# Menstrual factors, reproductive history, hormone use, and Urothelial carcinoma risk: A prospective study in the EPIC cohort

**Running title:** Reproductive factors and Urothelial carcinoma

Leila Lujan-Barroso 1,2,3, Edoardo Botteri 4, 5, Saverio Caini 6, Börje Ljungberg 7, Nina Roswall 8, Anne Tjønneland 8,9 , Bas Bueno-de-Mesquita 10, 11, 12, 13, Inger T Gram 14, Rosario Tumino 15, Lambertus A Kiemeney 16, Fredrik Liedberg 17, Tanja Stocks 18, Marc Gunter 19, Neil Murphy 19, Iris Cervenka 20, Agnès Fournier 20, Marina Kvaskoff 20, Christel Häggström 21, 22, Kim Overvad 23, Eiliv Lund 14, Marit Waaseth 24, Renée Turzanski Fortner 25, Tilman Kühn 25, Virginia Menéndez 26, Maria-Jose Sánchez 27,28, Carmen Santiuste 28,29, Aurora Perez-Cornago 30, Raul Zamora-Ros 1,2, Amanda J Cross 31, Antonia Trichopoulou 32, Anna Karakatsani 32,33, Eleni Peppa 32, Domenico Palli 6, Vittorio Krogh 34, Veronica Sciannameo 35, Amalia Mattiello 36, Salvatore Panico 36, Carla H. van Gils 37, N. Charlotte Onland-Moret 37, Aurelio Barricarte 28, 38, 39, Pilar Amiano 28, 40, Kay-Tee Khaw 41, Heiner Boeing 42, Elisabete Weiderpass\* 19, Eric J Duell\* 43, 44.

1. Unit of Nutrition and Cancer. Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), Gran Via de L'Hospitalet 199-203, 08908, L’Hospitalet de Llobregat, Barcelona, Spain.

2. Bellvitge Biomedical Research Institute – IDIBELL, Gran Via de L'Hospitalet 199-203, 08908, L’Hospitalet de Llobregat, Barcelona, Spain.

3. Department of Nursing of Public Health, Mental Health and Maternity and Child Health School of Nursing Universitat de Barcelona, Carrer de la Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain

4. Cancer Registry of Norway, Oslo University Hospital, Ullernchausseen 64, 0379, Oslo, Norway.

5. Norwegian National Advisory Unit for Women's Health, Women's Clinic, Oslo University Hospital, Sognsvannsveien 20, 0372, Oslo, Norway.

6. Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Via Cosimo il Vecchio 2, 50139, Florence, Italy

7. Department of surgical and perioperative sciences, urology and andrology, Umeå University, 901 85, Umeå, Sweden.

8. Diet, Genes and Environment, Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100, Copenhagen Copenhagen, Denmark.

9. Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Øster Farimagsgade 5, 1014 Copenhagen.

10. Former senior scientist, Dept. for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands.

11. Former associate professor, Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands.

12. Visiting professor, Dept. of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, St Mary’s Campus, Norfolk Place, London, W2 1PG London, United Kingdom.

13. Academic Icon / visiting professor, Dept. of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Pantai Valley, 50603, Kuala Lumpur, Malaysia.

14. Department of Community Medicine, University of Tromsø , The Arctic University of Norway, N – 9037, Tromsø, Norway.

15. Cancer Registry and histopathology Department, "Civic -M.P. Arezzo" Hospital, ASP Ragusa, 97100, Ragusa, Italy.

16. Radboud university medical center, Radboud Institute for Health Sciences, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

17. Department of Urology Skåne University Hospital and Institution of Translational Medicine, Lund University, Jan Waldenströms gata 5, 205 02, Malmö, Sweden.

18. Department of Clinical Sciences Lund, Lund University, Barngatan 4, 222 42, Lund, Sweden.

19. International Agency for Research on Cancer / World Health Organization, 150 cours Albert Thomas 69372, Lyon CEDEX 08, France.

20. Inserm U1018, Centre for Research in Epidemiology and Population Health (CESP) "Health across Generations" Team, Gustave Roussy 114 rue Edouard Vaillant, F-94805, Villejuif, France.

21. Department of Biobank Research, Umeå University, SE-901 87, Umeå, Sweden.

22. Department of Surgical Sciences, Uppsala University, Akademiska sjukhuset entrence 70, 1 tr SE-751 85, Uppsala, Sweden.

23. Department of Public Health, Section for Epidemiology, Aarhus University, Bartholins Allé 2 DK-8000, Aarhus, Denmark.

24. Department of Pharmacy, University of Tromsø , The Arctic University of Norway, N – 9037, Tromsø, Norway.

25. Division of Cancer Epidemiology, German Cancer Research Center (DFKZ), Im Neuenheimer Feld 280, · 69120, Heidelberg, Germany.

26. Public Health Directorate, C/Ciriaco Miguel Virgil 9, 33006, Oviedo, Asturias, Spain

27. Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.GRANADA. Hospitales Universitarios de Granada/Universidad de Granada, Cuesta del Observatorio 4, 18080, Granada, Spain

28. CIBER de Epidemiología y Salud Pública (CIBERESP), Av. Monforte de Lemos 3-5, 28029 Madrid, Spain

29. Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Ronda de Levante 11, 30008, Murcia, Spain.

30. Cancer Epidemiology Unit, Nuffield Department of Population Health University of Oxford, OX3 7LF,Oxford, United Kingdom.

31. Faculty of Medicine, Imperial College London, Norfolk Place, London W2 1PG, London, UK.

32. Hellenic Health Foundation, Kaisareias 13 & Alexandroupoleos, GR-115 27, Athens, Greece.

33. 2nd Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, “ATTIKON” University Hospital, 12462, Haidari, Greece.

34. Epidemiology and Prevention Unit. Fondazione IRCCS Istituto Nazionale dei Tumouri, Via Venezian 1, 20133 Milano-Italy.

35. Unit of Epidemiology, Regional Health Service ASL TO3, 10095 Grugliasco (Turin), Italy.

36. Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Via Pansini 5, 80131, Naples, Italy.

37. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, P.O. Box 85500, 3508 GA Utrecht, The Netherlands.

38. Navarra Public Health Institute, C/Leyre 15, 31003, Pamplona, Spain.

39. Navarra Institute for Health Research (IdiSNA), C/Irunlarrea 3, 31008, Pamplona, Spain.

40. Ministry of Health of the Basque Government, Public Health Division of Gipuzkoa. Biodonostia Research Institute: Paseo Doctor Begiristain s/N, 20014 Donostia/Gipuzkoa, Gipuzkoa, Spain

41. Department of Public Health and Primary Care, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Hills Rd, Cambridge CB2 0SP, United Kingdom.

42. German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114 – 116, 14558 Nuthetal, Germany.

43. Unit of Biomarkers and Susceptibility, Oncology Data Analytics Program, Catalan Institute of Oncology (ICO), Gran Via de L'Hospitalet 199-203, 08908, L’Hospitalet de Llobregat, Barcelona, Spain.

44. ONCOBELL Program, Bellvitge Biomedical Research Institute (IDIBELL), Gran Via de L'Hospitalet 199-203, 08908, L’Hospitalet de Llobregat, Barcelona, Spain.

\*These authors contributed equally to this work

**Corresponding author**:

Leila Luján-Barroso, MSC

Unit of Nutrition and Cancer

Cancer Epidemiology Research Program

Cantaln Institute of Oncology (ICO-IDIBELL)

Avda. Gran Via 199-203

08908 L’Hospitalet de Llobregat, Barcelona, Spain

Tel: +34 93 260 7401

Fax: +34 93 260 7787

email: llujan@iconcologia.net

ORCID: 0000-0001-6224-1764

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# Abstract:

**Background**

Urothelial carcinoma (UC) is the predominant (95%) bladder cancer cell type in industrialised nations. Animal and human studies suggest that hormonal factors may influence UC risk**.**

**Methods**

We used an analytic cohort of 333 919 women from the European Prospective Investigation into Cancer and Nutrition Cohort (EPIC). Associations between exposure variables and incident UC risk were evaluated using Cox proportional hazards models. All models were stratified by age at recruitment and study centre, and adjusted for smoking status and intensity, and fruit and vegetable intakes.

**Results**

During a mean of 15 years of follow-up, 529 women developed UC. A final mutually-adjusted model including number of full-term pregnancies (FTP), menopausal status, and menopausal hormone therapy (MHT) showed an inverse association between number of FTP and UC (HR≥5*vs*1=0.48, 0.25-0.90; *P*-trend in parous women=0.010). MHT-use (compared to non-use) was positively associated with UC (HR=1.27, 1.03-1.57). No modification of HRs by smoking status was observed. Sensitivity analysis in never-smokers showed similar HRs patterns for number of FTP and no association between MHT-use and UC.

**Conclusion**

We observed that increasing number of FTP may reduce UC risk and limited evidence of the role of MHT-use in UC. More detailed studies on parity are needed to understand any effect of perinatal hormone changes in urothelial cells.

**Key words:** Bladder cancer; menopausal hormone therapy; menstrual and reproductive factors; parity; urothelial carcinoma.

# Introduction:

Bladder cancer is the 12th most common cancer in the world, accounting for 4.8% and 1.5% of incident cancers in men and women, respectively(1). In 2018, the estimated male:female sex ratio in Europe was 4.7 to 1(1). The predominant bladder cancer cell type is urothelial carcinoma (UC), accounting for 95% of all cases in industrialise nations(2). Between 50-64% of UC cases in men and 20-50% in women are attributable to tobacco use; and the risk increases with both intensity and duration of smoking(3). Other established risk factors for UC include occupational exposure to aromatic amines and dyes, ingestion of inorganic arsenic via drinking water, a positive family history, and constitutional variants in at least a dozen genes(2,4).

Sex differences in UC incidence may be explained to a large extent by sex differences in the prevalence and intensity of exposure to known risk factors(2). However, several studies suggest that female hormones may have a beneficial effect on UC risk. An experimental animal study that examined effect of the hormones on oncogenesis in male rat bladders suggested that incidence of bladder cancer was higher in the group with testosterone supplementation than in the group with oestrogen supplementation (5). Moreover, castration of male mice and pregnancy and/or lactation in female mice can decrease the growth of bladder cancer(6). Previous epidemiological studies have reported a reduced risk of UC in parous women compared to nulliparous women(7–10); and an increased risk in postmenopausal women, particularly those with an earlier age at menopause(9,11,12). In general, no associations between age at menarche, the use of oral contraceptives (OC), age at first full-term pregnancy, and breastfeeding and UC have been observed(7–17). A meta-analysis by MHT formulation(9), based on four studies, showed a possible reduction in risk of UC in women who used oestrogen plus progestin MHT compared to never users of MHT. Nevertheless, in the Women's Health Initiative (WHI), which included a clinical trial component and an observational study component, no such association was observed(16).

The aim of the present study was to assess the associations between menstrual factors, reproductive history, use of exogenous hormones, and the risk of developing UC, both overall and by tumour grade and by tumour aggressiveness, and accounting for smoking status, within a prospective cohort study of European women.

# Methods:

**Study design and population**

The European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) is an ongoing multicentre cohort study that recruited participants from 23 centres located in ten European countries. At recruitment (baseline), information on diet, lifestyle, and anthropometric measurements was collected. Lifestyle questionnaires included questions on education, occupation, medical history, lifetime history of consumption of tobacco, alcoholic beverages, and physical activity. Questionnaires specific to women were used to collect information on menstrual factors, reproductive history, and use of exogenous hormones. Details on the study design have been described previously(18). A total of 521 324 participants were recruited between 1992 and 2000.

Participants with prevalent cancers, except non-melanoma skin cancer, or participants with missing follow-up information were excluded (n=29 332). Only women were eligible for the present analysis (n=343 985). Women with incomplete information on dietary intake or lifestyle or who had extreme or implausible caloric intake (top or bottom 1% of the ratio of energy intake to estimated energy required(19)) were excluded (n=10 066). After these exclusions, the present analysis included 333 919 women.

