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Reproductive and Hormone-Related Risk Factors for Epithelial Ovarian Cancer by Histologic Pathways, Invasiveness, and Histologic Subtypes: Results from the EPIC Cohort

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Abstract

Whether risk factors for epithelial ovarian cancer (EOC) differ by subtype (i.e., dualistic pathway of carcinogenesis, histologic subtype) is not well understood; however, data to date suggest risk factor differences. We examined associations between reproductive and hormone-related risk factors for EOC by subtype in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Among 334,126 women with data on reproductive and hormone-related risk factors (follow-up: 1992-2010), 1,245 incident cases of EOC with known histology and invasiveness were identified. Data on tumor histology, grade, and invasiveness, was available from cancer registries and pathology record review. We observed significant heterogeneity by the dualistic model (i.e., type I [low grade serous or endometrioid, mucinous, clear cell, malignant Brenner] vs. type II [high grade serous or endometrioid]) for full-term pregnancy (p_{het}=0.02). Full-term pregnancy was more strongly inversely associated with type I than type II tumors (ever vs. never: type I: Relative Risk (RR) 0.47 [95% confidence interval (CI): 0.33-0.69]; type II, RR: 0.81 [0.61-1.06]). We observed no significant differences in risk in analyses by major histologic subtypes of invasive EOC (serous, mucinous, endometrioid, clear cell). None of the investigated factors were associated with borderline tumors. Established protective factors, including duration of oral contraceptive use and full term pregnancy, were consistently inversely associated with risk across histologic subtypes (e.g., ever full-term pregnancy: serous, RR: 0.73 [0.58-0.92]; mucinous, RR: 0.53 [0.30-0.95]; endometrioid, RR: 0.65 [0.40-1.06]; clear cell, RR: 0.34 [0.18-0.64]; p_{het}=0.16). These results suggest limited heterogeneity between reproductive and hormone-related risk factors and EOC subtypes.

Keywords

ovarian cancer; reproductive factors; histologic subtype; dualistic model

Introduction

Reproductive and hormone-related risk factors for epithelial ovarian cancer (EOC) have been extensively investigated (reviewed in ref 1). However, EOC is increasingly recognized as a heterogeneous disease and risk factor differences across EOC subtypes, such as the recently proposed dualistic pathway of ovarian carcinogenesis (i.e., type I, type II1,2) and main histologic subgroups (i.e., serous, mucinous, endometrioid), are not well understood.

The dualistic model of ovarian carcinogenesis suggests that EOC develops by two pathways: 2 type I tumors are less aggressive and are thought to develop from defined precursor lesions (i.e. borderline tumors, endometriosis), while type II tumors are more aggressive, rapidly metastasize, and have no well-defined precursor lesion within the ovary.3 Type I EOC includes low grade serous and endometrioid EOC, as well as mucinous, clear cell, and malignant Brenner tumors, whereas type II tumors are primarily high grade serous or endometrioid EOC. To our knowledge, only one prior study has investigated reproductive and hormone-related risk factors by the dualistic pathway; this study observed significant heterogeneity in risk factors between type I and type II tumors.4 For example, parity exerted a stronger protective effect against type I tumors, whereas associations between duration of oral contraceptive (OC) use and breastfeeding duration were stronger for type II tumors.4 These findings have not yet been replicated.

Prior studies suggest risk factors for epithelial ovarian cancer may differ by histologic subtype.1,4–13 For example, a collaborative reanalysis of 45 epidemiologic studies found the risk reduction afforded by OC use was evident for serous, endometrioid and clear cell, but not mucinous, tumors13 and an analysis in the Ovarian Cancer Cohort Consortium (OCAC) found a positive association between body mass index (BMI) and risk of invasive endometrioid, mucinous and clear cell, but not high grade serous, tumors.12 However, heterogeneous associations between BMI and EOC histologic subgroups have not been observed in all studies.14 The extent to which reproductive and hormone-related factors impact risk differentially by histologic subtype remains unclear.

An improved understanding of heterogeneity in risk across EOC subtypes will ultimately improve our understanding of the etiology of this lethal disease. Therefore, we present a detailed investigation of reproductive and hormone-related risk factors and EOC by the dualistic pathway of carcinogenesis and major histologic subtypes in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Methods

The EPIC cohort was established between 1992-2000 at 23 centers in 10 countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Details of the study design have been published previously.15,16 Briefly,

more than 500,000 men and women between the ages of approximately 25-75 years of age were enrolled; participants provided detailed information on diet and lifestyle, including data on reproductive and menstrual history, hormone use, and medical history. In all countries except France, Germany, and Greece, as well as the center of Naples, Italy, follow-up is based on record linkage; the end of follow-up was the date of last follow-up for cancer incidence and vital status (2004-2009). In France, Germany, Greece, and Naples, Italy, a combination of active follow-up with participants and their next-of-kin, and outcome verification with medical and health insurance records was used. Vital status is available from mortality registries. End of follow-up for France, Germany, Greece, and Naples, Italy, was the earliest of date of last contact, cancer diagnosis, or death (2005-2010). All subjects provided written informed consent. The Institutional Review Boards of the International Agency for Cancer Research and the local ethics committees approved the study.

Study Population and Case Ascertainment

Participants were excluded if they reported history of prior cancer at recruitment (except non-melanoma skin cancer), had incomplete baseline data, or reported bilateral oophorectomy at baseline, leaving a study population of 334,225 women. We additionally excluded women missing data on all investigated reproductive and hormone-related risk factors (n=99). Our final study population included 334,126 women. Cases were defined as women diagnosed after recruitment with an incident epithelial borderline tumor (C569) or invasive ovarian (C569), fallopian tube (C570) or peritoneal cancer (C480, C481, C482, C488) according to the International Classification of Diseases for Oncology (ICD) O–3 topography codes. The majority of tumors identified were ovarian (borderline: 100%, n=106; invasive: 93%, n=1063), with a relatively small proportion of fallopian tube (3.4%, n=42) and peritoneal (2.7%, n=34) malignancies included. Data on invasiveness, histology, cancer stage, and tumor grade was available from cancer registries and pathology record review. A total of 1,245 EOC cases with data on tumor histology and invasiveness were identified. Grade information, used for type I and type II classification, was complete for 56% of cases (n=670).

