Ovarian cancer risk factors by tumor aggressiveness: an analysis from the Ovarian Cancer Cohort Consortium

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ijc.32075

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Running title: Ovarian cancer risk factors by aggressiveness

Key words: ovarian cancer, risk factors, subtypes, aggressiveness, prospective cohort

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Novelty and Impact:
Risk factor profiles by ovarian cancer subtypes defined by disease aggressiveness (time between diagnosis and death), were investigated under the hypothesis that these profiles are associated with tumor aggressiveness independent of histology. Risk factor profiles for the most aggressive disease categories clustered together independent of histotype suggesting that risk profiles may be directly associated with subtypes defined by tumor aggressiveness, rather than through differential effects on histology, providing impetus for future studies on mechanistic pathways.

Abstract

Ovarian cancer risk factors differ by histotype; however, within subtype there is substantial variability in outcomes. We hypothesized that risk factor profiles may influence tumor aggressiveness, defined by time between diagnosis and death, independent of histology. Among 1.3 million women from 21 prospective cohorts, 4,584 invasive epithelial ovarian cancers were identified and classified as highly aggressive (death in <1 year, n=864), very aggressive (death in 1-<3 years, n=1,390), moderately aggressive (death in 3-<5 years, n=639), and less aggressive (lived 5+ years, n=1,691). Using competing risks Cox proportional hazards regression, we assessed heterogeneity of associations by tumor aggressiveness for all cases and among serous and endometrioid/clear cell tumors. Associations between parity (p_{het}=0.01), family history of ovarian cancer (p_{het}=0.02), body mass index (BMI; $p_{het} \leq 0.04$) and smoking ($p_{het}<0.01$) and ovarian cancer risk differed by aggressiveness. A first/single pregnancy, relative to nulliparity, was inversely associated with highly aggressive disease (HR: 0.72; 95% CI [0.58-0.88]), no association was observed for subsequent pregnancies (per pregnancy, 0.97 [0.92-1.02]). In contrast, first and subsequent pregnancies were similarly associated with less aggressive disease (0.87 for both). Family history of ovarian cancer was only associated with risk of less aggressive disease (1.94 [1.47-2.55]). High BMI (≥35 vs. 20-<25 kg/m^2, 1.93 [1.46-2.56] and current smoking (vs. never, 1.30 [1.07-1.57]) were associated with increased risk of highly aggressive disease. Results were similar within histotypes. Ovarian cancer risk factors may be directly associated with subtypes defined by tumor aggressiveness, rather than through differential effects on histology. Studies to assess biological pathways are warranted.

Introduction

Ovarian cancer is one of the most fatal cancers in women, with over 150,000 deaths globally per year [1]. The five-year relative survival for ovarian cancer patients is about 45%, while the ten-year relative survival is only slightly lower at 35%.[2, 3] Further, across all stages of disease, the probability of surviving the next five years increases with longer survival.[4] This, in conjunction with data showing worse outcomes for high-grade serous tumors compared to other types,[5-7] suggests that some tumors may be intrinsically more aggressive than others. While differences in survival across tumor subtypes can be explained, in part, by surgical outcomes,[8] a recent study noted that changes in chemotherapy regimens did not substantially influence long-term survival.[9] More recently, studies have shown that exposures before diagnosis are differently associated with ovarian cancer subtypes [10-14], with each histologic type showing a distinct pattern of risk factor associations.[10] However, few studies have considered whether risk factor profiles may influence the development of ovarian cancer toward more aggressive (i.e., rapidly fatal) versus less aggressive subtypes.

One prior study that combined data from two prospective cohort studies (also included in the present study) and two case-control studies used time to death as a surrogate for characterizing more versus less aggressive disease (i.e., death within 3 years of diagnosis compared with longer survival).[15] Multiple established ovarian cancer risk factors, including age, parity, oral contraceptive (OC) use, and menopausal status, were differentially associated with risk by tumor aggressiveness for all invasive and serous tumors. For example, each birth was associated with a significant 13% lower risk of less aggressive disease but only a 2% lower risk for more aggressive tumors, although the first birth was associated with a similar ~20% lower risk of both tumor types. We expanded this analysis within the Ovarian Cancer Cohort Consortium (OC3), which included 21 prospective cohort studies across Australia, Europe, Asia, and North America. With 4,584 invasive ovarian cancer cases, we examined the relationship of 17 established and putative risk factors by tumor aggressiveness (defined by time to death (<1, 1-<3, 3-<5, 5+ years)) for all invasive tumors and within specific histologic subtypes.

Methods

Study population

The OC3 includes women participating in 23 prospective cohort studies, 21 of which had sufficient cases and follow-up for death (defined as at least 3 years of follow-up for >50 cases) to be included in this analysis (Table 1). Studies were required to have prospective follow-up for incident cases of ovarian cancer through questionnaires, medical records or cancer registries, as well as follow-up for death, along with data on age at study entry, OC use, and parity. Women with a history of cancer (other than non-melanoma skin cancer), with bilateral oophorectomy prior to study entry, or missing age at baseline were excluded. All studies obtained institutional approval for cohort maintenance as well as participation in the OC3. The OC3 Data Coordinating Center and analytic approaches were approved by the institutional review board of the Brigham and Women's Hospital (BWH).

