Menstrual Factors, Reproductive History, Hormone Use, and Urothelial Carcinoma Risk: A Prospective Study in the EPIC Cohort

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 J. 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[27,28,29,30], Carmen Santiuste[29,31], Aurora Perez-Cornago[32], Raul Zamora-Ros[1,2], Amanda J. Cross[33], Antonia Trichopoulou[34], Anna Karakatsani[34,35], Eleni Peppa[34], Domenico Palli[6], Vittorio Krogh[36], Veronica Sciannameo[37], Amalia Mattiello[38], Salvatore Panico[38], Carla H. van Gils[39], N. Charlotte Onland-Moret[39], Aurelio Barricarte[29,40,41], Pilar Amiano[29,42], Kay-Tee Khaw[43], Heiner Boeing[44], Elisabete Weiderpass[19], and Eric J. Duell[45,46]

ABSTRACT

Background: Urothelial carcinoma is the predominant (95%) bladder cancer subtype in industrialized nations. Animal and epidemiologic human studies suggest that hormonal factors may influence urothelial carcinoma risk.

Methods: We used an analytic cohort of 333,919 women from the European Prospective Investigation into Cancer and Nutrition Cohort. Associations between hormonal factors and incident urothelial carcinoma (overall and by tumor grade, tumor aggressiveness, and non–muscle-invasive urothelial carcinoma) risk were evaluated using Cox proportional hazards models.

Results: During a mean of 15 years of follow-up, 529 women developed urothelial carcinoma. In a model including number of full-term pregnancies (FTP), menopausal status, and menopausal hormone therapy (MHT), number of FTP was inversely associated with urothelial carcinoma risk ($HR_{\geq 5 vs 1} = 0.48$; 0.25–0.90; P_{trend} in parous women = 0.010) and MHT use (compared with nonuse) was positively associated with urothelial carcinoma 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 urothelial carcinoma risk was observed. Association between MHT use and urothelial carcinoma risk remained significant only in current smokers. No heterogeneity of the risk estimations in the final model was observed by tumor aggressiveness or by tumor grade. A positive association between MTH use and non–muscle-invasive urothelial carcinoma risk was observed.

Conclusions: Our results support that increasing the number of FTP may reduce urothelial carcinoma risk.

Impact: More detailed studies on parity are needed to understand the possible effects of perinatal hormone changes in urothelial cells.

[1]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), Gran Via de L'Hospitalet 199-203, L'Hospitalet de Llobregat, Barcelona, Spain. [2]Bellvitge Biomedical Research Institute – IDIBELL, Gran Via de L'Hospitalet 199-203, 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, L'Hospitalet de Llobregat, Barcelona, Spain. [4]Cancer Registry of Norway, Oslo University Hospital, Ullernchausseen 64, Oslo, Norway. [5]Norwegian National Advisory Unit for Women's Health, Women's Clinic, Oslo University Hospital, Sognsvannsveien 20, Oslo, Norway. [6]Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Via Cosimo il Vecchio 2, Florence, Italy. [7]Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden. [8]Diet, Genes and Environment, Danish Cancer Society Research Center, Strandboulevarden 49, Copenhagen, Denmark. [9]Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Øster Farimagsgade 5, Copenhagen, Denmark. [10]Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. [11]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, the Netherlands. [12]Department of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, St Mary's Campus, Norfolk Place, London, United Kingdom. [13]Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Pantai Valley, Kuala Lumpur, Malaysia. [14]Department of Community Medicine, University of Tromsø, The Arctic University of Norway, Tromsø, Norway. [15]Department of Cancer Registry and Histopathology, "Civic -M.P. Arezzo" Hospital, ASP Ragusa, Ragusa, Italy. [16]Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, the Netherlands. [17]Department of Urology, Skåne University Hospital and Institution of Translational Medicine, Lund University, Jan Waldenströms gata 5, Malmö, Sweden. [18]Department of Clinical Sciences Lund, Lund University, Barngatan 4, Lund, Sweden. [19]International Agency for Research on Cancer/World Health Organization, Lyon, France. [20]Inserm U1018, Centre for Research in Epidemiology and Population Health (CESP) "Health across Generations" Team, Gustave Roussy 114 rue Edouard Vaillant, Villejuif, France. [21]Department of Biobank Research, Umeå University, Umeå, Sweden. [22]Department of Surgical Sciences, Uppsala University, Akademiska sjukhuset entrence 70, Uppsala, Sweden. [23]Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark. [24]Department of Pharmacy, University of Tromsø, The Arctic University of Norway, Tromsø, Norway. [25]Division of Cancer Epidemiology, German Cancer Research Center (DFKZ), Im Neuenheimer Feld 280, Heidelberg, Germany. [26]Public Health Directorate, C/Ciriaco Miguel Virgil 9, Oviedo, Asturias, Spain. [27]Escuela Andaluza de Salud Pública (EASP), Cuesta del Observatorio 4, Granada, Spain. [28]Instituto de Investigación Biosanitaria ibs.GRANADA, Av. de las Fuerzas