Invasive tumors were classified as type I or type II as described by Shih and Kurman.2 Type I tumors were defined as low-grade (grade 1, well differentiated) tumors of serous and endometrioid histology, as well as mucinous, clear cell and malignant Brenner tumors; type II tumors include high-grade (grade 2 or 3, moderately or poorly differentiated) serous and endometrioid tumors, as well as undifferentiated and malignant mixed Mullerian tumors.

Exposure Assessment

Data on age at menarche, age at menopause, parity and number of full-term pregnancies, breast feeding, menstrual cycle regularity, OC use and duration, menopausal hormone replacement therapy (MHT) use, and hysterectomy were collected at baseline using standardized questionnaires. Height (cm) and weight (kg) were measured according to standardized procedures, except for the Oxford cohort, the Norwegian cohort, and part of the French cohort, where height and weight were predominantly self-reported.17 For participants from the Oxford cohort, where only self-reported data were available, linear regression models were used to recalibrate values using age-specific measurements from

subjects with both measured and self-reported body measures. These measures were used to calculate body mass index (BMI; kg/m^2).

Statistical Analysis

We used Cox proportional hazards models to estimate the association between reproductive and hormone-related factors and risk of overall invasive EOC (n=1,139) and borderline tumors (n=106), as well as invasive EOC by main histologic subtypes (serous (n=631), mucinous (n=79), endometrioid (n=131), and clear cell (n=57)), and type I (n=184) and type II (n=480) status. Age in years was the underlying time scale, and all analyses were stratified by age and study center. Main exposure variables were categorized as follows: age at menarche: ≤13, 14, ≥15 years; age at menopause: ≤48, 49-50, 51-54, ≥55 years; full-term pregnancy: yes/no; number of full-term pregnancies: 0, 1, 2, 3+; breastfed: yes/no; menstrual cycle regularity: ≤ 26 days, 27-29 days, 30+ days, none or irregular; OC use: yes/no; OC duration: never user, ≤ 1 year, 1-4 years, 5-9 years, ≥10 years; hysterectomy: yes/no; HRT use: yes/no; BMI: normal weight (<25 kg/m^2), overweight (25-30 kg/m^2), obese (≥30 mg/m^2). Tests for trend were conducted by modelling continuous variables.

Covariates for statistical adjustment were identified *a priori.* All analyses were adjusted for OC use (ever/never), HRT use (ever/never), age at menopause (continuous; pre-/perimenopausal assigned median age at menopause), menopausal status at baseline (pre- or perimenopausal/postmenopausal), and full-term pregnancy (ever/never), except when the variable was the main effect. Missing values for HRT use (7.8%) were coded in a “missing” category for statistical adjustment. Missing values for OC use (3.2%) were coded as “never” users; given the low prevalence of missing data for this covariate, we were unable to use separate “missing" category for statistical adjustment. Differences in risk associations by histologic subtype and borderline and type I/II status were assessed using the data augmentation method proposed by Lunn and McNeil.18 Heterogeneity (p_{het}) between subtypes was assessed using a likelihood ratio test comparing models assuming the same association between exposure and EOC across all outcomes (e.g., tumors of serous, mucinous, endometrioid, and clear cell histology as a single outcome) to one assuming different associations for each subtype (i.e., each histology considered individually as an outcome). In analyses by the dualistic model, heterogeneity was assessed between type I and type II tumors, as well as across borderline, type I and type II tumors. Results were similar, therefore p for heterogeneity between type I and type II tumors is presented.

We investigated the major individual components associated with duration of ovulatory lifespan and EOC risk.19 These analyses included ages at menarche and menopause, duration of OC use, and duration of full-term pregnancies (number of full-term pregnancies *0.75), mutually adjusted and as a composite variable to estimate total duration of ovulatory lifespan. We further examined associations between number of full-term pregnancies, age at first and last pregnancy, and time since last pregnancy in mutually adjusted models investigating risk associations among parous women. We used the approach described by Heuch et al.20 to ensure that observed risk estimates were not biased by multi-collinearity. In these analyses, nulliparous women were assigned to the reference category of age at first and last pregnancy, and time since last pregnancy, and indicator variables for parity were

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included in the model such that effect estimates reflect risk among parous women. Sensitivity analyses were conducted excluding women diagnosed with fallopian tube or peritoneal cancers.

P-values <0.05 were considered statistically significant; all p-values were two-sided. All analyses were conducted in SAS 9.3 (Cary, NC).

Results

Baseline characteristics by tumor invasiveness and the dualistic model are presented in Table 1. Briefly, women who remained free of EOC were somewhat younger at recruitment than those diagnosed with invasive disease during follow-up (median age at recruitment, non-cases: 51 years; invasive cases: 55 years), and a higher proportion of women subsequently diagnosed with invasive EOC were postmenopausal at recruitment (63%), relative to women diagnosed with borderline tumors (33%) and to women who remained free of EOC (45%). As expected, the majority of both borderline (58%) and invasive (55%) tumors were of serous histology. A total of 81% of type II tumors were serous, whereas type I tumors were predominantly of mucinous (43%) and clear cell (31%) histology.

Ever full-term pregnancy was differentially associated with risk across subgroups defined by type I and type II status (type I vs. II: ever full-term pregnancy, p_{het}=0.02) (Table 2). We observed a significant inverse association between ever full-term pregnancy and type I tumors (ever vs. never full-term pregnancy: Relative Risk (RR): 0.47 [95% Confidence Interval (CI) 0.33-0.69]), and no association with type II or borderline tumors (type II, RR: 0.81 [0.61-1.06]; borderline, RR: 1.12 [0.59-2.13]). There was no statistically significant heterogeneity by type I and type II status for any of the other investigated exposures. However, age at menopause was significantly associated with type I tumors (≥55 vs. ≤48 years, RR: 2.71 (1.17-6.30), p_{trend}=0.01; p_{het}=0.21) and only suggestively associated with type II tumors (≥55 vs. ≤48 years, RR: 1.57 (0.99-2.47), p_{trend}=0.04). Duration of OC use and number of full-term pregnancies were inversely associated with both type I and type II, but not borderline, tumors (e.g., ≥10 years vs never use of OC: borderline, RR: 0.75 [0.35-1.61], p_{trend}=0.22; type I, RR: 0.54 [0.31-0.94], p_{trend}=0.01; type II, RR: 0.71 [0.51-0.97], p_{trend}=0.01; p_{het}=0.22).