**Exposure of interests**

Self-reported menstrual factors, and exogenous hormone use included: age at menarche (<12, 12, 13, 14, >14 years), history (yes/no) and duration of OC use (non-user, >0-≤1, >1-5, >5-10 years), menopausal status at baseline (premenopausal: ≥9 cycles over the past 12 months, perimenopausal: <9 cycles, natural menopause in case of no menses, and surgical menopause in case of bilateral oophorectomy), age at natural menopause (surgical menopause were excluded, ≤46, 47-49, 50-52, ≥53 years) , age at any menopause (surgical and natural, ≤46, 47-49, 50-52, ≥53 years) , MHT-use (yes/no) and duration (non-user, >0-≤1.25, >1.25-4, >4 years), type of MHT (oestrogen alone, progestin alone, or oestrogen plus progestin), oophorectomy (yes/no), hysterectomy (yes/no), and calculated cumulative duration of menstrual cycling. Cumulative duration of menstrual cycling (in years) was calculated as follows: for postmenopausal women, it was the difference between the age at menopause and the age at menarche minus the total time pregnant (number of FTP x 9 months). For pre- and perimenopausal women, cumulative duration of menstrual cycling was the difference between age at recruitment and age at menarche minus the total time pregnant. Total time taking OCs was subtracted from cumulative duration of menstrual cycling(20) for pre-, peri-, and postmenopausal women.

Self-reported reproductive history included: parity (yes/no), number of full-term pregnancies (FTP, including livebirths and stillbirths; 0, 1, 2, 3, 4, ≥5), age at first FTP (in parous women; ≤20, 21-13, 24-25, 26-30, ≥30 years), number of induced (never pregnant, 0, 1, ≥2) and spontaneous abortions (never pregnant, 0, 1, ≥2), breastfeeding (in parous women; yes/no), and duration of breastfeeding (in parous women who breastfeed; 0>-≤3, >3-12, >12 months).

**Endpoint assessments**

Incident bladder cancers were identified through population registries (Denmark, Italy, The Netherlands, Norway, Spain, Sweden, and United Kingdom) and active follow-up, including use of health insurance records, hospital registries, and direct contacts with participants or next-of-kin (France, Germany, and Greece). For these analyses, the follow-up for UC was completed between December 2011 and December 2013, depending on the centre.

 Bladder cancers were defined by ICD-O-3, including first invasive cancer (coded C67 based) and UC (morphology codes 812\*–813\*)(21). Only incident UC was included in the present analyses; since it represents 95% of all bladder cancers. Definitions of UC subtype classifications are heterogeneous in the literature. In previous EPIC studies, UC was classified by pathology reports as aggressive (pT1 and higher or carcinoma *in situ* (CIS) or World Health Organization (WHO) Grade 3), and non-aggressive (pTa Grade 1 and 2)(21). We also analysed UC by tumour grade (using WHO-defined Grades 2 and 3 as “high-grade” and Grade 1 as “low-grade”)(22).

**Statistical analysis**

To evaluate associations between hormonal factors and UC risk, Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95%CI). Ordinal variables were scored and trend tests were calculated on these scores, “unknown” category was excluded for trend test calculation. Age was used as the time scale, with age at recruitment as the entry time, and age at the date of UC or the end of follow-up (whichever came first) as the exit time. Additional models were performed to describe the risk of UC by tumour aggressiveness and tumour grade. All models were stratified by age at recruitment (1 year-categories) and study centre, and adjusted for smoking status and intensity at baseline (never-smokers, current smokers ≤15 cigarettes/day, current smokers >15 cigarettes/day, ex-smokers ≤10 years, ex-smokers >10 years, current: pipe/cigar/occasional cigarette smokers, current/former: missing intensity, and unknown), and fruit (g/d) and vegetable (g/d) intakes(2). Physical activity and body mass index (BMI) were not included as adjustment covariates because they did not change effect estimates >10%. Other potential confounders were occupations at risk of potentially carcinogenic exposures. To adjust models for occupational risks a dichotomous score (yes/no) was defined, where it was coded as “yes” if the participant worked in occupations with exposure to heavy metals (present in foundries, in metal industries, and in occupation related to welding, turning and electroplating), aromatic amines (present in, e.g. dye production, textile and leather dying, and hairdressers), PAHs (polycyclic aromatic hydrocarbons; associated with refineries, asphalt work, the transport sector, and car repair stations), and environmental tobacco smoking (particularly elevated for workers in bars and restaurants), detailed information in Büchner *et al* (2009)(23). Nevertheless, occupation was ultimately not included in the multivariable-adjusted models because <7% of women worked in a potential high-risk job for UC, and adjusting for occupational exposure did not change any estimated HRs. To evaluate all identified factors in one model, mutually-adjusted models were evaluated. The proportional hazard assumption was checked using Schoenfeld residuals. Also, all the time-dependent variables (interactions of predictors and time) were included in the mutually-adjusted model and evaluated.

Modification of the HRs by tobacco use at baseline (never, former, and current) was evaluated using a likelihood ratio test (LRT). Joint effect variables (with a common referent group) for tobacco with each variable included in the final model were also evaluated.

Sensitivity analyses were performed in never smokers to reduce the likelihood of residual confounding by smoking at baseline. Finally, to address possible changes in the reproductive history during the follow-up, a sensitivity analysis including only women with completed reproductive history (peri-/postmenopausal women at recruitment) was performed for the final model.

All statistical tests were two-sided and evaluated at α-level 0.05. All analyses were performed using SAS v. 9.4 (Cary, North Carolina, USA).

# Results:

**Descriptive statistics**

After a median follow-up time of 15 years, 529 UC cases were identified including 146 non-aggressive tumours, 230 aggressive tumours, and 153 with unknown tumour aggressiveness; and among the 529 cases, there were 80 low-grade tumours, 233 high-grade tumours, and 216 with unknown tumour grade. The median age at recruitment was 51 years (y) (25th and 75th percentile (p25-p75): 45-58-y) for the whole cohort and 58-y (p25-p75: 52-63-y) for UC cases. The median age at diagnosis was 68-y (p25-p75: 62-74-y). Baseline characteristics of participants by country are presented in Supplemental Table 1.

**Menstrual factors, and exogenous hormone use**

Age at menarche, cumulative duration of menstrual cycling, history and duration of OC use, age at natural menopause, oophorectomy, and hysterectomy showed no association with UC risk (Table 1). Elevated and statistically significant HRs for UC were observed for postmenopausal status (natural or surgical) compared to premenopausal status (HRnatural*vs*pre: 1.88; 95%CI, 1.09-3.25; HRsurgical*vs*pre: 2.15; 95%CI, 1.10-4.20) (Table 1). MHT use in peri-/postmenopausal women (natural or surgical) was associated with overall UC independently of the duration of MHT use (Table 1). For the 67% (n=52,892, 82 cases) of women with information on formulation of MHT available, 25% (n=13,123, 32 cases) took oestrogen alone (HR: 1.43; 95%CI: 0.97-2.10). No association was observed for use of oestrogen plus progestin MHT formulations (HR: 1.08; 95%CI, 0.77- 1.51) (Table 1).

**Reproductive factors**

There was a statistically significant inverse association for number of FTP and UC risk (HR3*vs*1: 0.70; 95%CI, 0.52-0.94; HR≥5*vs*1FTP: 0.46; 95%CI, 0.25-0.88; *P*-trend in parous women only = 0.008). No statistically significant associations were observed for the other variables in Table 2.

Results on menstrual factors, reproductive factors, and exogenous hormone use by tumour aggressiveness and tumour grade are presented in supplemental table 2.

**Mutually-adjusted Cox proportional hazards regression for UC**

Models included number of FTP and menopausal status, where peri-/postmenopausal women were further classified by MHT history. Statistically significant inverse associations between number of FTP and UC risk were observed (HR3*vs*1: 0.70; 95%CI, 0.52-0.94; HR≥5*vs*1FTP: 0.48; 95%CI, 0.25-0.90; *P*-trend in parous women only 0.010) (Table 3). Further, the HR for peri-/postmenopausal MHT-users compared to peri-/postmenopausal women never-users was 1.27 (95%CI, 1.03-1.57) (Table 3).

**Modification of the HRs by tobacco**

No evidence for modification of HRs for each factor and UC by cigarette smoking status was found (all likelihood ratio statistics *P*-value>0.05) with the exception of induced abortions (*P*-value=0.028). Different estimations of the HR of the number of induced abortions were observed by smoking status. While no association between number of induced abortions and the risk of UC was observed; HR for never smoking women with at least 2 induced abortions compare to 0 abortions was 2.52 (95%CI: 1.33- 4.78, *P*-trend = 0.012) (Supplemental table 3).

No modification of HRs in the mutually-adjusted model by cigarette smoking status was observed. Nonetheless, the higher risk of MHT-use was only observed in peri-/postmenopausal women (natural or surgical) who were smokers at baseline (HR: 1.56; 95%CI: 1.10, 2.21) (Supplemental table 4). No statistically significant associations were observed when joint-effect variables for tobacco and FTP, and tobacco and menopausal status were evaluated.

**Sensitivity analyses**

In general, patterns of HRs did not change substantially when we restricted analyses to the subgroup of never smokers (Supplemental table 3 and Supplemental table 4), nor in the subgroup of participants who were peri-/postmenopausal at recruitment (data not shown).

# Discussion:

The present analyses based on 529 women, showed evidence that women who had experienced more than one birth are at lower risk of developing UC compared to uniparous women; further, we observed evidence of an inverse trend between UC risk and number of births. Furthermore, in peri-/postmenopausal women, MHT-use may increase the risk of UC. No associations were observed for the remaining menstrual factors, reproductive history variables, or exogenous hormone use variables. Never smoking women who had two or more induced abortions were at higher risk of UC compared to women with no abortions.

Previous studies(9,10,16) and two meta-analyses(8,15) observed a reduced risk of UC in parous women, independent of the number of births(8,9,11,12,14–16). Nearly all these studies used “nulliparous” as the referent category(9,11,12,14,15). Nulliparous women likely represent a heterogeneous group that includes women with and women without fertility problems. In our study, “one birth” was used as a referent category, and we found a linear trend of decreasing UC risk with increasing number of FTP. This reduction in risk with increasing FTP was also observed in never-smokers. The observed trend in our study was similar to the trend reported by Weibull et al. (HR for ≥3 vs. 1 FTP: 0.76; 95%CI: 0.68-0.86)(10).

Women experience several hormonal changes during pregnancy, including an increase in oestrogen and progesterone levels(24). An animal study observed that these increased levels, particularly progesterone levels, may be related with changes in the bladder structure related to greater bladder capacity and compliance(25). Further, it has been shown that oestrogen receptors (ER) and progesterone receptors (PR), that mediate oestrogen and progesterone levels, are expressed in both normal and cancerous urothelial cells(26,27). ERs have different roles in cancer biology, in general ER-α has been related with cell growth, while ER-β has been suggested to act as a suppressor of tumour growth, thus ER-α and ER-β may have opposing effects on cellular processes(28). It has been observed that ER-β is the dominant receptor expressed in urothelial carcinoma cells(6,26). Few studies have been done in relation to ERs and progesterone in urothelial carcinoma cells, but it has been suggested that progesterone suppress ER expression during pregnancy(29). [Consequently](http://paperrater.com/vocab_builder/show/consequently), It can be hypothesized that these increased levels of oestrogen and progesterone may reduce UC risk in parous women(7–10,15,30).

Two previous studies have examined the association between induced abortions and the risk of UC (13,31). These two case-control studies did not observe that the number of induced abortion was associated with UC risk. Our results on never-smokers were based in a small number of cases, and in view of the large number of associations tested, the association in never-smokers between induced abortion and UC risk may be due to chance.

It has been hypothesized that earlier age at menopause increases UC risk due to lower levels of oestrogen after menopause(12). Earlier age at menopause (natural or surgical) was associated with an increased risk of UC in a meta-analysis(15), that included 4 case-control studies and 3 cohort studies. We observed no association between earlier age at menopause and UC, in agreement with other recent prospective cohort studies(8,9,16).

The higher UC risk we observed in peri-/postmenopausal MHT users, when compared to peri-/postmenopausal non-users, is inconsistent with previous studies which found no relation(8,15,16). Since no association was observed in never-smokers, and the overall MHT effect only remained significant in current-smokers, residual confounding from tobacco smoking is a likely explanation for our MHT results. The WHI found no influence of the formulation of MHT on the risk of UC (results for oestrogen: n=136 cases; HR: 0.93; 95%CI: 0.74-1.17; results for oestrogen plus progestin: n=103 cases; HR: 1.05; 95%CI: 0.81-1.36)(16). A meta-analysis (based on 4 cohort studies) of MHT by formulation (oestrogen or oestrogen plus progestin) showed a 39% decreased UC risk in users of oestrogen plus progestin (n=84 cases; RR: 0.61; 95%CI: 0.47-0.78), and no effect for users of oestrogen alone (n=217 cases; RR: 1.03; 95%CI: 0.87-1.24)(9). Our results, based on smaller sample sizes (52 UC for oestrogen, and 30 UC for oestrogen plus progestin), were in agreement with those from the WHI.