Exposure assessment

Full baseline cohort data (19 studies) and case-cohort datasets with weights for subcohort members (2 studies) were centrally harmonized. We examined multiple ovarian cancer risk factors, including parity (no children, first child, linear term for subsequent children), age at first birth (per 1 year; and <20, 20-<25, 25-<30, 30+ years), age at last known birth (per 1 year; <25, 25-<30, 30-<35, 35+ years), duration of OC use (per 5 years of use; never, ≤1, >1-≤5, >5-≤10, >10 years), duration of breastfeeding (per 1 year; ever vs. never among parous women), age at menarche (per 1 year; ≤11, 12, 13, 14, ≥15 years), age at natural menopause (postmenopausal women only: per 5 years; ≤40, >40-≤45, >45-≤50, >50-≤55, >55 years), duration of menopausal hormone therapy (HT) use (postmenopausal women only: per 1 year; never, ≤5, >5 years), tubal ligation (yes vs. no), hysterectomy (yes vs. no), endometriosis (yes vs. no), first degree family history of breast cancer (yes vs. no), first degree family history of ovarian cancer (yes vs. no), BMI at baseline (per 5 kg/m^2; <20, 20-<25, 25-<30, 30-<35, ≥35 kg/m^2), BMI at age 18-20 years (per 5 kg/m^2; <18, 18-<20, 20-<22, ≥22 kg/m^2), height (per 0.05m; <1.60, 1.60-<1.65, 1.65-1.70, ≥1.70 m), and smoking at baseline (never, former, current). Studies that did not provide data on a specific risk factor were excluded from the analysis of that factor, leading to different numbers of cases for each exposure (Table S1).

Outcome definition

Epithelial ovarian or peritoneal cancer cases were confirmed through cancer registries or medical record review (ICD9: 183, 158; ICD10: C56); details were described previously.[10] For each case, we requested information on date of or age at diagnosis, histology (classified as serous/poorly differentiated, endometrioid, mucinous, clear cell, other/unknown), and date of or age at death (if applicable). All studies obtained information on deaths during the course of follow-up, primarily through mortality registries and family members, and had >95% mortality follow-up. We calculated the time between diagnosis and death for all cases who died and classified tumors as highly aggressive (death in <1 year, n=864), very aggressive (death in 1-<3 years, n=1,390), moderately aggressive (death in 3-<5 years, n=639), and less aggressive (lived 5+ years, n=1,691). For cases who did not die during follow-up, we excluded those who had less than 5 years of follow-up time after diagnosis (n=992).

Statistical methods

We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) using competing risks Cox proportional hazards regression to evaluate associations between exposures and ovarian cancer risk based on aggressiveness.[16] Follow-up time was calculated as the time between study entry and date of i) ovarian cancer diagnosis, ii) death, or iii) end of follow-up, whichever occurred first. Survivor function plots for exposures generally showed parallel curves, suggesting no relevant deviation from proportional hazards; the few deviations observed were due to small numbers of exposed cases within a specific category of aggressiveness. In primary analyses, we pooled data from all cohorts, and stratified by year of birth and cohort to account for potential differences in baseline hazards by these factors; associations were similar to those using random effects meta-analysis to combine cohort-specific estimates (data not shown). Statistical heterogeneity of associations across tumor aggressiveness categories was assessed via a likelihood ratio test comparing a model allowing the association for the risk factor of interest to vary by aggressiveness versus one not allowing the association to vary.[17] A trend test was calculated across the ordinal aggressiveness subtype beta coefficients using meta-regression. All models were adjusted for age at entry (enrollment), number of children, and duration of OC use, unless the exposure of interest was collinear with one of these factors. Hysterectomy analyses were additionally adjusted for HT use. For missing covariate data, we included a missing indicator in the model.

We considered all invasive cases together and conducted analyses among serous/poorly differentiated tumors only and endometrioid/clear cell tumors; we combined these latter subtypes due to their similar risk factor profiles, as observed in our prior analysis.[10] In an additional analysis, we evaluated endometrioid tumors separately; collapsed categories of aggressiveness were used due to limited sample size (i.e., highly/very aggressive: time between diagnosis and death <3 years; moderately/less aggressive: time between diagnosis and death or end of follow-up 3+ years). We also evaluated known high-grade serous tumors in a secondary analysis. We evaluated associations stratified by stage at diagnosis (stages 1 or 2 and stages 3 or 4) for all exposures for which we observed significant heterogeneity across aggressiveness categories. For BMI and smoking, we conducted sensitivity analyses excluding cases diagnosed within 2 years of baseline (to address potential for reverse causation), excluding all women with cardiovascular disease (CVD) or diabetes at baseline; for BMI, we also stratified by menopausal status and HT use. Two of the prospective cohort studies included in this study (AARP and NHS) were included in a previous study on tumor aggressiveness;[15] these studies were excluded in a sensitivity analysis.

We performed unsupervised hierarchical clustering of the four aggressiveness categories alone and further separated by histology (serous and endometrioid/clear cell) using beta estimates for exposures that had differential associations by tumor aggressiveness overall in invasive cases or within the serous or endometrioid/clear cell subsets using complete linkage and uncentered correlation (Pearson’s coefficient). SAS 9.4 was used to conduct the analyses. A p-value of <0.05 was considered statistically significant.

Results

Study population

During follow-up of 1,202,492 participants (1,298,977 including full cohort size for case-cohort studies), 4,584 incident invasive epithelial ovarian cancers were identified which could be classified by tumor aggressiveness. Case numbers ranged from 1,009 for breastfeeding to 4,529 for smoking status (Table S1). This study included 2,795 (73.6% of cases with known histology) serous, 506 (13.3%) endometrioid, 289 (7.6%) mucinous, and 208 (5.5%) clear cell carcinomas. Fifteen of 21 cohorts were based in North America, four in Europe, one in Australia, and one in Asia (Table 1); a majority of the cohorts started enrollment in the 1990s. The median age at diagnosis was 71.0 years for highly aggressive (death <1 years following diagnosis), 67.5 years for very aggressive (death 1-<3 years), 65.6 years for moderately aggressive (death 3-<5 years), and 62.7 years for less aggressive (lived at least 5 years). The majority of participants with known stage were diagnosed with distant (stage 3-4) disease, with little variation in the moderately (75.6%), very (76.2%) and highly aggressive (76.2%) subgroups, but a smaller proportion of women with less aggressive disease diagnosed at later stage (41.8% distant) (Table S2).

