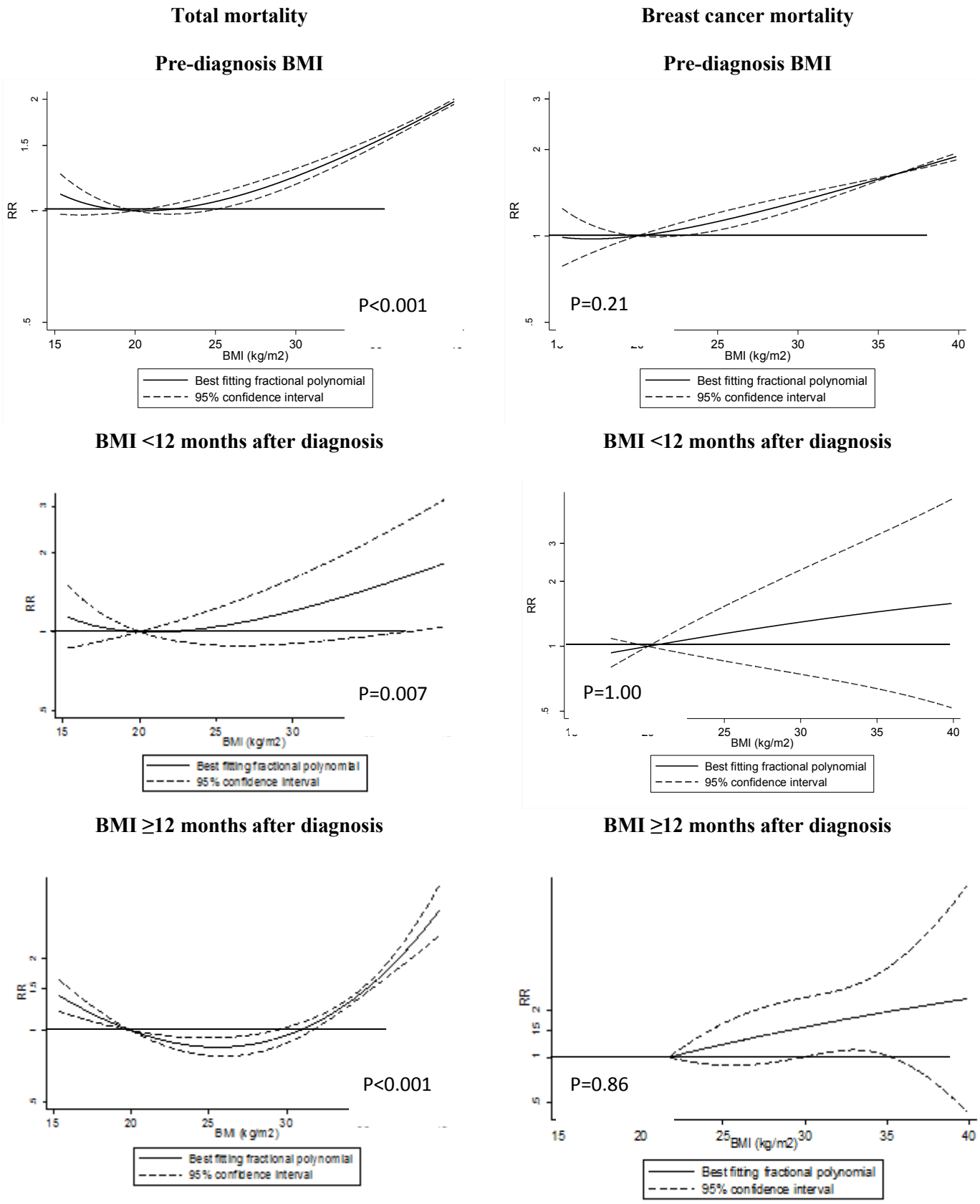

Figure 6.17 Non-linear dose-response curves of BMI and mortality after breast cancer

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Table 6.5 Summary of subgroup meta-analyses of BMI and total mortality after breast cancer

	Pre-diagnosis BMI					BMI <12 months after diagnosis				
	N	**RR (95% CI)**	I^2 **(%)**	**Phet**	**Pmet**	***N***	**RR (95% CI)**	I^2 **(%)**	**Phet**	**Pmet**
Obese versus normal weight meta-analysis										
Menopausal status										
Premenopausal	7	**1.75 (1.26-2.41)**	70	<0.01	Ref	3	**1.26 (1.03-1.54)**	17	0.30	Ref
Postmenopausal	9	**1.34 (1.18-1.53)**	27	0.20	0.28	5	**1.20 (1.01-1.43)**	43	0.14	0.58
Hormone receptor status										
Positive	2	**1.43 (1.16-1.78)**	0	0.32	Ref	5	**1.28 (1.06-1.53)**	47	0.11	Ref
Negative	2	1.18 (0.92-1.52)	0	0.72	0.37	4	**1.33 (1.05-1.70)**	52	0.10	0.86
Linear dose-response meta-analysis (per 5 kg/m^2 increase)										
Menopausal status										
Premenopausal	3	**1.25 (1.10-1.43)**	47	0.15	Ref	2	1.50 (0.65-3.47)	68	0.08	Ref
Postmenopausal	3	**1.16 (1.01-1.34)**	56	0.10	0.50	4	1.03 (0.96-1.11)	38	0.18	0.39
Number of deaths										
<400	7	**1.22 (1.14-1.31)**	20	0.28	Ref	6	**1.21 (1.13-1.28)**	0	0.66	Ref
401-800	5	**1.15 (1.09-1.22)**	0	0.94	0.27	2	**1.15 (1.07-1.25)**	0	0.73	0.44
>800	3	**1.16 (1.05-1.27)**	61	0.08	0.29	2	**1.06 (1.02-1.10)**	0	0.54	0.01
Length of follow-up										
≤5 y	3	**1.21 (1.06-1.38)**	35	0.22	Ref	2	**1.15 (1.07-1.25)**	0	0.73	Ref
>5-≤10 y	11	**1.17 (1.13-1.22)**	10	0.35	0.73	8	**1.09 (1.03-1.15)**	55	0.03	0.36
>10 y	1	1.11 (0.98-1.26)	-	-	0.43	2	**1.19 (1.09-1.30)**	0	0.42	0.75
Study design										
RCT-based	0	-	-	-	-	4	**1.12 (1.06-1.19)**	55	0.09	Ref
Prospective cohort	8	**1.18 (1.12-1.24)**	0	0.71	Ref	4	**1.07 (1.02-1.12)**	6	0.36	0.54
Retrospective cohort	1	1.14 (0.88-1.47)	-	-	0.62	2	1.02 (0.85-1.21)	69	0.07	0.16
Cases of case-control	6	**1.18 (1.10-1.26)**	50	0.08	0.89	2	**1.27 (1.13-1.44)**	0	0.85	0.13
Geographic location										
North America	10	**1.17 (1.12-1.22)**	13	0.33	Ref	4	**1.19 (1.12-1.28)**	0	0.55	Ref
Europe	4	**1.19 (1.08-1.32)**	35	0.20	0.87	2	1.01 (0.90-1.12)	67	0.08	0.02
Asia Pacific	1	**1.15 (1.01-1.32)**	-	-	0.86	3	**1.18 (1.05-1.33)**	0	0.41	0.95
International	0	-	-	-	-	3	**1.09 (1.04-1.14)**	16	0.31	0.10
Exposure assessment methods										
Measured	2	**1.18 (1.06-1.31)**	0	0.37	Ref	6	**1.17 (1.11-1.23)**	7	0.37	Ref
Self-reported	13	**1.17 (1.13-1.22)**	15	0.29	0.84	2	1.17 (0.98-1.38)	9	0.30	0.87
Medical records	0	-	-	-	-	4	**1.05 (1.01-1.10)**	32	0.22	0.01
Adjustment for confounders										
Tumour stage										
Yes	13	**1.16 (1.12-1.21)**	0	0.46	Ref	10	**1.09 (1.04-1.14)**	46	0.06	Ref
No	2	**1.26 (1.02-1.57)**	67	0.08	0.70	2	**1.19 (1.11-1.28)**	0	0.56	0.13
Cancer treatment										
Yes	4	**1.17 (1.09-1.26)**	0	0.59	Ref	8	**1.08 (1.03-1.14)**	28	0.20	Ref
No	11	**1.17 (1.12-1.22)**	23	0.22	0.93	3	**1.14 (1.02-1.28)**	78	0.01	0.48
Comorbidities/diabetes										
Yes	3	**1.12 (1.05-1.19)**	0	0.72	Ref	3	**1.11 (1.03-1.19)**	0	0.44	Ref
No	12	**1.19 (1.14-1.23)**	8	0.37	0.15	9	**1.11 (1.05-1.18)**	64	<0.01	0.93
Physical activity										
Yes	6	**1.18 (1.12-1.25)**	0	0.89	Ref	2	1.17 (0.98-1.38)	9	0.30	Ref
No	9	**1.17 (1.11-1.24)**	39	0.11	0.67	10	**1.11 (1.06-1.16)**	60	0.01	0.61
Alcohol use										
Yes	1	**1.26 (1.05-1.52)**	-	-	Ref	0	-	-	-	-
No	14	**1.17 (1.13-1.21)**	9	0.36	0.43	12	**1.11 (1.06-1.16)**	54.8	0.01	-
Smoking										
Yes	6	**1.20 (1.14-1.27)**	0	0.60	Ref	2	1.15 (0.89-1.49)	33	0.22	Ref
No	9	**1.15 (1.10-1.21)**	18	0.28	0.24	10	**1.11 (1.06-1.17)**	61	0.01	0.98

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6.3.3.7 Post-diagnosis body mass index and total mortality

For BMI ascertained <12 months post-diagnosis, 12 studies could be included in the dose-response meta-analysis (6,020 deaths)[422;441-451]. In addition, 24 studies on obese women[397;399;422;427;441-443;445;447;448;450-462], 22 on overweight women[397;399;422;427;441-443;445;447;448;450-459;461;462], and 11 on underweight women could be included in the categorical meta-analyses[397;422;427;442;443;445;455;456;458;462], respectively.

The corresponding numbers for BMI ascertained ≥ 12 months post-diagnosis were four studies in the dose-response meta-analysis (1,703 deaths)[424;428;429;463]; and five[105;424;428;429;463], four[424;428;429;463], and three studies[404;424;428] in the categorical meta-analyses.

Post-diagnosis BMI (ascertained <12 or ≥ 12 months after diagnosis) significantly increased the risk of total mortality in breast cancer survivors (summary RRs per 5 kg/m^2 = 1.11 (95% CI: 1.06-1.16) and 1.08 (95% CI: 1.01-1.15), respectively) (Figure 6.15, above). There was significant evidence of heterogeneity (I^2 = 55%, P heterogeneity = 0.01), and publication bias (P for Egger's test = 0.05) in the studies of <12 months post-diagnosis BMI (graph not shown). The findings on ≥12 months post-diagnosis BMI were consistent (I^2 = 0%, P heterogeneity = 0.52). The summary RR estimates remained significant in influence analysis with studies of <12 months post-diagnosis BMI but became 1.06 (95% CI: 0.98-1.15) per 5 kg/m^2 when Flatt *et al.*[463] was excluded from the studies of ≥ 12 months post-diagnosis BMI.

Increased risks were observed in the categorical meta-analyses. For BMI <12 months post-diagnosis, the summary RR estimates were 1.23 (95% CI: 1.12-1.33) (I^2 = 69%, P heterogeneity ≤0.01) for obese women, 1.07 (95% CI: 1.02-1.12) (21%, P heterogeneity 0.18) for overweight women, and 1.25 (95% CI: 0.99-0.57) (I^2 = 63%, P heterogeneity <0.01) for underweight women compared with normal weight women (Figure 6.18). For BMI ≥ 12 months post-diagnosis, the summary RR estimates for the same comparisons were 1.21 (95% CI: 1.06-1.38) (I^2 = 0%, P heterogeneity 0.70), 0.98 (95% CI: 0.86-1.11) (I^2 = 0%, P heterogeneity 0.72), and 1.29 (95% CI: 1.02-1.63) (I^2 = 0%, P heterogeneity 0.39) (Figure 6.19). Second-order fractional polynomial regression analyses showed J-shaped curves, which suggest normal weight women had the lowest risk of dying compared to women in other weight groups (both P-values for non-linearity <0.01) (Figure 6.17, above).

The summary RR estimates for obese versus normal weight ascertained <12 months post-diagnosis were 1.26 (95% CI: 1.03-1.54) (I^2 = 17%, P heterogeneity = 0.03) in women with premenopausal breast cancer and 1.20 (95% CI: 1.01-1.43) (I^2 = 43%, P heterogeneity 0.14) in women with postmenopausal breast cancer (P meta-regression = 0.58). Significant positive associations of similar magnitude were also observed by HR subtypes of breast cancer, with the summary RR estimates for the same comparison being 1.28 (95% CI: 1.06-1.53) (I^2 = 47%, P heterogeneity 0.11) in women with HR-positive breast cancer and 1.33 (95% CI: 1.05-1.70) (I^2 = 52%, P heterogeneity = 0.10) in women with HR-negative breast cancer (P meta-regression = 0.86) (Table 6.5, above).

Several studies of certain common characteristics appeared to explain partly the heterogeneity between the studies of BMI <12 months post-diagnosis and total mortality. Studies with larger number of deaths[441;448]; conducted in Europe[444;448]; or with weight and height assessed through medical records[444;447;448;451] tended to report weaker associations compared with other studies (P-values for meta-regression = 0.01, 0.02 and 0.01, respectively). Studies of different designs, length of follow-up and confounding factor adjustment did not find significantly different associations (all P-values for meta-regression >0.13) (Table 6.5, above). Subgroup meta-analyses were not conducted for the association of ≥12 post-diagnosis BMI because of low number of studies.

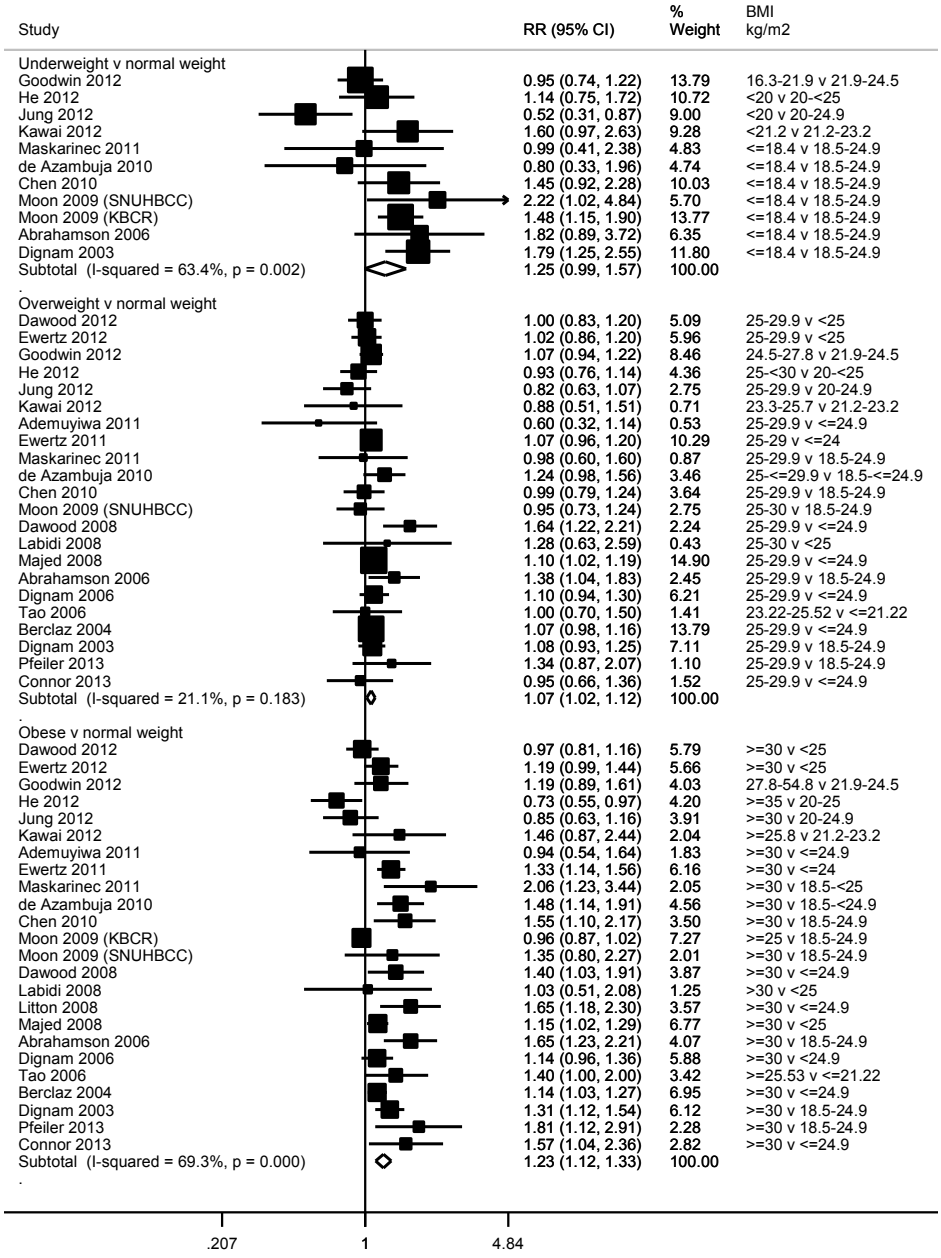

Figure 6.18 Relative risk and 95% CI of total mortality after breast cancer for obese, overweight, and underweight women compared with normal weight women ascertained less a year post-diagnosis

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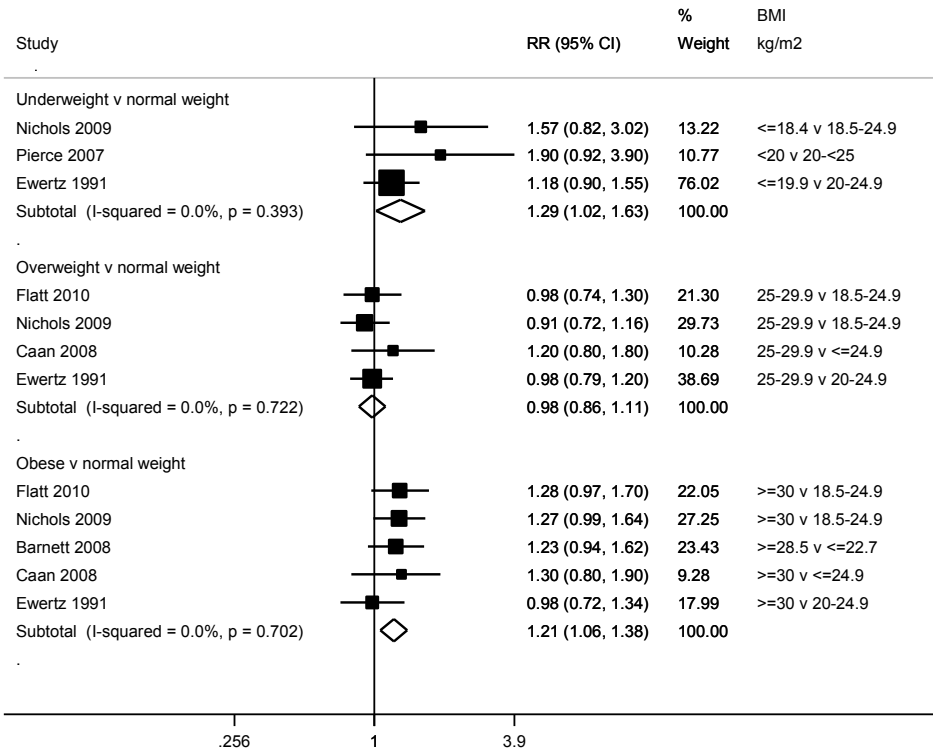

Figure 6.19 Relative risk and 95% CI of total mortality after breast cancer for obese, overweight, and underweight women compared with normal weight women ascertained more than a year post-diagnosis

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6.3.3.8 Pre-diagnosis body mass index and breast cancer mortality

Eighteen studies on pre-diagnosis BMI could be included in the dose-response meta-analysis (5,262 breast cancer deaths)[110-112;402;417;418;423;426;428-430;436-438;464-467]. In addition, 22 studies on obese women[110-112;114;400;402;416-418;423;426;428-430;436-438;464-468], 21 on overweight women[110-112;114;400;402;416-418;423;428-430;436-438;464-468], and 8 on underweight women[416;417;423;428;430;437;438;464] could be included in the categorical meta-analyses with normal weight women as reference group, respectively.

Pre-diagnosis BMI significantly increased the risk of breast cancer mortality (summary RR per 5 kg/m^2 = 1.18, 95% CI: 1.12-1.25) (Figure 6.20). Moderate heterogeneity was observed (I^2 = 47%, P heterogeneity = 0.01).

Statistically significant positive associations were also observed for obese women (summary RR = 1.35, 95% CI: 1.24-1.47) (I^2 = 36%, P heterogeneity = 0.05), and overweight women (1.11, 95% CI: 1.06-1.17) (I^2 = 0%, P heterogeneity = 0.66), but not for underweight women (1.02, 95% CI: 0.85-1.21) (I^2 = 31%, P heterogeneity = 0.18) compared with normal weight women (Figure 6.21). There was no significant evidence of non-linear relationship (P for non-linearity = 0.21) (Figure 6.17, above).

Obese women compared with normal weight women with HR-positive subtypes of the tumour had stronger risk of dying from breast cancer than women with HR-negative subtypes of the tumour (summary RRs = 1.42 (95% CI: 1.15-1.75) vs 1.01 (95% CI: 0.79-1.30)), although the different associations were not statistically significant (P for meta-regression = 0.09). Positive associations of similar magnitude were observed across the other subgroups (Table 6.6).

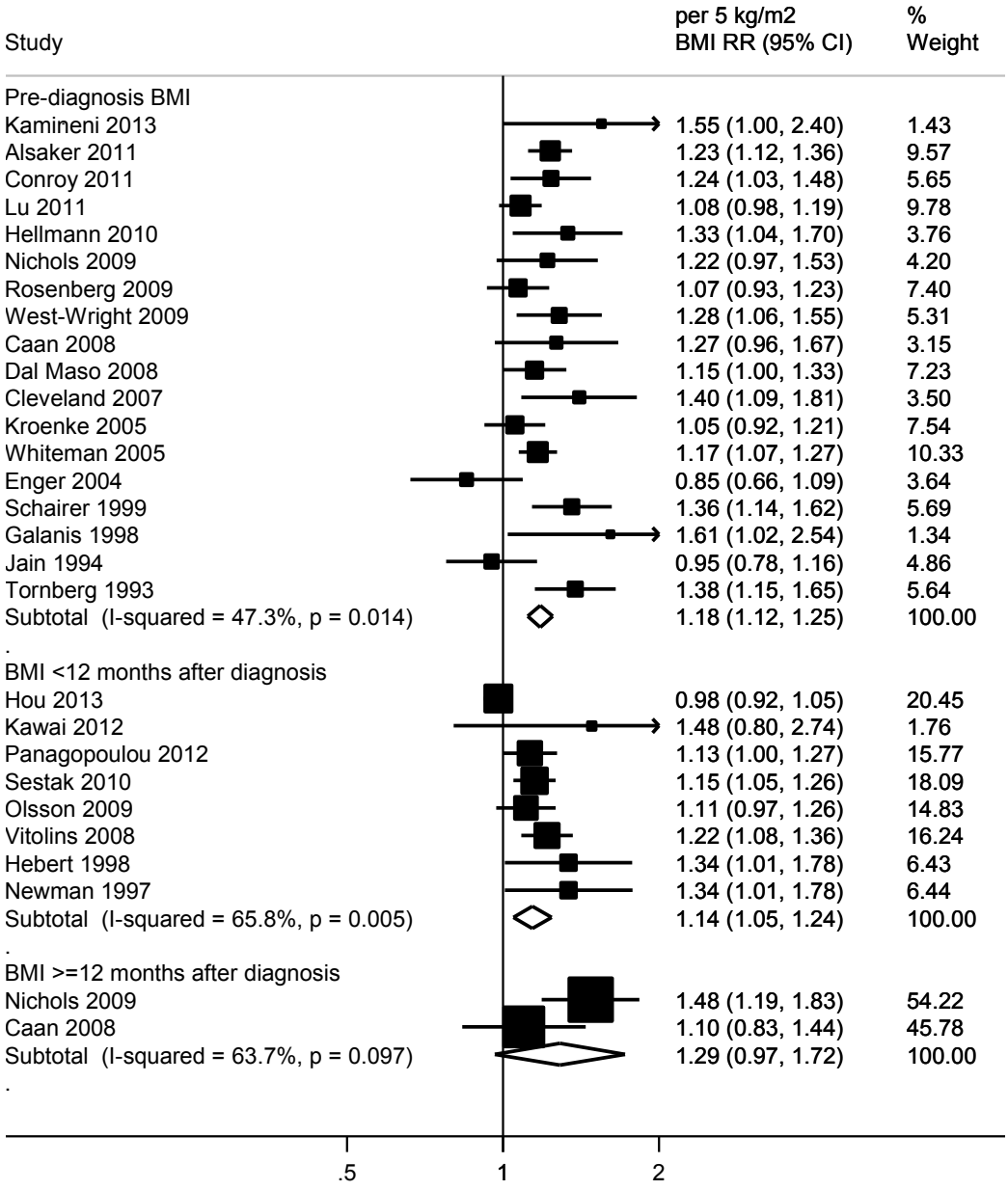

Figure 6.20 Relative risk and 95% CI of breast cancer mortality for 5 kg/m^2 increase of BMI ascertained before, a year or more post-diagnosis

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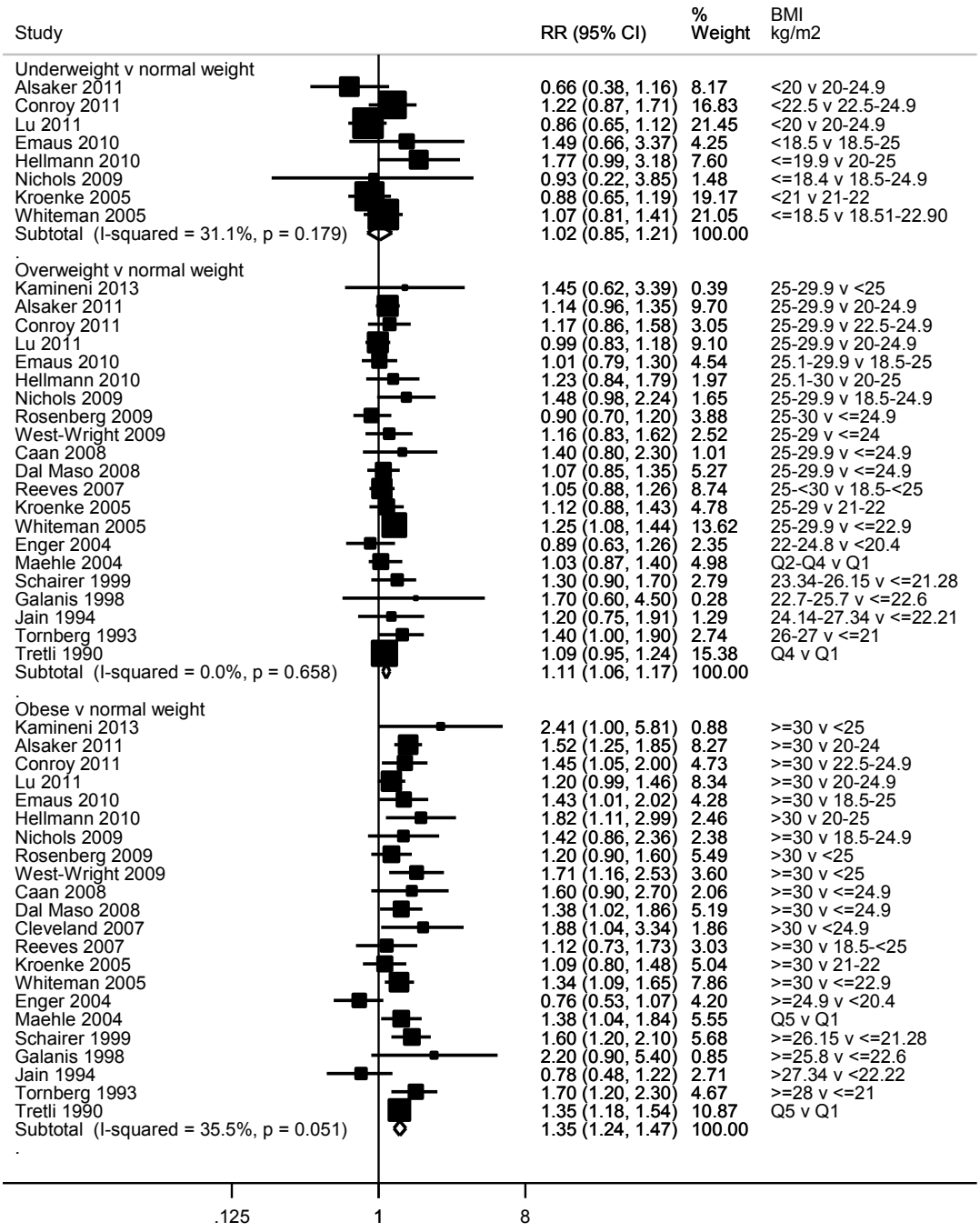

Figure 6.21 Relative risk and 95 % CI of breast cancer mortality for obese, overweight, and underweight women compared with normal weight women ascertained before diagnosis

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Table 6.6 Summary of subgroup meta-analyses of BMI and breast cancer mortality after breast cancer

	Pre-diagnosis BMI					BMI <12 months after diagnosis				
	N	RR (95% CI)	I^2 (%)	Phet	Pmet	*N*	RR (95% CI)	I^2 (%)	Phet	Pmet
Obese versus normal weight meta-analysis										
Menopausal status										
Premenopausal	8	**1.50 1.13-2.00**	70	<0.01	Ref	1	1.68 (0.61-4.64)	-	-	Ref
Postmenopausal	12	**1.34 1.21-1.48**	15	0.30	0.61	2	1.28 (0.99-1.66)	0	0.61	0.70
Hormone receptor status										
Positive	4	**1.42 1.15-1.75**	0	0.84	Ref	4	**1.33 (1.06-1.67)**	29	0.24	Ref
Negative	3	1.01 0.79-1.30	0	0.38	0.09	3	1.05 (0.86-1.28)	0	0.84	0.18
Linear dose-response meta-analysis (per 5 kg/m^2 increase)										
Menopausal status										
Premenopausal	5	1.12 (0.92-1.35)	72	0.01	Ref	2	**1.36 (1.03-1.79)**	0	0.67	Ref
Postmenopausal	7	**1.15 (1.05-1.25)**	54	0.04	0.89	1	1.05 (0.42-2.63)	-	-	0.69
Number of deaths										
<400	12	**1.18 (1.08-1.29)**	46	0.04	Ref	4	**1.25 (1.13-1.38)**	0	0.81	Ref
401-800	4	**1.24 (1.10-1.39)**	61	0.05	0.53	3	**1.13 (1.06-1.21)**	0	0.89	0.16
>800	2	**1.13 (1.04-1.21)**	29	0.23	0.60	1	0.98 (0.92-1.05)	-	-	0.01
Length of follow-up										
≤5 y	1	**1.38 (1.15-1.65)**	-	-	Ref	1	**1.34 (1.01-1.78)**	-	-	Ref
>5-≤10 y	12	**1.17 (1.10-1.24)**	38	0.09	0.25	6	**1.11 (1.01-1.21)**	64	0.02	0.30
>10 y	5	**1.17 (1.03-1.33)**	63	0.03	0.27	1	1.22 (1.08-1.36)	-	-	0.63
Study design										
RCT-based	1	0.95 (0.78-1.16)	-	-	Ref	3	**1.16 (1.09-1.24)**	0	0.56	Ref
Prospective cohort	9	**1.25 (1.17-1.33)**	17	0.30	0.05	3	**1.35 (1.12-1.64)**	0	0.95	0.22
Retrospective cohort	1	1.55 (1.00-2.40)	-	-	0.10	2	1.04 (0.91-1.19)	75	0.05	0.10
Cases of case-control	7	**1.12 (1.04-1.21)**	41	0.12	0.21	-	-	-	-	-
Geographic location										
North America	13	**1.17 (1.09-1.26)**	51	0.02	Ref	3	**1.25 (1.13-1.38)**	0	0.72	Ref
Europe	5	**1.21 (1.11-1.31)**	37	0.18	0.59	2	**1.12 (1.02-1.22)**	0	0.85	0.19
Asia Pacific	0	-	-	-	-	2	1.07 (0.77-1.50)	42	0.19	0.02
International	0	-	-	-	-	1	**1.15 (1.05-1.26)**	-	-	0.32
Exposure assessment methods										
Measured	4	**1.21 (1.05-1.40)**	63	0.04	Ref	4	**1.19 (1.12-1.28)**	0	0.58	Ref
Self-reported	14	**1.17 (1.10-1.24)**	42	0.05	0.62	1	1.48 (0.80-2.74)	-	-	0.56
Medical records	0	-	-	-	-	2	1.04 (0.91-1.19)	75	0.05	0.09
Adjustment for confounders										
Tumour stage										
Yes	14	**1.17 (1.10-1.24)**	39	0.07	Ref	7	**1.13 (1.03-1.23)**	63	0.01	Ref
No	4	**1.22 (1.05-1.42)**	66	0.03	0.53	1	**1.22 (1.08-1.36)**	-	-	0.48
Cancer treatment										
Yes	4	**1.16 (1.07-1.25)**	16	0.31	Ref	4	1.09 (0.97-1.22)	72	0.01	Ref
No	14	**1.19 (1.11-1.28)**	55	0.01	0.84	4	**1.19 (1.10-1.29)**	0	0.45	0.19
Comorbidities/diabetes										
Yes	3	**1.21 (1.03-1.42)**	62	0.07	Ref	2	1.07 (0.77-1.50)	42	0.19	Ref
No	15	**1.18 (1.11-1.25)**	48	0.02	0.85	6	**1.17 (1.10-1.23)**	0	0.65	0.01
Physical activity										
Yes	5	**1.18 (1.01-1.38)**	54	0.07	Ref	1	1.48 (0.80-2.74)	-	-	Ref
No	13	**1.18 (1.11-1.25)**	49	0.02	0.98	7	**1.14 (1.04-1.24)**	69	<0.01	0.44
Alcohol use										
Yes	3	1.24 (0.99-1.54)	56	0.10	Ref	0	-	-	-	-
No	15	**1.18 (1.11-1.25)**	49	0.02	0.87	8	**1.14 (1.05-1.24)**	66	0.01	-
Smoking										
Yes	5	**1.17 (1.07-1.28)**	4	0.38	Ref	1	1.48 (0.80-2.74)	-	-	Ref
No	13	**1.18 (1.10-1.26)**	57	0.01	0.87	7	**1.14 (1.04-1.24)**	69	<0.01	0.44

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6.3.3.9 Post-diagnosis body mass index and breast cancer mortality

Eight studies on BMI ascertained <12 months post-diagnosis could be included in the dose-response meta-analysis (3,857 breast cancer deaths)[443;449;469-474]. Twelve studies on obese women[399;443;452;458;461;462;469-472;474;475], 12 on overweight women[399;443;452;458;461;462;469-472;474;475], and five on underweight women[397;443;458;462;472] could be included in the categorical meta-analyses, respectively.

The respective numbers for the studies on BMI ascertained ≥ 12 months post-diagnosis were two studies in the dose-response meta-analysis (220 breast cancer deaths)[428;429], and two[428;429], two[428;429] and one[428] in the categorical meta-analyses.

BMI ascertained <12 months post-diagnosis was significantly positively associated with breast cancer mortality risk. The summary RR estimates were 1.14 (95% CI: 1.05-1.24) (I^2 = 66%, P heterogeneity = 0.005) for each 5 kg/m^2 increase in BMI (Figure 6.20, above); and 1.25 (95% CI: 1.10-1.42) (I^2 = 53%, P heterogeneity = 0.02) for obese women, 1.11 (95% CI: 1.03-1.20) (I^2 = 14%, P heterogeneity = 0.31) for overweight women, and 1.53 (95% CI: 1.27-1.83) (I^2 = 0%, P heterogeneity = 0.59) for underweight women compared with normal weight women, respectively (Figure 6.22).

For BMI ≥ 12 months post-diagnosis, the positive associations were not statistically significant. The summary RR estimates were 1.29 (95% CI: 0.97-1.72) (I^2 = 64%, P heterogeneity = 0.10) per 5 kg/m^2 (Figure 6.20, above); and 1.68 (95% CI: 0.90-3.15) (I^2 = 67%, P heterogeneity = 0.08) for obese women, and 1.37 (95% CI: 0.96-1.95) (I^2 = 0%, P heterogeneity = 0.90) for overweight women compared with normal weight women, respectively (Figure 6.23). The only study reported results on breast cancer mortality risk for underweight compared with normal weight women found a statistically non-significant association (RR = 1.10, 95% CI: 0.15-8.08) (Figure 6.23). Publication bias was detected in studies of <12 months post-diagnosis BMI (P for Egger' test = 0.03) (graph not shown). Second-order fractional polynomial regression analyses did not show non-linear relationships (P-values for non-linearity = 1.00 for BMI <12 months, and 0.86 for BMI ≥12 months post-diagnosis) (Figure 6.17, above).

Compared with normal weight women ascertained <12 months post-diagnosis, obese women with HR-positive breast cancers had stronger breast cancer mortality risk than obese women with HR-negative breast cancers, but the associations were not statistically significantly different (summary RRs = 1.33, 95 CI: 1.06-1.67 vs 1.05, 95% CI: 0.86-1.28, respectively) (P-values for meta-regression = 0.18) (Table 6.6, above). Heterogeneity between studies of <12 months post-diagnosis BMI could be explained partly by two studies that existed commonly across the subgroups. Studies with larger number of deaths[469], conducted in Asia[443;469], and adjusted for co-morbidity [443;469] had weaker non-significant associations (P-values for meta-regression = 0.01, 0.02 and 0.01, respectively). No other significantly different associations were observed in the subgroup meta-analyses (all P-values for meta-regression ≥0.09) (Table 6.6, above).

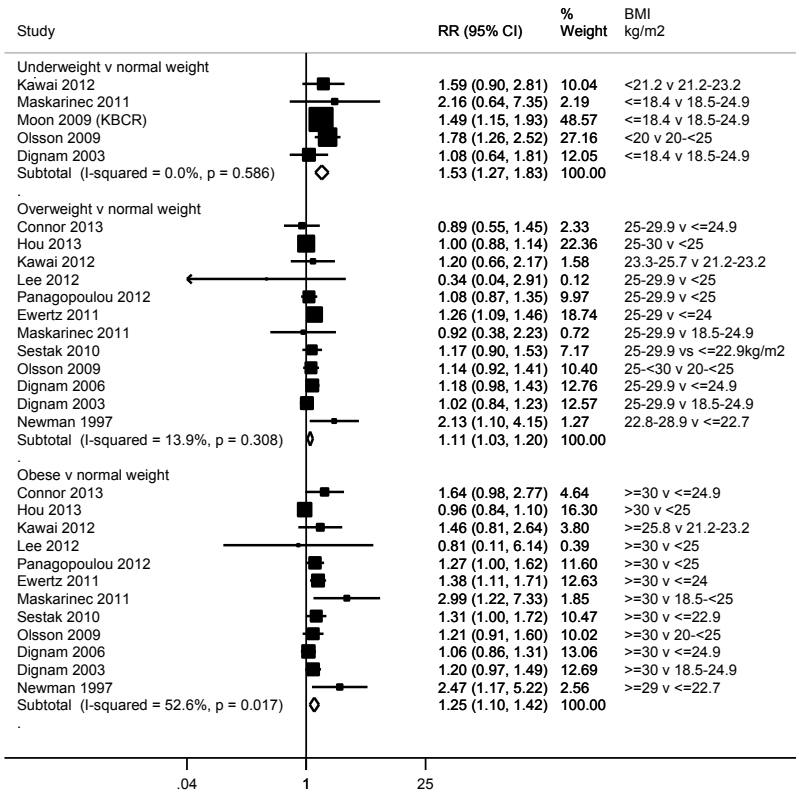

Figure 6.22 Relative risk and 95% CI of breast cancer mortality for obese, overweight, and underweight women compared with normal weight women ascertained less a year post-diagnosis

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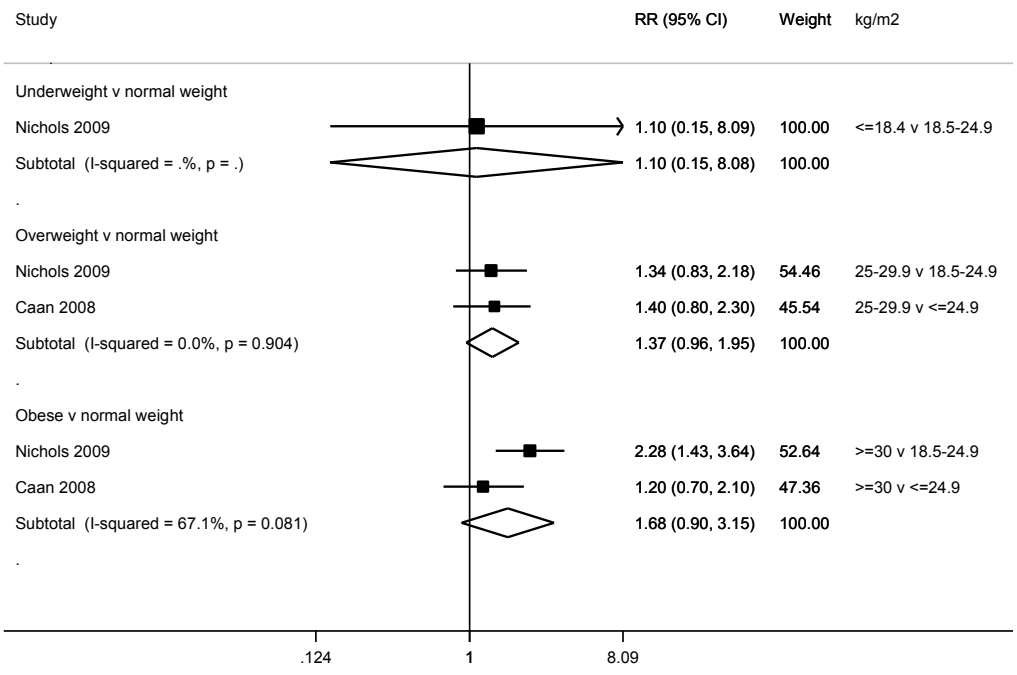

Figure 6.23 Relative risk and 95% CI of breast cancer mortality for obese, overweight, and underweight women compared with normal weight women ascertained more than a year post-diagnosis

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6.3.3.10 Waist circumference and total mortality

One study on pre-diagnosis waist circumference was identified. All three studies on <12 months post-diagnosis waist circumference could be included in the dose-response meta-analysis. No studies examined ≥12 months post-diagnosis waist circumference.

The only study (IWHS) reported results on pre-diagnosis waist circumference and total mortality risk found a non-significant positive association (RR for 36.6-56 vs 23-32 inches = 1.10, 95% CI: 0.60-2.10) (P trend = 0.77) (56 deaths, 698 breast cancer cases, average 2.9 years follow-up)[115].

Waist circumference ascertained <12 months after diagnosis was non-significantly positively associated with the risk of total mortality in breast cancer survivors (summary RR per 10 cm = 1.21, 95% CI: 0.97-1.49). Substantial proportion of heterogeneity was detected (I^2 = 75%, P heterogeneity = 0.02) (3 studies[422;442;450]) (664 deaths) (Figure 6.24). Studies did not include BMI in the statistical model. One study reported additional results that showed attenuation of association when BMI was adjusted (RR for ≥88 vs <79 = 1.75, 95% CI: 1.20-2.55) (P trend = 0.03)[422].

The Canadian study was small (134 deaths, among 535 breast cancer survivors from hospitals, after average 12.1 years)[442]. The Shanghai Breast Cancer Study (SBCS) from China had short follow-up (240 deaths, among 1,455 breast cancer cases, after average 5.1 years)[450]. The American follow-up study of women with breast cancer from a population-based case-control study had 290 deaths among 1,254 women with breast cancer after 9.8 years, treatment information was not available in the whole study[422]. The studies included pre- and postmenopausal women. Waist circumference was measured, soon after[442;450] or 4.2 months after[422] cancer diagnosis; therefore was not subjected to report bias, but body weight could change around diagnosis and during treatment.

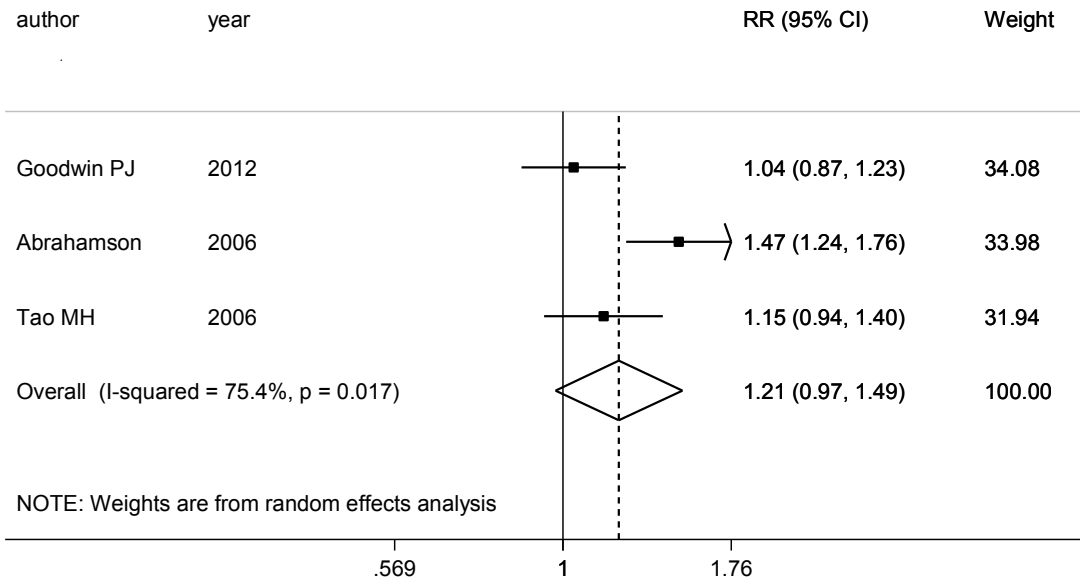

Figure 6.24 Relative risk and 95% CI of total mortality after breast cancer for 10 cm increase of waist circumference ascertained before diagnosis

6.3.3.11 Waist circumference and breast cancer mortality

No studies were identified.

6.3.3.12 Hip circumference and total mortality

One study on pre-diagnosis, two studies on <12 months post-diagnosis and no studies on ≥12 months post-diagnosis hip circumference were identified.

The IWHS reported a statistically non-significant positive association with total mortality risk (RR for 42.5-59.8 vs 21-39.1 inches = 1.8, 95% CI: 0.8-3.8) (P trend = 0.15) (56 deaths in total)[115].

Non-significant positive associations were also observed for the highest versus the lowest hip circumference measured <12 months post-diagnosis. The RR estimates were 1.21 (95% CI: 0.88-1.66) (P trend = 0.04) (290 deaths)[422] and 1.12 (95% CI: 0.80-1.55) (P trend = 0.71) (134 deaths)[442]. The association was attenuated after BMI adjustment (0.80, 95% CI: 0.49-1.3) (P trend = 0.54)[422].

6.3.3.13 Hip circumference and breast cancer mortality

IWHS was the only study identified. A 2.1-fold increased risk of breast cancer mortality was observed for 42.5-59.8 inches versus 21.0-39.1 inches pre-diagnosis hip circumference[115]. 95% CI and P-value was not reported in the study.

6.3.3.14 Waist-hip-ratio and total mortality

One study reported results on pre-diagnosis waist-hip-ratio. All four studies on <12 months post-diagnosis waist-hip-ratio could be included in the dose-response meta-analysis. No studies examined waist-hip-ratio ≥12 months post-diagnosis.

For waist-hip-ratio ascertained before diagnosis, the only study identified (IWHS) found a non-significant positive association (RR for 0.89-1.62 vs 0.58-0.80 unit = 1.10, 95% CI: 0.60-2.20) (P trend = 0.69) (40 breast cancer deaths)[115].