We additionally examined exposures related to total ovulatory lifespan (ages at menarche and menopause, OC use, and pregnancy) in mutually adjusted models (Table 3). We observed no heterogeneity in associations by the dualistic model (all p_{het} values ≥0.09). However, age at menopause was only significantly associated with type I tumors (per year younger age at menopause, RR: 0.92 [0.86-0.98], whereas duration of OC use was only associated with type II tumors (per year of OC use, RR: 0.97 [0.96-0.99]). Risk per year of being pregnant and total ovulatory life span were associated with both type I and type II tumors (per year reduction in ovulatory lifespan: type I, RR: 0.95 [0.92-0.98]; type II, RR: 0.97 [0.96-0.99]; p_{het}=0.17). We repeated these analyses restricted to women postmenopausal at recruitment, given that the data on reproductive history on these women was more complete (i.e., age at menopause was known, no additional pregnancies). Results were somewhat attenuated after restricting the analysis to women postmenopausal at

recruitment (i.e., per year reduction in ovulatory lifespan, postmenopausal women, type I RR: 0.96 [0.92-1.00]; type II RR: 0.99 [0.97-1.00]).

We observed no heterogeneity in the associations between evaluated risk factors and invasive EOC by main histologic subgroups (serous, mucinous, endometrioid, and clear cell; Table 4). While the heterogeneity between subgroups was not statistically significant, evaluated risk factors were associated with risk of individual EOC histologic subgroups. For example, duration of OC use was only significantly associated with reduced risk of serous tumors (e.g., OC use ≥10 years vs. never user, RR: 0.61 [0.46-0.82], $p_{trend}<0.01$, $p_{het}=0.86$), older age at menopause was only associated with risk of endometrioid and clear cell tumors (≥55 vs. ≤48 years, endometrioid: RR: 3.56 [1.63-7.76], $p_{trend}=0.01$; clear cell: RR: 2.27 (1.45-27.1), $p_{trend}=0.03$; $p_{het}=0.09$), and ever full-term pregnancy was significantly inversely associated with serous (RR: 0.73 [0.58-0.92]), mucinous (RR: 0.53 [0.30-0.95]), and clear cell tumors (RR: 0.34 [0.18-0.64]), but not endometrioid (RR: 0.65 [0.40-1.06]; $p_{het}=0.16$). Ever use of HRT was only significantly associated with serous and endometrioid tumors.

We observed no heterogeneity by histologic subgroup in analyses examining factors related to ovulatory lifespan (all $p_{het}\geq0.10$; Table 5). However, older age at menarche was associated with reduced risk of clear cell tumors (per year older age at menarche, RR: 0.77 [0.63-0.95]), while younger age at menopause was associated with reduced risk of both endometrioid and clear cell tumors (endometrioid: per year younger age at menopause, RR: 0.93 [0.87-0.99]; clear cell: RR: 0.88 [0.78-0.99]). Duration of OC use was associated with serous tumors (per year OC use, RR: 0.97 [0.95-0.98]). Pregnancy duration was associated with serous, endometrioid, and clear cell tumors (per year of being pregnant: serous, RR: 0.85 [0.77-0.94]); endometrioid, RR: 0.78 [0.62-0.98]; clear cell, RR: 0.56 [0.38-0.81]), as was total ovulatory lifespan (per year reduction of ovulatory lifespan: serous, RR: 0.97 [0.96-0.98]); endometrioid, RR: 0.96 [0.93-0.99]; clear cell, RR: 0.91 [0.85-0.97]). None of the investigated variables were associated with mucinous tumors. Results were attenuated after restricting the analysis to women postmenopausal at recruitment, except for a strengthened positive association between delayed age at menarche and risk of mucinous tumors (n=40; RR: 1.34 [1.08-1.67]). The association between total ovulatory lifespan and the histologic subtypes was heterogeneous ($p_{het}=0.02$) in analyses restricted to postmenopausal women.

We analysed the associations between the following pregnancy-related variables and risk among parous women in mutually adjusted models: number of full-term pregnancies, age at first and last pregnancy, and time since last pregnancy. We observed significant heterogeneity in the associations between age at first full-term pregnancy and type I and II tumors (p=0.02; Supplemental Table 1). However, the individual RRs were not statistically significant (age at first full-term pregnancy ≥30 vs. <25 years: type I, RR: 0.73 [0.35-1.52], $p_{trend}=0.17$; type II, RR: 1.37 [0.92-2.05], $p_{trend}=0.03$). We observed no heterogeneity in the associations between the examined pregnancy-related variables by the examined histologic subtypes (Supplemental Table 2). None of the pregnancy-related variables were significantly associated with the EOC subgroups, with the exception of a significant positive association between time since last pregnancy and serous tumors (>30 vs. ≤20 years since last full-term pregnancy, RR: 1.64 [1.05-2.54], $p_{trend}=0.09$).

We conducted sensitivity analyses restricted to ovarian tumors (C569; i.e., excluding fallopian tube and peritoneal tumors). This resulted in exclusion of 2 type I and 36 type II tumors from analyses by the dualistic pathway, and 46 serous, 1 mucinous, 4 endometrioid, and no clear cell tumors from analyses by histology. Results including all cases were very similar to those restricted to ovarian tumors, both in analyses by the dualistic pathway and by histologic subtype. For example, ever vs. never full-term pregnancy was associated with a 53% reduction in risk of type I EOC when all cases were included, and a 54% reduction in risk when restricted to ovarian type I cases (all type I, RR: 0.47 [0.33-0.69]; ovarian type I, RR: 0.46 [0.32-0.67], with comparable results for type II EOC (all type II, RR: 0.81 [0.61-1.06], ovarian type II, RR: 0.78 [0.59-1.04]; p_{het} comparing type I vs. II: all cases =0.02, ovarian cases=0.03. Results were similar in analyses by histology (e.g., ever vs. never full-term pregnancy: all serous, RR: 0.73 [0.58-0.92]; ovarian serous, RR: 0.71 [0.56-0.89]; all mucinous, RR: 0.53 [0.30-0.95]; ovarian mucinous, RR: 0.52 [0.29-0.93]; all endometrioid, RR: 0.65 [0.40-1.06]; ovarian endometrioid, RR: 0.63 [0.40-1.06]).

