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RESEARCH

Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies

OPEN ACCESS

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Abstract

Objective To investigate the association between intake of dietary fibre and whole grains and risk of colorectal cancer.

Design Systematic review and meta-analysis of prospective observational studies.

Data sources PubMed and several other databases up to December 2010 and the reference lists of studies included in the analysis as well as those listed in published meta-analyses.

Study selection Prospective cohort and nested case-control studies of dietary fibre or whole grain intake and incidence of colorectal cancer.

Results 25 prospective studies were included in the analysis. The summary relative risk of developing colorectal cancer for 10 g daily of total dietary fibre (16 studies) was 0.90 (95% confidence interval 0.86 to 0.94, I^2=0%), for fruit fibre (n=9) was 0.93 (0.82 to 1.05, I^2=23%), for vegetable fibre (n=9) was 0.98 (0.91 to 1.06, I^2=0%), for legume fibre (n=4) was 0.62 (0.27 to 1.42, I^2=58%), and for cereal fibre (n=8) was 0.90 (0.83 to 0.97, I^2=0%). The summary relative risk for an increment of three servings daily of whole grains (n=6) was 0.83 (0.78 to 0.89, I^2=18%).

Conclusion A high intake of dietary fibre, in particular cereal fibre and whole grains, was associated with a reduced risk of colorectal cancer. Further studies should report more detailed results, including those for subtypes of fibre and be stratified by other risk factors to rule out residual confounding. Further assessment of the impact of measurement errors on the risk estimates is also warranted.

Introduction

Colorectal cancer is the third most common type of cancer, with 1.2 million new cases diagnosed in 2008 worldwide, accounting for about 9.7% of all cases of cancer.[1] Evidence from ecological studies, migrant studies, and secular trend studies suggest that environmental risk factors are of major importance in the cause of colorectal cancer.[2-4] Dietary factors have been suspected as important, but only intakes of red and processed meat and alcohol are considered to be convincing dietary risk factors for colorectal cancer.[5]

In the 1970s, Burkitt proposed the hypothesis that dietary fibre reduces the risk of colorectal cancer, based on the observation of low rates of such cancer among rural Africans who ate a diet with a high fibre content.[6] Several plausible mechanisms have been proposed to explain the hypothesis, including increased stool bulk and dilution of carcinogens in the colonic lumen, reduced transit time, and bacterial fermentation of fibre to short chain fatty acids.[7] However, although many epidemiological studies have investigated the association between fibre intake and risk of colorectal cancer, the results have not been consistent and the possibility of residual confounding by folate intake remains a controversial issue.[8] Case-control studies have generally shown a protective association,[9 10] whereas the results from cohort studies have been mixed.[8 11-31] In addition, it is not clear whether only specific types or sources of fibre are associated with the risk. Although initial cohort studies generally reported no significant association between fibre intake and risk of colorectal cancer, the hypothesis regained interest when the

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High versus low intake of dietary fibre and whole grains and risk of colorectal cancer
High versus low intake of fruit, vegetable, legume, and cereal fibre and risk of colorectal cancer

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European Prospective Investigation into Cancer and Nutrition (EPIC) study reported a linear decrease in the risk of colorectal cancer with increasing fibre intake.[19] A subsequent pooled analysis of 13 North American and European cohort studies (not including the EPIC study) reported an 18% increased risk of colorectal cancer with low fibre intake (<10 g/day *v* 10-15 g/day), but no further reductions in risk were observed with higher intake.[31] More recently, results from additional large cohort studies[23-30] have been published and, together with the EPIC study, included more than 1.7 million participants and 12 000 cases and included several studies from Asian populations.[23 24 26 30] With such a large number of additional studies we had sufficient statistical power to clarify the dose-response relation between fibre intake and risk of colorectal cancer. In addition we examined whether specific types of fibre are associated with risk.

Whole grains are a major source of dietary fibre and contain germ, endosperm, and bran, in contrast with refined grains that contain only the endosperm. The germ and bran contain numerous nutrients, which are removed during the refining process. In addition, whole grains are a major source of several vitamins, minerals, and phytochemicals, which have anticancer properties and could plausibly influence the risk of colorectal cancer by several potential mechanisms.[32] An earlier review and meta-analysis of case-control studies of whole grain intake and colorectal cancer and polyps reported a summary odds ratio of 0.79 for the highest versus the lowest intake.[33] However, the interpretation of case-control studies is hampered by possible recall and selection biases, which make it difficult to draw firm conclusions. Over the past decade results from several cohort studies have been published on whole grain intake and risk of colorectal cancer, with mixed results.[16 20 25 27 34-39] Some studies suggested no association,[16 20 34 36] whereas others reported an inverse association with higher whole grain intake.[25 27 35 37-39] To clarify the association between dietary fibre and whole grain intake and risk of colorectal cancer we carried out a systematic review and meta-analysis of published prospective studies. We also did meta-regression and sensitivity analyses to evaluate potential sources of heterogeneity in the analyses.

Methods

Several reviewers at Wageningen University carried out the literature search and extracted data up to December 2005. They searched several databases, including PubMed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, Latin American and Caribbean Center on Health Sciences Information, Cochrane library, *Cumulative Index to Nursing and Allied Health Literature*, the Allied and Complementary Medicine Database, National Research Register, and In Process Medline. As all the relevant prospective studies were identified by the PubMed searches the protocol was modified and only PubMed was used for the updated searches from January 2006 to December 2010. No language restrictions were imposed. This review was done as part of the Continuous Update Project of the World Cancer Research Fund and has been published online (www.wcrf.org/PDFs/Colorectal-cancer-CUP-report-2010.pdf). A predefined protocol was used for the review (www.dietandcancerreport.org/downloads/SLR_Manual.pdf) and we followed standard criteria for meta-analyses of observational studies.[40] Abstracts, grey literature, and unpublished results or information were not included. We also searched the reference lists of the studies that were included in our analysis as well as those listed in the published meta-analyses.[33 41]

Study selection

To be included studies had to have a prospective cohort, case-cohort, or nested case-control design and investigate the association between dietary fibre or whole grain intake and incidence of colorectal cancer. We excluded retrospective case-control studies and cross sectional studies. The publication had to include estimates of the relative risk (hazard ratio, risk ratio) with the 95% confidence intervals. For the dose-response analysis, a quantitative measure of intake and the total number of cases and person years had to be provided. When several publications were from the same study we selected the publication with the largest number of cases. We identified 40 potentially relevant full text publications.[8 11-30 34-39 42-54] We excluded seven that reported mean exposure only,[42-48] seven that were duplicate publications,[19 49-54] and one that was on mortality from colorectal cancer.[34] Two publications that were included in the dietary fibre analyses reported on specific whole grain foods, not overall intake, and we excluded these from the whole grain analysis.[16 20] For the dose-response analysis we further excluded two publications that reported results only for the highest versus the lowest levels of intake,[30 37] and two publications that did not report quantities of intake.[11 15]

Data extraction

From each study we extracted data on the first author's last name, year of publication, country where the study was done, study name, follow-up period, sample size, sex, age, number of cases, method of dietary assessment (type, number of food items, and whether the assessment method had been validated), exposure (by type of outcome), quantity of intake, relative risks and 95% confidence intervals for the highest versus the lowest intake, and variables adjusted for in the analysis. Several reviewers at Wageningen University carried out the search and extracted data of articles published up to December 2005 during the systematic literature review for the World Cancer Research Fund and Association for International Cancer Research report (www.dietandcancerreport.org/downloads/SLR/Colon_and_Rectum_SLR.pdf). Two of the authors (DSMC and RL) did the search from January 2006 to December 2010. Three authors (DSMC, RL, and DA) extracted the data into a database, and two authors (TN and DA) checked these for accuracy.

Statistical analysis

We used random effects models to calculate summary relative risks and 95% confidence intervals for the highest versus the lowest levels of dietary fibre and whole grain intake and for the dose-response analysis. The average of the natural logarithm of the relative risks was estimated and we weighted the relative risk from each study by the inverse of its variance. A two tailed $P<0.05$ was considered statistically significant. For studies that reported results separately for colon and rectal cancer or for men and women separately, we combined the estimates using a fixed effects model to obtain an overall estimate for colorectal cancer or both sexes combined.

We used a previously described method[55] for the dose-response analysis and computed study specific slopes (linear trends) and 95% confidence intervals from the natural logs of the relative risks and confidence intervals across categories of dietary fibre and whole grain intake. The method requires that the distribution of cases and person years or non-cases and the relative risks with the variance estimates are known for at least three quantitative categories of use. We estimated the distribution of cases or person years in studies that did not report these but reported the total number of cases or person years if the results

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were analysed by quantiles (and could be approximated)—for example, the total number of person years was divided by 5 when data were analysed by quintiles to derive the number of person years in each fifth. We assigned the median or mean level of dietary fibre or whole grain intake in each category to the corresponding relative risk for each study. For studies that reported the intake by ranges of intake we estimated the midpoint in each category by calculating the average of the lower and upper bound. When the highest category was open ended we assumed the length of the open ended interval to be the same as that of the adjacent interval. When the lowest category was open ended we set the lower boundary to zero. If the intakes were reported in densities (servings per 1000 kcal) we recalculated the reported intakes to absolute intakes using the mean or median energy intake.[18 21 27 28] In studies that reported the whole grain intake in grams daily we used 30 g as a serving size for recalculation of the intakes to a common scale (servings daily). The dose-response results in the forest plots are presented for a 10 g daily increment for dietary fibre and for an increment of three servings daily (90 g) for whole grains. We examined a potential non-linear dose-response relation between dietary fibre and whole grain intake and colorectal cancer by using fractional polynomial models.[56] We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the non-linear and linear models to test for non-linearity.[57]

Heterogeneity between studies was assessed by the Q test and I^2 statistic.[58] I^2 is the amount of total variation that is explained by variation between studies. We did not use a score to assess study quality but in subgroup analyses we determined whether indicators of study quality, such as study size, number of cases, duration of follow-up, and adjustment for confounders modified the results. Heterogeneity between subgroups was evaluated by meta-regression.