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, accounting for 95% of all cases in industrialized nations (4) and almost 71% of men and 63% of women are diagnosed with non–muscle-invasive urothelial carcinoma (2).

Between 50% and 64% of urothelial carcinoma 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 urothelial carcinoma 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 urothelial carcinoma 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 urothelial carcinoma 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 estrogen supplementation (7). Moreover, castration of male mice and pregnancy and/or lactation in female mice can decrease the growth of bladder cancer (8). Previous epidemiologic studies have reported a reduced risk of urothelial carcinoma in parous women compared with 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, age at first full-term pregnancy (FTP), and breastfeeding and urothelial carcinoma 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 urothelial carcinoma in women who used estrogen plus progestin MHT compared with 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 urothelial carcinoma risk did not stratify by tumor characteristics (based on tumor grade and tumor stage).

We used a large number of cases (most of them with detailed urothelial carcinoma's characteristics) within a large multicentric 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 urothelial carcinoma, overall and by tumor grade, tumor aggressiveness, and non–muscle-invasive urothelial carcinoma, and accounting for smoking status.

Materials and Methods

Study design and population

The European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) is an ongoing multicenter cohort study that recruited participants from 23 centers located in 10 European countries. The EPIC study was performed in accordance with the Declaration of Helsinki. All participants signed an informed consent form, and each center 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 nonmelanoma skin cancer, or participants with missing follow-up information were excluded ($n = 29{,}332$). Only women were eligible for this 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; ref. 21) were excluded ($n = 10{,}066$). After these exclusions, this analysis included 333,919 women.

Armadas 2, Granada, Spain. [29]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Av. Monforte de Lemos 3-5, Madrid, Spain. [30]Universidad de Granada, Av. del Hospicio 1, Granada, Spain. [31]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Ronda de Levante 11, Murcia, Spain. [32]Cancer Epidemiology Unit, Nuffield Department of Population Health University of Oxford, Oxford, United Kingdom. [33]Faculty of Medicine, Imperial College London, Norfolk Place, London, United Kingdom. [34]Hellenic Health Foundation, Kaisareias 13 & Alexandroupoleos, Athens, Greece. [35]2nd Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" University Hospital, Haidari, Greece. [36]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumouri, Via Venezian 1, Milano, Italy. [37]Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco (Turin), Italy. [38]Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Via Pansini 5, Naples, Italy. [39]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. [40]Navarra Public Health Institute, C/Leyre 15, Pamplona, Spain. [41]Navarra Institute for Health Research (IdiSNA), C/Irunlarrea 3, Pamplona, Spain. [42]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. [43]Department of Public Health and Primary Care, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, United Kingdom. [44]German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114 – 116, Nuthetal, Germany. [45]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. [46]ONCOBELL Program, Bellvitge Biomedical Research Institute (IDIBELL), Gran Via de L'Hospitalet 199-203, 08908, L'Hospitalet de Llobregat, Barcelona, Spain.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

E. Weiderpass and E.J. Duell contributed equally to this article.

Corresponding Author: Leila Lujan-Barroso, Catalan Institute of Oncology (ICO-IDIBELL), Avda Gran Via 199, Barcelona 203 08907, Spain. Phone: 349-3260-7401; Fax: 349-3260-7787; E-mail: llujan@iconcologia.net