For waist-hip-ratio ascertained less than 12 months after diagnosis, there was a significant positive association with total mortality risk on average (summary RR per 0.1 unit = 1.31, 95% CI: 1.17-1.48) (I^2 = 0%, P heterogeneity = 0.73) (4 studies[418;422;427;450]) (1,475 deaths) (Figure 6.25). The summary RR estimate remained statistically significant in influence analysis. Two studies each used measured[422;450] or self-reported data[418;427], and the results were similar.

6.3.3.15 Waist-hip-ratio and breast cancer mortality

Only two studies were identified, both reported results on <12 months post-diagnosis waist-hip-ratio. The Italian study found a statistically non-significant positive association (RR [BMI unadjusted] for ≥0.85 vs ≤0.79 = 1.27, 95% CI: 0.98-1.64) (P trend = 0.06) (398 breast cancer deaths)[418]. The

Canadian study reported positive associations, that was significant in postmenopausal women (RR [BMI adjusted] for >0.848 vs <0.756 = 3.3, 95% CI: 1.1-10.4) and not in premenopausal women (1.2, 95% CI: 0.4-3.4) (112 breast cancer deaths)[476].

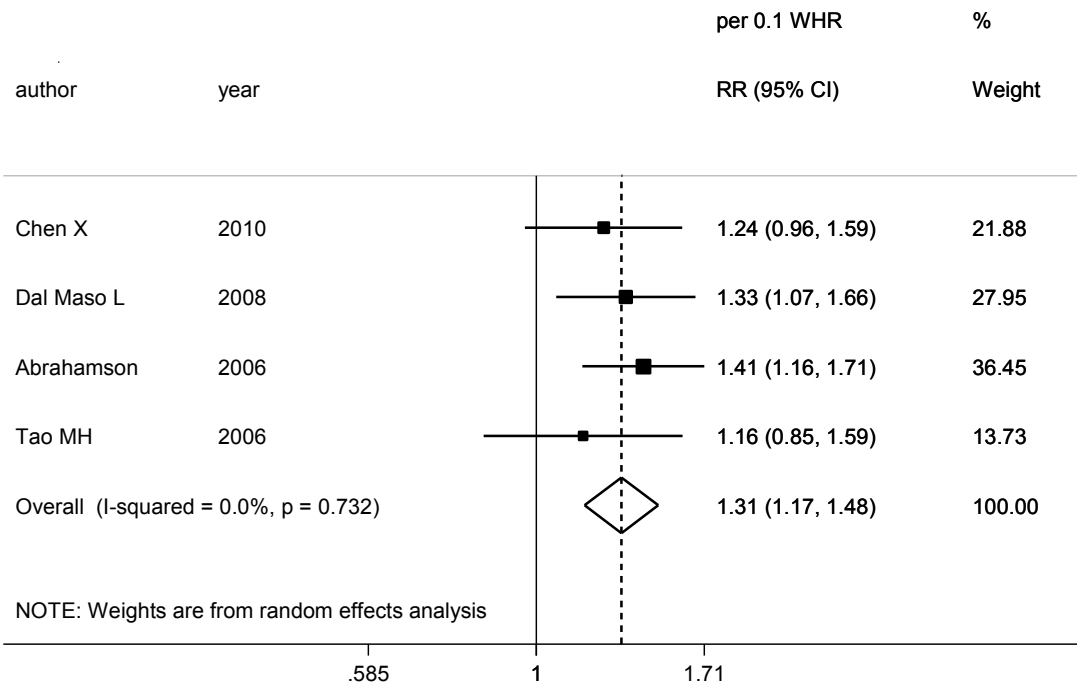

Figure 6.25 Relative risk and 95% CI of total mortality after breast cancer for 0.1 unit increase of waist-hip-ratio ascertained less than a year post-diagnosis

6.4 Summary of the meta-analyses

In summary, breast cancer survivors who performed high level of physical activity had generally lower risk of dying after cancer diagnosis. Specifically, women with the highest level of recreational physical activity performed prior to cancer diagnosis had statistically significantly reduced risk of total mortality and breast cancer mortality compared with women with the lowest level of activity. After cancer diagnosis, the inverse association of recreational physical activity performed during this period was statistically significant with total mortality risk. Moderate or vigorous physical activity before or after breast cancer diagnosis were also shown to associate inversely with total mortality risk in breast cancer survivors.

Overweight and obese breast cancer survivors, regardless of when the weight status was ascertained, had statistically significant higher risk of total mortality and breast cancer mortality. Underweight breast cancer survivors were also at higher risk of dying, but such findings could be due to reverse causation. Overall, it showed that women of normal weight had the most favourable survival after breast cancer. Furthermore, waist-to-hip ratio ascertained ≤12 months after breast cancer diagnosis and weight gain before and after breast cancer diagnosis were positively associated with risk of total

mortality, and weight gain after cancer diagnosis was significantly positively associated with breast cancer mortality risk.

As in the studies of breast cancer incidence, total energy intake was not significantly related to mortality risk in breast cancer survivors.

6.5 Grading of the evidence

Below is the full consideration of the robustness and quality of the evidence, and the judgement on the confidence of the observed evidence to infer causality, made based on the WCRF grading criteria (see section 4.1.6).

Number and size of studies

The body of evidence was relatively small for factors other than BMI, even though overall 149 publications were identified. Because the associations were examined by exposure timeframe and mortality outcome, some meta-analysis, particularly those on post-diagnosis factors and/or breast cancer mortality, comprised only a small number of studies. In addition, many studies only had a small number of deaths.

Dose-response relationship

Statistically significant dose-response relationships were observed for (≥12 months) post-diagnosis recreational physical activity and total mortality risk, pre-diagnosis BMI and BMI less than a year or more post-diagnosis and total mortality risk, and (<12 months) post-diagnosis waist-hip-ratio and total mortality risk. Pre-diagnosis BMI and (<12 months) post-diagnosis BMI were also significantly associated with the risk of breast cancer mortality.

The associations were modest in magnitude. The summary RR estimates ranged from 0.81 to 1.31, with narrow 95% CIs. The results for ≥ 12 months post-diagnosis BMI and total mortality risk became non-significant in influence analysis.

Heterogeneity

Significant proportions of heterogeneity were observed between the studies of ≥12 months post-diagnosis recreational physical activity and total mortality risk. It was not possible to explore the potential sources in a subgroup analysis because of the low number, but since all studies in the analysis found an inverse association, the difference detected was due to the variations in magnitude instead of direction of the association. Between-studies heterogeneity was also significant for post-diagnosis weight gain and total mortality risk. This is likely due to the diverse measurement of weight gain.

Significant proportions of heterogeneity were also observed in the analyses of BMI and risks of total and breast cancer mortality. As described, sources of heterogeneity were identified (see sections

6.3.3.6-3.3.9); and the positive associations were generally consistent in the dose-response meta-analysis.

Publication bias

Egger's tests were statistically significant for <12 months post-diagnosis BMI and risk of total mortality and breast cancer mortality. However, the overall evidence was supported by studies of larger sizes.

Other than BMI, publication bias could not be evaluated for other energy balance-related factors because of the low numbers.

Study quality

Factors related to study design, dietary intake, physical activity and body measurements assessment and/or confounding factors adjustment may have an impact on the results. Study quality was not evaluated using an overall score, but specific issues were noted, as detailed below.

Generalisation of study population and selection bias

The external validity of the studies of breast cancer survivors depends on the characteristics of the patients, timing of recruitment, and the length of follow-up, which could vary between the studies; although most studies include early stages breast cancer patients and the studies were from the US or Europe that have better medical facilities. The generalisation of findings from RCT of cancer survivors is in question, as such trials may recruit cancer patients of less advanced cancers, who are younger, stronger, with less complicated disease and co-morbidities, and were more likely to receive protocol treatments with high treatment completion rates. Selection bias because of survival benefit in healthier patients was detected in the LACE study and possibly in the WHEL trial.

The J-shaped relationship was more evident between ≥12 months post-diagnosis BMI and total mortality risk, suggesting the so-called 'obesity paradox' phenomenon (higher BMI is associated with more favourable survival)[477]. Obesity paradox could be real or a result of collider stratification, a specific type of selection bias, in which a risk factor such as obesity also drives selection into the study population, and can distort the findings.

Exposure assessment/measurement error

Studies of cancer survivors used the same exposure assessment methods as in the population studies, thus were subjected to the same measurement errors as described in section 5.5: exposure assessment/measurement error. Furthermore, recall bias was possible, in the studies that followed women with breast cancer from a case-control study and in the studies that asked breast cancer survivors for information before the cancer diagnosis.

Exposure factors were only measured once at study baseline and changes were not accounted for throughout the follow-up in most studies. This is particularly important because cancer survivors may change their lifestyles around diagnosis and during treatment[209].

Confounding adjustment

Most studies controlled for known prognostic factors, such as, age, tumour stage, size, and/or grade, and in some studies, treatment types. Subgroup analysis could be conducted for the associations of BMI and mortality risks, and generally did not find significantly different associations.

Nevertheless, treatment compliance and responses, co-morbidities, and quality of life-related factors, such as depression, fatigue and pain, which could relate to both the exposure and outcome of interest, were mostly not addressed in the studies. Treatment effect may be of particular concerns. Obese cancer patients may be at a higher mortality risk because of chemotherapy under-dosing and sub-optimal treatment, in addition to higher risk of cardiotoxicity, although the lack of type of surgery and adjuvant therapy information may not be as big an issue in studies that had adjusted for tumour stage and grade, as these variables have been shown to be correlated with systemic adjuvant therapy assignment[415].

Patient characteristics, for instance weight change that occur commonly during chemotherapy treatment, menopausal status of younger women who had ovarian ablation, and assigned treatment (new regimen for HER2-positive cancer patients, the switch of tamoxifen to aromatase inhibitors) may change along the survivorship and were not always captured by the studies. The associations observed post-diagnosis may reflect that of pre-diagnosis, for example obese cancer patients have perturbed hormonal factors since before the diagnosis. Most cancer survival studies did not take into account the pre-diagnostic factors.

Reverse causation

Reverse causation was likely a bigger problem for survival studies, as the percentage of sick participants was relatively high and the study outcome was mortality rather than incident events[478].

Specifically, body fatness could be changed due to the lifestyles, illness and/or treatment related to cancer. Comorbidity and advanced disease may limit physical activity performance. More severe or aggressive disease patients could perform physical activity more vigorously as a coping mechanism to the disease and treatment effects[409], which would lead to attenuation of the association.

Few studies had examined the potential bias, but reported no different associations

Follow-up

Cancer survivors were prospectively followed up for mortality events in the survival studies, however most studies were of relatively short follow-up (<5 years), which may miss any late effects on cancer survival.

Outcome definitions

Misclassification of causes of death is possible. Not all studies separated *in situ* from invasive breast cancer. Patients with i*n situ* breast cancer may have fewer events and better prognosis. Many *in situ* breast cancer cases are detected through mammography screening, which attendance disparity is possible (see section 3.1.1, socioeconomic factors).

Biological mechanisms

The same mechanistic pathways involved in breast cancer development are believed to implicate breast cancer progression.

6.6 Judging the evidence

Taken together, the findings on breast cancer survival were downgraded because of the likely reverse causation and confounding bias, and other issues.

Accordingly, there was no strong (convincing or probable) evidence that the associations on the risk of mortality in breast cancer survivors are likely causal (Table 6.7).

There is limited/suggestive evidence that:

- Physical activity before diagnosis decreases the risks of total mortality and breast cancer mortality in breast cancer survivors
- Physical activity (≥12 months) post-diagnosis decreases the risk of total mortality
- Body fatness (BMI) before diagnosis increases the risks of total mortality and breast cancer mortality
- Body fatness (BMI) (< or ≥12 months) post-diagnosis increases the risk of total mortality
- Body fatness (BMI) (< 12 months) post-diagnosis increases the risk of breast cancer mortality

These judgements were consistent to those made in the WCRF Second Expert Report (see section 3.2.1).

Table 6.7 Summary of judgements on energy balance-related factors and risk of mortality after breast cancer

	Decreases risk	**Increases risk**
Convincing		
Probable		
Limited – suggestive	Physical activity	Body fatness (BMI)
Limited – no conclusion	Total energy intake, weight gain, weight loss, waist circumference, waist-hip ratio, hip circumference	
Substantial effect on risk unlikely	None identified	

7 Systematic reviews of WCRF/AICR recommendations adherence and breast cancer

7.1 Results of the literature search

Ten relevant publications (8 from the general PubMed search, 1 from the reference list and 1 from the specific PubMed search) were identified.

Seven studies, of which six reported categorical results, could be included in the dose-response and the highest versus the lowest meta-analyses of overall adherence score and risk of breast cancer incidence, respectively. Further, six studies were pooled in the meta-analyses of adherence versus non-adherence to each individual component of the score.

Three publications were excluded from the meta-analyses. One was a consortium of seven elderly cohorts[479], which overlapped with the multi-centre cohort that was already included in the meta-analysis[14]. The consortium found a null association with breast cancer risk (RR per 1 point increase = 0.93, 95% CI: 0.86-1.00)[479]. One was a mortality study of two cohorts, which reported a statistically non-significant inverse association with high versus low lifestyle score (RR = 0.76, 95% CI: 0.45-1.30)[480]. One was a cohort that comprised breast cancer survivors, which observed a significant decreased risk of total mortality (RR for Q4 vs Q1 = 0.61, 95% CI: 0.39-0.96) (P trend = 0.01), but not mortality specific to breast cancer (0.88, 95% CI: 0.41-1.91) (P trend = 0.65), and cardiovascular disease (0.67, 95% CI: 0.33-1.37) (P trend = 0.10)[15].

7.2 Characteristics of the studies

The included studies were either from North America or Europe. One study was on American African women. Two studies were of postmenopausal women only. There was a mammography screening cohort, and a prospective study originated from a mammography screening RCT.

One study had limited number of cases, thus was of low statistical power (124 cases)[481]. The average follow-up was at least 6.7 years[482]. Cases ascertainment was mostly through record linkages to the health or cancer registries, and was therefore mostly complete. Studies either adjusted for or tested the inclusion of multiple confounding factors, including age, reproductive factors, education or smoking in the statistical models. No relevant issues regarding study quality were detected.

Appendix 6 shows the main characteristics of the studies included in the present review.

7.3 WCRF/AICR adherence scores operationalised in the studies

The construction of the WCRF/AICR adherence score was study-specific, depending on the applicability of the recommendations and the availability of data in the study. The scoring of the recommendations was based on expert decisions, existing recommendations and/or the distribution of data in the study. Appendix 7 shows the operationalisation of the score in the studies. All adherence

scores comprised the recommendations on body fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal foods and alcohol consumption. Four studies additionally operationalised the score for added salt, salty foods or sodium intake[255;481;483;484]. One study each also operationalised the score for dietary supplements[485] and breastfeeding[14].

The studies awarded maximum 1 point for full adherence to a recommendation. Occasionally, 0.5 point was awarded for partial adherence, to allow for greater variability of scores in the study population. Sub-component scores were either treated as scores for separate recommendations which were then added up[483] or taken as an average for the recommendation[14]. One study computed weighted average overall score[481].

Maximum adherence score was 6[14;482], 7[255;481;484;485] or 8[483] in the studies. Most study participants scored towards the higher end of the range, with 4-<5 out of 7[14;484;485] or 5 out of 8 points[483]; apart from one study, in which most women scoring <3 out of 7 points[255] and the another study, 2 out of 6 points[482] (see Appendix 6).

Alcohol consumption was the most likely met recommendation in all included studies[14;255;482-485], with 66%[14] to 95%[485] of the study participants scoring full point (see Appendix 6). Plant foods (2-20% adherence)[255;482;485] and animal foods (11-18% adherence)[14;483;484] were among the least likely met recommendations in the studies. In-between were the recommendations related to energy balance.

7.4 Results of the studies

7.4.1 WCRF/AICR overall adherence score and breast cancer risk

Table 7.1 is the summary of the meta-analyses of the present review.

Adherence to the recommendations was statistically significantly inversely associated with the risk of breast cancer incidence overall. For each 1 point increase of adherence score, the summary RR was 0.91 (95% CI: 0.88-0.94) (7 studies[14;255;481-485]) (18,495 cases) (Figure 7.1). When the categorical results were pooled, the summary RR for the highest versus the lowest adherence score was 0.72 (95% CI: 0.61-0.84) (6 studies[14;255;481-485]) (18,371 cases) (Figure 7.2).

There was evidence of significant between-study heterogeneity (I^2 = 63% and 73%, P heterogeneity = 0.012 and 0.003, respectively), which were not explained by geographic location of the studies (5 North American[255;481-484] and 2 European studies[14;485]), or HR subtypes of breast cancer (1,432 HR-positive and 517 HR-negative breast cancer cases in 3 studies[255;482;485]). Subgroup meta-analyses by these factors showed consistent inverse associations (Table 7.1). The heterogeneity remained high within the subgroups.

There was evidence of significant publication bias (P for Egger's test < 0.01) (Figure 7.3). Visual inspection of the funnel plot shows asymmetry, suggesting more small studies with a stronger than the average inverse association. Summary RRs remained significant in influence analyses. No threshold

effect was detected in the non-linear analysis (P for non-linearity = 0.67). Overall breast cancer risk decreased linearly with increasing adherence score (Figure 7.4).

Table 7.1 Summary of the meta-analyses of 2007 WCRF/AICR recommendation adherence and risk of breast cancer overall and postmenopausal breast cancer

		Any breast cancer				Postmenopausal breast cancer		
WCRF Adherence (increment/ comparison)	**Studies**	**RR (95% CI)**	**I^2 (%)**	**P heterogeneity**	**Studies**	**RR (95% CI)**	**I^2 (%)**	**P heterogeneity**
Overall adherence								
Overall (Per 1 score)	7	**0.91 (0.88-0.94)**	63	0.01	3	**0.88 (0.84-0.92)**	0	0.68
Overall (Highest vs lowest)	6	**0.72 (0.61-0.84)**	73	<0.01	3	0.70 (0.48-1.03)	79	<0.01
Subgroup by geographic location (Per 1 score)								
Europe	2	**0.93 (0.87-0.99)**	69	0.07	-	-	-	-
North America	5	**0.89 (0.84-0.94)**	61	0.04	3	**0.88 (0.84-0.92)**	0	0.68
Subgroup by HR type (Per 1 score)								
HR-positive	3	**0.89 (0.84-0.93)**	0	0.69	1	**0.90 (0.85-0.96)**	-	-
HR-negative	3	0.85 (0.73-1.00)	38	0.20	1	**0.84 (0.72-0.99)**	-	-
Adherence to component recommendation (Met vs not met recommendation)								
Body fatness	5	0.91 (0.80-1.02)	77	0.001	3	**0.85 (0.74-0.97)**	55	0.11
Physical activity	**5**	**0.91 (0.83-0.99)**	54	0.07	3	0.90 (0.79-1.03)	44	0.17
Foods and drinks that promote weight gain	3	0.95 (0.85-1.06)	45	0.17	1	1.04 (0.88-1.22)	-	-
Sugary drinks	1	0.90 (0.62-1.30)	-	-	1	0.90 (0.62-1.30)	-	-
Plant foods	4	0.93 (0.85-1.01)	0	0.44	2	0.89 (0.69-1.15)	30	0.23
Red meat and processed meat	4	**0.84 (0.77-0.91)**	0	0.60	2	0.90 (0.78-1.03)	0	0.33
Alcoholic drinks	5	**0.83 (0.70-0.98)**	71	<0.01	3	**0.74 (0.58-0.94)**	66	0.05
Sodium intake	2	0.99 (0.90-1.09)	0	0.98	1	1.10 (0.82-1.48)	-	-

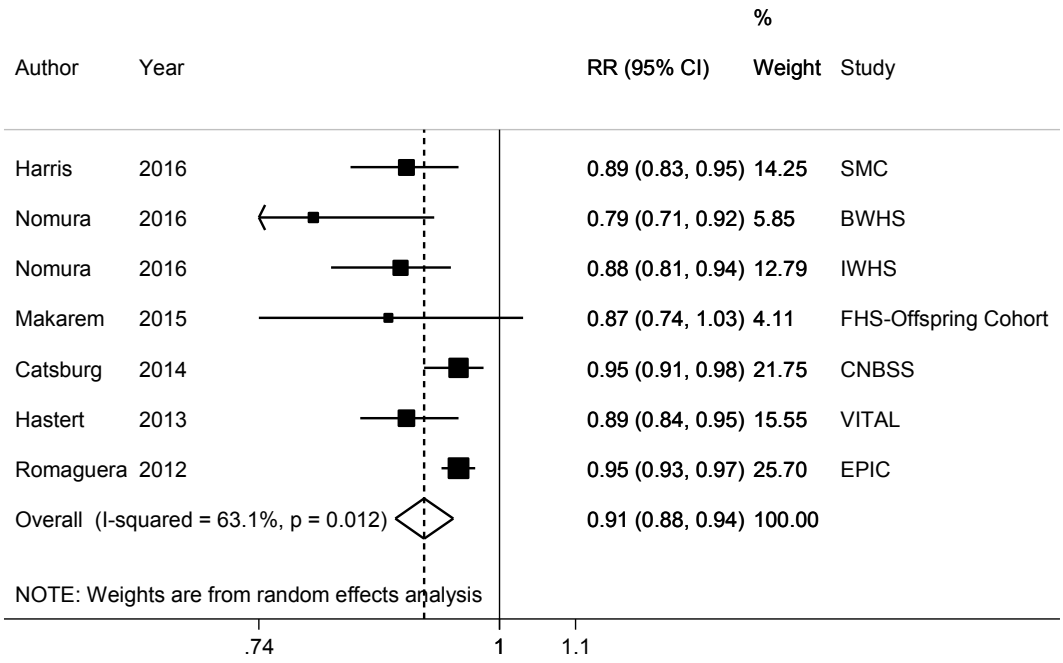

Figure 7.1 Relative risk and 95% CI of overall breast cancer for 1 point increase of adherence score

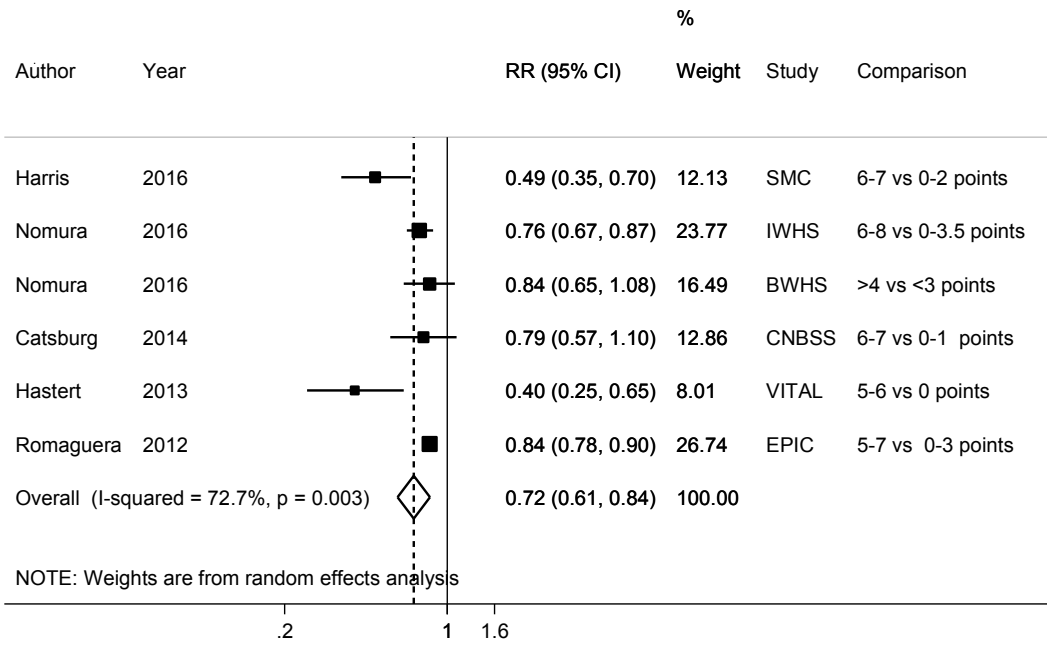

Figure 7.2 Relative risk and 95% CI of overall breast cancer for the highest compared with the lowest adherence

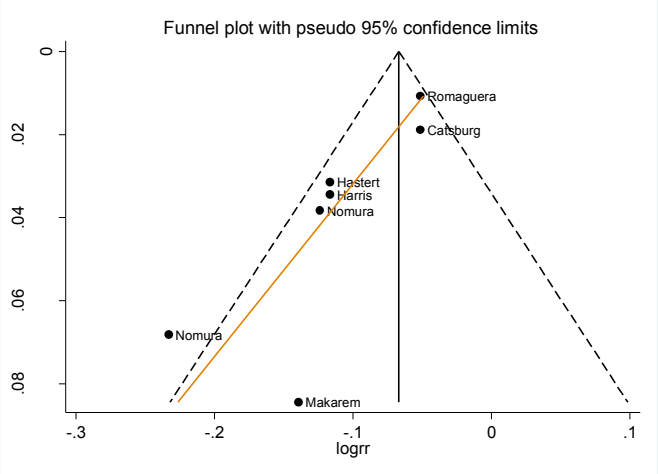

Figure 7.3 Funnel plot of studies included in the dose response meta-analysis of adherence score and breast cancer

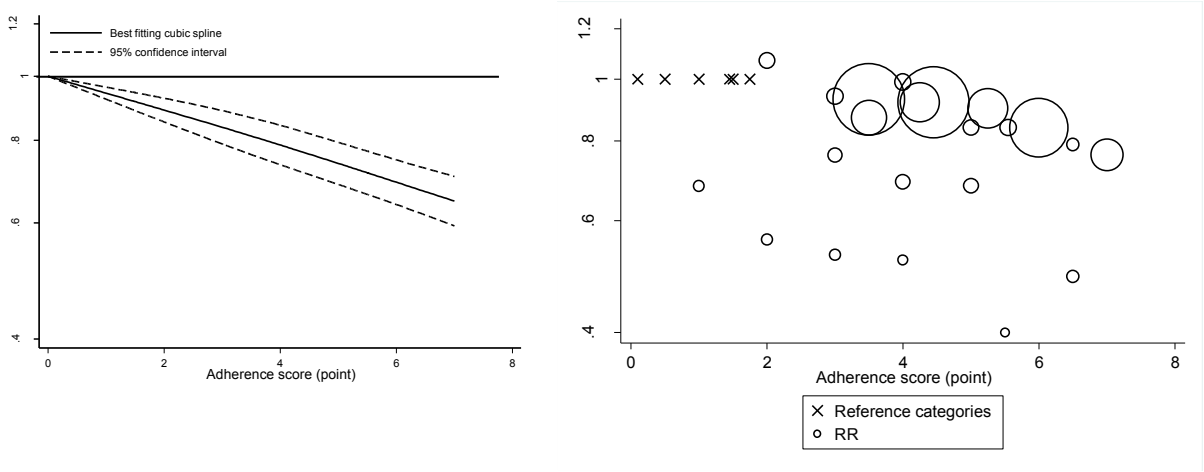

Figure 7.4 Non-linear analysis of adherence score and breast cancer

7.4.2 WCRF/AICR component adherence score and breast cancer risk

Adherence versus non-adherence to each individual recommendation/component score mostly showed an inverse association (Figures 7.5 and 7.6). Only small number of studies could be included in the analysis of postmenopausal breast cancer risk (graph not shown). Individual component scores were mutually adjusted in the studies.

Adherence to the recommendation on physical activity was statistically significantly inversely associated with overall breast cancer risk (summary RR = 0.91, 95% CI: 0.83-0.99) (I^2 = 54%, P heterogeneity = 0.07) (5 studies[255;482-485]) (Figure 7.5), but not with postmenopausal breast cancer risk (summary RR = 0.90, 95% CI: 0.79-1.03) (I^2 = 44%, P heterogeneity = 0.17) (graph not shown), compared with non-adherence. Adherence to the body fatness recommendation did not associate with overall breast cancer risk (summary RR = 0.91, 95% CI: 0.80-1.02) (I^2 = 77%, P heterogeneity = 0.001) (5 studies[255;482-485]) (9,137 cases) (Figure 7.5) but was significantly inversely associated with

postmenopausal breast cancer risk (0.85, 95% CI: 0.74 0.97) (I^2 = 55%, P heterogeneity = 0.11) (graph not shown). No significant association was observed for the recommendation on foods that promote weight gain and overall breast cancer risk (summary RR = 0.95, 95% CI: 0.85-1.06) (I^2 = 45%, P heterogeneity = 0.17) (3 studies[482;484;485]) (Figure 7.5). For the other recommendations, the summary RR estimates ranged from 0.83 (alcohol) to 0.99 (sodium intake) for overall breast cancer risk (Figure 7.6) and from 0.74 (alcohol) to 0.90 (red meat and processed meat) for postmenopausal breast cancer risk (graph not shown).

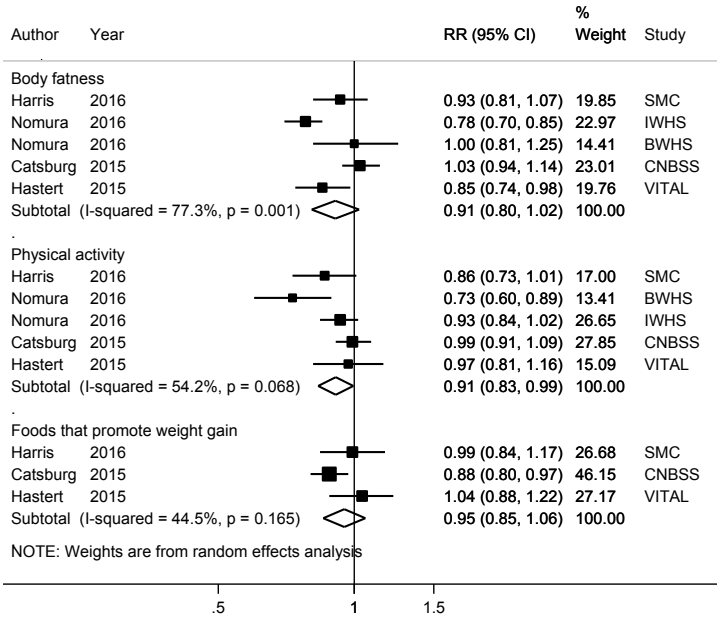

Figure 7.5 Relative risk and 95% CI of breast cancer for meeting versus not meeting recommendations related to energy balance

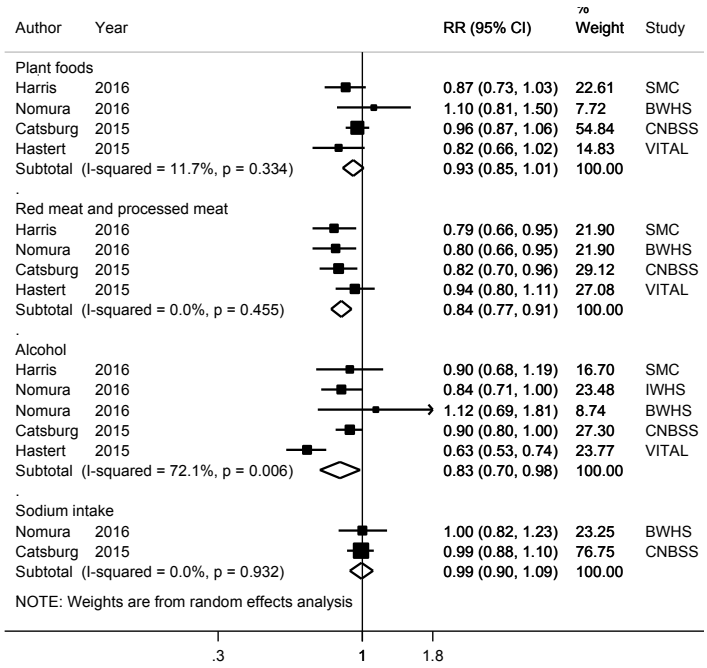

Figure 7.6 Relative risk and 95% CI of breast cancer for meeting versus not meeting others recommendations

7.5 Summary of the systematic review

The present systematic review and meta-analysis of the association of WCRF/AICR 2007 Cancer Prevention Recommendations adherence score and breast cancer risk showed that gaining just one point toward a healthier lifestyle pattern statistically significantly reduced the risks of overall breast cancer by 9% (95% CI: 6-12%), postmenopausal breast cancer by 12% (95% CI: 8-16%) and HR-positive breast cancers by 11% (95% CI: 7-16%), and suggestively, a risk reduction of HR-negative breast cancers risk by 15% (95% CI: 0-27%). For those who scored the most compared with the least, the associated risk reductions were 28% (95% CI: 16-39%) overall and 30% (95% CI: 52% decrease to 3% increase) for postmenopausal breast cancer risk. The protective effect was consistent, even though the studies had slightly different scoring criteria and between-study heterogeneity was significant.

Current results may be affected by small study bias such as publication bias, as indicated in the funnel plot there may be more small studies with a stronger inverse association than the average. However, the summary risk estimate may not change substantially with the addition of future results, because an adverse association of score adherence with breast cancer risk is unlikely. The inverse relation was consistent with those observed in the studies that examined adherence to the ACS guidelines[484;486].

In some studies, the least adhered recommendation was red meat and processed meat and the most adhered recommendation was alcohol intake. Whether a component recommendation is useful in predicting breast cancer risk may depend on the study population. On average, adherence to the recommendations for body fatness, physical activity, red meat and processed meat, and alcoholic drinks each showed an independent protective role in preventing the development of breast cancer, or specifically for body fatness, postmenopausal breast cancer. In particular, the association with alcohol showed the strongest inverse association with breast cancer risk.

This showed adopting to an overall healthful lifestyle, as well as adherence to certain components of the healthful lifestyle, are as important. These are encouraging results, supporting the purposeful systematic reviews and meta-analyses that contribute towards the making of these recommendations. Future studies need to investigate relative importance of each recommendation by excluding in turn each recommendation from the overall score (and including as a covariate in the regression model).

The independent role of the recommendations, for foods and drinks that promote weight gain (including sugary drinks) and plant foods was not substantial, and for sodium intake was minimal. As the recommendations are for the prevention of all cancer types and other chronic diseases; some recommendations, for instance for salt intake, may not have a role in breast cancer prevention, but more for other cancers. The null association with foods and drinks that promote weight gain could be explained by the inclusion of 'body fatness' in the modelling.

Although the recommendations for foods that promote weight gain and plant-based foods did not show significant additional protection against breast cancer risk. These foods contribute to weight control are an integral part of the recommendations. Currently, some studies show low adherence.

The WCRF/AICR recommendations aim to reduce the exposure to risk factors and increase the exposure to protective factors of breast cancer. As illustrated in Chapter 5 of the present thesis, obesity and weight gain is an established risk factor of postmenopausal breast cancer and recreational physical activity and/or vigorous physical activity is protective against pre- and postmenopausal breast cancer. Moreover, alcohol consumption is a strong risk factor of breast cancer, in both pre- and postmenopausal women (see section 3.1.4, alcohol). Therefore, the protective effect between the recommendations and breast cancer is underpinned by the biological mechanisms that involve sex hormones, insulin resistance, inflammation, adipocytokines, and the immune system (physical activity), and the generation of acetaldehyde and hydroxyl free radicals (alcohol); and possibly non-biologically, an overall healthy lifestyle. Women of higher adherence to the recommendations, particularly the energy balance-related recommendations, have been shown to have a more favourable biomarker profile of inflammation, hormonal, and insulin response[487].

The association between red meat and processed meat intake and breast cancer risk is not clear[117], but adherence to the related recommendation showed a statistically significant inverse association that was independent of other healthful behaviours. Unmeasured or residual confounding is possible, as factors contributed to a healthy lifestyle are closely related, although the studies adjusted for multiple confounding factors, including reproductive factors, education or smoking.

Currently, the evidence on premenopausal women is limited, and healthy cohort effect may create a downward bias to the risk estimate within specific study[482]. As observed, different associations of obesity with the risk of premenopausal breast cancer (inverse) and postmenopausal breast cancer (positive) had diluted the association overall; hence future studies should conduct separate analyses by menopausal status of the women. As seen in Chapter 5, adult weight gain increases the risk of postmenopausal breast cancer, adherence score with the component of weight change may better predict the risk of the disease; although currently many studies do not have (prospective) information on weight change. Healthy lifestyle index with the inclusion of waist circumference or waist-hip-ratio did not show improvement in prediction[488].

On-going trials such as the Women's Wellness after Cancer Program (WWACP) could provide more supporting evidence on whether following the WCRF/AICR recommendations would improve quality of life and survival after breast cancer diagnosis and treatment[489].

8 Discussion

In the present PhD study, I systematically reviewed and meta-analysed relevant findings from cohort studies and RCTs on energy balance-related factors and risk of breast cancer and mortality after breast cancer, as part of my work to update the evidence base for the WCRF International CUP[161]. A further aim of the present PhD study was to examine if the accumulated evidence supports the 2007 WCRF/AICR Cancer Prevention Recommendation. Therefore, I graded the accumulated evidence by their strength, using the WCRF evidence grading criteria (see sections 4.1.6 and 4.2.6), as only strong evidence from observational studies can be used to infer causality and contributes towards recommendation development. I then compared the judgements on the updated evidence with those reported in the WCRF/AICR Second Expert Report[7]. Below is a summary of the main findings.

8.1 Main findings

In reviewing the accumulated evidence, some new findings were revealed alongside some recognised associations that confirmed the past findings. The relationships are complex and vary not only according to the level of exposure, but also with the timing of exposure to these factors in the life course.

Higher levels of physical activity, particularly through recreational physical activity, may protect against the development of postmenopausal breast cancer (12% reduced risk), it may also reduce the risks of total mortality (26% when assessed before diagnosis and 39% after breast cancer diagnosis) and breast cancer mortality (24% when assessed before breast cancer diagnosis) in the survivors. It is possible that the protection is more evident with recreational physical activity because activity of this type tends to be more vigorous compared with other activities such as occupational or household activities; and that vigorous level of activity may be needed in order to have an effect against cancer.

Indeed, when taken into account the intensity of physical activity, the risks of both pre- and postmenopausal breast cancer development decrease with higher compared with lower levels of vigorous physical activity (21% and 10% reduced risk, respectively), and the risk of total mortality in breast cancer survivors decrease with higher levels of pre-diagnosis moderate and vigorous physical activities (25% and 28% reduced risk, respectively). Current evidence on moderate or moderate to vigorous physical activity assessed after breast cancer diagnosis and the subsequent risk of mortality is limited. Moderate instead of vigorous intensity may be more suitable for a wider range of survivors, and it warrants further investigation. Nevertheless, the present findings on physical activity in breast cancer survivors were in accord with the statistically significant reduced risk of total mortality (27%) and breast cancer mortality (25%), for ≥10 versus <10 MET-hours/week, reported in the After Breast Cancer Pooling Project (ABCPP) that combined data from four cohorts (Shanghai Breast Cancer Survival Study, WHEL, LACE, and NHS), not all of which were included in the present analysis[490].

The reduction of postmenopausal breast cancer risk in women with very high level of recreational physical activity compared with inactive women (>30 versus 0 MET-hour/week) was modest (6%). Such level corresponds to >60 minutes of daily physical activity, such as brisk walking, light bicycling or playing badminton. Because consistent high levels of physical activity throughout adult life has been shown to reduce breast cancer risk[232;262;280]; it is therefore possible that such high levels of (vigorous) daily physical activity is required to achieve protection against breast cancer. This is also in agreement with the recent finding from the Global Burden disease group[491], that estimated a 3.3% breast cancer risk reduction with 600-3999 versus <600 MET-minutes/week (10-66.65 vs <10 MET-hour/week) of total physical activity.

On the other hand, prolonged sedentary behaviour, that may independently reduce overall energy expenditure, has been proposed to be a risk factor for breast cancer[492;493]. In the present meta-analysis, we observed a 7% increase risk in postmenopausal breast cancer for each 5 hours increase of sitting/day. Most studies adjusted for BMI and physical activity, suggesting that physical inactivity may act through a separate pathway. However, more studies are needed for a definitive conclusion.

The hypothesised biological pathways underpinning physical activity and breast cancer development, are decreased levels of sex-hormones, insulin and IGF-1, inflammatory responses, and decreased levels of SHBG and adiponectin (obesity-related pathways); in addition to changes in breast tissue growth and differentiation, and menstrual characteristics in the young women, improved immunity and antioxidative defence[154]. In our meta-analyses, inverse associations were shown in the BMI adjusted studies, as well as among women of normal range of BMI, which suggests an independent effect. This could either be the result of lower numbers of overweight and obese women in the analyses, report bias by weight status, or the possibility that women who performed physical activity, likely attaining a vigorous level, had successfully modulated their adiposity at study baseline and therefore benefited from the protection. The inverse associations were not clearly different by HR subtypes. Also, no effect modification by MHT use was observed; it suggests that the above mentioned biological pathways, instead of just the hormonal pathway, may be at play. The same mechanisms are thought to underpin the inverse association between physical activity and mortality risk in breast cancer survivors, in addition to better adherence to treatment[494] and the promotion of cardiovascular health. Due to insufficient data, it was not possible to investigate the relationship of physical activity, or other factors related to energy balance and the risk of dying from cardiovascular disease in breast cancer survivors.

The relationships of body fatness with pre- and postmenopausal breast cancer risk differ across adult life. Total adiposity, as assessed by BMI, in early adulthood (age 18-<30 years) was inversely associated with pre- and postmenopausal breast cancer risk. The findings were generally consistent and supported by plausible biological mechanisms that relate to breast development and its susceptibility to carcinogenicity in early years[389;393]. In the present meta-analyses, the first being

conducted to my knowledge, we observed statistically significant summary RR estimates of 0.86 (95% CI: 0.78-0.96) for premenopausal breast cancer and 0.81 (95% CI: 0.75-0.87) for postmenopausal breast cancer per 5 kg/m^2 of BMI in early adulthood. The associations persisted in the studies that adjusted for subsequent weight gain or adult BMI, suggesting the inverse associations, especially for premenopausal breast cancer risk, were partially influenced by the status of adiposity during early adulthood. Further research is needed to establish if the association is explained by childhood adiposity, which is positively related to premenopausal weight and has been shown inversely associated with pre- and postmenopausal breast cancer risk[495]. Recent findings from the NHS showed that the inverse associations between weight at age 18 years and pre- and postmenopausal breast cancer risk was attenuated after controlling for somatotype at age 10 years[496]. Whether early adult BMI has any association with breast cancer survival is not clear, as evidence is limited; however, arguably, it is the study of post-diagnosis risk factors that is more informative to cancer patients, as post-diagnosis is the period during which patients may be able to modify their lifestyle and behaviours to influence energy balance and weight management.

Weight gain during adulthood, that is, between age 18 years and study baseline, consistently increased the risk of postmenopausal breast cancer (7% per 5 kg gain and 17% per 5 kg/m^2); while it showed no relation in younger women (summary RR = 1.00 for premenopausal breast cancer risk). The risk increase of postmenopausal breast cancer was monotonic, suggesting an effect even with a modest weight gain (8%, 17% and 26% for 5, 10 and 15 vs 0 kg weight gain, respectively). The association may be independent of early adult adiposity, but further confirmation is needed from subgroup analysis by initial body weight. The pattern of positive associations with ER+PR+ breast cancer and among MHT non-users, and non-significant associations with ER-PR- breast cancer and among MHT current users follows that of total body fatness (see below). As weight change takes into account measurements at two time points, it is possibly a better indicator of long-term energy balance and related metabolic consequences than one BMI measurement, and waist circumference and waist-to-hip ratio measurement. The pattern and duration of weight change may provide more clues to the complex relationships[497-499]. The timing of weight gain and the distribution of adipose tissue may be of particular importance. Breast cancer risk has been shown to associate positively with weight gain during middle adulthood[234], which may be implicated by more visceral fat deposited during middle adulthood[500]. Our review suggest that breast cancer survivors who gained or lost weight before, during, and after diagnosis/treatment had increased risk of mortality compared with those of stable weight, but the findings were not very consistent[418;422;424-435].

As previously reported in the Second Expert Report[7], BMI was associated inversely with premenopausal breast cancer risk and positively with postmenopausal breast cancer risk overall, with HR-positive tumours, and among MHT non-users. The evidence linking body adiposity (BMI) and breast cancer risk is abundant. More data is needed on other breast cancer subtypes and in MHT users.

Current evidence also suggested that obesity ascertained before or after cancer diagnosis led to higher risk of mortality in breast cancer survivors, regardless of their menopausal status. Across BMI categories, premenopausal breast cancer risk decreased, and postmenopausal breast cancer risk increased monotonously; but for total mortality after breast cancer diagnosis, the relationship was J-shaped, with normal weight patients having the most favourable survival and those with lower or higher weight having worse outcomes. The J-shape curve was more evident at higher BMI ascertained >12 months after diagnosis; this may reflect loss of body weight after cancer diagnosis and treatment or the obesity paradox phenomenon. Underweight breast cancer survivors showed increased risk of mortality, likely because of underlying illness and co-morbidities.

The obesity-related mechanistic pathways that drive the development of breast cancer are believed to implicate breast cancer progression and prognosis, but further research is needed to clarify these complex inter-related pathways. The hormonal pathway is likely the predominant pathway; this is suggested by the different associations by HR-status and MHT use observed in the present PhD study. Oestrogens may play a role in the early stage development of breast cancer regardless of the HR status. ER-negative tumours may arise from oestrogen-responsive precursor tumours or cells and oestrogen sensitivity may be lost at later stages of tumour development[352]. Use of exogenous hormones may mask the associations because it increases the levels of circulating oestrogens in both lean and obese women, trivialising the contribution of oestrogens from the conversion of androgens into oestrogens occurring in adipose tissue[236]. Significant associations maybe diluted in an overall analysis, if HR subtypes and MHT use are not differentiated.

Obese patients (BMI ascertained ≤12 months post-diagnosis) with either HR-positive or HR-negative breast cancers showed a significant increased risk of total mortality compared with normal weight patients; although for the other associations (pre-diagnosis obesity and total mortality, and pre- and ≤12 months post-diagnosis obesity and breast cancer mortality), significant increased risks were only observed among HR-positive patients, and not HR-negative patients. The increased risks were not statistically significantly different, which was consistent with the findings in other systematic review[501]. The Early Breast Cancer Trialist' Collaborative Group (EBCTCG) reported different findings, in which poorer survival was only observed in obese pre- or peri-menopausal women with ER-positive breast cancers, and not in obese postmenopausal women with ER-positive breast cancers, or in obese pre- and postmenopausal women with ER-negative breast cancers. EBCTCG is a pooled analysis of RCTs, with 80,000 patients from 70 trials followed for an average of 8 women-years, which could include patients of tumour and treatment characteristics different to the general populations. The data was published as Abstract to a conference in 2014 (http://meetinglibrary.asco.org/content/133648-144). The study has not been fully published. Nevertheless, more research is needed for patients of different tumour characteristics (ER/PR, HER-2 positive, triple-negative, or other aggressive tumours). Some studies found that obesity was not

significantly associated with overall survival in high risk breast cancer patients, leading to the suggestion that the impact of host factors on patient's prognosis is minor in aggressive biological subtypes[502].

Statistically significant increased risks of total and breast cancer mortality for overweight women were found in the present meta-analyses, as opposed to the non-significant associations in the ABCPP[68], probably because of the larger number of included studies in our meta-analyses along with the Shanghai Breast Cancer Survival Study, LACE, and NHS that were included in the ABCPP. Most studies included in the present meta-analysis reported an upper-most open-ended BMI category of 30 kg/m^2; therefore, we were unable to investigate the associations with severely and morbidly obese ($\geq$40 kg/m^2) women, and confirm the significant or borderline significant increased risks of 81% of total mortality and 40% of breast cancer mortality associated with morbidly obese compared with normal weight women found in the ABCPP study. Further studies are needed to confirm the substantial increased risks observed with extreme obese compared with normal weight patients, and women in general.

Abdominal obesity (measured by waist circumference or waist-to-hip-ratio) overall showed no significant association with premenopausal breast cancer risk. In postmenopausal women, the risk of developing breast cancer with higher abdominal obesity levels was significantly increased. When the associations were examined taking into account total adiposity (adjusting by BMI), studies showed increased risks in pre-and postmenopausal women on average; suggesting that fat distribution around the waist could be an independent risk factor for breast cancer development in women. The independent association requires further confirmation as total obesity and abdominal obesity are strongly correlated, although waist circumference varies in women of the same BMI categories[500]. For instance, central obesity can be substantially greater among Asian women compared to their Western counter-part of the same BMI[503;504], but currently only limited number of Asian studies reported results on abdominal obesity.