Discussion

We observed limited heterogeneity in risk between reproductive and hormone-related factors and epithelial ovarian cancer subtypes in this large, prospective investigation. Full-term pregnancy was significantly inversely associated with type I tumors, but not with borderline tumors or type II EOC. Associations for full-term pregnancy were not significantly different across main histologic subgroups (serous, mucinous, endometrioid and clear cell tumors). In analyses considering invasive EOC as the outcome, the associations with established reproductive factors were confirmed (i.e., parity, OC use).

The prevailing assumption that ovarian cancer originates in the ovary has been supplanted, with emerging data suggesting that many “ovarian” cancers originate in the fallopian tube. The recently proposed dualistic pathway of ovarian carcinogenesis suggests two distinct pathways. This model posits that type I tumors (predominantly low-grade serous) arise from precursor lesions such as borderline tumors or endometriosis, generally display KRAS, BRAF, or PTEN mutations and have low chromosomal instability, whereas type II tumors (predominantly high-grade serous) arise as aggressive neoplasms, and harbour TP53 mutations and exhibit high chromosomal instability.2,3 A proportion of both type I and type II tumors are hypothesized to be of extra-ovarian origin:2,3 serous ovarian carcinomas, the most common histologic subtype of ovarian cancer, are hypothesized to arise from serous tubal intraepithelial carcinoma (STIC) in the fimbriae of the fallopian tubes, mucinous tumors are suggested to originate in the colonic mucosa or endocervical epithelia, and clear cell and endometrioid tumors are linked to endometriosis and display characteristics of endometrial tissue.2,3 We hypothesized heterogeneity in risk associations given these differences between ovarian cancer subtypes.

One prior investigation has evaluated reproductive risk factors for EOC by the type I/II pathways,4 and one additional study investigated “rapidly fatal” (within 3 years; proxy for type II) vs. “less aggressive” (proxy for type I) disease.21 Consistent with these prior analyses, we observed a somewhat stronger protective effect for ever full-term pregnancy for type I vs. type II disease and a suggestively stronger positive association between older age

at menopause and type I vs. type II tumors. We did not replicate prior findings of heterogeneity suggesting stronger inverse associations for breastfeeding4 or duration of OC use4,21 with type II disease. However, case numbers were limited in some subgroups. Larger studies or pooled analyses investigating risk factors by tumor aggressiveness are needed to better characterize EOC risk.

Parity and number of full-term pregnancies are hypothesized to impact risk of EOC via (1) reduction in the number of ovulatory cycles (i.e., reducing incessant ovulation),22 (2) the well-established changes in the hormonal milieu during gestation, and (3) the cell clearance hypothesis.23 It is plausible that pregnancy differentially impacts risk of type I vs. type II tumors, given the proposed different pathways leading to the development of these tumors. We observed a stronger association between ever full-term pregnancy and type I vs. type II EOC. Given that type I tumors are slower growing malignancies, it is plausible that exposure to the “cell clearance” and hormonal milieu of a single pregnancy is sufficient to afford protection against these tumors. Given the rapid development of type II tumors (predominantly high-grade serous), more recent pregnancy-associated “cell clearance”, represented by shorter time since last pregnancy, may be the most relevant pregnancy-related exposure for risk reduction in this subgroup. This is in line with the significant positive association between time since last pregnancy and serous tumors observed in this study. However, we did not observe significant heterogeneity across subgroups for time since last pregnancy, nor did we observe a significant association between time since last pregnancy and type II tumors.

Age at menopause was suggestively more strongly associated with type I tumors in our study. Type I tumors are more slowly growing malignancies than type II disease and it is plausible that type I tumors are more sensitive to the premenopausal hormonal milieu (i.e., relatively high endogenous estrogens). To our knowledge, there are no data to date examining the association between circulating estrogens and ovarian cancer by the dualistic pathway. However, in our previous investigation on the role of androgens and EOC by subtype, we observed a significant positive association between androstenedione and type I EOC, and an inverse association for type II disease.24 Androstenedione is a precursor to estradiol, and higher androstenedione may represent a higher estrogen environment. Our findings are compatible with the hypothesis that a higher estrogen environment is differentially associated with type I vs. type II EOC.

Epidemiologic data to date on reproductive risk factors for EOC by histologic subtype is mixed.1,4–13 A longer ovulatory lifespan, or higher number of cumulative ovulatory cycles, is consistently associated with increased risk of EOC, and has been associated with tumors of serous,4,25 endometrioid,4,25 and clear cell4 histology, with some evidence of heterogeneity between histologic subtypes.25 Shorter total ovulatory lifespan was associated with lower risk of serous, endometrioid, and clear cell tumors in the current study; no association was observed for mucinous tumors. Serous, endometrioid and clear cell tumors originate in the female reproductive tract, and thus may be more directly impacted by ovulation and/or menstruation; mucinous tumors, which may originate in other pelvic organs, may be less susceptible to menstrual cycle related events. Age at menopause was only significantly associated with endometrioid and clear cell tumors in our analysis.

Findings for endometrioid tumors are consistent with prior data linking older age at menopause with increased risk of both endometrioid EOC25 and endometrial carcinoma.19,26 Recent investigations in large, well-characterized cohorts suggest parity27 and breastfeeding25 may differentially impact risk by histologic subtype. We did not observe heterogeneity by either of these factors, though breastfeeding was suggestively inversely associated with serous tumors.