Associations of putative and established risk factors

Parity (p_{het}=0.01), family history of ovarian cancer (p_{het}=0.02), adult BMI ($p_{het} \leq 0.04$), and smoking status (p_{het}<0.01) were differentially associated with risk of ovarian cancer by disease aggressiveness (Table 2). Both higher parity and family history of ovarian cancer were most strongly associated with less aggressive disease, though in opposing directions, whereas very high and very low BMI and current smoking at baseline were both more strongly associated with increased risk of highly aggressive disease.

Specifically, a first child (i.e., parity of 1) conferred significant protection against highly and very aggressive disease, relative to nulliparity (e.g., highly aggressive, HR: 0.72 [95% CI: 0.58-0.88]); subsequent pregnancies conferred no additional protection (per pregnancy, HR: 0.97 [0.92-1.02]). For less aggressive disease, both the first and subsequent pregnancies were associated with lower risk (first/single pregnancy, HR: 0.87 [0.74-1.01]; subsequent pregnancies, HR: 0.87 [0.83-0.91]); p_{trend} across aggressiveness categories=0.002). Family history of ovarian cancer was associated with higher risk of all but the highly aggressive ovarian cancers, with risk increasing stepwise with lower aggressiveness (e.g., highly aggressive, HR: 0.70 [0.38-1.32]); less aggressive, HR: 1.94 [1.47-2.55]; $p_{trend\_aggressiveness}$ =0.01).

In contrast higher BMI and current smoking were associated with higher risk of highly aggressive, but not less aggressive, disease ($p_{trend\_aggressiveness}$, BMI ≥35 kg/m^2 category=0.002; current smoking=0.002). Notably, relative to women in the normal weight category (BMI 20-<25 kg/m^2), higher risk of highly aggressive disease was observed in women in both the lowest (<20 kg/m^2; HR: 1.36 [1.04-1.77]) and highest (≥35 kg/m^2; HR: 1.93 [1.46-2.56]) BMI categories. This association was not affected by additional adjustment for smoking (e.g., <20 kg/m^2; HR: 1.36 [1.04-1.78]).

We also observed a significant trend across aggressiveness categories for duration of HT use (>5 years; p=0.03) and family history of breast cancer (p=0.03), both suggestive of higher risk of less aggressive disease, and tubal ligation (p=0.02), suggestive of lower risk for less aggressive disease. However, the p for heterogeneity overall using the likelihood ratio test was not statistically significant (all p=0.12). No heterogeneity in associations was observed for the other examined risk factors.

Analyses in Histologic Subgroups

We next evaluated the associations separately for (i) serous/poorly differentiated (n=2,795; Table S3), (ii) high-grade serous disease (data not shown), and (iii) endometrioid /clear cell (n=714; Table S4). In a sensitivity analysis, we evaluated endometrioid tumors separately using collapsed aggressiveness categories (i.e., very/highly aggressive and less/moderately aggressive) (Table S5). Overall, results were of similar magnitude and in the same direction as those observed for invasive ovarian cancer overall. Among cases of endometrioid/clear cell disease, we observed a significant trend across aggressiveness categories for one height category (<1.60 meters; p=0.01); however, the p for overall heterogeneity for height was not statistically significant (p=0.28). Restricting the analysis to endometrioid disease, taller height appeared to be significantly associated with higher risk of more aggressive, but not less aggressive, disease (per 0.05 meters, p_{het}=0.04), although the association with height as a categorical variable was not consistent with a linear association. For BMI at age 18-20, both lower and higher young adult BMI were significantly associated with more aggressive disease while no association was observed with less aggressive disease (p_{het}=0.01). Finally, current (vs. never) smoking was associated with significantly lower risk of less aggressive endometrioid cancers (p_{het}<0.01). In analyses restricted to high-grade serous disease, heterogeneity by aggressiveness was statistically significant for duration of HT use (p_{het}=0.02), with longer duration associated with significantly higher risk of disease in all aggressive subgroups except highly aggressive (e.g., >5 years vs. never, less aggressive, HR: 2.25 [1.76-2.89]; highly aggressive, HR: 0.98 [0.64-1.50]).

Sensitivity Analyses

We conducted sensitivity analyses for parity, family history of ovarian cancer, BMI and smoking to evaluate associations by stage at diagnosis (data available for >75% of cases; Tables S6-S8). For BMI and smoking, we conducted additional sensitivity analyses excluding cases diagnosed within 2 years of baseline or diagnosed with CVD or diabetes at baseline; we further evaluated BMI associations by menopausal status at baseline and for postmenopausal women by HT use, as well as HT associations stratified by BMI (<25 vs. ≥25 kg/m^2) (data not shown). Patterns of association were similar for these subgroups, with the exception of analyses restricted to women diagnosed at stages 1 or 2, in which the associations of both BMI and smoking with highly aggressive disease, and family history of ovarian cancer and less aggressive disease, were attenuated. Further, in analyses restricted to stages 3 or 4, the association for parity and less aggressive disease was attenuated. Results were similar after excluding the two studies (AARP and NHS) included in a prior investigation on risk factors for ovarian cancer by aggressiveness (data not shown).

After adjusting for multiple comparisons using Bonferroni correction for 17 tests, none of the p_{het} remained statistically significant. However, the p_{trend} across aggressiveness categories for parity, BMI (≥35 kg/m^2 category), and current smoking met the stricter p<0.003 criterion.

We further considered clustering of risk factor associations by disease aggressiveness alone and when further stratifying by histology (Figure 1). Overall, the risk factor profile for highly aggressive disease was distinct from the other aggressiveness categories (Figure 1a). Further, risk factor associations for highly aggressive and very aggressive disease clustered together independent of histotype (Figure 1b). Moderately and less aggressive subtypes tended to cluster by histology (e.g., less/moderately aggressive and very aggressive serous disease, and less/moderately aggressive and highly aggressive non-serous disease). Certain risk factors, such as age at menopause and having more than one child, tended to be more strongly associated with one histotype (e.g., non-serous tumors) regardless of disease aggressiveness.