Cancer Epidemiol Biomarkers Prev 2020;29:1654–64

doi: 10.1158/1055-9965.EPI-20-0184

Hormonal and reproductive factors

Self-reported menstrual factors and exogenous hormone use included: age at menarche (<12, 12, 13, 14, and >14 years), history (yes/no), and duration of oral contraceptive use (nonuser, >0–≤1, >1–5, and >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, and ≥53 years), age at any menopause (surgical and natural, ≤46, 47–49, 50–52, and ≥53 years), MHT use (yes/no) and duration (nonuser, >0–≤1.25, >1.25–4, and >4 years), type of MHT (estrogen alone, progestin alone, or estrogen 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 FTPs × 9 months, due to the absence of menstrual cycles for 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 oral contraceptives 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 oral contraceptive use, those models were additionality adjusted for number of FTP and oral contraceptive use.

Self-reported reproductive history included: parity (yes/no), number of FTP (including livebirths and stillbirths; 0, 1, 2, 3, 4, and ≥5), age at first FTP (in parous women; ≤20, 21–13, 24–25, 26–30, and ≥30 years), number of induced (never pregnant, 0, 1, and ≥2) and spontaneous abortions (never pregnant, 0, 1, and ≥2), breastfeeding (in parous women; yes/no), and duration of breastfeeding (in parous women who breastfeed; 0>–≤3, >3–12, and >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 urothelial carcinoma was completed between December 2011 and December 2013, depending on the center.

Bladder cancers were defined by ICD-O-3, including first invasive cancer (coded C67 based) and urothelial carcinoma (morphology codes 812*–813*; ref. 23). Only incident urothelial carcinoma was included in this analysis because it represents 95% of all bladder cancers. Definitions of urothelial carcinoma subtype classifications are heterogeneous in the literature. In previous EPIC studies, urothelial carcinoma was classified by pathology reports as aggressive [pT1 and higher or carcinoma *in situ* (CIS) or World Health Organization (WHO) grade 3] and nonaggressive (pTa grade 1 and 2; ref. 23). We also analyzed urothelial carcinoma by tumor grade (using WHO-defined grades 2 and 3 as "high-grade" and grade 1 as "low-grade"; ref. 24). Finally, in centers where tumor stage information was available (available in all centers except San Sebastian, United Kingdom, Greece, Malmö, and Norway), we analyzed urothelial carcinoma restricted to non–muscle-invasive subtype (pT1, pTa, or CIS).

Statistical analysis

To evaluate associations between hormonal factors and urothelial carcinoma risk, Cox proportional hazards regression was used to estimate 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 urothelial carcinoma or the end of follow-up (whichever came first) as the exit time. Additional models were performed to describe the risk of urothelial carcinoma by tumor aggressiveness, tumor grade (using the Wald test statistic to assess the heterogeneity of the risk between outcomes using the SAS macro *%subtype*; ref. 25), and non–muscle-invasive urothelial carcinoma. All models were stratified by age at recruitment (1-year categories) and study center. 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. Furthermore, 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/day; ref. 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 confounders given the established effect of a number of chemicals and substances [e.g., heavy metal, dyes, and polycyclic aromatic hydrocarbons (PAH)] on sex hormones' levels among healthy women (26–28). 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 and colleagues (29). Nevertheless, occupation was ultimately not included in the multivariate-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 was used to select the best representation of the relation between number of FTP (among parous women) and urothelial carcinoma risk (Supplementary Fig. S1).

Modification of the HRs by tobacco use at baseline (never, former, and current) was evaluated using a likelihood ratio test. 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.

Results

Descriptive statistics

After a median follow-up time of 15 years, 529 urothelial carcinoma cases were identified including 146 nonaggressive tumors, 230 aggressive tumors, and 153 with unknown tumor aggressiveness; and among the 529 cases, there were 80 low-grade tumors, 233 high-grade tumors, and 216 with unknown tumor 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 urothelial carcinoma 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 oral contraceptive use, age at natural menopause, oophorectomy, and hysterectomy showed no association with urothelial carcinoma risk (**Tables 2** and **3**). Elevated and statistically significant HRs for urothelial carcinoma were observed for postmenopausal status (natural or surgical) compared with premenopausal status ($HR_{postnaturalvspre}$: 1.88; 95% CI, 1.09–3.25; $HR_{postsurgicalvspre}$: 2.15; 95% CI, 1.10–4.20; **Table 1**). MHT use in peri-/postmenopausal women (natural or surgical) was positively associated with overall urothelial carcinoma independently of the duration of MHT use (**Table 3**). For the 67% (n = 52,892; cases = 82) of women with information on formulation of MHT available, 25% (n = 13,123; cases = 32) took estrogen alone (HR, 1.43; 95% CI, 0.97–2.10). No association was observed for use of estrogen 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 urothelial carcinoma risk ($HR_{3vs1FTP}$: 0.70, 95% CI, 0.52–0.94; $HR_{\geq 5vs1FTP}$: 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 urothelial carcinoma