Our study has important strengths and limitations. We conducted the largest prospective analysis to date on reproductive and hormone-related risk factors and EOC in the well-characterized EPIC cohort. However, sample size for several subtypes was limited. Extensive baseline data is available for EPIC cohort members, however, data was not available, or had a substantial proportion missing, for some EOC risk factors, including tubal ligation, endometriosis, and family history of breast and ovarian cancer. Further, we used exposure data collected at baseline for this analysis, as updated exposure data was not available; this likely resulted in some misclassification for exposures including parity, duration of OC use and HRT use. We expect any misclassification would bias our results toward the null.

In this large, prospective study, we observed limited differences in risk in EOC subgroups defined by the dualistic model of carcinogenesis, with full-term pregnancy associated with plausible differences in risk of type I vs. type II tumors. Large, collaborative studies are needed to further our understanding of reproductive and hormone-related risk factors for the least common EOC subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact

Ovarian cancer is increasingly recognized as a heterogeneous disease, but risk factor differences across subtypes are not well understood. We present a detailed prospective investigation on reproductive and hormone-related risk factors for borderline tumors and epithelial ovarian cancer by main histologic subtypes and the dualistic pathway (type I and type II tumors). To our knowledge, our investigation is the first prospective study on reproductive and hormone-related risk factors for ovarian cancer by the dualistic pathway.

Table 1

Baseline characteristics of non-cases and epithelial ovarian cancer cases classified by tumor invasiveness and type I / type II status (median (5th and 95th percentile) or number (percentage)): EPIC cohort

Population characteristics	Non-Cases (n=332,881)	All Invasive (n=1,139)	Borderline (n=106)	Type I (n=184)	Type II (n=480)
Age at recruitment, years	51 (33-66)	55 (41-69)	49 (30-65)	53 (36-64)	54 (41-67)
Age at diagnosis, years	-	61 (47-76)	55 (37-71)	59 (41-71)	60 (47-75)
Age at menarche, years	13.0 (11-16)	13 (11-16)	13 (11-15)	13 (11-16)	13 (11-16)
Menstrual Cycle Regularity					
None or Irregular	21,507 (8%)	66 (7%)	5 (6%)	10 (7%)	30 (9%)
≤ Every 26 days	62,866 (24%)	245 (27%)	17 (20%)	36 (26%)	89 (26%)
Every 27-29 days	132,795 (51%)	433 (48%)	47 (55%)	63 (46%)	173 (50%)
≥ Every 30 days	44,272 (17%)	159 (18%)	17 (20%)	29 (21%)	55 (16%)
Ever Full-Term Pregnancy					
No	48,170 (15%)	182 (17%)	15 (15%)	41 (24%)	63 (14%)
Yes	268,972 (85%)	905 (83%)	88 (85%)	130 (76%)	393 (86%)
Ever Breastfed[1]					
No	38,591 (15%)	126 (15%)	12 (15%)	23 (20%)	62 (17%)
Yes	213,901 (85%)	718 (85%)	69 (85%)	93 (80%)	302 (83%)
OC use					
No	132,434 (41%)	574 (52%)	37 (36%)	85 (48%)	223 (48%)
Yes	191,677 (59%)	530 (48%)	66 (64%)	91 (52%)	244 (52%)
Duration of OC use, years[2]	5.0 (1-15)	4.0 (1-15)	3.0 (1-15)	3.0 (1-15)	4.5 (1-15)
History of Hysterectomy	25,595 (9%)	94 (10%)	8 (8%)	10 (7%)	34 (9%)
Menopausal Status					
Premenopausal	119,047 (36%)	224 (20%)	43 (41%)	58 (31%)	96 (20%)
Perimenopausal	64,669 (19%)	194 (17%)	28 (26%)	35 (19%)	92 (19%)
Postmenopausal	149,165 (45%)	723 (63%)	35 (33%)	91 (49%)	192 (61%)
Age at menopause, years[3]	50 (40-55)	50 (40-56)	48 (42-54)	50 (42-58)	50 (42-55)
Ever postmenopausal hormone use[3]					
No	81,356 (58%)	387 (58%)	21 (60%)	53 (63%)	149 (56%)
Yes	59,844 (42%)	284 (42%)	14 (40%)	31 (37%)	116 (44%)
BMI, kg/m^2	24 (19-33)	25 (20-34)	24 (19-34)	25 (20-34)	24 (20-33)
Histology					
Serous	-	631 (55%)	61 (58%)	28 (15%)	390 (81%)
Mucinous	-	79 (7%)	43 (41%)	79 (43%)	
Endometrioid	-	131 (11%)		17 (9%)	76 (16%)
Clear cell	-	57 (5%)		57 (31%)	
NOS	-	188 (16%)			
Other	-	53 (5%)	2 (2%)	3 (2%)	14 (3%)

[1] Among parous women

[2]Among women reporting ever OC use

[3]Among postmenopausal women

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Table 2

Reproductive and hormone-related factors and risk of borderline tumors and invasive type I and type II epithelial ovarian cancer: EPIC cohort, 1992-2010