Discussion

We identified parity, family history of ovarian cancer, BMI, and smoking as risk factors that were differentially associated with ovarian cancer defined by subgroups of tumor aggressiveness, overall and within specific histologic subtypes, in this first large-scale, prospective investigation. Notably, high BMI and smoking, two modifiable risk factors, were most strongly associated with higher risk of the most aggressive, rapidly fatal, ovarian cancers. Further, clustering analysis showed that risk factor profiles for the most aggressive categories (i.e., highly and very aggressive disease) largely tracked by tumor aggressiveness rather than histology. Risk factors differentially impacting risk by subtype may act via their influence on: (i) whether an aggressive disease subtype develops; (ii) whether an already initiated malignancy develops toward an aggressive phenotype; and/or, (iii) prognostic factors, independent of the etiologic process (e.g., efficacy of chemotherapy, surgery).

The first pregnancy was inversely associated with risk of more aggressive ovarian cancer; however, the inverse association for pregnancies beyond the first was stronger for less aggressive disease. The first pregnancy is associated with long-term permanent alterations in hormone regulation, including circulating lower prolactin levels;[18, 19] higher circulating prolactin has been associated with ovarian cancer risk.[20] This may impact etiology of all tumor types similarly. In contrast, more recent pregnancy may lead to a clearance of premalignant or malignant cells (i.e., a “wash out” effect).[21] This may be more relevant for slowly progressing tumors (i.e., developing over a period of years), than rapidly progressing disease that is more likely to have developed in the interval since pregnancy. That said, there was no clear pattern of association for age at last birth and ovarian cancer risk by aggressiveness (regardless of adjustment for parity), although relatively few studies had these data (data not shown). Parity-related reductions in ovulatory cycles[22] are unlikely to explain the observed heterogeneity, given we observed no differences by aggressiveness for oral contraceptive use, or ages at menarche or menopause, all contributors to the number of lifetime ovulatory cycles.

Family history of ovarian cancer was most strongly associated with less aggressive ovarian cancer, with a similar trend observed for family history of breast cancer. This is consistent with prior investigations suggesting a survival benefit proximal to diagnosis for women carrying an inherited *BRCA* mutation,[23, 24] potentially due to better response to platinum-based chemotherapies and PARP inhibitors.[25] This survival benefit is evident in the relative short term after diagnosis (i.e., 3-5 years),[23] as would be captured in our moderately and less aggressive disease categories.

Higher BMI was positively associated with risk of highly aggressive ovarian cancer, but not less aggressive disease. The association between BMI and ovarian cancer did not differ by aggressiveness in the study by Poole et al.;[15] however, results on ovarian cancer survival are in line with our findings.[25, 26] Obesity may potentiate an ovarian cancer toward an aggressive pathway via its impact on the metabolic milieu, or may influence disease aggressiveness by providing a permissive local microenvironment for metastases, reducing efficacy of treatment, or poor post-surgical performance. The associations between BMI and adipokines, insulin resistance and the metabolic syndrome,[27] and oxidative stress and chronic low-grade inflammation[28] are well described; in turn, these factors have been hypothesized to be associated with ovarian cancer progression.[29-33] Further, adiposity is associated with higher endogenous estrogen concentrations, as a result of an upregulation of aromatase activity,[34] particularly in postmenopausal women.[35, 36] However, the trends we observed for HT use were in the opposite direction of those observed for BMI, providing no support for endogenous estrogens as an intermediate mechanism. Omental adipose tissue has been identified as a tumor promoting microenvironment;[37] thus, this adipose depot proximate to the ovarian tumor may promote tumor progression and metastasis. In terms of treatment-related factors, suboptimal surgical cytoreductive (i.e., debulking) surgery and insufficient chemotherapy dosing may result in more rapidly fatal disease[38-41] in obese women. Finally, we also observed that individuals with BMI less than 20 kg/m^2 were at increased risk for highly aggressive disease; this association was unchanged after adjustment for smoking. This should be confirmed in other studies and mechanisms explored to better understand this potential relationship.

We observed suggestive heterogeneity in the associations between duration of postmenopausal HT use and tubal ligation and ovarian cancer risk by aggressiveness. The associations between HT use and tubal ligation did not differ by aggressiveness in the prior analysis by Poole et al.,[15] nor are they consistently associated with survival.[25] In the current study, longer duration of HT use was more strongly associated with increased risk of less aggressive disease. Data on circulating sex steroid hormones suggest heterogeneity by disease subtype, with a study in the OC3 reporting significantly different associations between circulating pre-diagnosis endogenous androgens and ovarian cancer risk by the dualistic pathway.[42] Higher androgen concentrations increased risk of type I (less aggressive) ovarian cancer risk, but not type II (more aggressive) disease, providing indirect support for our findings. Androgens are a substrate for estrogen production, and are correlated in postmenopausal women (e.g. testosterone and estradiol, postmenopausal women, r=0.23-0.38).[43, 44]

Current smoking was associated with highly aggressive, but not less aggressive, disease in this study. Smoking may drive development of a more aggressive phenotype via its well-described inflammation- and oxidative stress-inducing effects[45] and is associated with higher risk of death following an ovarian cancer diagnosis[46] (reviewed in[25]). Further, limited data suggest that smoking may impact the effectiveness of neoadjuvant therapy,[47] particularly for mucinous tumors. This is in agreement with observed differences between smoking and ovarian cancer mortality by histology in OCAC,[46] with the strongest associations between smoking and mortality observed for mucinous disease. We observed similar associations in serous and endometrioid/clear cell subgroups in the current study; case numbers precluded evaluating smoking by aggressiveness among mucinous cases.

