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

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Running title: Reproductive factors and Urothelial carcinoma

Abbreviations list:

UC: Urothelial carcinoma

EPIC: European Prospective Investigation into Cancer and Nutrition Cohort

FTP: Number of full-term pregnancies

MHT: Menopausal hormone therapy

OC: Oral contraceptives

WHI: Women's Health Initiative

CIS: Carcinoma *in situ*

HR: Hazard ratio

CI: Confidence interval

BMI: Body mass index

AIC: Akaike information criterion

LRT: Likelihood ratio test

PAHs: Polycyclic aromatic hydrocarbons

ER: Oestrogen receptors

PR: Progesterone receptors

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Abstract:

Background: Urothelial carcinoma (UC) is the predominant (95%) bladder cancer subtype in industrialised nations. Animal and epidemiological 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 hormonal factors and incident UC (overall and by tumour grade, tumour aggressiveness, and non-muscle invasive UC) risk were evaluated using Cox proportional hazards models.

Results: During a mean of 15 years of follow-up, 529 women developed UC. In a model including number of full-term pregnancies (FTP), menopausal status, and menopausal hormone therapy (MHT), number of FTP was inversely associated with UC risk ($HR_{\geq 5 vs 1}$=0.48, 0.25-0.90; *P*-trend in parous women=0.010) and MHT-use (compared to non-use) was positively associated with UC risk (HR=1.27, 1.03-1.57), but no dose-response by years of MHT-use was observed. No modification of HRs by smoking status was observed. Finally, sensitivity analyses in never-smokers showed similar HR patterns for the number of FTP, while no association between MHT-use and UC risk was observed. Association between MHT-use and UC risk only remained significant in current-smokers. No heterogeneity of the risk estimations in the final model was observed by tumour aggressiveness or by tumour grade. A positive association between the MTH-use and non-muscle invasive UC risk was observed.

Conclusion: Our results support that increasing the number of FTP may reduce UC risk.

Impact: More detailed studies on parity are needed to understand the possible effects 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). Although, men are at higher risk than women of developing bladder cancer; women present more advanced stages at diagnosis(2). In Europe, the 5-year relative survival rate is 84% in men and 75% in women(3). The predominant bladder cancer subtype is urothelial carcinoma (UC), accounting for 95% of all cases in industrialised nations(4) and almost 71% of men and 63% of women are diagnosed non-muscle invasive UC(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(5). 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(4,6).

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(4). However, after adjusting for these factors differential risk of bladder cancer persists(2). Thus, several studies support that female hormones may have a beneficial effect on UC risk. An experimental animal study that examined the effect of the hormones on oncogenesis in male rat bladders showed that induced incidence of bladder cancer was higher in the group injected with testosterone supplementation than in the group injected with

oestrogen supplementation(7). Moreover, castration of male mice and pregnancy and/or lactation in female mice can decrease the growth of bladder cancer(8). Previous epidemiological studies have reported a reduced risk of UC in parous women compared to nulliparous women(9–12); and an increased risk in postmenopausal women, particularly those with an earlier age at menopause(11,13,14). In general, no associations between age at menarche, use of oral contraceptives (OC), age at first full-term pregnancy, breastfeeding and UC risk were observed(9–19). A meta-analysis by menopausal hormone therapy (MHT) formulation(11), 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 of MHT component and an observational study of MHT component, no such association was observed(18). To our knowledge, previous studies examining the association of reproductive factors with UC risk did not stratified by tumour characteristics (based on tumour grade and tumour stage).

We used a large number of cases (most of them with detailed UC's characteristics) within a large multi-centric prospective study of European women with a long follow-up (15-years) to assess the associations between menstrual factors, reproductive history, use of exogenous hormones, and the risk of developing UC, overall and by tumour grade, tumour aggressiveness, and non-muscle invasive UC, and accounting for smoking status.

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. 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. 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(20). 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(21)) were excluded (n=10 066). After these exclusions, the present analysis included 333 919 women.

Hormonal and reproductive factors

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) is an accepted proxy for total endogenous exposure and was calculated as follows(14,22): for postmenopausal women, it was the difference between the age at menopause and the age at menarche minus the total time pregnant (number of full-term pregnancies (FTP) x 9 months, due to the absence of menstrual cycles of 9 months for each pregnancy). 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 for pre-, peri-, and postmenopausal women. To assess for hormonal changes during pregnancy and exogenous hormones through OC use, those models were additionality adjusted for number of FTP and OC-use.