	Borderline (n = 106)			Type I (n = 184)			Type II (n = 480)		
Reproductive factor	**Case n**	**HR[1]**	**95% CI**	**Case n**	**HR[1]**	**95% CI**	**Case n**	**HR[1]**	**95% CI**
Age at Menarche									
<13 years	42	Reference		67	Reference		150	Reference	
14 years	48	0.85	(0.56-1.29)	79	0.83	(0.60-1.16)	230	1.07	(0.87-1.32)
≥15 years	12	0.70	(0.36-1.34)	27	0.82	(0.52-1.30)	85	1.07	(0.81-1.40)
P for trend[2]			*0.46*			*0.36*			*0.47*
P for subtype heterogeneity[3]									*0.24*
Menstrual Cycle Regularity									
None or Irregular	5	0.69	(0.27-1.79)	10	1.01	(0.51-1.99)	30	1.06	(0.71-1.59)
≤ 26 days	17	0.76	(0.43-1.34)	36	1.17	(0.77-1.78)	89	1.09	(0.84-1.41)
27-29 days	47	Reference		63	Reference		173	Reference	
30+ days	17	0.88	(0.50-1.54)	29	1.37	(0.88-2.15)	55	0.96	(0.70-1.30)
P for trend[2]			*0.49*			*0.58*			*0.46*
P for subtype heterogeneity[3]									*0.39*
Oral Contraceptive Use									
Never	37	Reference		85	Reference		223	Reference	
Ever	66	1.17	(0.74-1.84)	91	0.85	(0.60-1.20)	244	0.94	(0.76-1.16)
Duration ≤1 year	18	1.50	(0.83-2.72)	27	1.41	(0.89-2.22)	55	1.13	(0.83-1.54)
>1-4 years	17	1.11	(0.60-2.07)	25	1.02	(0.63-1.66)	57	0.98	(0.72-1.34)
5-9 years	15	1.11	(0.57-2.14)	12	0.53	(0.28-1.01)	54	0.96	(0.70-1.33)
>10 years	10	0.75	(0.35-1.61)	18	0.54	(0.31-0.94)	60	0.71	(0.51-0.97)
P for trend[2]			*0.22*			*0.01*			*0.01*
P for subtype heterogeneity[3]: Ever/Never									*0.63*
P for subtype heterogeneity[3]: Duration									*0.22*
Ever Full-Term Pregnancy									
No	15	Reference		41	Reference		63	Reference	
Yes	88	1.12	(0.59-2.13)	130	0.47	(0.33-0.69)	393	0.81	(0.61-1.06)
1 child	15	1.22	(0.56-2.70)	16	0.33	(0.18-0.59)	83	0.97	(0.69-1.35)
2 children	49	1.39	(0.69-2.79)	60	0.46	(0.30-0.70)	193	0.87	(0.65-1.17)
3+ children	19	0.70	(0.32-1.55)	48	0.53	(0.34-0.83)	108	0.67	(0.48-0.92)
P for trend[2]			*0.18*			*0.16*			*0.01*
P for subtype heterogeneity[3]: Parity, yes/no									*0.02*
P for subtype heterogeneity[3]: Number of children									*0.84*
History of Breast feeding[4]									
No	12	Reference		23	Reference		62	Reference	

	Borderline (n = 106)			Type I (n = 184)			Type II (n = 480)		
Reproductive factor	**Case n**	**HR[1]**	**95% CI**	**Case n**	**HR[1]**	**95% CI**	**Case n**	**HR[1]**	**95% CI**
Yes	69	1.02	(0.54-1.93)	93	0.67	(0.41-1.08)	302	0.85	(0.64-1.13)
P for subtype heterogeneity[3]									*0.39*
History of Hysterectomy									
No	87	Reference		137	Reference		329	Reference	
Yes	8	1.06	(0.49-2.32)	10	0.79	(0.40-1.55)	34	0.85	(0.58-1.25)
P for subtype heterogeneity[3]									*0.84*
Age at Menopause[5]									
≤48 years	13	Reference		22	Reference		84	Reference	
49-50 years	5	0.52	(0.17-1.54)	26	1.66	(0.90-3.07)	66	0.99	(0.71-1.38)
51-54 years	4	0.57	(0.17-1.88)	17	1.53	(0.77-3.06)	57	1.23	(0.86-1.76)
>55 years	1	0.42	(0.05-3.49)	9	2.71	(1.17-6.30)	27	1.57	(0.99-2.47)
P for trend[2]			*0.72*			*0.01*			*0.04*
P for subtype heterogeneity[3]									*0.21*
Ever Use of Postmenopausal Hormones[5]									
No	21	Reference		53	Reference		149	Reference	
Yes	14	0.62	(0.33-1.03)	31	0.92	(0.56-1.51)	116	1.12	(0.85-1.48)
P for subtype heterogeneity[3]									*0.49*
Body Mass Index, kg/m^2									
<25	62	Reference		96	Reference		270	Reference	
25-30	29	1.07	(0.68-1.70)	67	1.33	(0.95-1.84)	134	0.88	(0.71-1.09)
≥30	15	1.52	(0.84-2.75)	19	0.82	(0.49-1.38)	71	1.10	(0.83-1.45)
P for trend[2]			*0.27*			*0.25*			*0.63*
P for subtype heterogeneity[3]									*0.23*

[1]Stratified by age at recruitment and study center and adjusted for ever full-term pregnancy, ever OC use, menopausal status at recruitment, age at menopause, and ever HRT use

[2]P for trend on continuous scale

[3]P for subtype heterogeneity comparing type I and type II tumors.

[4]Among parous women

[5]Among postmenopausal women

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Table 3

Factors related to ovulatory lifespan and total ovulatory lifespan and risk of borderline tumors and invasive type I and type II epithelial ovarian cancer: EPIC cohort, 1992-2010

	Borderline HR (95% CI)[1]	Type I HR (95% CI)[1]	Type II HR (95% CI)[1]	p_{het}[2]
Risk per year older age at menarche	0.94 (0.81-1.10)	0.95 (0.85-1.07)	1.02 (0.95-1.09)	0.34
Risk per year younger age at menopause[3,4]	0.98 (0.89-1.08)	0.92 (0.86-0.98)	0.98 (0.95-1.01)	0.09
Risk per year of OC use	0.96 (0.91-1.01)	0.97 (0.94-1.00)	0.97 (0.96-0.99)	0.73
Risk per year of being pregnant[5]	0.84 (0.64-1.10)	0.78 (0.64-0.95)	0.84 (0.75-0.94)	0.53
Risk per year reduction of total ovulatory lifespan[6]	0.96 (0.91-1.00)	0.95 (0.92-0.98)	0.97 (0.96-0.99)	0.17
Restricted to Women Postmenopausal at Baseline				
Risk per year older age at menarche	1.14 (0.87-1.50)	1.13 (0.97-1.31)	1.07 (0.98-1.16)	0.54
Risk per year younger age at menopause[3]	1.00 (0.91-1.11)	0.91 (0.85-0.97)	0.97 (0.94-1.00)	0.08
Risk per year of OC use	0.94 (0.81-1.08)	0.98 (0.93-1.02)	0.99 (0.97-1.02)	0.53
Risk per year of being pregnant[5]	1.01 (0.66-1.56)	0.88 (0.68-1.14)	0.88 (0.76-1.02)	0.97
Risk per year reduction of total ovulatory lifespan[7]	0.99 (0.92-1.06)	0.96 (0.92-1.00)	0.99 (0.97-1.00)	0.19

[1] Age and center stratified and further adjusted for menopausal status at recruitment, ever OC use and ever HRT use, and mutually adjusted for the risk factors presented in this table.