We hypothesized that pre-diagnosis exposures may influence whether ovarian cancers develop toward “less” vs. “more” aggressive phenotypes, defined by survival time following an ovarian cancer diagnosis. Overall, results were similar by histologic subgroups, suggesting the observed heterogeneity was not principally driven by tumor histology. Importantly, in clustering analysis, our results suggested that risk factor associations for highly and very aggressive disease track more clearly by tumor aggressiveness rather than by histology. This suggests that metrics of tumor heterogeneity beyond histotype should be evaluated to identify potential etiologic mechanisms that relate risk factors to disease development. For example, Kurman and colleagues suggested that ovarian cancer develops along two pathways: type I disease, a less aggressive phenotype including low grade serous, endometrioid, mucinous, clear cell, and malignant Brenner tumors, and; type II disease, more aggressive disease, primarily including high grade serous tumors.[48, 49] Prognosis for type I tumors is significantly better than that observed for type II disease.[5, 50] An alternative, complementary, approach to that implemented here would be to evaluate risk by the proposed dualistic model,[48] classifying tumors using histology and grade. However, grade data were not available for a large portion of cases in this study.

We conducted analyses by stage at diagnosis for exposures where we observed significant heterogeneity by aggressiveness to explore whether the observed results were due to associations between the exposure and later stage at diagnosis (e.g., if smoking status were more strongly associated with highly aggressive disease due to delayed detection and/or diagnosis). For BMI, family history of ovarian cancer, and smoking, patterns observed in the overall analysis were consistently observed for cases diagnosed at higher stage (stages 3 or 4; 63% of the study population). However, while data on stage at diagnosis were relatively complete, data on sub-stage were not available. As one example, the association between current smoking and highly aggressive disease was limited to women diagnosed at stage III/IV. It is possible that a higher proportion of smokers were diagnosed at more advanced sub-stage (e.g., IIIB, IIIC) than nonsmokers, explaining the association. A further limitation of this investigation is the lack of detailed information on comorbidities and lack of data on post-diagnosis treatment information, including chemotherapy regimen and debulking status. Poole et al.[15] observed minimal impact on the differences between rapidly fatal vs. less aggressive disease before and after adjusting for both chemotherapy regimen and debulking status, suggesting that these factors may not be important covariates in an analysis of risk of ovarian cancer by tumor aggressiveness. The aggressiveness classification was based on death from any cause, as data on ovarian-cancer specific death were not readily available. We evaluated cause of death following ovarian cancer diagnosis in the NHS/NHSII, NLCS and EPIC cohorts, and the large majority of deaths following ovarian cancer diagnosis were due to ovarian cancer, particularly within 5 years of diagnosis (percentages of deaths due to ovarian cancer: highly aggressive: >90%; very aggressive >85%, moderately aggressive >83%, less aggressive >50%). Finally, despite the relatively large sample size, data availability for the investigated risk factors varied by cohort and was limited for some exposures (e.g., endometriosis, duration of breastfeeding) and analyses by disease aggressiveness within histologic subgroups were limited; these analyses were restricted to the two major histologic subgroups identified in our earlier investigation.[10]

We provide novel data on risk factors for ovarian cancer by aggressiveness, defined by time to death, in this pooled analysis in the OC3, identifying obesity and current smoking as modifiable risk factors predominantly associated with higher risk of highly aggressive (i.e., rapidly fatal) ovarian cancer. Further research is required to more fully describe the mechanistic pathways underlying these associations. However, our study supports a role for maintaining healthy weight and smoking cessation in reducing risk of ovarian cancers with the least favorable outcomes.

Additional Information

Ethics approval and consent to participate

All studies obtained institutional approval for cohort maintenance as well as participation in the OC3. The OC3 Data Coordinating Center and analytic approaches were approved by the institutional review board of the Brigham and Women's Hospital (BWH).

Availability of data and material

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. For information on data access for the OC3, please see the instructions at: https://sites.google.com/a/channing.harvard.edu/oc3/ .

Conflict of interest

The authors report no conflicts of interest.

Funding

Supported by Department of Defense Ovarian Cancer Research Program Grant No. W81XWH-12-1-0561. Also supported by K05 CA154337 from the National Cancer Institute (NCI) and Office of Dietary Supplements (VITAL [Vitamins and Lifestyle study cohort]); R01 CA39742 (Iowa Women's Health Study); National Institutes of Health/NCI grant UM1 CA182876 (Singapore Chinese Health Study); CA047988, HL043851, HL080467, and HL099355 (Women's Health Study); CA164973 (Multiethnic Cohort); R01CA77398 and UM1 CA169417 (California Teachers Study); UM1 CA186107, P01 CA87969, UM1 CA176726, and R01 CA67262

(Nurses' Health Study, Nurses' Health Study II); National Institutes of Health UM1 CA182934 and center grants P30 CA016087 and P30 ES000260 (NYU Women's Health Study); grants from the Swedish Cancer Society and Swedish Research Council (Swedish Women's Lifestyle and Health cohort study); and the Swedish Research Council (Swedish Mammography Cohort). All aspects of the Cancer Prevention Study II were funded by the Intramural Research Program of the American Cancer Society and by the NCI Intramural Research Program, Intramural Research Program of the National Institutes of Health, and National Institute of Environmental Health Sciences. The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, 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) (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Nordforsk (Norway); Health Research Fund (FIS), PI13/00061 to Granada; , PI13/01162 to EPIC-Murcia), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford) (United Kingdom). The Melbourne Collaborative Cohort Study was funded by VicHealth and Cancer Council Victoria, and Australian National Health and Medical Research Council grants 209057 and 396414.

Authors' contributions

All authors contributed to the design of the study or the acquisition, analysis, or interpretation of data. RTF, EMP, and SST drafted the manuscript. All authors contributed to revision of the manuscript for intellectual content. The authors assume full responsibility for analyses and interpretation of these data.

Acknowledgements

We would like to thank the participants and staff of the participating cohorts for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY.

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Figure 1.