Self-reported reproductive history included: parity (yes/no), number of 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).

Bladder cancer 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*)(23). 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)(23). We also analysed UC by tumour grade (using WHO-defined Grades 2 and 3 as "high-grade" and Grade 1 as "low-grade")(24). Finally, in centres where tumour stage information was available (available in all centres except San Sebastian, United Kingdom, Greece, Malmö, and Norway), we analysed UC restricted to non-muscle invasive subtype (pT1, pTa, or CIS).

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. Estimations of "unknown" categories were provided when more than 10% of the cases were classified as "unknown". 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, tumour grade (using the Wald test statistic to assess the heterogeneity of the risk between outcomes using the SAS macro *%subtype*(25)), and non-muscle invasive UC. All models were stratified by age at recruitment (1 year-categories) and

study centre. Stratified models by center allowed us to give each center its own baseline hazard, thus the variation in menstrual and reproductive history, hormone use, and cancer patterns across centers were included in the model. Further, stratified by age provided left truncation of the data (the risk of developing the outcomes of interest was only included during the follow-up). Finally, these stratified models assumed proportional hazard between the centers. All models were 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 and vegetable intakes (both entered as continuous variable g/d) (4), which change estimate effect of the hormone variables by more than >10%. Physical activity and body mass index (BMI) were not included as adjustment covariates because they did not change effect estimates >10%. Occupations with potential exposure to bladder carcinogens are potential confounder given the established effect of a number of chemicals and substances (e.g. heavy metal, dyes, and polycyclic aromatic hydrocarbons [PAHs]) on sex hormones levels among healthy women(26–28). Other potential confounders were occupations with potential exposure to bladder carcinogens. To adjust models for occupational exposure a dichotomous score (yes/no) was defined, where it was coded as “yes” if the participant worked in occupations with potential exposure to heavy metals (present in foundries, in metal industries, and in occupations related to welding, turning and electroplating), aromatic amines (present in, e.g. dye production, textile and leather dying, and hairdressers), PAHs (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)(29). Nevertheless, occupation was ultimately not

included in the multivariable-adjusted models because <7% of women worked in a job/occupation with potential exposure to bladder carcinogens, 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. Restricted cubic splines with 3-5 knots were used to explore linearity in the trend in the risk with number of FTP. Akaike information criterion (AIC) was used to select the best representation of the relation between number of FTP (among parous women) and UC risk (Supplemental Figure 1).

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) (25^{th} and 75^{th} 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 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 2, Table 3). Elevated and statistically significant HRs for UC were observed for postmenopausal status (natural or surgical) compared to premenopausal status ($HR_{postnatural vs pre}$: 1.88; 95%CI, 1.09-3.25; $HR_{postsurgical vs pre}$: 2.15; 95%CI, 1.10-4.20) (Table 1). MHT use in peri-/postmenopausal women (natural or surgical) was positively associated with overall UC independently of the duration of MHT use (Table 3). 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 3).

Reproductive factors

There was a statistically significant inverse association for number of FTP and UC risk ($HR_{3 vs 1FTP}$: 0.70; 95%CI, 0.52-0.94; $HR_{\geq 5 vs 1FTP}$: 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 4.

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 ($HR_{3vs1FTP}$: 0.70; 95%CI, 0.52-0.94; $HR_{\geq 5vs1FTP}$: 0.48; 95%CI, 0.25-0.90; *P*-trend in parous women only 0.010) (Table 5). 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 5).

Study of the heterogeneity of the risk between non-aggressive tumours and aggressive tumours

MHT-use was positively associated with risk of non-aggressive UC ($HR_{yesvsno}$: 1.93; 95%CI, 1.29- 2.87). Parity was inversely associated with non-aggressive UC risk ($HR_{yesvsno}$: 0.59; 95%CI, 0.39- 0.90). Natural and surgical menopause were statistically significantly associated with risk of aggressive UC ($HR_{naturalvspre}$: 2.47; 95%CI, 1.01-6.03; $HR_{surgicalvspre}$: 3.25; 95%CI, 1.18-8.97) (Supplemental Table 1). Despite these statistically significant individual associations, statistically significant heterogeneity of the risk for menstrual factors and exogenous hormone use by tumour aggressiveness was not observed for each individual model, and for the mutually-adjusted model (all P_{het}-value > 0.05).