Abdominal obesity may influence breast cancer risk through different biological pathways in pre- and postmenopausal women. In premenopausal women, abdominal obesity is not associated with elevated oestradiol levels[395]; whilst in postmenopausal women, abdominal obesity is closely related to general obesity and visceral fat that produce oestrogens[38]. Gluteofemoral obesity, as indicated by hip circumference, is related inversely with premenopausal breast cancer risk, but positively with postmenopausal breast cancer risk. Evidence on abdominal and gluteofemoral obesity and mortality risk after breast cancer is limited, but there was also a suggestion of increased risks in the studies.

Although we found that weight loss was inversely associated with pre- and postmenopausal breast cancer risk, it is unclear if weight loss would benefit overweight or obese women, as most studies did not assess the intentionality of weight loss. Large weight loss may reflect treatment and disease

complications rather than voluntary lifestyle improvement. Weight loss in overweight women has been shown to lower circulating levels of oestrogen[505], cytokines[506], and other tumour markers and circulating biomarkers[507]; and is feasible even for breast cancer survivors[507;508]. Whether this would translate to beneficial effect requires investigations.

Total energy intake was not related to postmenopausal breast cancer risk, although adiposity was. Energy intake is poorly assessed in FFQ[371], and BMI (or other measure of adiposity) is a better indicator of the balance between energy intake-energy expenditure. From a mechanistically point of view, it is the abovementioned biological pathways that link excess adiposity and physical activity to breast cancer development.

Collectively, the body of evidence on breast cancer development and energy balance-related factors was large, with little evidence of publication bias. The evidence on waist circumference, waist-to-hip ratio and hip circumference has added support to the evidence on BMI, and together with weight gain, has made a solid evidence base for judgement on body fatness. Conclusions on physical activity, particularly for vigorous physical activity could be made, but without the support of a dose-response trend that would strengthen the inference of causality.

The accumulated findings, supported by good quality studies, were generally consistent; if not, the inconsistency could be partially explained, by study quality (occupational physical activity and pre- and postmenopausal breast cancer risk); geographic region of the studies (BMI and pre- and postmenopausal breast cancer risk); and HR breast cancer subtypes and proportion of MHT users in the studies (adult weight gain and BMI and postmenopausal breast cancer risk).

The different associations by HR subtypes of the tumour inform plausible biological mechanisms underlying the energy balance-related factors in breast cancer development and progression. This is particularly important, as most breast cancers are hormone-sensitive; it means a large proportion of breast cancers can be prevented by modifying exposures related to energy balance. Nevertheless, as there were generally less numbers of ER-negative breast cancer, studies may have lacked statistical power and caution is needed to interpret the results.

Two recent Mendelian randomisation studies reported opposite results to observational studies, in that inverse association was observed between genetically determined higher BMI and postmenopausal breast cancer risk [509;510]. The Mendelian randomisation approach is based on the principle that genetic variants are fixed at conception and generally independent of confounders. The results of the two Mendelian randomisation studies had raised the issue that the positive association between BMI and postmenopausal breast cancer risk in observational studies could be a result of confounding and reverse causation. However, this observation is consistent in a large number of studies. One possible explanation could be that the genetic risk score for BMI is a stronger determinant of early adult BMI

instead of BMI later in adult life[511], which will be consistent with the inverse associations of BMI in early adulthood with pre- and postmenopausal breast cancer risk shown in the present PhD study.

Although the evidence related to energy balance and risk of mortality in breast cancer survivors has grown in numbers, a majority of the studies investigated adiposity. Several limitations were identified. First, most studies assessed energy balance-related factors only once at or shortly after cancer diagnosis, a period when lifestyle factors may undergo changes; possible reverse causation may have distorted the observed associations. This is in addition to the possible report bias in exposure assessment. Second, information on treatment – the main determinant of prognosis for a given stage – was not available and not controlled for in most studies. Treatment (including type, time to treatment and compliance) is closely related to socioeconomic status, which in turn shows survival disparity and difference in obesity prevalence. Third, selection bias was detected in several studies that recruited the survivors long after the diagnosis, and may have distorted the associations.

All evidence in the present PhD study came from observational studies, apart from the few dietary intervention trials in breast cancer survivors (WINS, WHEL) that were not specifically designed to investigate the effect of weight change and breast cancer risk. Although RCT is considered the gold standard for determining causal factors[512]; due to implicational complications, there is a lack of information from lifestyle intervention trials with breast cancer as study endpoint, and such information will likely remain scanty. Alternatively, intervention trials with intermediate endpoints such as biomarkers related to breast cancer development had been conducted. For instance, improved levels of oestradiol, insulin, and biomarkers related to inflammation[513], and reduced circulating hs-CRP and leptin levels with weight loss were reported[514].

The association between WCRF Cancer Prevention Recommendations adherence and breast cancer risk was meta-analysed for the first time. As shown, breast cancer risk was reduced in women who followed the recommendations compared with women who did not. Despite the different recommendations and/or criteria for operationalising the overall adherence score in the studies, the inverse associations with breast cancer, HR-positive breast cancer, and possibly HR-negative breast cancer were consistent across the studies. Risk reductions were also observed with the recommendations specific for body fatness and physical activity, as well as for animal foods (red meat and processed meat) and alcoholic drinks. Women who adhered to the most compared with the least numbers of recommendations showed the greatest benefit. This reflects the importance of the recommendations as a whole as well as individually in breast cancer prevention; although further research is needed to confirm the findings, as current evidence suggested possible residual confounding and publication bias.

8.1.1 New knowledge

It is important to recognise the new knowledge generated in the present PhD study. Compared to the Second Expert Report[7], the work presented in the current thesis is mainly based on large amount of high quality data from prospective cohort studies, which gives strong evidence on the relations between energy balance-related factors and breast cancer.

The previous work showed limited suggestive inverse association between physical activity and premenopausal breast cancer risk. In our work, the association remained the same, but we have further shown that vigorous physical activity probably protects against the cancer in premenopausal women, as well as in postmenopausal women. On the other hand, the new analysis on sitting time and postmenopausal breast cancer risk has shown a positive association, although more evidence is needed to draw a conclusion.

For the first time, we have presented summarised results on early adult adiposity, which shows probable inverse associations with pre- and postmenopausal breast cancer risk, but future studies are needed to clarify possible influence from early life adiposity. Such findings have pointed to the importance of life course research.

We have shown a stronger and more consistent positive association between adult weight gain and postmenopausal breast cancer risk, which led to the upgrade of conclusion on the evidence, from probable to convincing level. In regard to premenopausal breast cancer, we have shown that there is limited suggestion of an association. On the other hand, as seen in the new analysis, overall weight loss may inversely associate with both pre- and postmenopausal breast cancer risk, but higher quality data and evidence from mechanistic studies are needed to clarify these findings. Our research also suggests that higher abdominal obesity may independently increase the risk of breast cancer in premenopausal women, which is a new finding that requires further confirmation.

With the accumulated evidence, we were able to conduct subgroup meta-analyses and meta-regression analyses to explore potential sources of between-study heterogeneity. The findings on molecular subtype of the tumour have provided evidence that excess adiposity and weight gain may primarily act through the hormonal pathway in postmenopausal breast cancer development (increase risk was restricted to ER+PR+ breast cancer and among MHT non-users, and no association with ER-PR- breast cancer and among MHT current users).

However, the majority of the evidence was from the US and Europe, and on Caucasian women. There was limited information from Asia (China, Japan, Korea, and Taiwan); and from populations such as the African Americans and Hispanics, who have lower risk of developing breast cancer, despite the higher prevalence of obesity[515]. There was not enough data to elucidate if the lower risk of breast cancer in African American and Hispanic women is due to genetic factors or lifestyle factors. Nevertheless, we were able to conduct subgroup meta-analyses, which suggest stronger increase in

risk of postmenopausal breast cancer with adult weight gain and abdominal obesity (waist-hip-ratio) in Asian women. These new findings add to the confirmed stronger positive association between total adiposity (BMI) and postmenopausal breast cancer risk in these women. Such differential associations have reinforced the importance of exploring ethnic-specific total and regional adiposity cut-off points for cancer risk prediction, which is an area that requires more research.

On the whole, the new findings in the present thesis have provided a more cohesive picture on the complex relationship between energy balance-related factors and breast cancer risk in pre- and postmenopausal women.

We have developed a new protocol for reviewing the literature on lifestyle factors and survival after breast cancer. The protocol has been discussed and approved by the Panel of Experts, and could serve as a template for reviewing the literature on other cancers survivors.

We were able to conduct meta-analyses using the accumulated evidence from follow-up studies of breast cancer survivors. Because of limited data at the time of the Second Expert Report[7], the previous systematic review was focused on the health outcomes of cancer survivors in nutritional and physical activity intervention trials. We have shown that pre- and post-diagnosis recreational physical activity may reduce the risks and excess adiposity may increase the risks of total mortality and breast cancer mortality in breast cancer survivors, for which the evidence was graded as limited suggestive evidence.

From the methodological point of view, new techniques that employ the second-order fractional polynomial regression model and the restricted cubic spline regression model to explore potential non-linear dose-response relationship have allowed threshold detection and the determination of cut-points for recommendations, and therefore is a particularly useful tool for the CUP. We have shown that >60 minutes of daily moderate recreational physical activity are needed to achieve protection against postmenopausal breast cancer, which suggests that the current recommendation on physical activity could be revised. The non-linear relationships detected for BMI and total mortality risk in breast cancer survivors suggest that women of normal BMI have the most favourable survival.

We have demonstrated in the first meta-analysis that overall adherence as well as adherence to each individual WCRF Cancer Prevention Recommendation may protect against the development of breast cancer. We have identified moderate adherence to the recommendations on body weight and physical activity and low adherence to the recommendation on energy-dense foods that promote weight gain. Our work carries important public health implications; particularly, it has provided insight on prevention targets.

8.2 Implications for cancer prevention

Current findings on energy balance-related factors and pre- and postmenopausal breast cancer development are consistent with those reported previously in the WCRF/AICR Second Expert Report[7].

Specifically, higher body fatness convincingly increases and physical activity probably reduces the risk of postmenopausal breast cancer, and body fatness is probably inversely related to premenopausal breast cancer risk. The evidence that suggests risk reduction in premenopausal breast cancer with physical activity in general remained limited. Importantly, the judgement on adult weight gain had been upgraded from a probable to a convincing risk factor in postmenopausal breast cancer development.

These grading coincide with the judgements published in a recent umbrella review that applied statistical criteria to empirically classified the grading of the evidence, which concluded that the evidence on weight gain increases the risk of postmenopausal breast cancer among HRT non-users, BMI increases postmenopausal breast cancer risk, and BMI decreases premenopausal breast cancer risk are strong, highly suggestive and suggestive, respectively[511].

For breast cancer survival, although the evidence has pointed to probable causes, limitations in the studies had led to more conservative judgements, that there were limited suggestions that body fatness increases and physical activity decreases the risks of total mortality and breast cancer mortality in breast cancer survivors.

Therefore, the accumulated evidence supported the 2007 WCRF Cancer Prevention Recommendations (see section 3.2.1 for details):

- Be as lean as possible within the normal range of body weight, avoiding adult weight gain and gain around the waist.
- Being physically active as part of everyday life.
- Limit consumption of energy-dense foods and avoid sugary drinks.

These recommendations are in line with the current recommendations from the European Code Against Cancer (https://cancer-code-europe.iarc.fr/index.php/en/ecac-12-ways) and the American Cancer Society[516].

As suggested above, from the perspective of breast cancer prevention, the recommended levels of physical activity could increase, to encourage people to always aim for 60 minutes or more of moderate to vigorous physical activity every day.

Although new evidence had pointed to possible risk reductions of pre- and postmenopausal breast cancer with higher adiposity in early adult life, it may have little role in the recommendations. First, it

is difficult to lose and keep off weight later in life when obesity is a strong risk factor of postmenopausal breast cancer. Second, obese women generally have poorer lifestyle pattern including low physical activity and high energy intake. Third, overweight and obese breast cancer patients have poorer survival. Fourth, obesity is associated with a range of other adverse health outcomes.

Cancer survivors are a diverse community with specific needs along the course of survivorship[517]. Current evidence on breast cancer survival is too limited for making tailored guidelines for cancer survivors, but there is no evidence of harm in following the current recommendations for cancer prevention[7].

It is possible to achieve full adherence to the WCRF Cancer Prevention Recommendations and attain the greatest benefit in breast cancer prevention. The moderate adherence to the recommendations on body weight and physical activity may reflect that these recommendations are better promoted and understood, with clear recommendations levels; while the low adherence to the recommendation on energy dense foods that promote weight gain suggests that the recommendation may be harder to comprehend and act on.

Our findings have reinforced that whilst it is important to keep an up-to-date evidence base for formulating new or revised recommendations, the promotion of these recommendations is just as important. Better implementation through stronger public health policy is needed.

8.3 Limitations of the PhD study

Several limitations were identified in the present PhD study.

The main limitation of our conclusions is that inference has to be drawn from observational studies, due to lack of randomised controlled trials on physical activity and body fatness, and breast cancer risk and prognosis. Randomised controlled trials on cancer outcomes are complicated, because it is unclear what moment in life is the most relevant for intervention. Also, weight changes can only happen through diet modification and increased physical activity. It will be difficult, rather impossible, to disentangle the individual effect of each component in a trial. Instead, global approaches on lifestyle are more likely to be feasible in future trials. We have used the observational study type (prospective studies) less prone to bias and standardised criteria to assess the likelihood that the observed associations are causal. We did not include case-control studies in our review. Evidence from the Second Expert Report and elsewhere showed that the results of case-control studies were not always concordant with those of cohort studies, although biases and residual confounding are still possible in this study design.

We searched only in PubMed for relevant publications on breast cancer risk. Although the source has been shown to cover at least 95% of the relevant articles published before 2006[518], we do not know if the same coverage would apply to the recent articles. The main difference between the journals

indexed in MEDLINE and Embase (the two main medical and health databases) is that the latter includes more journals on pharmacology, drug research and toxicology, which may not be applicable to the CUP. Nevertheless, it would be useful to extend the search; and search, for instance, in multi-disciplinary databases (e.g. Web of Science and Scopus) and in the registries that are set up to facilitate complete public reporting and address publication bias and reporting bias (e.g. ClincialTrials.gov and WHO Primary Registries)[519].

Not all identified studies could be included in a meta-analysis, specifically, dose-response meta-analysis, because of missing data. However, majority of the studies were included. Dose-response curves are useful for detecting threshold and determining recommendation levels. These are either not constructed because of insufficient data, or in some cases the curve could be driven by few data points.

The current focus on BMI as an obesity measure is a limitation. Whilst BMI is an easy, simple, inexpensive and non-invasive measure of excess weight relative to height, that has been commonly used clinically and in epidemiological studies, and shows strong correlation with the prevalence of obesity and predicts health risks and death on the population level; it does not reflect body fat distribution as does the measure of waist circumference, and cannot differentiate fat and muscle mass[520]. For the same BMI, the distribution and composition of body fat vary between women of different ethnicity, age and health status[503;504;521], which may incur different breast cancer risks. In addition, body composition of breast cancer survivors may change, possibly accelerated by the chemotherapy induced menopause, without a change in BMI[522].

In many studies, body fatness and its distribution was assessed by self-report or measured only once; measurement error may have attenuated the observed associations, in the case of random misclassification. Measurement errors in confounders are of unpredictable direction. However, the meta-analyses stratified by level of adjustment or self-reported versus measured data are not showing strong evidence of bias.

Also, while there are many studies on postmenopausal breast cancer risk, the statistical power and the number of studies is lower for premenopausal breast cancer, due to a lower incidence of this cancer. Future studies will provide more information. Breast cancer is one of the few cancers for which the therapy is now decided according to the molecular characteristics of the tumour. It is likely that lifestyle factors may influence differently the development and progression of the different breast cancer subtypes, but there is still little data to raise firm conclusions, in particular for the less frequent subtypes.

Some evidence suggests that energy balance during adolescence and probably childhood may play a role in breast cancer risk later in life. Our conclusions in this regard have to be considered cautiously due to the limited data. Similarly, we cannot reach definitive conclusions on weight change and breast

cancer risk. The precautionary principle – and the implications for total survival – indicates that weight loss in women with excess body weight should be beneficial, but specific data on impact of weight loss on breast cancer risk is warranted. Weight loss induced by bariatric surgery showed no significant effect on breast cancer risk in earlier, smaller studies[523;524], whereas a 42% reduction of postmenopausal breast cancer risk was recently reported in a large multisite cohort of bariatric surgery patients[525].

More research on cancer survivors is needed. A 2.7 kg (3.7%) weight loss over 5 years and a 24% reduction of breast cancer recurrence in the WINS study are suggestive[130]. Ongoing studies such as the Breast Cancer WEight Loss Study (BWEL Study) (ClinicalTrials.gov Identifier: NCT02750826) will add to the evidence. This is one of the ongoing trials using digital technologies (e.g. smart phones) for intervention and follow-up.

Finally, another limitation is that excess body weight and physical activity may influence outcomes that we did not investigate in this review, such as breast cancer recurrence and quality of life.

8.4 Strength of the PhD study

The present PhD study has several strengths.

First, the systematic literature review we conducted allows the formulation of evidence-based recommendations for cancer prevention. All the available information from RCT and cohort studies has been reviewed. We examined body adiposity looking at different measures in different moments of life; and for physical activity, all domains reported in the existing research were considered. The analyses were conducted by menopausal status and breast cancer subtype to take into account the breast cancer heterogeneity collected in the existing studies.

The systematic reviews and meta-analyses were conducted by following a standard protocol, with transparent and rigorous methodology. The process is consistent with the methods recommended by the Cochrane Reviews group (http://www.cochranelibrary.com/).

Second, a large number of studies, many from well-designed cohort studies that were less subjected to biases inherent in case-control studies, were comprehensive reviewed and meta-analysed. This allowed thorough examination and quantification of the shape and the magnitude of the associations, and identification of factors that may explain heterogeneity in the study findings. Publications were identified through the major sources of search[518], so it is unlikely that relevant publications were missed. Another method that is considered more superior is the pooling of individual patients data; but it is not always practical, for instance the process requires harmonisation of data, which may not be collected by all participating studies.

Third, we used a modified NOS to evaluate the quality of the studies on breast cancer incidence. Study quality assessment has been increasingly recognised as one important step of systematic

reviews of observational studies in nutritional epidemiology, and the NOS is a representative tool for such purpose[205]. We also used the clear and well-defined grading system tested in the Second Expert Report[7] to evaluate the strength of the evidence. This facilitates the making of recommendations that are accurate, reliable, and unlikely be invalidated over time.

Finally, we extended our review from examining the association of energy balance-related factors and breast cancer risk to investigating whether existing recommendations predict breast cancer risk.

8.5 Recommendations for future research

Our works have shown gaps in the data that require future research.

More longitudinal studies with updated/repeated sampled life course exposure factors (or biomarkers that reflect the exposures), long follow-up, and larger numbers of breast cancer cases of different molecular subtypes are needed. It is important to investigate the latency period and critical timing of these exposure factors to have an effect on breast cancer development and progression.

More data on all types of physical activity, and indeed physical inactivity/sedentary behaviour, with uniform details on intensity, duration, frequency and consistency of the activities are needed. Adolescent and early adult adiposity, class II and III obesity (BMI 35-39.9 and ≥40 kg/m^2, respectively), and intentional weight loss among overweight and obese women (and whether such changes would reverse the carcinogenic events associated with obesity) should be further investigated. Future studies could also examine muscle tissue mass, visceral fat mass and subcutaneous fat mass; and validate somatotype, abdominal and gluteofemoral adiposity with the use of body imaging technologies (computerised tomography, dual-energy X-ray absorptiometry, magnetic resonance imaging) to examine the relative importance of these measures in relation to the risk of breast cancer development and survival, particularly in different ethnic populations who may have different risk patterns.

Different obesity measures may help with disentangling 'obesity paradox', as the crudeness of BMI may be one of the reasons for the phenomenon[526;527]. Trajectory of body weight and other anthropometric measures would be informational, as weight change has been shown in the present PhD study as a better indicator of energy balance. Another area that may benefit by more research is obesity phenotypes, in which as much as 30% of obese individuals in the US do not develop metabolic abnormalities that are hypothesised to underpin the obesity-breast cancer relationship[528].

This implies accurate measurement using modern technologies (mobile devices, wearable sensors and other emerging digital technologies) and 'omic' technologies (genomics, metabolomics, and epigenomics). Objective assessment of dietary intake[529], physical activity and sedentary behaviours[530] will provide better categorisation of these exposure factors, and allows for full investigation of the dose-response relationship. For measures of adiposity, recently established prospective studies such as

UKBiobank (https://www.ukbiobank.ac.uk/) use modern technology to more accurately assess body fatness and its distribution. This will indicate whether the surrogate measures used in other studies remain of etiological and clinical value, as well as provide a better estimate of the associations, which might have been underestimated due to measurement error. Metabolomics will be a useful tool for identifying biomarkers of dietary exposure[531].

The majority of the accumulated evidence comes from economically developed Western countries; more research studies are needed from other low and middle income countries and countries undergoing demographic transition. Studies on women of ethnic background other than white Caucasian will provide more definitive conclusions on the appropriate cut-off points of different adiposity measures for cancer risk prediction in these populations[532-534].

More studies on women of different breast cancer subtypes, along the cancer trajectory, with long follow-up, and study endpoints other than mortality (recurrence, metastases, second primary cancer, quality of life, and comorbidities) would provide much needed knowledge in these populations. Studies should aim to collect updated cancer and treatment-related information, as well as information on comorbidies of the cancer patients. It is imperative for researchers to conduct the studies and interpret the results taking into account reverse causality, confounding, detection bias, and selection bias that are particularly problematic for cancer survival studies.

Data from large biobanks will increase statistical power and allows for more subgroup analyses and analyses of interactions and effect modifications (gene-exposure factor, physical activity-sedentary behaviour, BMI-physical activity, BMI-other anthropometric factors).

RCTs are needed in order to move away from investigating aetiology and proving causality to finding effective intervention (dose, timing, target group, mode of action, and acceptability). RCTs along the cancer trajectory (shortly after diagnosis, during cancer treatment, and long after diagnosis) would provide useful information for short- and long-term survivors.

Outside the scope of the present PhD study, socio-epidemiological research is needed to evaluate how to effectively deliver the recommendations and implement cancer prevention programmes, and whether to target the mass public, the communities or individuals at high risk of developing the disease. Local research is needed for implementation in different countries and populations.

8.6 Future work

Future work could include investigation of biological mechanisms that link energy balance-related factors to breast cancer risk and survival, such as the meta-analysis of circulating CRP and breast cancer risk that we conducted[151], for which chronic low-grade inflammation – a condition that is associated with obesity – may have a role in breast cancer development.

In addition, systematic reviews on other dietary factors and other breast cancer subtypes, as well as breast cancer recurrence and quality of life in cancer survivors could be conducted.

Future methodological work could include the validation of the modified NOS for the studies of cancer incidence and the development of a scoring system for the studies of cancer survivors; the grading of the accumulated evidence using the empirical grading system in an umbrella review, which includes the analysis of possible excess statistical significance findings that indicates report bias[535]; and a validation study to evaluate the association between adherence to the WCRF/AICR Cancer Prevention Recommendations and breast cancer risk, using a separate cohort that has not contributed towards the evidence base for formulating these recommendations.

8.7 Conclusion and implications

The complex and time-specific relationships between energy balance-related factors and risk of breast cancer development and mortality continue to unravel, but the overall picture is cohesive. Collectively, the evidence base is strong and supports the previous WCRF/AICR Cancer Prevention Recommendations for women, as well as breast cancer survivors after cancer treatment, to aim to have normal body weight (BMI 18.5-24.9 kg/m^2 or appropriate ranges issued by national governments), be physically active (≥ 30 minutes/day moderate physical activity) and sit less, prevent gain in weight and waist circumference, and limit consumption of energy-dense foods (< 225–275 kcal per 100 g) and avoid sugary drinks. The consistency has provided assurance that the guidelines can be used reliably by the public to make healthful lifestyle choices, by healthcare professionals to convey health-related messages, and by public health policy makers to make informed decisions.

The important message is that breast cancer prevention strategies should include weight control and physical activity. Although the effects of lifestyle factors on breast cancer development and survival are modest, tackling these highly prevalent factors would have a potentially huge impact on the cancer burden. It was estimated that 12% of breast cancer in the UK could be avoided through increased levels of physical activity and 16% through the elimination of excessed adiposity[178]; which is comparable to the 22% through drinking less alcohol[178], and much higher than the 3% each through minimising MHT use and breastfeeding if possible[536]. Because the evidence is particularly strong, for breast cancer, and for a number of other cancers and common chronic diseases[7], factors related to energy balance will remain one of the main focuses of cancer prevention.

Under the precautionary principle, the next big step would be to deliver the recommendations and implement cancer prevention programmes, but this is not without challenges. First, public awareness of the link between lifestyle and cancer is low. Only about 25% of the public in the UK know about obesity and cancer[537] and less than 50% of Americans is aware that lack of exercise, unhealthy food choices and obesity causes most cancer[538]. Second, current obesogenic environment in economically developed countries promotes poor dietary intakes and sedentary behaviour, as well as discourages

adequate physical activity; making it hard to maintain a healthy body weight, or for those who are overweight or obese to lose weight[539] – a problem clearly reflected by the global upward trend of obesity[11;12].

Hence, cancer prevention programmes should aim to engage and raise the awareness of cancer risk factors among women, which are often risk factors for other diseases. For this reason, cancer prevention programmes could be implemented along with other health promotion programmes using shared resources. In the UK, health promotion during mammography screening has been tested and showed promising results[540]; but prevention at any key stages, preferably along the life course, are useful.

The programmes should give emphasis on establishing and maintaining a healthy diet from a young age, by promoting foods that are not energy dense (vegetables, fruits, and whole grains) and limiting sugary drinks and fruit juices; along with the promotion of physical activity and healthy body weight, for which the recommendations had shown better adherence. More research is needed to evaluate whether the programmes are better implemented population-wide or directed to those most likely to benefit [541].

The main successes of changes in lifestyle and cancer prevention are the reduction in tobacco smoking and lung cancer, and the reduction of salt intake and stomach cancer. These lifestyle changes were not achieved only by individual actions; instead they were collective effort of many stakeholders (people, organisations, the government, policy makers, and the industry) and at different social levels (individual, interpersonal, and environmental). Only coordinated actions, driven by clear and strong public health policy agendas, can result in established social norms, changed environment and sustainable changes. My role is to provide through this PhD study the scientific evidence for those actions.

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Appendix 1 WCRF/AICR criteria for grading evidence[7]

Grade	Criteria
Convincing: These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates.	All of the following were generally required: • Evidence from more than one study type. • Evidence from at least two independent cohort studies. • No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect. • Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias. • Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly. • Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.
Probable: These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.	All the following were generally required: • Evidence from at least two independent cohort studies, or at least five case-control studies. • No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect. • Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias. • Evidence for biological plausibility.

Limited – suggestive: These criteria are for evidence that is too limited to permit a probable or convincing causal judgement, but where there is evidence suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions to this require special explicit justification.	All the following were generally required: • Evidence from at least two independent cohort studies or at least five case-control studies. • The direction of effect is generally consistent though some unexplained heterogeneity may be present. • Evidence for biological plausibility.
Limited — no conclusion: Evidence is so limited that no firm conclusion can be made. This category represents an entry level, and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited — no conclusion' for a number of reasons. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors. When an exposure is graded 'limited — no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.	
Substantial effect on risk unlikely: Evidence is strong enough to support a judgement that a particular food, nutrition, or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.	All of the following were generally required: • Evidence from more than one study type. • Evidence from at least two independent cohort studies. • Summary estimate of effect close to 1.0 for comparison of high versus low

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, an insufficient range of exposure in the study population, and inadequate statistical power. Defects in these and other study design attributes might lead to a false conclusion of no effect. The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or in humans that a specific mechanism exists, or that typical exposures can lead to cancer outcomes, argues against such a judgement. Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful, and could overlap with judgements of 'limited — suggestive' or 'limited — no conclusion'.	exposure categories. • No substantial unexplained heterogeneity within or between study types or in different populations. • Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias. • Absence of a demonstrable biological gradient ('dose response'). • Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes.
Special upgrading factors: These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. So an exposure that might be deemed a 'limited — suggestive' causal factor in the absence, say, of a biological gradient, might be upgraded to 'probable' in its presence.	The application of these factors requires judgement, and the way in which these judgements affect the final conclusion in the matrix are as below: • Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly. • A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders. • Evidence from randomised trials in humans. • Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans. • Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Appendix 2 List of publications identified in the search and included in the meta-analyses of risk of breast cancer incidence, and details of studies excluded from each specific meta-analysis

Overall

347 potential relevant publications were identified:
150 publications were included in the meta-analyses[101;104;111;121;123;211-244;247-251;253-267;269-274;277-284;290;293-306;308-321;324-365;367-369;542-544]
197 publications were excluded:
100 publications on unspecified breast cancer[122;307;481;484;485;545-639]
61 publications were superseded by publications of the same study or an overlapping study population[268;286-289;384;482;488;640-692]
12 publications did not have sufficient data to be included in a dose-response meta-analysis[374;693-703]
2 publications had no measure of association[704;705]
22 publications were not meta-analysed[252;275;276;285;291;292;322;323;366;370;483;706-716]

Total energy intake and premenopausal breast cancer

Overall 5 publications were identified[220;237-239;651]
3 publications from 3 studies were included in the dose-response meta-analysis[237-239]
1 superseded publication[651]
1 excluded publication[220]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Silvera, 2006[220], CNBSS, Canada	818/ 327,994 (PY) 16.4 years	Cases and non-cases per category not available	Semi-quantitative FFQ RR = 1.45, 95% CI: 1.13-1.85, P for trend = 0.001 for ≥2406 vs ≤1629 kcal/day Age, leisure-time physical activity, BMI, reproductive factors, alcohol, OC use, MHT use, smoking

Total energy intake and postmenopausal breast cancer

Overall 21 publications were identified[214;218;220;228;237-244;374;482;644;686;696;701-703;705]
9 publications from 9 studies were included in the dose-response meta-analysis[214;228;237;238;240-244]
5 superseded publications[218;239;482;644;686]
7 excluded publications[220;374;696;701-703;705]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Hartz, 2013[696], WHI, USA	-/ 147 202 8 years	Incompatible increment unit	Questionnaire RR = 1.00, 95% CI: 0.98-1.03 per 1 SD increase of energy intake Age, alcohol, family history of prostate cancer, history of cancer, history of polyp diagnosis, medication, number of cigarettes smoked, osteoporosis, psychological character, race, study, weight
2	Prentice, 2013[374], WHI-DM & OS, USA	5 061/ 103 426	Incompatible increment unit	4-day food record and FFQ RRs without and with BMI adjustment = 1.22, 95% CI: 1.15-1.30 and 0.94, 95%

		16 years		CI: 0.73-1.22, respectively, per 20 % increase of doubly-labelled water calibrated energy intake Age, recreational physical activity, MHT use, education, smoking, cohort and randomisation group
3	Prentice, 2009[701], WHI-DM & OS, USA	1 703/ 80 816 12 years	Incompatible increment unit	FFQ RRs without and with BMI adjustment = 1.24, 95% CI:1.11-1.38 and 1.11 95% CI: 0.81-1.53 per 20% increase of calibrated energy intake Age, alcohol, educational level, oestrogen use, Gail model risk, hormone use, physical activity, smoking status
4	Sieri, 2002[702], ORDET, Italy	56 cases/ 214 controls 5.5 years	Cases and non-cases per category not available	Semi-quantitative FFQ RR = 1.02, 95% CI: 0.48-2.16, P for trend = 0.96 for 1786.4-3474.4 vs ≤1410.6 kcal/day Birth cohort, educational level, parity/pregnancies
5	Silvera, 2006[220], CNBSS, Canada	662/ 2,244,616 (PY) 16.4 years	Cases and non-cases per category not available	Semi-quantitative FFQ RR = 0.94, 95% CI: 0.72-1.23, P for trend = 0.86 for ≥2406 vs ≤1629 kcal/day Age, leisure-time physical activity, BMI, reproductive factors, alcohol, OC use, MHT use, smoking
6	Velie, 2000[703], BCDDP, USA	996/ 40 022 5.3 years	Exposure values per category not available	FFQ RR = 0.94, 95% CI: 0.77-1.16, P for trend = 0.39 for quantile 5 vs quantile 1 (Q5 vs Q1) BMI, reproductive factors, alcohol, education
7	Wirfalt, 2004[705], MDCS, Sweden	-/ 12 803 8 years	Only reported mean energy intake for cases and non-cases	7-day food record and questionnaire Mean intake (kcal/day) = 2117 in cases and 2125 in controls, P = 0.82
Total physical activity and premenopausal breast cancer Overall 6 publications were identified[233;247-249;285;286] 4 publications from 5 studies were included in the highest versus the lowest meta-analysis[233;247-249] 1 publication from 1 study included in the dose-response meta-analysis[248] 1 superseded publication[286] 1 excluded publication[285]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Steindorf, 2012[285], EPIC, Europe	138/ 728,907 (PY) 11.7 years	Breast cancer *in situ*	Questionnaire, total physical activity index RR = 1.32, 95% CI: 0.69-2.52, P trend = 0.90 for active vs inactive Age, reproductive factors, alcohol consumption, BMI, educational level, HRT use, occupational physical activity, OC history, smoking
Total physical activity and postmenopausal breast cancer Overall 11 publications were identified[215;233;247;248;250;252;285;286;289;295;488] 5 publications from 6 studies were included in the highest versus the lowest meta-analysis[215;233;247;248;250] 3 publications from 3 studies were included in the dose-response meta-analysis[215;248;250]				

4 superseded publications[252;286;289;488]
2 excluded publications[285;295]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Cohen, 2013[295], SCCS, USA	371/ - 9 years	Results on white women only, no overall result	Questionnaire RR = 0.64, 95% CI: 0.32-1.27 for ≥27.1 vs ≤8.9 MET-hours/day among white women Age, BMI, reproductive factors, MHT use, education, smoking
2	Steindorf, 2012[285], EPIC, Europe	921/ 2,388,524 (PY) 11.7 years	Breast cancer *in situ*	Questionnaire, total physical activity index RR = 1.03 (0.77-1.39), P trend = 0.66 for active vs inactive Age, reproductive factors, alcohol consumption, BMI, educational level, HRT use, occupational physical activity, OC history, smoking

Total physical activity over life course and postmenopausal breast cancer
1 publication identified[252]
No meta-analysis

Change of total physical activity and postmenopausal breast cancer
1 publication identified[252]
No meta-analysis

Recreational physical activity and premenopausal breast cancer
Overall 18 publications were identified[227;232;233;247;253-260;268;271;285;286;289;716]
11 publications from 12 studies were included in the highest versus the lowest meta-analysis[227;233;247;253-260]
3 publications from 3 studies were included in the dose-response meta-analysis[247;256;257]
4 superseded publications[232;268;286;289]
3 excluded publications[271;285;716]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Maruti, 2008[271], NHS II, USA	363 (ER+)/ 103 (ER-)/ 64 777 6 years	Breast cancer by HR status	Questionnaire, for recreational and occupational physical activities for different age periods RRs = 0.76, 95% CI: 0.54-1.06, P trend = 0.15 for ER-positive cases and 0.89, 95% CI: 0.48-1.63, P trend = 0.21, for ER-negative cases for the highest vs lowest categories of activity Age, reproductive factors, alcohol Intake, benign breast disease, body shape, OC use
2	Steindorf, 2012[285], EPIC, Europe	138/ 728,907 (PY) 11.7 years	Breast cancer *in situ*	Questionnaire RR = 0.81, 95% CI: 0.51-1.31, P trend = 0.96 for ≥42 vs ≤12 MET-hour/week Age, reproductive factors, alcohol consumption, BMI, educational level, HRT use, occupational physical activity, OC history, smoking, other types of physical activity

3	Wyshak, 2000[716] College alumnae, 1981 USA	12/ 3,940 overall 15 years	Cohort of athletes	Questionnaire RR = 0.16, 95% CI:0.04-0.64 for athletes vs non-athletes Age, current exercise, percent body fat, ever pregnant, OC use, MHT use, ever smoked
Recreational physical activity and postmenopausal breast cancer Overall 39 publications were identified[121;218;227;232;233;235;240;247;251;253-256;258-270;272-274;285-289;482;483;674;691;711] 26 publications from 27 studies were included in the highest versus the lowest meta-analyses[121;218;227;233;235;247;251;253-256;258-267;269;270;272-274] 6 publications from 6 studies were included in the dose-response meta-analysis[235;247;256;261;262;267] 11 superseded publications[232;240;268;286-289;482;483;674;691] 2 excluded publications[285;711]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Kabat, 2010[711], WHI, USA	450/ 58,055 8 years	Breast cancer *in situ*	Questionnaire RR = 0.97, 95% CI:0.70-1.34, P trend =0.65 for ≥20 MET-hours/week vs none Age, reproductive factors, BMI, educational level, HRT use, mammogram in past 2 years, OC history, smoking, waist circumference
2	Steindorf, 2012[285], EPIC, Europe	921/ 2,388,524 (PY) 11.7 years	Breast cancer *in situ*	Questionnaire RR = 1.01, 95% CI: 0.82-1.23, P trend = 0.97 for ≥42 vs ≤12 MET-hour/week Age, reproductive factors, alcohol consumption, BMI, educational level, HRT use, occupational physical activity, OC history, smoking, other types of physical activity
Recreational physical activity over life course and premenopausal breast cancer 1 publication identified[275] No meta-analysis				
Recreational physical activity over life course and postmenopausal breast cancer 3 publications identified[266;269;275] No meta-analysis				
Recent recreational physical activity and postmenopausal breast cancer 1 publication identified[272] No meta-analysis				
Long-term recreational physical activity and premenopausal breast cancer 2 publications identified[232;271] No meta-analysis				
Long-term recreational physical activity and postmenopausal breast cancer 2 publications identified[232;262] No meta-analysis				
Change of recreational physical activity and postmenopausal breast cancer 2 publications identified[262;272] No meta-analysis				
Light physical activity and postmenopausal breast cancer				

1 publication identified[276]
No meta-analysis

Moderate physical activity and premenopausal breast cancer
1 publication identified[271]
No meta-analysis

Moderate physical activity and postmenopausal breast cancer
3 publications identified[215;270;273]
No meta-analysis

Vigorous physical activity and premenopausal breast cancer
Overall 5 publications were identified[220;231;248;271;277]
5 publications from 5 studies were included in the highest versus the lowest meta-analysis[220;231;248;271;277]
3 publications from 3 studies were included in the dose-response meta-analysis[231;248;271]

Vigorous physical activity and postmenopausal breast cancer
Overall 15 publications were identified[121;215;220;231;248;262;266;267;270;273;277-280;713]
14 publications from 14 studies were included in the highest versus the lowest meta-analysis[121;215;220;231;248;262;266;267;270;273;277-280]
3 publications from 3 studies were included in the dose-response meta-analysis[231;248;267]
1 excluded publications[713]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Nyante, 2013[713], NIH-AARP, USA	5 334 (ductal carcinomas)/ 836 (lobular carcinomas) 192 076 9.6 years	Breast cancer subtypes	Questionnaire RRs = 0.90, 95% CI:0.82-0.99, P trend = 0.03 for ductal carcinomas and 0.90, 95% CI: 0.70-1.16, P trend = 0.37 for lobular carcinomas for ≥5 vs ≤0 times/week Age, reproductive factors, alcohol Intake, BMI, educational level, HRT use, OC use, weight

Vigorous physical activity over life course and postmenopausal breast cancer
2 publications identified[267;276]
No meta-analysis

Recent moderate-vigorous physical activity and postmenopausal breast cancer
1 publication identified[276]
No meta-analysis

Long-term vigorous physical activity and premenopausal breast cancer
2 publications identified[271;277]
No meta-analysis

Long-term vigorous physical activity and postmenopausal breast cancer
3 publications identified[262;277;280]
No meta-analysis

Occupational physical activity and premenopausal breast cancer
Overall 12 publications were identified[247;253;259;260;281-286;672;687]
8 publications from 8 studies were included in the highest versus the lowest meta-analysis[247;253;259;260;281-284]

3 superseded publications[286;672;687]
1 excluded publication[285]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Steindorf, 2012[285], EPIC, Europe	138/ 728,907 (PY) 11.7 years	Breast cancer *in situ*	Questionnaire RR = 1.35, 95% CI: 0.65–2.80 for manual and heavy manual work vs sedentary occupation Age, reproductive factors, alcohol consumption, BMI, educational level, HRT use, occupational physical activity, OC history, smoking, other types of physical activity

Occupational physical activity and postmenopausal breast cancer
Overall 15 publications were identified[247;253;259;260;264;266;281-286;289;672;687]
9 publications from 9 studies were included in the highest versus the lowest meta-analysis[247;253;259;260;264;266;281-283]
4 superseded publications[286;289;672;687]
2 excluded publications[284;285]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Moradi, 1999[284], Swedish cohorts, 1971, Sweden	6,684/ 982,270 18 years	No overall result, results were subgroup by attained age at follow-up	Questionnaire RRs = 1.30, 95% CI: 1.10-1.70, P trend = 0.005 for age 50 – 59 years, 1.00, 95% CI: 0.80-1.30, P trend > 0.5 for age 60 – 69 years, and 0.82, 95% CI: 0.60-1.10, P trend = 0.5 for age ≥70 years for sedentary vs high activity level Age, year of follow-up, SES, are of residence
2	Steindorf, 2012[285], EPIC, Europe	921/ 2,388,524 (PY) 11.7 years	Breast cancer *in situ*	Questionnaire RR = 1.04, 95% CI: 0.77-1.39 for manual and heavy manual work vs sedentary occupation Age, reproductive factors, alcohol consumption, BMI, educational level, HRT use, occupational physical activity, OC history, smoking, other types of physical activity

Occupational physical activity over life course and premenopausal breast cancer
1 publication identified[271]
No meta-analysis

Household physical activity and premenopausal breast cancer
3 publications identified[247;285;286]
No meta-analysis

Household physical activity and postmenopausal breast cancer
6 publications identified[247;285-289]
No meta-analysis

Non-recreational physical activity and postmenopausal breast cancer

1 publication identified[290]
No meta-analysis

Non-occupational physical activity and premenopausal breast cancer
3 publications identified[247;286;337]
No meta-analysis

Non-occupational physical activity and postmenopausal breast cancer
5 publications identified[247;286;291;292;337]
No meta-analysis

Walking and premenopausal breast cancer
3 publications were identified[248;257;271]
2 publications from 2 studies were included in the highest versus the lowest meta-analysis[248;257]
1 superseded publication[271]

Walking and postmenopausal breast cancer
6 publications were identified[235;248;266;272;293;696]
4 publications from 4 studies were included in the highest versus the lowest meta-analysis[235;248;272;293]
1 superseded publication[696]
1 excluded publication[266]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Dirx, 2001[266], NLCS, Netherlands	941/ 62 573 7.3 years	Walking and cycling	Questionnaire RR = 0.81, 95% CI: 0.60-1.09, P trend = 0.001 for ≥61 vs ≤9 min/day of cycling and walking Age , reproductive factors, alcohol, educational level, energy Intake

Other physical activities and premenopausal breast cancer
3 publications identified[256-258]
No meta-analysis

Other physical activities and postmenopausal breast cancer
5 publications identified[256;258;266;272;290]
No meta-analysis

Sitting and premenopausal breast cancer
Overall 2 publications were identified[256;294]
Overall 2 publications from 2 studies were included in the highest versus the lowest meta-analyses[256;294]

Sitting and postmenopausal breast cancer
Overall 6 publications were identified[235;256;266;290;294;295]
Overall 6 publications from 6 studies were included in the highest versus the lowest meta-analyses[235;256;266;290;294;295]
Overall 5 publications from 5 studies were included in the dose-response meta-analyses[235;256;266;290;294]

Early adult BMI and premenopausal breast cancer
Overall 15 publications were identified[211;212;226;230;256;296-300;336;543;689;697;715]
10 publications from 13 studies were included in the dose-response meta-analysis[211;212;226;230;256;296-300]
3 superseded publications[336;543;689]

2 excluded publications[697;715]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Horn-Ross, 2016[697], CTS, USA	248/ 46 822 10 years	ER-positive breast cancers	Self-reported weight at early years, validated RR = 0.51, 95% CI:0.31-0.86 for ≥25 vs ≤19 kg/m^2 for ER-positive breast cancers Age as time metric and stratified by age at baseline, adjusted for history of benign breast disease and family history of breast cancer in a first-degree relative
2	Warner, 2016[715], NHS and NHSII, USA	2 983/ 233,214 6,129,327 PY (overall)	Breast cancer subtypes	Self-reported weight at early years RRs = 0.58, 95% CI: 0.41-0.82, P trend = 0.0004 for 624 luminal A cancers, 0.71, 95% CI: 0.44-1.13, P trend = 0.16 for 302 luminal B cancers, 0.66, 95% CI: 0.22-1.96, P trend = 0.16 for 55 HER2-positive cancers and 0.42, 95% CI: 0.15-1.19, P trend = 0.15 for 126 TNBCs for ≥25 vs 20.0-21.9 kg/m^2 Age, reproductive factors, physical activity, weight change since 18 years, interaction between menopausal status and weight change since 18, menopausal status and MHT use, recent alcohol consumption
Early adult BMI and postmenopausal breast cancer Overall 26 publications were identified[123;211;212;226;230;236;256;273;297;298;300-306;312;316;370;543;641;654;697;712;715] 15 publications from 18 studies were included in the dose-response meta-analysis[123;212;226;230;236;256;297;298;300-306] 3 superseded publications[543;641;654] 8 excluded publications[211;273;312;316;370;697;712;715]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Ahn, 2007[312], NIH-AARP, USA	948 (MHT non-users)/ 1 162 (MHT users)/ 99 039 4 years	Cases and non-cases per category not available	Self-reported weight at early years RRs = 0.48, 95% CI: 0.27-0.86, P trend <0.001 and 0.65, 95% CI: 0.35-1.23, P trend = 0.01 for ≥30 vs 18.5-22.4 kg/m^2 among MHT non-users and MHT current users, respectively Age, reproductive factors, alcohol consumption, educational level, physical activity, smoking habits, current BMI
2	Canchola, 2012[316], CTS, USA	1 348 (ER+PR+)/ 280 (ER+PR-)/ 276 (ER-PR-)/ 56 542 12.1 years	Breast cancer subtypes	Self-reported weight at early years RRs = 0.98, 95% CI: 0.80-1.19, P trend = 0.76 for ER+PR+ breast cancer and 0.89, 95% CI: 0.58-1.35, P trend = 0.34 for ER-PR- breast cancer for ≥25 vs <20 kg/m^2 Age at baseline, reproductive factors, alcohol, HRT use
3	Horn-Ross, 2016[697], CTS, USA	1 056/ 21 788 (never/past MHT users)	Two BMI categories only	Self-reported weight at early years, validated RRs = 1.10, 95% CI: 0.90-1.34 and 0.87, 95% CI: 0.70-1.08 for ≥25 vs ≤19 kg/m^2 for ER-positive breast cancers among never/past MHT users and current MHT