Our study strengths include its prospective cohort design and a relatively large number of incident cases from 10 European countries, which allowed us to investigate associations by strata of smoking status. To our knowledge, this is the first study on menstrual factors, reproductive history, hormone use, and UC risk that includes information on tumour classification.

One potential weakness of our analysis is that information on reproductive history and hormone use was available only at cohort enrolment; however, we noted that 78.7% of the cases were postmenopausal at recruitment, so reproductive history was essentially complete for most participants. We performed sensitivity analyses restricted to postmenopausal women, whose reproductive exposures were unlikely to change. We observed similar results for the final mutually-adjusted model in the analysis restricted to postmenopausal women as we observed for all study participants. Thus, our results were unlikely to be affected by changes in reproductive history during the follow-up. Another potential weakness of our study was the large number of missing values in the MHT variables (duration and formulation). We observed almost twice of missing MHT information in women diagnosed with UC who were current-smokers than those who were never-smokers. Thus, it seems than current-smokers tended to omit their use of MHT and their risk of UC maybe was underestimated. Also, information on MHT was not periodically updated, and therefore, we could not evaluate risk in women who started using MHT or who modified their use after enrolment. Further, tumour grade and tumour aggressiveness had a large number of missing values which could bias HR estimates. We would also like to highlight that information on smoking habits, and fruit and vegetables intakes were not periodically updated, so habits changes of these variables were not collected during the follow-up. Results from the sensitivity analyses in never smoking women showed that our results in general were not affected by residual confounding by smoking status. Finally, we could not consider occupational exposure in our analysis, as not all EPIC-centres collected such information. Further, occupational exposure was available for 32% (n=169) of UC cases; of which 10% (n=17) reported jobs considered at risk. Despite this, a sensitivity analysis was performed including occupational exposures in the final UC model and similar HR estimates for menopausal status, MHT-use, and number of full-term pregnancies were observed.

# Conclusion:

Our results confirm the increasing benefit of each birth after the first on UC risk. Our results provided little support for the hypothesis that MHT-use lowers the risk of UC. Results from other large cohorts and consortia with a large sample of never-smokers, might help to clarify the evidence provided by this analysis. More studies on number of FTP are needed to elucidate the putative “protective” effects of parity. Further investigations of the role of perinatal hormonal changes and how these changes may affect to ER and PR levels and urothelial cells in the bladder are needed.

# Additional Information:

**Ethics approval and consent to participate:** The EPIC study was performed in accordance with the Declaration of Helsinki. All participants signed an informed consent form, and each centre obtained approval from the local Ethics Committee.

**Consent for publication:** Not applicable.

**Data availability:** Dataset of the study can be found with the corresponding author.

**Conflict of interest:** The authors declare that they have no conflicts of interest.

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**Author’s contribution**

LLB, EB, SC, EW, and EJD analyzed and interpreted the data. LLB, EW, and EJD wrote the manuscript. BL, NR, AT, BBdM, ITG, RT, LAK, FL, TS, MG, NM, IC, AF,MK, CH, KO, EL, MW, RTF, TK, VM, MJS, CS, APC, RZR, AJC, AT, AK, EP, DP, VK, VS, AM, SP, CHvG, NCOM, AB, PA, KTK, HB, and EW collected the data and provided critical comments on the manuscript.

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Table 1: Multivariable-adjusted models for each individual menstrual factor, and exogenous hormone use in relation to UC risk in EPIC Women.

|  |  |  |
| --- | --- | --- |
|  |  | **Overall** |
|  | **Person-years** | **Cases (%)****n=529** | **HR (95%CI) a** |
| **Age at menarche, years** |  |  |  |
| **<12** | 678 236 | 64 (12.1) | 1.00 (referent) |
| **12** | 955 271 | 103 (19.5) | 1.10 (0.80- 1.51) |
| **13** | 1 166 665 | 128 (24.2) | 1.05 (0.78- 1.43) |
| **14** | 976 383 | 108 (20.4) | 0.92 (0.67- 1.26) |
| **>14** | 718 342 | 113 (21.4) | 1.07 (0.78- 1.48) |
| **Unknown** | 166 304 | 13 (2.5) |  |
| ***P* trend** |  |  | 0.845 |
| **Cumulative duration of menstrual cycling, accounting for OC use, years b** |  |  |  |
|  |  |  |
| **<23** | 960 018 | 72 (13.6) | 1.00 (referent) |
| **23- <30** | 693 105 | 96 (18.2) | 1.01 (0.73- 1.39) |
| **30- <35** | 920 740 | 108 (20.4) | 0.87 (0.63- 1.21) |
| **≥35** | 805 979 | 142 (26.8) | 1.00 (0.71- 1.40) |
| **Unknown** | 1 011 360 | 111 (21.0) | 1.05 (0.74- 1.48) |
| ***P* trend** |  |  | 0.924 |
| **Use of OC** |  |  |  |
| **No** | 1 859 302 | 278 (52.6) | 1.00 (referent) |
| **Yes** | 2 668 828 | 239 (45.2) | 0.93 (0.77- 1.14) |
| **Unknown** | 133 072 | 12 (2.3) |  |
| **Duration OC use, years**  |  |  |  |
| **No** | 1 859 302 | 278 (52.6) | 1.00 (referent) |
| **>0- ≤1** | 495 753 | 34 (6.4) | 0.70 (0.49- 1.01) |
| **>1- 5** | 780 263 | 63 (11.9) | 0.94 (0.71- 1.26) |
| **>5- 10** | 594 859 | 69 (13.0) | 1.22 (0.92- 1.63) |
| **>10** | 546 567 | 51 (9.6) | 0.82 (0.59- 1.13) |
| **Unknown duration** | 251 386 | 22 (4.2) |  |
| **Missing use of OC** | 133 072 | 12 (2.3) |  |
| ***P* trend** |  |  | 0.259 |
| **Menopausal status** |  |  |  |
| **Premenopausal** | 1 654 703 | 49 (9.3) | 1.00 (referent) |
| **Perimenopausal** | 896 065 | 64 (12.1) | 1.32 (0.77- 2.8) |
| **Natural postmenopausal** | 1 992 700 | 394 (74.5) | 1.88 (1.09- 3.25) |
| **Surgical postmenopuasal** | 117 733 | 22 (4.2) | 2.15 (1.10- 4.20) |
| **Age at natural menopause, years c** |  |  |  |
| **≤46** | 385 834 | 85 (21.6) | 1.17 (0.87- 1.58) |
| **47- 49** | 337 177 | 68 (17.3) | 1.08 (0.79- 1.48) |
| **50 - 52** | 509 460 | 97 (24.6) | 1.00 (referent) |
| **≥53** | 305 850 | 79 (20.1) | 1.33 (0.99- 1.80) |
| **Unknown** | 454 379 | 65 (16.5) | 1.21 (0.86- 1.70) |
| ***P* trend** |  |  | 0.527 |
| **Age at any menopause, years** |  |  |  |
| **≤46** | 450 220 | 100 (24.0) | 1.21 (0.91- 1.60) |
| **47- 49** | 360 268 | 70 (16.8) | 1.04 (0.76- 1.42) |
| **50 - 52** | 527 478 | 101 (24.3) | 1.00 (referent) |
| **≥53** | 315 160 | 80 (19.6) | 1.31 (0.97- 1.77) |
| **Unknown** | 457 307 | 65 (15.6) | 1.20 (0.86- 1.68) |
| ***P* trend** |  |  | 0.853 |
| **Use of MHT d** |  |  |  |
| **No** | 1 740 862 | 247 (51.5) | 1.00 (referent) |
| **Yes** | 1 072 357 | 172 (35.8) | 1.28 (1.04- 1.58) |
| **Unknown** | 193 278 | 61 (12.7) | 1.32 (0.90- 1.95) |
| **Duration MHT use, years d** |  |  |  |
| **No** | 1 740 862 | 247 (51.5) | 1.00 (referent) |
| **>0- ≤1.25** | 321 348 | 51 (10.6) | 1.33 (0.98- 1.81) |
| **>1.25-4** | 336 578 | 47 (9.8) | 1.37 (0.99- 1.90) |
| **>4** | 310 366 | 56 (11.7) | 1.27 (0.93- 1.73) |
| **Unknown duration** | 104 065 | 18 (3.8) |  |
| **Unknown use of MHT** | 193 278 | 61 (12.7) | 1.03 (0.74- 1.43) |
|  ***P* trend** |  |  | 0.152 |
| **Type of MHT  d, e** |  |  |  |
| **Non-users of MHT** | 1 527 202 | 215 (58.0) | 1.00 (referent) |
| **Oestrogen alone** | 178 339 | 32 (8.6) | 1.43 (0.97- 2.10) |
| **Oestrogen + Progestin** | 527 153 | 50 (13.5) | 1.08 (0.77- 1.51) |
| **Unknown type of MHT** | 329 620 | 74 (20.0) | 1.37 (1.04- 1.81) |
| **Oophorectomy f** |  |  |  |
| **No** | 3 407 081 | 344 (76.1) | 1.00 (referent) |
| **Unilateral** | 145 533 | 28 (6.2) | 1.32 (0.90- 1.95) |
| **Bilateral** | 131 175 | 23 (5.1) | 1.12 (0.73- 1.72) |
| **Unknown if unilateral or bilateral** | 11 831 | 2 (0.4) |  |
| **Unknown** | 965 580 | 55 (12.2) | 0.91 (0.47- 1.78) |
| **Hysterectomy f** |  |  |  |
| **No** | 3 640 275 | 344 (76.1) | 1.00 (referent) |
| **Yes** | 472 260 | 76 (16.8) | 1.09 (0.84- 1.40) |
| **Unknown** | 548 667 | 32 (7.1) |  |

UC: Urothelial Carcinoma // OC: oral contraceptive // MHT: menopause hormone therapy

Estimation of “Unknown” category is provided when more than 10% of the cases are classified as “Unknown”.

a Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity, fruits and vegetables intake.

b Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity, fruits and vegetables intake, OC use, and full-term pregnancies

c Women who had surgical menopause were excluded.

d In peri- and postmenopausal (natural or surgical).

e Available in France, Italy, Spain, United kingdom, The Netherlands, Germany, Denmark, and Norway.

f Available in all centres except Malmö.