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 urothelial carcinoma 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**). Furthermore, the HR for peri-/postmenopausal MHT users compared with peri-/postmenopausal women never users was 1.27 (95% CI, 1.03–1.57; **Table 5**).

Study of the heterogeneity of the risk between nonaggressive tumors and aggressive tumors

MHT use was positively associated with risk of nonaggressive urothelial carcinoma ($HR_{yesvsno}$, 1.93; 95% CI, 1.29–2.87). Parity was inversely associated with nonaggressive urothelial carcinoma risk ($HR_{yesvsno}$, 0.59; 95% CI, 0.39–0.90). Natural and surgical menopause were statistically significantly associated with risk of aggressive urothelial carcinoma ($HR_{naturalvspre}$: 2.47, 95% CI, 1.01–6.03; $HR_{surgicalvspre}$: 3.25, 95% CI, 1.18–8.97; Supplementary Table S1). Despite these statistically significant individual associations, statistically significant heterogeneity of the risk for menstrual factors and exogenous hormone use by tumor aggressiveness was not observed for each individual model and for the mutually adjusted model (all $P_{het} > 0.05$).

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

MHT use was positively associated with low-grade tumors (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 tumors. Parity was inversely associated with low-grade tumors ($HR_{yesvsno}$, 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 urothelial carcinoma risk (Supplementary Table S1).

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

Risk estimation between hormonal and reproductive factors and non–muscle-invasive urothelial carcinoma

Positive association was observed between MHT users and non–muscle-invasive urothelial carcinoma risk (HR, 1.38; 95% CI, 1.01–1.90), especially in women whose treatment's formulation was estrogen alone (HR, 1.90; 95% CI, 1.15–3.13; Supplementary Table S1).

Modification of the HRs by tobacco

No evidence for modification of HRs for each factor and urothelial carcinoma by cigarette smoking status was found (all likelihood ratio statistics $P > 0.05$) with the exception of induced abortions ($P = 0.028$). 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 urothelial carcinoma was observed, HR for never smoking women with at least two induced abortions compare with zero abortions was 2.52 (95% CI, 1.33–4.78; P_{trend} = 0.012; Supplementary Table S2).

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; Supplementary Table S3). 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 (Supplementary Tables S2 and S5), or in the subgroup of participants who were peri-/postmenopausal at recruitment (**Table 5**). In never smokers, no

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/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)	11,101 (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)

Note: 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, PAHs, and environmental tobacco smoke.

Table 2. Multivariate-adjusted models for each individual menstrual factor in relation to urothelial carcinoma 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 postmenopausal	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)	

Note: 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."

Abbreviations: FTP, full-term pregnancies; OC, oral contraceptive.

[a]Cox proportional hazards model stratified by center and age at recruitment and adjusted by smoking status and intensity and fruits and vegetables intake.

[b]Cox proportional hazards model stratified by center and age at recruitment and adjusted by smoking status and intensity, fruits and vegetables intake, OC use, and FTP.

[c]Women who had surgical menopause were excluded.

[d]Available in all centers except Malmö.

association between MHT use and urothelial carcinoma risk was observed in the final mutually adjusted model (**Table 5**).

Discussion

These analyses, based on 529 women, showed evidence that women who had experienced more than one birth are at lower risk of developing urothelial carcinoma compared with uniparous women; furthermore, we observed evidence of an inverse trend between urothelial carcinoma 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 urothelial carcinoma risk by the number of FTPs or other menstrual factors, reproductive history factor, or exogenous hormone use according to tumor characteristics (based on tumor grade and tumor stage).

Previous studies (11, 12, 18) and two meta-analyses (10, 17) observed a reduced risk of urothelial carcinoma 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 urothelial carcinoma risk with increasing number of FTP. This reduction in

Table 3. Multivariate-adjusted models for each individual exogenous hormone use in relation to urothelial carcinoma risk in EPIC women.