		1 219/ 36 977 (current MHT users) 10 years		users, respectively Age as time metric and stratified by age at baseline, adjusted for reproductive factors, history of benign breast disease, family history of breast cancer in a first-degree relative, alcohol, neighbourhood, plant-based diet (MHT non-users)
4	Kotsopoulos, 2010[712], NHS, USA	4 048 (ductal carcinomas) / 582 (lobular carcinomas) 107 759 26 years	Breast cancer subtypes	Self-reported weight at early years RRs = 0.74, 95% CI: 0.67-0.81 for ductal carcinomas and 0.69, 95% CI: 0.54-0.88 for lobular carcinomas for ≥23 vs 19-<21 kg/m^2 Age, reproductive factors, alcohol Intake, menopausal age, menopausal type, MHT use, BMI
5	Manders, 2011[211], HEBON, Netherlands, *BRCA1/2* mutation carriers	63/ 299 10 years	Two BMI categories only	Self-reported weight at early years RR = 0.94, 95% CI: 0.37-2.39 for ≥22.5 vs ≤22.4 kg/m^2 Stratified by genes and birth cohort, clustered on family, adjusted for HRT use, parity, physical activity, type of menopause
6	Phipps, 2011[273], WHI-CT-OS, USA	1 426 (ER+)/ 177 (TNBC)/ 155 723 7.9 years	Breast cancer subtypes	Self-reported weight at early years RRs = 0.83, 95% CI: 0.69-0.98, P trend = <0.01 for ER+ cancers and 0.94, 95% CI: 0.56-1.56, P trend = 0.59 for TNBCs for ≥22.42 vs ≤19.33 kg/m^2 Age, educational level, mammography at baseline and during follow-up, recreational activity, BMI at baseline
7	Potter, 1995[370], IWHS, USA	411 ER+PR+/ 97 ER+PR-/ 79 ER-PR-/ 16 ER-PR+/ 37 105 7 years	Breast cancer subtypes	Self-reported weight at early years RRs = 0.62, 95% CI: 0.47-0.81 for ER+PR+ and 1.38, 95% CI: 0.82-2.31 for ER-PR- breast cancers for ≥23 vs ≤22.9 kg/m^2 Age, reproductive factors, hormone use, alcohol consumption, BMI, WHR
8	Warner, 2016[715], NHS and NHS II, USA	2 983/ 233,214 6,129,327 PY (overall)	Breast cancer subtypes	Self-reported weight at early years RRs = 0.88, 95% CI: 0.73-1.05, P trend = 0.0009 for 1 747 luminal A cancers, 0.70, 95% CI: 0.52-0.94, P trend = 0.57 for 741 luminal B cancers, 0.32, 95% CI: 0.13-0.80, P trend = <0.0001 for 201 HER2-positive cancers and 0.65, 95% CI: 0.33-1.28, P trend = 0.03 for 184 TNBCs for ≥25 vs 20.0-21.9 kg/m^2 Age, reproductive factors, physical activity, weight change since 18 years, interaction between menopausal status and weight change since 18, menopausal status and MHT use, recent alcohol consumption
Adult weight gain and premenopausal breast cancer Overall 15 publications were identified[211;230;232;254;256;298;300;308;309;315;318;543;676;690;697] 8 publications from 9 studies were included in the dose-response meta-analysis[211;230;232;254;256;308;308;309;318] 6 superseded publications[298;300;315;543;676;690] 1 excluded publication[697]				
Publications	**Author Year**	**No. of cases Study size**	**Exclusion reasons**	**Exposure assessment Main results**

	Study Country	Average follow-up years		Main confounding factors adjustment
1	Horn-Ross, 2016[697], CTS, USA	248/ 46 822 10 years	Breast cancer subtypes	Self-reported height and weight at early years and baseline, validated RR = 1.04, 95% CI: 0.79-1.37 for weight gain ≥25 lb vs loss ≥10 lb for ER-positive breast cancers Age as time metric and stratified by age at baseline, adjusted for history of benign breast disease and family history of breast cancer in a first-degree relative
Adult weight gain and postmenopausal breast cancer Overall 38 publications were identified[211;225;230;232;254;256;298;300-304;306;309-320;349;369;543;641;647;652;663;676;681;690;696;697;700] Overall 20 publications from 18 studies were included in the dose-response meta-analyses[225;230;232;254;256;302-304;306;309-318;320] 11 superseded publications[298;300;369;543;641;647;652;663;676;681;690] 7 excluded publications[211;301;319;349;696;697;700]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Han, 2014[301], ARIC, USA	372/ 7 569 20 years	Incompatible increment unit	Self-reported weight at early years, baseline weight measured by study personnel RR = 1.05, 95% CI:1.02-1.07 per 5% increase weight gain Age, reproductive factors, alcohol, BMI at age 25 years, cigarette smoking status, education years, height, physical activity
2	Hartz, 2013[696], WHI, USA	-/ 147 202 8 years	Incompatible increment unit	Self-reported weight at different periods, change from minimal weight RR = 1.05, P >0.01 per 1 SD Age, race, study
3	Horn-Ross, 2016[697], CTS, USA	1 056/ 21 788 (never/past MHT users) 1 219/ 36 977 (current MHT users) 10 years	Two weight gain categories only	Self-reported height and weight at early years and baseline, validated RRs for ER-positive breast cancers = 1.42, 95% CI: 1.19-1.70 for weight gain ≥10 lb vs stable among never/past MHT users and 1.11, 95% CI: 0.95-1.28 for weight gain 10-24 lb vs stable among current MHT users Age as time metric and stratified by age at baseline, adjusted for reproductive factors, history of benign breast disease, family history of breast cancer in a first-degree relative, alcohol, neighbourhood, plant-based diet (MHT non-users)
4	Krebs, 2006[349], SOF, USA	350/ 9 704 11.3 years	Incompatible increment unit	Self-reported weight and height at age 25 years, current anthropometrics were measured at second health examination RR = 1.64, 95% CI:1.15-2.34, P trend = 0.002 for ≥29.8 vs <5.1 % weight gain Age , reproductive factors, educational level, HRT use, walking, smoking habits
5	Manders, 2011[211], HEBON, Netherlands, BRCA1/2 mutation carriers	63/ 299 10 years	Two weight gain categories only	Self-reported weight at early years and the time of questionnaire completion RR = 1.56, 95% CI: 0.85-2.87 for ≥5 kg gain vs <5 kg gain Stratified by genes and birth cohort, clustered on family, adjusted for HRT use, parity, physical activity, type of menopause
6	Manjer, 2001[700], MPP, Sweden	50/ 2 082 13.3 years	Two weight gain categories only	Self-reported weight gain at early years (>10 kg), weight and height measured at study baseline RR = 1.10, 95% CI:0.63-1.92, for yes vs no

		Ex-smokers		Age, HRT use, OC use
7	Welti, 2017[319], WHI, USA	5 564/ 80 943 20 years	Two weight gain categories only	Self-reported information on adult weight change RR = 1.11, 95% CI:1.03-1.20 for weight gain vs stable weight Age, education, smoking status, alcohol intake, physical activity, HT use, healthy eating index, BMI at baseline
BMI gain and premenopausal breast cancer Overall 4 publications were identified[212;297;299;710] 3 publications from 6 studies were included in the dose-response meta-analysis[212;297;299] 1 excluded publication[710]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Hilakivi-Clarke, 2005[710], Finland, 1990, Finland	98 cases/ 392 non-cases 6 years	Exposure was change of BMI during pregnancy	Self-reported weight change RR = 0.60, 95% CI:0.32-1.11 for >7 vs <3.49 kg/m^2 Age at first child, age at menarche, educational level, family history, other anthropometric factors
BMI gain and postmenopausal breast cancer Overall 6 publications were identified[212;236;297;302;305;306] 6 publications from 9 studies were included in the dose-response meta-analysis[212;236;297;302;305;306]				
Weight gain over life course and premenopausal breast cancer 2 publications identified[234;676] No meta-analysis				
Weight gain over life course and postmenopausal breast cancer 7 publications identified[234;236;311;312;315;323;676] No meta-analysis				
Adult weight loss and premenopausal breast cancer Overall 11 publications were identified[211;232;297;299;300;308;309;315;318;543;676] 6 publications from 8 studies were included in the highest versus the lowest meta-analysis[211;297;299;308;309;318] 4 superseded publications[300;315;543;676] 1 excluded publication[232]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Breslow, 2001[232], NHEFS, USA	41/ 6 160 (overall) 9.2 years	Women of low nutritional status	Self-reported weight at age 25 years; measured by skilled personnel in 1982-1984 RR = 1.63, 95% CI:0.20-13.38 for ≥5.0 kg lost vs ±4.9 lb Age, height, physical activity , SES, BMI at 25 years
Adult weight loss and postmenopausal breast cancer Overall 21 publications were identified[232;297;300-302;304;306;309-312;314-316;318-321;543;676;697] 13 publications from 14 studies were included in the highest versus the lowest meta-analysis[297;301;302;304;306;309;311;312;314;318-321]				

4 publications from 4 studies were included in the dose-response meta-analysis[304;312;314;320]
4 superseded publications[300;315;543;676]
4 excluded publications[232;310;316;697]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Breslow, 2001[232], NHEFS, USA	94/ 6 160 (overall) 9.2 years	Women of low nutritional status	Self-reported weight at age 25 years; measured by skilled personnel in 1982-1984 RR = 3.26, 95% CI: 1.44-7.38 for ≥5.0 kg lost vs ±4.9 lb Age, height, physical activity , SES, BMI at 25 years
2	Canchola, 2012[316], CTS, USA	Overall 1 355 (ER+PR+)/ 282 (ER+PR-)/ 279 (ER-PR-)/ 56 542 12.1 years	Breast cancer subtypes	Self-reported weight at early years RRs = 1.07, 95% CI: 0.85-1.34 for ER+PR+ breast cancer and 1.80, 95% CI: 1.08-3.02 for ER-PR- breast cancer for weight loss ≥10 lb vs stable weight Age at baseline, reproductive factors, alcohol, HRT use, height, weight at age 18
3	Horn-Ross, 2016[697], CTS, USA	1 056/ 21 788 (never/past MHT users) 1 219/ 36 977 (current MHT users) 10 years	Breast cancer subtypes	Self-reported height and weight at early years and baseline, validated RRs = 1.35, 95% CI: 1.05-1.73 and 1.16, 95% CI: 0.94-1.44 for weight loss ≥10 lb vs stable for ER-positive breast cancers among never/past MHT users and current MHT users, respectively Age as time metric and stratified by age at baseline, adjusted for reproductive factors, history of benign breast disease, family history of breast cancer in a first-degree relative, alcohol, neighbourhood, plant-based diet (MHT non-users)
4	Zhang, 2015[310], NHS, USA	1 520 androgen receptor-(AR) positive breast cancers/ 446 AR-negative breast cancers 103 577 (overall) 26 years	Breast cancer subtypes	Self-reported weight at age 18 years and study baseline in questionnaire RRs = 0.98, 95% CI: 0.70-1.36 for AR-positive and 1.40, 95% CI: 0.74-2.64 for AR-negative breast cancers for ≥5 kg lost vs ±<2.0 kg Stratified by age and year of questionnaire return, adjusted for reproductive factors, alcohol Intake, height, MHT use, BMI at age 18 years

Weight loss over lifecourse and premenopausal breast cancer
1 publication identified[234]
No meta-analysis

Weight loss over lifecourse and postmenopausal breast cancer
9 publications identified[234;311;312;314;315;319;320;322;323]
No meta-analysis

BMI and premenopausal breast cancer

Overall 62 publications were identified[111;211;212;216;217;220-222;224;230;234;237;249;256;297;298;300;318;324;325;327-330;332;333;335-337;343;352;354;360;362;384;543;648;662;670;677;680;682;683;694;697-699;704;708;714 104;213;296;299;326;331;334;338;350;684;689;690]

27 publications from 41 studies were included in the main dose-response meta-analysis[104;111;211-213;216;217;221;222;224;230;237;256;296;299;318;324-334]
Further 5 publications included in other meta-analyses[335-338;543]
19 superseded publications[220;234;297;298;300;350;360;362;384;648;662;670;677;680;682-684;689;690]
11 excluded publications[249;343;352;354;694;697-699;704;708;714]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Bjorge, 2010[694], Me-Can, pooled analysis, Austria, Norway, Sweden	3 043/ 287 320 (overall) 11 years	Subgroup by attained age, cases and non-cases per category not available	Weight and height measured by study personnel RR = 0.70, 95% CI: 0.57-0.85, P trend <0.001 for ≥31.7 vs ≤ 20 kg/m^2 Year of birth, age at measurement, smoking, stratified for cohort
2	Davey Smith, 2009[708], SIMS, Sweden	-/ 1 018 012 (overall) 50 years	BMI of offspring	Measured by study personnel RR = 0.92, 95% CI: 0.88-0.97 for 1 SD increase for breast cancer mortality Educational level, parental age, social class
3	Fagherazzi, 2012[354], E3N, France	223 ER+PR+/ 54 ER-PR- breast cancers/ (premenopausal) 63 726 582 144 (PY) (overall)	Breast cancer subtypes	Self-reported height and weight RRs = 0.40, 95% CI: 0.16-1.00, P trend = 0.04 for ER+PR+ and 1.45, 95% CI: 0.38-5.59, P trend = 0.20 for ER-PR- breast cancers for ≥30 vs ≤19.9 kg/m^2 Age underlying Cox proportional hazard model, stratified on year of birth, adjusted for reproductive factors, alcohol Intake, educational level, mammography, non-alcohol energy, OC use, smoking status, total physical activity, use of HRT
4	Guo, 2014[343], Northern China 2006-2011, China	34/ 26 643 (overall) 4.28 years	Cases and non-cases per category not available	Measured by study personnel RR = 1.09, 95% CI:0.31-3.78 for ≥28 vs 18.5-23.9 kg/m^2 Age, alcohol consumption, educational level, smoking
5	Horn-Ross, 2016[697]	248/ 46 822 10 years	Two BMI categories only	Self-reported height and weight at baseline, validated RR = 0.94, 95% CI:0.71-1.24 for ≥25 vs ≤24 kg/m^2 for ER-positive breast cancers Age as time metric and stratified by age at baseline, adjusted for history of benign breast disease and family history of breast cancer in a first-degree relative
6	Kerlikowske, 2017[698], BCSC, USA	4 335 ER+/ 1 243 ER- breast cancers/ 506 871 8.3 years	Cases and non-cases per category not available	Self-reported height and weight RRs = 1.21, 95% CI:1.08-1.36 for ER+ and 1.52, 95% CI: 1.19-1.94 for ER- breast cancers for ≥39 vs ≤22 kg/m^2 Age at entry, race/ethnicity, with interactions between Breast Imaging Reporting

				and Data System density and age at entry
7	Le Marchand, 1988[699], Hawaii 1942, 1960, 1972, USA	101 cases/ 444 non-cases	Cases and non-cases per category not available	From drive licence RR = 0.45, 95% CI: 0.23-0.86, P trend = 0.016 for Q3 vs Q1 Matched on race of the parents and month and year of birth, adjusted for occupation of the chief of the household, change in Quetelet index
8	Lee, 2003[249], KWC, Korea	360/ 110 604 6 years	Two BMI categories only	Collected at physical examination RR = 1.00, 95% CI: 0.80-1.30, P trend = 0.7575 for ≥23 vs ≤22.9 kg/m^2 Age, reproductive factors, OC use, physical activity , smoking habits
9	Rissanen, 2003[704], Mobile Clinic Health Examination Survey, Finland	-/ 8 196 10 years	Only reported mean BMI for cases and non-cases	Measured by study personnel Mean BMI among cases = 23.1 kg/m^2 and mean BMI among non-cases = 24.4 kg/m^2
10	Ritte, 2012[352], EPIC, Europe	390 ER+PR+/ 64ER+PR-/ 71 ER-PR+/ 147 ER-PR-/314 760 3 399 178 (PY) (overall)	Breast cancer subtypes (joint hormonal receptor types)	Measured or reported RRs = 0.80, 95% CI:0.69-0.93 for ER+PR+ and 0.90, 95% CI: 0.71-1.13 for ER-PR- breast cancers per 5 kg/m^2 Age, reproductive factors, alcohol, centre location, educational level, height, menopausal status, OC history, smoking
11	Schairer, 2013[714], BCSC, USA	1 744 non-inflammatory breast cancers/ 182 inflammatory breast cancers 93 654 (overall) -	Breast cancer subtypes	Self-reported height and weight RRs = 0.98, 95% CI: 0.69-1.39 for non-inflammatory and 3.62, 95% CI:1.30-10.04 for inflammatory breast cancers for ≥30 vs ≤24.9 kg/m^2 Matched on age and year at diagnosis and mammography registry, adjusted for reproductive factors, educational level, height, mammographic density
BMI and postmenopausal breast cancer Overall 150 publications were identified[101;104;111;123;211-214;216-225;228-230;234;236;237;240;241;250;253;256;261;273;274;278;288;289;297;298;300;302-306;310;312;313;316;318;324-333;335;337-359;362-365;368-370;482;483;488;542-544;642;645-650;653-659;661;662;664;665;667-671;673-675;677;680-686;688-692;694;695;697-701;704-708;711-714] 42 publications from 65 studies were included in the main dose-response meta-analysis[101;104;111;212;213;217;221-224;230;234;237;250;253;256;261;302;303;305;313;318;324-327;330-333;339-350] Further 28 publications were included in other meta-analyses[123;219;229;236;273;274;278;297;306;312;316;328;329;335;337;338;351-359;542-544] 64 superseded publications[214;216;218;220;225;240;241;288;289;298;300;304;363-365;368-370;482;488;642;645-650;653-659;661;662;664;665;667-671;673-675;677;680;700;701;310;362;681-686;688-692;705] 16 excluded publications[211;228;483;694;695;697-699;704;706-708;711-714]				
Publications	**Author Year Study**	**No. of cases Study size Average**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**

	Country	follow-up years		
1	Arnold, 2016[706], WHI, USA	3 723/ 73 913 12.6 years	Duration and intensity of being overweight and obese	Self-reported height and weight RRs = 1.05, 95% CI:1.03-1.07 per 10 years being overweight, 1.07, 95% CI: 1.04-1.10 per 10 years being obese, 1.08, 95% CI: 1.05-1.12 per 100 units of weighted cumulative overweight years and 1.07, 95% CI: 1.02-1.12 per 100 units of weighted cumulative obese years Age, ethnicity, education, physical activity, smoking status, dietary intake (in kilocalories), and diet quality score
2	Arnold, 2016[707], CHANCES Consortium, Europe and the US	6 369/ 139 784 18 years (max)	Duration and intensity of being overweight and obese	Self-reported or measured height and weight RRs = 1.26, 95% CI: 0.88-1.63 per 10 years being overweight and 1.16, 95% CI: 0.80-1.51 per 100 units of weighted cumulative overweight years Age, sex, alcohol consumption, education, smoking status, vigorous physical activity
3	Barrett-Connor, 1993[228], Rancho Bernardo, 1972, USA	15/ 590 15 years	Only reported mean BMI for cases and non-cases	Weight and height measured by study personnel Mean BMI among cases = 24.7 kg/m^2 and mean BMI among non-cases = 24.3 kg/m^2, P = 0.62 Age adjusted
4	Bjorge, 2010[694], Me-Can, pooled analysis, Austria, Norway, Sweden	1 106 (age 50-59 years)/ 713 (age ≥60 years) 287 320 (overall) 11 years	Subgroup by attained age, cases and non-cases per category not available	Weight and height measured by study personnel RRs = 0.87, 95% CI: 0.71-1.07, P trend = 0.2 for women of age 50-59 years and 1.21, 95% CI: 1.01-1.43, P trend = 0.003 for age ≥60 years for ≥31.7 vs ≤ 20 kg/m^2 Year of birth, age at measurement, smoking, stratified for cohort
5	Davey Smith, 2009[708], SIMS, Sweden	-/ 1 018 012 (overall) 50 years	BMI of offspring	Measured by study personnel RR = 1.02, 95% CI: 0.98-1.07 for 1 SD increase for breast cancer mortality Educational level, parental age, social class
6	Harding, 2015[695], ANZDCC, pooled analysis, Australia and New Zealand	1 323/ 38 724 16 years	Incompatible increment unit	Measured by study personnel RR = 1.06, 95% CI:1.01-1.12 per 1 SD Age as timescale in model, adjusted for smoking status, education, study cohort
7	Horn-Ross, 2016[697]	1 056/ 21 788 (never/past MHT users) 1 219/ 36 977 (current MHT users) 10 years	Two BMI categories only	Self-reported height and weight at baseline, validated RRs = 1.21, 95% CI: 1.07-1.37 and 1.07, 95% CI: 0.95-1.21 for ≥25 vs ≤24 kg/m^2 for ER-positive breast cancers among never/past MHT users and current MHT users, respectively Age as time metric and stratified by age at baseline, adjusted for reproductive factors, history of benign breast disease, family history of breast cancer in a first-degree relative, alcohol, neighbourhood, plant-based diet (MHT non-users)
8	Kabat, 2010[711], WHI, USA	450/ 58,055	Breast cancer *in situ*	Measured by study personnel RR = 1.13, 95% CI 0.68-1.87, P trend = 0.97 for ≥33.8 vs ≤23.9 kg/m^2

		8 years		Age, reproductive factors, educational level, HRT use, mammogram in past 2 years, OC history, smoking, physical activity
9	Kerlikowske, 2017[698], BCSC, USA	9 010 ER+/ 1 913 ER- breast cancers/ 594 090 8.3 years	Cases and non-cases per category not available	Self-reported height and weight RRs = 1.78, 95% CI:1.61-1.98 and 1.28, 95% CI: 1.11-1.47 for ER+ breast cancers among HRT non-current users and HRT current users, respectively for ≥39 vs ≤22 kg/m^2 RRs = 1.72, 95% CI: 1.36-2.17 and 1.44, 95% CI: 1.06-1.94, respectively for ER- breast cancers for ≥39 vs ≤22 kg/m^2 Age at entry, race/ethnicity, with interactions between Breast Imaging Reporting and Data System density and age at entry
10	Kotsopoulos, 2010[712], NHS, USA	4 566 ductal carcinomas / 645 lobular carcinomas 107 759 26 years	Breast cancer subtypes	Self-reported height and weight RRs = 1.60, 95% CI: 1.42-1.80 for ductal carcinomas and 1.47, 95% CI: 1.08-2.00 for lobular carcinomas for ≥30 vs ≤20.99 kg/m^2 Age, reproductive factors, alcohol Intake, BMI at age 18 years, menopausal age, menopausal type, MHT use
11	Le Marchand, 1988[699], Hawaii 1942, 1960, 1972, USA	39 cases/ 172 non-cases among postmenopausal women	Cases and non-cases per category not available	From drive licence RR = 0.72, 95% CI: 0.24-2.19, P trend = not significant for Q3 vs Q1 for postmenopausal breast cancer risk Matched on race of the parents and month and year of birth, adjusted for occupation of the chief of the household, change in Quetelet index
12	Manders, 2011[211], HEBON, Netherlands, BRCA1/2 mutation carriers	63/ 299 10 years	Two BMI categories only	Self-reported height and weight at the time of questionnaire completion RR = 1.46, 95% CI: 0.86-2.51 for ≥25 vs ≤24 kg/m^2 Stratified by genes and birth cohort, clustered on family, adjusted for HRT use, parity, physical activity, type of menopause
13	Nomura, 2016[483], IWHS, USA	3 189/ 36 626 23 years (max)	Adherence to recommendation	Height and weight, and physical activity self-reported RRs = 0.78, 95% CI: 0.70-0.85, P trend <0.001 for fully met vs not met body weight recommendation and = 0.93, 95% CI: 0.84-1.02, P trend = 0.23 for fully met vs not met physical activity recommendation
14	Nyante, 2013[713], NIH-AARP, USA	5 334 ductal carcinomas/ 836 lobular carcinomas/ 192 076 9.6 years	Breast cancer subtypes	Height and weight self-reported RRs = 1.29, 95% CI:1.19-1.39, P trend = <0.01 for ductal carcinomas and 1.23, 95% CI: 1.01-1.51, P trend = 0.01 for lobular carcinomas for ≥30 vs 18.5-24.9 kg/m^2 Age, reproductive factors, alcohol Intake, educational level, HRT use, OC use, vigorous physical activity
15	Rissanen, 2003[704], Mobile Clinic Health Examination Survey, Finland	-/ 8 196 10 years	Only reported mean BMI for cases and non-cases	Measured by study personnel Mean BMI among cases = 24.9 kg/m^2 and mean BMI among non-cases = 25.6 kg/m^2
16	Schairer, 2013[714], BCSC, USA	5 856 non-inflammatory breast cancers/	Breast cancer subtypes	Self-reported height and weight RRs = 1.41, 95% CI: 1.08-1.84 for non-inflammatory and 3.75, 95% CI:1.92-7.34 for inflammatory breast cancers for ≥30 vs ≤24.9 kg/m^2

		435 inflammatory breast cancers 93 654 (overall) -		Matched on age and year at diagnosis and mammography registry, adjusted for reproductive factors, educational level, height, mammographic density
BMI over lifecourse and postmenopausal breast cancer 3 publications identified[236;273;312] No meta-analysis				
Waist circumference and premenopausal breast cancer Overall 11 publications were identified[213;222;230;256;329;354;360-362;640;643] 7 publications from 7 studies were included in the dose-response meta-analysis of studies not adjusted for BMI[213;222;230;256;329;360;361] 4 publications from 4 studies were included in the dose-response meta-analysis of studies adjusted for BMI[213;329;360;361] 3 superseded publications[362;640;643] 1 excluded publication[354]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Fagherazzi, 2012[354], E3N, France	223 ER+PR+/ 54 ER-PR- breast cancers/ 63 726 582 144 person-years (overall)	Breast cancer subtypes	Self-reported waist and hip circumferences RRs = 0.67, 95% CI: 0.46-0.96, P trend = 0.04 for ER+PR+ and 1.52, 95% CI: 0.75-3.07, P trend = 0.25 for ER-PR- breast cancers for ≥77 vs ≤70.9 cm Age underlying Cox proportional hazard model, stratified on year of birth, adjusted for reproductive factors, alcohol Intake, educational level, mammography, non-alcohol energy, OC use, smoking status, total physical activity, use of HRT
Waist circumference and postmenopausal breast cancer Overall 44 publications were identified[123;213;222;225;229;230;236;250;256;273;310;312;316;318;329;339;342;349;354;356;361-366;368;369;640;643;649;655-657;660;666;675;691-693;695;705;709;711] 14 publications from 14 studies were included in the dose-response meta-analysis of studies not adjusted for BMI[213;222;229;230;250;256;312;339;342;349;361;363-365] 7 publications from 7 studies were included in the dose-response meta-analysis of studies adjusted for BMI[123;213;229;329;339;342;361] 17 superseded publications[225;310;362;368;369;640;643;649;655-657;660;666;675;691;692;705] 11 excluded publications[236;273;316;318;354;356;366;693;695;709;711]				
Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Agnoli, 2010[693], ORDET, Italy	163 cases/ 629 non-cases 13.5 years	Two waist circumference categories only	Measured by trained nurse RR = 1.23, 95% CI: 0.83-1.81 for 86 vs ≥85 cm Matched on age, date of recruitment and laboratory batch, adjusted for reproductive factors, alcohol Intake, educational level, HRT use, menopausal age, OC use, smoking habits
2	Borgquist, 2009[356],	26 ERα ≤10%/	Breast cancer subtypes	Measured by study personnel

	MDCS, Sweden	194 ERα >10%/ 93 ERβ≤10%/ 83 ERβ>10%/ 9 685 10.3 years		RRs = 2.00, 95% CI: 0.60-6.64, P trend = 0.19 for breast cancers with ERα expression ≤10%, 1.88, 95% CI: 1.21-2.90, P trend = 0.02 for ERα expression >10%, 2.89, 95% CI: 1.49-5.61, P trend = 0.002 for ERβ expression ≤10% and 1.14, 95% CI: 0.63-2.06, P trend = 0.70 for ERβ expression >10% for ≥0.85 vs ≤0.7 m Age, reproductive factors, alcohol consumption, educational level, OC use, smoking habits
3	Canchola, 2012[316], CTS, USA	829 (ER+PR+)/ 181 (ER+PR-)/ 156 (ER-PR-)/ 56 542 12.1 years	Breast cancer subtypes	Self-reported waist and hip circumferences RRs = 1.33, 95% CI: 1.09-1.62, P trend = 0.02 for ER+PR+ breast cancer and 1.10, 95% CI: 0.70-1.73, P trend = 0.69 for ER-PR- breast cancer for ≥36 vs <30 inch Age at baseline, reproductive factors, alcohol, HRT use, height
4	Fagherazzi, 2012[354], E3N, France	944 ER+PR+/ 243 ER-PR- breast cancers/ 63 726 582 144 person-years (overall)	Breast cancer subtypes	Self-reported waist and hip circumferences RRs = 1.21, 95% CI: 1.02-1.44, P trend = 0.03 for ER+PR+ and 0.81, 95% CI: 0.59-1.12, P trend = 0.20 for ER-PR- breast cancers for ≥77 vs ≤70.9 cm Age underlying Cox proportional hazard model, stratified on year of birth, adjusted for reproductive factors, alcohol Intake, educational level, mammography, non-alcohol energy, OC use, smoking status, total physical activity, use of HRT
5	Fourkala, 2014[709], UKCTOCS, UK	1 018/ 92 834 3.19 years	Dress size as proxy measure for waist circumference	Self-reported skirt size RR = 1.05, 95% CI:1.01-1.09 for 1 dress size up Age underlying Cox proportional hazard model, reproductive factors, alcohol consumption, derivation category, educational level, HRT use, OC use, smoking
6	Harding, 2015[695], ANZDCC, pooled analysis, Australia and New Zealand	1 323/ 38 724 16 years	Incompatible increment unit	Measured by study personnel RR = 1.06, 95% CI:1.01-1.12 per 1 SD Age as timescale in model, adjusted for smoking status, education, study cohort
7	Kabat, 2010[711], WHI, USA	450/ 58,055 8 years	Breast cancer *in situ*	Measured by study personnel RR = 0.90, 95% CI: 0.39-2.09, P trend = 0.50 for ≥100.7 vs ≤76.2 cm Age, reproductive factors, educational level, HRT use, mammogram in past 2 years, OC history, smoking, physical activity
8	Liu, 2016[318], SWHS, China	522/ 32 948 15.1 years	Incompatible increment unit	Measured by study personnel RR = 1.29, 95% CI: 1.19-1.41 per 1 SD Age-underlying cox models, alcohol consumption, educational level, energy intake, HRT use, leisure time physical activity, smoking, year of birth
9	Morimoto, 2002[236], WHI-OS, USA	708/ 85 917 34.8 months	Cases and non-cases per waist circumference category among MHT users and non-users not available	Measurements performed by clinical staff RRs = 1.99, 95% CI: 1.30-3.02, P trend = 0.001 and 0.89, 95% CI: 0.68-1.18, P trend = 0.71 for ≥95.1 vs ≤73 cm among HRT non-users and HRT users, respectively Age , reproductive factors, alcohol, educational level, energy Intake, leisure time physical activity, smoking habits

10	Phipps, 2011[273], WHI-CT-OS, USA	2 607 (ER+)/ 307 (TNBC)/ 155 723 7.9 years	Breast cancer subtypes	Waist and hip circumferences measured by study personnel RRs = 1.34, 95% CI: 1.09-1.64, P trend = 0.01 for ER+ cancers and 0.66, 95% CI: 0.37-1.20, P trend = 0.23 for TNBCs for ≥95 vs ≤76 cm Age, educational level, mammography at baseline and during follow-up, recreational activity, BMI at baseline
11	Reeves, 2012[366], SOF, USA	385 ER+/ 303 PR+ 8 956 14.4 years Age 65+ years	Breast cancer subtypes	Measured by study personnel RRs = 1.30, 95% CI: 1.03-1.66 for ER+ and 1.51, 95 %CI: 1.16-1.97 for PR+ breast cancers for ≥88 vs ≤87.9 cm Age, diabetes, HRT use, hypertension

Hip circumference and premenopausal breast cancer
Overall 6 publications were identified[222;329;354;360-362]
4 publications from 4 studies were included in the dose-response meta-analysis of studies not adjusted for BMI[222;329;360;361]
3 publications from 3 studies were included in the dose-response meta-analysis of studies adjusted for BMI[329;360;361]
1 superseded publication[362]
1 excluded publication[354]

Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Fagherazzi, 2012[354], E3N, France	223 ER+PR+/ 54 ER-PR- breast cancers/ 63 726 582 144 person-years (overall)	Breast cancer subtypes	Self-reported waist and hip circumferences RRs = 1.05, 95% CI: 0.74-1.48, P trend = 0.77 for ER+PR+ and 2.85, 95% CI: 1.33-6.13, P trend <0.01 for ER-PR- breast cancers for ≥99 vs <93 cm Age underlying Cox proportional hazard model, stratified on year of birth, adjusted for reproductive factors, alcohol Intake, educational level, mammography, non-alcohol energy, OC use, smoking status, total physical activity, use of HRT

Hip circumference and postmenopausal breast cancer
Overall 14 publications were identified[222;236;273;312;329;339;354;361-364;368;649;695]
7 publications from 7 studies were included in the dose-response meta-analysis of studies not adjusted for BMI[222;236;312;339;361;363;364]
3 publications from 3 studies were included in the dose-response meta-analysis of studies adjusted for BMI[329;339;361]
2 publications were included in non-linear analysis only[362;368]
1 superseded publication[649]
3 excluded publications[273;354;695]

Publications	**Author Year Study Country**	**No. of cases Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Fagherazzi, 2012[354], E3N, France	944 ER+PR+/ 243 ER-PR- breast cancers/ 63 726	Breast cancer subtypes	Self-reported waist and hip circumferences RRs = 1.31, 95% CI: 1.10-1.55, P trend <0.01 for ER+PR+ and 0.98, 95% CI: 0.71-1.36, P trend = 0.90 for ER-PR- breast cancers for ≥99 vs <93 cm Age underlying Cox proportional hazard model, stratified on year of birth,

		582 144 person-years (overall)		adjusted for reproductive factors, alcohol Intake, educational level, mammography, non-alcohol energy, OC use, smoking status, total physical activity, use of HRT
2	Harding, 2015[695], ANZDCC, pooled analysis, Australia and New Zealand	1 323/ 38 724 16 years	Incompatible increment unit	Measured by study personnel RR = 1.09, 95% CI:1.03-1.15 per 1 SD Age as timescale in model, adjusted for smoking status, education, study cohort
3	Phipps, 2011[273], WHI-CT-OS, USA	2 607 (ER+)/ 307 (TNBC)/ 155 723 7.9 years	Breast cancer subtypes	Waist and hip circumferences measured by study personnel RRs = 1.28, 95% CI: 1.03-1.58, P trend = 0.01 for ER+ cancers and 0.81, 95% CI: 0.44-1.50, P trend = 0.54 for TNBCs for ≥113 vs ≤97.9 cm Age, educational level, mammography at baseline and during follow-up, recreational activity, BMI at baseline

Waist-to-hip ratio and premenopausal breast cancer
Overall 13 publications were identified[213;221;222;230;256;298;318;329;354;360-362;367]
10 publications from 10 studies were included in the dose-response meta-analysis of studies not adjusted for BMI[213;221;222;230;256;318;329;360;361;367]
7 publications from 7 studies were included in the dose-response meta-analysis of studies adjusted for BMI[213;221;318;329;360;361;367]
2 superseded publications[298;362]
1 excluded publication[354]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Fagherazzi, 2012[354], E3N, France	223 ER+PR+/ 54 ER-PR-breast cancers/ 63 726 582 144 person-years (overall)	Breast cancer subtypes	Self-reported waist and hip circumferences RRs = 0.66, 95% CI: 0.46-0.95, P trend = 0.02 for ER+PR+ and 0.84, 95% CI: 0.44-1.62, P trend = 0.64 for ER-PR- breast cancers for ≥0.80 vs <0.75 Age underlying Cox proportional hazard model, stratified on year of birth, adjusted for reproductive factors, alcohol Intake, educational level, mammography, non-alcohol energy, OC use, smoking status, total physical activity, use of HRT

Waist-to-hip ratio and postmenopausal breast cancer
Overall 39 publications were identified[123;213;221;222;225;230;236;250;256;273;298;310;312;318;329;339;342;349;354;361-365;367-370;649;654;656;657;671;675;678;679;681;695;705]
17 publications from 20 studies were included in the dose-response meta-analysis of studies not adjusted for BMI[213;221;222;230;256;312;318;339;342;349;361;362;364;365;367-369]
8 publications from 8 studies were included in the dose-response meta-analysis of studies adjusted for BMI[123;213;221;318;329;339;361;367]
1 publication were included in the meta-analysis by MHT use only[236]
13 superseded publications[225;298;363;649;654;656;657;671;675;678;679;681;705]
6 excluded publications[250;273;310;354;370;695]

Publications	Author Year Study Country	No. of cases Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Bellocco, 2016[250], Swedish National	609/ 19196	Two waist-to-hip ratio categories only	Self-reported waist and hip circumferences RRs = 1.15, 95% CI: 0.94-1.41 for >0.8 vs ≤0.8

	March Cohort, Sweden	13.2 years		Age, age at first child, age at menarche, alcohol drinking, cigarette smoking status, educational level, HRT use, number of children, OC use, treatment for childlessness, vitamin / mineral supplement use
2	Fagherazzi, 2012[354], E3N, France	944 ER+PR+/ 243 ER-PR- breast cancers/ 63 726 582 144 person-years (overall)	Breast cancer subtypes	Self-reported waist and hip circumferences RRs = 1.02, 95% CI: 0.86-1.21, P trend = 0.80 for ER+PR+ and 0.86, 95% CI: 0.62-1.19, P trend = 0.42 for ER-PR- breast cancers for ≥0.80 vs <0.75 Age underlying Cox proportional hazard model, stratified on year of birth, adjusted for reproductive factors, alcohol Intake, educational level, mammography, non-alcohol energy, OC use, smoking status, total physical activity, use of HRT
3	Harding, 2015[695], ANZDCC, pooled analysis, Australia and New Zealand	1 323/ 38 724 16 years	Incompatible increment unit	Measured by study personnel RR = 1.01, 95% CI: 0.95-1.07 per 1 SD Age as timescale in model, adjusted for smoking status, education, study cohort
4	Phipps, 2011[273], WHI-CT-OS, USA	2 607 (ER+)/ 307 (TNBC)/ 155 723 7.9 years	Breast cancer subtypes	Waist and hip circumferences measured by study personnel RRs = 1.06, 95% CI: 0.93-1.21, P trend = 0.21 for ER+ cancers and 0.99, 95% CI: 0.66-1.49, P trend = 0.82 for TNBCs for ≥0.857 vs ≤0.757 cm Age, educational level, mammography at baseline and during follow-up, recreational activity, BMI at baseline
5	Potter, 1995[370], IWHS, USA	412 ER+PR+/ 99 ER+PR-/ 78 ER-PR-/ 17 ER-PR+/ 37 105 7 years	Breast cancer subtypes	Waist and hip measured by a friend with tape provided RRs = 1.33, 95% CI: 1.05-1.70 for ER+PR+ and 0.79, 95% CI: 0.42-1.47 for ER-PR- breast cancers for ≥0.90 vs <0.90 Age, reproductive factors, hormone use, alcohol consumption, BMI, BMI at age 18
6	Zhang, 2015[310], NHS, USA	857 androgen receptor-(AR) positive breast cancers/ 257 AR-negative breast cancers 103 577 (overall) 26 years	Breast cancer subtypes	Self-reported waist and hip circumferences in questionnaire RRs = 1.20, 95% CI: 0.96-1.49 for AR-positive and 1.08, 95% CI: 0.70-1.67 for AR-negative breast cancers for ≥0.84 vs ≤0.72 Stratified by age and year of questionnaire return, adjusted for reproductive factors, alcohol Intake, height, MHT use, BMI

Appendix 3 Main characteristics of studies included in the meta-analyses of risk of breast cancer incidence

Author, publication year	Study, country, age of women at study baseline, special characteristics	Years of follow-up, case ascertainment	Number of women/ No. cancer cases (in analysis)	Exposures, details	Exposure comparison	Adjustment	Study quality score
Ahn, 2007[312]	NIH-AARP, USA, age >50, postmenopausal	4 years, record linkage with cancer registry	99 039 women/ 1 162 postBC, 202 ER+PR+, 53 ER-PR-, 44 ER+PR-	BMI, Early adult BMI, WC, WHR, Weight gain, self-reported	BMI: ≥40 vs 18.5-22.4 kg/m^2, WC: ≥104 vs ≤75 cm, WHR: ≥0.95 vs ≤0.7, Weight gain: ≥50 vs ±1.9 kg	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, family history of cancer, fat Intake, oophorectomy/hysterectomy, parity, physical activity, race, smoking habits, initial BMI	13/ 12.5 (weight gain)
Albanes, 1989[260]	NHANES I, USA, age 25-74, pre- and postmenopausal	10 years, medical records and death certificate	7 413 women/ 46 preBC, 76 postBC	PA, interviewed	Occupational PA: inactive vs moderately active Recreational PA: little/no exercise vs moderate exercise	Age (Adjustment for race, economic and smoking status, BMI (or stature), energy intake, age at menarche and menopause, parity, age at first birth, family history of breast cancer, dietary fat intake did not materially alter any of the findings)	6 (premenopausal) 7 (postmenopausal)
Alsaker, 2013[311]	HUNT2, Norway, age >=55, postmenopausal	12.8 years, record linkage with cancer registry, almost complete follow-up	28 153 women/ 471 postBC, ICD-7 code 170	Weight gain, measured in exams	≥7.5 vs ±2.5 kg gain/10 years	Age, age at menarche, alcohol, educational level, exercise, height, parity and age at first birth, smoking status, attained age, stratified on year of birth, BMI at first survey	11.5
Andreotti, 2010[542]	Agricultural Health Study (AHS), USA, Spouse of pesticide applicator	10 years, record linkage with cancer registry	28 319 women (overall)/ 464 postBC	Self-reported height and weight	BMI: ≥35 vs 18.5-24.9 kg/m^2	Age underlying Cox proportional hazard model, adjusted for diabetes, family history of breast cancer, parity, vitamin supplement	7

Bardia, 2006[263]	IWHS, USA, age 55-69, postmenopausal	18 years, record linkage with health registry	41 836 women/ 2 548 postBC, 1 643 ER+, 298 ER-, 1 366 PR+, 497 PR-, 1 323 ER+PR+, 252 ER+PR-, 244 ER-PR-, 42 ER-PR+	PA, self-reported questionnaire	high vs low	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, BMI, educational level, family history, HRT use, OC use, parity/pregnancies, smoking habits	12
Barrett-Connor, 1993[228]	Rancho Bernardo, 1972, USA, age 40-79, postmenopausal	15 years, medical records and death certificate	590 women/ 15 postBC	Total energy, 24-recall	per 500 kcal/day	Age, age at menopause, alcohol, BMI, parity/pregnancies	8
Bellocco, 2016[250]	SNMC, Sweden, age 56 years, postmenopausal	13.2 years, record linkage to cancer registry, complete follow-up	19 196 women/ 708 postBC, invasive	BMI, WC, PA, self-reported	BMI: ≥30 vs 18.5-24.9 kg/m^2 WC: ≥88 vs ≤79.8 cm PA: ≤31.1 vs ≥38.2 MET-hour/day	Age, age at first child, age at menarche, alcohol drinking, cigarette smoking status, educational level, HRT use, number of children, OC use, treatment for childlessness, vitamin / mineral supplement use	14 (BMI, waist) 15 (PA)
Benn, 2016[324]	CGPS and CCHS, age 20-100	4.7 years, record linkage to cancer registry	108 812 women/ 507 preBC 2 351 postBC	BMI, measured	BMI: ≥30 vs 18.5-24.9 kg/m^2	Age, alcohol consumption, educational level, pack years of smoking, physical activity, serum C-reactive protein, year of birth	12 (premenopausal) 13 (postmenopausal)
Bessonova, 2011[358]	CTS, USA, age 53 years	1 322 634 (PY, overall), teacher's retirement system	115 433 women (overall)/ 222 postBC	BMI, self-reported	BMI: ≥30 vs 18.5-24.9 kg/m^2	Age, alcohol consumption, calories derived from fat, HRT use, morbidity, physical activity, smoking, weight change	8
Bhaskaran, 2014[325]	CPRD, UK, age >16, pre- and postmenopausal	25 years, medical records	2 864 658 women/ 6 298 preBC, 28 409 postBC,	BMI, measured	BMI: >35 vs 18.5-24.9 kg/m^2	Age, alcohol, calendar year, diabetes, smoking, socio-economic status	13 (premenopausal) 12 (postmeno

			invasive				pausal)
Borgquist, 2009[356]	MDC, Sweden, mean age 61 years, postmenopausal MHT non-users	10.3 years, record linkage with cancer registry, low loss to follow-up	9 685 women/ 231 postBC, 26 ERalpha-, 194 ERalpha+, 93 ERbeta-, 83 ERbeta+, 108 PR-, 100 PR+, invasive	BMI, WC, measured	BMI: ≥28 vs ≤22.9 kg/m^2	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, marital status, occupation, oophorectomy/hysterectomy, oral contraceptive use, parity, smoking habits	14.5
Brasky, 2010[261]	VITAL, USA, age 50-76, postmenopausal	6 years, record linkage to cancer registry	35 016 women/ 880 postBC, invasive	BMI PA, self-reported	BMI: ≥30 vs ≤24.9 kg/m^2 PA: ≥10.62 vs ≤0 MET-hours/week	Age	12 (BMI, PA)
Breslow, 2001[232]	NHEFS, USA, age 24-75, pre and postmenopausal	9.2 years, self-reported and medical records	6 160 women/ 41 preBC, 94 postBC	Weight gain, measured, PA, self-reported	≥20 vs +/-4.9 kg gain	Age, ethnicity, height, income, physical activity , SES, BMI at 25 years	6 (premenopausal) 7 (postmenopausal)
Brinton, 2014[278]	NIH-AARP, USA, age 50-71, postmenopausal	9.3 years, record linkage with cancer registry	190 872 women/ 7 299 postBC (1 604 ER+, 297 ER-), Invasive	BMI, PA, self-reported questionnaire	≥5 vs 0-0.9 times/month	Age, age at menarche, alcohol Intake, BMI, breast biopsies, educational level, family history of breast cancer In first degree relatives, marital status, menopausal age, menopausal status, parity and age at first birth, postmenopausal hormone use, race	14 (postmenopausal)
Burton, 2010[226]	Glasgow Alumni Cohort study, UK, age >20, pre- and postmenopausal	49 years, record linkage with cancer registry and death certificates	2 657 women/ 30 preBC, 69 postBC, ICD-9 code 174, ICD-10 code C50	BMI, Early adult BMI, measured	>25 vs 19-23 kg/m^2	Age, age at menarche, height, smoking, social class	9 (premenopausal) 8 (postmenopausal)