Publication bias was assessed with Egger's test[59] and Begg's test,[60] with the results considered to indicate publication bias when P<0.10. In addition, we visually explored funnel plots for asymmetry. We carried out sensitivity analyses excluding one study at a time to explore whether the results were driven by one large study or by a study with an extreme result.

Results

Dietary fibre

Twenty one prospective studies[8 11-18 20-30 36] were identified and included in the analysis of the highest versus the lowest intake of dietary fibre and risk of colorectal cancer, 18 of which[8 12-14 16-18 20-29 36] were included in the dose-response analyses (table 1⇓, fig 1⇓). Twelve of the studies were from the United States, five from Europe, and four from Asia. Table 1 summarises the characteristics of the included studies. The ranges of intake varied: 6.3-21.4 g/day for total dietary fibre, 1.8-15.5 g/day for fruit fibre, 1.9-16.8 g/day for vegetable fibre, 3.0-16.9 g/day for cereal fibre, and 1.3-3.8 g/day for legume fibre (results not shown).

Total dietary fibre

High versus low intake

Nineteen prospective studies (18 publications) were included in the analysis of high versus low intake of total dietary fibre and risk of colorectal cancer (table 1).[8 11 12 15-18 20-30] The summary relative risk was 0.88 (95% confidence interval 0.82 to 0.94), with no evidence of heterogeneity (I^2=0%, P=0.48, see web extra figure 1a).

Dose-response analysis

Sixteen prospective studies (15 publications)[8 12 16-18 20-29] were included in the dose-response analysis, with 14 514 cases among 1 985 552 participants. The summary relative risk was 0.90 (0.86 to 0.94) for each 10 g/day intake, with no significant heterogeneity (I^2=0%, P=0.48, fig 2⇓). A statistically significant inverse association was seen for colon cancer[8 12-14 21 23 24 26-29 36] (13 studies, summary relative risk 0.89, 0.81 to 0.97, I^2=35%, P=0.11) but not for rectal cancer[8 12 21 23 24 26-29] (10 studies, 0.91, 0.83 to 1.03, I^2=15%, P=0.31), although evidence was lacking for heterogeneity between subsites (P=0.86, see table 3). Publication bias was not evident with either Egger's test (P=0.62) or Begg's test (P=0.56). In a sensitivity analysis excluding one study at a time, the summary relative risk for colorectal cancer ranged from 0.89 (0.85 to 0.93) when the National Institutes of Health-American Association for Retired Persons (NIH-AARP) Diet and Health Study was excluded to 0.91 (0.88 to 0.96) when the EPIC study was excluded. A non-linear association was not evident between intake of total dietary fibre and risk of colorectal cancer (P=0.32 for non-linearity, fig 2).

Fruit fibre

High versus low intake

Nine cohort studies (eight publications)[8 17 18 21 22 26-28] were included in the analysis of high versus low intake of fruit fibre and risk of colorectal cancer. The summary relative risk was 0.94 (0.85 to 1.04; see also web extra figure 2a), with little evidence of heterogeneity (I^2=39%, P=0.11).

Dose-response analysis

Nine cohort studies (eight publications)[8 17 18 21 22 26-28] were included in the dose-response analysis of fruit fibre and risk of colorectal cancer, with 9930 cases among 1 514 871 participants. The summary relative risk for each 10 g/day intake was 0.93 (0.82 to 1.05, fig 3⇓), with little evidence of heterogeneity (I^2=23%, P=0.24). Publication bias was not evident with Egger's test (P=0.83) or Begg's test (P=0.47). The summary relative risk ranged from 0.87 (0.78 to 0.96) when the NIH-AARP Diet and Health Study was excluded to 0.95 (0.84 to 1.07) when the Nurses' Health Study was excluded.

Vegetable fibre

High versus low intake

Nine cohort studies (eight publications)[8 17 18 21 22 26-28] were included in the analysis of high versus low intake of vegetable fibre and risk of colorectal cancer. The summary relative risk was 0.98 (0.91 to 1.06, also see web extra figure 2b), with no evidence of heterogeneity (I^2=0%, P=0.48).

Dose-response analysis

Nine cohort studies (eight publications)[8 17 18 21 22 26-28] were included in the dose-response analysis of vegetable fibre and risk of colorectal cancer, with 9930 cases among 1 514 871 participants. The summary relative risk for each 10 g/day intake was 0.98 (0.91 to 1.06, fig 3), with no evidence of heterogeneity (I^2=0%, P=0.60). Publication bias was not evident with Egger's test (P=0.51) or Begg's test (P=0.92). The summary relative risk ranged from 0.96 (0.89 to 1.04) when the Nurses' Health

Study was excluded to 1.02 (0.94 to 1.10) when the Multiethnic Cohort Study was excluded.

Legume fibre

High versus low intake

Four cohort studies[8 18 22 27] were included in the analysis of high versus low intake of legume fibre and risk of colorectal cancer. The summary relative risk was 0.89 (0.78 to 1.02, see also web extra figure 2c), with moderate heterogeneity (I^2=40.8%, P=0.17).

Dose-response analysis

Four cohort studies[8 18 22 27] were included in the dose-response analysis of legume fibre intake and risk of colorectal cancer, with 5405 cases among 1 095 056 participants. The summary relative risk for each 10 g/day intake was 0.62 (0.27 to 1.42, fig 3), with moderate to high heterogeneity (I^2=58%, P=0.07). The summary relative risk ranged from 0.38 (0.08 to 1.87) when excluding the NIH-AARP Diet and Health Study to 0.84 (0.65 to 1.09) when excluding the Women's Health Study.

Cereal fibre

High versus low intake

Eight cohort studies (seven publications)[8 17 18 21 22 27 28] were included in the analysis of high versus low intake of cereal fibre and risk of colorectal cancer. The summary relative risk was 0.90 (0.83 to 0.96, also see web extra figure 2d), with no significant heterogeneity (I^2=0%, P=0.94).

Dose-response analysis

Eight cohort studies (seven publications)[8 17 18 21 22 27 28] were included in the dose-response analysis of cereal fibre and risk of colorectal cancer, with 9487 cases among 1 471 756 participants. The summary relative risk for each 10 g/day intake was 0.90 (0.83 to 0.97, fig 3), with no evidence of heterogeneity (I^2=0%, P=0.78). Publication bias was not evident with Egger's test (P=0.90) or Begg's test (P=1.00). The summary relative risk ranged from 0.85 (0.76 to 0.95) when the Multiethnic Cohort Study was excluded to 0.93 (0.85 to 1.03) when the NIH-AARP Diet and Health Study was excluded.

Whole grains

Seven cohort studies were included in the analysis of total whole grain intake and risk of colorectal cancer (table 2⇓, fig 1⇓).[25 27 35-39] Two studies were from Europe and the other five from the United States (table 2). Total whole grains included whole grain rye breads, whole grain breads, oatmeal, whole grain cereals, high fibre cereals, brown rice, and porridge. The range of whole grain intake varied from and 61-128 g/day (results not shown).

High versus low intake

Four cohort studies[25 27 35 38] were included in the analysis of high versus low intake of whole grains and risk of colorectal cancer. The summary relative risk was 0.79 (0.72 to 0.86), with no evidence of heterogeneity (I^2=0%, P=0.98, see web extra figure 1b). The results for colon and rectal cancer were similar: summary relative risks 0.82 (0.72 to 0.92, I^2=23%, P=0.27)[27 35-38] and 0.80 (0.59 to 1.07, I^2=58%, P=0.10).[27 35 38] The results for rectal cancer were, however, not statistically significant.

Dose-response analysis

Six studies (five publications)[25 27 35 38 39] were included in the dose-response analysis, with a total of 7941 cases among 774 806 participants. The summary relative risk for colorectal cancer with an increment of three servings daily (90 g/day) of whole grains was 0.83 (0.78 to 0.89, fig 4⇓), with no evidence of heterogeneity (I^2=18%, P=0.30). The summary relative risk for colon cancer[27 35 36 38] was 0.86 (0.79 to 0.94), with no evidence of heterogeneity (I^2=0%, P=0.42), and for rectal cancer[27 35 38] was 0.80 (0.56 to 1.14), with substantial heterogeneity (I^2=91%, P<0.001, table 4). In a sensitivity analysis excluding one study at a time, no particular study explained the results for colorectal cancer; the summary relative risk ranged from 0.82 (0.77 to 0.88) when the Swedish Mammography Study was excluded to 0.86 (0.80 to 0.92) when the NIH-AARP Diet and Health Study was excluded. Publication bias was not evident with Egger's test (P=0.54) or Begg's test (P=1.00), although the number of studies was low. However, the funnel plots did not suggest asymmetry. A non-linear association between whole grain intake and risk of colorectal cancer was not indicated (P=0.26, fig 4).