	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]				
None	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]				
Nonusers of MHT	1,527,202	215 (58.0)	1.00 (referent)	
Estrogen alone	178,339	32 (8.6)	1.43 (0.97–2.10)	
Estrogen + 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)	

Note: Estimation of "unknown" category is provided when more than 10% of the cases are classified as "unknown."
Abbreviations: MHT, menopausal hormone therapy; OC, oral contraceptive.
[a]Cox proportional hazards model stratified by center and age at recruitment and adjusted by smoking status and intensity and fruits and vegetables intake.
[b]In peri- and postmenopausal (natural or surgical).
[c]Available in France, Italy, Spain, United Kingdom, the Netherlands, Germany, Denmark, and Norway.

risk with increasing FTP was also observed in never smokers. The observed trend in our study was similar to the trend reported by Weibull and colleagues (HR for ≥3 vs. 1 FTP: 0.76; 95% CI, 0.68–0.86; ref. 12).

Women experience several hormonal changes during pregnancy, including an increase in estrogen 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). Furthermore, it has been shown that estrogen receptors (ER) and progesterone receptors (PR), that mediate estrogen 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 tumor 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 estrogen and progesterone may reduce urothelial carcinoma risk in parous women (9–12, 17, 36).

Two previous studies have examined the association between induced abortions and the risk of urothelial carcinoma (15, 37). These two case–control studies did not observe that the number of induced abortions was associated with urothelial carcinoma 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 urothelial carcinoma risk may be due to chance.

It has been hypothesized that earlier age at menopause increases urothelial carcinoma risk due to lower levels of estrogen after menopause (14). Earlier age at menopause (natural or surgical) was associated with an increased risk of urothelial carcinoma in a meta-analysis (17), that included four case–control studies and three cohort studies. We observed no association between earlier age at menopause and urothelial carcinoma, in agreement with other recent prospective cohort studies (10, 11, 18).

The higher urothelial carcinoma risk we observed in peri-/postmenopausal MHT users, when compared with peri-/postmenopausal nonusers, 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 urothelial carcinoma (results for estrogen: $n = 136$ cases; HR, 0.93; 95% CI, 0.74–1.17;

Table 4. Multivariate-adjusted models for each individual reproductive factor in relation to urothelial carcinoma 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 FTPs[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 FTP, 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)	
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)	

Note: 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."

Abbreviation: FTP, full-term pregnancy.

[a]Cox proportional hazards model stratified by center and age at recruitment and adjusted by smoking status and intensity and fruits and vegetables intake.

[b]Available in all centers except Bilthoven.

[c]Including nulliparous women and women without FTPs.

[d]In parous women.

[e]Available in all centers except Bilthoven and Umeå.

[f]In parous women who have ever breastfed.

[g]Available in all centers except Bilthoven, Malmö, Umeå, and Norway.

[h]Available in all centers except Bilthoven, Umeå, and Norway.

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

results for estrogen plus progestin: $n = 103$ cases; HR, 1.05; 95% CI, 0.81–1.36; ref. 18). A meta-analysis (based on four cohort studies) of MHT by formulation (estrogen or estrogen plus progestin) showed a 39% decreased urothelial carcinoma risk in users of estrogen plus progestin ($n = 84$ cases; RR, 0.61; 95% CI, 0.47–0.78), and no effect for users of estrogen alone ($n = 217$ cases; RR, 1.03; 95% CI, 0.87–1.24; ref. 11). Our results, based on smaller sample sizes (52 urothelial carcinomas for estrogen and 30 urothelial carcinomas for estrogen plus progestin), were in agreement with those from the WHI; however, we observed a positively statistically significant estimation in current smokers who used estrogen alone or reported unknown type of MHT. Because 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 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,

Table 5. Mutually adjusted models for menopause status, MHT, and parity in relation to urothelial carcinoma 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 and use of MHT									
Premenopausal	49 (9.3)	0.73 (0.43–1.22)		18 (9.2)	1.23 (0.52–2.43)				
Peri-/postmenopausal and nonusers of MHT	247 (46.7)	1.00 (referent)		105 (53.9)	1.00 (referent)		247 (51.5)	1.00 (referent)	
Peri-/postmenopausal and 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 and unknown MHT use	61 (11.5)	1.35 (0.88–2.07)		20 (10.3)	1.12 (0.53–2.39)		61 (12.7)	1.34 (0.89–2.02)	
Number of FTPs[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)	

Note: 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."