Canchola, 2012[316]	CTS, USA, age 56-70, postmenopausal	12,1 years, record linkage with cancer registry, National death index	56 542 women/ postBC, 1371 ER+PR+, 287 ER+/PR-, 280 ER-/PR-, invasive	BMI, Weight gain, self-reported, validated	BMI:≥30 vs <25 kg/m^2; Weight gain: ≥40 vs ±9.9 lbs gain	Age, age at first child birth, age at menarche, alcohol, breast biopsies, family history of breast cancer, height, HRT use, parity, (weight at 18 years)	13.5/ 12.75 (weigt gain)
Catsburg, 2014[256]	CSDLH, Canada, pre- and postmenopausal	15 years, record linkage with cancer registry, loss to follow-up 3%	4 417 women/ 548 preBC, 724 postBC, invasive	BMI, Early adult BMI, WC, WHR, Weight gain, PA, Sitting self-reported, validated	BMI: ≥30 vs 18.5-24.99 kg/m^2, WC: ≥92.8 vs ≤72.9 cm, WHR: ≥0.89 vs ≤0.75, Weight gain: ≥16 vs ≤0 kg, Recreational PA: ≥31 vs ≤2.9 MET-hours, Sitting: ≥54.1 vs ≤12.4 hours/week, Sitting for TV: ≥21 vs ≤1 hours/week	Stratified by age, adjusted for age at first child birth, age at menarche, alcohol Intake, family history of breast cancer, HRT use, menopausal status, number of childbirths, OC use, physical activity	14 (BMI/waist) 13 (early adult BMI)/ 13.5 (weight gain)/ 15 (PA)
Cecchini, 2012[224]	NSABP-P-1 and STAR, USA, high risk women participating in breast cancer prevention trial (tamoxifen), mammography screening, P-1: pre- and postmenopausal; STAR: postmenopaus	Follow-up in RCT, every 6 months for the first 5 years and annually thereafter	31 731 women/ 126 preBC, 77 ER+, 39 ER-, 650 postBC, 472 ER+, 154 ER-, invasive	BMI, measured	≥30 vs ≤25 kg/m^2	Age, diabetes, oestrogen use, gail score, oral contraceptive history, smoking	9 (premenopausal) 11.75 (postmenopausal)

	al						
Chang, 2006[218]	PLCO, USA, age 55-75, cancer screening RCT, postmenopausal	4.9 years, self-reported and verified by medical records	38 660 women/ 764 postBC	PA, question on hours of vigorous activities per week	≥4 vs ≤0 hours/week	Age, age at first child, age at menarche, age at menopause, benign breast disease, BMI, educational level, energy Intake , ethnicity, family history, height, HRT use, parity/pregnancies, recruitment center (The association between energy and breast cancer was not weakened by the addition of either energy-adjusted alcohol intake or energy-adjusted fat intake)	11
Chen, 2016[340]	TBCSS, Taiwan, age 35+ years, screening programme	13 years, cancer registry and death certificates	1 393 985 women/ 6 023 postBC	BMI, measured	≥35 vs 18.5-23.9 kg/m^2	Age, age at menarche, breastfeeding, family history of breast cancer, number of birth, parous/nulliparous, age at first birth	11
Chlebowski, 2007[274]	WHI, USA, age 50-79, postmenopausal	5 years (min), self-reported and verified by medical records	147 916 women/ postBC, 2 391 ER+, 459 ER-, invasive	BMI, measured PA, self-reported, validated	≥30 vs ≤24.9 kg/m^2	Age at screening, age at first child birth, age at menarche, age at menopause, alcohol consumption, breast biopsies, breastfeeding, oestrogen use, ethnicity, family history of breast cancer, parity, physical activity, progestin + oestrogen use, smoking	15
Cohen 2013[295]	SCCS, USA, age 40-79, postmenopausal, mainly low income and uninsured persons	9 years, record linkage with cancer registry	371 postBC, 546 non-cases, Invasive	Sitting, questionnaire	≥12 vs ≤5.4 hours/day	Age, age at menarche, BMI at 21 years, educational level, ethnicity, family history of breast cancer, health Insurance, household Income, HRT use, parity, smoking habits, source type (Alcohol consumption, BMI at study entry, total energy consumption, and age at first birth did not change the ORs appreciably)	12
Colditz, 2003[257]	NHS II, USA, age 25-42, nurses, pre- and postmenopausal	10 years, self-reported verified by medical records, <1% loss to follow-up	110 468 women/ 849 pre, invasive	PA, self-reported questionnaire, validated	Recreational PA: ≥27 vs ≤2.9 MET-hour/week, Walk: ≥4 vs ≤0.32 hours/week	Age, age at first child, age at menarche, alcohol, benign breast disease, BMI, family history, height, OC use	15

Couto, 2013[237]	WLHS, Sweden, age 30-49, pre- and postmenopausal	16 years, record linkage with cancer registry, almost complete follow-up	49 258 women/ 736 preBC, 448 postBC	BMI, self-reported, Total energy, validated 80-item semi-quantitative FFQ for diet 6 months prior to study baseline	BMI: ≥25 vs ≤20 kg/m^2, Energy: ≥7725 vs <5590 kJ	Age, age at first child birth, age at menarche, alcohol, benign breast disease, contraception, educational level, height, history of breast cancer, hormone use, number of childbirths, smoking,	13.5 (premenopausal) 11.5 (postmenopausal)
Dallal, 2007[277]	CTS, USA, age 27-86, pre- and postmenopausal	6.6 years, record linkage with cancer registry	110 599 women/ 1 062 preBC, 1 587 postBC, Invasive	PA, self-reported questionnaire	≥5.01 vs 0-0.5 hours/week	Age, age at first child, alcohol, BMI, breast biopsies, ethnicity, family history, hormonal variables , mammography, menopausal status, parity/pregnancies, smoking habits	12 (premenopausal) 13 (postmenopausal)
Dartois, 2016[337]	E3N, France, age 42-72, pre- and postmenopausal	15 years, pathology reports	67 634 women/ 497 preBC (314 ER+, 97 ER-) 3 138 postBC (2 050 ER+, 466 ER-)	Height and weight self-reported	BMI: ≥30 vs ≤24.9 kg/m2	Age, age at first full-term pregnancy, age at menarche, age at menopause, alcohol consumption, birth weight, body shape at menarche, breastfeeding, dietary pattern, educational level, family history of breast cancer in first degree relatives, height at adulthood, history of benign breast disease, HRT use, number of children, oral contraceptive or progesterone use, physical activity level, tobacco smoking status, vitamin d intake and UV radiation	11 (premenopausal) 14 (postmenopausal)
De Stavola, 1993[333]	Guernsey G2 and G3, UK, pre- and postmenopausal	15 years, histology reports, quality follow-up	4 528 women/ 73 preBC, 95 postBC	BMI, measured	BMI: ≥26.5 vs ≤21.9 kg/m^2	Age	10.5 (premenopausal) 9.5 (postmenopausal)
Dirx, 2001[266]	NLCS, The Netherlands, age 55-69, postmenopausal	7.3 years, record linkage with cancer registries and a pathology register, complete follow-up	62 573 women/ 943 postBC, invasive	PA, sitting self-reported questionnaire	Recreational PA: ≥2.1 vs ≤0 hours/week, Vigorous PA: ≥6.01 vs ≤4 MET score, Occupational PA: ≥12.1 vs ≤7.9 kj/minute, Sit at work: <2 vs 6-8	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, height, educational level, maternal breast carcinoma, breast carcinoma in sister(s), parity, energy Intake	13

					hours/day		
Dite, 2017[212]	ABCFR, kConFab, ACCFR, Australia, mean age 45.9 years, family of BC cases	10 years, self-report verified by pathology reports and medical records	9 126 women/ 288 BC, invasive	BMI, Early adult BMI, BMI gain, self-reported height and current weight and weight at age 18-21 years	BMI: 27.69-65.75 vs 11.72-21.45 kg/m^2 per 5 kg/m^2	Age-underlying cox models, BMI and genetic risk score interaction, genetic risk score, HRT use, smoking, change in BMI (in early adult BMI analysis), BMI at 18-21 years (in BMI gain analysis)	6 (early adult BMI-premenopausal) 6.5 (BMI gain-premenopausal) 7 (BMI-premenopausal) 7 (early adult BMI-postmenopausal) 7.5 (BMI gain-postmenopausal) 8 (BMI-postmenopausal)
Ekenga, 2015[281]	Sister Study, USA, age 30-74, kins of BC cases	4.7 years, self-report verified by pathology reports and medical records	45 373 women/ 422 pre BC 1 363 post BC	PA, self-reported	Ever vs never	Age-underlying cox models, age at menopause, educational level, income, parity, race/ethnicity, recreational physical activity, work at night, BMI	11
Eliassen, 2006[320]	NHS, USA, age 30-55, nurses, postmenopausal	26 years, self-reported verified by medical records, loss to follow-up 5%	121 700 women/ 4 393 postBC, Invasive	Weight gain, self-reported	≥25 vs +/-2 kg	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, body weight, family history, height, HRT use, other design Issue, parity/pregnancies	13.75
Eliassen, 2010[262]	NHS, USA, age 30-55, nurses, postmenopausal	20 years, self-reported verified by medical records, loss to follow-up 8.9%	95 396 women/ 4 782 postBC, invasive	PA, self-reported questionnaire, validated	Recreational and vigorous PA: ≥27 vs <3 MET-hour/week	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI at age 18 years, family history of breast cancer, height, history of breast disease, HRT use, parity	15

Emaus, 2014[234]	EPIC-PANACEA, Europe, age 25-70, pre- and postmenopausal	1 396 538 person-years, active follow-up and cancer registry, loss to follow-up 3.7%	205 723 women/ 298 preBC, 2370 postBC, Invasive	BMI, self-reported or measured	28.1-59.7 vs 16-21.3 kg/m^2	Age, age at first child birth, age at menarche, alcohol consumption, alcohol drinking, educational level, energy Intake, physical activity, smoking, study center, time between measurements, use of oral contraception, BMI at baseline	16
Fagherazzi, 2012[354]	E3N EPIC-France, age 40-65	582 144 person-years, self-reported verified by medical records and pathology reports, low loss to follow-up (see Fournier, 2014)	63 726 women/ preBC, 223 ER+PR+ 54 ER-PR- postBC, 944 ER+PR+, 243 ER-PR-, Invasive	BMI, self-reported	≥30 vs ≤19.9 kg/m^2	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, breastfeeding, educational level, family history of breast cancer, history of benign breast disease, mammography, non-alcohol energy, OC use, parous/nulliparous, smoking status, total physical activity, use of HRT, year of birth	14
Feigelson, 2004[313]	CPS II, USA, age 50-74, postmenopausal	9 years, self-reported, medical records, death certificate, loss to follow-up 4 394 women	62 756 women/ 1 934 postBC, invasive	BMI; Weight gain, self-reported	BMI: ≥35 vs ≤21 kg/m^2, Weight gain: ≥71 vs ±5lb	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, educational level, ethnicity, family history, height, mammography, OC use, parity/pregnancies, physical activity	14.5
Feigelson, 2006[317]	CPS-II Nutrition Cohort, USA, age 50-74, postmenopausal	Cancer registries and medical records, loss to follow-up 2 428 women	97 786 women/ postBC, 445 ER+PR+, 98 ER-PR-, 108 ER+PR-/ER-PR+, invasive	Weight gain, self-reported	≥61 vs 5-20 lbs	Age, age at first child, age at menarche, age at menopause, alcohol, breast diseases , educational level, ethnicity, family history, height, mammography, oc use, other factors , parity/pregnancies, physical activity	15.5
Folsom, 1990[225]	IWHS, USA, age 55-69, 99% white, postmenopausal	2 years, histology reports	225 postBC, 1 804 non-cases, ICD-O code 174	BMI, WC, WHR, Weight gain, self-reported, validated	≥17.31 vs ≤8.19 kg	Age (Adjustment for other breast cancer risk factors and sociodemographic characteristics did not appreciably alter the findings.)	9.75
Folsom, 2000[365]	IWHS, USA, age 55-69, postmenopausal	10 years, active follow-up, record linkage with cancer registries, and death certificates	31 702 women/ 1 299 postBC	BMI, WC, WHR, self-reported, validated	WC: ≥96 vs ≤74.3 cm, WHR: ≥0.9 vs ≤0.76	Age, age at first child, alcohol Intake, educational level, energy, fish Intake, fruits and vegetables Intake, keys score, pack years of smoking, physical activity, red meat Intake, smoking status, vitamin use, whole grains, oestrogen use	12.5

Fournier, 2014[272]	E3N France, postmenopausal	8.5 years, self or next of kin reported, death registry, loss of follow-up 4 659 women	59 308 women/ 2 097 postBC (1 337 ER+, 315 ER-) Invasive	PA, validated	≥24 vs ≤5.9 MET-hour/week	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, BMI, family history of breast cancer In first degree relatives, history of benign breast disease, menopausal oestrogen use, parity, sport, total energy Intake, year of birth	15
Freisling, 2017 [339]	CHANCE consortium, Europe, mean age 63 years, postmenopausal	12 years, self-report, cancer registries, medical records	24 751 women/ 555 postBC	BMI, WC, HC, WHR	BMI: ≥30 vs ≤24.9 kg/m^2 WC: ≥88 vs ≤87.9 cm	Age, alcohol consumption, education, height, smoking, vigorous physical activity, year of recruitment	9.81 (BMI) 10 (WC/HC/ WHR)
Galanis, 1998[111]	Hawaii State Department of Health, 1975, Hawaii, mean age 43 years, pre- and postmenopausal	14.9 years, histology reports, loss to follow-up low with low rate of out-migration	17 628 women/ 86 preBC, 292 postBC, invasive	BMI, self-reported	≥26.1 vs ≤19.5 kg/m^2	Age, alcohol, educational level, ethnicity	10.5 (premenopausal) 9.5 (postmenopausal)
Gaudet, 2010[347]	Columbia, MO cohort, USA, postmenopausal	25 years, histology reports, loss to follow-up<10%	229 postBC, 227 non-cases	BMI, self-reported	≥30 vs ≤25 kg/m^2	Age, time of blood collection	9
Gaudet, 2014[229]	CPS II, USA, MHT non-users, postmenopausal	11.58 years, self-reported verified by medical records, or by record linkage with cancer registries, response to follow-up <=86%	28 965 women/ 1 088 postBC, 791 ER+, 128 ER-, invasive	BMI, WC, self-reported	BMI: ≥30 vs ≤24.9 kg/m^2, WC: 97-139 vs 39-74 cm	Age, age at first child birth, age at menopause, alcohol Intake, benign breast disease, diabetes, educational level, exercise, family history of breast cancer, height, mammography, oral contraceptive use, parity, postmenopausal hormone use, race, smoking	14
George, 2010[290]	NIH-AARP, USA, age 50-71, postmenopausal	7 years, record linkage with cancer registry	97 039 women/ 2 866 postBC, invasive	PA, sitting self-reported questionnaire	Occupational PA: heavy lifting or carrying vs sitting all day,	Age, alcohol Intake, BMI, breast biopsies, educational level, energy Intake, HRT use, parity, race, recreational activity	13

					Sit: ≥9 vs <3 hours/day		
Graham, 1992[241]	NYSC, USA, age 50-107, postmenopausal	8 years, histology reports, few lost	18 586 women/ 344 postBC	Total energy, 130-item semi quantitate FFQ	62-318 vs 7-35 *1000 kcal/month	Age, educational level; parity not in final model	7
Grenier, 2011[355]	Manitoba Cancer Registry Study, Canada, age >50, postmenopausal	5.4 years, record linkage with cancer registry	37 860 women/ 484 postBC	BMI, measured	per 5.26 kg/m^2	Age, age, lumbar spine bone mass density	8
Gunter, 2009[357]	WHI-OS, USA, age 50-79, postmenopausal	77 months, self-reported verified by medical records, loss to follow-up 1.6%	1 651 women/ 831 postBC	BMI, measured	30.0 vs 18.5 kg/m^2	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, educational level, oestrogen use, family history of cancer, hormonal variables, HRT use, nsaid use, ocp use, parity, physical activity, race, smoking habits	14
Guo, 2014[343]	Northern China, China, 2006-2011, age >18, pre- and postmenopausal	4.28 years, self-reported, reported by kin, medical and pathologicla records	26 643 women/ 34 preBC, 57 postBC	BMI, measured	≥28 vs 18.5-23.9 kg/m^2	Age, alcohol consumption, educational level, smoking	9
Han, 2014[301]	ARIC, USA, age 45-64, postmenopausal	20 years, record linkage with cancer registry and medical records	7 569 women/ 372 postBC	Early adult BMI, Weight gain, self-reported	≥30 vs 18.5-24.9 kg/m^2	Age, menopause status at baseline, age at menarche, age at menopause, alcohol consumption, smoking status, cigarette smoking status, education, height, physical activity, race-center; model + weight change from age 25 to baseline	8
Harlid, 2012[346]	MSP and VIP, Sweden, age 27-95, postmenopausal	Record linkage with cancer registry	3 994 women/ 850 post BC(MSP+VIP), invasive	BMI, self-reported	≥30 vs 18.5-25 kg/m^2	Age	10

Harris, 2011[360]	NHS II, USA, age 25-42, nurses, premenopausal	426 164 person-years, self-reported verified by medical records, high follow-up rates	45 799 women/ 620 preBC, 415 ER+, 131 ER-, invasive	BMI, WC, WHR, self-reported	WC: ≥34.25 vs ≤26.99 in, WHR: ≥0.84 vs ≤0.73	Age, age at first child birth, age at menarche, alcohol consumption, benign breast disease, family history of breast cancer, height, oral contraceptive use, parity, physical activity; model + BMI	14.5
Hildebrand, 2013[235]	CPS II-Nutrition Cohort, USA, age 50-74, postmenopausal	14.2 years, self-reported verified by medical records, loss to follow-up 3 111 women	73 615 women/ 4 760 postBC, ICD-O C50 (invasive)	PA, sitting self-reported questionnaire	Recreational PA: ≥42.1 vs 0.1-7 MET-hours/week, Walk: ≥7 plus other activities vs ≤3 hours/week, Sitting for TV: ≥6 vs ≤2.9 hours/day	Age, age at first child birth, age at menopause, alcohol, BMI, breast diseases , educational level, family history of breast cancer, HRT use, mammography, number of childbirths, oophorectomy/hysterectomy, race, smoking status, weight change	16
Holmes, 1999[239]	NHS, USA, age 30-55, nurses, pre- and postmenopausal	14 years, self-reported verified by medical notes	121 700 women/ 784 preBC, 1 913 postBC, invasive	Total energy, 61-item semi-quantitative FFQ in 1980, expanded in follow-ups, validated, recorded diet a year prior to baseline	per 100 kcal/day	Age, time period, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI at 18 years, body weight change since age 18 years, family history, height, menopausal status and HRT use, parity, vitamin A	13
Horn, 2014[344]	NNTHS, Norway, age ≥55 , postmenopausal	409 377 person-years, cancer registries	18 562 women/ 1 069 postBC, 614 luminal, 120 non-luminal, 361 luminal A, 205 luminal B, 50 basal-like, 30 five negative phenotype, invasive	BMI, measured	≥30 vs ≤24 kg/m^2	Age, birth cohort (Adjustment for marital status, place of residence and occupation, age at menarche, parity and age at first birth did not substantially influence the results and were not included in the final analyses)	13
Howard,	USRT, USA,	8.9 years,	45 631	PA,	Total PA: ≥97	Age, age at first child birth, age at menarche, age at menopause,	10

2009[248]	mean age 47 years, radiologic technologists, pre- and postmenopausal	self-reported verified by medical records	women/ 440 preBC, 285 postBC, invasive	self-reported questionnaire	vs 0-9.5 MET score, Vigorous PA: ≥10 vs ≤0 hours/week, Walking/hiking for exercise: ≥10 vs ≤0 hours/week	alcohol consumption, BMI, breast diseases , family history of cancer, menopausal hormone use, OC use, parity, race, smoking habits	
Huang, 1999[361]	NHS, USA, age 30-55, nurses, pre- and postmenopausal	Self-reported verified by medical records, follow-up rate as of 1994 was 95%	47 832 women/ 197 preBC, 840 postBC, invasive	Self-reported height, weight, waist and hip circumferences	WC: 36-55 vs 15-27.9 inch, WHR: ≥0.84 vs ≤0.72	Age, age at first child, age at menarche, benign breast disease, family history, height, parity/pregnancies, physical activity; model BMI	11.5 (premenopausal) 12.5 (postmenopausal)
Huang,1997[543]	NHS, USA, age 30-55, nurses, pre- and postmenopausal	16 years, self-reported verified by medical records	95 256 (overall)/ 1 000 pre BC 1 517 postBC	Self-reported height, weight, waist and hip circumferences	BMI: ≥31.1 vs ≤20 kg/m^2 (nonlinear analyses only)	Age , age at first child, age at menarche, family history, height, parity/pregnancies	12.5
Iwasaki, 2007[335]	JPHC I and II, Japan, age 40-69, pre- and postmenopausal	9.9 years, record linkage with cancer registry, low rate of loss to follow-up	53 857 women/ 201 preBC, 62 ER+, 41 ER-, 53 PR+, 42 PR-, 229 postBC, 65 ER+, 41 ER-, 46 PR+, 55 PR-, ICD-O code 500-509 (invasive)	BMI, self-reported	≥30 vs ≤18 kg/m^2	Age, age at first child, area, height, parity/pregnancies (Other factors, such as a family history of breast cancer in female first-degree relatives, history of benign breast disease, age at menarche, age at menopause, use of exogenous female hormones, smoking status, alcohol consumption, and food intake of such items as meat, vegetables, fruit, and soy foods also were examined as confounders, but not included in the final multivariate-adjusted model.)	14.5 (premenopausal) 13.5 (postmenopausal)

Johnsson, 2017 [253]	SSGPS, Sweden, age 25-65	19.8 years, record linkages to cancer and mortality registries	29 524 women/ 423 preBC 1 083 postBC	BMI, PA, self-reported	BMI: ≥29.1 vs ≤24.9 kg/m^2 Competitive sports: no vs yes Occupation activity: sedentary vs non-sedentary	Age, age at first child, age at menarche, BMI, education years, family history of breast cancer, OC use, occupational physical activity, HRT use (postmenopausal women)	10 (BMI) 9 (PA)
Kaaks, 1998[222]	DOM-project Utrecht, The Netherlands, age 39-73, mammography screening cohort, pre- and postmenopausal	7.1 years, histology reports	11 480 women/ 147 preBC, 76 postBC	BMI, WC, WHR, measured	BMI: ≥27.15 vs ≤22.5 kg/m^2, WC: ≥83.51 vs ≤71 cm, WHR ≥0.8 vs ≤0.73	Age, age at first child, age at menarche, menopausal status, parity/pregnancies	8 (premenopausal) 9 (postmenopausal)
Kabat, 2015[342]	WHI, USA, age 50-79, postmenopausal	12.7 years, self-reported verified by medical records and pathology reports	143 901 women/ 7 039 postBC, invasive	BMI, WC, WHR, measured	Q5 vs Q1	Age, age at menarche, alcohol, aspirin use, diabetes, educational level, ethnicity, family history of colon cancer, HRT use, met-hours per week, parity, smoking, treatment allocation; model + BMI	14
Kawai, 2010[304]	MIYAGI-I, Japan, age 40-64, postmenopausal	129 891 person-years, record linkage with cancer registry, loss to follow-up 4.9%	10 106 women/, 108 postBC, ICD-O code C50-.9 (invasive)	BMI, Early adult BMI, Weight gain, self-reported	Early adult BMI:≥23.8 vs ≤20.4 kg/m^2, Weight gain: ≥ +12 vs ±1.9kg	Age, age at menarche, age at menopause, alcohol Intake, educational level, family history of breast cancer, exogenous female hormone use, occupation, parity, smoking, walking, body weight at 20 years (for current BMI and weight change) and current BMI (for BMI at age 20 years; omitting cases that occurred within 2 years of recruitment yielded almost the same results.)	12 (early adult BMI) 12.5 (weight gain)
Kerlikowske, 2008[101]	BCSC, USA, age >40, underwent mammography screening, postmenopausal	Record linkage with cancer registry	287 115 women/ 4 446 postBC, 2 466 ER+, 495 ER-	BMI, self-reported	≥35 vs 18.5-24.9 kg/m^2	Age, centre location, mammography, race	10

Kim, 2006[242]	NHS, USA, age 30-55, nurses, postmenopausal	20 years, self-reported verified by medical records	121 701 women/ 3 537 postBC, 1 653 ER+PR+, 517 ER-PR-, 477 ER+PR-, 83 ER-PR-, invasive	Total energy, 61-130 item validated semi-quantitative FFQ	per 500 kcal	Age, time period, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI at age 18 years, body weight change since age 18 years, energy Intake , family history, height, HRT use, other design Issue, parity/pregnancies	14.5
Krebs, 2006[349]	SOF, USA, mean age 73.5 years, postmenopausal	11.3 years, self-reported verified by medical records, loss to follow-up 2%	9 704 women/ 350 postBC, invasive	BMI, WC, WHR, Weight gain, measured	BMI: ≥29 vs ≤23 kg/m^2, WC: ≥91.3 vs ≤75.7 cm, WHR: ≥0.89 vs ≤0.78	Age, age at menarche, age at menopause, anthropometry, benign breast disease, educational level, family history, HRT use, parity/pregnancies, physical activity , smoking habits (Alcohol did not differed by incident breast cancer status (P = 0.8) and not included in model)	13
Krishnan, 2013[302]	MCCS, Australia, age 39-76, postmenopausal	16.5 years, cancer registry, pathology reports, complete follow-up	14 441 women/ 668 postBC, 261 ER+, 59 ER-, 175 PR+, 129 PR-, 168 ER+/PR+, 77 ER+/PR-, 52 ER-PR-, 86 HER-2+, 234 HER-2-, 190 luminal A, 68 luminal B, 38 triple negative, invasive	BMI. Measured; Early adult BMI, self-reported; Weight gain (kg/BMI)	BMI: ≥30 vs ≤24.9 kg/m^2, BMI at 18-21 years: ≥25 vs 18.5-24.9 kg/m^2, Weight gain: ≥18.7 vs 0-10 kg, Gain in BMI ≥7.4 vs 0-3.9 kg/m^2	Age, age at menarche, alcohol, breastfeeding, country of birth, educational level, energy Intake, HRT use, ocp use, parity, phyisical activity, smoking, weight at 18 to 21 years (for baseline BMI and weight gain	15.5 (BMI)/ 13.5 (early adult BMI)/ 14.5 (weight gain)
Kushi, 1992[244]	IWHS, USA, age 55-69, postmenopausal	4 years, histology reports	34 388 women/ 459 postBC, ICD code 174	Total energy, 127-item validated semi-quantitative FFQ	2264 vs 1168 kcal/day	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, BMI at 18 years, family history, WHR	9.5

Kwan, 2014[293]	WHI, USA, age 50-79, postmenopausal	12.4 years, medical records	14 719 women/ 762 postBC, invasive	Walking	≥1.33 vs ≤0.98 minute	Age, age, alcohol consumption, BMI, oestrogen plus progesterone use, ethnicity, gail model risk, health status, Income, mammogram In the past 2 years, smoking status, trial Intervention group	13
Lacey Jr, 2009[544]	PLCO, USA, age 55-74, postmenopausal	4.98 years Self-reported/ death certificate/ medical records	70 575/ 2 063 postBC	Self-reported height and weight	≥35 vs 18.5-24.9 kg/m^2	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, calendar period, family history of cancer, height, HRT use, study center	12
Lahmann, 2003[369]	MDC, Sweden, age 50-73, postmenopausal	5.7 years, record linkage with cancer registry and death certificate, 50 women emigrated during follow-up	12 159 women/ 236 postBC	BMI, WC, WHR, Weight gain, measured	WHR: ≥0.84 vs ≤0.75	Age, age at first child, age at menarche, alcohol, height, marital status, OC use, occupation, parity/pregnancies, smoking habits	12.5
Lahmann, 2004[329]	EPIC, Europe, age 18-80, pre- and postmenopausal	4.7 years, record linkage with cancer registries and active follow-up	176 886 women/ 494 preBC, 1 405 postBC, invasive	BMI, WC, WHR, measured	BMI: ≥28.8 vs ≤21.5 kg/m^2, WC: ≥89.3 vs ≤70.9 cm, WHR ≥0.85 vs ≤0.74	Age, age at first child, age at menarche, alcohol, educational level, OC use, parity/pregnancies, smoking habits, study centre; model + BMI	12 (premenopausal) 14 (postmenopausal)
Lahmann, 2005[309]	EPIC, Europe, age 25-70, pre- and postmenopausal	5.8 years, histology reports	98 352 women/ 254 preBC, 626 postBC, invasive	Weight gain, self-reported earlier weight, measured at baseline	> 20 kg vs +/- 2 kg	Stratified by age and centre, adjusted for age at menarche, age at first birth/parity, OC use, education, height, alcohol intake, smoking status, leisure physical activity, weight at age 20	11 (premenopausal) 12 (postmenopausal)

Lee, 2001[121]	WHS, USA, age >45, nurses, postmenopausal	48 months, self-reported, medical records, and death certificate, loss to follow-up ≤1%	39 322 women/ 261 postBC, 157 ER+PR+	PA, self-reported questionnaire	Recreational PA: ≥6300 vs ≤839 kj/week, Vigorous PA: ≥4200 vs ≤0 kj/week	Age, randomised treatment assignment, age at first child, age at menarche, alcohol, BMI, family history, HRT use, menopausal status, OC use, parity/pregnancies	12
Lee, 2003[249]	KWC, Korea, age ≥20, premenopausal parous women	6 years, medical records and death certificate	110 604 women/ 348 preBC, ICD-10 code C50 (invasive)	PA, self-reported questionnaire	yes vs no	Age, age at first child, age at menarche, BMI, OC use, parity/pregnancies, physical activity , smoking habits	8
Leitzmann, 2008[215]	BCDDP, USA, postmenopausal	11 years, self-reported/death certificate/medical records	32 269 women/ 1 506 postBC, 706 ER+, 161 ER-, 588 PR+, 248 PR-, 555 ER+PR+, 126 ER-PR-, 115 ER+PR-, 29 ER-PR+	PA, self-reported	Total PA: 395-721 vs 105-244 MET hr/week, Vigorous PA: 126.1-588 vs ≤0 MET-hour/week	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, benign breast disease, dietary fat, educational level, family history of cancer, health screening, height, menopausal hormone use, oral contraceptive use, smoking habits; model + BMI + (type of activity)	12
Li, 2006[298]	SWHS, China, age 40-70, pre- and postmenopausal	5.66 years, medical records, loss to follow-up 0.1%	73 410 women/ 221 preBC, 213 postBC	BMI, Early adult BMI, WHR, Weight gain, all measured, apart from self-reported earlier weight	Current BMI: ≥25.21 vs ≤22.34 kg/m^2, BMI at 20 years: ≥20.46 vs ≤18.36 kg/m^2, WHR: ≥0.84 vs ≤0.79, Weight gain: ≥13.6 vs ≤6 kg	Age, age at first child birth, breastfeeding, educational level, energy Intake, family history, family history of cancer; model + BMI	12 (BMI, waist)/ 10 (early adult BMI)/ 11 (weight gain)

Liu, 2016[318]	SWHS, China, age 40-70, pre- and postmenopausal	15.1 years, cancer registry, follow up by home visit, medical and hospital records, response rate 92.7% 5 women lost	68 253 640 preBC 522 postBC (ICD-9 174)	BMI Weight gain Weight loss WHR	BMI: ≥30 vs 23-24.9 kg/m^2 WHR: ≥0.86 vs ≤0.77 unit Weight loss: Any loss vs 0-5 kg gain	Age-underlying cox models, alcohol consumption, educational level, energy intake, family history of cancer, fruits and vegetables consumption, hormone replacement therapy, leisure time physical activity, meat intake, menopausal status, parity, smoking, year of birth	14 (BMI, WHR) 13 (weight gain/loss)
London, 1989[300]	NHS, USA, age 30-55, nurses, pre- and postmenopausal	743 716 person-years, self-reported verified by medical records, response rate to follow-ups ~97%	115 534 women/ 598 preBC, 384 postBC, invasive	BMI, Early adult BMI, Weight gain, self-reported	≥25 vs ≤19.9 kg/m^2	Age, age at first child, age at menarche, family history of breast cancer, history of benign breast disease, parity, smoking	14.5 (premenopausal) 12.5 (postmenopausal)
Lukanova, 2006[328]	MSP and VIP, Sweden, age 27-61, pre- and postmenopausal	8.2 years, record linkage with cancer registry	74 207 women/ 92 preBC, 422 postBC, invasive	BMI, measured	≥26 vs 18.5-21.5 kg/m^2	Age, calendar year, smoking habits	9
Lundqvist, 2007[327]	Sweden,Finland Co-twin study,1975, mean age 44 years, twins, pre- and postmenopausal	25.2 years, record linkage with cancer registry	36 490 women/ 881 preBC, 756 post BC, ICD-7 code 170	BMI, self-reported	≥30 vs 18.5-24.9 kg/m^2	Age, country of birth, diabetes, educational level, physical activity , smoking habits, parity (older subjects) (The adjustment did not change the risk estimates by >10%, physical activity at work and alcohol intake were not included in the final model)	9
Luoto, 2000[258]	Finnish adult health behaviour survey, 1978-1993, Finland, age 15-64, pre- and postmenopaus	Record linkage with cancer registry, complete follow-up	30 548 women/ 332 BC (overall)	PA, self-reported questionnaire	daily vs <one/week	Stratified by age and calendar time, may be adjusted for education, parity and age at first birth, BMI, physical activity when communting to work	10.5 (premenopausal) 9.5 (postmenopausal)

	al						
Ma, 2016[280]	CTS, USA, Age 22-79	14.7 years, pathology reports	53 394 postmenopausal women/ 1 672 Luminal A-like BC 202 TNBC,	PA	≥3.51 vs ≤0.5 hours/week/year	Age underlying Cox proportional hazard model, adjusted for race, family history of breast cancer in first-degree relatives, combined age at first full-term pregnancy and parity variable, BMI at baseline, history of smoking, alcohol intake during the past year of baseline, screening mammogram in the past 2 years of baseline, history of a breast biopsy, and a corresponding moderate recreational physical activity variable	13
MacInnis, 2004[364]	MCCS, Australia, age 27-75, postmenopausal	9.1 years, medical records	13 598 women/ 357 postBC, 97 ER+, 29 ER-, 84 PR+, 42 PR-, invasive	BMI, WC, WHR, measured	WC: ≥87 vs ≤70.9 cm, WHR: ≥0.83 vs ≤0.73	Age, birthplace, educational level, HRT use, physical activity (Physical activity, alcohol consumption, maternal family history of cancer, parity, duration of lactation, age at first gestation, age at menarche, HRT, and OC use were not adjusted as inclusion did not change the HRs by ≥5%)	13
Manders, 2011[211]	HEBON, BRCA1/2 carriers, pre- and postmenopausal	10 years, record linkage with cancer registry	155 preBC, 719 non-cases; 63 postBC, 2 922 non-cases	BMI, Early adult BMI, Weight gain, self-reported	BMI and BMI at age 18 years–preBC: ≥25 vs 18.5-22.49 kg/m^2, Weight gain: ≥25 vs 4-12.9 %	Age, stratified for birth cohort and genes, clustered on family, adjusted for lifetime spots activity (Did not adjust for reproductive factors and alcohol because it did not change RR estimate)	7 (BMI) 6 (early adult BMI) 6.5 (weight gain)
Manjer, 2001[330]	MPP, Sweden, mean age 55 years, pre- and postmenopausal	13.1 years, record linkage with cancer registries	9 738 women/ 112 preBC, 157 postBC, invasive	BMI, measured	BMI–preBC: ≥25.47 vs ≤20.61 kg/m^2 , BMI–postBC: ≥26.55 vs ≤21.98 kg/m^2	Age	10 (premenopausal) 11 (postmenopausal)
Maruti, 2008[271]	NHS II, USA, age 33-51, nurses, premenopausal	6 years, self-reported verified by medical records, response rate to	64 777 women/, 550 preBC (363 ER+, 103 ER-),	PA (lifetime), self-reported questionnaire, validated	≥4 vs ≤0.9 hours/week	Age, age at first child birth, alcohol Intake, benign breast disease, body shape, family history of cancer, height, oc use, parity (After adjusting for age at menarche, regularity and length of	15

		follow-ups ~90%	invasive,			menstrual cycle during youth and adulthood and BMI(at age 18, current and cumulatively updated), RR for total lifetime activity and BC did not appreciably different.)	
McTiernan, 2003[267]	WHI-OS, USA, age 50-79, postmenopausal	4.7 years, medical record, pathology reports, family report, loss to follow-up 3.2%	74 171 women/ 1 768 postBC	PA, Early adult PA, self-reported questionnaire,validated	Recreational PA: ≥40.1 vs ≤0 MET-hour/week, Vigorous PA: ≥7 vs ≤0 hours/week	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, educational level, ethnicity, family history, HRT use, Income, mammography, oophorectomy/hysterectomy, parity/pregnancies, place of residence, smoking habits	15
Mellemkjaer, 2006[368]	DCH, Denmark, age 50-65, postmenopausal	6.1 years, record linkage with cancer registry	23 788 women/ 633 postBC	BMI, WC, WHR, measured	≥0.85 vs 0.79-0.84	Age, age at first child birth, alcohol consumption, benign breast disease, educational level, parity, (current use of MHT and duration of use)	12
Mertens, 2006[264]	ARIC, USA, age 45-64, postmenopausal	13.1 years, histology reports	7 994 women/ 342 postBC	PA, self-reported questionnaire, validated	Q4 vs Q1	Age, age at first child, age at menopause, ethnicity, family history, recruitment center	12
Miao Jonasson, 2014[345]	Swedish National Diabetes Register Cohort Study, Sweden, age 30-90, type 2 diabetic, postmenopausal	8.6 years, record linkage with cancer registry and death registry	11 093 women/ 263 postBC, ICD-10 code C50 (invasive)	BMI, From records	≥30 vs 18.5-24.9 kg/m^2	Age, diabetes, diabetes medication use, hba1c, smoking	7
Michels, 2006[336]	NHS II, USA, age 25-42, nurses, premenopausal	14 years, self-reported verified by medical notes	116 609 women/ 1 398 preBC, 669 ER+, 285 ER-, 636 PR+, 300 PR-, invasive	BMI, Early adult BMI, self-reported	BMI: ≥30 vs 20-22.4 kg/m^2, BMI at 18 years: ≥27.5 vs 20-22.4 kg/m^2	Age, age at first child, age at menarche, alcohol, benign breast disease, family history of cancer, height, OC use, parity/pregnancies, physical activity, (BMI)	14.5

Michels, 2012[308]	NHS, age 30-55; NHS II, age 25-42, USA, nurses, premenopausal	1 014 175 person-years, self-reported verified by medical records, response rate to follow-ups 95% (NHS) and 94% NHSII	165 608 women/ 1 811 preBC, invasive	Weight gain, self-reported	gained ≥25 kg vs stable	Age, age at first child birth, age at menarche, alcohol, contraception, family history of breast cancer, height, history of breast disease, parity, physical activity, weight at 18 yrs	14.5
Moore, 2000[270]	IWHS, USA, age 55-69, postmenopausal	10 years, record linkage with cancer registry and death certificate	41 837 women/ 1 371 postBC	PA, self-reported questionnaire	>4 times/week vs rarely or never	Age, age at first child, age at menopause, BMI, BMI at 18 years, educational level, family history, HRT use, WHR	12
Moradi,1999[284]	Sweden, 1971, age 50-59, pre- and postmenopausal	18 years, histology records, complete long-term follow-up	982 270 women/ 1 597 preBC, 6 684 postBC, invasive	PA, self-reported questionnaire	sedentary vs high	Age, place of residence, calendar year of follow-up, socioeconomic status	11.5
Morimoto, 2002[236]	WHI-OS, USA, age 50-79, postmenopausal	34.8 months, self-reported and medical records, loss to follow-up 1.9%	85 917 women/ 1019 postBC, invasive	BMI, WC, WHR (measured) Early adult BMI (self-reported), BMI gain	BMI at 18 years: ≥22.32 vs ≤18.6 kg/m^2 Gain in BMI: ≥9.71 vs ≤0 kg/m^2	Age, age at first child, age at menarche, age at menopause, alcohol, educational level, energy Intake , ethnicity, family history, leisure time physical activity, parity/pregnancies, smoking habits	14 (early adult BMI) 15 (BMI gain)
Muti, 2000[367]	ORDET, USA, age 35-69 years	5.5 years, record linkage with cancer registry	70 preBC, 277 non-cases; 64 postBC, 253 non-cases, invasive	WHR, measured	WHR–preBC: ≥0.80 vs ≤0.75, WHR–postBC: ≥0.84 vs ≤0.79	Age, recruitment center, time of recruitment; model + BMI	9 (premenopausal) 10 (postmenopausal)
Neuhouser, 2015[351]	WHI, USA, age 50-79 postmenopausal	13 years, medical records	13 518 post BC 2 143 ER+PR+ 415 ER-PR-	BMI, measured	≥35 vs ≤24 kg/m^2	Age, alcohol consumption, diabetes, e+p use and duration, e-alone use and duration, education, family history of breast cancer, history of bilateral oophorectomy, parity, race/ethnicity, smoking status, age at first birth , stratified by cad randomization group, stratified by ht trial randomization group, stratified by baseline age group, stratified by dietary trial randomization group, stratified by extended follow-up, stratified	15

						by hysterectomy status	
Nitta, 2016[254]	JACC, Japan, age 40-79	13 years, hospital records/cancer registries	38 610 women/ 81 preBC 153 postBC	Weight gain, PA, self-reported questionnaire	Weight gain ≥10 vs ≤3.2 kg PA: mostly physically active vs inactive	Age, age at first child birth, age at menarche, alcohol consumption, height, number of birth, mutually adjusted for weight gain and physical activity	8.5 (weight gain) 9 (PA)
Nomura, 2016[294]	BWHS, USA, age 21-69 years African America	15.4 years, self-report, linkage to cancer registries and medical records, follow-up rate 87%	46 734 women/ 752 preBC 965 postBC 1 008 ER+ or PR+ 433 ER-PR- 173 ER-PR-HER2-, ICD-9 code 174/ICD-10 code C50	Sitting	Overall: ≥10 vs ≤4.9 hours/day	Age, age at menarche, area of residence, BMI, calories intake, education years, family history of breast cancer, mammography, menopausal hormone use, OC use, parity, recreational activity, smoking (Results did not differ when excluding participants diagnosed with breast cancer within 4 years of baseline)	14 (premenopausal) 13 (postmenopausal)
Nomura, 2016[255]	BWHS, USA, age 21-69 years African America	13.86 years, self-report, linkage to cancer registries and medical records	49103 women/ 698 preBC 861 postBC Invasive	PA	Met vs not met PA recommendations	Age, geographic region of residence, kilocalories/day, smoking, family history of breast cancer, education, menopausal status (pre/post), OC use, parity, MHT use, BMI, alcohol	15 (premenopausal) 14 (postmenopausal)
Palmer, 2007[230]	BWHS, USA, age 21-69, Black women, pre- and postmenopausal	10 years, self-reported, medical records, and death certificates, follow-up rate ~80%	59 000 women/ 490 preBC, 454 postBC, 84 ER+PR+, 52 ER-PR-, 36 ER+PR- or ER-PR+	BMI, Early adult BMI, WC, WHR, Weight gain, self-reported	BMI: ≥30 vs ≤24 kg/m^2, WC: ≥37 vs ≤27 inch, Weight gain: ≥25 vs ≤9 kg	Age, age at first child birth, age at menarche, age at menopause, educational level, family history of cancer, parity, physical activity, BMI at 18 years (for weight gain)	10 (BMI, waist) 9 (early adult BMI) 9.5 (weight gain)
Parker, 2003[321]	IWHS, USA age 55-69, postmenopausal	Record linkage to cancer registry	21 707 women/ 772 post BC	Weight loss, self-reported	Intentional and unintentional weight loss episodes of ≥20 pounds vs never lost ≥20 pounds	Age, BMI, BMI^2, waist-to-hip ratio, physical activity, education, marital status, smoking status, pack-years cigarettes, current oestrogen use, alcohol use, parity, and multivitamin use	9

Patel, 2003[269]	CPSII, USA, age 63 years, postmenopausal	5 years, histologically confirmed	72 608/ 1 503 postBC	Interviewed	Recreational PA: ≥42 vs 0.1-7 MET-hour	Age , age at menarche, age at menopause, alcohol, benign breast disease, BMI, body weight, duration of oc use, educational level, energy Intake , ethnicity, family history, HRT use, mammography, parity/pregnancies, smoking habits	15
Peters, 2009[279]	NIH-AARP, age 50-71 years, postmenopausal	7 years Record linkage to cancer registry	182 862/ 6 609 postBC (2 083 ER+, 411 ER-)	PA: Self-administered questionnaire	Vigorous PA: ≥5 vs ≤0 times/week	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, educational level, ethnicity, family history of cancer, menopausal hormone use, parity, smoking status	13
Petrelli, 2002[359]	CPSII, USA age ≥30 years	14 years, histologically confirmed	424 168 (overall)/ 2 852 postBC	Self-reported height and weight	BMI: ≥30 vs ≤24.99 kg/m^2	Age , age at first child, age at menarche, age at menopause, alcohol, benign breast disease, educational level, ethnicity, family history, height, HRT use, menopausal status, OC use, parity/pregnancies, physical activity , smoking habits	15
Phipps, 2011[273]	WHI, USA, age 50-79, postmenopausal	7.9 years, self-reported	155 723 women/ postBC 2 592 ER+, 306 triple-negative, invasive	BMI, WC, WHR (measured) Early adult BMI (self-reported), PA, validated	≥30 vs ≤25 kg/m^2	Age, educational level, family history of breast cancer, income, history of mammography at baseline, mammography during follow-up, race, recreational activity	15
Radimer, 2004[314]	FHS, USA, age 28-62 , postmenopausal	48 years, histology reports	2 873 women/ 165 postBC	Weight gain, measured weights	≥25.1 vs +/-2 kg	Age, age at first child, alcohol, HRT use, parity/pregnancies, smoking habits, BMI at start of period	11
Reeves, 2007[217]	MWS, UK, age 50-64, MHT non-users, pre- and postmenopausal	5.4 years, National health records	1 222 630 women/ 1 179 preBC, 637 postBC, ICD-10 code C50 (Invasive)	BMI, self-reported	≥30 vs 22.5-24.9 kg/m^2	Age, alcohol consumption, geographic area, physical activity, reproductive factors, smoking habits, socio-economic status, time since menopause (post only)	12 (premenopausal) 13 (postmenopausal)
Reinier, 2007[216]	VMC, USA, pre- and postmenopausal	3.1 years, screening examinations, 21.9% no exit mammography/biopsy (loss to	61 844 women/ 231 preBC, 572 postBC, invasive	BMI, self-report	≥30 vs ≤21.9 kg/m^2	Age, age at first child birth, breast density, family history of cancer	9

		follow-up)					
Rinaldi, 2006[363]	EPIC, Europe, postmenopausal	Record linkage with cancer registries and active follow-up	613 postBC, 1 139 non-cases	BMI, WC, WHR, measured and self-reported	Q 5 vs Q 1	Matched by centre, age, time of the day of blood collection, and fasting status, adjusted for age at first child, parity, (steroid levels in different models) (Age at menarche, age at menopause, age, past use of exogenous hormones, time since menopause not in final model as did not alter regression coefficients by >=5%)	11
Rintala, 2002[283]	Finland, age 25-55, pre- and postmenopausal	24 years (maximum), record linkage with cancer registry	-women/ 1694 preBC, 10 801 postBC	PA, self-reported questionnaire of the census	Class 5 (excluding agricultural workers) vs class 1+2	Age, social class and reproductive factors	8 (premenopausal) 6 (postmenopausal)
Rintala, 2003[282]	FFTC, Finland, age 25-80, pre- and postmenopausal	34 years, record linkage with cancer registry	10 049 women/ 123 preBC, 342 postBC	PA, self-reported questionnaire	physical education vs teacher vs language teacher	Age, age at first child birth, calendar year of follow-up, number of children	7 (premenopausal) 6 (postmenopausal)
Ritte, 2012[352]	EPIC, Europe, age 25-70, postmenopausal	3 399 178 person-years, cancer and pathology registries	314 760 women/, postBC, 3196 ER+PR+, 1022 ER+PR-142 ER-PR+, 874 ER-PR-	BMI, self-reported or measured	≥25.9 vs ≤22.5 kg/m^2	Age, age at first child birth, age at menarche, age at menopause, alcohol, centre location, educational level, height, menopausal status, oral contraceptive history, parity, smoking	14
Rosenberg, 2014[231]	BWHS, USA, age >30, Black women, pre- and postmenopausal	307 672 person-years, self-reported, record linkage with cancer registries, medical and pathology reports, follow-up rate ~80%	44 708 women/ 483 preBC, 661 postBC, invasive	PA, Early adult PA, self-reported questionnaire, PA validated	≥7 vs ≤0.9 hours/week	Age, fruits and vegetables consumption, meat consumption, parity, time period, years of education (Models that further controlled for age at menarche, age at first birth, oral contraceptive use, supplemental female hormone use, menopausal status, age at menopause, history of breast cancer in a first-degree relative, alcohol consumption, and cigarette smoking yielded IRR estimates that were within 2% of the estimates)	13

Rosner, 2017[315]	NHS, USA, Age 30-55	1 595 695 PY, self-report verified by pathology reports and medical records	74 177 women/ 4 207 postBC (2 084 ER+PR+, 544 ER-PR-)	Weight gain , self-reported height and weight	≥20 vs stable weight	Age, age at menarche, age at menopause, alcohol intake, benign breast disease, duration and type of hormone therapy, family history of breast cancer in first degree relatives, height, parity and age at first birth, postmenopausal hormone use, postmenopausal weight change, type of menopause	14.5
Schnohr, 2005[265]	CCPPS, Denmark, age 20-91, postmenopausal	14 years, histology reports	13 216 women/ 417 postBC	PA, self-reported questionnaire	vigorous vs low	Age, alcohol, birth cohort, study cohort membership, BMI, educational level, parity, smoking habits, occupational physical activity, (MHT)	10
Schonfeld, 2011[223]	Four NCI cohorts, USA, mean age 60.8 years, Caucasian, postmenopausal	7.1 to 11.5 years in cohorts, record linkage with cancer and death registry, or self-reported with/without verification by medical records	236 911 women/ 9 792 postBC	BMI, self-reported	≥30 vs <25 kg/m^2	Age, birth year, calendar year of entry, OC use, study, age at menarche, age at a natural menopause, MHT use, family history of BC, benign breast disease, alcohol consumption, (number of live births)	11.9
Sczaniecka, 2012[240]	VITAL, USA, age 50-76, postmenopausal	6 years, record linkage with cancer registries, 5.3% moved out of catchment area but were identified and follow-up	30 252 women/ 771 postBC, invasive	Total energy, 120-item semi-quantitative FFQ for diet a year prior to baseline	Energy: ≥1910 vs ≤1015 kcal/day,	Age	12.5
Sebastiani, 2016[341]	MSP, Modena, Italy, age 55-69, postmenopausal, mammography screening programme	70.61 months, record linkage to cancer registry	14 684 women/ 366 post BC	BMI, self-report height, weight measured by personnel	≥30 vs ≤18.5-24.9 kg/m^2	Age	8.5