Study of the heterogeneity of the risk between low-grade tumours and high-grade tumours

MHT-use was positively associated with low-grade tumours (HR: 2.37; 95%CI, 1.37-4.12), while the number of spontaneous abortions (comparisons based on 17 women in the referent group) was statistically significant and inversely associated with the risk of low-grade tumours. Parity was inversely associated with low-grade tumours ($HR_{yesvsno}$:

0.44; 95%CI, 0.26- 0.75; comparisons based on 18 women in the referent group). No associations were observed between hormonal factors and high-grade UC risk (Supplemental Table 1).

Statistically significant heterogeneity in the risk estimates by tumour grade was observed in relation to the number of spontaneous abortions (P_{het}-value=0.026) and parity (P_{het}-value=0.011). Finally, once the identified variables were included in one model, estimations of the risk were similar by tumour grade (P_{het}-value=0.079).

Risk estimation between hormonal and reproductive factors and non-muscle invasive UC

Positive association was observed between MHT-users and non-muscle invasive UC risk (HR: 1.38; 95%CI, 1.01-1.90), especially in women which treatment's formulation was oestrogen alone (HR: 1.90; 95%CI, 1.15-3.13) (Supplemental Table 1).

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 2).

No modification of HRs by cigarette smoking status in the mutually-adjusted model 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 3). 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 2 and Table 5), or in the subgroup of participants who were peri-/postmenopausal at recruitment (Table 5). In never smokers, no association between MHT-use and UC risk was observed in the final mutually adjusted model (Table 5).

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. No associations were observed for the remaining menstrual factors, reproductive history variables, or exogenous hormone use variables. We observed no evidences of differences in the estimations of UC risk by the number of full-term pregnancies or other menstrual factors, reproductive history factor, or exogenous hormone use according to tumour characteristics (based on tumour grade and tumour stage).

Previous studies(11,12,18) and two meta-analyses(10,17) observed a reduced risk of UC in parous women, independent of the number of births(10,11,13,14,16–18). Nearly all these studies used “nulliparous” as the referent category(11,13,14,16,17). 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)(12).

Women experience several hormonal changes during pregnancy, including an increase in oestrogen and progesterone levels(30). 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(31). 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(32,33). 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(34). It has been observed that ER-β is the dominant receptor expressed in urothelial carcinoma cells(8,32). Few studies have been done in relation to ERs and progesterone in urothelial carcinoma cells, but it has been suggested that progesterone suppresses ER expression during pregnancy(35). Consequently, it can be hypothesized that these increased levels of oestrogen and progesterone may reduce UC risk in parous women(9–12,17,36).

Two previous studies have examined the association between induced abortions and the risk of UC (15,37). These two case-control studies did not observe that the number of induced abortions was associated with UC risk. Our results on never-smokers were based on 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(14). Earlier age at menopause (natural or surgical) was associated with an increased risk of UC in a meta-analysis(17), 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(10,11,18).

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(10,17,18). Our results and previous studies showed no dose-response by years of MHT-use(10,11,13,16,18). 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)(18). 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)(11). 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, however we observed a positively statistically significant estimation in current-smokers who used oestrogen alone or reported unknown type of MHT. Since we observed no association in never-smokers, and the MHT effect (overall and by formulation) only remained significant in current-smokers, residual confounding from tobacco smoking and possible chance are a likely explanation for our MHT results.

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. However, non-muscle invasive UC classification was not available in San Sebastian, Oxford, Cambridge, Malmö, and Norway centres.

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, suggesting our results were unlikely to be affected by any changes in reproductive history after enrolment. Another potential weakness of our study was the large number of missing values in the MHT variables (duration and formulation). 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 could not evaluate changes after baseline for any variables. Results from the sensitivity analyses in never smoking women showed that, except for MHT, our results 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. 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 ER and PR levels and urothelial cells in the bladder are needed.