Subgroup, sensitivity, and meta-regression analyses

In subgroup analyses defined by sex, subsite, adjustment for confounders, number of cases, duration of follow-up, geographical location, and range of intake, total dietary fibre intake was inversely associated with risk of colorectal cancer in most subgroups, with no evidence of significant heterogeneity between subgroups with meta-regression analyses (table 3⇓). Similar results were observed for intake of cereal fibre and whole grains (table 4⇓). Intake of fruit fibre was not significantly associated with risk of colorectal cancer in most subgroup analyses. In the subgroups of studies that adjusted for alcohol intake and body mass index or weight, however, inverse associations were significant, with evidence of heterogeneity between subgroups (P=0.04, table 3). When stratified by the range of intake, an inverse association was observed for intake of fruit fibre in studies with a range of 10 g/day or more but not among studies with a range of 10 g/day or less (P=0.04 for heterogeneity), but evidence of a difference in the results for the other fibre types was lacking when stratified by the range of intake (tables 3 and 4). Intake of vegetable fibre consistently was not associated with risk of colorectal cancer in subgroup analyses (table 3⇓). Too few studies of legume fibre precluded any meaningful subgroup analyses.

In addition, the effect on the results of excluding studies from the dose-response analysis was explored. When the analysis of high versus low intake was restricted to the studies that were included in the dose-response analysis of total dietary fibre, the summary relative risk was 0.86 (0.80 to 0.92, I^2=0%, P=0.46 for heterogeneity), similar to the original analysis including all studies.

The influence on the results of the method used to estimate total fibre intake was assessed. For the eight studies[17 21 22 24 26-28] using the Association of Official Analytical Chemists method, the summary relative risk was 0.91 (0.85 to 0.97, I^2=13.3%, P=0.33 for heterogeneity), for the four studies[8 16 21] using the Englyst method it was 0.91 (0.81 to 1.02, I^2=37.0%, P=0.19 for heterogeneity), and for the six studies[12 18 20 23 25 29] with an unknown method it was 0.93 (0.86 to 1.00, I^2=0%, P=0.89 for heterogeneity). In this sensitivity analysis no heterogeneity was found between subgroups (P=0.39 for heterogeneity). In addition, in one study the results did not differ materially between the two methods.[21]

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Discussion

Our meta-analysis supports an inverse association between intake of dietary fibre, cereal fibre, and whole grains and risk of colorectal cancer, but we found no significant evidence for an association with intake of fibre from fruit, vegetables, or legumes.

Comparison with other studies

Our results for total dietary fibre are consistent with a previous meta-analysis of case-control studies, which found an inverse association between fibre intake and risk of colorectal cancer. Our results, based on prospective studies, are not, however, as strong as the previous results from case-control studies.[9] The size of the summary estimates from our analyses is more in line with those of a pooled analysis of cohort studies,[31] which found an 18% increased risk among people with a low intake of dietary fibre (<10 g/day). In that analysis, however, no further reduction in risk occurred with higher intake of fibre, whereas we observed a linear inverse association with increasing intake, such as shown in the EPIC study.[8] Several differences between our analysis and the pooled analysis could explain the differences between the results. For example, although some overlap occurs between the studies included in the two analyses, some differences also exist. Our dose-response analysis included results from seven[16-18 21 22 25] of the 13 studies in the Pooling Project of Prospective Studies of Diet and Cancer, but included nine additional studies[8 12 20 23 24 26-29] not included in the pooled analysis, some of which were large. Thus our analysis included more than 14 000 cases among 1.9 million participants compared with 8000 cases among 700 000 participants in the pooled analysis. It is therefore possible that these additional studies contributed to a better assessment of the dose-response relation between fibre intake and risk of colorectal cancer. In line with the pooled analysis we found no evidence for an association between fruit or vegetable fibre and risk of colorectal cancer. However, in a previous meta-analysis of prospective studies we showed a reduction in risk with high intake of fruit and vegetables,[61] suggesting the potential role of components other than fibre in fruits and vegetables in explaining this result. In addition, we cannot exclude the possibility that the range of fruit fibre intake was too low to detect an inverse association in the overall analysis, although no difference in the summary estimates was observed for the other fibre types when stratified by the range of intake. Inverse associations were evident between intakes of cereal fibre and whole grain and risk of colorectal cancer in our analysis, and the results for whole grain intake are consistent with a previous meta-analysis of case-control studies, which reported a 20% reduction in risk with high whole grain intake.[33] The pooled analysis found a marginally significant inverse association between whole grain intake and colorectal cancer: pooled relative risk 0.92 (95% confidence interval 0.84 to 1.00).[31] In contrast to our results, the Women's Health Initiative Trial did not find a reduction in risk of colorectal cancer among participants who were randomised to an intervention with increased intakes of fruits, vegetables, grains, and fibre and reductions in fat intake.[62] However, fibre intake increased by only 2.5 g/day from baseline to the three year follow-up, from 15.4 to 17.9 g/day, whereas the intake in the comparison group did not materially change (from 15.4 to 14.8 g/day). Thus the changes in fibre intake in that trial may have been too small to significantly reduce the risk of colorectal cancer. Given that our results show a 10% reduction in risk of colorectal cancer for each 10 g intake of fibre daily, only a 2-3% reduction in risk would be expected with such a small increase in fibre intake.

Limitations of the study

Our meta-analysis has limitations that affect the interpretation of the results. It is possible that the weak inverse associations between dietary fibre or whole grain intake and risk of colorectal cancer could result from unmeasured or residual confounding by other dietary or lifestyle factors. Higher intakes of dietary fibre and whole grain are typically associated with other health behaviours, such as higher intakes of calcium and folate; higher levels of physical activity; lower prevalence of smoking, overweight, or obesity; and lower intakes of alcohol and red and processed meat.[22 27 63] Many but not all of the studies adjusted for potential confounding factors, although not all potential confounders were adjusted for in every study. In analyses stratified by adjustment for confounding factors, however, we found that the association between dietary fibre, cereal fibre, and whole grains persisted in most subgroups, with adjustment for potential confounding factors. In addition, in meta-regression analyses evidence that the results for these exposures differed significantly whether confounders had been adjusted for or not was lacking. Only in the analysis of fruit fibre was heterogeneity evident between studies that did or did not adjust for body mass index or weight and alcohol intake, with significant inverse associations among the studies with such adjustments. None of the included studies reported results stratified by alcohol, smoking, body mass index, or meat intake. Any further studies should report analyses stratified by other risk factors to better be able to rule out residual confounding.

Although publication bias can be a problem in meta-analyses of published literature we found no evidence of such bias in this analysis. In addition, the few studies that were excluded from the dose-response analysis of dietary fibre are unlikely to have altered the results because the results from the analyses of high versus low intake were similar when we repeated the analyses with the same dataset as in the dose-response analysis.

Accurate assessment of dietary fibre intake and other food constituents is a challenge. The definition of dietary fibre may differ between studies and may contribute to heterogeneity in the results. Some studies used the Englyst definition of fibre, which distinguishes non-starch polysaccharides from starch, whereas other studies calculated fibre intake using the Association of Official Analytical Chemists method, which includes some starch as dietary fibre. The summary relative risks were generally similar, however, no matter which method was used, and there was no evidence of heterogeneity between subgroups when stratified by the method used to calculate fibre intake.

Most studies carried out to date have used food frequency questionnaires to assess dietary intake. Concern is, however, increasing that measurement errors associated with the use of food frequency questionnaires may obscure associations between dietary intake and risk of chronic disease.[64] Few studies have reported results corrected for measurement errors. In the EPIC study the relative risk of colorectal cancer was 0.75 (95% confidence interval 0.59 to 0.95) for the highest compared with lowest fifths of fibre intake, and after calibration with more detailed data the relative risk was 0.58 (0.41 to 0.85).[19] In the Pooling Project of Prospective Studies the adjusted relative risk for less than 10 g/day compared with 10 g/day or more was 1.22 (1.10 to 1.35), but this increased to 2.16 (1.12 to 4.16) after correction for measurement error.[31] In a pooled analysis of seven UK based cohort studies, a stronger association was observed when food diaries were used to assess dietary fibre intake; an odds ratio of 0.66 (95% confidence interval 0.45 to 0.96) for the highest versus lowest fifths of fibre density compared with 0.88 (0.57 to 1.36) when food frequency questionnaires were

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used to measure dietary intake.[65] The latter was of similar size to our summary estimate for the highest versus lowest intake (summary relative risk 0.88, 95% confidence interval 0.82 to 0.94). The results using food diaries were further strengthened when corrected for measurement errors: odds ratio 0.68 (95% confidence interval 0.48 to 0.96) for a 0.7 g/MJ increase in fibre intake (uncorrected odds ratio 0.83, 95% confidence interval 0.70 to 0.97).[65] The results from these studies suggest that our results for dietary fibre and risk of colorectal cancer are likely to be conservative estimates of the true underlying risk and that any further studies should incorporate correction for measurement error in the analyses.

Strengths of the study

Our meta-analysis also has several strengths. Because we based our analysis on prospective studies, our findings are unlikely to be explained by recall bias and selection bias. Our meta-analysis included a large number of studies and more than 14 500 cases, and almost two million participants in the dietary fibre analysis. Thus we had adequate statistical power to clarify the shape of the dose-response relation between dietary fibre intake and risk of colorectal cancer and to detect moderate reductions in risk. We also carried out sensitivity analyses to investigate whether any particular study explained the results, but the findings were generally robust. We quantified the association between intake of dietary fibre and whole grain and risk of colorectal cancer by carrying out linear and non-linear dose-response analyses.