Abbreviations: FTP, full-term pregnancy; MHT, menopausal hormone therapy.

[a]Cox proportional hazards model stratified by center and age at recruitment and adjusted by menopausal status and MHT, number of FTPs, smoking status and intensity, and fruits and vegetables intake.

[b]Cox proportional hazards model stratified by center and age at recruitment and adjusted by menopausal status and MHT, number of FTPs, and fruits and vegetables intake.

[c]Available in all centers having information except Bilthoven.

[d]Including nulliparous women and women without FTPs.

[e]In parous women

reproductive history, hormone use, and urothelial carcinoma risk that includes information on tumor classification. However, non–muscle-invasive urothelial carcinoma classification was not available in San Sebastian, Oxford, Cambridge, Malmö, and Norway centers.

One potential weakness of our analysis is that information on reproductive history and hormone use was available only at cohort enrollment; 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 enrollment. 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 enrollment. Furthermore, tumor grade and tumor 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 centers collected such information. Furthermore, occupational exposure was available for 32% ($n = 169$) of urothelial carcinoma cases; of which 10% ($n = 17$) reported jobs considered at risk. Despite this, a sensitivity analysis was performed including occupational exposures in the final urothelial carcinoma model and similar HR estimates for menopausal status, MHT use, and number of FTPs were observed.

Conclusion

Our results confirm the increasing benefit of each birth after the first on urothelial carcinoma 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.

Disclosure of Potential Conflicts of Interest

B. Ljungberg reports receiving speakers bureau honoraria from Novartis, Pfizer, IPSEN, and Bristol-Myers Squibb; participation in trials by Janssen, Astellas, and Medivation; consultancy with Janssen, Ipsen, and MSD; and other from EAU. No potential conflicts of interest were disclosed by the other authors.

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.

Authors' Contributions

Conception and design: L. Lujan-Barroso, S. Caini, N. Roswall, A. Tjønneland, B. Bueno-de-Mesquita, R. Tumino, K. Overvad, E. Lund, A. Barricarte, K.-T. Khaw, H. Boeing, E.J. Duell

Development of methodology: E. Botteri, N. Roswall, B. Bueno-de-Mesquita, A. Karakatsani, H. Boeing, E.J. Duell

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Ljungberg, A. Tjønneland, B. Bueno-de-Mesquita, R. Tumino, L.A. Kiemeney, C. Häggström, K. Overvad, E. Lund, T. Kühn, M.-J. Sánchez, A. Trichopoulou, A. Karakatsani, D. Palli, V. Krogh, A. Mattiello, S. Panico, C.H. van Gils, A. Barricarte, P. Amiano, K.-T. Khaw, H. Boeing, E. Weiderpass
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Lujan-Barroso, E. Botteri, S. Caini, N. Roswall, I.T. Gram, M.J. Gunter, M. Kvaskoff, R.T. Fortner, E.J. Duell
Writing, review, and/or revision of the manuscript: L. Lujan-Barroso, E. Botteri, S. Caini, B. Ljungberg, N. Roswall, A. Tjønneland, B. Bueno-de-Mesquita, I.T. Gram, R. Tumino, L.A. Kiemeney, F. Liedberg, T. Stocks, M.J. Gunter, N. Murphy, I. Cervenka, A. Fournier, M. Kvaskoff, C. Häggström, K. Overvad, E. Lund, M. Waaseth, R.T. Fortner, M.-J. Sánchez, C. Santiuste, A. Perez-Cornago, R. Zamora-Ros, A.J. Cross, A. Trichopoulou, A. Karakatsani, E. Peppa, D. Palli, V. Krogh, V. Sciannameo, A. Mattiello, S. Panico, C.H. van Gils, N.C. Onland-Moret, A. Barricarte, P. Amiano, K.-T. Khaw, H. Boeing, E. Weiderpass, E.J. Duell
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Liedberg, V. Menéndez, R. Zamora-Ros, A. Karakatsani
Study supervision: R. Tumino, L.A. Kiemeney, E.J. Duell