Additional Information:

Disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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Author's contribution

LLB, EB, SC, EW, and EJD analyzed and interpreted the data. LLB 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: 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)
Body mass index(kg/m^2)[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)
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)
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], yes	6 920 (6.4)			1 177 (4.7)	599 (5.2)		465 (3.1)	2 479 (9.1)		2 200 (7.7)	6 920 (6.4)
Diabetes [b], 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)

Numbers may not sum to totals due to missing values

[a] Median (percentile 25th and percentile 75th) // [b] n (%) // [c] Available in Spain, Cambridge, Greece, Germany, Denmark, and Norway // [d] Job exposure was coded as "yes" if the participant worked in jobs with potential exposure to heavy metals, aromatic amines, polycyclic aromatic hydrocarbons, and environmental tobacco smoke.

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

	Person-years	Cases (%) n=529	HR (95%CI) [a]	*P*-trend
Age at menarche, years				
<12	678 236	64 (12.1)	1.00 (referent)	0.845
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)	
Cumulative duration of menstrual cycling, accounting for OC use, years [b]				
<23	960 018	72 (13.6)	1.00 (referent)	0.924
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)	
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)	0.527
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)	
Age at any menopause, years				
≤46	450 220	100 (24.0)	1.21 (0.91- 1.60)	0.853
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)	
Oophorectomy [d]				
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	965 580	55 (12.2)	0.91 (0.47- 1.78)	
Hysterectomy [d]				
No	3 640 275	344 (76.1)	1.00 (referent)	
Yes	472 260	76 (16.8)	1.09 (0.84- 1.40)	

UC: Urothelial Carcinoma // OC: oral contraceptive // Numbers may not sum to totals due to missing values

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] Available in all centres except Malmö.

663 Table 3: Multivariable-adjusted models for each individual exogenous hormone use in relation to UC
664 risk in EPIC Women.
665

	Person-years	Cases (%) n=529	HR (95%CI) [a]	*P*-trend
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)	0.259
>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)		
Use of MHT [b]				
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 [b]				
No	1 740 862	247 (51.5)	1.00 (referent)	0.152
>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)	
Type of MHT [b, c]				
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)	

666 UC: Urothelial Carcinoma // OC: oral contraceptive // MHT: menopause hormone therapy
667 Estimation of "Unknown" category is provided when more than 10% of the cases are classified as "Unknown".
668 a Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity,
669 fruits and vegetables intake.
670 [b] In peri- and postmenopausal (natural or surgical).
671 [c] Available in France, Italy, Spain, United Kingdom, The Netherlands, Germany, Denmark, and Norway.

Table 4: 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]	*P*-trend
Parity				
No	686 624	73 (13.8)	1.00 (referent)	
Yes	3 774 138	440 (83.2)	0.87 (0.68- 1.12)	
Number of full-term pregnancies [b]				
0 [c]	686 624	69 (13.5)	0.92 (0.67- 1.25)	0.008[d]
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)	
Age at first full-term pregnancy, years [d]				
≤20	546 150	68 (15.5)	1.00 (referent)	0.688
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)	
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)	
Duration of breastfeeding, all pregnancies, months [e, f]				
>0-≤3	854 602	115 (33.7)	1.00 (referent)	0.092
>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)	
Induced abortions [g]				
Never pregnant	483 030	48 (12.4)	1.19 (0.91- 1.56)	0.759
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)	
***P*-trend**				
Spontaneous abortions [h]				
Never pregnant	508 626	56 (12.1)	1.14 (0.85- 1.52)	0.497
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)	
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 // Numbers may not sum to totals due to missing values

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 5: Mutually-adjusted models for menopause status, MHT, and parity in relation to UC risk in EPIC women.