Unsupervised hierarchical clustering of ovarian cancer subtypes defined by disease aggressiveness using β-estimates, with complete linkage and uncentered correlation (Pearson coefficient). Unsupervised hierarchical clustering of (A) aggressiveness categories and (B) aggressiveness further categorized by serous vs. non-serous histology . Aggressiveness categories defined as: highly aggressive: death within <1 year of diagnosis; very aggressive; death in 1-<3 years; moderately aggressive: death in 3-<5 years; less aggressive: lived 5+ years. The color scale shows the range of β-values for each exposure.

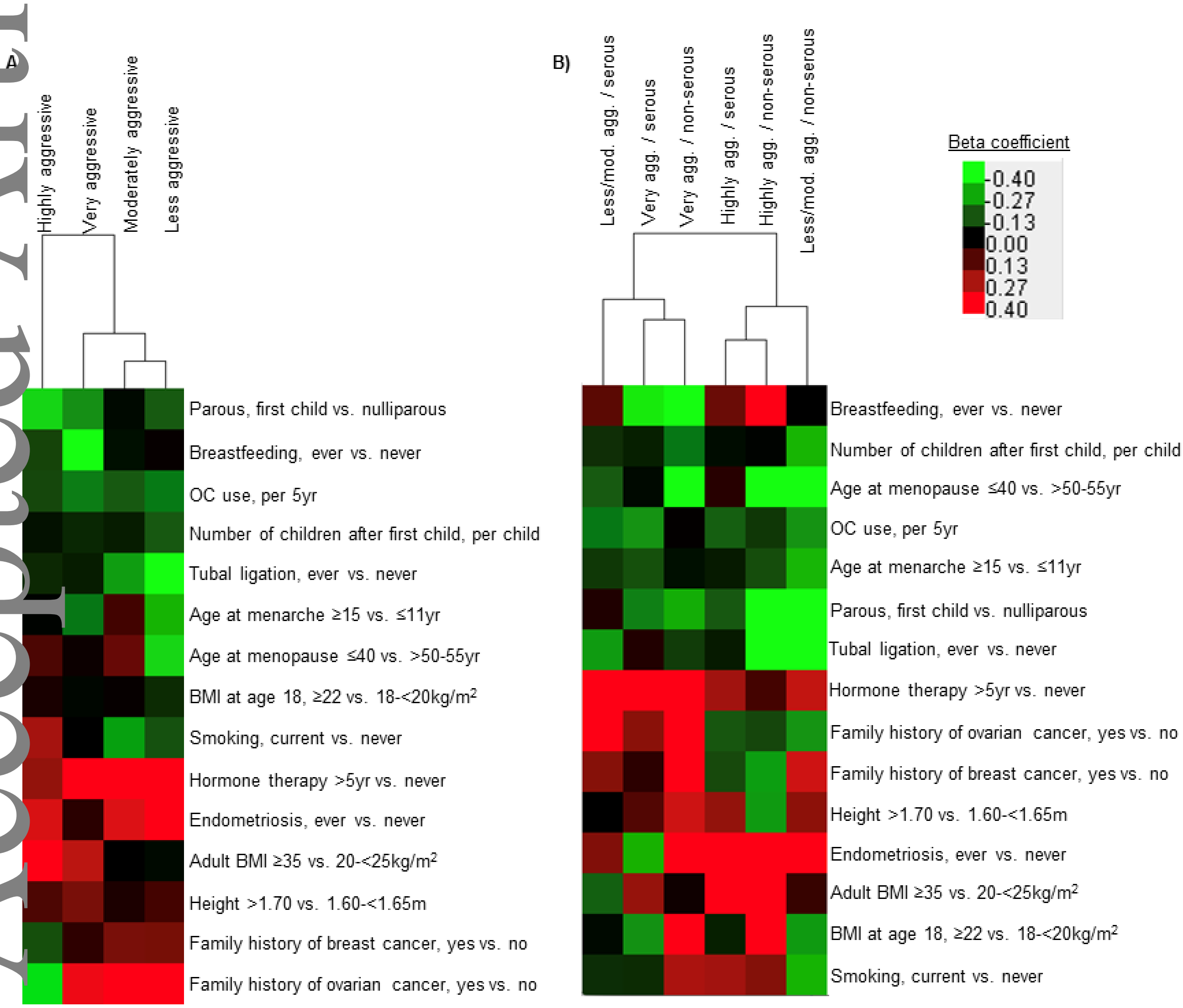

Table 1. Characteristics of cohorts in the Ovarian Cancer Cohort Consortium

Study name	Study abbreviation	Location	Baseline enrollment period	Baseline cohort size[a]	Median study participant age	Median follow-up (years)	Last year of follow-up	Invasive ovarian cancer cases
Adventist Health Study II	AHS	U.S.	2002-2007	39,014	53	8	2015	41
Breast Cancer Detection Demonstration Project Follow-up Study	BCDDP	U.S.	1987-1989	36,168	61	9	1999	104
California Teachers Study	CTS	U.S.	1995-1999	43,744	50	15	2012	151
Campaign against Cancer and Stroke	CLUEII	U.S.	1989	12,380	46	22	2012	80
Canadian Study of Diet, Lifestyle, and Health	CSDLH	Canada	1991-1999	2,733[b]	58	16	2010	78
Cancer Prevention Study II Nutrition Cohort	CPSII-NC	U.S.	1992-1993	65,795	62	15	2009	444
European Prospective Investigation into Cancer and Nutrition	EPIC	Europe	1992-2000	263,644	51	13	2010	519
Iowa Women's Health Study	IWHS	U.S.	1986	30,526	61	23	2010	252
Melbourne Collaborative Cohort Study	MCCS	Australia	1990-1994	20,827	55	16	2009	86
Multiethnic/Minority Cohort Study[c]	MEC	U.S.	1993-1998	16,454	57	11	2011	55
New York University Women's Health Study	NYU	U.S.	1984-1991	12,407	49	24	2012	109
Netherlands Cohort Study on diet and cancer	NLCS	Netherlands	1986	2,755[b]	62	17	2009	446
NIH-AARP Diet and Health Study	AARP	U.S.	1995-1997	152,850	62	11	2006	504
Nurses' Health Study 1980[d]	NHS80	U.S.	1980-1982	86,624	46	16	2010	351
Nurses' Health Study 1996[d]	NHS96	U.S.	1996-1998	67,454	62	14	2010	342
Nurses' Health Study II	NHSII	U.S.	1989-1990	111,882	35	20	2011	159
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	PLCO	U.S.	1993-2002	60,103	62	12	2009	270
Singapore Chinese Health Study	SCHS	Singapore	1993-1999	31,925	56	14	2011	81
Swedish Mammography Cohort Study	SMC	Sweden	1997	34,388	60	14	2011	124
VITamins And Lifestyle Cohort	VITAL	U.S.	2000-2002	28,297	60	10	2011	96
Women's Health Study	WHS	U.S.	1993-1996	33,518	53	18	2012	174
Women's Lifestyle and Health	WLHS	Sweden	1991-1992	49,004	40	21	2012	118