Mechanisms

A protective effect of dietary fibre and whole grain consumption on risk of colorectal cancer is biologically plausible. Whole grain foods are important sources of dietary fibre and may decrease the risk of colorectal cancer by increasing stool bulk, diluting faecal carcinogens, and decreasing transit time, thus reducing the contact between carcinogens and the lining of the colorectum.[7] In addition, bacterial fermentation of fibre results in the production of short chain fatty acids, which may have protective effects against colorectal cancer.[66] Other components of whole grains may also protect against colorectal cancer, including antioxidants, vitamins, trace minerals, phytate, phenolic acids, lignans, and phytoestrogens.[66-68] Whole grains have a high content of folate and magnesium, which have been associated with a reduced risk of colorectal cancer.[69-71] Higher intakes of dietary fibre and whole grain also protect against weight gain[72 73] and type 2 diabetes,[74 75] and it is possible that part of the potential effect of fibre intake is mediated through improved weight control and reduced insulin resistance, although these may not be the main mechanisms. However, the results persisted in studies that adjusted for both folate and body mass index, suggesting an association independent of folate and body mass index.

Conclusions and policy implications

Our results indicate a 10% reduction in risk of colorectal cancer for each 10 g/day intake of total dietary fibre and cereal fibre and a about a 20% reduction for each three servings (90 g/day) of whole grain daily, and further reductions with higher intake. These findings thus have important public health implications. Our results provide further support for public health recommendations to increase the intake of dietary fibre in the prevention of colorectal cancer. However, they suggest a particular benefit of increasing cereal fibre and whole grain intake. Increasing the intake of dietary fibre and whole grains is also likely to reduce the risk of cardiovascular disease,[76-78] type 2 diabetes,[74 75] overweight and obesity,[72 73] and possibly overall mortality,[76 78] thus there are several health benefits by increasing fibre intake and replacing refined grains with whole grains.

In summary, our meta-analysis suggests that a high intake of dietary fibre, particularly from cereal and whole grains, is associated with a reduced risk of colorectal cancer. Further studies should report more detailed results, including those for subtypes of fibre, stratify the results by subsites within the colorectum, and stratify the results by other risk factors to be able to rule out residual confounding. Further assessment of the impact of measurement errors on the risk estimates is also warranted.

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Contributors: The systematic literature review team at Wageningen University carried out the search, and selected and extracted data up to the end of December 2005. RV developed and managed the database for the Continuous Update Project. RL and DSMC did the updated literature search. RL, DSMC, and DA did the updated data extraction. DA and DSMC selected the studies and carried out the statistical analyses. DCG was statistical adviser and contributed to the statistical analyses. All authors revised the manuscript. EK was principal investigator of the Systematic Literature Reviews at Wageningen University. TN is principal investigator of the Continuous Update Project and wrote the protocol and implemented the study. DA wrote the first draft of the original manuscript. All authors had full access to all of the data in the study and prepared the manuscript. DA is guarantor. The sponsor of this study had no role in the decisions about the design and conduct of the study; collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript. The views expressed in this review are the opinions of the authors. They may not represent the views of the World Cancer Research Fund International/American Institute for Cancer Research and may differ from those in future updates of the evidence related to food, nutrition, physical activity, and cancer risk.

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What is already known on this topic

Colorectal cancer is the third most common cancer worldwide, with 1.2 million new cases annually

Intake of dietary fibre and whole grains has been established as protective against cardiovascular disease, but the association with colorectal cancer is not convincing

It is unclear whether only specific types of fibre or sources of fibre are associated with the risk of colorectal cancer

What this study adds

Intakes of dietary fibre, cereal fibre, and whole grains are associated with linear decreases in the risk of colorectal cancer

Evidence of an association between intake of fruit, vegetable, or legume fibre and risk of colorectal cancer was lacking

Intake of dietary fibre, particularly cereal fibre and whole grains, was associated with a small reduction in the risk of colorectal cancer

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Tables

Table 1 | **Prospective studies of dietary fibre intake and incidence of colorectal cancer**

Study, country	Study name	Follow-up period	Study size, sex, age, No of cases*	Diet assessment, No of items, fibre definition	Exposure	Quantity	Relative risk (95% CI)	Adjustment for confounders
Kabat 2008[29], USA	Women's Health Initiative	1993-8, 7.9 years	158 800 women, age 50-79, 1476 cases	Validated food frequency questionnaire, 122 food items, NA	Total fibre	≥21.2 *v* <9.9 g/day	1.06 (0.67 to 1.70)	Age, education, daily cigarette consumption, body mass index, height, HRT, diabetes mellitus, family history of colorectal cancer, physical activity, observational study participant, energy, dietary calcium
Butler 2008[30], Singapore	Singapore Chinese Health Study	1993-2005, 9.8 years	61 321 men and women, age 45-74, 961 cases	Validated food frequency questionnaire, 165 food items, NA	Dietary fibre	Fourths: 4 *v* 1	0.98 (0.81 to 1.19)	Age, sex, dialect group, interview year, diabetes mellitus, smoking, body mass index, alcohol, education, physical activity, family history of colorectal cancer, energy
Nomura 2007[28], USA	Multiethnic Cohort Study	1993-2001, 7.3 years	85 903 men and 105 108 women, age 45-75, 1138/972 cases	Validated food frequency questionnaire, 180 food items, AOAC method	Dietary fibre, men	16.5 *v* 6.1 g/1000 kcal/day	0.62 (0.48 to 0.79)	Age, ethnicity, time since cohort entry, family history of colorectal cancer, history of colorectal polyps, pack years of cigarette smoking, body mass index, hours of vigorous activity, aspirin use, multivitamin use, HRT, alcohol, red meat, folate, vitamin D, calcium, energy
					Fruit fibre, men	12.6 *v* 0.9 g/1000 kcal/day	0.78 (0.63 to 0.97)	
					Vegetable fibre, men	18.4 *v* 3.0 g/1000 kcal/day	0.78 (0.62 to 0.97)	
					Grain fibre, men	15.6 *v* 2.8 g/1000 kcal/day	0.86 (0.69 to 1.07)	
					Legume fibre, men	7.6 *v* 0.3 g/1000 kcal/day	0.87 (0.68 to 1.10)	
					Dietary fibre, women	18.6 *v* 7.5 g/1000 kcal/day	0.88 (0.67 to 1.14)	
					Fruit fibre, women	14.0 *v* 1.2 g/1000 kcal/day	0.82 (0.64 to 1.05)	
					Vegetable fibre, women	17.2 *v* 3.0 g/1000 kcal/day	0.95 (0.75 to 1.20)	
					Grain fibre, women	14.0 *v* 2.4 g/1000 kcal/day	1.00 (0.78 to 1.27)	
					Legume fibre, women	5.8 *v* 0.2 g/1000 kcal/day	1.16 (0.90 to 1.49)	
Schatzkin 2007[27], USA	NIH-AARP Diet and Health Study	1995-2000, 4.5 years	291 988 men and 197 623 women, age 50-71, 2974 cases	Validated food frequency questionnaire, 124 food items, AOAC method	Dietary fibre	15.9 *v* 6.6 g/1000 kcal/day	0.99 (0.85 to 1.15)	Age, sex, physical activity, smoking, HRT (women), red meat, dietary calcium, dietary folate, energy
					Grain fibre	5.7 *v* 1.7 g/1000 kcal/day	0.86 (0.76 to 0.98)	
					Fruit fibre	4.8 *v* 0.5 g/1000 kcal/day	1.08 (0.95 to 1.23)	
					Vegetable fibre	6.0 *v* 1.7 g/1000 kcal/day	1.01 (0.89 to 1.15)	
					Bean fibre	2.3 *v* 0.2 g/1000 kcal/day	0.93 (0.83 to 1.04)	

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Table 1 (continued)