Table 2: Multivariable-adjusted models for each individual reproductive factor in relation to UC risk in EPIC Women.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Person-years** | **Cases (%)****n=529** | **HR (95%CI)a** |
| **Parity** |  |  |  |
| **No**  | 686 624 | 73 (13.8) | 1.00 (referent) |
| **Yes** | 3 774 138 | 440 (83.2) | 0.87 (0.68- 1.12) |
| **Unknown** | 200 439 | 16 (3.0) |  |
| **Number of full-term pregnancies b** |  |  |  |
| **0 c** | 686 624 | 69 (13.5) | 0.92 (0.67- 1.25) |
| **1** | 663 853 | 99 (19.4) | 1.00 (referent) |
| **2** | 1 787 539 | 192 (37.6) | 0.80 (0.62- 1.02) |
| **3** | 845 995 | 89 (17.4) | 0.70 (0.52- 0.94) |
| **4** | 253 868 | 35 (6.9) | 0.79 (0.53- 1.18) |
| **≥5** | 110 467 | 11 (2.2) | 0.47 (0.25- 0.88) |
| **Unknown parity** | 200 439 | 16 (3.1) |  |
| ***P-*trendd** |  |  | 0.008 |
| **Age at first full-term pregnancy, years d** |  |   |   |
| **≤20**  | 546 150 | 68 (15.5) | 1.00 (referent) |
| **21- 23**  | 1 001 554 | 119 (27.1) | 1.03 (0.76- 1.40) |
| **24- 25**  | 742 124 | 73 (16.6) | 0.86 (0.61- 1.20) |
| **26- 30**  | 1 086 162 | 139 (31.6) | 1.03 (0.76- 1.39) |
| **≥30**  | 382 435 | 40 (9.1) | 0.89 (0.59- 1.32) |
| **Unknown**  | 15 713 |  1 (0.2) |   |
|  **P-trend** |  |  | 0.688 |
| **Breastfeeding d, e** |  |   |   |
|  **No** | 523 624 | 57 (14.1) | 1.00 (referent) |
|  **Yes** | 2 984 829 | 341 (83.8) | 0.85 (0.64- 1.14) |
| **Unknown** | 63 513 | 9 (2.2) |   |
| **Duration of breastfeeding, all pregnancies, months e, f** |  |   |   |
| **>0-≤3**  | 854 602 | 115 (33.7) | 1.00 (referent) |
| **>3- 12** | 1 327 975 | 142 (41.6) | 0.73 (0.56- 0.95) |
| **>12**  | 771 517 | 79 (23.2) | 0.78 (0.55- 1.09) |
| **Unknown** | 31 193 |  5 (1.5) |   |
|  **P-trend** |  |  | 0.092 |
| **Induced abortions g** |  |  |  |
| **Never pregnant** | 483 030 | 48 (12.4) | 1.19 (0.91- 1.56) |
| **0** | 2 466 069 | 269 (69.7) | 1.00 (referent) |
| **1** | 404 767 | 45 (11.7) | 1.12 (0.81- 1.56) |
| **≥2** | 176 646 | 19 (4.9) | 1.01 (0.62- 1.64) |
| **Unknown** | 69 032 | 5 (1.3) |  |
| ***P-*trend** |  |  | 0.759 |
| **Spontaneous abortions h** |  |  |  |
| **Never pregnant** | 508 626 | 56 (12.1) | 1.14 (0.85- 1.52) |
| **0** | 2 469 123 | 295 (63.7) | 1.00 (referent) |
| **1** | 587 558 | 78 (16.9) | 1.10 (0.86- 1.42) |
| **≥2** | 200 186 | 27 (5.8) | 1.05 (0.71- 1.56) |
| **Unknown** | 73 119 | 7 (1.5) |  |
| ***P*-trend** |  |  | 0.497 |
| **Infertility problems i** |  |  |  |
| **No** | 2 872 888 | 255 (83.3) | 1.00 (referent) |
| **Yes** | 142 531 | 16 (5.2) | 1.61 (0.97- 2.69) |
| **Unknown** | 151 702 | 35 (11.4) | 1.72 (0.24- 12.51) |

UC: Urothelial Carcinoma

Estimation of “Unknown” category is provided when more than 10% of the cases are classified as “Unknown”.

a Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity, fruits and vegetables intake.

b Available in all centres except Bilthoven.

c Including nulliparous women and women without full-term pregnancies.

d In parous women.

e Available in all centres except Bilthoven and Umeå.

f In parous women who has ever breastfed.

g Available in all centres except Bilthoven, Malmö, Umeå, and Norway.

h Available in all centres except Bilthoven, Umeå, and Norway.

i Available in France, Italy, Spain, United Kingdom, Utrecht, Greece, and Germany.

Table 3: Mutually-adjusted models for menopause status, MHT, and parity, and UC

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall** |  |  | **Never smokers** |
|  | **Cases** **(%)** | **HR (95%CI)a** |  | **Cases** **(%)** | **HR (95%CI)b** |
| **Full cohort** | n=529 |  |  | n=195 |  |
|  **Menopausal status & use of MHT** |  |  |  |  |  |
| **Premenopausal**  | 49(9.26) | 0.73 (0.43- 1.22) |  | 18 (9.23) | 1.23 (0.52- 2.43) |
| **Peri-/Postmenopausal & non-users of MHT** | 247(46.7) | 1.00 (referent) |  | 105 (53.9) | 1.00 (referent) |
| **Peri-/Postmenopausal & users of MHT** | 172(32.5) | 1.27 (1.03- 1.57) |  | 52 (26.7) | 1.02 (0.71- 1.47) |
| **Peri-/Postmenopausal & unknown MHT-use** | 61 (11.5) | 1.35 (0.88- 2.07) |  | 20 (10.26) | 1.12 (0.53- 2.39) |
|  **Number of full-term pregnancies c** |  |  |  |  |  |
| **0 d** | 69 (13.5) | 0.92 (0.67- 1.25) |  | 19(9.7) | 0.72 (0.40- 1.29) |
| **1** | 99 (19.4) | 1.00 (referent) |  | 32 (16.4) | 1.00 (referent) |
| **2** | 192 (37.6) | 0.80 (0.62- 1.02) |  | 83 (42.6) | 0.95 (0.63- 1.45) |
| **3** | 89 (17.4) | 0.70 (0.52- 0.94) |  | 39 (20.0) | 0.85 (0.52- 1.37) |
| **4** | 35(6.9) | 0.80 (0.54- 1.19) |  | 9(4.6) | 0.57 (0.27- 1.21) |
| **≥5** | 11(2.2) | 0.48 (0.25- 0.90) |  | 5(2.6) | 0.49 (0.18- 1.29) |
| **Unknown parity** | 16(3.1) |  |  | 8(4.1) |  |
| **Information not available**  | 18 |  |  |  |  |
| ***P*-trend e** |  | 0.010 |  |  | 0.069 |

UC: Urothelial Carcinoma // MHT: menopausal hormone therapy

a Cox proportional hazards model stratified by centre and age at recruitment and adjusted by menopausal status and MHT, number of full-term pregnancies, smoking status and intensity, fruits and vegetables intake.

b Cox proportional hazards model stratified by centre and age at recruitment and adjusted by menopausal status and MHT, number of full-term pregnancies, fruits and vegetables intake.

c Available in all centres have information except Bilthoven.

d Including nulliparous women and women without full-term pregnancies.

e In parous women

Supplemental Table 1: Baseline characteristics of women in the EPIC cohort by country

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | **Cohort****(n= 333 919)** | **France****(n= 67 403)** | **Italy** **(n= 30 513)** | **Spain****(n= 24 850)** | **United** **Kingdom****(n= 52 566)** | **The** **Netherlands****(n= 26 912)** | **Greece****(n= 15 233)** | **Germany****(n= 27 379)** | **Sweden****(n= 26 368)** | **Denmark****(n= 28 720)** | **Norway****(n= 33 975)** |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **Urothelial Carcinoma cases** | 529 | 40 | 72 | 32 | 68 | 80 | 7 | 25 | 105 | 80 | 20 |
| **Age at recruitment(years)a** | 51(45- 58) | 51(47- 57) | 51(44- 57) | 48(41- 55) | 48(36- 58) | 53(46- 59) | 54(43- 64) | 48(41- 57) | 51(47- 60) | 56(53- 60) | 48(44- 52) |
| **Age at diagnosis(years)a** | 68(62- 74) | 65(60- 71) | 65(59- 71) | 64(57- 71) | 63(52- 73) | 67(59- 73) | 65(54- 75) | 59(52- 67) | 69(60- 78) | 72(68- 76) | 61(58- 65) |
| **BMI(kg/m2)a** | 24.1(21.9- 27.2) | 22.5(20.8- 24.7) | 25.0(22.6- 27.9) | 27.5(24.7- 30.9) | 23.4(21.4- 26.1) | 24.5(22.3- 27.3) | 28.2(24. 8- 31.6) | 24.7(22.3- 28.0) | 24.1(21. 9- 27.0) | 24.8(22.5- 27.8) | 23.8(21.8- 26.2) |
| **Physical activity b** |  |  |  |  |  |  |  |  |  |  |  |
| **Inactive** | 73 114(21.9) | 12 623(18.7) | 11 201(36.7) | 12 071(48.6) | 12 581(23.9) | 1 897(7.1) | 8 157(53.6) | 4 756(17.4) | 5 532(21.0) | 3 050(10.6) | 1 246(3.7) |
| **Moderately inactive** | 113 292(33.9) | 26 969(40.0) | 11 940(39.1) | 8 745(35.2) | 18 867(35.9) | 6 410(23.8) | 3 997(26.2) | 10 378(37.9) | 9 480(36.0) | 9 235(32.2) | 7 271(21.4) |
| **Moderately active** | 90 980(27.3) | 21 813(32.4) | 4 557(14.9) | 2 983(12.0) | 12 075(23.0) | 6 480(24.1) | 2 460(16.2) | 7 110(26.0) | 6 912(26.2) | 7 148(24.9) | 19 442(57.2) |
| **Active** | 50 782(15.2) | 5 998(8.9) | 2 815(9.2) | 1 051(4.2) | 8 056(15.3) | 9 399(34.9) | 619(4.1) | 5 129(18.7) | 4 400(16.7) | 9 265(32.3) | 4 050(11.9) |
| **Unknown** | 5 751(1.7) |  |  |  | 987(1.9) | 2 726(10.1) |  | 6(0.02) | 44(0.2) | 22(0.1) | 1 966(5.8) |
| **Smoking status b** |  |  |  |  |  |  |  |  |  |  |  |
| **Never** | 186 228(55.8) | 44 938(66.7) | 16 376(53.7) | 17 740(71.4) | 31 544(60.0) | 10 984(40.8) | 11 144(73.2) | 15 333(56.0) | 13 957(52.9) | 12 563(43.7) | 11 649(34.3) |
| **Former** | 75 216(22.5) | 12 896(19.1) | 6 162(20.2) | 2 446(9.8) | 14 457(27.5) | 8 425(31.3) | 816(5.4) | 7 017(25.6) | 6 004(22.8) | 7 074(24.6) | 9 919(29.2) |
| **Current** | 64 756(19.4) | 5 807(8.6) | 7 974(26.1) | 4 652(18.7) | 5 543(10.5) | 7 409(27.5) | 2 594(17.0) | 4 980(18.2) | 6 282(23.8) | 9 021(31.4) | 10 494(30.9) |
| **Unknown** | 7 719(2.3) | 3 762(5.6) | 1(0.0) | 12(0.1) | 1 022(1.9) | 94(0.4) | 679(4.5) | 49(0.2) | 125(0.5) | 62(0.2) | 1 913(5.6) |
| **Smoking status and intensity b** |  |  |  |  |  |  |  |  |  |  |  |
| **Never** | 161 061(48.2) | 25 164(37.3) | 12 657(41.5) | 17 740(71.4) | 31 544(60.0) | 10 938(40.6) | 1 1101(72.9) | 15 333(56.0) | 12 436(47.2) | 12 563(43.7) | 11 585(34.1) |
| **Current ≤15 cigarettes/day** | 40 802(12.2) | 2 971(4.4) | 4 611(15.1) | 2 950(11.9) | 3 675(7.0) | 4 435(16.5) | 1 425(9.4) | 3 491(12.8) | 4 482(17.0) | 5 978(20.8) | 6 784(20.0) |
| **Current >15 cigarettes/day** | 21 318(6.4) | 1 924(2.9) | 3 360(11.0) | 1 660(6.7) | 1 409(2.7) | 2 540(9.4) | 1 162(7.6) | 1 467(5.4) | 1 512(5.7) | 2 954(10.3) | 3 330(9.8) |
| **Former quit ≤ 10 years** | 27 394(8.2) | 3 628(5.4) | 2 959(9.7) | 1 473(5.9) | 4 887(9.3) | 3 011(11.2) | 478(3.1) | 2 363(8.6) | 2 349(8.9) | 2 322(8.1) | 3 924(11.6) |
| **Former quit >10 years** | 44 918(13.5) | 8 581(12.7) | 3 188(10.5) | 936(3.8) | 8 977(17.1) | 5 215(19.4) | 298(2.0) | 4 361(15.9) | 3 482(13.2) | 4 268(14.9) | 5 612(16.5) |
| **Current, pipe/cigar/occasional** **cigarette smokers** | 27 610(8.3) | 21 818(32.4) | 3 719(12.2) | 13(0.1) | 145(0.3) | 46(0.2) | 44(0.3) | 21(0.1) | 1 672(6.3) | 68(0.2) | 64(0.2) |
| **Current/Former, missing** | 4 854(1.5) | 1 312(2.0) | 18(0.1) | 66(0.3) | 907(1.7) | 633(2.4) | 46(0.3) | 294(1.1) | 310(1.2) | 505(1.8) | 763(2.3) |
| **Unknown** | 5 962(1.8) | 2 005(3.0) | 1(0.0) | 12(0.1) | 1022(1.9) | 94(0.4) | 679(4.5) | 49(0.2) | 125(0.5) | 62(0.2) | 1 913(5.6) |
| **Vegetables intake(g/day)a** | 186(118-286) | 264(189-356) | 162(109-232) | 216(138-315) | 256(186-347) | 127(98-162) | 412(317-527) | 117(89-156) | 119(70-184) | 172(112-244) | 126(87-179) |
| **Fruit intake(g/day)a** | 216(125-332) | 242(153-339) | 320(221-443) | 286(176-436) | 229(143-345) | 195(123-288) | 344(244-457) | 126(92-204) | 179(114-269) | 172(100-276) | 138(79-219) |
| **Job exposure b, c, d** |  |  |  |  |  |  |  |  |  |  |  |
| **No** | 100 681(93.6) |  |  | 23 673(95.3) | 10 971(94.8) |  | 14 730(96.9) | 24 900(91.0) |  | 26 407 (92.3) |  |
| **Yes** | 6 920(6.4) |  |  | 1 177(4.7) | 599(5.2) |  | 465(3.1) | 2 479(9.1) |  | 2 200(7.7) |  |
| **Diabetes b** |  |  |  |  |  |  |  |  |  |  |  |
| **No** | 300 864(97.3) | 65 960 (98.0) | 29 846 (97.9) | 23 681(95.5) | 35 647(98.3) | 26 229(97.8) | 14 182(93.3) | 26 590(97.1) | 24 437(98.2) | 27 117(94.8) | 27 175(98.5) |
| **Yes** | 7 422(2.4) | 1 379 (2.1) | 633(2.1) | 1 124(4.5) | 633(1.7) | 581(2.2) | 1 016(6.7) | 775(2.8) | 445(1.8) | 430(1.5) | 406(1.5) |
| **Do not known** | 1 078(0.4) |  |  |  |  |  |  | 8(0.03) |  | 1 070(3.7) |  |