	Overall			Never smokers			Postmenopausal		
	Cases (%) n=529	**HR (95%CI)[a]**	***P*-trend**	**Cases (%) n=195**	**HR (95%CI)[b]**	***P*-trend**	**Cases (%) n=195**	**HR (95%CI)[b]**	***P*-trend**
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)		247 (51.5)	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)		172 (35.8)	1.28 (1.04- 1.59)	
Peri-/Postmenopausal & unknown MHT-use	61 (11.5)	1.35 (0.88- 2.07)		20 (10.26)	1.12 (0.53- 2.39)		61 (12.7)	1.34 (0.89- 2.02)	
Number of full-term pregnancies [c]									
0 [d]	69 (13.5)	0.92 (0.67- 1.25)	0.010[e]	19 (9.7)	0.72 (0.40- 1.29)	0.069[e]	66 (14.1)	1.03 (0.73- 1.39)	0.008 [e]
1	99 (19.4)	1.00 (referent)		32 (16.4)	1.00 (referent)		88 (18.8)	1.00 (referent)	
2	192 (37.6)	0.80 (0.62- 1.02)		83 (42.6)	0.95 (0.63- 1.45)		171 (36.5)	0.79 (0.61- 1.03)	
3	89 (17.4)	0.70 (0.52- 0.94)		39 (20.0)	0.85 (0.52- 1.37)		82 (17.5)	0.71 (0.52- 0.97)	
4	35 (6.9)	0.80 (0.54- 1.19)		9 (4.6)	0.57 (0.27- 1.21)		35 (7.5)	0.85 (0.57- 1.27)	
≥5	11 (2.2)	0.48 (0.25- 0.90)		5 (2.6)	0.49 (0.18- 1.29)		11 (2.4)	0.51 (0.27- 0.97)	

UC: Urothelial Carcinoma // MHT: menopausal hormone therapy // Numbers may not sum to totals due to missing values
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 menopausal status and MHT, number of full-term pregnancies, smoking status and intensity, fruits and vegetables intake.

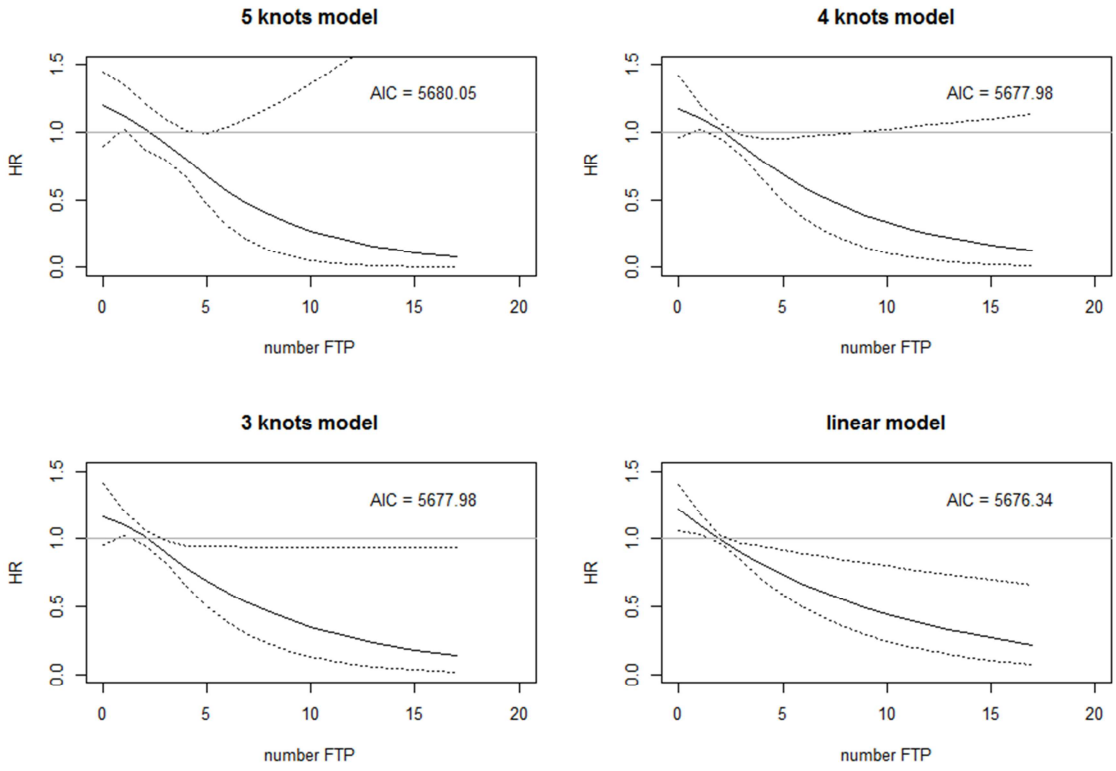
[b] Cox proportional hazards model stratified by centre and age at recruitment and adjusted by menopausal status and MHT, number of full-term pregnancies, fruits and vegetables intake.