Sellers, 2002[123]	IWHS, USA, age 55-69, postmenopausal	13 years, histology reports	37 105 women/ 1650 postBC, 1 043 ER+, 232 ER-, 993 PR+, 362PR-	BMI, Early adult BMI, WC, WHR, self-reported, validated	BMI: ≥30.7 vs ≤22.89 kg/m^2, BMI at 18 years: ≥22.91 vs ≤18.6 kg/m^2, WC: ≥39.1 vs ≤29.75 inch, WHR: ≥0.91 vs ≤0.76	Age at first child, age at menarche, age at menopause, alcohol, BMI, body weight, educational level, family history, HRT use, OC use, parity/pregnancies, physical activity , smoking habits, (WHR), (BMI), (BMI at 18 years)	13.5 (BMI, waist) 12 (early adult BMI)
Sesso, 1998[227]	CAHS, USA, age 37-69 ,	31 years, self-reported, medical records, and death certificate, loss to follow-up 34%	1 566 women/ 28 preBC, 81 postBC	PA, self-reported questionnaire, validated	≥1000 vs ≤499 kcal/week	Age, BMI (Adjustment for age at menarche, age at menopause, family history of breast cancer, MHT use, and parity did not substantially change any of the previous RR estimates)	9 (premenopausal) 8 (postmenopausal)
Setiawan, 2009[353]	MEC, USA, age 45-75, postmenopausal	10.4 years, record linkage with cancer registry	84 427 women/ post BC, 1 182 ER+PR+, 217 ER+PR-, 327 ER-PR-, invasive	BMI, self-reported	30.0 vs ≥24.9 kg/m^2	Age, age at first child birth, age at menarche, alcohol consumption, ethnicity, family history of cancer, HRT use, menopausal status, parity, study center, year of recruitment	14.5
Silvera, 2006[220]	CNBSS, Canada, age 40-59, pre- and postmenopausal	16.4 years, histology reports, complete follow-up	38 645 women/ 818 preBC, 662 postBC	PA, self-reported	≥61 vs 0-30 min/day	Age, age at first child, age at menarche, alcohol, BMI, breast diseases , energy Intake , family history, HRT use, menopausal status, oc use, other design Issue, parity/pregnancies, recruitment center, smoking habits	11.5
Song, 2008[348]	KNHIC, Korea, age 40-64, postmenopausal	8.75 years, cancer registry and national insurance database	179 481 women/ 612 postBC, ICD-10 code C50 (invasive)	BMI, measured	≥30 vs 21-22.9 kg/m^2	Age, alcohol consumption, height, Income, physical activity, smoking status (Results did not materially change in an analysis restricted to women reporting natural menopause and not use HRT)	11

Sonnenschein, 1999[221]	NYUWHS, USA, age 35-65, recruited in BC screening clinic, pre- and postmenopausal	6.6 years, histology reports	8 416 women/ 109 preBC, 150 postBC	BMI, self-reported; waist and hip circumference, measured	BMI–preBC: ≥26.37 vs ≤21.4 kg/m^2, BMI–postBC: ≥27.47 vs ≤22.31 kg/m^2, WHR: ≥0.78 vs ≤0.7	Age, age at first child, age at menarche, breast biopsies, family history; model + BMI	7 (BMI-premenopausal) 8 (BMI-postmenopausal) 8 (waist-premenopausal) 9 (waist-postmenopausal)
Steindorf, 2013[247]	EPIC, Europe, age 35-70, pre- and postmenopausal	11.6 years, record linkage with cancer registry	257 805 women/ 936 preBC, 7 098 postBC, invasive	PA, self-reported questionnaire/interviewed, validated	Total PA: active vs inactive, Recreational PA: ≥42 vs ≤13.5 MET-hours/week Occupational PA: manual/heavy vs sedentary	Age, age at first child, age at menarche, age at menopause, alcohol, BMI, breastfeeding, centre location, educational level, household physical activity, HRT use, menopausal status, number of full-term pregnancies, occupational activity, oral contraceptive history, recreational activity, smoking, total physical activity	14 (premenopausal) 13 (postmenopausal)
Sue, 2009[214]	PLCO, USA, age 55-75, cancer screening RCT, screening arm only postmenopausal	8.7 years, self-reported verified by medical records, response rate to annual follow-up 95.7%	29 170 women/ 1 319 postBC	Total energy, dietary questionnaire/137-item FFQ at baseline	≥2081 vs ≤1311 kcal/day	Age, age at first child birth, age at menarche, age at menopause, benign breast disease, duration of HRT use, educational level, family history of cancer, height, mammography, parity, race, study center; alcohol/OC use not in final model; also model + BMI and physical activity	13.5
Suzuki, 2006[219]	SMC, Sweden, age <70, postmenopausal	8.3 years, record linkage with cancer registry	51 823 women/ 1 284 postBC, 716 ER+PR+, 279 ER+PR-, 50 ER-PR+, 143 ER-PR-, 766 PR+, 422 PR-, invasive	BMI, self-reported	≥30 vs 18.5-24.9 kg/m^2	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, educational level, energy Intake , family history, food, height, HRT use, menopausal status, nutrients, OC use, parity/pregnancies	13

Suzuki, 2011[297]	JPHC I and II, Japan, age 40-69, pre- and postmenopausal	14 years, hospital records and cancer registry, low loss to follow-up	41 594 women/ 220 preBC (49 ER+PR+, 24 ER-PR-), 232 postBC (45 ER+PR+, 36 ER-PR-), invasive	BMI, Early adult BMI, Gain in BMI, self-reported	BMI: ≥24 vs 20-23.9 kg/m^2, Gain in BMI: ≥5 vs ≥-2.5 to >2.5 kg/m^2	Age, age at first child birth, age at menarche, parity, use of exogenous female hormones, smoking status, leisure-time physical activity, alcohol intake, green-yellow vegetables, meat and meat products, isoflavones intake, change in BMI from age 20 years, (BMI at 20 years)	12.5 (BMI-postmenopausal) 13.5 (early adult BMI-premenopausal) 12.5 (early adult BMI-postmenopausal) 14 (BMI gain-premenopausal) 13 (BMI gain-postmenopausal)
Suzuki, 2011[233]	JPHC, Japan, age 40-69, pre- and postmenopausal	14.5 years, record linkage with cancer registry, low loss to follow-up	53 578 women/ 240 preBC, (55 ER+PR+, 25 ER+PR-, 25 ER-PR) 239 postBC, (46 ER+PR+, 21 ER+PR, 36 ER-PR-) WHO code C500-509 (invasive)	PA, self-reported questionnaire/interviewed, validated	Total PA: Q3 vs Q1, Recreational PA: ≥3d/week vs ≤3d/month	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, area, energy-adjusted Intake of Isoflavones, height, HRT use, parity, physical activity, smoking; model + BMI	15.5 (premenopausal) 14.5 (postmenopausal)
Tehard, 2006[362]	E3N, France, age 40-65, pre- and postmenopausal	3.6 years, active follow-up, health insurance, and medical records	69 116 women/ 212 preBC, 1 071 postBC, invasive	BMI, WC, WHR, self-reported	WHR: ≥0.82 vs ≤0.74	Age, age at first child, age at menarche, alcohol, benign breast disease, educational level, family history, marital status, parity/pregnancies, physical activity	13
Tehard, 2006[251]	E3N, France age 40-65, pre- and postmenopaus	11.4 years, active follow-up, health insurance, and medical	98 995 women/ 2 637 (overall)	PA: Self-reported in questionnaire	Recreational PA: ≥33.8 vs ≤0 MET-hour/week	Age at first child, age at menarche, age-underlying cox models, benign breast disease, BMI, family history, HRT use, marital status, menopausal status, OC use, occupation, parity/pregnancies	12

	al	records					
Thune, 1997[259]	NNHSS, three counties, Norway, age 20-49, pre- and postmenopausal	13.7 years, histology reports	25 624 women/ 98 preBC, 248 postBC, invasive	PA, self-reported questionnaire	Recreational PA: regular exercise vs sedentary, Occupational PA: lifting or heavy manual labour vs sedentary	Age, BMI, height, parity/pregnancies, place of residence (Women in whom cancer developed or who died within the first year of the study were excluded in the study)	9 (premenopausal) 10 (postmenopausal)
Torio, 2010[305]	CLUE II, USA, mean age 63 years, postmenopausal	Record linkage with cancer registry	5 642 women/ 172 postBC, ICD code 174	BMI, Early adult BMI; Gain in BMI, self-reported	per 1 kg/m^2	Age, age at first child birth, breastfeeding, educational level, HRT use, parity, social class	9 (BMI) 8 (early adult BMI) 8.5 (BMI gain)
Tornberg, 1994[332]	Sweden, 1971, age 25-75, pre- and postmenopausal	25 years, histology reports	47 003 women/ 373 preBC, 1 093 postBC	BMI, measured	≥28 vs ≤21.9 kg/m^2	Age	9 (premenopausal) 11 (postmenopausal)
Trichopoulou, 2010[238]	EPIC-Greece, age 20-68, pre- and postmenopausal	9.8 years, medical records and pathology reports, loss to follow-up 520 women	14 807 women/ 113 preBC, 127 postBC, ICD-O code C50 (invasive)	Total energy, validated semi-quantitative, interviewer-administered 150-item FFQ for usual diet a year prior to baseline	per 568 kcal/day	Age, age at first child birth, age at menarche, BMI, educational level, energy Intake, height, metabolic equivalents, parity, smoking, (age at menopause, HRT)	11.5 (premenopausal) 12.5 (postmenopausal)
Tulinius, 1997[331]	Reykjavik Study, 1968, Iceland, age 45-59, pre- and postmenopausal	27 years, histology reports, loss to follow-up 0.6%	11 580 women/ 91 preBC, 343 post BC, ICD-7 code 170	BMI, measured	per 1 kg/m^2	Age	10 (premenopausal) 11 (postmenopausal)

van den Brandt, 2000[104]	The Pooling Project, USA, age 28-93, pre- and postmenopausal	3-7 years in cohorts, follow-up questionnaires and inspection of medical records and/or tumour registry linkage	337 819 women/ 723 preBC, 3 208 postBC, invasive	BMI, self-reported	≥33 vs <21 kg/m^2	Stratified by year of birth and calendar year or study-specific matching factors, adjusted for age at menarche, parity, age at birth of first child, postmenopausal hormone use, oral contraceptive use, history of benign breast disease, maternal history of breast cancer, history of breast cancer in a sister, smoking status, education, fat intake, fibre intake, energy intake, alcohol intake	13.45 (premenopausal) 12.85 (postmenopausal)
van den Brandt,1997[306]	NLCS, The Netherlands, age 55-69, postmenopausal	4.3 years, histology reports, no loss to follow-up	500 postBC, invasive	BMI, early adult BMI, Weight gain (kg/BMI), self-reported	BMI: ≥27 vs ≤19.9 kg/m^2, Weight gain: ≥20 vs <5 kg, Gain in BMI: ≥10 vs 0-1.9 kg/m2/20 yr	Age, age at first child, age at menarche, alcohol, parity	12 (early adult BMI) 12.5 (weight gain)
Vatten, 1990[350]	NNHSS, Norway, age 35-51, pre- and postmenopausal	11.9 years, histology reports	23 826 women/ 137 preBC, 99 postBC	BMI, measured	≥2.68 vs ≤2.19 g/cm^2	Age	9
Vatten, 1992[334]	NNHSS, age 26-49 years, premenopausal	14 years, histology reports	25 967 women/ 164 preBC	BMI, measured	≥28 vs ≤21 kg/m^2	Age, age at first child, occupation, parity/pregnancies, place of residence	9
Voorrips, 2002[243]	NLCS, The Netherlands, age 55-69, postmenopausal	6.3 years, histology records, loss to follow-up 4%	62 573 women/ 783 postBC, invasive	Total energy, 150-item semi-quantitative FFQ, validated against 9-day diet record, Pearson correlation coefficient for energy was 0.74	9247 vs 5079 kJ/day	Age, age at first child, age at menarche, age at menopause, alcohol, benign breast disease, BMI, educational level, family history, OC use, parity/pregnancies, smoking habits	14.5

Wada, 2014[326]	Eight Japanese cohorts, Japan, mean age 55.3 years, pre- and postmenopausal	11.93 years, record linkage with cancer registries and active follow-up with hospitals	183 940 women/ 301 preBC, 1 482 post BC, ICD-10 code C50 (invasive)	BMI, self-reported	≥30 vs 23-24.9 kg/m^2	Age, area, smoking status, alcohol consumption, age at menarche, age at first delivery, parity number	10.87 (premenopausal) 10.86 (postmenopausal)
Weiderpass, 2004[299]	WLHS, Norway and Sweden, age 30-49, premenopausal	8 years, histology reports, 789 women emigrated during follow-up	99 717 women/ 716 preBC, invasive	BMI, Early adult BMI, Gain in BMI, self-reported	BMI: ≥30 vs 20-24.9 kg/m^2, BMI at 18 years: ≥25 vs 20-24.59 kg/m^2, Weight gain: ≥4.1 vs 0-1.4 kg/m^2	Age, age at first child, age at menarche, duration of breastfeeding, family history of breast cancer, OC use, parity, place of residence; model + current BMI	12.5 (BMI) 11.5 (early adult BMI) 12 (BMI gain)
Welti, 2017[319]	WHI-OS, USA postmenopausal	20 years, annual mailed questionnaires, medical record review, pathology reports	80 943 women/ 5 564 postBC	Weight loss	Weight loss vs stable weight (within 10 lb)	Age, race/ethnicity, education, income, smoking status, alcohol intake, physical activity, HT use, healthy eating index, BMI at baseline	9
White, 2015[213]	Sister study, USA, Puerto Rico, age 35-74, sisters of BC cases	5.4 years, Self-report verified by medical record and pathology report	47 166 women/ 413 preBC (204 ER+PR+, 157 ER-PR-) 1 582 postBC (682 ER+PR+)	BMI WC WHR	BMI: ≥35 vs 18.5-24.9 kg/m^2 WC: ≥89 vs ≤80 cm WHR: ≥0.86 vs ≤0.74	Age, age at first child birth, age at menarche, age at menopause, alcohol consumption, breastfeeding, educational level, parity, physical activity, postmenopausal hormone use, race, smoking, pack-years, BMI (in analyses of WC and WHR)	13 (premenopausal) 15 (postmenopausal)
White, 2012[303]	MEC, Hawai, California, age 45-75, postmenopausal	9 years, cancer registry and National death index	82 971 women/ 3080 postBC, invasive	BMI, Early adult BMI, Weight gain, self-reported compared with the driving license	BMI: ≥30 vs 20-24.9 kg/m^2, Weight gain: ≥22.7 vs 3.65-9.09 kg	Age, age at first child birth, age at menarche, age at menopause, alcohol Intake, energy intake, family history of breast cancer, height, HRT use, number of childbirths, physical activity, smoking status, type of menopause, (BMI at baseline)	13.5 (BMI) 12 (early adult BMI) 12.75 (weight gain)

Whitlock, 2009[338]	PSC, Pooled analysis, International, age 46 years	8 years, death certificates, medical records and autopsy findings	353 124 women (overall)/ 462 preBC 420 postBC	BMI, self-reported	15-50 kg/m^2	Age at risk, study, smoking status	
Xue, 2016[296]	NHS II, USA, age 25-42, nurses, premenopausal	1 133 893 person-years, self-report, next of kin, medical and pathological records	90 101 women/ 1 574 preBC Invasive	BMI, Early adult BMI, self-reported	BMI: ≥27.5 vs <20 kg/m^2 Early adult BMI: ≥27.5 vs <18.5 kg/m^2	Age at first child birth, age at menarche, alcohol consumption, body fatness factors earlier in life, body fatness factors later in life, family history of breast cancer, height, history of benign breast disease, interaction between parity, oral contraceptive use, physical activity, body fatness factors (somatotype or BMI) later in life (in analysis of early adult BMI)	11.5
Zhang, 2015[310]	NHS, USA, age 30-55, nurses, postmenopausal	26 years, self-reported verified by medical records, loss to follow-up <10%	103 577 women/ 5 191 postBC, (1 701 androgen receptor-positive, 497 androgen receptor-negative) Invasive,	Weight gain/loss, self-reported height and weight	10-19.9 vs ±1.9 kg	Stratified by age, and year of questionnaire return, adjusted for age at menarche, age at menopause, alcohol Intake, family history of breast cancer, height, history of benign breast disease, parity and age at first birth, MHT use, BMI at age 18 years	13.75

Appendix 4 List of publications identified in the search and included in the meta-analyses of risk of mortality after breast cancer, and details of studies excluded from each specific meta-analysis

Overall

149 potential relevant publications:

80 publications were included in the meta-analyses[105;106;110;111;114;115;128;129;397-402;404;409-433;436-445;447-475;717]

69 publications were excluded:

14 publications were superseded by publications of the same study or an overlapping study population[108;113;718-729]

18 publications did not have sufficient data to be included in a meta-analysis[109;396;403;730-744]

16 publications had no measure of association[745-760]

13 publications were not meta-analysed[112;405-408;434;435;476;761-765]

7 publications reported unadjusted results[107;766-771]

1 publication from a pooled study of 4 cohorts[68]

Pre-diagnosis total energy intake and total mortality after breast cancer

Overall 4 publications were identified[115;398;402;403]

3 publications from 3 studies were included in the dose-response meta-analysis[115;398;402]

1 excluded publication [403]

1	Goodwin, 2003[403], breast cancer survivor cohort, Canada	52/ 477 6.1 years	Insufficient information	FFQ, completed on average 9.3 weeks after diagnosis, for diet over preceding 12 months P for linear = 0.35, P for non-linear = 0.15 Age, tumour stage, nodal status, hormonal therapy, chemotherapy, energy intake, BMI

≥12 months post-diagnosis total energy intake and total mortality after breast cancer

Overall 3 publications identified[404-406]

No meta-analysis

Pre-diagnosis total energy intake and breast cancer mortality

Overall 3 publications identified[112;402;764]

No meta-analysis

<12 months post-diagnosis total energy intake and breast cancer mortality

Overall 1 publication identified[407]

No meta-analysis

≥12 months post-diagnosis total energy intake and breast cancer mortality

Overall 2 publications identified[406;408]

No meta-analysis

Pre-diagnosis total physical activity and total mortality after breast cancer

Overall 2 publications were identified[410;413]

2 publications from 2 studies were included in the highest versus the lowest meta-analysis[410;413]

≥12 months post-diagnosis total physical activity and total mortality after breast cancer

Overall 3 publications were identified [409-411]

3 publications from 3 studies were included in the highest versus the lowest meta-analysis[409-411]

3 publications from 3 studies were included in the dose-response meta-analysis[409-411]
Pre-diagnosis total physical activity and breast cancer mortality Overall 2 publications were identified [410;413] 2 publications from 2 studies were included in the highest versus the lowest meta-analysis[410;413]
≥12 months post-diagnosis total physical activity and breast cancer mortality Overall 2 publications identified[409;410] 2 publications from 2 studies included in the highest versus the lowest meta-analysis[409;410]
Pre-diagnosis recreational physical activity and total mortality after breast cancer Overall 8 publications were identified[129;402;413-418] 8 publications from 8 studies were included in the highest versus the lowest meta-analysis[129;402;413-418]
≥12 months post-diagnosis recreational physical activity and total mortality after breast cancer Overall 5 publications were identified[128;412;415;419;420] 5 publications from 5 studies were included in the highest versus the lowest meta-analysis[128;412;415;419;420] 5 publications from 5 studies were included in the dose-response meta-analysis[128;412;415;419;420]
Pre-diagnosis recreational physical activity and breast cancer mortality Overall 7 publications were identified[110;402;413;414;416-418] 7 publications from 7 studies were included in the highest versus the lowest meta-analysis[110;402;413;414;416-418]
<12 months post-diagnosis recreational physical activity and breast cancer mortality Overall 1 publication identified [407] No meta-analysis
≥12 months post-diagnosis recreational physical activity and breast cancer mortality Overall 2 publications were identified 2 publications from 2 studies were included in the highest versus the lowest meta-analysis[128;421]
Pre-diagnosis moderate physical activity and total mortality after breast cancer Overall 3 publications were identified[413-415] 3 publications from 3 studies were included in the highest versus the lowest meta-analysis[413-415]
≥12 months post-diagnosis moderate physical activity and total mortality after breast cancer Overall 1 publication identified[412] No meta-analysis
≥12 months post-diagnosis moderate-vigorous physical activity and total mortality after breast cancer Overall 3 publications were identified[409;411;415] 3 publications from 3 studies were included in the highest versus the lowest meta-analysis[409;411;415]
Pre-diagnosis vigorous physical activity and total mortality after breast cancer Overall 2 publications were identified[413;414] 2 publications from 2 studies were included in the highest versus the lowest meta-analysis[413;414]
≥12 months post-diagnosis vigorous physical activity and total mortality after breast cancer Overall 1 publication identified[412] No meta-analysis
Pre-diagnosis early adult BMI and total mortality after breast cancer Overall 1 publication identified[422] No meta-analysis
Pre-diagnosis early adult BMI and breast cancer mortality

Overall 1 publication identified[423]
No meta-analysis

Pre-diagnosis adult weight gain and total mortality after breast cancer
Overall 4 publications were identified[418;424-426]
4 publications from 4 studies were included in the highest versus the lowest meta-analysis[418;424-426]

Post-diagnosis weight gain and total mortality after breast cancer
Overall 8 publications were identified[422;427-431;720;756]
6 publications from 6 studies were included in the highest versus the lowest meta-analysis[422;427-431]
1 superseded publication[720]
1 excluded publication[756]

Publication	Author Year Study Country	No. of deaths Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Makari-Judson, 2007[756], clinical trials participants, USA Breast cancer stage I-IIIB	- 185 38 months (max)	No measure of association	From chart records, for weight at diagnosis and 1 year post-diagnosis Survival comparison between women of ≤2.5kg gain and >2.5kg gain Log-rank test P = 0.58

Weight gain during treatment and total mortality after breast cancer
Overall 6 publications identified [422;432;433;747;750;752]
3 publications from 3 studies were included in the highest versus the lowest meta-analysis[422;432;433]
3 excluded publications[747;750;752]

Publication	Author Year Study Country	No. of deaths Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Chlebowski, 1986[747], clinical trials participants, USA Recruited ≤6 weeks after mastectomy All ≥4 nodes positive breast cancer patients	- 62 112 months	No measure of association	Weight recorded weekly during period of adjuvant therapy The amount of weight increase was not directly correlated with survival in either 5-FU arm or CMF arm. None of the five women who gained more than 10kg survived.
2	Heasman, 1985[750], clinical trials participants, Canada	- 237 12 months (min)	No measure of association	From medical records, for weight before and after treatment No statistically significant differences in overall survival between the weight groups
3	Kumar, 1997[752], breast cancer survivor cohort, USA Breast cancer stage IA-IIB	- 200 40 months (max)	No measure of association	From medical records, for weight at diagnosis, during treatment and follow-up period Weight gain during treatment was not related with survival

Pre-diagnosis adult weight gain and breast cancer mortality
Overall 4 publications were identified[110;418;423;426]
4 publications from 4 studies were included in the highest versus the lowest meta-analysis[110;418;423;426]
3 publications from 3 studies were included in the dose-response meta-analysis [110;423;426]

Post-diagnosis weight gain and breast cancer mortality
Overall 4 publications were identified[428;430;431;720]
3 publications from 3 studies were included in the highest versus the lowest meta-analysis[428;430;431]
1 superseded publication[720] (not tabulated)

Pre-diagnosis adult weight loss and total mortality after breast cancer
Overall 3 publications identified[424;426;434]
No meta-analysis

Post-diagnosis weight loss and total mortality after breast cancer
Overall 7 publications were identified[422;427-431;720]
6 publications from 6 studies were included in the highest versus the lowest meta-analysis[422;427-431]
1 superseded publication[720] (not tabulated)

Weight loss during treatment and total mortality after breast cancer
Overall 2 publications identified[422;435]
No meta-analysis

Pre-diagnosis adult weight loss and breast cancer mortality
Overall 1 publication identified[426]
No meta-analysis

Post-diagnosis weight loss and breast cancer mortality
Overall 3 publications were identified[428;430;431]
3 publications from 3 studies were included in the highest versus the lowest meta-analysis[428;430;431]

Pre-diagnosis BMI and total mortality after breast cancer
Overall 30 publications were identified[68;106;108;113;115;400-402;405;416-419;422;425-430;436-440;721;724;730;736;768]
Overall 21 publications from 21 studies were included in the categorical meta-analyses[106;115;400-402;416-419;422;425-430;436-440]
15 publications from 15 studies were included in the dose-response meta-analysis[115;401;402;416-418;422;427-430;436-439]
5 superseded publications[108;113;405;721;724]
4 excluded publications [68;730;736;768]

Publication	Author Year Study Country	No. of deaths Study size Average follow-up years	Exclusion reasons	Exposure assessment Main results Main confounding factors adjustment
1	Allemani, 2011[730], ORDET, Europe breast cancer patients of all stages, including T1-3N+M0/T4/M1	43/ 264 7.6 years	Reported relative excess risk	Assessed during study enrolment Relative excess risk = 2.20, 95% CI: 1.01-4.70 for $\geq$ 25 vs <25 kg/m^2 Non-alcohol energy intake
2	Eley, 1994[768], breast cancer survivor cohort, USA	350/ 1130 5 years (max)	Unadjusted results	Self-reported after diagnosis for height and usual weight or from medical records RR = 2.5, 95% CI: 1.8-3.4 for high vs low/normal

	Breast cancer stage I-IV			
3	Gregorio, 1985[736], breast cancer survivor cohort, USA	- 854 -	Insufficient data	0.99, P>0.05 per 1 QI (kg/cm2 x 1000) Age, tumour stage, treatment delay, fat intake
4	Kwan, 2012[68], ABCPP, pooled analysis of breast cancer survivor cohorts AJCC stage I-III	2 166/ 14 948 7.8 years	Pooled analysis	Self-reported and measured RRs = 1.58, 95% CI: 1.18-2.13 for <18.5 kg/m^2 1.01, 95% CI: 0.91-1.12 for 25-29.9 kg/m^2 1.11, 95% CI: 0.97-1.27 for 30-34.9 kg/m^2 1.09, 95% CI: 0.88-1.36 for 35-39,9 kg/m^2 1.81, 95% CI: 1.42-2.32 for ≥40 kg/m^2 compared with 18.5-24.9 kg/m^2 Age, AJCC stage, race/ethnicity, education, menopausal status, hormone receptor status, surgery, chemotherapy, radiation therapy, hormonal therapy, smoking, comorbidity, physical activity

<12 months post-diagnosis BMI and total mortality after breast cancer

Overall 60 publications were identified[109;399;422;427;432;441-445;447;451;452;454-457;459-462;718;719;722;725;726;731;733-735;737;739;740;745;746;751;754;755;766;769 107;396-398;433;448-450;453;458;728;729;742-744;757-760;770]

Overall 23 publications from 24 studies were included in the categorical meta-analyses[397;399;422;427;441-443;445;447;448;450-462]
12 publications from 12 studies were included in the dose-response meta-analysis[422;427;441-445;447-451] (two publications reported only dose-response results) [444;449]
7 superseded publications[718;719;722;725;726;728;729]
28 excluded publications [107;109;396;398;432;433;731;733-735;737;739;740;742-746;751;754;755;757-760;766;769;770]

Publication	**Author Year Study Country**	**No. of deaths Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Albain, 1992[745], clinical trial participants, USA All node-positive breast cancer patients	263/ 768 -	No measure of association	Pre-treatment BMI No independent prognostic significance for >28 v ≤28 kg/m^2
2	Allin, 2011[766], breast cancer survivor cohort, Denmark Breast cancer patients of all stages, including 1.4% distant metastases	383/ 2910 3 years	Unadjusted results	RR = 1.45, 95% CI: 1.01-2.09 for ≥30 vs 18.5-24.9 kg/m^2
3	Bergmann, 2011[746], breast cancer survivor cohort, Brazil Breast cancer stage IIA-IIIB	62/ 196 18.69 months	No measure of association	BMI prior to neoadjuvant or palliative treatment Survival time was 23 months and 27 months for non-overweight or obese women and overweight or obese women, respectively Log-rank test: P = 0.0294

4	Camoriano, 1990[432], clinical trial participants, USA All node-positive breast cancer patients	- 646 6.6 months	Two BMI categories only	Measured within 8 weeks of primary breast surgery RR = 1.70, 95% CI: 0.99-2.94 for >28 vs ≤28 kg/m^2 among premenopausal women (n=330) Age, nodal status, oestrogen receptor level, tumour size, weight change, nuclear grade
5	Carmichael, 2004 [731], breast cancer survivor cohort, UK Breast cancer stage I-III	- 1 579 6 years	Two BMI categories only	Self-reported at diagnosis RR = 0.81, 95% CI: 0.62-1.06 for <30 vs ≥30 kg/m^2 Adjusted, unknown factors
6	Clough-Gorr, 2010 [733], breast cancer survivor cohort, USA Age ≥65 years Breast cancer stage I-III	- 660 7 years (max)	Two BMI categories only	Self-reported 3 months after definitive surgery RR = 1.27, 95% CI: 0.89-1.81 for >30 vs ≤30 kg/m^2 Age, tumour stage, social class, comorbidity, physical function, mental health index
7	Contiero, 2013 [734], breast cancer survivor cohort, Breast cancer stage I-III	317/ 1 261 9.5 years	Two BMI categories only	From medical records, peri-diagnostic BMI RR = 1.22, 95% CI: 0.93-1.60 for ≥25 vs <25 kg/m^2 Menopausal status, stratified by oestrogen and progesterone receptor status, stage, age
8	Gonzalez-Angulo, 2005[735], breast cancer survivor cohort, USA AJCC stage 0-X	84/ 452 3 years	Two BMI categories only	From medical records RR = 1.42, 95% CI: 0.99-2.04 for ≥30 vs <30 kg/m^2 Adjusted, unknown factors
9	Gordon, 1992 [769], clinical trial participants, USA All had mastectomy	-/ 1 392 16 years	Unadjusted results	Measured by study personnel RR = 1.43, 95% CI: 1.09-1.88 for ≥36 vs ≤19 kg/m^2
10	Haakinson, 2012 [737], breast cancer survivor cohort, USA Breast cancer stage 1-4	- 1 352 2.5 years	Two BMI categories only	From clinical records RR = 1.53, 95% CI: 0.965-2.431 for ≥30 vs <30 kg/m^2 Adjusted, unknown factors
11	Kimura, 1990 [751], breast cancer survivor cohort, Japan breast cancer stage I-III All had radical operation	-/ 593 16 years (max)	No measure of association	From medical records Survival comparison between women of <21, 21.1-23.0 and >23.1 kg/m^2 5-year overall survival: Not significant 10-year overall survival: P<0.05
12	Kumar, 2000[739], cases from a case-control	83/ 166	Two BMI categories only	Measured within 3 months of diagnosis, but before treatment RR = 0.92, 95% CI: 0.87-0.98 for obese vs non-obese

	study, USA Breast cancer stage 1-IV	10 years (min)		Tumour stage
13	Kyogoku, 1990 [109], cases from a case-control study, Japan Breast cancer stage I-III	64/ 213 12 years	Insufficient data	Interviewed 1-3 months after operation RR = 2.51, P trend <0.01 for ≤25 vs <20 kg/m^2 Tumour stage, age of menarche, age at first birth, menopausal status, history of abortion, smoking, radiotherapy, chemotherapy, hormonal therapy, type of operative procedure, history of benign breast disease
14	Lethaby, 1996 [754], Auckland Breast Cancer Study Group, New Zealand, Non-metastatic, node-negative breast cancer	-/ 1 138 10.2 years	No measure of association	Survival comparison between women of ≥28 and <28 kg/m^2 Log-rank test: P = 0.29 among women age <50 years Log-rank test: P = 0.13 among women age ≥50 years
15	Loehberg, 2013 [755], breast cancer survivor cohort, Germany Metastatic breast cancer	373/ 467 1.5 years	No measure of association	From medical records 2-year overall survival rates: <23 kg/m^2 0.48 (0.40-0.58) 23-27 kg/m^2 0.38 (0.29-0.48) ≥28 kg/m^2 0.42 (0.34-0.52) Log-rank test: P = 0.02
16	Loi, 2005[740], cases from a case-control study, Australia Non-metastatic breast cancer survivors	184/ 1 101 5 years	Two BMI categories only	Self-reported on average 8 months after diagnosis RR = 1.56, 95% CI: 1.01-2.40 for ≥30 vs <30 kg/m^2 Age, tumour grade, nodal status, progesterone receptor level
17	Menon, 1999[107], clinical trial participants, UK	162/ 448 6 years	Unadjusted results	Self-reported height, BMI calculated at the time of diagnosis RR = 1.00, 95% CI: 0.968-1.034 per 1 kg/m^2 increase
18	Mohle-Boetani, 1988 [742], cases of a case-control study, USA AJCC equivalent stage I-IV	257/ 838 6 years	Insufficient data	Obtained at-diagnosis RR = 1.4, P trend = 0.02 for ≥34.7 v ≤30.4 lbs/inch^2 Age at diagnosis, tumour stage, follow up time
19	Mousa, 2012[757], breast cancer survivor cohort, Turkey	41/ 433 -	No measure of association	Mean overall survival: <18.5 kg/m^{2}8.9 years 18.5-24.99 kg/m^{2}16.4 years 25-29.99 kg/m^2 23.55 years >30 kg/m^2 16.79 years Comparisons not significant
20	Saxe, 1999[398], breast cancer survivor cohort, USA	26/ 149 5 years	Unadjusted results	Measured close to the time of diagnosis RR = 0.74, 95% CI: 0.32-1.71 for >27 vs ≤27 kg/m^2

	Breast cancer stage in situ, I-IV			
21	Schuetz, 2007 [770], breast cancer survivor cohort, Germany Breast cancer stage 1-4	163/ 1 072 6.1 years	Unadjusted results	From medical records RR = 1.01, 95% CI: 0.96-1.05 per 1 kg/m^2 increase among postmenopausal women (n = 793, 124 deaths)
22	Sendur, 2012[758], breast cancer survivor cohort, Turkey Postmenopausal women, breast cancer stage 1-4	-/ 501 25.1 years	No measure of association	From medical records 3-year overall survival: 18.5-24.9 kg/m^2 98.3% ≥25 kg/m^2 98.0% Log-rank test: P = 0.57
23	Singh, 2011[759], breast cancer survivor cohort, India	-/ 309 4 years (max)	No measure of association	Measured at admission for surgery Obesity is a significant risk factor for 3-year mortality
24	Sparano, 2012 [743], clinical trials participants, USA E1199 trial 88% node-positive and 12% high risk node-breast cancer patients	891/ 4770 (3 411 HR-positive; 940 HER2-positive; 878 TNBC) 7.9 years	Two BMI categories only	Measured after surgery and before chemotherapy RRs = 1.37, 95% CI: 1.13-1.67 among women with HR-positive and HER2 negative or unknown disease, 1.11, 95% CI: 0.85-1.46 among women with TNBC and 0.99, 95% CI: 0.73-1.34 among women with HER2 positive breast cancers for ≥30 vs <30 kg/m^2 Age, race, menopausal status, tumour size, axillary nodal status, surgery
	E5188 trial ER-positive and node-positive premenopausal breast cancer patients	-/ 1 502 14 years		Measured after surgery and before chemotherapy RR = 1.51, 95% CI: 1.24-1.83 for ≥30 vs <30 kg/m^2 Age, race, tumour size, axillary nodal status, surgery, radiation therapy, systemic therapy, adherence to hormonal therapy
	E3189 trial ER-negative and node-positive breast cancer patients	-/ 613 14.4 years		Measured after surgery and before chemotherapy RR = 0.83, 95% CI: 0.63-1.09 for ≥30 vs <30 kg/m^2 Age, race, menopausal status, tumour size, axillary nodal status, surgery, radiation therapy, systemic therapy, chemotherapy treatment
25	Suissa, 1989[744], clinical trial participants, Canada 31% stage II	-/ 68 13 years	Insufficient data	Records of height and weight at mastectomy RR = 3.35, P = 0.002 per 1 unit increase (1 unit = 0.01 X weight[lbs] / height^2 [inches]) Age, tumour stage, menopausal status, treatment
26	Taylor, 1989[760], clinical trial participants, USA Postmenopausal women, node-positive	-/ 265 74 months	No measure of association	Obesity was a significant independent risk factor for overall survival

	breast cancer			
27	Thivat, 2010[433], breast cancer survivor cohort, France breast cancer stage 1-4, all undergone chemotherapy	57/ 111 20.4 years	Two BMI categories only	Measured at the beginning of treatment RR = 1.49, 95% CI: 0.81-2.74 for ≥24 vs <24 kg/m^2 Node involvement, tumour stage, menopausal status, hormonal therapy, weight variation
28	von Drygalski, 2011 [396], breast cancer survivor cohort, USA breast cancer stage I-IV, including metastatic breast cancer, undergone high-dose chemotherapy with autologous stem cell support treatment	-/ 96 5.42 years	Two BMI categories only	From medical records at time of treatment RR = 1.82, 95% CI: 1.03-3.23 for ≥30 vs <30 kg/m^2 Tumour stage, metastasis
≥12 months post-diagnosis BMI and total mortality after breast cancer Overall 7 publications were identified[105;404;424;428;429;463;723] Overall 6 publications from 6 studies were included in the categorical meta-analyses[105;404;424;428;429;463] 4 publications from 4 studies were included in the dose-response meta-analysis[424;428;429;463] 1 superseded publication[723] (not tabulated)				
Pre-diagnosis BMI and breast cancer mortality Overall 27 publications were identified[68;110;111;114;400;402;416-418;423;426;428-430;436-438;464-468;717;724;727;764;768] Overall 22 publications from 22 studies were included in the categorical meta-analyses[110;111;114;400;402;416-418;423;426;428-430;436-438;464-468;717] 18 publications from 18 studies were included in the dose-response meta-analysis[110;111;402;417;418;423;426;428-430;436-438;464-467;717] 3 superseded publications[724;727;764] 2 excluded publications [68;768]				
Publication	**Author Year Study Country**	**No. of deaths Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Eley, 1994[768], breast cancer survivor cohort, USA Breast cancer stage I-IV	237/ 1130 5 years (max)	Unadjusted results	Self-reported after diagnosis for height and usual weight or from medical records RR = 2.2, 95% CI: 1.5-3.2 for high vs low/normal BMI
2	Kwan, 2012[68], ABCPP, pooled analysis of breast cancer survivor cohorts	1 438/ 14 948 7.8 years	Pooled analysis	Self-reported and measured RRs = 1.33, 95% CI: 0.92-1.92 for <18.5 kg/m^2 1.04, 95% CI: 0.92-1.18 for 25-29.9 kg/m^2 1.12, 95% CI: 0.94-1.32 for 30-34.9 kg/m^2

	AJCC stage I-III			0.92, 95% CI: 0.68-1.24 for 35-39,9 kg/m^2 1.40, 95% CI: 1.00-1.96 for ≥40 kg/m^2 compared with 18.5-24.9 kg/m^2 Age, AJCC stage, race/ethnicity, education, menopausal status, hormone receptor status, surgery, chemotherapy, radiation therapy, hormonal therapy, smoking, comorbidity, physical activity
<12 months post-diagnosis BMI and breast cancer mortality Overall 26 publications were identified[397;399;408;443;449;452;458;461;462;469-475;729;732;738;741;743;748;749;753;766;767] Overall 13 publications from 13 studies were included in the categorical meta-analyses[397;399;443;452;458;461;462;469-472;474;475] 8 publications from 8 studies were included in the dose-response meta-analysis[443;449;469-474] 1 superseded publication[729] 10 excluded publications [408;732;738;741;743;748;749;753;766;767]				
Publication	**Author Year Study Country**	**No. of deaths Study size Average follow-up years**	**Exclusion reasons**	**Exposure assessment Main results Main confounding factors adjustment**
1	Allin, 2011[766], breast cancer survivor cohort, Denmark breast cancer patients of all stages, including 1.4% distant metastases	225/ 2910 3 years	Unadjusted results	RR = 1.62, 95% CI: 1.05-2.52 for ≥30 vs 18.5-24.9 kg/m^2
2	Chang, 2000[732], breast cancer survivor cohort, USA Inflammatory breast cancer patients, participants of chemotherapy trial	101/ 177 8.33 years	Two BMI categories only	From medical records at time of diagnosis RR = 1.34, 95% CI: 0.88-2.05 for ≥30 vs <30 kg/m^2 Nodal status, chemotherapy protocols
3	Coates, 1990[748], breast cancer survivor cohort, Georgia Breast cancer stage 1-4	-/ 1 960 5 years (min)	No measure of association	Measured at enrolment Cumulative 5-year breast cancer survival: ≤20.5 kg/m^{2}73.5% 20.6-24.5 kg/m^{2}76.8% ≥24.6 kg/m^{2}67.4% Wilcoxon test: P <0.001
4	Crujeiras, 2012 [749], breast cancer survivor cohort, Spain Breast cancer stage I-IV	18/ 159 3 years (max)	No measure of association	From medical records Survival comparison among BMI <25, 25-30, ≥30 kg/m^2 Log-rank test: P = 0.77
5	den Tonkelaar, 1995 [767], DOM-project,	39/ 241	Unadjusted results	measured during screening and at diagnosis Incident density ratio = 0.95, 95% CI: 0.51-1.78 for ≥26 vs <26 kg/m^2

	Netherlands Postmenopausal women	9.1 years		
6	Katoh, 1994[738], breast cancer survivor cohort, USA Postmenopausal women, breast cancer stage I-IV	94/ 301 5 years (min)	Two BMI categories only	From medical records RR = 0.99, 95% CI: 0.41-2.42 for >27 vs ≤27 kg/m^2 Age, ER status, PR status, treatment, tumour stage, tumour size, nodal status
7	Lara-Medina, 2011 [753], breast cancer survivor cohort, Mexico Breast cancer stage I-IV	209 deaths overall/ 2 074 1.42 years	No measure of association	From clinical records Estimated 5-year breast cancer survival: <30 kg/m^2 76.10% ≥30 kg/m^{2}78.10% P = 0.121
8	Mason, 1990[741], breast cancer survivor cohort, Australia	586/ 2 706 7 years	Two BMI categories only	From records RR = 0.67, 95% CI: 0.55-0.83 for <28 vs ≥28 kg/m^2 Age, age at first birth, age of menarche, parity, lactation, season
9	Rohan, 1993[408], cases of a case-control study, Australia	112/ 412 5.5 years	Unadjusted results	Interviewed on average 4.8 months after diagnosis RR = 3.39, 95% CI: 1.84-6.25 for ≥30 vs <23 kg/m^2
10	Sparano, 2012 [743], clinical trials participants, USA E1199 trial 88% node-positive and 12% high risk node-breast cancer patients	695/ 4770 (3 411 HR-positive; 940 HER2-positive; 878 TNBC) 7.9 years	Two BMI categories only	Measured after surgery and before chemotherapy RRs = 1.40, 95% CI: 1.11-1.76 among women with HR-positive and HER2 negative or unknown disease, 1.00, 95% CI: 0.74-1.36 among women with TNBC and 1.00, 95% CI: 0.71-1.40 among women with HER2 positive breast cancers for ≥30 vs <30 kg/m^2 Age, race, menopausal status, tumour size, axillary nodal status, surgery
	E5188 trial ER-positive and node-positive premenopausal breast cancer patients	-/ 1 502 14 years		Measured after surgery and before chemotherapy RR = 1.54, 95% CI: 1.26-1.88 for ≥30 vs <30 kg/m^2 Age, race, tumour size, axillary nodal status, surgery, radiation therapy, systemic therapy, adherence to hormonal therapy
	E3189 trial ER-negative and node-positive breast cancer patients	-/ 613 14.4 years		Measured after surgery and before chemotherapy RR = 0.85, 95% CI: 0.63-1.15 for ≥30 vs <30 kg/m^2 Age, race, menopausal status, tumour size, axillary nodal status, surgery, radiation therapy, systemic therapy, chemotherapy treatment
≥12 months post-diagnosis BMI and breast cancer mortality Overall 2 publications were were identified[428;429] Overall 2 publications from 2 studies were included in the categorical meta-analyses[428;429] 2 publications from 2 studies included in the dose-response meta-analysis[428;429]				

Pre-diagnosis, <12 months, and ≥12 months post-diagnosis BMI and non-breast cancer mortality Overall 1 publication identified[771] No meta-analysis
<12 months post-diagnosis other measurements of adiposity and total mortality after breast cancer Overall 2 publications identified[761;763] No meta-analysis
<12 months post-diagnosis other measurements of adiposity and breast cancer mortality Overall 2 publications identified[762;765] No meta-analysis
Pre-diagnosis waist circumference and total mortality after breast cancer Overall 1 publication identified[115] No meta-analysis
<12 months post-diagnosis waist circumference and total mortality after breast cancer Overall 3 publications identified[422;442;450] 3 publications from 3 studies included in the dose-response meta-analysis
Pre-diagnosis hip circumference and total mortality after breast cancer Overall 1 publication identified[115] No meta-analysis
<12 months post-diagnosis hip circumference and total mortality after breast cancer Overall 2 publications identified[422;442] No meta-analysis
Pre-diagnosis hip circumference and breast cancer mortality Overall 1 publication identified[115] No meta-analysis
Pre-diagnosis waist-hip ratio and total mortality after breast cancer Overall 1 publication identified[115] No meta-analysis
<12 months post-diagnosis waist-hip ratio and total mortality after breast cancer Overall 4 publications identified[418;422;427;450] 4 publications from 4 studies included in the dose-response meta-analysis[418;422;427;450]
<12 months post-diagnosis waist-hip ratio and breast cancer mortality Overall 2 publications identified[418;476] No meta-analysis

Appendix 5 Main characteristics of studies included in the meta-analyses of risk of mortality after breast cancer

Author Year	Study, country	Diagnosed / recruitment dates, end of follow-up, years of follow-up	Study type, response rate, loss to follow-up	Participants characteristics	Tumour characteristics	Hormone receptor status, nodal status	Treatment info	Outcome events Number in analysis, outcome confirmation	Exposure assessment Timeframe	Exposure comparison	Adjustments
Abrahamson, 2006[129]	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000, 8.5 years	Follow-up of cases of a population-based case-control study, response rate 86%, <2% loss to follow-up	1264 participants 42 years (mean) 20 - 54 years 78% premenopausal	Invasive breast cancer; AJCC; any stage; 57% local, 43% regional/distant	62% ER+VE, 59% PR+ve		1264 participants 290 deaths, Cancer registry	Measured 4.2 months after diagnosis; PA at age 12 to 13 years, age 20 years, and the year before diagnosis	PA: 35.1-98 vs 1.6-3.4 MET/week	Age at diagnosis, ethnicity, tumour stage, menopausal status, receptor status, education, WHR, BMI, household income
Abrahamson, 2006[422]	Atlanta, Seattle, New Jersey Follow-up Study United States	Cancer diagnosis:1990-1992; Study follow up: until 2000, 9.8 Years (max)	Follow-up of cases of a population-based case-control study, response rate 86%, <2% loss to follow-up	1254 participants 20 - 54 years 75% white 25% nonwhite 78% premenopausal, 22% postmenopausal and unknown <1%	Invasive breast cancer; AJCC; any stage ; 57% local, 40% regional, 3% distant, <1% unknown	56% ER+ve, 35%ER-ve, 3% borderline, 6% unknown		1217 participants 290 deaths, 280 deaths included in analysis, Cancer registry + National Death Index	Measured 4.2 months after diagnosis; self-reported weight and height at age 20 years and the year before diagnosis	BMI: ≥30 vs 18.5-24.9 kg/m^2 Early BMI: ≥30 vs 18.5-24.9 kg/m^2 Weight gain: >25 vs ±3% Weight loss: >3 vs ±3% WC: ≥88 vs ≤79 cm HC: 109.9-223 vs 50.7-96 cm WHR: ≥0.87 vs ≤0.75	Tumor stage, income (Result further adjusted for waist-hip-ratio was also provided in the article)