UC: Urothelial Carcinoma // BMI: Body mass index

a Median(percentile 25th and percentile 75th)

b n (%)

c Available in Spain, Cambridge, Greece, Germany, and Denmark, Germany.

d Job exposure was coded as “yes” if the participant worked exposure to heavy metals, aromatic amines, polycyclic aromatic hydrocarbons, and environmental tobacco smoking.

Supplemental Table 2: Reproductive factors, menstrual, menopausal factors, and exogenous hormone use in relation to UC by aggressiveness and by grade in EPIC Women.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | **Nonaggressive (n=146)** | **Aggressive (n=230)** | **Low-Grade (n=80)** | **High-Grade (n=233)** |
|   | **Cases (%)** | **HR (95%CI) a** | **Cases (%)** | **HR (95%CI) a** | **Cases (%)** | **HR (95%CI) a** | **Cases (%)** | **HR (95%CI) a** |
| **Age at menarche, years** |   |   |   |   |   |   |   |   |
| **<12**  | 12 (8.4) | 1.00 (referent) | 33 (14.4) | 1.00 (referent) | 10(12.5) | 1.00 (referent) | 25(10.7) | 1.00 (referent) |
| **12** | 26 (17.8) | 1.39 (0.70- 2.76) | 45 (19.6) | 0.96 (0.61- 1.51) | 7( 8.8) | 0.47(0.18-1.24) | 51(21.9) | 1.41(0.87-2.29) |
| **13** | 37 (25.3) | 1.64 (0.85- 3.17) | 55 (23.9) | 0.91 (0.59- 1.41) | 23(28.8) | 1.29(0.61-2.75) | 60(25.8) | 1.36(0.85-2.19) |
| **14** | 36 (24.7) | 1.74 (0.90- 3.39) | 45 (19.6) | 0.74 (0.47- 1.18) | 20(25.0) | 1.26(0.58-2.76) | 50(21.5) | 1.23(0.75-2.00) |
| **>14**  | 32 (21.9) | 1.80 (0.91- 3.57) | 47 (20.4) | 0.81 (0.51- 1.29) | 19(23.8) | 1.46(0.65-3.24) | 41(17.6) | 1.13(0.68-1.89) |
| **Unknown**  | 3 (2.1) |   | 5 (2.2) |   | 1 (1.3) |   | 6 (2.6) |   |
| ***P*-trend** |   | 0.075 |   | 0.188 |   | 0.057 |   | 0.903 |
| **Cumulative duration of menstrual cycling, accounting for OC use, years b** |   |   |   |   |   |   |   |   |
| **<23**  | 17 (11.6) | 1.00 (referent) | 29 (12.6) | 1.00 (referent) | 9(11.3) | 1.00 (referent) | 28(12.0) | 1.00 (referent) |
| **23- <30**  | 31 (21.2) | 1.29 (0.70- 2.36) | 41 (17.8) | 1.09 (0.67- 1.78) | 18(22.5) | 1.59(0.69-3.65) | 44(18.9) | 0.98(0.60-1.59) |
| **30- <35**  | 32 (21.9) | 1.14 (0.62- 2.12) | 47 (20.4) | 0.94 (0.58- 1.53) | 19(23.8) | 1.48(0.63-3.46) | 42(18.0) | 0.74(0.45-1.22) |
| **≥35**  | 37 (25.3) | 1.14 (0.61- 2.12) | 63 (27.4) | 1.17 (0.73- 1.87) | 21(26.2) | 1.57(0.66-3.71) | 65(27.9) | 0.99(0.61-1.61) |
| **Unknown**  | 29 (18.9) |  1.19 (0.60-2.35) | 50 (21.7) |  1.01 (0.61- 1.67) | 13 (16.3) |  1.53 (0.59-3.98) | 54 (23.2) | 1.01 (0.60- 1.71) |
| ***P*-trend** |   | 0.396 |   | 0.610 |   |  0.348 |   | 0.982 |
| **Use of OC** |   |   |   |   |   |   |   |   |
| **No** | 80 (54.8) | 1.00 (referent) | 123 (53.5) | 1.00 (referent) | 38(47.5) | 1.00 (referent) | 137(58.8) | 1.00 (referent) |
| **Yes** | 65 (44.5) | 0.79 (0.54- 1.15) | 103 (44.8) | 0.90 (0.67- 1.21) | 42(52.5) | 0.98(0.59-1.63) | 94(40.3) | 0.80(0.59-1.08) |
| **Unknown** | 1 (0.7) |   | 4 (1.7) |   |   |   | 2(0.9) |   |
| **Duration OC use, years**  |  |  |  |  |  |  |  |  |
| **No** | 80 (54.8) | 1.00 (referent) | 123 (53.5) | 1.00 (referent) | 38 (47.5) | 1.00 (referent) | 137 (58.8) | 1.00 (referent) |
| **>0- ≤1** | 6 (4.1) | 0.40 (0.17- 0.82) | 19 (8.3) | 0.84 (0.51- 1.39) | 5 (6.3) | 0.65 (0.25- 1.70) | 14 (6.0) | 0.57 (0.32-1.00) |
| **>1- 5** | 16 (11.0) | 0.79 (0.45- 1.40) | 24 (10.4) | 0.85 (0.54- 1.35) | 10 (12.5) | 0.94 (0.45- 1.98) | 19 (8.2) | 0.65 (0.39- 1.07) |
| **>5- 10** | 19 (13.0) | 1.03 (0.60- 1.78) | 28 (12.2) | 1.12 (0.72- 1.74) | 15 (18.8) | 1.53 (0.79- 2.99) | 25 (10.7) | 0.96 (0.61- 1.52) |
| **>10** | 17 (11.6) | 0.86 (0.48- 1.53) | 22 (9.6) | 0.74 (0.46- 1.21) | 6 (7.5) | 0.41 (0.20- 1.31) | 25 (10.7) | 0.93 (0.58- 1.50) |
| **Unknown duration** | 7 (4.8) |  | 10 (4.4) |  | 6 (7.5) |  | 11 (4.7) |  |
| **Unknown use of OC** | 1 (0.7) |  | 4 (1.7) |  |  |  | 2 (0.9) |  |
| ***P* trend** |  | 0.769 |  | 0.469 |  | 0.712 |  | 0.549 |
| **Menopausal status** |   |   |   |   |   |   |   |   |
| **Premenopausal** | 18 (12.3) | 1.00 (referent) | 15 (6.5) | 1.00 (referent) | 12(15.0) | 1.00 (referent) | 23( 9.9) | 1.00 (referent) |
| **Perimenopausal** | 21 (14.4) | 0.87 (0.37- 2.04) | 22 (9.6) | 1.64 (0.67- 4.00) | 15(18.8) | 1.19(0.39-3.58) | 25(10.7) | 1.56(0.71-3.43) |
| **Natural postmenopausal** | 102 (69.9) | 1.26 (0.52- 3.02) | 180 (78.3) | 2.47 (1.01- 6.03) | 51(63.8) | 1.16(0.35-3.81) |  175(75.1) | 1.60(0.60-4.22) |
| **Surgical postmenopuasal** |  5 (3.4) | 1.11 (0.33- 3.75) | 13 (5.7) | 3.25 (1.18- 8.97) | 2( 2.5) | 0.80(0.13-4.81) | 10( 4.3) | 1.08(0.50-2.36) |
| **Age at natural menopause, years c** |   |   |   |   |   |   |   |   |
| **≤46**  | 21 (20.6) | 1.14 (0.64- 2.05 | 39 (21.7) | 1.14 (0.73- 1.76) | 8(15.7) | 0.84 (0.35- 2.02) | 39(22.3) | 1.16 (0.75- 1.79) |
| **47- 49** | 23 (22.6) | 1.40 (0.79- 2.47) | 28 (15.6) | 1.00 (0.62- 1.63) | 12(23.5) | 1.32 (0.60- 2.89) | 25(14.3) | 0.87 (0.53- 1.43) |
| **50 - 52**  | 26 (25.5) | 1.00 (referent) | 43 (23.9) | 1.00 (referent) | 14(27.5) | 1.00 (referent) | 45(25.7) | 1.00 (referent) |
| **≥53**  | 16 (15.7) | 1.01 (0.54- 1.91) | 40 (22.2) | 1.49 (0.96- 2.31) | 10(19.6) | 1.21 (0.52- 2.79) | 36(20.6) | 1.35 (0.86- 2.10) |
| **Unknown**  | 16 (15.7) | 1.26 (0.63- 2.51) | 30 (16.7) |  1.18 (0.72- 1.95) | 7 (13.7) |  1.11 (0.41- 3.06) | 30(17.1) | 1.26 (0.76- 2.09) |
| ***P*-trend** |   | 0.688 |   | 0.324 |   | 0.53 |   | 0.571 |
| **Age at menopause, years** |  |  |  |  |  |  |  |  |
| **≤46**  | 24 (22.4) | 1.14 (0.65- 2.0) | 49 (25.4) | 1.19 (0.79- 1.80) | 9 (17.0) | 0.83 (0.36- 1.96) | 47 (25.4) | 1.17 (0.76- 1.76) |
| **47- 49** | 24 (22.4) | 1.37 (0.78- 2.38) | 28 (14.5) | 0.92 (0.57- 1.47) | 13 (24.5) | 1.37 (0.64- 2.95) | 25 (13.5) | 0.82 (0.50- 1.34) |
| **50 - 52**  | 27 (25.2) | 1.00 (referent) | 46 (23.8) | 1.00 (referent) | 14 (26.4) | 1.00 (referent) | 47 (25.4) | 1.00 (referent) |
| **≥53**  | 16 (15.0) | 0.98 (0.52- 1.83) | 40 (20.7) | 1.43 (0.93- 2.20) | 10 (18.9) | 1.21 (0.53- 2.79) | 36 (19.5) | 1.30 (0.83- 2.02) |
| **Unknown**  | 16 (15.0) | 1.31 (0.66- 2.60) | 30 (15.5) | 1.11 (0.68- 1.82) | 7 (13.2) | 1.20 (0.44- 3.29) | 30 (16.2) | 1.24 (0.75- 2.05) |
| ***P*-trend** |  | 0.635 |  | 0.479 |  | 0.532 |  | 0.681 |
| **Use of MHT d** |   |   |   |   |   |   |   |   |
| **No** | 60 (46.9) | 1.00 (referent) | 122 (56.7) | 1.00 (referent) | 28(41.2) | 1.00 (referent) | 124(62.9) | 1.00 (referent) |
| **Yes** | 53 (41.4) | 1.93 (1.29- 2.87) | 85 (39.5) | 1.27 (0.94- 1.71) | 31(45.6) | 2.37(1.37-4.12) | 73(37.1) | 1.33(0.97-1.82) |
| **Unknown** | 15 (11.7) |  1.72 (0.76-3.87) | 8 (3.7) |   | 9(13.2) | 2.93 (0.94- 9.11) | 13(6.2) |   |
| **Duration MHT use, years d** |   |   |   |   |   |   |   |   |
| **No** | 60 (46.9) | 1.00 (referent) | 122 (56.7) | 1.00 (referent) | 28 (41.2) | 1.00 (referent) | 124 (59.1) | 1.00 (referent) |
|  **≤1.25** | 19 (14.8) | 2.31 (1.35- 3.94) | 22 (10.2) | 1.11 (0.70-1. 77) | 15(22.1) | 3.77 (1.95- 7.31) | 19(9.1) | 1.10 (0.67-1.80) |
| **>1.25-4** | 12 (9.4) | 1.47 (0.77- 2.80) | 27 (12.6) | 1.60 (1.03- 2.48) | 9(13.2) | 2.28 (1.03- 5.04) | 18( 8.6) | 1.16 (0.69- 1.94) |
| **>4** | 17 (13.3) | 2.32 (1.29- 4.17) | 29 (13.5) | 1.11 (0.72- 1.72) | 6(8.8) | 1.79 (0.70- 4.60) | 24(11.4) | 1.48 (0.92- 2.38) |
| **Unknown duration** | 5 (3.9) |  | 7 (3.3) |   | 1(1.5) |   | 12 (5.7) |   |
| **Unknown use of MHT** | 15 (11.7) | 1.56 (0.67- 3.61) | 8 (3.7) |  | 9(13.2) | 2.26 (0.68- 7.49) | 13 (6.2) |  |
|  ***P*-trend** |  | 0.002 |  | 0.242 |  | 0.023 |  | 0.100 |