[c] Available in all centres have information except Bilthoven.

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

[e] In parous women

Supplemental Figure 1: Restricted cubic splines plots of the association between number of full-term pregnancies and UC risk in EPIC women.



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.

Supplemental Table 1: Reproductive factors, menstrual, menopausal factors, and exogenous hormone use in relation to UC by aggressiveness, grade, and non-muscle invasive tumour in EPIC Women.

	Nonaggressive (n=146)		Aggressive (n=230)		Low-Grade (n=80)		High-Grade (n=233)		Non-muscle invasive (n=198)[a]	
	Cases(%)	**HR(95%CI)** [b]	**Cases(%)**	**HR(95%CI)** [b]	**Cases(%)**	**HR(95%CI)** [b]	**Cases(%)**	**HR(95%CI)** [b]	**Cases(%)**	**HR(95%CI)** [b]
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)	31(15.7)	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)	37(18.7)	0.85(0.53-1.38)
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)	41(20.7)	0.76(0.48-1.23)
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)	45(22.7)	0.87(0.54-1.39)
>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)	42(21.2)	0.90(0.55-1.45)
Unknown	3(2.1)		5(2.2)		1(1.3)		6(2.6)		2(1.0)	
***P*-trend**		0.075		0.188		0.057		0.903		0.796
Cumulative duration of menstrual cycling, accounting for OC use, years [c]										
<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)	31(15.7)	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)	36(18.2)	0.95(0.58-1.55)
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)	39(19.7)	0.75(0.46-1.23)
≥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)	52(26.3)	0.89(0.55-1.45)
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)	40(20.2)	0.72(0.43-1.22)
***P*-trend**		0.396		0.610		0.348		0.982		0.674
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)	96(48.5)	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)	98(49.5)	1.03(0.76-1.42)
Unknown	1(0.7)		4(1.7)				2(0.9)		4(2.0)	

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)	96(48.5)	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)	16(8.1)	0.84(0.49-1.45)
>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)	24(12.1)	1.09(0.68-1.75)
>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)	28(14.1)	1.41(0.90-2.22)
>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)	22(11.1)	0.93(0.57-1.54)
Unknown duration	7(4.8)		10(4.4)		6(7.5)		11(4.7)		8(4.0)	
Unknown use of OC	1(0.7)		4(1.7)				2(0.9)		4(2.0)	
***P* trend**		0.769		0.469		0.712		0.549		0.809
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)	15(7.6)	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)	145(73.2)	2.05(0.83-5.03)
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)	26(13.1)	1.59(0.66-3.81)
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)	12(6.1)	2.64(0.94-7.43)
Age at natural menopause, years [d]										
≤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)	31(21.4)	1.14(0.70-1.86)
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)	24(16.6)	1.07(0.63-1.81)
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)	35(24.1)	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)	30(20.7)	1.41(0.86-2.33)
Unknown	16(15.7)	1.26(0.63-2.51)	30(16.7)	1.18(0.72-.95)	7(13.7)	1.11(0.41-.06)	30(17.1)	1.26(0.76-2.09)	25(17.2)	1.17(0.68-2.03)
***P*-trend**		0.688		0.324		0.53		0.571		0.499
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)	40(25.5)	1.24(0.78-1.95)
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)	25(15.9)	1.01(0.60-1.69)
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)	37(23.6)	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)	30(19.1)	1.38(0.84-2.25)
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)	25(15.9)	1.14(0.66-1.66)
***P*-trend**		0.635		0.479		0.532		0.681		0.415
Use of MHT [e]										
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)	102(55.7)	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)	79(43.2)	1.38(1.01-1.90)
Unknown	15(11.7)	1.72(0.76-.87)	8(3.7)		9(13.2)	2.93(0.94-9.11)	13(6.2)		2(1.1)	
Duration MHT use, years [e]										
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)	102(55.7)	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)	23(12.6)	1.39(0.88-2.22)
>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)	23(12.6)	1.54(0.96-2.47)
>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)	29(15.9)	1.28(0.82-2.02)
Unknown duration	5(3.9)		7(3.3)		1(1.5)		12(5.7)		4(2.2)	
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)		2(1.1)	
***P*-trend**		0.002		0.242		0.023		0.100		0.199
Type of MHT [e, f]										
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)	97(55.4)	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)	20(11.4)	1.90(1.15-3.13)
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)	25(14.3)	1.10(0.68-1.78)
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)	33(18.9)	1.32(0.87-1.99)
Oophorectomy [g]										
No	102(81.0)		171(77.4)	1.00(referent)	56(82.4)		170(78.7)	1.00(referent)	163(82.3)	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)	10(5.1)	0.96(0.51-1.83)
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)	13(6.6)	1.27(0.72-2.26)
Unknown if unilateral or bilateral	0(0)		1(0.5)		19(10.3)		24(11.1)	0.85(0.31-2.28)	1(0.5)	
Unknown	14(11.1)		19(8.6)						11(5.6)	