Ademuyiwa, 2011[457]	Roswell Park Cancer Institute, Buffalo Review Study United States	Cancer diagnosis: 1996-2010, 37.2 months	Retrospective cohort study	418 participants 54 years (mean) 26 - 92 years 77.8% Caucasian, 22.2$ others	Triple-negative breast cancer; AJCC stages: 36.8% I, 47.6% II, 15.6% III; Grades: 9.6% 1/2, 85.2% 3, 5.3% unknown; Histology: 90% ductal, 2.2% inflammatory, 3.6% lobular, 4.1% other	Nodal status 38.5% +ve, 61.5% -ve	Breast conserving surgery: 72% yes; Chemotherapy: 80.6% yes, 19.4% no	418 participants 87 deaths, Medical records	From medical records; BMI at diagnosis	BMI: ≥30 vs ≤24.9 kg/m^2	Age at diagnosis, race, chemotherapy, year of diagnosis, grade, histology, stage, lymphovascular invasion
Alsaker, 2011[464]	Norwegian Breast Cancer Screening Cohort Study Norway	Study recruitment:1956-1959, Cancer diagnosis: 1961-2007, Study follow-up: Until 2007 Recruited on average 23.9 years before diagnosis, 5.75 years	Cancer survivors of population-based prospective cohort study, response rate 74.20%	2640 participants; ≥55 years Postmenopausal, participants of breast cancer screening cohort	Stages: 53% I, 34% II, 6% III, 6% IV, 1% unknown			2640 participants, 2301 deaths, 1022 breast cancer mortality, 745 breast cancer deaths from 1992 participants, age ≥55 years were included in analysis, Death certificate	Measured at screening on average 19 years prior to diagnosis	BMI: ≥30 vs 20-24 Kg/m^2 ≥ age 55 years	Age at diagnosis, time-period at diagnosis
de Azambuja, 2010[445]	BIG 02-98 adjuvant study null	Study recruitment: 1998-2001; 62.5 months	Randomised controlled trial of chemotherapy; ancillary analysis	2887 participants 18 - 70 years 53.7% premenopausal, 40.6% postmenopausal, 5.6% others Comorbidities: 15.7%	Node+ve breast cancer; 39.6% pTumour size ≤ 2cm, 52.7% size 2.1-5 cm, 7.1% size >5cm and 0.4% unknown	75.5% at least 1 ER+ve, 24.5% ER-ve; among those with data 51% ER+ve and PR+ve, 20.5% ER+ve and PR-ve, 42%	Surgery: among those with data 42.4% breast conservation, 57.6% mastectomy; Adjuvant endocrine therapy: 73.6% yes	2887 participants 403 deaths, 368 breast cancer mortality and 35 other causes of death; 70 second primary tumour	Measured at trial baseline, after surgery, before first cycle of chemotherapy	BMI: ≥35 vs 18.5-24.9 Kg/m^2 5-year survival	

				cardiac, 2.6% diabetes		ER-ve and PR+, 24.5%ER-ve and PR –ve, nodal status All node+ve: 54.3% 1-3 nodes+ve, 32.8% 4-10 nodes+ve and 12.8% >10 nodes+ve		including 20 second primary breast tumour, Trial medical staff			
Barnett, 2008[105]	Studies of Epidemiology and Risk Factors in Cancer Heredity Breast Cancer Study UK	Cancer diagnosis: 1991-2005, 6.82 years	Prospective cohort study of breast cancer survivors, response rate 67%	4560 participants 51.5 years (mean) 23 - 69 years 98% white Among those with data: 55.2% pre-menopausal, 44.7% postmenopausal HRT use: 62 % never usage, 37.9% ever usage	Invasive breast cancer; 73% incident and 27% prevalent; among those with data: 49.7% stage I, 45.8% stage II, 3.3% stage III, 1.1% stage IV; 24.1% grade 1, 47.2% grade 2, 28.6% grade 3	18.7% ERve, 81.2% ER+ve		4346 participants, 586 deaths included in analysis, Cancer registry + death certificate	Self-reported at study baseline	BMI: >28.5 vs ≤22.7 Kg/m^2	Age at diagnosis, tumour stage, tumour grade
Baumgartner, 2011[444]	Munchen University Breast Cancer Center Review Study Germany	Cancer diagnosis: 1984-2006 Recruited after diagnosis, 88 months	Retrospective cohort study	1053 participants 27 - 94 years 18.8% premenopausal, 12% perimenopausal, 69.2% postmenopausal HRT use:37.1% yes, 51.5% no, 11.4% unknown	Primary invasive, nonmetastatic breast cancers; Tumour stages: 55.1% T1, 33.1% T2, 5.4% T3, 6.5% T4 among peri-postmenopausal women with data	Nodal status 36.8% +ve, 63.2% -ve among peri-postmenopausal women with data	Mastectomy: 37.1% yes; Breast conserving surgery: 62.9% yes; Chemotherapy: 48.2% yes; Radiotherapy: 74.5% yes; Hormonal therapy: 87.6% yes among peri-postmenopau	1053 participants, medical records	From medical records	BMI: Per 1 Kg/m^2 increase	Age, tumour stage, nodal status, hormonal therapy, Histology, tumour grade, surgery, adjuvant therapy, adjuvant chemotherapy

							sal women with data				
Berclaz, 2004[451]	International Breast Cancer Study Group Switzerland	Study recruitment:1978 - 1993; 14 years	Follow up of cases of a randomised controlled trial of adjuvant treatment	6370 participants years (mean) 55% pre/perimenopausal, 45% postmenopausal	43% tumour size ≤2 cm, 53% size >2 cm, 4% unknown; 14% tumour grade 1, 44% grade 2, 35% grade 3 and 7% unknown	28% ER-ve, 57% ER+ve, 15% unknown; 33.6% PR-ve, 47.6% PR+ve and 18.8% unknown, nodal status 20% node -ve, 80% node +ve	Hormone therapy with or without chemotherapy: 32% ;Chemotherapy only: 58% and 10% no adjuvant therapy	6370 participants 55% overall survival in obese group, 57% in intermediate weight group and 61% in normal weight group, Death record	Height and weight previously recorded in database	BMI: ≥30 vs ≤24.9 Kg/m^2 10-year survival	ER status, menopausal status, nodal status, tumour size, treatment, chemotherapy, hormone+chemotherapy
Bernstein, 2002[425]	Cancer and Steroid Hormone Study United States	Cancer diagnosis:1980-1982 (1st breast cancer) and before 1999 (2nd breast cancer); Study follow up: until 1998, 18 Years (max)	Follow-up of cases of a population-based case-control study, 28 patients lost	369 participants 20 - 54 years Multi-ethnic	First primary breast cancer and a second primary in the contralateral breast; any stages including In situ breast cancer		81 and 71 patients had radiation treatment following first and second primary breast cancer respectively	369 participants 160 deaths (90% death from cancer including 87% breast cancer mortality), Cancer registry	Interviewed within 6 months of diagnosis of primary cancer for data at age 18 years and adulthood	BMI: ≥25 vs 18.5-24.9 Kg/m^2 ≥30 vs ≤9% gain in Quetelet's index	Age at diagnosis, education, tumour stage, time between primary cancers
Bertram, 2011[411]	Women's Healthy Eating and Living Study United States	Study recruitment:1995-2000, Follow up: until June 2006, 7.1 years	Randomised controlled trial of dietary intervention, 1 patient lost	2361 participants 80.7 % postmenopausal, 9.8% premenopausal, 9.4%perimenopausal	Invasive breast cancer: 40.5% stage I, 32.8% stage IIA, 12.4% stageIIB, 11.3% stage IIIA, 3% stage IIIC	Nodal status 87.7% 0-3 node+ve, 12.3% >3 node+ve	68.2% chemotherapy, 61.6% radiation	2361 participants 163 death from all causes, 295 additional breast cancer events, Medical record + death certificate	Assessed at baseline and at various follow-up points after diagnosis	PA: 24.7-107 vs 0-2.5 MET-h/week PA change	Age at randomization, race, fruit and vegetable consumption, BMI at randomization, menopausal status, tumour type, tumour grade, tumour stage, anti-oestrogen use, clinical site, time from diagnosis to randomization,

											hot flashes, and study group
Bradshaw, 2012[431]	Long Island Breast Cancer Study United States	Cancer diagnosis: 1996-1997, Study follow-up: until 2005 Recruited on average 3 months after diagnosis, 8.8 years	Follow up of cases of a population-based case-control study, response rate 82%, 55 patients lost	1436 participants 59 years (mean) 25-98 years 32% premenopausal, 68% postmenopausal	Primary in situ or invasive breast cancer; 76% tumour size <2cm , 24% ≥2 cm, 453 unknown	26% ER-ve, 74% ER+ve, 483 missing; 36% PR -ve, 64% PR +ve, 487 missing	Chemotherapy: 41% yes, 59% no, 459 unknown	1436 participants 292 deaths, 156 breast cancer mortality, death record	Self-reported at baseline and during follow up; height and weight 1 yr prior to diagnosis, at diagnosis and post diagnosis weight change	Weight gain: >10 vs ±5% Weight lost: >5vs ±5%	Age, chemotherapy, ER status, PR status, tumour size (result further adjusted for BMI 1 year before diagnosis and weight change from 20 years to 1 year before diagnosis was also provided in the article)
Buck, 2011[419]	Hamburg and Rhein-Neckar-Karlsruhe, Germany Follow-up Study Germany	Cancer diagnosis: 2002-2005, Study follow-up: Until 2009, 6.1 years	Follow-up of cases of population-based case-control study	1140 participants 50 - 74 years Postmenopausal HRT use:39.8% current, 59.2% past/ever Diabetes: 10.5% yes, 89.4% no; Cardiovascular disease: 51.2% yes, 48.8% no	5.9% In situ, Grades: 63.7% 1-2, 24.1% 3, 17.7% HER2+, 66.3% HER2-, 3.9% metastasis, 6% unknown	54% ER+/PR+, 17.8% ER+/PR- or ER-/PR+, 16.2% ER-/PR-, nodal status 29.8% +ve, 58.1% -ve	Surgery: 2.6% ablation, 26.4% ablation + axilla, 11.4% breast conserving surgery, 58.5% breast conserving surgery + axilla; Chemotherapy: 39% adjuvant, 6% neoadjuvant, 54.1% no; Radiotherapy: 76% yes, 23.9% no; Tamoxifen use: 59.8% yes, 30.4%	1140 participants 162 deaths, 124 breast cancer mortality, 15 deaths from cardiovascular disease, 23 other causes of deaths, Death certificate	Self-reported at baseline; PA at age 50y	PA: ≥28 vs <28 MET-h/week BMI: ≥30 vs 18.5-24.9 Kg/m^2	Age at diagnosis, tumour size, nodal status, tumour grade, ER status, detection type, diabetes, HRT, BMI, physical activity

							no				
Caan, 2008[429]	LACE United States	Cancer 46% diagnosis:1997-2000; Study follow up: until 2007 Diagnosed 11–39 months before study enrolment, 83.9 months	Prospective cohort study of breast cancer survivors, response 46%	1692 participants 58.3 years (mean) 18 - 70 years 22.8% premenopausal, 63.8% postmenopausal	Early stage invasive breast cancer; AJCC; 46.7% Stage I, 50.2% Stage II, 3.1% Stage IIIA	69.2% ER+/PR+, 13.6% ER+/PR-, 1.7% ER-/ PR+, 15.5% ER-/PR-. Nodal status 63.2% o node+ve, 26.3% 1-3 nodes+ve, 5.7% 4-6 nodes+ve, 1.7% 7-9 nodes+ve, 3.1% ≥10 nodes+ve	19% chemotherapy; 24.8% radiotherapy; 38.4% chemo- and radiotherapy; 49.2% mastectomy; 50.8% breast-conserving surgery; 70.9% current tamoxifen users, 6.7% past tamoxifen users	1689 participants 162 deaths, 99 breast cancer mortality, 160 deaths included in the analysis, Medical records	Self-reported at baseline; one year pre-diagnosis and also after diagnosis at baseline From before diagnosis to study entry ~22.7 months after diagnosis	BMI: ≥30 vs ≤24.9 Kg/m^2 ≥10 vs ±5% weight gain weight lost	Tumour stage, age at diagnosis, tamoxifen use, treatment, nodal status, oestrogen receptor level, progesterone receptor level, smoking, physical activity
Camorian o, 1990[432]	Review of Adjuvant Chemotherapy Trials of Node-Positive Breast Cancer United States	Follow-up 6.6 years	Randomised controlled trial of adjuvant treatment trial; ancillary analysis	545 participants 20 - 75 years 60.5% premenopausal, 39.5% postmenopausal	Node-positive breast cancer; mastectomy; any stages	All node +ve		545 participants Included 330 premenopausal women only in analysis, Active follow-up and review	BMI measured at randomisation, within 8 weeks of primary breast surgery	Weight gain: > vs ≤ median From randomization to after 60 weeks, end of treatment and total mortality	Age, nodal status, oestrogen receptor level, tumour size, weight change, nuclear grade
Chen, 2011[420]	Shangai Breast Cancer Study China	Study recruitment: 2002-2006 6 months after Diagnosis, 4.3 years	Prospective cohort of breast cancer survivors, response rate 80%	4826 participants 53.5 years (mean) 20 - 75 years 48.6% premenopausal, 51.4% postmenopausal	TNM stages: 37.2% 0-I, 33.1% IIA, 16.6% IIB, 8.7% III-IV, 4.4% unknown	51.2% ER+/PR+, 26.9% ER-/PR-, 20.2% ER/PR mixed, 1.8% ER/PR unknown	Surgery: 94.3% mastectomy, 2.7% conservation surgery, 2.7% unknown type, 0.3% no surgery; Chemotherapy: 91% yes,	4826 participants 436 deaths and 450 recurrences or breast cancer-related deaths, Cancer registry	PA assessed approximately 6, 18, and 36 months post-diagnosis	PA: ≥8.3 vs <8.3 MET-h/week	Date of birth, BMI at baseline, waist-to-hip ratio at baseline, menopausal status, income, education, QOL, cruciferous vegetable

							9% no; Tamoxifen use: 66.3% yes, 33.7% no; Radiotherapy: 31.2% yes, 68.8% no; Immunotherapy: 14.9% yes, 84.8% no, 0.2% unknown				intake, soy protein intake, tea consumption, chemotherapy, radiotherapy, tamoxifen use, TNM status, and ER/PR status
Chen, 2010[427]	Shanghai Breast Cancer Survival Study China	Study recruitment: 2002-2006; Recruited on average 6 months after diagnosis, 46 months	Prospective cohort of breast cancer survivors, response rate 80%	5042 participants 53.5 years (mean) 20 - 75 years 51.1% postmenopausal	TNM; 36.4% stage 0-I, 32.6% IIA, 16.6% IIB, 9.8% IIIIV, 4.6% unknown	49.9% ER+ve/PR+ve, 27.6% ER-ve/PR-ve, 20.4% mixed (ER+ve PR-ve/ER-ve PR+ve), 2.1% unknown	Mastectomy: 93.9% ; Chemotherapy: 91.2%; Radiotherapy: 32.1% ; Tamoxifen usage: 52%	5042 participants 442 deaths, Cancer register	Self-reported weight 1 year prior to diagnosis and at diagnosis, measured at baseline interview approximately 6 months after diagnosis	BMI: ≥30 vs 18.5-24.9 Kg/m^2 Weight gain: ≥5 vs ±1Kg Weight loss: >1 vs ±1Kg WHR: ≥0.87 vs ≤0.795	Age at diagnosis, education, income, marital status, exercise, meat intake, cruciferous vegetables, soy protein, time from diagnosis to study enrollment, menopausal status, menopausal symptoms, chemotherapy, surgery type, radiotherapy, tamoxifen use, nodal status, immunotherapy, TNM stage, comorbidity, oestrogen/progesterone receptor status
Cleveland, 2012[414]	Long Island Breast	Cancer diagnosis: 1996-1997,	Follow-up of cases of population-	1508 participants 58.9 years	First primary in situ or invasive			1508 participants 196 deaths,		PA: ≥9 vs 0 MET-h/week	Age at diagnosis, body mass

	Cancer Study Project United States	Study follow-up: Until Soon after Diagnosis, 66.7 months	based case-control study, ~27% lost to follow-up	(mean)	breast cancer			128 breast cancer mortality, Death certificate			index and menopausal status
Cleveland, 2007[426]	Long Island Breast Cancer Study Project United States	Cancer diagnosis:1996-1997; Study follow up: 2002-2004, 66.7 months	Follow up of cases of a case-control study, 410 patients loss to follow-up	1508 participants 58.8 years (mean) 25 - 98 years Mostly white 32.2% premenopausal, 67.8% postmenopausal HRT use: 86.8% ever, 13.2% never	84.4% invasive and 15.6% In situ	26.7% ER-ve, 73.3% ER +ve, 35.8% PR-ve, 64.2% PR+ve, Nodal status73.7% no nodes involved, 26.3% nodes involved	Radiation therapy, chemotherapy, hormone therapy	1508 participants 196 deaths (of which 21% from cardiovascular disease), 127 breast cancer mortality, 9 death from brain and lung metastases, National Death Index Analysis included postmenopausal women only	Self-reported shortly after diagnosis; weight and height at each decade of life from age 20 years until 1 year before diagnosis	BMI: >30 vs <24.9 Kg/m^2 Per 1 Kg/m2 increase Premenopausal ≥16 vs ±3Kg gain Postmenopausal ≥22.3 vs ±3Kg gain Weight loss	Age at diagnosis, hypertension
Connor, 2013[452]	Follow-up of a population-based case-control study, New Mexico, US	breast cancer diagnosis: 1992-1994, Study follow-up: 13 years	Follow-up of a population-based case-control study	577 participants 20-80 years Non-Hispanic white and Hispanic	Invasive breast cancer	184 cases ER+, 164 cases ER-	200 patients surgery only, 123 patients surgery and radiation, 107 patients surgery and chemotherapy, 107 patients surgery, chemotherapy and radiation, 7 patients no treatment	215 deaths, 129 breast cancer mortality	Self-reported at study enrolment	BMI: ≥30 v ≤24.9 kg/m^2	Age, history of high blood pressure, history of stroke, smoking status, total physical activity, total energy intake (total mortality) BMI at age 18, total physical activity, duration of oestrogen use,

											stage, total energy intake, post-breast cancer diagnosis (BC mortality)
Conroy, 2011[437]	The Multiethnic Cohort Study Hawaii	Study recruitment: 1993-1996, Study follow-up: Until 2007, 6.2 years	Cancer survivors of population-based prospective cohort study	3842 participants 68.8 years (mean) 50 - 89 years Multi-ethnic Postmenopausal Comorbidities: Heart disease/stroke: 9% yes; Hypertension: 37% yes	Incident, invasive breast cancer; SEER stages: 71% local, 25% regional, 3% distant; Size (cm): 61% ≤2 61%, >2 24%, 16% unknown	45% ER+ PR+, 13% ER- PR-, 10% ER+PR-/ER-PR+, 31% other/unknown	Surgery: 56% conserving surgery, 38% mastectomy, 6% none/unknown; Chemotherapy: 24% yes; Radiotherapy: 47% yes	3842 participants 804 deaths, 376 breast cancer mortality, Death certificate	Self-reported BMI at cohort baseline on average 6.5 years before diagnosis	BMI: ≥30 vs 22.5 - 24.9 Kg/m^2	Stage, hormonal receptor status, smoking, years between diagnosis and study entry
Dal Maso,2008[418]	Six Italian Regions Follow-up Study Italy	Cancer diagnosis: 1991-1994; Study follow up: until 2005-2006 diagnosed no longer than 1 year before the interview, 12.6 years	Follow-up of cases of a case-control study, 2.70% loss to follow-up	1453 participants 55 years (mean) 23 - 74 years Among those with data, pre diagnosis data: 45.5 % peri/pre menopausal, 54.9% postmenopausal HRT use: 91.3% never, 8.6% ever	Invasive breast cancer; TNM; 32.7% Stage I, 44.1% stage II, 13.2% stage III-IV, 9.8% unknown	41.5% ER+ve/PR+ve, 3.5% ERve/ PR+ve, Nodal status 45.6% no node+ve, 44.2% node+ve, 10.1%		1453 participants 503 deaths, 398 breast cancer mortality, 6.2% death from other cancers, 7.4% from cardiovascular disease, Cancer registry	Self-reported (questionnaire) at study baseline	PA: ≥2 vs <2h/week BMI: ≥30 vs ≤24.9 Kg/m^2 Weight gain: ≥5 vs <1.4 kg/m^2 WHR: ≥0.85 vs ≤0.79	Region, age at diagnosis, year of diagnosis, TNM stage, receptor status
Dawood, 2012[454]	MD Anderson Cancer Center United States	Cancer diagnosis: 1990-2010, 3.25 years	Retrospective survivorship cohort study	2311 patients Pre- and postmenopausal White, black and others	Tumour stage I-III	Triple-negative breast cancer; 645 cases lymphovascular invasion, 1609 cases	24 cases no breast surgery; 893 cases neoadjuvant chemotherapy; 80.9% anthracycline, 66.5%	753 deaths	From medical records	BMI: ≥30 v <25 kg/m^2	Adjusted, unknown variables

						no invasion	taxane; 64.6% radiation				
Dawood, 2008[447]	MD Anderson Cancer Center, Texas Review Study United States	Cancer diagnosis:1974- 2000, 6 years	Retrospective cohort study of breast cancer survivors	606 participants 44.4% premenopausal, 44.9% postmenopausal and 10.7% unknown	18% nonmetastatic inflammatory(IBC), 82% noninflammatory locally advanced breast cancers (non-IBC LABC); AJCC stage III; 1.98% grade 1, 23.4% grade 2, 51% grade 3 and 23.6% unknown	26.7% HR-ve, 39.3% HR+ve and 34% unknown	Surgery: 115% BCS, 79.9% mastectomy, 6.6% none, 2.4% unknown; Chemotherapy: 794% A, 20.95% A+T; X-ray therapy: 794% adjuvant, 4.6% neoadjuvant, 9.6% none, 6.7% unknown	606 participants 341 death, 325 recurrence, Trial medical staff	From medical records; height and weight at time of initial diagnosis	BMI: ≥30 vs ≤24.9 Kg/m^2	Tumour type, year of diagnosis, number of positive lymph nodes, menopausal status, pathological complete response, age, chemotherapy
Dignam, 2006[461]	National Surgical Adjuvant Breast and Bowel Project B-13, B-19, B-23 Trials United States	Study recruitment:1981-1988; Study follow up: until 2005	Follow up of cases of a randomised controlled trial of adjuvant treatment trial	4077 participants white: 81.7%, black: 12%, others/unknown: 6.3%, 54.5% pre/perimenopausal, 45.5% postmenopausal	Node-negative, ER-negative breast cancer; 54.9% tumour size≤2cm, 38.2% size 2.1-4cm, 6.9% size ≥4.1cm	All ER-ve All node -ve	Participants of different adjuvant therapy trials	4077 participants 820 deaths, 624 deaths following a BC events,196 other causes of death, 242 total second primary contralateral breast cancer, Medical records	Measurement obtained only at baseline and during treatment; BMI at diagnosis was used	BMI: ≥35 vs ≤24.9 Kg/m^2	Treatment, tumour size, age, ethnicity
Dignam, 2003[462]	National Surgical Adjuvant Breast and Bowel Project B-14 Trial United	Study recruitment:1982-1988; Study follow up: until 2001, 166 months	Randomised controlled trial of adjuvant treatment trial	3385 participants white: 91.1%, black: 4.3%, unknown: 4.6% 30.6% peri/premenopausal,	Early stage breast cancer; 60.7% tumour size ≤ 2cm, 34.6% size 2.1-4 cm, 4.7% size ≥ 4 cm	All ER +ve All node -ve	64.9% tamoxifen, 35.1% placebo	3385 participants 983 deaths, 595 deaths following a BC events, 388 other causes of death,, 193	From the records of original study	BMI: ≥30 vs 18.5-24.9 Kg/m^2	Age, menopausal status, ethnicity, tumour size, oestrogen receptor level, progesterone receptor

	States			69.4% postmenopausal				contralateral breast cancer, 232 other second primary cancers (plus 51 endometrium cancer), Trial medical staff (blinded)			level, treatment
Emaus, 2010[416]	Norwegian Health Surveys Follow-up Study, three counties Norway	Cancer diagnosis: 1975–2005; 8.2 years	Cancer survivors of a population-based prospective cohort study, response rate 91% in the 1st, 91% in the 2nd and 88% in the 3rd survey, Complete follow up	1364 participants 57.5 years (mean) 27 - 79 years 61% postmenopausal HRT use: 30 patients, only measured in 3rd survey. Participants of a health screening cohort. Comorbidities : 8 diabetic patients	Invasive breast cancer; TNM; 49% Stage 1, 41% Stage 2, 4.5% stage 3, 5.3% stage 4			1364 participants 429 deaths, 355 breast cancer mortality, 27 death from other cancers, 23 death from cardiovascular disease, and 24 from other causes, Death record	Measured during health screening, prior to diagnosis (usual level of physical activity during leisure time in the year preceding each survey)	PA: Hard vs sedentary BMI: ≥30 vs 18.5-24.9 Kg/m^2	Age at diagnosis, pre-diagnostic observation time, tumour stage, region of residence, year at diagnosis before and after 1995 and BMI
Enger, 2004[110]	University of Southern California Cancer Surveillance Program United States	Cancer diagnosis: 1983-89, Study follow-up: Until 2000, 10.4 years	Follow-up of cases of population-based case-control study, response rate 76.80%	717 participants 40 years White or Hispanic Premenopausal	Stages: 9.9% in situ, 47.4% localized, 39.1% regional, 3.6% distant metastasis	Nodal status 41.1% +ve, 57.3% -ve, 1.5% unknown		717 participants 251 breast cancer mortality, 2 deaths from coronary/CVD, 10 other causes of deaths, Death certificate	Self-reported data for age 18, a year prior to diagnosis in interview at study baseline	PA: >5 vs 0h/week BMI: ≥24.9 vs <20.4 Kg/m2 Weight gain: >10 vs 0 Kg	Age, tumour stage, BMI
Ewertz, 2012[441]	BIG-1098 study International	Recruitment in 1998-2003, 8.7 years	Survivors cohort study based on patients in a randomised	4760 patients 38-90 years Postmenopausal	Early stage breast cancer; 2005 cases node+, 2750 cases node-;	3413 cases ER+, 61 cases ER-; 3051 cases PR+, 422	1215 patients prior chemotherapy; breast surgery		Recorded before adjuvant endocrine treatment	BMI: ≥30 v <25 kg/m^2	Age at randomization, region, nodal status, tumour grade, tumour

			controlled trial			cases PR-; 250 cases HER2+, 3275 cases HER2-;	with/without radiation; received tamoxifen or letrozole				size, radiotherapy, mastectomy, oestrogen and progesterone receptor status, Her-2/neu status, prior hormone replacement therapy, diabetes, smoking, hypertension, stratified by randomisation arm and chemotherapy
Ewertz, 2011[399]	Danish Breast Cancer Cooperative Group Denmark	Study follow up: until 2008, 7.1 years	Follow up of cases of randomised controlled trials of adjuvant treatment, Complete follow-up for first events (loco regional recurrences and distant metastases)	18967 participants 39 - 70 years 18688 (34.7%) premenopausal and 35128 (65.3%) postmenopausal	Early stage - 14077 patients had ductal grade 1, 19456 grade 2, 9282 grade 3, 5532 lobular breast cancer	9780 ER-ve, 32276 ER+ve, 11760 unknown, nodal status 29660 with 0 +ve node, 15486 with 1-3 +ve nodes, 8666 with 4+ nodes, 4 unknown	22968 patients had no adjuvant treatment, 10230 chemotherapy, 16148 endocrine therapy, 4470 combined therapy	For those with BMI data, 18967 participants 5868 death from breast cancer and 1529 death from unknown causes, Death certificate	From medical records; weight and height at diagnosis	BMI: ≥30 vs ≤24.9 Kg/m^2 >10 years follow-up	Age, menopausal status, tumour size, nodal status, tumour grade, histology , ER status, fascia invasion, protocol year, systemic therapy
Ewertz, 1991[424]	Danish Breast Cancer Cooperative Group Denmark	Cancer diagnosis:1983-1984; Study follow up: until 1990, 7 Years (max)	Follow up of cases of population-based case-control study, response rate 87%	2445 participants ≤70 years Among those with data, HRT use: 66.1% never usage, 33.8% ever usage	Primary Invasive breast cancer; 44.8%Grade I, 42.3% Grade II, 12.8% Grade III breast cancer	58.5% none node+ve, 28.6% 1-3 node+ve, 12.8% >4 node+ve		2445 participants 805 deaths, Cancer registry	Self-reported 1 year after diagnosis	BMI: ≥30 vs 20-24.9 Kg/m^2 Weight gain: >5 vs ±5kg Weight loss	Age, tumour size, nodal status, tumour grade, skin invasion, area of residence
Flatt, 2010[463]	Women's Healthy Eating and Living Study United	Cancer diagnosis: 1991-2000; Study recruitment:1995-	Randomised controlled trial of dietary intervention; ancillary	3088 participants 52 years (mean) 18 - 70 years	Invasive breast cancer: 38.5% stage I (=1 cm), 45.5% stage II, 15.9%	Among those with data: 24.8% ER-ve, 75.1%		3088 participants 315 deaths (83% of which were BC–related,	Measured on average 2 y, and a maximum of 4 y after diagnosis	BMI: ≥30 vs 18.5-24.9 Kg/m^2	Tumour grade, tumour stage, years between diagnosis and study entry, alcohol intake,

	States	2000, Follow up: until June 2006 Up to 4 years; 1698 patients <2y and 1390 patients 2-4 y, 7.3 years	analysis, response rate 96%		stage III; 15.7% grade 1, 40.1% grade2, 35.9% grade 3, 8.2% unspecified			and only 8% of which were not from any cancer), 518 breast cancer events (69% of which were distal recurrences), Death certificate			education, ethnicity, smoking, parity, physical activity
Friedenreich, 2009[413]	Alberta Cancer Registry Follow-up Study Canada	Cancer diagnosis: 1995-1997; Study follow up: until 2008, 8.3 years	Prospective cohort study of breast cancer survivors	1225 participants 56 years (mean) 62.4% postmenopausal HRT use: 34% 47.3% with comorbidities	Incident in situ and invasive breast cancer; 9% stage 0, 42.3% stage I, 39.8% stage II, 8.8% stage III+, 0.2% missing	68.2% ER+ve, 62.7% PR+ve	35.6% chemotherapy, 38.6% hormonal therapy, 54.7% radiotherapy	1225 participants 341 deaths, 223 breast cancer mortality, SEERS	Self-reported at baseline; lifetime PA	PA: >151 vs ≤95 MET-h/week/year	Age, tumour stage, treatment (chemotherapy, hormone therapy and radiation therapy), SBR grade, BMI and other comorbidity conditions
Galanis, 1998[111]	Multiethnic Cohort in Hawaii, 75-80	Study recruitment: 1975-1980; Study follow up: until 1994, 14.9 years	Prospective cohort study of cancer survivors	378 participants 43 years (mean) 86 (22.75%) premenopausal cases, 292 (77.25%) postmenopausal cases				378 participants 34 breast cancer mortality, Cancer registry	Self-reported; height and weight before diagnosis	BMI: >25.8 vs <22.6 kg/m^2	Age, ethnicity, tumour stage, education, alcohol intake
Goodwin, 2012[442]	University of Toronto Hospitals Follow-up Study Canada	Cancer diagnosis:1989-1996; Study follow up: until 2007, 12.1 years	Prospective cohort of breast cancer survivors, 23 patients lost	535 participants 50.3 years (mean) ≤75 years Multi-ethnic 57.2% premenopausal, 4.9% perimenopausal, 37.9% postmenopaus	Early M0 invasive breast cancer; non-diabetic women; 55.5% T1, 32.5% T2, 5% T3, 6.9% Tx, N0-1,	67.7% ER+ve, 18.7% ER-ve, 13.6% unknown; 61.7% PR+ve, 23.4% PR-ve, 15% unknown; 69.2% N0,	22.8% mastectomy, 77.2% lumpectomy; adjuvant chemotherapy: 39.8% yes, 60.2% no; hormone therapy: 39.1% yes, 60.9% no	535 participants 134 deaths, 113 breast cancer mortality, 21 deaths from other causes, Hospital records	Measured post diagnosis; median, 7 weeks postoperatively before systemic therapy	BMI: 31.1 vs 23.2 Kg/m^2 Waist: 95.5 vs 76 cm HC: 113 vs 98.5 cm	Age, tumour stage, tumour grade, hormone receptor status, adjuvant chemotherapy, hormonal therapy

				al		30.8% N1					
He, 2012[455]	MD Anderson Cancer Center, Texas Review Study United States	BC diagnosis: 1998-2010	Retrospective survivorship cohort study	1983 patients Pre- and peri/postmenopausal; Multi-ethnic	Tumour stage ≥2-4	HER2+ breast cancer; 54.2% ER/PR+, 45.8% ER- & PR-			From medical records at diagnosis	BMI: ≥35 v 20-<25 kg/m^2	Age, race, diabetes, tumour grade, tumour nuclear grade, hormone receptor status, tumour stage, treatment, insulin use, insulin secretagogue use, metformin use, thiazolidinedione use
Hebert, 1998[473]	Memorial Sloan-Kettering Cancer Center Follow-up Study United States	Cancer diagnosis: 1982-1984; Study follow up: until 1991, 10 Years (max)	Prospective cohort of breast cancer survivors, response rate Approximately 95%, 1 patient lost	472 participants 52.2 years (mean) 20 - 80 years 86.8% white 47.3% premenopausal, 52.7% postmenopausal	Early-stage breast cancer; TNM; 39, 7% Stage I, 40.6% Stage II, 19.7% Stage III	57.1% ER+ve		472 participants 87 deaths, 73 breast cancer mortality, Cancer registry	Interviewed at the time of diagnosis	BMI: Per 1 Kg/m^2 increase	Tumour stage, age, meat, butter/margarine/lard, beer, menopausal status, ER status
Hellmann, 2010[417]	Copenhagen City Heart Study Denmark	Study recruitment:1976; Study follow up: until 2007, 7.8 years	Cancer survivors of a population-based prospective cohort study, response rate 74% at the 1st, 70% at the 2nd , 61% at the 3rd and 50% at the 4th examination, 1% loss to follow-up	528 participants 66.9 years (mean) 33.1 - 95.4 years 16.1% premenopausal, 83.9% postmenopausal HRT use: 71.2% unexposed, 28.8%	Primary breast cancer, one sarcoma, 527 carcinomas; TNM; 56.2% local, 33.7 regional, 6.3 metastatic, 3.8% unknown		7.4% radiotherapy, 7.4% chemotherapy, 22.4% hormonal therapy	528 participants 323 deaths, 174 breast cancer mortality, 126 other causes of death including 43.6% death from cardiovascular disease and 25.6% other cancers,	Measured at study baseline	PA: >4 vs 0 h/w BMI: ≥30 vs 20-25 Kg/m2	Alcohol, smoking, physical activity, body mass index, hormone replacement therapy, age, disease stage, menopausal status, parity, education, and adjuvant treatment

				exposed				Cancer registry			
Holick, 2008[412]	Colloborative Women's Longevity Study United States	Cancer diagnosis: 1988-2001; Study follow up: until 2004 Within 2 years of Diagnosis, 5.5 years	Prospective cohort of breast cancer survivors	4482 participants 58.5 years (mean) 20 - 79 years 72.7% postmenopausal	Invasive breast cancer: 72.6% local, 27.4% regional			4482 participants 412 deaths, 109 breast cancer mortality, National Death Index	Self-reported after diagnosis; post diagnosis PA	PA: ≥21 vs <2.8MET-h/week	Age at diagnosis, stage of disease at diagnosis, state of residence at diagnosis, and interval between diagnosis and physical activity assessment, post-diagnosis BMI, post-diagnosis menopausal status, post-diagnosis hormone therapy use, total energy intake year before enrollment in the CWLS, education level at diagnosis, family history of breast cancer at diagnosis, and initial treatment modality
Holmberg, 1994[401]	Swedish and Norwegian Cancer Registries Follow-up Study Sweden	Cancer diagnosis: original studies 1984-1985, Study follow-up: Until	Follow-up of cases of case-control study,0% loss to follow-up	422 participants ≤45 years Premenopausal	Invasive breast cancer; any stages		422 participants 94 deaths, 92 breast cancer mortality, Cancer registry	88.3%, 92.1% in original studies	Self-reported BMI 18 months prior to diagnosis during interview 3-12	BMI: 1 Kg/m^2 increase ≥29 vs <19 Kg/m^2	Age, study centre

	and Norway	1989, 5 Years (max)					+ National Death Index		months after diagnosis		
Holmes, 2005[128]	Nurses' Health Study United States	Cancer diagnosis:1984 and 1998; Study follow up: until June 2002 Recruitment in 1976, Diagnosis in 1984-1998, 96 months	Cancer survivors of population-based prospective cohort study	2987 participants 30 - 55 years Among those with data: 531 premenopausal and 2242 postmenopausal 986 postmenopausal HRT use:986 postmenopausal women only	Invasive breast cancer; stage I, II and III		991 patients had chemotherapy	2987 participants 463 deaths, 280 breast cancer mortality, Family+ National Death Index	Measured first at 2 years after diagnosis (1986) and reassessed in 1988, 1992, 1994, 1996, 1998, and 2000	PA: ≥24 vs <3 MET-h/week	Age, time from diagnosis to exposure assessment, smoking, BMI, menopausal status, hormonal therapy, age at first birth, parity, oral contraceptive, energy intake, tumour stage, tamoxifen use, chemotherapy
Hou, 2013[469]	Tianjin Medical University Cancer Institute and Hospital , China	BC diagnosis: 2002-2006, 5.67 years	Retrospective survivorship cohort study	5634 patients Pre- and postmenopausal 1013 patients with diabetes, 4621 patients without diabetes	Tumour stage 1-4 2483 cases node+, 3151 cases node-	3685 cases ER+, 1949 cases ER-; 3906 cases PR+, 1728 cases PR-; 1353 cases HER2+, 4281 cases HER2-	2688 patients anthracycline , 2946 patients non-anthracycline ; 419 patients metformin	1424 breast cancer deaths	From medical records	BMI: >30 v <25 kg/m^2	Diabetic/metformin subgroups, age, cardio-cerebrovascular complications, menopausal status, stage, lymph node status, vessel carcinoma embolus, ER status, PR status, HER-2 status, chemotherapy
Irwin, 2011[415]	Women's Heath Initiave United States	Study recruitment: 1993-1998, Study follow-up: Until 2005, 7 years	Cancer survivors of population-based prospective cohort study or clinical trials	4643 participants 50 - 79 years Postmenopausal	Stages I-IIIA		Chemotherapy: 25% yes among stage I, 78% yes among stageII/III patients	4643 participants 350 deaths, 194 breast cancer mortality, Death certificate	On average 4.1 years from pre-diagnosis physical activity assessment to cancer diagnosis. On average	PA: ≥9 vs 0 MET-h/week PA change	Age, ethnicity, WHI study arm, previous hormone therapy use, BMI, diabetes, alcohol, smoke, total calories, percentage

									1.8 years from diagnosis to post-diagnosis physical activity assessment		calories from fat, and servings of fruit and vegetable
Irwin, 2008[410]	Health Eating Activity and Lifestyle Study United States	Cancer diagnosis:1995-1998; Study follow up: until 2004, 6 years	Prospective cohort study of breast cancer survivors	933 participants 18 - 64 years Multi-ethnic	Primary breast cancer			933 participants 164 deaths, 115 breast cancer mortality, 56 breast cancer recurrence, 40 new breast cancer primaries, Cancer register	Assessed the year before & 2 years after diagnosis (during baseline interview (approximately 6 months after diagnosis)	PA: ≥9 vs 0 MET-h/week PA change	Age, race, disease stage, initial treatment, and tamoxifen use
Jain, 1994[717]	National Breast Screening Study Canada	Study recruitment: 1980-1985; Cancer diagnosis:1981-1982; Study follow up: until 1988, 5.2 years	Randomised controlled trial of mammography screening trial	1033 participants 52.2 years (mean) 40 - 66 years Trial group screened; 48% detected by screening	Invasive breast cancer; any stage	341 node+ve women		1033 participants 133 breast cancer mortality, Death certificate	Measured during screening prior to diagnosis	BMI: Per 1 Kg/m^2 increase >27.34 vs <22.22 Kg/m^2	Age at diagnosis, nodal status
Jung, 2012[456]	UPMC, UPCI Breast Cancer Program Review Study United States	Cancer diagnosis: 1999-2008; Study follow up: until 2010, 9 years	Retrospective cohort study of breast cancer survivors, a hospital clinic-based	557 participants 55 years (mean) 26 - 88 years Majority non-black: 93.5%, Black:6.6%, 25.5% premenopausal, 74.5% postmenopausal 79.5% Charlson	Metastatic breast cancer; 34.5% HER2 +ve, 65.5% HER2 -ve, and metastatic at only one site (69.8%)	73.2% ER/PR +ve, 26.8% ER/PR –ve		557 participants 403 deaths, National Death Index	From medical records, assessed at diagnosis	BMI: ≥30 vs 20-24.9 Kg/m^2	Age, race, education, menopausal status, hypertension, comorbidity, heart failure, chronic pulmonary disease, mild liver disease, diabetes, receptor status, metastasis-free survival, metastasis

				comorbidity condition free; 6.6% diabetes, 2.3% heart failure							location
Kamineni, 2013[436]	Breast Cancer Screening Program, United States	Cancer diagnosis: 1988-1993, 10 years (max)	Retrospective survivorship cohort study	485 patients 40-93 years White and non-white	AJCC stage I-II	294 cases ER+/PR+, 60 cases ER+/PR-, 14 cases ER-/PR+, 47 cases ER-/PR-	293 patients breast conserving with radiation, 6 patients breast conserving without radiation, 185 patients mastectomy with or without radiation; 87 patients chemotherapy; 230 patients tamoxifen	97 deaths 31 breast cancer deaths	Self-reported at screening	BMI: ≥30 v <25 kg/m^2	Age, stage, tamoxifen use
Kawai, 2012[443]	Miyagi Cancer Center Hospital, Japan	Cancer diagnosis: 1997-2005, 5.85 years	Hospital-based prospective survivorship cohort study	653 patients 57 years (mean) Pre- and postmenopausal	39.2% in situ or localised, 35.7% lymph node metastasis, 8.7% local invasion, 3.1% distant metastasis	62.8% ER+ or PR+, 26.6% ER-/PR-	23.7% chemotherapy, 18.7% radiation therapy, 24.5% hormonal therapy	136 deaths, 108 (79.4%) breast cancer deaths	Self-reported before treatment	BMI: ≥25.8 v ≥21.2-<23.3 kg/^{m2}	Age, tumour stage, hormone receptor status (overall analysis only), radiation therapy, chemotherapy, hormonal therapy, smoking, physical activity, menopausal status (overall analysis only), family history of breast cancer, comorbidity

Keegan, 2010[440]	Australia, Canada and the US Registries Follow-up Study Australia, Canada, United States	Cancer diagnosis:1991-2000; Study follow up: ranged from Jan 1994 - July 2007 Newly diagnosed patients recruited, 7.8 years	Prospective population-based cohort study of cancer survivors	4153 participants Multi-ethnic	Invasive breast cancer; 62% tumour size ≤20 mm, 31% size>20 mm, 7% missing; 19% grade 1, 36% grade 2, 37% grade 3, 8% unknown	24% ER-ve, 65% ER+ve, 11% unknown; 26% PR-ve, 63% PR+ve, 11% unknown, nodal status 54% none, 23% 1-3nodes, 12% ≥4 nodes, 11% missing	Chemotherapy: 34% no, 49% yes, 18% unknown; Tamoxifen: 47% no, 39% yes, 14% missing	4153 participants 725 deaths, Cancer registry + death certificate	Self reported at baseline; height and weight 1 year prior to diagnosis, lifetime PA and 3 yrs prior to diagnosis	BMI: ≥30 vs ≤24.9 Kg/m^2	Study centre, age at diagnosis, race/ethnicity, number of axillary invaded nodes,time since last full term pregnancy, ER status, PR status, tumour grade,tumour size,tumour type, physical activity
Kroenke, 2005[430]	Nurses' Health Study United States	Cancer diagnosis: 1976 - 2000, Study follow-up: Until 2002, 9 years	Cancer survivors of population-based prospective cohort study	5204 participants 30 - 55 years	Invasive non metastatic breast cancer, any stages; 86.9% tumour size >2cm	73.2% ER+ Nodal status 85.2% +ve	Chemotherapy: 63.9% yes; Tamoxifen: 64.8% yes	5204 participants 860 deaths, 533 breast cancer mortality, Family+ National Death Index	Self-reported at cohort baseline; pre and post-diagnosis weight	BMI: ≥30 vs 21-22 Kg/m^2 BMI gain: ≥2 vs ±0.5 BMI BMI loss: >0.5 vs ±0.5 BMI	Age, oral contraceptive, birth index, menopausal status, age at menopause, hormonal therapy, smoking, tumour size, nodal status, chemotherapy, tamoxifen use, protein intake
Labidi, 2008[459]	Salah Azaiz Institute Tunisia Review Study Tunisia	Cancer treatment: 1994-2000, 6 Years (max)	Retrospective study	100 participants 44 years (mean) 23 - 71 years Among those with data: 70% premenopausal, 30% postmenopausal	Nonmetastatic inflammatory breast cancer; AJCC; 30% tumour size ≤ 5cm, 46% size >5 cm, 24% unknown; Scarf and Bloom: 4% grade 1, 39% grade 2, 37% grade 3, 20% unknown	40% ER-ve, 17 %ER +ve, 43% unknown; 27% PR-ve, 12 %PR +ve, 61% unknown Nodal status 91% axillary node+ve: 23% 1-3 nodes+ve, 60% >4	99% neo-adjuvant chemotherapy, 93% mastectomy, 83% radiotherapy, 84% adjuvant chemotherapy, 60% hormone therapy	100 participants 70 deaths, Medical records	From medical records: height and weight at the time of diagnosis, before treatment;	BMI: >30 vs <25 Kg/m^2 3-year survival	Chemotherapy, hormonal therapy

						nodes+ve, 9% unknown; 8% node-ve					
Lee, 2012[475]	Seoul National University Hospital, Korea	Cancer diagnosis 1994-2008 2.95 years	Hospital-based retrospective survivorship cohort study	438 patients 20-84 years	Tumour stage II-III	210 cases ER+, 228 cases ER-, 144 cases PR+, 294 cases PR-; 267 cases HER2+, 168 cases HER2-	Received neoadjuvant regimens; had breast surgery; 379 patients radiation therapy; 197 patients hormonal therapy	49 breast cancer deaths	Measured	BMI: ≥30 v <25 kg/m^2	Age, tumour stage, nodal stage, ER status, PR status, HER2 status, age x BMI interaction
Litton, 2008[460]	MD Anderson Cancer Center, Texas Review Study United States	Cancer diagnosis: 1990-2004 Recruited after treatment with NC and before surgical treatment, 14 years	Retrospective cohort study	1169 participants 50 years (mean) white: 70%, Hispanic: 12.3%, African American: 12.1%, Asian/others: 5.6%, 44.9% premenopausal, 3.8% perimenopausal, 51.3% postmenopausal	Cancer stages: 4.1% I, 63% II, 32.9% III; Tumour stages: 0.2% T0, 11.5% T1, 56.5% T2, 17.7% T3; 14.1% T4; Histology: 92.9% ductal, 7.1% lobular	60.1% ER+, 39.9% ER-; 51.2% PR+, 48.8% PR-; 22.8% HER-2+, 77.2% HER-2-, nodal status 56.4% +ve, 43.6% -ve	Mastectomy: 61% yes; Breast-conserving surgery: 38% yes; No surgery: 1% yes; Anthracycline-based regimen: 91% yes	1169 participants 194 deaths, 167 breast cancer mortality, 18 other causes of deaths, 9 unknown causes of deaths, Cancer registry	From medical records	BMI: ≥30 vs ≤24.9 Kg/m^2	Race, age, menopausal status, chemotherapy, receptor status, nodal status, pathological complete response, time from chemo to surgery, nuclear grade
Lu, 2011[438]	The Women's Contraceptive and Reproductive Experiences (CARE) Study United States	Cancer diagnosis: 1994-1998, Study follow-up: Until 2005/2007, 8.6 years	Follow-up of cases of population-based case-control study, response rate 76.50%	4538 participants 35 - 64 years White: 64.7%, Black: 35.3%, 46.2% premenopausal, 42.2% postmenopausal, 11.6% unknown	SEER stages: 60.3% localized, 38.5% non-localized, 1.2% unknown; Invasive breast cancer	58.7% ER+, 28.8% ER-, 12.5% unknown	No info on breast cancer therapies	4538 participants 1053 deaths, 828 breast cancer mortality, SEER record	Self-reported on average 5.1 months post-diagnosis; BMI of 5 years before diagnosis	BMI: ≥30 vs 20 -24.9 Kg/m^2	Age at diagnosis, education, Study centre, tumour stage, ER status, number of comorbidities, race