Acknowledgments

The authors thank CERCA Program/Generalitat de Catalunya for institutional support. The coordination of EPIC was financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts were supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, and Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, and Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Compagnia di San-Paolo (Naples, Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Comprehensive Cancer Center The Netherlands (IKNL), Zorg Onderzoek Nederland Medische Wetenschappen (ZONMW), World Cancer Research Fund (WCRF), Dutch Cancer Society (KWF), Statistics Netherlands (the Netherlands); Health Research Fund (FIS) - Instituto de Salud Carlos III (ISCIII), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, and the Catalan Institute of Oncology - ICO (Spain); Swedish Cancer Society and Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); and Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford) and Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford; United Kingdom). R. Zamora-Ros thanks the "Miguel Servet" program (CP15/00100) from the Institute of Health Carlos III and European Social Fund (ESF). For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Received February 7, 2020; revised April 7, 2020; accepted May 19, 2020; published first May 28, 2020.

References

1. Global Cancer Observatory [homepage on the Internet]. Lyon (France): International Agency for Research on Cancer; 2020. Available from: http://gco.iarc.fr/.
2. Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH. The effect of age and gender on bladder cancer: a critical review of the literature. BJU Int 2010;105:300–8.
3. ECIS - European Cancer Information System [database on the Internet]. Brussels (Belgium): European Commission. Available from: https://ecis.jrc.ec.europa.eu/explorer.php?$0-2.
4. Malats N, Real FX. Epidemiology of bladder cancer. Hematol Oncol Clin North Am 2015;29:177–89.
5. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA 2011;306:737–45.
6. Bladder cancer statistics; [about 6 screens]. Available from: http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/bladder-cancer-statistics.
7. Tanahashi NK, Suzawa N, Azuma C. Effects of sex hormones on oncogenesis in rat urinary bladder by N-butyl-N-(4-hydroxybutyl)-nitrosamine. Int J Clin Pharmacol Biopharm 1977;15:101–5.
8. Johnson AM, O'Connell MJ, Messing EM, Reeder JE. Decreased bladder cancer growth in parous mice. Urology 2008;72:470–3.
9. Huang A-T, Kogevinas M, Silverman DT, Malats N, Rothman N, Tardon A, et al. Bladder cancer and reproductive factors among women in Spain. Cancer Causes Control 2009;20:1907–13.
10. Davis-Dao CA, Henderson KD, Sullivan-Halley J, Ma H, West D, Xiang YB, et al. Lower risk in parous women suggests that hormonal factors are important in bladder cancer etiology. Cancer Epidemiol Biomarkers Prev 2011;20:1156–70.
11. Daugherty SE, Lacey JV, Pfeiffer RM, Park Y, Hoover RN, Silverman DT. Reproductive factors and menopausal hormone therapy and bladder cancer risk in the NIH-AARP Diet and Health Study. Int J Cancer 2013;133:462–72.
12. Weibull CE, Eloranta S, Altman D, Johansson ALV, Lambe M. Childbearing and the risk of bladder cancer: a nationwide population-based cohort study. Eur Urol 2013;63:733–8.
13. McGrath M, Michaud DS, De Vivo I. Hormonal and reproductive factors and the risk of bladder cancer in women. Am J Epidemiol 2006;163:236–44.
14. Prizment AE, Anderson KE, Harlow BL, Folsom AR. Reproductive risk factors for incident bladder cancer: Iowa Women's Health Study. Int J Cancer 2007;120:1093–8.
15. Pelucchi C, La Vecchia C, Negri E, Dal Maso L, Franceschi S. Smoking and other risk factors for bladder cancer in women. Prev Med 2002;35:114–20.
16. Cantwell MM, Lacey JV, Schairer C, Schatzkin A, Michaud DS. Reproductive factors, exogenous hormone use and bladder cancer risk in a prospective study. Int J Cancer 2006;119:2398–401.
17. Dietrich K, Demidenko E, Schned A, Zens MS, Heaney J, Karagas MR. Parity, early menopause and the incidence of bladder cancer in women: a case-control study and meta-analysis. Eur J Cancer 2011;47:592–9.
18. Kabat GC, Kim MY, Luo J, Hou L, Cetnar J, Wactawski-Wende J, et al. Menstrual and reproductive factors and exogenous hormone use and risk of transitional cell bladder cancer in postmenopausal women. Eur J Cancer Prev 2013;22:409–16.
19. Fernandez E, Gallus S, Bosetti C, Franceschi S, Negri E, La Vecchia C. Hormone replacement therapy and cancer risk: a systematic analysis from a network of case-control studies. Int J Cancer 2003;105:408–12.
20. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24.
21. Ferrari P, Slimani N, Ciampi A, Trichopoulou A, Naska A, Lauria C, et al. Evaluation of under- and overreporting of energy intake in the 24-hour diet recalls in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5:1329–45.
22. Duell EJ, Travier N, Lujan-Barroso L, Boutron-Ruault MC, Clavel-Chapelon F, Palli D, et al. Menstrual and reproductive factors, exogenous hormone use, and gastric cancer risk in a cohort of women from the European Prospective Investigation into Cancer and Nutrition. Am J Epidemiol 2010;172:1384–93.
23. Roswall N, Freisling H, Bueno-de-Mesquita HB, Ros M, Christensen J, Overvad K, et al. Anthropometric measures and bladder cancer risk: a prospective study in the EPIC cohort. Int J Cancer 2014;135:2918–29.
24. Compérat EM, Burger M, Gontero P, Mostafid AH, Palou J, Rouprêt M, et al. Grading of urothelial carcinoma and the new "World Health Organisation Classification of Tumours of the Urinary System and Male Genital Organs 2016." Eur Urol Focus 2018;5:457–66.
25. Wang M, Spiegelman D, Kuchiba A, Lochhead P, Kim S, Chan AT, et al. Statistical methods for studying disease subtype heterogeneity. Stat Med 2016;35:782–800.
26. Nagata C, Wada K, Tsuji M, Hayashi M, Takeda N, Yasuda K. Association of hair dye use with circulating levels of sex hormones in premenopausal Japanese women. Eur J Public Health 2015;25:895–9.
27. Yin S, Tang M, Chen F, Li T, Liu W. Environmental exposure to polycyclic aromatic hydrocarbons (PAHs): the correlation with and impact on reproductive hormones in umbilical cord serum. Environ Pollut 2017;220:1429–37.