| **Type of MHT d, e** |   |   |   |   |   |   |   |   |
| **Non-users of MHT** | 55 (53.4) | 1.00 (referent) | 111 (58.4) | 1.00 (referent) | 26(48.2) | 1.00 (referent) | 114(64.0) | 1.00 (referent) |
| **Oestrogen alone** | 7 (6.8) | 1.47 (0.65- 3.30) | 19 (10.0)  | 1.59 (0.96- 2.64) | 5(9.3) | 2.59 (0.97- 6.95) | 13(7.3) | 1.26(0.69-2.28) |
| **Oestrogen + Progestin** | 17 (23.3) | 1.57 (0.84- 2.94) | 22 (11.6) | 0.92 (0.56- 1.50) | 9( 16.7) | 1.59 (0.67-3.77) | 23( 12.9) | 1.09(0.65-1.80) |
| **Unknown type** | 24 (23.3) | 2.37 (1.44- 3.91) | 38 (20.0) |  1.16 (0.79- 1.70) | 14(25.9) | 2.76 (1.40- 5.46) | 28(15.7) |  1.23 (0.80- 1.87) |
| **Oophorectomy f** |   |   |   |   |   |   |   |   |
|  **No** | 102 (81.0) |   | 171 (77.4) | 1.00 (referent) | 56(82.4) |   | 170(78.7) | 1.00 (referent) |
| **Unilateral** | 5 (4.0) |   | 16 (7.2) | 1.51 (0.90- 2.52) | 3( 4.4) |   | 11( 5.1) | 1.06(0.57-1.95) |
| **Bilateral** | 5 (4.0) |   | 14 (6.3) | 1.36 (0.78- 2.36) | 2(2.9) |   | 11( 5.1) | 1.04(0.56-1.94) |
| **Unknown if unilateral or bilateral** | 0 (0) |   | 1 (0.5) |   | 19(10.3) |   | 24 (11.1)  | 0.85 (0.31- 2.28) |
| **Unknown** | 14 (11.1) |   | 19 (8.6) |   |   |   |   |   |
| **Hysterectomy f** |   |   |   |   |   |   |   |   |
| **No** | 99 (78.6) | 1.00 (referent) | 169 (76.5) | 1.00 (referent) | 55(80.5) | 1.00 (referent) | 166(78.7) | 1.00 (referent) |
| **Yes** | 20 (15.9) | 0.96 (0.59 1.57) | 38 (17.2) | 1.11 (0.78- 1.59) | 11(16.2) | 1.03(0.53-1.99) | 37(17.1) | 1.06(0.73-1.52) |
| **Unknown** | 7 (5.6) |   | 14 (6.3) |   | 2 (2.9) |   | 13(6.0) |   |
| **Parity** |  |  |  |  |  |  |  |  |
|  **No** | 27 (18.5) | 1.00 (referent) | 29 (12.6) | 1.00 (referent) | 18(22.5) | 1.00 (referent) | 29(12.5) | 1.00 (referent) |
|  **Yes** | 115 (78.8) | 0.59 (0.39- 0.90) | 196 (85.2) | 0.91 (0.62- 1.35) | 59(73.8) | 0.44(0.26-0.75) | 199(85.4) | 0.96(0.65-1.43) |
|  **Unknown** | 4 (2.7) |   | 5 (2.2) |   | 3(3.8) |   | 5(2.2) |   |
| **Number of full-term pregnancies g** |   |   |   |   |   |   |   |   |
| **0 h** | 26 (18.7) | 1.42 (0.81- 2.51) | 26 (11.9) | 0.79 (0.48- 1.29) | 18(23.1) | 1.70 (0.83- 3.46) | 25(11.5) | 0.80 (0.48-1.33) |
| **1** | 23 (16.5) | 1.00 (referent) | 43 (19.6) | 1.00 (referent) | 14(18.0) | 1.00 (referent) | 39(18.0) | 1.00 (referent) |
| **2** | 43 (30.9) | 0.71 (0.42- 1.19) | 89 (40.6) | 0.81 (0.56- 1.17) | 24(30.8) | 0.65 (0.33-1.28) | 77(35.5) | 0.78(0.53-1.16) |
| **≥3**  | 43 (30.9) | 0.83 (0.49- 1.41) | 56 (25.6) | 0.59 (0.39- 0.90) | 19(24.4) | 0.63 (0.30-1.29) | 71(32.7) | 0.81(0.53-1.21) |
| **Unknown**  | 4 (2.9) |   | 5 (2.3) |   | 3(3.9) |   | 5 (2.3) |   |
| ***P-*trend i** |   | 0.039 |   | 0.067 |   | 0.002 |   | 0.674 |
| **Age at first full term****pregnancy, years j** |  |  |  |  |  |  |  |  |
| **≤20**  | 15 (13.0) | 1.00 (referent) | 33 (16.8) | 1.00 (referent) | 12 (20.3) | 1.00 (referent) | 28 (14.1) | 1.00 (referent) |
| **21- 23**  | 30 (26.1) | 0.98 (0.52- 1.83) | 57 (29.1) | 1.09 (0.70- 1.68) | 13 (22.0) | 0.57 (0.26-1.26) | 49 (24.6) | 0.84 (0.53-1.35) |
| **24- 25**  | 21 (18.3) | 0.83 (0.42- 1.64) | 33 (16.8) | 0.88 (0.53- 1.44) |  9 (15.3) | 0.51 (0.21-1.25) | 38 (19.1) | 0.81 (0.49-1.35) |
| **26- 30**  | 38 (33.0) | 0.94 (0.50- 1.74) | 55 (28.1) | 0.96 (0.61- 1.52) | 22 (37.3) | 0.79 (0.37-1.65) | 60 (30.2) | 0.80 (0.50-1.27) |
| **≥30**  | 11 (9.6) | 0.85 (0.38- 1.88) | 17 (8.7) | 0.96 (0.53- 1.76) |  3 (5.1) | 0.33 (0.09-1.22) | 23 (11.6) | 0.95 (0.54-1.68) |
| **Unknown**  |   |  | 1 (0.5) |   |  |  | 1(0.5) |  |
|  ***P-*trend** |   | 0.702 |  | 0.661 |  | 0.402 |  | 0.713 |
| **Breastfeeding  i, j** |  |  |  |  |  |  |  |  |
|  **No** | 19 (18.1) | 1.00 (referent) | 24 (13.4) | 1.00 (referent) | 11 (20.0) | 1.00 (referent) | 32 (17.8) | 1.00 (referent) |
|  **Yes** | 83 (79.1) | 0.82 (0.49- 1.36) | 155 (86.6) | 0.97 (0.62- 1.51) | 43 (78.2) | 0.66 (0.33-1.32) | 146 (81.1) | 0.83 (0.56-1.24) |
| **Unknown** | 3 (2.9) |   |  |   | 1(1.8) |  | 2 (1.1) |  |
| **Duration of breastfeeding, all** **pregnancies, months j, k** |   |   |   |   |  |  |  |  |
| **>0-≤3**  | 26 (31.3) | 1.00 (referent) | 53 (34.2) | 1.00 (referent) | 14 (32.6) | 1.00 (referent) | 46 (31.5) | 1.00 (referent) |
| **>3- 12**  | 39 (47.0) | 0.98 (0.58- 1.66) | 66 (42.6) | 0.75 (0.51- 1.11) | 16 (37.2) | 0.83 (0.39-1.76) | 68 (46.6) | 0.93 (0.63-1.39) |
| **>12**  | 18 (21.7) | 0.82 (0.41- 1.65) | 33 (21.3) | 0.75 (0.45- 1.24) | 13 (30.2) | 1.42 (0.60-3.34) | 31 (21.2) | 0.69 (0.40-1.16) |
| **Unknown** |   |   | 3 (1.9) |   |  |  | 1 (0.7) |  |
|  ***P-*trend** |  | 0.600 |  | 0.234 |  | 0.388 |  | 0.219 |
| **Induced abortions l** |   |   |   |   |   |   |   |   |
| **Never pregnant** | 17 (15.9) | 1.70 (1.00- 2.91) | 19 (9.8) | 1.01 (0.63- 1.64) | 13(21.7) | 2.66 (1.40- 5.07) | 16(9.0) | 0.83 (0.49- 1.40) |
| **0** | 69 (64.5) | 1.00 (referent) | 137 (70.6) | 1.00 (referent) | 35(58.3) | 1.00 (referent) | 134(74.4) | 1.00 (referent) |
| **1** | 14 (14.0) | 1.90 (1.05- 3.42) | 25 (12.9) | 1.04 (0.67- 1.62) | 9(15.0) | 1.67 (0.77- 3.61) | 18( 10.0) | 1.22 (0.73- 2.04) |
| **≥2** | 5 (3.5) | 1.22 (0.47- 3.16) | 11 (5.7) | 1.00 (0.53- 1.90) | 2( 3.3) | 0.67 (0.16- 2.91) | 10( 5.6) | 1.19 (0.60- 2.36) |
| **Unknown** | 1 (0.9) |   | 2 (1.0) |   | 1(1.7) |   | 2(1.1) |   |
| ***P-*trend** |   | 0.657 |   | 0.947 |   | 0.119 |   | 0.261 |
| **Spontaneous abortions m** |   |   |   |   |   |   |   |   |
| **Never pregnant** | 22 (17.3) | 1.77 (1.10- 2.86) | 19 (9.4) | 0.95 (0.59- 1.55) | 17(23.6) | 2.83 (1.59- 5.03) | 17(8.6) | 0.80(0.48-1.34) |
| **0** | 76 (59.8) | 1.00 (referent) | 135 (66.5) | 1.00 (referent) | 40(55.6) | 1.00 (referent) | 128(65.0) | 1.00 (referent) |
| **1** | 21 (16.5) | 1.15 (0.71- 1.86) | 33 (16.3) | 1.01 (0.69- 1.48) | 10(13.9) | 1.05 (0.53- 2.11) | 35(17.8) | 1.13(0.78-1.65) |
| **≥2** | 7 (5.5) | 0.96 (0.44- 2.09) | 14 (6.9) | 1.25 (0.72- 2.17) | 4( 5.6) | 1.16 (0.41- 3.24) | 15( 7.6) | 1.26(0.72-2.15) |
| **Unknown** | 1 (0.8) |   | 2 (1.0) |   | 1(1.4) |   |  2 (1.0) |   |
| ***P-*trend** |   | 0.225 |   | 0.710 |   | 0.048 |   | 0.164 |
| **Fertility problems n** |   |   |   |   |   |   |   |   |
| **No** | 82 (73.2) |  | 107 (77.5) |   | 45(75.0) |  - | 142(75.5) |  |
| **Yes** | 7 (6.3) |  | 4 (2.9) |   | 2( 3.3) |  - | 8(4.3) |  |
| **Missing** | 23 (20.5) |   | 27 (19.6) |   | 13 (21.7) |   |  38(20.2) |   |

OC: oral contraceptive // MHT: menopause hormone therapy

Estimation of “Unknown” category is provided when more than 10% of the cases are classified as “Unknown”.

aCox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity, fruits and vegetables intake.

bCox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity, fruits and vegetables intake, OC use, and full-term pregnancies.

c Women who had surgical menopause were excluded

d In peri and postmenopausal women (natural or surgical).

e Available in France, Italy, Spain, United kingdom, The Netherlands, Germany, Denmark, and Norway.

f Available in all centres except Malmö.

g Available in all centres excepte Bilthoven.

h Including nulliparous women and women without full-term pregnancies.

i In parous women.

j Available in all centres except Bilthoven and Umeå.

k In parous women who has ever breastfed.

l Available in all centres excepte Bilthoven, Umeå, Malmö, and Norway

m Available in all centres excepte Bilthoven, Umeå, and Norway.

n Available in France, Italy, Spain, United Kingdom, Utrecht, Greece, and Germany.