Study, country	Study name	Follow-up period	Study size, sex, age, No of cases*	Diet assessment, No of items, fibre definition	Exposure	Quantity	Relative risk (95% CI)	Adjustment for confounders
Wakai 2007[26], Japan	Japan Collaborative Cohort Study	1988-97, 7.6 years	43 115 men and women, age 40-79, 443 cases	Validated food frequency questionnaire, 40 food items, AOAC method	Total dietary fibre	13.4/13.4 *v* 6.7/7.4 g/d men and women	0.73 (0.51 to 1.03)	Age, sex, area, education, family history of colorectal cancer, alcohol, smoking, body mass index, walking, exercise, sedentary work, beef/pork, energy, folate, calcium, vitamin D
McCarl 2006[25], USA	Iowa Women's Health Study	1986-2001, 15 years	35197 women, age 55-69, 954 cases	Validated food frequency questionnaire, 131 food items, NA	Fibre	≥25.4 *v* ≤13.2 g/day	0.75 (0.61 to 0.92)	Age
Shin 2006[23], China	Shanghai Women's Health Study	1997-2004, 5.74 years	73 314 women, age 40-70, 283 cases	Validated food frequency questionnaire, 77 food items, NA	Fibre	Fifths: 5 *v* 1	1.1 (0.6 to 1.8)	Age, menopausal status, education, smoking, alcohol, exercise, family history of colorectal cancer, energy, vitamin supplements
Otani 2006[24], Japan	Japan Public Health Center-based Prospective Study	Cohort 1: 1995-2002; Cohort 2: 1998-2002, 5.8 years	78 326 men and women, age 40-59 (cohort 1) and 40-69 (cohort 2), 522 cases	Validated food frequency questionnaire 138 food items, AOAC method	Dietary fibre, men	18.7 *v* 6.4 g/day	0.85 (0.53 to 1.4)	Age, alcohol, smoking, body mass index, physical exercise, folate, calcium, vitamin D, red meat, study area, energy
					Dietary fibre, women	20.0 *v* 8.3 g/day	0.58 (0.31 to 1.1)	
Bingham 2005[8], Europe	European Prospective Investigation into Cancer and Nutrition	1992-2004, 6.2 years	519 978 men and women, age 25-70, 1721 cases	Validated food frequency questionnaire, 300-350 food items, diet records, Englyst method (UK)	Dietary fibre	30.1/24.3 *v* 18.2/15.9 g/day, men and women	0.79 (0.63 to 0.99)	Age, sex, energy from non-fat sources, energy from fat sources, height, weight, folate, red and processed meat, physical activity, alcohol, smoking status, educational level
					Fruit fibre	5.3/5.4 *v* 2.7/2.8 g/day	0.81 (0.68 to 0.97)	
					Cereal fibre	13.1/9.2 *v* 6.6/4.9 g/day	0.93 (0.76 to 1.15)	
					Vegetable fibre	5.3/5.4 *v* 2.7/2.8 g/day	0.94 (0.76 to 1.16)	
					Legume fibre	1.9/1.0 *v* 0 g/day	0.98 (0.82 to 1.17)	
Michels 2005[21], USA	Nurses' Health Study	1984-2000, 16 years	76 947 women, age 38-63, 919 cases	Validated food frequency questionnaire, 131 food items, AOAC method	Dietary fibre	>14.0 *v* <8.0 g/1000 kcal/day	0.98 (0.70 to 1.37)	Age, time period, family history of colorectal cancer, sigmoidoscopy or colonoscopy, height, body mass index, physical activity, aspirin use and duration, pack years of early onset smoking, multivitamins, energy, alcohol, dietary folate, calcium, red meat, processed meat, glycaemic load, methionine, HRT (women), menopausal status (women)
					Cereal fibre	11.45 *v* 2.8 g/1000 kcal/day	0.79 (0.60 to 1.05)	
					Fruit fibre	9.3 *v* 1.4 g/1000 kcal/day	0.92 (0.68 to 1.23)	
					Vegetable fibre	12.2 *v* 3.6 g/1000 kcal/day	1.09 (0.83 to 1.42)	
	Health Professionals Follow-up Study	1986-2000, 14 years	47 279 men, age 40-75, 593 cases	Validated food frequency questionnaire, 131 food items, AOAC method	Dietary fibre	>14.0 *v* <8.0 g/1000 kcal/day	0.91 (0.65 to 1.28)	
					Cereal fibre	8.0 *v* 2.3 g/1000 kcal/day	0.89 (0.71 to 1.12)	
					Fruit fibre	7.3 *v* 1.4 g/1000 kcal/day	0.88 (0.68 to 1.13)	
					Vegetable fibre	10.0 *v* 3.6 g/1000 kcal/day	1.20 (0.94 to 1.56)	

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Table 1 (continued)

Study, country	Study name	Follow-up period	Study size, sex, age, No of cases*	Diet assessment, No of items, fibre definition	Exposure	Quantity	Relative risk (95% CI)	Adjustment for confounders
Lin 2005[22], USA	Women's Health Study	1993-2003, 10 years	39 976 women, age ≥45, 223 cases	Validated food frequency questionnaire, 131 food items, AOAC method	Total fibre	26 *v* 12 g/day	0.75 (0.47 to 1.18)	Age, body mass index, randomised treatment assignment, family history of colorectal cancer, colon polyps, physical activity, smoking status, aspirin, red meat, alcohol, energy, menopausal status, HRT
					Fruit fibre	6.0 *v* 2.5 g/day	1.00 (0.67 to 1.49)	
					Vegetable fibre	8.0 *v* 5.9 g/day	1.00 (0.65 to 1.56)	
					Cereal fibre	6.1 *v* 3.1 g/day	0.97 (0.66 to 1.42)	
					Legume fibre	1.8 *v* 0.4 g/day	0.60 (0.40 to 0.91)	
Sanjoaquin 2004[20], England	Oxford Vegetarian Study	1980-9, 17 years	10 998 men and women, age 16-89: 95 cases	Validated food frequency questionnaire, NA	Total dietary fibre	36.7 *v* 17.0 g/day	0.82 (0.43 to 1.56)	Age, sex, alcohol, smoking
McCullough 2003[36], USA	Cancer Prevention Study 2 Nutrition Cohort	1992-7, 4.5 years	62 609 men and 70 554 women, age 50-74, 298 and 210 cases	Validated food frequency questionnaire, 68 food items, NA	Dietary fibre, men	≥16.6 *v* <9.3 g/day	1.11 (0.72 to 1.70)	Age, exercise metabolic equivalent of tasks, body mass index, aspirin, smoking, family history of colorectal cancer, education, energy, multivitamins, total calcium, red meat intake, and HRT (women)
					Dietary fibre, women	≥14.4 *v* <8.0 g/day	0.86 (0.52 to 1.42)	
Mai 2003[18], USA	Breast Cancer Detection Demonstration Project	1987-8, 8.5 years	45 491 women, mean age 62, 487 cases	Validated food frequency questionnaire, 62 food items, NA	Total fibre	>12 *v* <6.3 g/1000 kcal/day	0.94 (0.70 to 1.26)	Age, non-steroidal anti-inflammatory drugs, smoking, alcohol, calcium, vitamin D, red meat, height, body mass index, education
					Fruit fibre	>3.57 *v* <0.90 g/1000 kcal/day	1.10 (0.83 to 1.46)	
					Vegetable fibre	>3.48 *v* <1.44 g/1000 kcal/day	0.92 (0.69 to 1.21)	
					Bean fibre	>1.38 *v* <0.20 g/1000 kcal/day	0.84 (0.63 to 1.10)	
					Grain fibre	>4.75 *v* <1.80 g/1000 kcal/day	1.02 (0.76 to 1.37)	
Terry 2001[17], Sweden	Swedish Mammography Cohort Study	1987-98, 9.6 years	61 463 women, age 40-74, 460 cases	Food frequency questionnaire, 67 items, AOAC method	Cereal fibre	13.6 *v* 5.7 g/day	0.91 (0.69 to 1.20)	Age, red meat, dairy products, energy
					Total dietary fibre	21.8 *v* 12.3 g/day	0.96 (0.70 to 1.33)	
					Fruit fibre	5.2 *v* 0.8 g/day	0.97 (0.69 to 1.38)	
					Vegetable fibre	2.5 *v* 0.6 g/day	1.17 (0.85 to 1.61)	
Pietinen 1999[16], Finland	ATBC Cancer Prevention Study	1985-95, 8 years	27 111 male smokers, age 50-69, 185 cases	Validated food frequency questionnaire, 276 items, Englyst method	Dietary fibre	34.1 *v* 16.0 g/day	1.0 (0.6 to 1.5)	Age, tobacco years, body mass index, alcohol, education, physical activity, calcium, energy
Kato 1997[15], USA	New York University Women's Cohort Study	1985-94, mean 7.1 years	15 785 women, age 34-65, 100 cases	Food frequency questionnaire, 70 items, NA	Dietary fibre	Fourths: 4 *v* 1	1.51 (0.85 to 2.68)	Age, energy, place at enrolment, highest level of education
Gaard 1996[14], Norway	Norwegian National Health Screening Study	1977-91, 11.4 years	505 35 men and women, age 20-54, 143 cases of colon cancer	Validated food frequency questionnaire, 80 food items, NA	Fibre, men	≥17.9 *v* ≤13.5 g/day	0.82 (0.46 to 1.46)	Age, body mass index, height, smoking status, energy
					Fibre, women	≥11.3 *v* 8.5 g/day	2.10 (0.90 to 4.87)	

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Table 1 (continued)

Study, country	Study name	Follow-up period	Study size, sex, age, No of cases*	Diet assessment, No of items, fibre definition	Exposure	Quantity	Relative risk (95% CI)	Adjustment for confounders
Steinmetz 1994[13], USA	Iowa Women's Health Study	1986-91, 5 years	41 837 women, age 55-69, 212 cases of colon cancer	Validated food frequency questionnaire, 127 food items, NA	Dietary fibre	>24.7 *v* <14.5 g/day	0.80 (0.49 to 1.31)	Age, energy
Heilbrun 1989[12], USA	Honolulu Heart Program	1965-85, 16 years	8006 American Japanese men: 102 cases of colon cancer, 60 cases of rectal cancer, 361 controls	Dietary recall, 24 hour, 54 food items, NA	Dietary fibre, colon cancer	≥14.80 *v* <7.50 g/day	0.71 (0.38 to 1.32)	Age, alcohol intake
					Dietary fibre, rectal cancer	≥14.80 *v* <7.50 g/day	1.20 (0.51 to 2.83)	
Wu 1987[11], USA	Leisure World Cohort Study	1981-5, 3.5 years	11 564 men and women, age ≤64 to ≥85, 58 and 68 cases	Validated food frequency questionnaire, 56 food items, NA	Dietary fibre, men	Thirds: 3 *v* 1	1.13 (0.60 to 2.10)	Age
					Dietary fibre, women	Thirds: 3 *v* 1	0.64 (0.40 to 1.20)	

NA=not available; HRT=hormone replacement therapy; AOAC=Association of Official Analytical Chemists.