[a]Stratified on birth year and cohort, and adjusted for age at study entry, parity, and duration of oral contraceptive use (except when parity or oral contraceptive use was the primary exposure of interest and then we adjusted only for the other risk factor) using pooled analyses of all cohorts combined. [b]These cohorts were included as a case-cohort design, reflecting a total cohort population of 39,445 women in the CSDLH and 62,528 women for the NLCS. Appropriate weights for subcohort selection were applied in all analyses; [c]Including only Caucasian women; [d]The Nurses' Health Study was broken into two study periods (1980-June 1996 and July 1996-2010) because the follow-up was nearly twice as long as any other study. We updated the exposures in 1996 for that follow-up period.

Table 2: Associations[a] of ovarian cancer risk factors with invasive epithelial ovarian cancer by tumor aggressiveness in the Ovarian Cancer Cohort Consortium

	Highly aggressive HR (95% CI)	Very Aggressive HR (95% CI)	Moderately aggressive HR (95% CI)	Less aggressive HR (95% CI)	p_{het} by aggressiveness[b]	p_{trend} across categories of aggressiveness[c]
Time between diagnosis and death	***<1 year***	***1 to <3 years***	***3 to <5 years***	***5+ years***		
Parity						
No children	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
First child	0.72 (0.58,0.88)	0.80 (0.67,0.94)	0.98 (0.76,1.28)	0.87 (0.74,1.01)	**0.01**	0.13
Subsequent children	0.97 (0.92,1.02)	0.94 (0.90,0.98)	0.95 (0.90,1.01)	0.87 (0.83,0.91)		**0.002**
Age at first birth, per yr	0.99 (0.97,1.00)	1.00 (0.98,1.01)	0.99 (0.97,1.01)	1.01 (1.00,1.02)	0.19	0.08
<20	1.13 (0.85,1.50)	1.07 (0.86,1.33)	1.05 (0.78,1.41)	1.01 (0.83,1.24)		0.54
20-<25	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	0.56	
25-<30	0.98 (0.81,1.17)	0.92 (0.80,1.05)	0.97 (0.79,1.19)	1.05 (0.92,1.19)		0.30
30+	0.85 (0.65,1.10)	1.02 (0.84,1.23)	0.81 (0.60,1.09)	1.10 (0.93,1.31)		0.18
Age at last birth, per yr	1.00 (0.97,1.02)	1.01 (0.99,1.03)	0.98 (0.95,1.00)	1.01 (0.99,1.03)	0.26	0.51
<25	1.31 (0.86,2.01)	0.96 (0.67,1.39)	1.01 (0.64,1.58)	0.89 (0.66,1.19)		0.20
25-<30	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	0.32	
30-<35	1.20 (0.88,1.62)	1.14 (0.90,1.43)	1.04 (0.75,1.43)	1.08 (0.89,1.31)		0.56
35+	1.19 (0.85,1.68)	1.06 (0.82,1.39)	0.59 (0.37,0.92)	1.06 (0.84,1.33)		0.51
Duration of breastfeeding, per yr[d]	0.96 (0.80,1.15)	0.82 (0.68,0.98)	1.00 (0.86,1.18)	0.97 (0.87,1.09)	0.24	0.48
Ever vs never	0.90 (0.58,1.39)	0.67 (0.48,0.93)	0.98 (0.59,1.61)	1.01 (0.77,1.33)	0.27	0.20
Duration of oral contraceptive use, per 5 yr	0.89 (0.81,0.99)	0.82 (0.76,0.89)	0.87 (0.78,0.97)	0.82 (0.77,0.88)	0.48	0.38
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
≤1	0.91 (0.68,1.21)	0.90 (0.73,1.10)	1.03 (0.77,1.37)	1.02 (0.86,1.21)		0.31
>1-≤5	0.83 (0.65,1.06)	0.87 (0.73,1.03)	0.98 (0.77,1.24)	0.84 (0.73,0.98)	0.95	0.99
>5-≤10	0.74 (0.56,0.99)	0.66 (0.54,0.82)	0.80 (0.59,1.07)	0.76 (0.64,0.91)		0.52
>10	0.72 (0.52,1.01)	0.59 (0.45,0.77)	0.60 (0.41,0.88)	0.57 (0.46,0.72)		0.37
Age at menarche, per 1 yr	0.99 (0.95,1.04)	0.97 (0.94,1.00)	1.01 (0.96,1.06)	0.97 (0.94,1.01)	0.64	0.78
≤11	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
12	0.88 (0.70,1.10)	0.84 (0.71,0.99)	1.00 (0.78,1.28)	0.95 (0.82,1.10)		0.32
13	0.96 (0.79,1.18)	0.86 (0.74,1.00)	1.14 (0.91,1.43)	0.90 (0.79,1.04)	0.13	0.98
14	0.83 (0.65,1.06)	0.81 (0.67,0.98)	0.89 (0.67,1.19)	1.00 (0.85,1.18)		0.10
≥15	0.99 (0.78,1.26)	0.83 (0.69,1.01)	1.11 (0.83,1.48)	0.75 (0.62,0.91)		0.17
Age at menopause, per 5 yr	1.02 (0.94,1.12)	1.04 (0.97,1.11)	0.98 (0.89,1.09)	1.09 (1.02,1.16)	0.37	0.30
≤40	1.13 (0.83,1.54)	1.02 (0.79,1.33)	1.18 (0.81,1.71)	0.71 (0.54,0.95)		0.05
>40-≤45	0.89 (0.67,1.19)	0.71 (0.55,0.90)	1.08 (0.77,1.51)	0.82 (0.65,1.03)		0.87
>45-≤50	1.02 (0.85,1.23)	0.95 (0.82,1.10)	1.04 (0.83,1.31)	0.89 (0.77,1.03)	0.51	0.33
>50-≤55	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
>55	1.20 (0.87,1.64)	1.02 (0.78,1.33)	1.14 (0.77,1.69)	0.94 (0.72,1.24)		0.35