[2] P for heterogeneity comparing type I and type II tumors.

[3] Age at menopause was entered in the model with a minus sign to compare with other factors.

[4] For women not postmenopausal at recruitment, age at menopause was replaced by age at recruitment.

[5] Calculated as: (number of FTP) x 0.75.

[6] Calculated as: (age at menopause – age at menarche – duration of OC use – cumulative duration of FTP), and entered into the model with a minus sign; Age and center stratified and further adjusted for menopausal status at recruitment and ever HRT use.

[7] Calculated as: (age at menopause – age at menarche – duration of OC use – cumulative duration of FTP), and entered into the model with a minus sign; Age and center stratified and adjusted for ever HRT use.

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Table 4

Reproductive and hormone-related factors and risk of invasive epithelial ovarian cancer overall and by main histologic subtypes: EPIC cohort, 1992-2010

	Invasive EOC (n=1,139)		Serous (n=631)		Mucinous (n=79)		Endometrioid (n=131)		Clear Cell (n=57)	
	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI
Age at Menarche										
<13 years	366	Reference	197	Reference	27	Reference	45	Reference	26	Reference
14 years	515	0.96 (0.84-1.10)	302	1.04 (0.87-1.25)	30	0.78 (0.46-1.32)	57	0.84 (0.57-1.25)	20	0.52 (0.28-0.94)
≥15 years	210	0.99 (0.83-1.18)	112	1.00 (0.79-1.27)	17	1.26 (0.67-2.38)	25	0.95 (0.57-1.57)	6	0.40 (0.16-0.98)
P for trend[2]		0.99		0.90		0.52		0.83		0.01
P for subtype heterogeneity[3]										0.08
Menstrual Cycle Regularity										
None or Irregular	66	0.86 (0.73-1.25)	39	1.03 (0.73-1.46)	6	1.47 (0.59-3.69)	9	1.25 (0.60-2.59)	1	0.25 (0.03-1.93)
≤26 days	245	1.14 (0.97-1.33)	139	1.19 (0.96-1.47)	14	1.15 (0.58-2.24)	24	1.03 (0.62-1.68)	10	0.78 (0.37-1.66)
27-29 days	433	Reference	233	Reference	23	Reference	49	Reference	24	Reference
30+ days	159	1.19 (0.99-1.43)	88	1.19 (0.93-1.53)	12	1.61 (0.79-3.25)	13	0.84 (0.45-1.55)	8	1.03 (0.46-2.32)
P for trend[2]		0.55		0.95		0.86		0.40		0.18
P for subtype heterogeneity[3]										0.46
Oral Contraceptive Use										
Never	574	Reference	298	Reference	35	Reference	56	Reference	26	Reference
Ever	530	0.84 (0.73-0.96)	316	0.92 (0.77-1.10)	41	0.88 (0.53-1.47)	71	1.12 (0.75-1.67)	27	0.87 (0.47-1.63)
Duration <=1 year	122	1.02 (0.83-1.25)	75	1.13 (0.87-1.47)	7	0.89 (0.39-2.07)	14	1.15 (0.62-2.12)	11	2.15 (1.01-4.58)
2-4 years	135	0.96 (0.78-1.17)	76	0.98 (0.75-1.28)	14	1.43 (0.73-2.81)	17	1.16 (0.65-2.07)	6	0.81 (0.32-2.09)
5-9 years	116	0.88 (0.71-1.09)	70	0.96 (0.73-1.27)	7	0.75 (0.31-1.78)	18	1.35 (0.76-2.41)	2	0.31 (0.07-1.35)
≥10 years	113	0.57 (0.45-0.70)	68	0.61 (0.46-0.82)	10	0.70 (0.32-1.51)	13	0.62 (0.32-1.20)	5	0.47 (0.17-1.32)
P for trend[2]		< 0.01		<0.01		0.15		0.09		0.07
P for subtype heterogeneity[3]: Ever OC use										0.82
P for subtype heterogeneity[3]: Duration of OC use										0.86

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	Invasive EOC (n=1,139)		Serous (n=631)		Mucinous (n=79)		Endometrioid (n=131)		Clear Cell (n=57)		
	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	
Ever Full-Term Pregnancy											
No	182	Reference	91	Reference	17	Reference	20	Reference	15	Reference	
Yes	905	0.68 (0.57-0.80)	518	0.73 (0.58-0.92)	58	0.53 (0.30-0.95)	102	0.65 (0.40-1.06)	34	0.34 (0.18-0.64)	
1 child	172	0.77 (0.62-0.95)	108	0.89 (0.67-1.18)	5	0.25 (0.09-0.68)	16	0.64 (0.32-1.26)	6	0.37 (0.14-0.98)	
2 children	436	0.71 (0.59-0.85)	239	0.71 (0.56-0.91)	29	0.56 (0.30-1.07)	56	0.82 (0.48-1.41)	15	0.32 (0.15-0.69)	
3+ children	279	0.61 (0.50-0.74)	161	0.64 (0.49-0.83)	22	0.64 (0.32-1.27)	29	0.62 (0.34-1.13)	11	0.33 (0.14-0.76)	
P for trend[2]		*<0.01*		*<0.01*		*0.78*		*0.28*			*0.01*
P for subtype heterogeneity: Parity, yes/no[3]											*0.16*
P for subtype heterogeneity: Number of pregnancies[3]											*0.37*
History of Breast feeding[4]											
No	126	Reference	72	Reference	11	Reference	10	Reference	4	Reference	
Yes	718	0.93 (0.76-1.13)	413	0.95 (0.74-1.24)	39	0.59 (0.29-1.20)	87	1.25 (0.64-2.46)	27	0.96 (0.33-2.83)	
P for subtype heterogeneity[3]											0.51
History of Hysterectomy											
No	855	Reference	464	Reference	53	Reference	90	Reference	43	Reference	
Yes	94	0.87 (0.69-1.10)	60	1.00 (0.74-1.34)	6	0.92 (0.37-2.32)	10	1.00 (0.50-2.01)	1	0.30 (0.04-2.28)	
P for subtype heterogeneity[3]											0.60
Age at Menopause[5]											
≤48 years	192	Reference	108	Reference	12	Reference	20	Reference	5	Reference	
49-50 years	175	1.18 (0.96-1.46)	97	1.11 (0.83-1.47)	11	1.18 (0.50-2.77)	14	1.00 (0.49-2.05)	12	3.47 (1.09-11.0)	
51-54 years	139	1.30 (1.03-1.63)	77	1.20 (0.89-1.63)	6	0.85 (0.30-2.40)	14	1.43 (0.69-2.98)	6	2.73 (0.74-10.1)	
≥55 years	67	1.62 (1.21-2.17)	30	1.18 (0.77-1.79)	3	1.53 (0.40-5.82)	13	3.56 (1.63-7.76)	4	2.27 (1.45-27.1)	
P for trend[2]		<0.01		0.15		0.68		0.01			0.03
P for subtype heterogeneity[3]											0.09
Ever Use of Postmenopausal Hormones[5]											
No	387	Reference	192	Reference	22	Reference	35	Reference	20	Reference	