*Cases refer to colorectal cancer unless specified otherwise.

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Table 2| **Prospective studies of whole grain intake and incidence of colorectal cancer**

Study, country	Study name	Follow-up period	Study size, sex, age, No of cases*	Diet assessment, No of items	Exposure	Quantity	Relative risk (95% CI)	Adjustment for confounders
Fung 2010[39], USA	Nurses' Health Study	1980-2006, 26 years	87 256 women, age 34-59, 1432 cases	Validated food frequency questionnaire, 61-116 food items	Whole grains	Per serving/day	0.95 (0.89 to 1.02)	Age, body mass index, alcohol, family history of colorectal cancer, physical activity, aspirin, colonoscopy, history of polyps, pack years of smoking, energy, multivitamins
Fung 2010[39], USA	Health Professionals Follow-Up Study	1986-2006, 20 years	45 490 men, age 40-75, 1032 cases	Validated food frequency questionnaire, about 140 food items	Whole grains	Per serving/day	0.94 (0.88 to 0.99)	Age, body mass index, alcohol, family history of colorectal cancer, physical activity, aspirin, colonoscopy, history of polyps, pack years of smoking, energy, multivitamins
Egeberg 2010[38], Denmark	The Diet Cancer and Health Cohort Study	1993-2006, 10.2 years	26 630 men and 29 189 women, age 50-64, 461 cases of colon cancer and 283 cases of rectal cancer	Validated food frequency questionnaire, 192 food items	Whole grains, colon cancer, men	>160 *v* ≤75 g/day	0.61 (0.43 to 0.86)	Age, body mass index, alcohol intake, school education, red and processed meat, HRT (women), leisure time physical activity
					Whole grains, rectal cancer, men	>160 *v* ≤75 g/day	0.88 (0.57 to 1.36)	
					Whole grains, colon cancer, women	>160 *v* ≤75 g/day	0.92 (0.63 to 1.35)	
					Whole grains, rectal cancer, women	>160 *v* ≤75 g/day	0.81 (0.50 to 1.30)	
Schatzkin 2007[27], USA	NIH-AARP Diet and Health Study	1995-2000, 5 years	291 988 men and 197 623 women, age 50-71, 2974 cases	Validated food frequency questionnaire, 124 food items	Whole grains	1.3 *v* 0.2 serv/1000 kcal/day	0.79 (0.70 to 0.89)	Age, sex, physical activity, smoking, HRT (women), red meat, dietary calcium, dietary folate, energy
McCarl 2006[25], USA	Iowa Women's Health Study	1986-2000, 14 years	35 197 women, age 55-69, 954 cases	Validated food frequency questionnaire, 127 food items	Whole grains	≥19 *v* ≤3.5 servings/week	0.81 (0.66 to 0.99)	Age
Larsson 2005[35], Sweden	Swedish Mammography Cohort Study	1987-2004, 14.8 years	61 433 women, age 40-76, 805 cases	Validated food frequency questionnaire, 67 food items	Whole grain	≥4.5 *v* <1.5 servings/day	0.80 (0.60 to 1.06)	Age, body mass index, education, energy, saturated fat, calcium, red meat, fruits and vegetables
Wu 2004[37], USA	Health Professional's Follow-up Study	1986-2000, 14 years	47 311 men, age 45-75, 561 cases of colon cancer	Validated food frequency questionnaire, 131 food items	Whole grain	Fifths: 5 *v* 1	0.75 (0.57 to 1.00)	Age, family history of colorectal cancer in first degree relative, history of endoscopy, physical activity, pack years of smoking before age 30, race, aspirin use, energy
McCullough 2003[36], USA	Cancer Prevention Study 2	1992-7, 4.5 years	62 609 men and 70 554 women, age 50-74, 298/210 cases of colon cancer	Validated food frequency questionnaire, 68 items	Whole grains, men	≥11.0 *v.* <2.0 servings/week	0.95 (0.64 to 1.42)	Age, exercise metabolic equivalent of tasks, aspirin, smoking, family history of colorectal cancer, body mass index, education, energy, multivitamin use, total calcium, red meat intake, and HRT (women)
					Whole grains, women	≥11.2 *v* <2.5 servings/week	1.17 (0.73 to 1.87)	

HRT=hormone replacement therapy.

*Cases refer to colorectal cancer unless specified otherwise.

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Table 3| **Subgroup analyses of fibre intake and risk of colorectal cancer, dose-response analysis**

	Total dietary fibre					Fruit fibre					Vegetable fibre				
				P for heterogeneity					P for heterogeneity					P for heterogeneity	
Subgroups	**No of studies**	**Relative risk (95% CI)**	**I^2 (%)**	*	†	**No of studies**	**Relative risk (95% CI)**	**I^2 (%)**	*	†	**No of studies**	**Relative risk (95% CI)**	**I^2 (%)**	*	†
All studies	16	0.90 (0.86 to 0.94)	0	0.48	—	9	0.93 (0.82 to 1.05)	23	0.24	—	9	0.98 (0.91 to 1.06)	0	0.60	—
Duration of follow-up:															
<10 years	10	0.91 (0.84 to 0.97)	33.2	0.14	0.77	6	0.97 (0.82 to 1.14)	37.6	0.16	0.26	6	0.96 (0.88 to 1.04)	0	0.51	0.27
≥10 years	6	0.91 (0.85 to 0.98)	0	0.97		3	0.80 (0.64 to 1.00)	0	0.91		3	1.10 (0.90 to 1.35)	0	0.74	
Sex:															
Men	7	0.92 (0.82 to 1.03)	54.4	0.04	0.72	2	0.83 (0.72 to 0.97)	0	0.80	0.45	2	0.94 (0.78 to 1.14)	44.3	0.18	0.34
Women	11	0.94 (0.89 to 0.99)	0	0.74		5	0.91 (0.78 to 1.06)	0	0.80		5	1.02 (0.89 to 1.17)	0	0.54	
Subsite:															
Colon	13	0.90 (0.83 to 0.98)	33.9	0.11	0.86	3	0.90 (0.34 to 2.38)	59.2	0.42	0.85	3	0.89 (0.57 to 1.40)	30.9	0.24	0.24
Rectum	10	0.91 (0.83 to 1.03)	14.7	0.31		1	1.26 (0.09 to 18.24)	—	—		1	6.40 (0.97 to 42.34)	—	—	
Geographical location:															
Europe	4	0.87 (0.78 to 0.96)	9.2	0.35	0.74	2	0.75 (0.46 to 1.23)	0	0.39	0.34	2	1.30 (0.35 to 4.84)	58.2	0.12	0.70
USA	9	0.92 (0.88 to 0.96)	0	0.69		6	0.93 (0.81 to 1.07)	38.0	0.15		6	0.98 (0.91 to 1.06)	0	0.61	
Asia	3	0.78 (0.60 to 1.03)	24.7	0.29		1	1.90 (0.40 to 9.04)	—	—		1	0.71 (0.26 to 1.91)	—	—	
No of cases:															
<500	8	0.92 (0.82 to 1.03)	0	0.64	0.35	4	1.08 (0.73 to 1.60)	0	0.87	0.98	4	1.05 (0.61 to 1.79)	8.0	0.35	0.37
500-1499	5	0.92 (0.87 to 0.99)	0	0.68		2	0.80 (0.64 to 1.00)	0	0.70		2	1.09 (0.89 to 1.34)	0	0.93	
≥1500	3	0.88 (0.80 to 0.97)	64.0	0.06		3	0.94 (0.75 to 1.17)	71.4	0.03		3	0.96 (0.88 to 1.04)	0	0.41	
Range of intake:															
<15 to <10 g/day‡	11	0.90 (0.84 to 0.96)	11.9	0.33	0.80	6	1.07 (0.94 to 1.23)	0	0.61	0.04	6	1.03 (0.89 to 1.18)	0	0.58	0.54
≥15 to ≥10 g/day‡	5	0.90 (0.85 to 0.95)	0	0.51		3	0.86 (0.77 to 0.96)	0	0.71		3	0.96 (0.88 to 1.05)	0	0.38	
Adjustment for confounders															
Alcohol:															
Yes	12	0.87 (0.83 to 0.92)	0	0.63	0.08	7	0.86 (0.78 to 0.96)	0	0.75	0.04	7	0.95 (0.87 to 1.04)	0	0.75	0.32
No	4	0.95 (0.88 to 1.01)	0	0.51		2	1.10 (0.95 to 1.28)	0	0.75		2	1.34 (0.54 to 3.34)	45.0	0.18	
Smoking:															
Yes	13	0.90 (0.85 to 0.95)	15.7	0.29	0.84	8	0.92 (0.81 to 1.05)	32.5	0.17	0.89	8	0.98 (0.90 to 1.05)	0	0.74	0.20
No	3	0.95 (0.88 to 1.01)	0	0.51		1	0.97 (0.45 to 2.09)	—	—		1	3.15 (0.63 to 15.64)	—	—	
Body mass index, weight, waist to hip ratio:															

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Table 3 (continued)