28. Pollack AZ, Schisterman EF, Goldman LR, Mumford SL, Albert PS, Jones RL, et al. Cadmium, lead, and mercury in relation to reproductive hormones and anovulation in premenopausal women. Environ Health Perspect 2011;119: 1156–61.
29. Büchner FL, Bueno-de-Mesquita HB, Ros MM, Kampman E, Egevad L, Overvad K, et al. Consumption of vegetables and fruit and the risk of bladder cancer in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2009;125:2643–51.
30. Modugno F, Laskey R, Smith AL, Andersen CL, Haluska P, Oesterreich S. Hormone response in ovarian cancer: time to reconsider as a clinical target? Endocr Relat Cancer 2012;19:R255–79.
31. Rodrìguez LV, Wang B, Shortliffe LMD. Structural changes in the bladder walls of pregnant and hormonetreated rats: correlation with bladder dynamics. BJU Int 2004;94:1366–72.
32. Shen SS, Smith CL, Hsieh J-T, Yu J, Kim IY, Jian W, et al. Expression of estrogen receptors-alpha and -beta in bladder cancer cell lines and human bladder tumor tissue. Cancer 2006;106:2610–6.
33. Blakeman PJ, Hilton P, Bulmer JN. Oestrogen and progesterone receptor expression in the female lower urinary tract, with reference to oestrogen status. BJU Int 2000;86:32–8.
34. Thomas C, Gustafsson J-Å. The different roles of ER subtypes in cancer biology and therapy. Nat Rev Cancer 2011;11:597.
35. Batra SC, Iosif CS. Progesterone receptors in the female lower urinary tract. J Urol 1987;138:1301–4.
36. Bai Y, Wang X, Yang Y, Tang Y, Wang J, Han P. Parity and bladder cancer risk: a dose-response meta-analysis. BMC Cancer 2017;17:31.
37. La Vecchia C, Negri E, Franceschi S, Parazzini F. Long-term impact of reproductive factors on cancer risk. Int J Cancer 1993;53:215–9.