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	Invasive EOC (n=1,139)		Serous (n=631)		Mucinous (n=79)		Endometrioid (n=131)		Clear Cell (n=57)	
	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI	Case n	HR[1] 95% CI
Yes	284	1.17 (0.98-1.39)	171	1.27 (1.01-1.60)	14	0.93 (0.44-1.94)	36	1.79 (1.07-3.01)	9	0.68 (0.29-1.63)
P for subtype heterogeneity[3]										0.22
Body Mass Index, kg/m^2										
<25	604	Reference	358	Reference	39	Reference	64	Reference	27	Reference
25-30	343	0.98 (0.85-1.12)	168	0.81 (0.67-0.98)	31	1.63 (1.00-2.67)	46	1.31 (0.89-1.94)	22	1.56 (0.86-2.83)
≥30	173	1.14 (0.95-1.36)	98	1.12 (0.88-1.42)	8	1.00 (0.46-2.21)	17	1.23 (0.71-2.16)	7	1.04 (0.43-2.52)
P for trend[2]		0.07		0.92		0.36		0.22		0.21
P for subtype heterogeneity[3]										0.49

[1] Stratified by age at recruitment and study center and adjusted for ever full-term pregnancy, ever OC use, menopausal status at recruitment, age at menopause, and ever HRT use

[2] P for trend on continuous scale

[3] P for subtype heterogeneity comparing serous, mucinous, endometrioid, and clear cell tumors.

[4] Among parous women

[5] Among postmenopausal women

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Table 5

Factors related to ovulatory lifespan and total ovulatory lifespan and risk of invasive epithelial ovarian cancer overall and by main histologic subtypes: EPIC cohort, 1992-2010

	Invasive HR (95% CI)[1]	Serous HR (95% CI)[1]	Mucinous HR (95% CI)[1]	Endometrioid HR (95% CI)[1]	Clear Cell HR (95% CI)[1]	p_{het}[2]
Risk per year older age at menarche	1.01 (0.96-1.05)	1.00 (0.95-1.06)	1.06 (0.90-1.25)	1.00 (0.88-1.14)	0.77 (0.63-0.95)	0.10
Risk per year younger age at menopause[3,4]	0.97 (0.95-0.99)	0.98 (0.96-1.01)	0.97 (0.89-1.06)	0.93 (0.87-0.99)	0.88 (0.78-0.99)	0.11
Risk per year of OC use	0.97 (0.95-0.98)	0.97 (0.95-0.98)	0.98 (0.94-1.02)	0.97 (0.94-1.01)	0.96 (0.90-1.02)	0.92
Risk per year of being pregnant[5]	0.83 (0.77-0.90)	0.85 (0.77-0.94)	0.88 (0.66-1.18)	0.78 (0.62-0.98)	0.56 (0.38-0.81)	0.17
Risk per year reduction of total ovulatory lifespan[6]	0.97 (0.96-0.98)	0.97 (0.96-0.98)	0.98 (0.94-1.02)	0.96 (0.93-0.99)	0.91 (0.85-0.97)	0.18
Restricted to Women Postmenopausal at Baseline						
Risk per year older age at menarche	1.05 (0.99-1.10)	1.03 (0.96-1.11)	1.34 (1.08-1.67)	1.08 (0.91-1.27)	0.88 (0.68-1.15)	0.08
Risk per year younger age at menopause[3]	0.97 (0.95-0.98)	0.98 (0.95-1.00)	0.97 (0.88-1.06)	0.93 (0.87-1.00)	0.85 (0.75-0.97)	0.10
Risk per year of OC use	0.98 (0.96-0.99)	0.98 (0.96-1.00)	1.01 (0.95-1.06)	0.98 (0.93-1.03)	0.94 (0.84-1.05)	0.67
Risk per year of being pregnant[5]	0.87 (0.80-0.96)	0.90 (0.80-1.02)	0.94 (0.64-1.37)	0.80 (0.60-1.06)	0.51 (0.32-0.83)	0.13
Risk per year reduction of total ovulatory lifespan[7]	0.97 (0.96-0.99)	0.98 (0.96-1.00)	1.01 (0.96-1.06)	0.96 (0.92-1.00)	0.87 (0.79-0.95)	0.02

[1] Age and center stratified and further adjusted for menopausal status at recruitment, ever OC use and ever HRT use, and mutually adjusted for the risk factors presented in this table.

[2] P for heterogeneity comparing serous, mucinous, endometrioid, and clear cell tumors.

[3] Age at menopause was entered in the model with a minus sign to compare with other factors.

[4] For women not postmenopausal at recruitment, age at menopause was replaced by age at recruitment.

[5] Calculated as: (number of FTP) × 0.75.

[6] Calculated as: (age at menopause – age at menarche – duration of OC use – cumulative duration of FTP), and entered into the model with a minus sign; Age and center stratified and further adjusted for menopausal status at recruitment and ever HRT use.

[7] Calculated as: (age at menopause – age at menarche – duration of OC use – cumulative duration of FTP), and entered into the model with a minus sign; Age and center stratified and adjusted for ever HRT use.