Subgroups	Total dietary fibre					Fruit fibre					Vegetable fibre				
	No of studies	Relative risk (95% CI)	I^2 (%)	P for heterogeneity *	P for heterogeneity †	No of studies	Relative risk (95% CI)	I^2 (%)	P for heterogeneity *	P for heterogeneity †	No of studies	Relative risk (95% CI)	I^2 (%)	P for heterogeneity *	P for heterogeneity †
Yes	10	0.89 (0.83 to 0.95)	19.4	0.26	0.22	7	0.86 (0.78 to 0.96)	0	0.75	0.04	7	0.95 (0.87 to 1.04)	0	0.75	0.32
No	6	0.93 (0.87 to 1.00)	0	0.91		2	1.10 (0.95 to 1.28)	0	0.75		2	1.34 (0.54 to 3.34)	45.0	0.18	
Physical activity:															
Yes	11	0.90 (0.85 to 0.96)	27.7	0.18	0.70	7	0.91 (0.79 to 1.05)	40.0	0.13	0.56	7	0.95 (0.87 to 1.04)	0	0.75	0.77
No	5	0.92 (0.85 to 0.99)	0	0.97		2	1.06 (0.68 to 1.65)	0	0.79		2	1.34 (0.54 to 3.34)	45.0	0.18	
Red, processed meat:															
Yes	10	0.89 (0.84 to 0.95)	21.3	0.25	0.32	9	0.93 (0.82 to 1.05)	23	0.24	NC	9	0.98 (0.91 to 1.06)	0	0.60	NC
No	6	0.93 (0.87 to 1.00)	0	0.86		0	—	—	—		0	—	—	—	
Dairy products, calcium:															
Yes	10	0.93 (0.87 to 0.98)	9.6	0.35	0.20	7	0.94 (0.82 to 1.07)	32.2	0.18	0.35	7	0.98 (0.91 to 1.06)	0	0.51	0.81
No	6	0.87 (0.82 to 0.92)	0	0.74		2	0.69 (0.40 to 1.19)	0	0.58		2	0.94 (0.42 to 2.07)	8.0	0.30	
Folate:															
Yes	7	0.89 (0.82 to 0.95)	41.3	0.12	0.27	6	0.90 (0.77 to 1.06)	49.9	0.08	0.60	6	0.98 (0.90 to 1.05)	0	0.62	0.59
No	9	0.93 (0.87 to 1.00)	0	0.94		3	1.04 (0.69 to 1.56)	0	0.93		3	1.33 (0.61 to 2.87)	21.7	0.28	
Energy intake:															
Yes	11	0.90 (0.84 to 0.96)	27.3	0.18	0.62	9	0.93 (0.82 to 1.05)	23	0.24	NC	9	0.98 (0.91 to 1.06)	0	0.60	NC
No	5	0.92 (0.86 to 0.98)	0	0.98		0	—	—	—		0	—	—	—	

NC=not calculable.

*Within each subgroup.

†Between subgroups with meta-regression analysis.

‡Total dietary fibre: ≥15 *v* <15 g/day, fruit and vegetable fibre: ≥10 *v* <10 g/day.

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Table 4| **Subgroup analyses of cereal fibre and whole grain intake and risk of colorectal cancer, dose-response analysis**

	Cereal fibre					Whole grains				
Subgroups	**No of studies**	**Relative risk (95% CI)**	**I^2 (%)**	**P for heterogeneity***	**P for heterogeneity†**	**No of studies**	**Relative risk (95% CI)**	**I^2 (%)**	**P for heterogeneity***	**P for heterogeneity†**
All studies	8	0.90 (0.83 to 0.97)	0	0.78	—	6	0.83 (0.78 to 0.89)	18.2	0.30	—
Duration of follow-up:										
<10 years	5	0.90 (0.82 to 0.98)	0	0.42	0.84	1	0.73 (0.63 to 0.84)	—	—	0.12
≥10 years	3	0.87 (0.71 to 1.08)	0	0.99		5	0.86 (0.80 to 0.92)	0	0.72	
Sex:										
Men	2	0.92 (0.80 to 1.06)	0	0.60	0.69	3	0.79 (0.72 to 0.87)	0	0.44	0.14
Women	5	0.96 (0.83 to 1.11)	0	0.98		5	0.88 (0.81 to 0.95)	0	0.58	
Subsite:										
Colon	3	1.03 (0.80 to 1.32)	0	0.45	0.45	4	0.86 (0.79 to 0.94)	0	0.58	0.53
Rectum	1	1.39 (0.78 to 2.48)	—	—		3	0.80 (0.56 to 1.14)	90.5	<0.001	
Geographical location:										
Europe	2	0.94 (0.73 to 1.21)	0	0.48	0.70	2	0.87 (0.78 to 0.96)	58.8	0.12	0.13
USA	6	0.89 (0.82 to 0.97)	0	0.65		4	0.79 (0.72 to 0.86)	0	0.57	
Asia	0	—	—	—		0	—	—	—	
No of cases:										
<500	3	1.01 (0.77 to 1.32)	0	0.99	0.48	0				0.12
500-1499	2	0.87 (0.71 to 1.08)	0	0.92		5	0.86 (0.80 to 0.92)	0	0.72	
≥1500	3	0.88 (0.77 to 1.00)	35.1	0.21		1	0.73 (0.63 to 0.84)	—	—	
Range of intake:										
<7 to <90 g/day‡	3	0.91 (0.68 to 1.21)	0	0.85	0.90	1	0.73 (0.63 to 0.84)			0.18
≥7 to ≥90 g/day‡	5	0.89 (0.82 to 0.97)	0	0.45		3	0.87 (0.80 to 0.94)	0	0.39	
Adjustment for confounders										
Alcohol:										
Yes	6	0.93 (0.84 to 1.02)	0	0.98	0.27	3	0.86 (0.79 to 0.93)	0	0.92	0.51
No	2	0.86 (0.68 to 1.08)	41.9	0.19		3	0.81 (0.70 to 0.93)	60.6	0.08	
Smoking:										
Yes	7	0.89 (0.82 to 0.97)	0	0.76	0.47	3	0.79 (0.71 to 0.87)	1.6	0.36	0.21
No	1	1.02 (0.73 to 1.43)	—	—		3	0.87 (0.80 to 0.94)	0	0.39	
Body mass index, weight, waist to hip ratio:										
Yes	7	0.89 (0.82 to 0.97)	0	0.76	0.27	4	0.87 (0.81 to 0.94)	0	0.82	0.09

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Table 4 (continued)

	Cereal fibre					Whole grains				
Subgroups	No of studies	Relative risk (95% CI)	I^2 (%)	P for heterogeneity*	P for heterogeneity†	No of studies	Relative risk (95% CI)	I^2 (%)	P for heterogeneity*	P for heterogeneity†
No	1	1.02 (0.73 to 1.43)	—	—		2	0.75 (0.67 to 0.84)	0	0.52	
Physical activity:										
Yes	6	0.89 (0.81 to 0.96)	0	0.68	0.38	4	0.82 (0.76 to 0.89)	20.1	0.29	0.60
No	2	1.02 (0.77 to 1.34)	0	0.97		2	0.86 (0.73 to 1.01)	47.5	0.17	
Red, processed meat:										
Yes	8	0.90 (0.83 to 0.97)	0	0.78	NC	3	0.84 (0.74 to 0.95)	64.0	0.06	0.81
No	0	—	—	—		3	0.82 (0.74 to 0.91)	0	0.81	
Dairy products, calcium:										
Yes	6	0.90 (0.83 to 0.98)	0	0.56	0.82	2	0.82 (0.65 to 1.03)	79.7	0.03	0.79
No	2	0.85 (0.59 to 1.23)	0	0.87		4	0.84 (0.78 to 0.91)	0	0.81	
Folate:										
Yes	5	0.88 (0.81 to 0.96)	0	0.54	0.38	1	0.73 (0.63 to 0.84)			0.12
No	3	1.01 (0.77 to 1.32)	0	0.99		5	0.86 (0.80 to 0.92)	0	0.72	
Energy intake:										
Yes	6	0.90 (0.82 to 0.98)	0	0.56	0.83	4	0.83 (0.74 to 0.92)	41.1	0.17	0.91
No	2	0.87 (0.71 to 1.08)	0	0.92		2	0.85 (0.77 to 0.93)	0	0.35	

NC=not calculable.

*Within each subgroup.

†Between subgroups with meta-regression analysis.

‡Cereal fibre: ≥7 versus <7 g/day, whole grains: ≥90 versus <90 g/day.

