Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin

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OBJECTIVE: To evaluate factors associated with type of ovarian cancer, a surrogate for cell of origin.

DESIGN: Case-control study and two cohort studies.

RESULTS: Among 1,771 invasive epithelial ovarian cancer cases, we observed 1,089 tumors with a dominant mass and 682 with no dominant mass. Dominant tumors were more likely to be mucinous, endometrioid, or clear cell, whereas non-dominant tumors were more likely to be serous. Tubal ligation, two or more births, endometriosis, and age were more strongly associated with dominant tumors (RRs = 0.60, 0.83, 1.58, 1.37, respectively) than non-dominant tumors (RRs = 1.03, 0.93, 0.84, 1.14 p-difference = 0.0001, 0.01, 0.0003, 0.01, respectively). These data suggest that risk factors for tumors putatively arising from ovarian versus fallopian tube sites may differ; in particular, reproductive factors may be more important for ovarian-derived tumors. As this is the first study to evaluate ovarian cancer risk factors by tumor dominance, these results need to be validated by other studies.

CONCLUSION: These results suggest that reproductive factors may be more important for ovarian-derived tumors, whereas serous tumors may be more strongly associated with age.

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Keywords
ovarian cancer; cell of origin; epidemiology; risk factors

Introduction
Ovarian cancer is the fifth leading cause of cancer death for women in the United States and seventh most fatal cancer worldwide.\(^1,2\) Despite extensive study, the etiology of ovarian cancer is not fully understood. Historically, ovarian tumors were thought to arise from the ovarian surface epithelium or related cortical inclusion cysts.\(^3\) Recent pathology studies suggest that as many as half of high-grade serous tumors originate in the distal fallopian tube.\(^4-6\) Furthermore, precursor lesions have been identified in the fallopian tube (called ‘p53 signatures’). These signatures have conserved \(p53\) mutations that are identical to co-located tubal intraepithelial carcinomas (TICs), a potential non-invasive precursor that can metastasize without undergoing direct invasion,\(^7\) as well as invasive carcinomas.\(^8\) Other characteristics of this ‘p53 signature’ include its location in the distal fallopian tube, involvement of secretory cells, strong immunostaining for \(p53\), and evidence of DNA damage.\(^4\) Thus, the etiology of ovarian cancer has been reconsidered in the framework of two sites of origin that may have distinct developmental pathways.\(^9,10\)

From an epidemiologic perspective, primary prevention recommendations for ovarian cancer are limited. Of the modifiable risk factors, consistent findings have been observed with oral contraceptive use (OC) and tubal ligation,\(^11,12\) while the relationship with other exposures remains unclear. Inconsistent associations with other potential risk factors (e.g., body mass index) may be explained if these factors are only associated with a specific subset of tumors. For example, several studies have observed different risk factor associations by histology.\(^13-19\) Despite this, there have been no epidemiologic studies to date classifying ovarian cancers by cell of origin. Characterizing risk factor relationships by cell of origin could elucidate how these factors alter risk, the etiology of the disease, and help improve prevention efforts.

Thus, we undertook this study to evaluate risk factor associations by a surrogate measure for cell of origin among 1,771 invasive epithelial ovarian tumors diagnosed in the Nurses’ Health Study (NHS), NHSII, and the New England Case-Control (NECC) study of ovarian cancer. Ideally, classification of tumor origin (e.g., ovarian vs. fallopian tube) would come from direct identification of a TIC or \(p53\) signature in the tube, but this requires extensive morphologic and immunohistochemical examination of the fallopian tube, and thus is possible only in a clinical setting. Alternatively, Roh and colleagues reported that ovarian versus tubal carcinomas may be classified using tumor dominance, which can be obtained from pathology reports and is a classification method amenable to epidemiologic studies.\(^20\) Thus, we evaluated the association of known and putative ovarian cancer risk factors for cases with dominant (tumor restricted to one ovary or twice as large as the tumor in the other ovary) versus non-dominant tumors (equally spread across peritoneal cavity or only tumor foci on ovaries), as a surrogate for cell of origin (ovarian vs. fallopian, respectively).