Supplemental table 3: Multivariable-adjusted models for each individual reproductive factor, menstrual, menopausal factors, and exogenous hormone use in relation to UC by smoking status in EPIC Women.

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Never**  | **Former** | **Current** |
|   | **Cases (%)** **n =195** | **HR (95%CI)a** | **Cases (%) n=133** | **HR (95%CI)b** | **Cases (%) n=197** | **HR (95%CI)b** |
| **Age at menarche, years** |   |   |   |   |   |   |
| **<12** | 25 (12.8) | 1.00 (referent) | 13 (9.8) | 1.00 (referent) | 26 (13.2) | 1.00 (referent) |
| **12** | 35 (18.0) | 0.95 (0.57- 1.60) | 31 (23.3) | 1.73 (0.90- 3.34) | 37 (18.8) | 0.99 (0.60- 1.65) |
| **13** | 46 (23.6) | 0.96 (0.59- 1.58) | 26 (19.6) | 1.01 (0.51- 1.99) | 55 (27.9) | 1.17 (0.72- 1.90) |
| **14** | 40 (20.5) | 0.86 (0.52- 1.43) | 32 (24.1) | 1.24 (0.64- 2.41) | 35 (17.8) | 0.76 (0.45- 1.29) |
| **>14** | 43 (22.1) | 1.07 (0.64- 1.78) | 29 (21.8) | 1.26 (0.64- 2.49) | 39 (19.8) | 0.97 (0.57- 1.63) |
| **Unknown** | 6 (3.1) |   | 2 (1.5) |   | 5 (2.5) |   |
| ***P* trend** |   | 0.847  |   |  0.874 |   | 0.506 |
| **Cumulative duration of menstrual cycling, accounting for OC use, years c** |   |   |   |   |   |   |
|   |   |   |   |   |   |
| **<23** | 26 (13.3) | 1.00 (referent) | 13 (9.8) | 1.00 (referent) | 33 (16.6) | 1.00 (referent) |
| **23- <30** | 27 (13.9) | 0.62 (0.35- 1.09) | 30 (22.6) | 1.86 (0.93- 3.71) | 39 (19.8) | 0.99 (0.60- 1.61) |
| **30- <35** | 37 (19.0) | 0.55 (0.31- 0.96) | 33 (17.3) | 1.18 (0.56- 2.49) | 47 (23.9) | 1.05 (0.64- 1.74) |
| **≥35** | 64 (32.8) | 0.75 (0.43- 1.28) | 31 (23.3) | 1.24 (0.58- 2.64) | 45 (22.8) | 1.15 (0.67- 1.97) |
| **Unknown** | 41 (21.0) | 0.93 (0.53- 1.64) | 36 (27.1) | 1.81 (0.87 -3.77) | 33 (16.8) | 0.73 (0.40- 1.33) |
| ***P* trend** |   | 0.863 |   | 0.857 |   | 0.725 |
| **Use of OC** |   |   |   |   |   |   |
| **No** | 123 (63.1) | 1.00 (referent) | 64 (48.1) | 1.00 (referent) | 90 (45.7) | 1.00 (referent) |
| **Yes** | 68 (34.9) | 0.84 (0.60- 1.18) | 66 (49.6) | 1.07 (0.72- 1.59) | 102 (51.8) | 0.93 (0.67- 1.28) |
| **Unknown** | 4 (2.1) |   | 3 (2.3) |   | 5 (2.5) |   |
| **Duration OC use, years**  |   |   |   |   |   |   |
| **No** | 123 (63.1) | 1.00 (referent) | 64 (48.1) | 1.00 (referent) | 90 (45.7) | 1.00 (referent) |
| **>0- ≤1** | 11 (5.6) | 0.71 (0.38- 1.33) | 4 (3.0) | 0.38 (0.14- 1.06) | 19 (9.6) | 0.85 (0.51- 1.44) |
| **>1- 5** | 15 (7.7) | 0.69 (0.40- 1.21) | 17 (12.8) | 1.03 (0.58- 1.82) | 30 (15.2) | 1.08 (0.69- 1.68) |
| **>5- 10** | 20 (10.3) | 1.20 (0.72- 1.99) | 24 (18.1) | 1.76 (1.05- 2.95) | 23 (11.7) | 0.93 (0.57- 1.53) |
| **>10** | 17 (8.7) | 0.93 (0.53- 1.61) | 9 (6.8) | 0.59 (0.28- 1.24) | 25 (12.7) | 0.92 (0.57- 1.51) |
| **Unknown duration** | 5 (2.6) |   | 12 (9.0) |   | 5 (2.5) |   |
| **Missing use of OC** | 4 (2.1) |   | 3 (2.3) |   | 5 (2.5) |   |
| ***P* trend** |   | 0.359 |   | 0.72 |   | 0.615 |
| **Menopausal status** |   |   |   |   |   |   |
| **Premenopausal** | 18 (9.5) | 1.00 (referent) | 9 (6.8) | 1.00 (referent) | 22 (11.2) | 1.00 (referent) |
| **Perimenopausal** | 19 (10.0) | 1.05 (0.46- 2.39) | 100 (75.2) | 1.48 (0.46- 4.78) | 140 (71.1) | 3.57 (1.55- 8.24) |
| **Natural postmenopausal** | 150 (78.9) | 0.78 (0.34- 1.78) | 18 (13.5) | 1.22 (0.39- 3.89) | 27 (13.7) | 2.31 (1.01- 5.30) |
| **Surgical postmenopuasal** | 8 (1.6) | 1.07 (0.38- 3.05) | 6 (4.5) | 2.06 (0.51- 8.33) | 8 (4.1) | 3.81 (1.33- 10.94) |
| **Age at natural menopause, years d** |   |   |   |   |   |   |
| **≤46** | 25 (16.7) | 1.15 (0.67- 1.93) | 19 (19.0) | 1.01 (0.55- 1.85) | 41 (29.3) | 1.23 (0.76- 1.97) |
| **47- 49** | 26 (17.3) | 1.25 (0.75- 2.10) | 16 (16.0) | 1.14 (0.60- 2.15) | 26 (18.6) | 0.92 (0.54- 1.55) |
| **50 - 52** | 36 (24.0) | 1.00 (referent) | 26 (26.0) | 1.00 (referent) | 35 (25.0) | 1.00 (referent) |
| **≥53** | 35 (23.3) | 1.25 (0.75- 2.10) | 22 (22.0) | 1.27 (0.71- 2.29) | 19 (13.6) | 1.12 (0.63- 2.00) |
| **Unknown** | 28 (18.7) | 1.84 (1.07- 3.16) | 17 (17.0) | 1.07 (0.55- 2.10) | 19 (13.6) | 1.05 (0.57- 1.93) |
| ***P* trend** |   | 0.532 |   | 0.592 |   | 0.562 |
| **Age at any menopause, years** |   |   |   |   |   |   |
| **≤46** | 29 (18.4) | 1.11 (0.68- 1.81) | 24 (22.6) | 1.13 (0.64- 2.00) | 47 (31.8) | 1.28 (0.81- 2.02) |
| **47- 49** | 26 (16.5) | 1.13 (0.68- 1.88) | 16 (15.1) | 1.05 (0.56- 1.97) | 28 (18.9) | 0.96 (0.57- 1.60) |
| **50 - 52** | 39 (24.7) | 1.00 (referent) | 27 (25.5) | 1.00 (referent) | 35 (23.7) | 1.00 (referent) |
| **≥53** | 36 (22.8) | 1.44 (0.91- 2.29) | 22 (20.8) | 1.25 (0.70- 2.22) | 19 (12.8) | 1.13 (0.64- 2.02) |
| **Unknown** | 28 (17.7) | 1.75 (1.02- 2.97) | 17 (16.0) | 1.05 (0.54- 2.03) | 19 (12.8) | 1.07 (0.59- 1.96) |
| ***P* trend** |   | 0.464 |   | 0.954 |   | 0.424 |
| **Use of MHT e** |   |   |   |   |   |   |
| **No** | 105 (59.3) | 1.00 (referent) | 63 (47.4) | 1.00 (referent) | 77 (39.1) | 1.00 (referent) |
| **Yes** | 52 (29.4) | 1.02 (0.71- 1.47) | 45 (33.8) | 1.21 (0.80- 1.84) | 73 (37.1) | 1.58 (1.12- 2.23) |
| **Unknown** | 20 (11.3) | 1.14 (0.58- 2.25) | 25 (18.8) | 0.87 (0.41- 1.85) | 47 (23.9) | 2.55 (1.34- 4.86) |
| **Duration MHT use, years e** |   |   |   |   |   |   |
| **No** | 105 (59.3) | 1.00 (referent) | 63 (47.4) | 1.00 (referent) | 77 (39.1) | 1.00 (referent) |
| **>0- ≤1.25** | 18 (10.2) | 1.16 (0.69- 1.95) | 10 (7.5) | 1.07 (0.54- 2.11) | 22 (11.2) | 1.73 (1.06- 2.82) |
| **>1.25-4** | 12 (6.8) | 0.87 (0.47- 1.62) | 14 (10.5) | 1.50 (0.82- 2.76) | 21 (10.7) | 1.87 (1.12- 3.10) |
| **>4** | 19 (10.7) | 1.24 (0.73- 2.11) | 14 (10.5) | 1.23 (0.66- 2.30) | 22 (11.2) | 1.26 (0.75- 2.11) |
| **Unknown duration** | 3 (1.7) |   | 7 (5.3) |   | 8 (4.1) |   |
| **Unknown use of MHT** | 20 (11.3) |   | 25 (18.8) |   |   |   |
|  ***P* trend** |   | 0.567 |   | 0.412 |   | 0.421 |
| **Type of MHT  e, f** |   |   |   |   |   |   |
| **Non-users of MHT** | 88 (63.8) | 1.00 (referent) | 52 (57.1) | 1.00 (referent) | 73 (52.5) | 1.00 (referent) |
| **Oestrogen alone** | 7 (5.1) | 0.87 (0.40- 1.92) | 8 (8.8) | 1.41 (0.65- 3.07) | 17 (12.2) | 2.08 (1.19- 3.62) |
| **Oestrogen + Progestin** | 22 (15.9) | 1.22 (0.72- 2.08) | 14 (15.4) | 1.21 (0.63- 2.32) | 13 (9.4) | 0.79 (0.42- 1.48) |
| **Unknown type of MHT** | 21 (15.2) | 1.10 (0.67- 1.80) | 17 (18.7) | 1.49 (0.84- 2.66) | 36 (25.9) | 1.68 (1.10- 2.56) |
| **Oophorectomy g** |   |   |   |   |   |   |
| **No** | 141 (82.0) | 1.00 (referent) | 76 (70.4) | 1.00 (referent) | 125 (74.4) | 1.00 (referent) |
| **Unilateral** | 9 (5.2) | 1.21 (0.61- 2.40) | 6 (5.6) | 1.03 (0.44- 2.39) | 13 (7.7) | 1.51 (0.84- 2.70) |
| **Bilateral** | 8 (4.7) | 0.91 (0.44- 1.87) | 6 (5.6) | 1.21 (0.52- 2.83) | 9 (5.4) | 1.25 (0.62- 2.52) |
| **Unknown if unilateral or** **bilateral** |   |   | 1 (0.93) |   |   |   |
| **Unknown** | 14 (8.1) | 0.07 (0.00- 1.29) | 19 (17.6) | 1.25 (0.45- 3.48) | 21 (12.5) | 2.00 (0.79- 5.03) |
| **Hysterectomy g** |   |   |   |   |   |   |
| **No** | 139 (80.8) | 1.00 (referent) | 76 (70.4) | 1.00 (referent) | 127 (75.6) | 1.00 (referent) |
| **Yes** | 23 (13.4) | 0.83 (0.53- 1.30) | 20 (18.5) | 1.11 (0.67- 1.84) | 32 (19.1) | 1.38 (0.92- 2.08) |
| **Unknown** | 10 (5.8) | 0.61 (0.19- 1.95) | 12 (11.1) | 1.22 (0.42- 3.53) | 9 (5.4) | 0.89 (0.27- 2.94) |
| **Parity** |   |   |   |   |   |   |
| **No**  | 19 (9.7) | 1.00 (referent) | 26 (19.6) | 1.00 (referent) | 27 (13.7) | 1.00 (referent) |
| **Yes** | 170 (87.2) | 1.23 (0.76- 1.99) | 103 (77.4) | 0.61( 0.39- 0.95) | 164 (83.3) | 1.35( 0.51- 3.61) |
| **Unknown** | 6 (3.1) |   | 4 (3.0) |   | 6 (3.1) |   |
| **Number of full-term pregnancies h** |   |   |   |   |   |   |
| **0 i** | 19 (9.8) | 0.72 (0.40- 1.28) | 25 (19.7) | 1.17 (0.67- 2.06) | 27 (12.8) | 0.81 (0.48- 1.35) |
| **1** | 32 (16.6) | 1.00 (referent) | 26 (20.5) | 1.00 (referent) | 40 (21.4) | 1.00 (referent) |
| **2** | 83 (43.0) | 0.96 (0.63- 1.45) | 36 (28.4) | 0.57 (.34- 0.96) | 72 (38.5) | 0.78 (0.52- 1.16) |
| **3** | 39 (20.2) | 0.85 (0.52- 1.37) | 25 (19.7) | 0.74 (0.42- 1.31) | 24 (12.8) | 0.47 (0.27- 0.79) |
| **4** | 9 (4.7) | 0.56 (0.26- 1.20) | 11 (8.7) | 0.93 (0.45- 1.93) | 15 (8.0) | 1.00 (0.54- 1.85) |
| **≥5** | 5 (2.6) | 0.48 (0.18- 1.28) | 0 (0) |   | 6 (3.2) | 0.77 (0.32- 1.86) |
| **Unknown parity** | 6 (3.1) |   | 4 (3.2) |   | 6 (3.2) |   |
| ***P-*trendj** |   | 0.064 |   | 0.208 |   | 0.127 |
| **Age at first full-term pregnancy, years j** |   |   |   |   |   |   |
| **≤20**  | 19 (11.2) | 1.00 (referent) | 13 (12.6) | 1.00 (referent) | 36 (22.0) | 1.00 (referent) |
| **21- 23**  | 40 (23.5) | 0.95 (0.55- 1.65) | 32 (31.1) | 1.31 (0.68- 2.51) | 45 (27.4) | 0.91 (0.58- 1.44) |
| **24- 25**  | 34 (20.0) | 0.90 (0.51- 1.61) | 15 (14.6) | 0.77 (0.36- 1.66) | 24 (14.6) | 0.79 (0.46- 1.35) |
| **26- 30**  | 57 (33.5) | 0.93 (0.54- 1.58) | 35 (34.0) | 1.18 (0.61- 2.29) | 47 (28.7) | 1.01 (0.64- 1.60) |
| **≥30**  | 20 (11.8) | 0.98 (0.51- 1.86) | 7 (6.8) | 0.73 (0.28- 1.85) | 12 (7.3) | 0.78 (0.40- 1.54) |
| **Unknown**  |   |   | 1 (1.0) |   |   |   |
|  **P-trend** |   | 0.906 |   | 0.552 |   | 0.745 |
| **Breastfeeding j, k** |   |   |   |   |   |   |
|  **No** | 24 (14.9) | 1.00 (referent) | 9 (9.9) | 1.00 (referent) | 24 (15.7) | 1.00 (referent) |
|  **Yes** | 133 (82.6) | 0.78 (0.50- 1.22) | 79 (86.8) | 1.17 (0.58- 2.38) | 127 (83.0) | 0.70 (0.45- 1.11) |
| **Unknown** | 4 (2.5) |   | 3 (3.3) |   | 2 (1.3) |   |
| **Duration of breastfeeding, all pregnancies, months k, l** |   |   |   |   |   |   |
| **>0-≤3**  | 49 (36.8) | 1.00 (referent) | 28 (35.4) | 1.00 (referent) | 38 (29.9) | 1.00 (referent) |
| **>3- 12** | 49 (36.8) | 0.51 (0.34- 0.78) | 32 (40.5) | 0.60 (0.36- 1.02) | 61 (48.0) | 1.00 (0.65- 1.53) |
| **>12**  | 34 (25.6) | 0.47 (0.29- 0.76) | 19 (24.1) | 0.78 (0.42- 1.44) | 25 (19.7) | 1.02 (0.60- 1.76) |
| **Unknown** | 1 (0.8) |   |   |   |   |   |
|  **P-trend** |   | 0.015 |   | 0.341 |   | 0.937 |
| **Induced abortions m** |   |   |   |   |   |   |
| **Never pregnant** | 14 (9.0) | 0.90 (0.51- 1.59) | 17 (19.8) | 1.77 (1.01- 3.09) | 16 (11.3) | 1.05 (0.61- 1.81) |
| **0** | 114 (73.1) | 1.00 (referent) | 56 (65.1) | 1.00 (referent) | 98 (68.0) | 1.00 (referent) |
| **1** | 15 (9.6) | 1.29 (0.73- 2.26) | 9 (10.5) | 1.23 (0.58- 2.86) | 21 (14.8) | 1.04 (0.63- 1.69) |
| **≥2** | 12 (7.7) | 2.52 (1.33- 4.78) | 2 (2.3) | 0.65 (0.15- 2.74) | 5 (3.5) | 0.43 (0.17- 1.08) |
| **Unknown** | 1 (0.6) |   | 2 (2.3) |   | 2 (1.4) |   |
| ***P-*trend** |   | 0.012 |   | 0.091 |   | 0.175 |
| **Spontaneous abortions n** |   |   |   |   |   |   |
| **Never pregnant** | 16 (8.9) | 0.84 (0.49- 1.42) | 20 (18.0) | 1.65 (0.99- 2.77) | 19 (11.1) | 1.16 (0.68- 1.84) |
| **0** | 120 (67.0) | 1.00 (referent) | 67 (60.4) | 1.00 (referent) | 108 (63.2) | 1.00 (referent) |
| **1** | 35 (19.6) | 1.26 (0.86- 1.84) | 15 (13.5) | 0.91 (0.52- 1.60) | 27 (15.8) | 1.08 (0.71- 1.67) |
| **≥2** | 7 (3.9) | 0.69 (0.32- 1.49) | 6 (5.4) | 1.06 (0.46- 2.46) | 14 (8.2) | 1.52 (0.86- 2.68) |
| **Unknown** | 1 (0.6) |   | 3 (2.7) |   | 3 (1.8) |   |
| ***P*-trend** |   | 0.679 |   | 0.185 |   | 0.375 |
| **Infertility problems o** |   |   |   |   |   |   |
| **No** | 122 (89.7) | 1.00 (referent) | 57 (79.2) | 1.00 (referent) | 75 (77.3) | 1.00 (referent) |
| **Yes** | 4 (2.9) | 0.93 (0.34- 2.55) | 7 (9.7) | 3.12(1.38- 7.04) | 5 (5.2) | 1.32(0.50- 3.49) |
| **Unknown** | 10 (7.4) |   | 8 (11.1) | 2.34(0.95- 5.74) | 17 (17.5) | 0.44(0.12- 1.55) |