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Figures

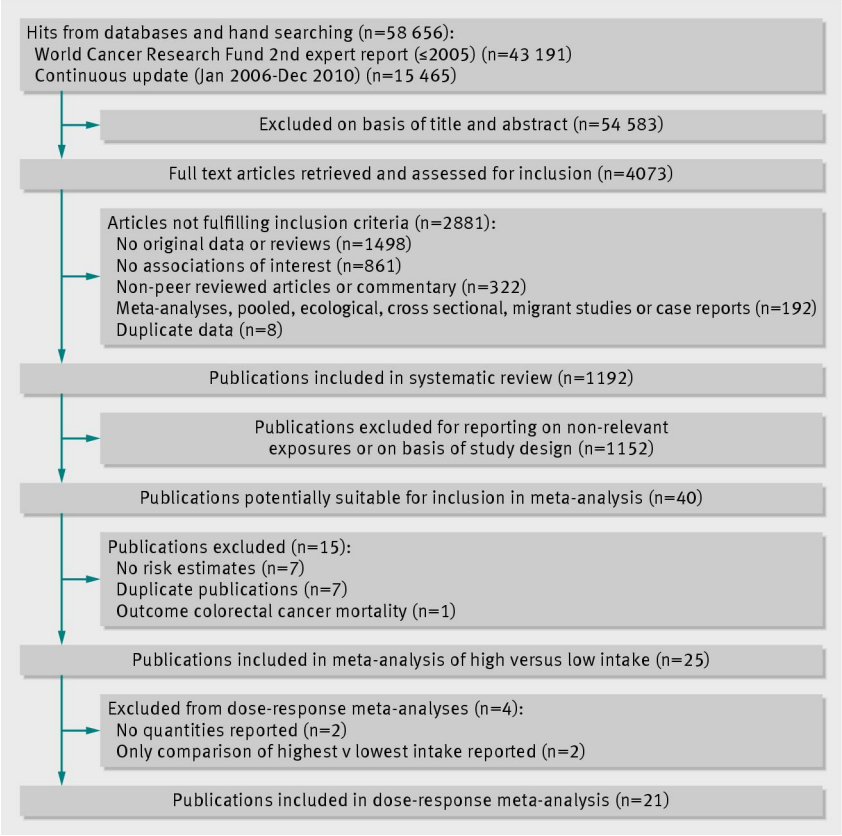

Fig 1 Flow chart of publications included in systematic review

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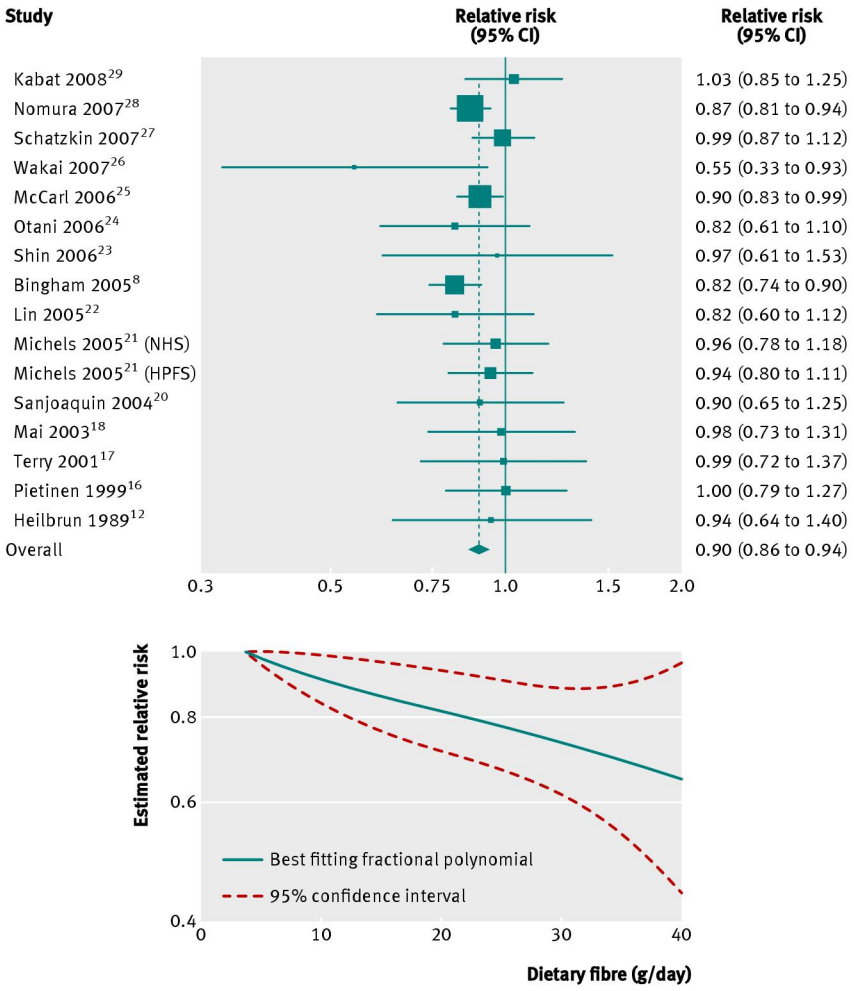

Fig 2 Dose-response analyses between dietary fibre and risk of colorectal cancer. NHS=Nurses' Health Study; HPFS=Health Professionals Follow-up Study

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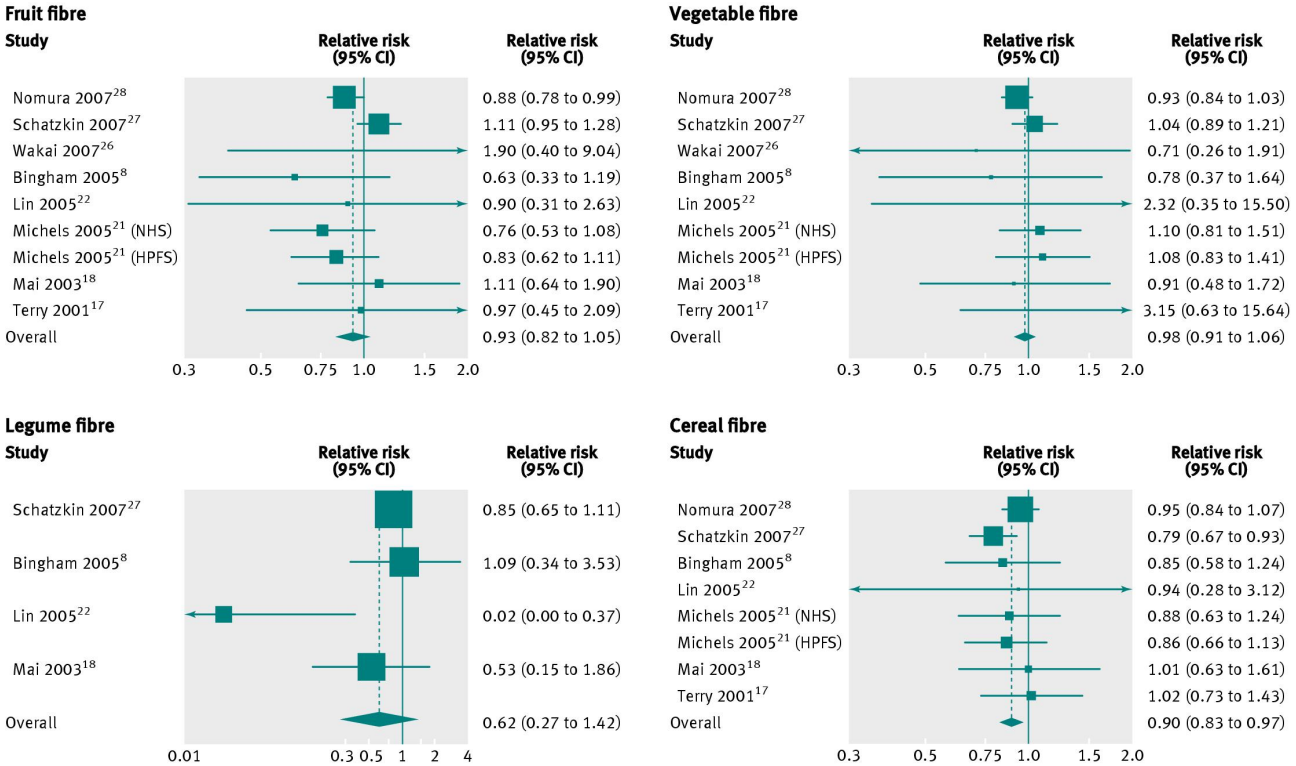

Fig 3 Risk of colorectal cancer according to fibre types. NHS=Nurses' Health Study; HPFS=Health Professionals Follow-up Study

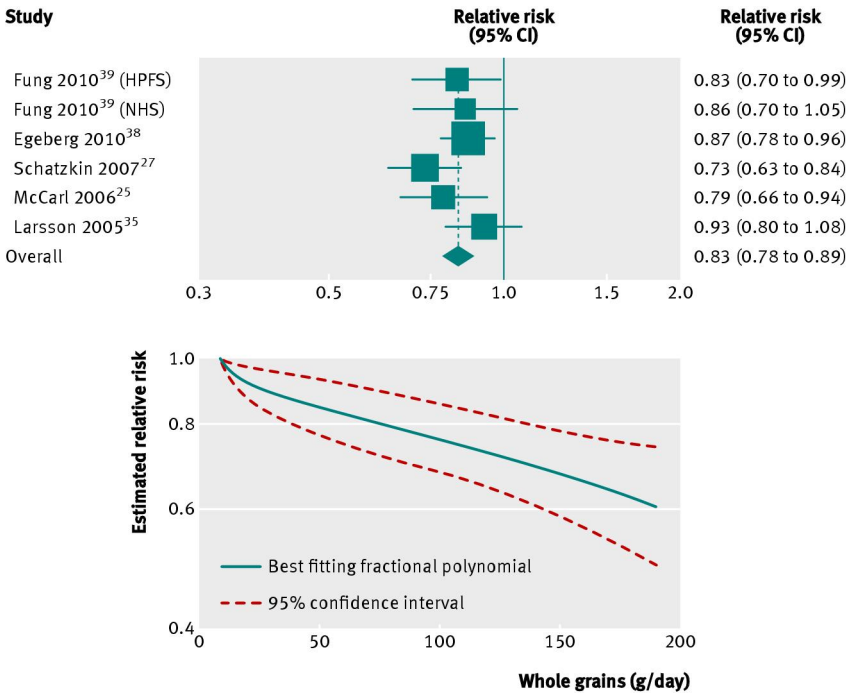

Fig 4 Dose-response analyses between whole grains and risk of colorectal cancer. NHS=Nurses' Health Study; HPFS=Health Professionals Follow-up Study

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