Duration of hormone therapy use, per 1 yr[e]	1.03 (1.01,1.04)	1.03 (1.02,1.04)	1.05 (1.03,1.06)	1.04 (1.03,1.05)	0.27	0.12
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
≤5 years	0.92 (0.74,1.14)	1.18 (0.99,1.40)	1.29 (1.00,1.66)	1.26 (1.06,1.47)	0.12	**0.05**
>5 years	1.26 (1.01,1.58)	1.52 (1.28,1.80)	1.87 (1.47,2.39)	1.69 (1.43,1.99)		**0.03**
Tubal ligation, ever vs. never	0.94 (0.65,1.36)	0.95 (0.75,1.21)	0.78 (0.55,1.11)	0.66 (0.53,0.82)	0.12	**0.02**
Hysterectomy, ever vs. never[f]	0.88 (0.73,1.06)	0.83 (0.72,0.97)	1.09 (0.89,1.34)	0.92 (0.80,1.06)	0.21	0.36
Endometriosis, ever vs. never	1.41 (0.66,3.00)	1.07 (0.59,1.95)	1.41 (0.75,2.68)	1.58 (1.06,2.33)	0.76	0.46
Family history of breast cancer, yes vs. no	0.88 (0.70,1.11)	1.08 (0.91,1.28)	1.21 (0.95,1.54)	1.21 (1.04,1.41)	0.12	**0.03**
Family history of ovarian cancer, yes vs. no	0.70 (0.38,1.32)	1.45 (1.04,2.04)	1.62 (1.01,2.60)	1.94 (1.47,2.55)	**0.02**	**0.01**
BMI in adulthood, per 5kg/m²	1.15 (1.07,1.23)	1.04 (0.98,1.10)	1.03 (0.95,1.12)	0.99 (0.94,1.04)	**0.01**	**0.002**
<20	1.36 (1.04,1.77)	1.02 (0.81,1.27)	0.98 (0.71,1.36)	0.94 (0.78,1.15)		0.06
20-<25	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
25-<30	1.15 (0.98,1.35)	0.99 (0.87,1.12)	0.94 (0.78,1.13)	0.95 (0.85,1.07)	**0.04**	0.10
30-<35	1.34 (1.07,1.67)	0.96 (0.80,1.16)	1.10 (0.85,1.42)	0.96 (0.81,1.14)		0.07
≥35	1.93 (1.46,2.56)	1.34 (1.07,1.69)	1.01 (0.70,1.45)	0.98 (0.78,1.24)		**0.0002**
BMI at age 18-20, per 5kg/m²	1.11 (0.97,1.28)	1.06 (0.95,1.19)	1.01 (0.86,1.18)	0.97 (0.87,1.08)	0.45	0.10
<18	1.04 (0.76,1.42)	0.84 (0.64,1.11)	0.83 (0.57,1.21)	1.04 (0.83,1.3)		0.71
18-<20	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	0.62	
20-<22	1.09 (0.87,1.36)	1.05 (0.87,1.25)	0.84 (0.65,1.10)	1.06 (0.91,1.24)		0.79
≥22	1.04 (0.83,1.31)	0.99 (0.82,1.19)	1.01 (0.78,1.31)	0.93 (0.79,1.10)		0.46
Height, per 0.05m	1.06 (1.01,1.12)	1.09 (1.04,1.13)	1.04 (0.98,1.10)	1.07 (1.03,1.11)	0.71	0.86
<1.60m	0.81 (0.67,0.98)	0.89 (0.76,1.03)	0.88 (0.70,1.09)	0.94 (0.82,1.07)		0.30
1.60-<1.65m	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	0.70	
1.65-<1.70m	0.90 (0.75,1.08)	1.05 (0.91,1.21)	1.07 (0.87,1.31)	1.10 (0.97,1.26)		0.12
≥1.70m	1.13 (0.93,1.37)	1.21 (1.04,1.41)	1.05 (0.83,1.32)	1.11 (0.97,1.28)		0.63
Smoking						
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)		
Former	0.91 (0.77,1.08)	1.07 (0.95,1.21)	1.02 (0.85,1.22)	0.95 (0.85,1.07)	**0.004**	0.79
Current	1.30 (1.07,1.57)	1.00 (0.85,1.17)	0.78 (0.60,1.01)	0.88 (0.76,1.02)		**0.002**

[a]Stratified on birth year and cohort, and adjusted for age at study entry, parity, and duration of oral contraceptive use (except when parity or oral contraceptive use was the primary exposure of interest and then we adjusted only for the other risk factor) using pooled analyses of all cohorts combined; [b]Assessed using a likelihood ratio test comparing a Cox proportional hazards competing risks model allowing the association to vary by subtype to a model forcing the association to be the same across subtypes; [c]Trend across the ordinal aggressiveness subtypes using meta-regression with a subtype-specific random effect term; [d]Parous women only; [e]Postmenopausal women only; [f]Additionally adjusted for duration of hormone therapy use