UC: urothelial carcinoma // OC: oral contraceptive // MHT: menopause hormone therapy

Estimation of “Unknown” category is provided when more than 10% of the cases are classified as “Unknown”.

All *P* value for the interaction were >0.05, with the exception of the induced abortions were *P* for interaction = 0.028

a Cox proportional hazards model stratified by centre and age at recruitment and adjusted by fruits and vegetables intake.

b Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking intensity (number of cigarettes per day in current-smokers and time since quitting smoking in former-smokers) , fruits and vegetables intake.

c Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity, fruits and vegetables intake, OC use, and full-term pregnancies

d Women who had surgical menopause were excluded

e In peri- and postmenopausal (natural or surgical).

f Available in France, Italy, Spain, United kingdom, The Netherlands, Germany, Denmark, and Norway.

g Available in all centres except Malmö.

h Available in all centres except Bilthoven.

i Including nulliparous women and women without full-term pregnancies.

j In parous women.

k Available in all centres except Bilthoven and Umeå.

l In parous women who has ever breastfed.

m Available in all centres except Bilthoven, Malmö, Umeå, and Norway.

n Available in all centres except Bilthoven, Umeå, and Norway.

o Available in France, Italy, Spain, United Kingdom, Utrecht, Greece, and Germany.

Supplemental table 4: Mutually adjusted models for menopause status, MHT, and parity, and UC by smoking status

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Never** | **Former** | **Current** |
|  | **Cases (%)** **n =195** | **HR (95%CI)a** | **Cases (%)** **n =133** | **HR (95%CI)b** | **Cases (%)** **n =197** | **HR (95%CI)b** |
|  **Menopausal status & use of MHT** |  |  |  |  |  |  |
| **Premenopausal**  | 18 (9.23) | 1.23 (0.52- 2.43) | 9 (6.8) | 0.83 (0.27- 2.54) | 22 (11.2) | 0.50 (0.22- 1.11) |
| **Peri-/Postmenopausal & non-users of MHT** | 105 (53.9) | 1.00 (referent) | 63 (47.4) | 1.00 (referent) | 77 (39.1) | 1.00 (referent) |
| **Peri-/Postmenopausal & users of MHT** | 52 (26.7) | 1.02 (0.71- 1.47) | 45 (33.8) | 1.20 (0.79- 1.83) | 73 (37.1) | 1.56 (1.10- 2.21) |
| **Peri-/Postmenopausal & unknown MHT-use** | 20 (10.26) | 1.12 (0.53- 2.39) | 16 (12.0) | 0.89 (0.40- 2.00) | 25 (12.7) | 2.31 (1.16- 4.62) |
|  **Number of full-term pregnancies c** |  |  |  |  |  |  |
| **0 d** | 19 (9.7) | 0.72 (0.40- 1.29) | 26 (19.6) | 1.17 (0.67- 2.06) | 27 (13.7) | 0.83 (0.49- 1.39) |
| **1** | 32 (16.4) | 1.00 (referent) | 26 (19.6) | 1.00 (referent) | 40 (20.3) | 1.00 (referent) |
| **2** | 83 (42.6) | 0.95 (0.63- 1.45) | 36 (27.1) | 0.57 (0.34- 0.96) | 72 (36.6) | 0.78 (0.49- 1.39) |
| **3** | 39 (20.0) | 0.85 (0.52- 1.37) | 25 (18.8) | 0.74 (0.42- 1.30) | 24 (12.2) | 0.48 (0.28- 0.81) |
| **4** | 9 (4.6) | 0.57 (0.27- 1.21) | 11 (8.3) | 0.94 (0.45- 1.95) | 15 (7.6) | 1.01 (0.54- 1.88) |
| **≥5** | 5 (2.6) | 0.49 (0.18- 1.29) |  |  | 6 (3.1) | 0.80 (0.33- 1.95) |
| **Unknown** | 8 (4.1) |  | 9 (6.8) |  | 13 (6.6) |  |
| ***P*-trend e** |  | 0.069 |  | 0.209 |  | 0.149 |

UC: urothelial carcinoma // MHT: menopause hormone therapy

Estimation of “Unknown” category is provided when more than 10% of the cases are classified as “Unknown”.

All *P* value for the interaction were >0.10

a Cox proportional hazards model stratified by centre and age at recruitment and adjusted by fruits and vegetables intake.

b Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking intensity (number of cigarettes per day in current-smokers and time since quitting smoking in former-smokers) , fruits and vegetables intake.

c Available in all centres except Bilthoven.

d Including nulliparous women and women without full-term pregnancies.

e In parous women.