				62.8% comorbidity free, 29.7% one, 7.5% ≥2 of either hypertension, myocardial infraction, stroke, diabetes, or other cancers excluding nonmelanoma skin cancers							
Maehle, 2004[468]	Norwegian Health Surveys Follow-up Study Norway	Study recruitment:1963-1975; Cancer diagnosis: 1970-1990; Study follow up: until 2000, 189 months	Cancer survivors of a population-based prospective cohort study, few patients lost	1211 participants 60.85 years (mean) 28 - 90 years, participants of a health screening cohort		42% node+ve metastases	Detailed information about adjuvant treatment was not available	1211 participants 471 breast cancer mortality, 275 deaths from other causes, Death record	Measured at screening programme; on average 12.5 years before diagnosis	BMI: Q5 vs Q1	Tumour size, nodal status, nuclear grade
Majed, 2008[448]	Curie Institute Breast Cancer Study France	Breast cancer treatment: 1981-1999, Study follow-up: Until 2004, 8 years	Prospective cohort of breast cancer survivors	14709 participants 44.8% premenopausal, 55.2% postmenopausal Obesity: 7.9% yes 20.2% cancers detected by mammography	Stages: 36.2% I, 51.1% II, 12.6% III; SBR grades: 22.9% I, 23% II weak, 18.8% II strong, 16.2% III, 9.4% non gradation, 9.7% NA; Tumour size (cm): 12% ≤1, 23.9% 1-2, 44.4% 2-5, 13.5% >5, 6.2% NA; Tumour histology: 73.7% ductal, 8.5% lobular, 6.9	50.9% ER+, 17.4% ER-, 31.7% NA; 50.2% PR+, 24.2% PR-, 25.6% NA, nodal status Clinical node involvement: 82.1% N0-N1a, 17.9% N1b-N3	Conservative surgery: 57.2% yes; Non-conservative surgery: 29% yes; Non surgical local treatment: 13.8% yes; Hormonal therapy: 33.1% yes; Chemotherapy: 30.8%; Radiotherapy: 86.6% yes	14709 participants 3693 deaths, 555 second cancers, Cancer registry	From medical records	BMI: Per 1 Kg/m^2 increase ≥30 vs <25 Kg/m^2	Age, tumour dimension, clinical node development, menopausal status, year of diagnosis, tumour oestrogen, progesterone receptor level, clinical tumour extension, number of axillary invaded nodes, Scarf-Bloom-Richardson grade

Maskarinec, 2011[458]	Patterns of Care and Outcomes Breast Cancer Follow-up Study Hawaii	Cancer diagnosis: 1995-1996, Study follow-up: Until 2009, 13.2 years	Prospective cohort of breast cancer survivors, response rate 48.20%	382 participants 59.3 years (mean) Multi-ethnic Close to 30% had either CVD, pulmonary disease, liver disease, neuromuscular/skeletal disorders, or kidney disease	Stages 0-IV		Adhered to treatment guidelines according to Physicians Data Query, no other details	382 participants 115 deaths, 43 breast cancer mortality, 72 other causes of deaths, cancer registry	From medical records	BMI: ≥30 vs 18.5-<25 Kg/m^2	Ethnicity, age at diagnosis, menopausal status, adherence to treatment guidelines, tumour stage, hormone receptor status, toxicity, comorbidity, health insurance
Moon, 2009[397]	KBCR, SNUHBCC Database Study, Korea Korea	Breast surgery: 1982-2006	Retrospective cohort study	29043 participants 48 years (mean)	Nonmetastatic, invasive breast cancer; histologic grades of KBCR patients: 62.8% 1-2, 37.2% 3; histologic grades of SNUHBCC patients: 57.1% grade 1-2, 42.9% grade 3	KBCR: 59% ER+, 41% ER-, 53.7% PR+, 46.3% PR-; SNUHBCC: 58% ER+, 42% ER-, 46.6% PR+, 53.4% PR-, nodal status KBCR: 43% +ve, 57% -ve; SNUHBCC: 42.3% +ve, 57.7% -ve	Among those with data: Chemotherapy: 79.6% yes, 20.4% no KBCR patients, 73.4% yes, 26.6% no SNUHBCC; Hormonal treatment: 62.5% yes, 37.5% no KBCR patients, 50.7% yes, 49.3% no SNUHBCC	29 043 participants, Cancer registry	From hospital records	BMI: SNUHBCC: ≥30 vs 18.5-24.9 Kg/m^2 KBCR: ≥25 vs 18.5-24.9 Kg/m^2	Age, tumour size, tumour stage, nodal status, ER status, PR status, tumour grade, lymphovascular invasion, chemotherapy, hormonal therapy Age,Tumour size,Tumour stage,Nodal status,ER status,PR status,Tumour grade,Lympho vascular invasion
Newman, 1997[474]	Northern Alberta Breast Cancer Registry Canada	Cancer diagnosis: 1978-1979, Study follow-up: Until 1990, 4.35 years	Prospective cohort of breast cancer survivors, 7.30% loss to follow-up	1169 participants 56.1 years (mean) 25 - 98 years 39% premenopausal, 61% postmenopaus	Early stage breast cancer (excluded advanced disease); Stages: 32.1% I, 61.6% II,	67.3% ER+, 32.7% ER-, nodal status 54.2% 0 +ve, 32.3% 1-3 +ve, 13.5% 4+ +ve		1169 participants 244 breast cancer mortality, Cancer registry	From cancer registry records	BMI: ≥29 vs ≤22.7 Kg/m^2	Tumour size, nodal status, oestrogen receptor level, age

				al	6.3% III						
Nichols, 2009[428]	Collaborative Women's Longevity Study United States	Study recruitment: 1988-2001; Cancer diagnosis: 1988-1999; Study follow up: until 2005 Recruited 5.8 years after breast cancer diagnosis, 6.3 years	Follow-up of cases of case-control studies, response rate 40%	3993 participants 58.4 years (mean) 20 - 79 years Mostly white: 98%, 28.1% premenopausal; 71.9% postmenopausal HRT use: 38.9% (postmenopausal hormone use)	Invasive nonmetastatic breast cancer; 64.1% local, 24.7% regional, 0.6% distant, 10.6% unknown			3993 participants 421 deaths, 121 breast cancer mortality, 95 deaths from cardiovascular disease, Death record	Self-reported body weight 1-5 years before diagnosis at study baseline	BMI: ≥30 vs 18.5-24.9 Kg/m^2 Weight gain: 10.1-103 vs ±2Kg Weight loss: 10.1-50 vs ±2Kg	Age, tumour stage, time from diagnosis to exposure assessment, family history, smoking, physical activity, menopausal status
Olsson, 2009[472]	Malmo Mammographic Screening Trial Sweden	Cancer diagnosis:1961-1991; Study followup: until 2006, 10 Years (max)	Randomised controlled trial of mammography screening	2794 participants 45 - 69 years Mammographic screening trial; 656 women invited to screening	Invasive breast cancer; any stages including distant metastasis			2794 participants 1318 deaths including 862, 210 and 246 in pre-screening group, invited to screening and control groups, respectively; 817 breast cancer mortality including 564 in pre-screening groups, 111 in invited to screening and 142 in control group, death records	Measured (up until 1982 yr) and selfreported (after 1982yr) at diagnosis and recorded in clinical notes	BMI: ≥30 vs 20-<25 Kg/m^2	Age at diagnosis, menopausal status, histology , tumour size, date of diagnosis, nodal status, clinical site, metastasis

Panagopoulou, 2012[470]	Hellenic Cooperative Oncology Group, Greece	Recruitment 1997-2008, 5.72 years	Hospital-based retrospective survivorship cohort study	2789 patients 21-79 years	Tumour grade: 1-3 1239 cases node 0-3, 1550 cases node 4+;	2121 cases hormone receptor+, 668 cases hormone receptor-; 306 cases triple-negative disease 787 cases HER2+, 1243 cases HER2-	Had breast surgery, patients undergone clinical trials	507 breast cancer deaths	From medical records	BMI: ≥30 v 25-29.9 kg/m^2	Age, menopausal status, tumour size/grade, positive nodes, hormone receptor status, HER2 overexpression, surgery type/treatment protocol
Pfeiler, 2013[453]	ABCSG-06 trial	Recruitment in 1990-1995, 5 years	Survivorship cohort study based on patients in a randomised controlled trial	1509 patients 41-80 years; postmenopausal	Tumour stage 1-3; 604 cases node+, 905 cases node-	Hormone receptor +	Had breast surgery; tamoxifen with or without aminogluteth imide	162 deaths, 101 (62.3%) breast cancer deaths	At trial enrolment	BMI: ≥30 v18.5-24.9 kg/m^2	Treatment, stage, nodal stage, grade, ER, PR, age
Pierce, 2007[404]	Women's Healthy Eating and Living Study United States	Cancer diagnosis:1991-2000; Study follow up: until 2005 Within 48 months of diagnosis (average, 24 months), 6.7 years	Randomised controlled trial of dietary intervention; ancillary analysis, 7 patients lost	1490 participants 50 years (mean)	Early stage breast cancer; AJCC; 40% Stage I (≥1cm), 45% Stage II, 15% stage III, 15.9% grade I, 39.8% grade II, 35.8% grade III, 8.3% unknown	63.1% ER+ve/PR+ve, 10.8% ER+ve/PR-ve, 5.1%ER-ve/PR+ve, 20.8% ER-ve/PR-ve	31.4% none-chemotherapy, 25.7% nonanthracycline, 42.8% anthracycline; 42% adjuvant tamoxifen, 58% no adjuvant tamoxifen	1490 participants 135 deaths, 118 breast cancer mortality, 10 death from other cancers, 7 death from non-cancer, 236 breast cancer events, Death certificate	Measured on average 2 y, and a maximum of 4 y after diagnosis	BMI: <19.9 vs 20-24.9 Kg/m^2 Energy: 1981-3553 vs 584-1435 kcal/day	Age, alcohol intake, receptor status, time from diagnosis to randomization
Reding, 2008[439]	Fred Hutchinson Cancer Research Center Follow-up study United States	Cancer diagnosis: 1983-1992, Study follow-up: Until 2002 Recruited at Diagnosis, 9 Years (max)	Follow-up of cases of case-control studies, response rate 83.3%, 83.9% in original studies, loss to follow-up 93.1% contacted within 12	1286 participants ≤45 years White: 95.2%, Black: 1.7%, Othes: 3.1% Premenopausal HRT use: 41.4% ever had, 58.6%	First primary invasive breast cancer; 57.94% local, 409% regional, 1.97% distant	59.3% ER+ve, 40.7% ER-ve, 60.5% PR+ve, 39.5% PR-ve, nodal status 41.1% +ve, 58.9% -ve,	Chemotherapy: 68.9% yes, 31.1% no; Radiotherapy 53.8% yes, 46.2% no; Hormone therapy 35.3% yes, 64.7% no, among those	1286 participants 364 deaths, 335 breast cancer mortality, 22 other causes of deaths, 7 unknown causes of deaths,	5 years before diagnosis were recalled at interview	BMI: ≥25.8vs ≤20.6 Kg/m^2	Age, diagnosis year, and mammography.

			months of end of F/U, 6.9% loss	had not among those with data		among those with data	with data	Medical records			
Reeves, 2007[400]	Study of Osteoporotic Fractures United States	Study recruitment:1986-1988; Study follow up: until 2006 Diagnosed 7.5 years on average after enrolling into SOF, 8.1 years	Cancer survivors of a population-based prospective cohort study, 1% loss to follow-up	533 participants 78 years (mean) ≥65 years Caucasian All postmenopausal 6.3% diabetes, Comorbidities : 0.9% history of congestive heart failure	15% In situ, 75.2% Stage I or II, 5.1% Stage III/IV, 4.7% unknown	68.9% ER+ve, 10.5% ER-ve, 20.6% unknown; 54% PR+ve, 23.5% PR-ve, 22.5% unknown		533 participants 206 deaths, 45 breast cancer mortality, 68 deaths from any cancer, 56 deaths from cardiovascular disease, Death certificate	Measured at clinical examinations at study baseline 128 participants	BMI: 34 vs 22.6 Kg/m^2	Age,smoking,hypertension, tumour stage, ER status,diabetes
Reeves, 2000[106]	Six London Hospitals Follow-up Study UK	Study recruitment: 1968-1984; Cancer diagnosis: 1968-1980 for 1st study and 1980-1984 for 2nd study; Study follow up: until 1994, 25 Years (max)	Follow-up of cases of case-control studies, 39 women lost	1208 participants 24 - 59 years 74% premenopausal, 26% postmenopausal HRT use: Among those with data: 5% yes, 95% no use	TNM; 49.6% Stage I, 32% stage II, 17.2% stage III, 1.2% stage IV	36% node-ve, 47.8% node+ve, 16.2% unknown		1208 participants 608 deaths, Medical records	from records of original studies	BMI: ≥27 vs ≤24 Kg/m^2	Age at diagnosis, year of diagnosis, hospital
Rohan, 1995[421]	Diet and Breast Cancer in Australia Follow-up Study Australia	Cancer diagnosis: 1982-1984, Study follow-up: Until 1989, 5.5 years	Follow-up of cases of population-based case-control study, response rate 80.7% (16.7% refused/untraceable, 2.7% died)	451 participants 55.1 years (mean) 20 - 74 years				451 participants 112 breast cancer mortality, 11 other causes of deaths, Cancer registry	The average interval between diagnosis and interview was 4.8 months	Recreational PA: >4000 vs 0 kcal/week Moderate PA: > 0 vs 0 kcal/week Light PA: >2000 vs 0 kcal/week	Age, receptor status, tumour size, education, history of benign breast disease, age at first birth, age of menarche, height, Quetelet Index, energy intake, menopausal status

Rosenberg, 2009[465]	Swedish Hormone Replacement Therapy Follow-up Study Sweden	Cancer diagnosis: 1993-1995, Study follow-up: Until 2003 Recruited at diagnosis, 9.5 years	Follow-up of cases of population-based case-control study, response rate 84%	2640 participants 63.7 years (mean) 50 - 74 years Postmenopausal	Invasive breast cancer, any stages; Tumour grades: 15.3% 1, 41.7% 2, 43% 3 among those with data. About 33% of cases missing data	78.3% ER+, 21.7% ER-; 66.7% PR+, 33.3% PR - among those with data. About 33% of cases missing data, nodal status 31.8% +ve, 68.2 -ve among those with data		2640 participants 354 breast cancer mortality, Death certificate	Self-reported data for 1 year before questionnaire, filled in about 4.3 months after diagnosis	BMI: >30 vs <25 Kg/m^2	Age at diagnosis, alcohol intake, tumour size, nodal status
Saxe, 1999[398]	Medical Center, Michigan University Follow-up Study United States	Study recruitment: 1989-1991, Recruited during first medical center visit for suspected or newly diagnosed, 5 years (min)	Prospective cohort of breast cancer survivors, 0% loss to follow-up	149 participants 57.8 years (mean) 26 - 95 years White: 90.6%, black:7.2% and other: 2.2%, 34.2% premenopausal, 65.8% postmenopausal	Primary breast cancer, stages: 19.6% in situ, 34.5% I, 34.5% II, 8.8% III, 2.7% IV	73.4% ER+, 26.6% ER-, nodal status 43% +ve, 57% -ve		149 participants 26 deaths, Hospital records	Interviewed close to time of diagnosis for diet a year prior to diagnosis, NCI semi-quantitative FFQ; 100-item	Energy: Per 1000kcal/d increase	Tumour stage, body mass index/arm muscle circumference ratio
Schairer, 1999[466]	Breast Cancer Detection Demonstration Project United States	Study recruitment: 1973-1980 Cancer diagnosis: 1973-1981, Study follow-up: Until 1995, 14.1 years	Follow-up of a breast cancer screening cohort, response rate 72.3%, 87% at different occasions	2614 participants years (mean) Multi-ethnic Postmenopausal HRT use: 122 (15.3%) current users, 82 (8.3%) non-users, 72(10.4%) past users	Incident breast cancer, any stages including in situ cancer			2614 participants 978 deaths, 486 breast cancer mortality, Death certificate	Self-reported at baseline of screening study	BMI: ≥26.15 vs ≤21.28 Kg/m^2	Tumour stage, race
Sestak, 2010[471]	The Arimidex, Tamoxifen Alone or	Follow-up for 100 months	Randomised controlled trial of adjuvant	4939 participants All postmenopaus	Early-stage breast cancer	All ER+ve and/or PgR +ve)	Participants of adjuvant treatment (anastrozole	4939 participants, 481 death after breast	Measured at baseline after diagnosis	BMI: ≥35 vs ≤22.9 Kg/m^2	Age, mastectomy, tumour size, tumour grade,

	in Combination (ATAC) United Kingdom		treatment trial	al			alone, tamoxifen alone, or combined) trial	cancer recurrence, 504 death without breast cancer recurrence, Trial medical staff (blinded)			nodal status, chemotherapy, radiotherapy, region
Sternfeld, 2009[409]	LACE United States	Cancer diagnosis:1997-2000; Diagnosed within 39 months of enrolment in the original study, 87 months	Prospective cohort study of breast cancer survivors, 15 patients lost	1970 participants 18 - 79 years Among those with data: 21 % premenopausal, 65.3% postmenopausal, 13.7% unknown	Early-stage breast cancer; AJCC; among those with data: 47.6% stage I, 33.4% stage IIa, 16% stage IIb, 2.9% stage IIIa	Among those with data: 68.2% ER+/ PR+, 14.2% ER+/ PR-, 1.8% ER-/ PR+, 15.8% ER-/ PR- Nodal status: Among those with data: 64.2% node-ve, 35.8% node+ve (25.5 % 1-3 nodes+ve, 10.3% ≥ 3 nodes +ve)	Among those with data: Surgery: 50.4% conserving, 49.6% mastectomy; Chemotherapy: 56.3% yes, 43.7% no; Radiation therapy: 62.9 % yes, 37.1% no	1970 participants 187 deaths, 102 breast cancer mortality, Death certificate	Self-reported at baseline; PA after diagnosis (6 month prior to enrolment)	PA: ≥62 vs <29 MET-h/week	Age, number of positive nodes, stage, weight at 18 y, education level and smoking status
Tao, 2006[450]	Shanghai Breast Cancer Study China	Cancer diagnosis: 1996-1998; Study follow up: until 2002 Recruited/interview on average 67 days after diagnosis, 5.1 years	Follow-up of cases of a population-based case-control study, response rate 91%, 126 patients lost (assumed to be still living)	1455 participants 25 - 64 years	Primary breast cancer; TNM; 24.6% Stage 0-I, 34.9% stage IIA, 21.9% stage IIB, 11.3% stage III-IV, 7.1% unknown	44.4% ER+ve, 25.5% ER-ve, 30% unknown; 43.5% PR+ve, 25.2% PR-ve, 31.1% unknown	Surgery: 99%; Adjuvant chemotherapy: 94% ; adjuvant chemotherapy and traditional Chinese medicine: 63%; radiotherapy: 38.9% yes, 47.4% no, 13.6% unknown;	1455 participants 240 deaths, Death certificate	Measured at or soon after diagnosis at study baseline	BMI: ≥25.53 vs ≤21.22 Kg/m^2 WC: ≥84 vs ≤71 cm WHR: ≥0.84 vs ≤0.76	Age at diagnosis, education, menopausal status, tumour stage, chemotherapy, tamoxifen use, radiotherapy, oestrogen receptor level, progesterone receptor level

							tamoxifen use: 63.2% yes, 18 no, 18.6% unknown				
Thivat, 2010[433]	Jean Perrin Center, Clermont-Ferrand Review Study France	Cancer treatment:1976-1989; Study follow up: until 2009, 20.4 years	Hospital-based retrospective cohort study of cancer survivors, 0% loss to follow-up	111 participants 54 years (mean) 32 - 74 years 45% premenopausal, 55% post-menopausal	Early stage and locally advanced breast cancer; 19% T1, 44% T2, 15% T3, 22% T4; 8% patients had Scarff-Bloom-Richardson Grade I, 55% II, 20% III	42% ER+ve, 44% ER-ve, 35% PR+ve, 47% PR-ve, nodal status 50% N0, 44% N1, 5% N2, 1% N3	Anthracycline-based chemotherapy: all patients; Tumourectomy: 66 patients; Mastectomy: 44 patients; Radiation: 97% (after chemotherapy); Hormonal therapy: 44% (90% with tamoxifen)	111 participants 57 deaths, Hospital records	Measured at the beginning of treatment and in the last chemotherapy cycle	Weight gain: >5 vs <5% before and after treatment	Nodal status, tumour stage, menopausal status, hormonal therapy, weight variation
Tornberg, 1993[467]	Swedish General Health Screening Cohort Sweden	Study recruitment: 1963-1965, Cancer diagnosis: before 1983, Study follow-up: Until 1987, 4 Years (max)	Follow-up of a health screening Cohort, response rate 80%	1170 participants 62.4 years (mean) White	Stages I-IV			1170 participants 407 breast cancer mortality, death records	Before diagnosis; examined during health screening	BMI: ≥28 vs ≤21 Kg/m^2	Age
Tretli, 1990[114]	Norwegian Health Surveys Follow-up Study Norway	Cancer diagnosis: 1963-1975; Study follow up: until 1981, 4.3 years	Cancer survivors of a population-based prospective cohort study, response rate 85%	8427 participants 30 - 69 years, participants of a health screening cohort	Any TNM stages I-IV; 47.7% stage I, 33.3% stage II, 5.5% stage III, 7.5% stage IV			8427 participants 2383 breast cancer mortality, 430 death from other causes, death certificates	Measured during screening	BMI: Q5 vs Q1	
Vitolins, 2008[449]	Phase II Doxorubicin-Based Drug Trial for Node-	Study recruitment: 1980-1985, Study follow-up:	Randomised controlled trial of adjuvant treatment	636 participants 52 years (mean) 25 - 73 years	Stages II-III; lymphnode positive breast cancer	62% ER+ve, 38% ER-ve; 49% PR+ve, 51% PR-ve	Participants of doxorubicin-based multidrug	636 participants 341 deaths, 303 breast cancer	Measured at time of enrolment for trial	BMI: Per 1 Kg/m^2 increase	

	Positive Breast Cancer United States	Until 1999 Post-diagnosis, post-surgery, 13.7 years	trial; ancillary analysis	Caucasian: 90%, African-American: 10% 41% premenopausal, 59% postmenopausal		among those with data, nodal status 52% 1-3 +ve, 32% 4-9 +ve, 16% 10+ +ve	regimen as adjuvant therapy trial; had mastectomy	mortality, 38 other causes of deaths, Active follow-up and review			
West-Wright, 2009[402]	California Teachers Study United States	Study recruitment: 1995; Cancer diagnosis: 1995-2004; Study follow up: until 2005, 9 Years (max)	Cancer survivors of a population-based prospective cohort study	3539 participants 58.9 years (mean) 26 - 94 years Mostly white: 89.7% Comorbidities: 111 diabetes, 106 cardiovascular disease; 24.5 %	Incident first primary invasive breast cancer; 68.9% localized, 28.4% regional, 1.86 metastatic, 0.8 % missing	72% ER+ve, 12.7% ERve, 15.3% unknown		3539 participants 460 deaths, 221 breast cancer mortality, 69 death from other causes including 24 death from other cancers, 68 cardiovascular disease deaths; 38 cerebrovascular disease deaths; 28 cardiopulmonary or pulmonary disease deaths; 4 diabetes death, Death certificate	Self-reported at baseline; PA within the 3 years prior to cohort entry, prior to diagnosis	PA: >3 vs 0-0.5 h/week/y Energy: >1682 vs <1271 kcal/d BMI: ≥30 vs <25 Kg/m^2	Age, for race, BMI, total caloric intake, number of comorbid conditions and oestrogen receptor status
Whiteman, 2005[423]	Cancer and Steroid Hormone Study United States	Cancer diagnosis:1980-1982; Study follow up: until 1997, 14.6 years	Follow-up of cases of a population-based case-control study, response rate 80.40%, 4.10% loss to follow-up	3924 participants 20 - 54 years White: 87.5%, black: 12.5% and other 47% premenopausal, 18% postmenopausal Comorbidities	Primary invasive incident breast cancer; 51.4% local, 45.4% regional, 3.2% distant		22.4% radiation therapy; info on adjuvant treatment not available	3924 participants 1671 deaths, 1, 347 breast cancer mortality, SEER record	Self-reported at interview on average 2.5 months of diagnosis; BMI at age 18 years and after diagnosis	BMI: ≥30 vs ≤22.9 Kg/m^2 Weight gain: ≥31 vs 0 lb Early BMI: ≥25.5 vs ≤21.59 lb	Age at diagnosis, race, radiotherapy, history of benign breast disease, education, menopausal status, tumour stage

				: 37.2% due to diabetes, high blood pressure, blood clots, kidney disease, gallbladder disease, heart attack, paralysis, rheumatoid arthritis, stroke, other cancer							
Zhang, 1995[115]	Iowa Women's Health Study United States	Study recruitment:1986; Study follow up: until 1991, 2.9 years	Cancer survivors of population-based prospective cohort study, response rate 42.60%, < 1% migration rate	698 participants 55 - 69 years Mostly white: 98%, Postmenopausal	Unilateral breast cancer; 10% in situ, 58% local, 28% regional, 3%distant, and 1% unknown; 55% tumour size <2cm, 33% size ≥ 2cm and 11% unknown	Among those with data: 85% ER+ve and 72% PR+ve		698 participants 56 deaths, 40 breast cancer mortality (among the causes of death) and 2 death from coronary heart disease, Death certificates, National death index	Self reported within 6 years before diagnosis, semi-quantitative FFQ; adapted from 126-item questionnaire in NHS	Energy: 2467vs 1225 kcal/d BMI: 28.9-45.9 vs 16-24 Kg/m^2 WC: 36.6-56 vs 23-32 inches HC: 42.5-59.8 vs 21.0-39.1 inches WHR: 0.88-1.62 vs 0.58-0.80	Age, smoking, education, tumour stage, ER status, tumour size

Appendix 6 Main characteristics of the studies included in the systematic review of 2007 WCRF/AICR Cancer Prevention Recommendations adherence and breast cancer risk

Author, publication year	Study, country, age of women, study baseline, special	Years of follow-up, case ascertainment	Number of subjects, no. cancer cases	Operationalised recommendations	Adherence scores (distribution, adherence)	Highest vs lowest score comparison	Adjustment
Jankovic, 2017[479] (overlapped with Romaguera, 2012[14], not included in meta-analysis)	CHANCES, consortium of 7 cohorts, Europe and USA, mean age from 60 to 70 years	Median follow-up from11 to 15 years, active follow-up and cancer registries	154,163 women 6,931 BC	4+2 recommendations: Food and drinks that promote weight gain Plant foods Animal foods Alcoholic drinks + Body fatness Physical activity	Mainly evaluated diet score, then diet+ score including physical activity and body fatness. No significant association in both. Range of score 0 – 6 overall, 0 – 4 for diet only score Average dietary score 2.3 out of 4 Proportion meeting recommendations: 74% alcohol 56% fruit and vegetables 53% sugary drinks 52% energy density 11% red meat and processed meat 5% dietary fibre intake	Per 1 point only	Age, educational level, chronic diseases at baseline, energy intake, smoking status, intensity of smoking/years since quitting smoking, and vigorous physical activity, BMI (in diet score analysis) (sensitivity analysis included menopausal status, OC use, parity, HRT in one cohort with data)
Harris, 2016[485]	SMC, Sweden, mean age 61.4, 88.9% postmeno	15 years, record linkage with cancer registers	31,514 women 1,388 invasive post BC, 746 ER+PR+ 118 ER-PR-	7 recommendations: Body fatness Physical activity Food and drinks that promote weight gain Plant foods Animal foods Alcoholic drinks Dietary supplements	Range of score 0 – 7 Most met 4 out of 7 recommendations Proportion meeting recommendations: 95% alcohol 77% physical activity, dietary supplements, and energy density recommendations 22% red meat and processed meat	6-7 vs 0-2 Per recommendation/ point	Age, height, education, OC use, HRT use, age at menarche, age at menopause, family history of breast cancer, history of benign breast disease, smoking status (for component

					20% plant foods		score analysis, one model simultaneously including all recommendations was used)
Lohse, 2016[480] (BC mortality, not included in meta-analysis)	MONICA and NRPIA, 2 cohorts, Switzerland, age 25-74	21.7 years, record linkage with census data	8,561 women 98 BC deaths	7 recommendations, 9 including sub-recommendations: Body fatness Physical activity Sedentary behaviour Food and drinks that promote weight gain Plant foods (fruits and vegetables, grains) Animal foods Alcoholic drinks Salt	BC deaths only Range of score 0 – 9 Proportion meeting recommendations (in whole study): 15.7% 0-3.5 points 22.0% 4-4.5 points 43.3% 5-9 points 19.0% points imputed 51.1% body fatness 49.7% salt 43.9% grains 43.4% alcohol 31.9% fruit and vegetables 30.7% energy density 20.6% physical activity 17.2% processed meat 9.7% sedentary behaviour	5-9 vs 0-3.5 Per 1 point	Stratified by age, adjusted for education, marital status, study, language region, nationality, and smoking status
Nomura, 2016[255]	BWHS, USA, age 21-69, Black women	13.86 years, self-reported verified by records from cancer registries, 13% loss to follow-up	49,103 women, 1,827 invasive BC, 686 ER+PR+ 196 ER+PR- or ER-PR+ 399 ER-PR- 166 triple-negative breast cancers	7 recommendations: Body fatness Physical activity and sedentary behaviour Food and drinks that promote weight gain Plant foods Animal foods Alcoholic drinks Salt	Range of score 0 – 7 overall, 0 – 5 for diet only score Most met <3 out of 7 recommendations Proportion meeting recommendations: 46.0% <3 points 45.5% 3-4 points 8.5% >4 points 94.2% alcohol 24.6% physical activity 17.5% red meat and processed meat 22% sodium intake	5-7 vs 0-2	Age, geographic region of residence, kilocalories/day, smoking, family history of breast cancer, education, menopausal status, OC use, parity, MHT use (adjusted for BMI, physical activity, and alcohol when these factors were not under

					15% body fatness 1.8% sugary drinks 1.8% plant foods		investigation)
Nomura, 2016[483]	IWHS, USA, age 55-69 postmeno	1986-2010, record linkage with health registry	36,626 women 3,189 post BC	7 recommendations, 8 including sub-recommendation: Body fatness Physical activity Food and drinks that promote weight gain Plant foods (fruit and vegetables, dietary fibre intake) Animal foods Alcoholic drinks Salt	Range of score 0.5 – 8 overall, 0 – 6 for diet only score Average adherence score 5 out of 8 Proportion meeting recommendations: 16.4% 0-3.5 32.9% 4-4.5 32.4% 5-5.5 18.4% 6-8 88.2% alcohol 62.8% fruits and vegetables 45.6% sugary drinks 38.5% body fatness 21.5% physical activity 21.3% dietary fibre 20.6% sodium intake 17.8% red meat and processed meat sign reduced risk among women with or without non-modifiable risk factors	6-8 vs 0-3.5	Age, smoking, education, HRT, family history of breast cancer, menarche age, menopause age, and parity (adjusted for BMI, physical activity, and alcohol when these factors were not under investigation)
Makarem, 2015 [481]	Framingham Offspring Cohort, USA, mean age 66, 63.9% postmeno	11.5 years, ascertained by pathology reports and death certifications	1,602 women 124 BC	7 recommendations: Body fatness Physical activity Food and drinks that promote weight gain Plant foods Animal foods Alcoholic drinks Salt/sodium	Range of score 0 – 7 The overall score was computed by obtaining the weighted average such that each component contributed a maximum score of one. data-driven tertiles	Per 1 unit only (1 score for overall adherence, weighted differently for the components)	Age, smoking status (additional adjustment for energy, menopausal status, hormone use and preexisting

					were used to assign the subcomponent scores		conditions did not alter these results) (models evaluating score components are not mutually adjusted for each other)
Catsburg, 2014 [484]	CNBSS, Canada, Age 40-59	16.6 years, record linkage with cancer registry	49,613 women, 2,503 BC	7 recommendations: Body fatness Physical activity Food and drinks that promote weight gain Plant foods Animal foods Alcoholic drinks Salt	Range of recommendations met 0 – 7 Most met 4 out of 7 recommendations Proportion meeting recommendations (among non-cases): 80.7% alcohol 63.9% sodium intake 60.7% body fatness 54.7% physical activity 51.6% plant foods 36.2% energy density 10.7% red meat and processed meat	6-7 vs 0-1 Per 1 recommendation met	Age, age at menarche, OC use, HRT use, parity, age at first live birth, family history of breast cancer, history of breast disease, menopausal status, study center (for component score analysis, model was mutually adjusted for all other recommendations)
Hastert, 2013 [482]	VITAL, USA, age 50-76, postmeno	6.7 years, record linkage with cancer registry	30,797 women, 899 post BC	6 recommendations: Body fatness Physical activity Food and drinks that promote weight gain Plant foods Animal foods Alcoholic drinks	Range of recommendations met 0 – 6 Proportion meeting recommendations: 1.9% 0 16.3% 1 33.5% 2 28.0% 3 14.3% 5 6.0% 5-6 86.5% alcohol 73.5% red meat and processed meat 38.8% body fatness 24.9% energy density	5-6 vs 0	Age, education, race, mammography, family history, age at menarche, age at first birth, age at menopause, years of hormone therapy, energy intake (for component score analysis, model was mutually adjusted for all

					17.2% physical activity 14.8% plant foods		other recommendations)
Inoue-Choi, 2013[15] Survivors (Not included in meta-analysis)	IWHS, USA, age 55-69, postmeno	8.6 years since cancer diagnosis, record linkage with health registry	938 breast cancer survivors, 203 deaths, (75 BC deaths, 66 deaths from cardiovascular disease)	7 recommendations, 8 including sub-recommendations: Body fatness Physical activity Food and drinks that promote weight gain Plant foods (fruit and vegetables, dietary fibre) Animal foods Alcoholic drinks Salt	Range of score 0 – 8 Most scored 5 – 5.5 point out of 8 Proportion meeting recommendations: 92.4% alcohol 61.4% fruit and vegetables 37.5% body fatness 31.8% dietary fibre 27.3% sodium intake 22.2% physical activity 18.9% red meat and processed meat 6.8% sugary drinks	6-8 vs 1.5-4.0	Age, total number of comorbid conditions, perceived general health and current smoking, cancer stage, cancer type, cancer treatment, subsequent cancer diagnosis before 2004 (start of follow-up), current cancer treatment, person-years since cancer diagnosis
Romaguera, 2012[14]	EPIC, Europe, age 25-70	11 years, active follow-up and cancer registry	260,098 women 9,358 BC	6 recommendations + 1 special recommendation Body fatness Physical activity Food and drinks that promote weight gain Plant foods Animal foods Alcoholic drinks + Breastfeeding	Range of score 0 – 7 Proportion meeting recommendations: 22.2% 0-3 27.7% >3-<4 35.4% 4-<5 13.1% 5-<6 1.7% 6-7 66.3% alcohol 48.0% body fatness 42.5% fruit and vegetables 35.3% breastfeeding 27.3% dietary fibre 23.9% physical activity 23.0% energy density 21.2% sugary drinks 15.0% red meat and processed meat	5-7 vs 0-3	Centre, age, sex, energy intake, level of education, smoking, contraceptive pill use, hormone replacement therapy use, age first menarche, age first pregnancy, menopausal status

Appendix 7 Table of WCRF/AICR Cancer Prevention Recommendations adherence score operationalisation in the studies reviewed

Study/Operationalisation of WCRF/AICR recommendations	**Jankovic, 2017[479], CHANCES**	**Harris, 2016[485], SMC**	**Lohse, 2016[480], MONICA and NRPIA**	**Nomura, 2016[255], BWHS**	**Nomura, 2016[483]; Inoue-Choi, 2013[15] IWHS**	**Makarem, 2015[481], FOC**	**Catsburg, 2014[484], CNBSS**	**Hastert, 2013[482], VITAL**	**Romaguera, 2012, EPIC[14]**
1 - BODY FATNESS Be as lean as possible without becoming underweight 1a - Ensure that body weight through childhood and adolescent growth projects towards the lower end of the normal BMI range at age 21 1b - Maintain body weight within the normal range from age 21 1c - Avoid weight gain and increases in waist circumference throughout adulthood									
Operationalisation	(1b) BMI kg/m^2	(1b) BMI kg/m^2	(1b) BMI kg/m^2	(1b) BMI kg/m^2 & weight gain from age 18 kg	(1b) BMI kg/m^2	(1b) BMI kg/m^2	(1b) BMI kg/m^2	(1b) BMI kg/m^2	(1b) BMI kg/m^2
1	18.5-24.9	18.5-24.9	18.5-24.9	18.5-24.9 & ≤6.8	18.5-24.9	18.5-24.9	18.5-24.9	18.5-24.9	18.5-24.9
0.5	25-29.9		25-29.9	25-29.9 &/or 6.81-13.61	25-29.9	25-29.9			25-29.9
0	<18.5 or ≥30	<18.5 or ≥25	<18.5 or ≥30	≥30 &/or ≥13.62	<18.5 or ≥30	<18.5 or ≥30	<18.5 or ≥25	<18.5 or ≥25	<18.5 or ≥30
2 - PHYSICAL ACTIVITY (PA): Be physically active as part of your everyday life 2a - Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day 2b - As fitness improves, aim for 60 minutes or more of moderate or for 30 minutes or more of vigorous, physical activity every day 2c - Limit sedentary habits such as watching television									
Operationalisation	Vigorous physically active	≥30 min/d walking/cycling/leisure time exercise	Physical activity day/week	≥3-4 h/w vigorous PA or ≥5-6 h/w walking (high PA) AND ≤5 h/d sitting (low sedentary) or >5-<8 h/d sitting (moderate sedentary	≥2 times/w vigorous PA or ≥5 times/w moderate activities	Physical activity index	≥210 min PA per week	≥30 min/d of moderate or fast walking and/or moderate or strenuous activity on ≥5 days/week in ≥ 7 of past 10 years	Manual/heavy manual job, or >2 h/w of vigorous PA or >30 min/d of cycling/sports
1	Yes		≥2			>33			
0.5			PA 1 day/week	High PA AND ≥8 h/d sitting (high sedentary) OR 1-2 h/w vigorous PA or 1-4 hr/w walking (moderate PA) AND low or moderate sedentary OR <1 h/w	2-4 times/w moderate or 1 time/w vigorous and moderate activities	PA index 30-33		<30 min/day or <5 days/week or <7 of previous 10 years of moderate or fast walking and/or moderate or strenuous activity	15-30 min/d of cycling/sports
0								N/A	

				vigorous PA or walking (low PA) AND low sedentary					
0	No	Otherwise	PA<1 day/week	Moderate PA AND high sedentary OR low PA AND moderate/high sedentary	Otherwise	PA index <30	<210 min PA per week		<15 min/d of cycling/sports
1	N/A	N/A	Sedentary behaviour: Regular exercise or exhausting physical activity		N/A	N/A	N/A		N/A
0.5			Walking, cycling, other regular activities or average activities such as walking						
0			Mostly sitting or sedentary						
3 - FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN: Limit consumption of energy-dense foods; avoid sugary drinks 3a - Consume energy-dense foods sparingly 3b - Avoid sugary drinks 3c - Consume fast foods sparingly, if at all									
Operationalisation	Energy density kcal/100g/d	Energy dense foods servings/w & soda/juice glasses/d	Sparingly use of fat for cooking, bread, or salad & cut away fat from meat & no sweets or chocolate	N/A	N/A	Energy dense foods servings/w	Energy density & soda or drinks with added sugar	Energy density kcal/100g/d & sugary drinks/w	Energy density kcal/100g/d
1	≤125	<14 & <2				<29.8	<125 & none	<125 & <1	≤125
0.5	>125-≤175					29.8-48.8			>125-≤175
0	>175	Otherwise	Otherwise			≥48.9	Otherwise	≥125 or ≥1	>175
	Sugary drinks intake g/d	N/A	N/A	Sugary drinks intake g/d	Sugary drinks intake g/d	Sugary drinks servings/w	N/A	N/A	Sugary drinks intake g/d
1	0			0	0	<4			0
0.5	≤250			<250	≤250	4-9.4			≤250
0	>250			≥250	>250	>9.4			>250
4 - PLANT FOODS: Eat mostly foods of plant origin 4a - Eat at least five portions / servings (at least 400 g) of a variety of non-starchy vegetables (V) and of fruits (F) every day									

4b - Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal 4c - Limit refined starchy foods 4d - People who consume starchy roots or tubers as staples should also ensure sufficient intake of non-starchy vegetables, fruits, and pulses (legumes)									
Operationalisation	F & V g/d	F & V & unprocessed grains and legumes g/d	F &/or V g/d	F&V serving/d & fibre intake g/d	F&V servings/d	F & V servings/d	F & V & unprocessed grains and legumes g/d	F & V & whole grains and/or legumes servings/d	F & V g/d
1	≥400	≥400 & ≥25	F & V ≥400	≥5 & ≥25	≥5	≥5	≥400 & ≥25	≥5 & ≥1	≥400
0.5	200-<400		F or V	3-<5 &/or 12.5-<25	3-<5	2.5-<5			200-<400
0	<200	Otherwise	No F or V	<3 &/or <12.5	<3	<2.5	Otherwise	<5 &/or <1	<200
	Dietary fibre g/d		Unprocessed cereals and/or pulses		Dietary fibre g/d	Refined grains g/d			Dietary fibre g/d
1	≥25		Yes every meal		≥25	<2.8			≥25
0.5	12.5-<25				12.5-<25	2.8-4.4			12.5-<25
0	<12.5		No		<12.5	>4.4			<12.5
						Starchy V & non-starchy V g/w			
1						<503 & >2,471.4			
0.5						>503 & >2,471.4			
0						>/<503 & <2,471.4			
5 - ANIMAL FOODS: Limit intake of red meat (RM) and avoid processed meat (PM) 5a - People who eat red meat to consume less than 500 g a week, very little if any to be processed									
Operationalisation	RM g/w & PM g/d	RM & PM g/w	RM or PM	RM and PM & PM g/w	RM and PM g/w & PM g/d	RM and PM g/w & PM g/d	RM & PM g/w	RM and/or PM oz/w	RM and PM g/w & PM g/d
1	<500 & <3	<500 & <25	None	<500 & <3	<500 & <3	<500 & <3	<500 & <25	<18	<500 & <3
0.5	<500 & 3-<50		Yes (meat)	<500 & 3-<50	<500 & 3-<50	<500 & 3-<50			<500 & 3-<50
0	≥500 or ≥50	Otherwise	Sausage products	≥500 & ≥50	≥500 or ≥50	≥500 or ≥50	Otherwise	≥18	≥500 or ≥50
6 - ALCOHOLIC DRINKS: Limit alcoholic drinks 6a - If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women									
Operationalisation	Ethanol g/d	Alcohol g/d	Alcohol drink/d	Alcoholic drinks serving (10g)/w	Ethanol g/d	Ethanol g/d	Drinks/d	Drinks/d	Ethanol g/d
1	≤10	<10	<1	<7	≤10	≤14	≤1	≤1	≤10
0.5	>10-20			7-13	>10-20	>14-21			>10-20
0	>20	Otherwise	≥1	≥14	>20	>21	>1	>1	>20
7 – PRESERVATION, PROCESSING, PREPARATION: Limit consumption of salt. Avoid mouldy cereals (grains) or pulses (legumes) 7a – Avoid salt-preserved, salted or salty foods; preserve foods without using salt 7b – Limit consumption of processed foods with added salt to ensure an intake of less than 6g (2.4g sodium)/day 7c – Do not eat mouldy cereals (grains) or pulses (legumes)									
Operationalisation	N/A	N/A	Adding salt	Sodium intake mg/d	Sodium intake mg/d	Sodium intake g/d	Sodium intake g/d	N/A	N/A
1			Never	≤1,500	≤1500	<2.4	<2.4		

0.5 0 1 0.5 0	 N/A	 N/A	Sometimes or seldom/almost never Always or always/often N/A	>1,500-2,400 >2,400	>1500-2400 >2400	2.4-3.6 >3.6 Salty foods servings/w <41.1 41.1-62.7 >62.7	 Otherwise		
8 – DIETARY SUPPLEMENTS: Aim to meet nutritional needs through diet alone 8a – Dietary supplements are not recommended for cancer prevention									
Operationalisation 1 0.5 0	N/A	Supplements Not use Otherwise	N/A	N/A	N/A	N/A	N/A	N/A	N/A
S1 – BREASTFEEDING: Mothers to breastfeed; children need to be breastfed S1a – Aim to breastfeed infants exclusively up to 6 months and continue with complementary feeding thereafter									
Operationalisation 1 0.5 0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Cumulative feeding ≥6 m <6 m No

Appendix 8 List of publications and presentations at conferences

Results of the current PhD study were presented in the following journals and conferences.

Publications:

- Chan DS, Norat T. Obesity and breast cancer: not only a risk factor of the disease. *Curr Treat Options Oncol* 2015; 16(5):22.

- Chan DS, Bandera EV, Greenwood DC, Norat T. Circulating C-Reactive Protein and Breast Cancer Risk-Systematic Literature Review and Meta-analysis of Prospective Cohort Studies. *Cancer Epidemiol Biomarkers Prev* 2015; 24(10):1439-1449.

- Chan DS, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* 2014; 25(10):1901-1914.

Poster presentations:

- Doris SM Chan, Rita Vieira, Dagfinn Aune, Elisa Bandera, Darren C. Greenwood, Anne McTiernan, et al. Body fatness and mortality in women with breast cancer – a meta-analysis. VLAG course Diet and Cancer: from Prevention to Survival, Wageningen University, the Netherlands. 1 to 3 October 2014.

- Doris SM Chan, Snieguole Vingeliene, Dagfinn Aune, Elli Polemiti, Leila Abar, et al. Obesity and breast cancer risk by hormone receptor status and menopausal hormone therapy use – meta-analysis of prospective studies. IARC 50th Anniversary Conference Global Cancer: Occurrence, Causes, and Avenues to Prevention, Lyon, France. 7 to 10 June 2016.

- Doris SM Chan, Elisa Bandera, Darren C. Greenwood, Teresa Norat. Circulating C-reactive protein and breast cancer risk – meta-analysis of prospective studies. IARC 50th Anniversary Conference Global Cancer: Occurrence, Causes, and Avenues to Prevention, Lyon, France. 7 to 10 June 2016.

Oral presentations:

- Doris SM Chan. Epidemiologic evidence – Energy balance-related factors and pre- and postmenopausal breast cancer risk. World Cancer Research Fund and World Obesity Federation Hot Topic Conference – Life course influences and mechanisms: Obesity, Physical Activity and Cancer (OPAC2). 1 to 2 Sept 2016.

Appendix 9 Permission to republish third party copyrighted works

Page No.	Type of work	Name of work	Source of work	Copyright holder and contact	permission requested on	I have permission yes /no	Permission note
47	figure	Summary of judgements of the 2007 WCRF/AICR Second Expert Report	World Cancer Research Fund International Continuous Update Project	© World Cancer Research Fund International wcrf@wcrf.org	22.12.17	yes	Permission granted via email