Hysterectomy [g]										
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)	152(76.8)	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)	35(17.7)	1.19(0.82-1.73)
Unknown	7(5.6)		14(6.3)		2(2.9)		13(6.0)		11(5.6)	
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)	28(14.1)	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)	164(82.8)	0.80(0.54-1.20)
Unknown	4(2.7)		5(2.2)		3(3.8)		5(2.2)		6(3.0)	
Number of full-term pregnancies [h]										
0 [i]	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)	25(13.2)	0.90(0.53-1.52)
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)	34(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)	70(37.0)	0.75(0.49-1.13)
≥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)	54(28.6)	0.68(0.44-1.07)
Unknown	4(2.9)		5(2.3)		3(3.9)		5(2.3)		6(3.2)	
***P*-trend** [j]		0.039		0.067		0.002		0.674		0.111
Age at first full term pregnancy, years [k]										
≤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)	23(14.0)	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)	54(32.9)	1.38(0.84-2.26)
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)	35(21.3)	1.13(0.65-1.94)
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)	39(23.8)	0.88(0.52-1.51)
≥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)	12(7.3)	0.91(0.44-1.87)
Unknown			1(0.5)				1(0.5)		1(0.6)	
***P*-trend**		0.702		0.661		0.402		0.713		0.196
Breastfeeding [j, k]										
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)	26(17.1)	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)	124(81.6)	0.78(0.50-1.20)
Unknown	3(2.9)				1(1.8)		2(1.1)		2(1.3)	
Duration of breastfeeding, all pregnancies, months [k, l]										
>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)	40(32.3)	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)	55(44.4)	0.77(0.51-1.18)
>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)	27(21.8)	0.75(0.44-1.26)
Unknown			3(1.9)				1(0.7)		2(1.6)	
***P*-trend**		0.600		0.234		0.388		0.219		0.264
Induced abortions [m]										
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)	18(10.0)	1.08(0.66-1.78)
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)	118(65.6)	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)	28(15.6)	1.28(0.83-1.96)
≥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)	14(7.80	1.36(0.76-2.43)
Unknown	1(0.9)		2(1.0)		1(1.7)		2(1.1)		2(1.1)	
***P*-trend**		0.657		0.947		0.119		0.261		0.733
Spontaneous abortions [n]										
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)	18(10.0)	1.12(0.68-1.85)
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)	109(60.7)	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)	36(20.0)	1.34(0.91-1.95)
≥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)	15(8.3)	1.61(0.93-2.77)
Unknown	1(0.8)		2(1.0)		1(1.4)		2(1.0)		2(1.1)	
***P*-trend**		0.225		0.710		0.048		0.164		0.095
Fertility problems [o]										
No	82(73.2)		107(77.5)		45(75.0)		142(75.5)	90(69.2)		
Yes	7(6.3)		4(2.9)		2(3.3)		8(4.3)	9(6.9)		
Missing	23(20.5)		27(19.6)		13(21.7)		38(20.2)	31(23.9)		

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] Available in all centres except San Sebastian, United Kingdom, Greece, Malmö, and Norway.
[b]Cox proportional hazards model stratified by centre and age at recruitment and adjusted by smoking status and intensity, 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 women (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, Umeå, Malmö, 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 2: 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*-trend[j]**		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 3: 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.