Materials and Methods
New England Case-Control Study (NECC)

Study Population—The NECC study of ovarian cancer was conducted in three enrollment phases (1992–1997, 1998–2002, 2003–2008). Briefly, 3,957 women residing in eastern Massachusetts or New Hampshire with an incident diagnosis of ovarian cancer were identified through hospital tumor boards and statewide cancer registries. Women were
excluded if they were less than 18 years of age, moved, had no phone, did not speak English, died, physician declined permission to contact, or had a non-ovarian primary upon review. Of the 3,083 eligible cases, 2,203 (71%, 2076 epithelial cases) agreed to participate. Diagnosis, invasiveness, and histologic subtype were confirmed by a gynecologic pathologist blinded to exposure status who reviewed the pathology reports for every enrolled case. Controls were identified through a combination of random digit dialing, drivers’ license lists, and town resident lists. In addition to the exclusion criteria applied to the cases, controls with bilateral oophorectomy were also excluded. In the first phase, 421 (72%) of the eligible controls were identified through random digit dialing agreed to participate and 102 (51%) through town resident lists agreed to participate. In the second and third phases, 4,366 potential controls were identified, 2,940 were eligible, 1,362 declined to participate by phone or by mail via an “opt-out” postcard, and 1,578 (54%) were enrolled. Controls were frequency matched to cases on age and state of residence. The institutional review boards of the Brigham and Women’s Hospital and Dartmouth Medical School approved all phases of the study.

**Exposure data**—We interviewed all participants in person at enrollment. We collected information about known and suspected ovarian cancer risk factors, including reproductive history, gynecologic conditions and procedures, height and weight, genital talc use, smoking, medication use, and family cancer history. To avoid the influence of pre-clinical disease, cases were asked about exposures that occurred at least one year before diagnosis, and controls were asked about exposures that occurred more than one year before the interview date.

For women with natural menopause, age at menopause was coded as age at last menstrual period without use of hormones. Women who had a hysterectomy, received medical treatment that led to menopause, or reported use of postmenopausal hormones (PMH) before their periods stopped, were excluded from the age at menopause analyses. Use of powders (e.g., cornstarch, talc, baby, or deodorizing powder) at least once per week on the genital/rectal area, on sanitary napkins or tampons, or to underwear was classified as weekly genital powder use. Women who smoked 100 or more cigarettes in their lifetime were considered smokers. Those who stopped more than a year before diagnosis or interview were considered past smokers. Data regarding analgesic use came from questions that asked about over the counter medication use for six months or longer and, in the last two phases of the study, participants also were asked about analgesic use for menstrual pain. Women with a mother or sister with breast or ovarian cancer were considered to have a family history of these cancers. Duration of breastfeeding was summed across all pregnancies.

**Nurses’ Health Study (NHS) and NHSII**

**Study Population**—The NHS was established in 1976 and the NHSII in 1989 with 121,700 female registered nurses aged 30–55 and 116,430 female registered nurses aged 25–42, respectively. Participants completed an initial questionnaire and biennial follow-up questionnaires, providing information on lifestyle factors and disease diagnoses. Follow-up is high in both cohorts; we obtained 95.2% of the total possible person-years through June 2008 in NHS and 94.2% through June 2007 in the NHSII. The institutional review board of the Brigham and Women’s Hospital approved both studies.

**Exposure Data**—We obtained exposure information from biennial questionnaires. At baseline, participants reported their date of birth, age at menarche, and height. We requested information on reproductive history, tubal ligation, hysterectomy, PMH use, weight, smoking, and family history of breast/ovarian cancer on multiple questionnaires during follow-up. In our analysis, we updated the values for these covariates when new data were
available and otherwise carried forward values from the previous cycle. We requested data
on total duration of breastfeeding across all pregnancies in 1986 (NHS) and 1993 (NHSII).
Frequency of genital talc use was collected in 1982 (NHS only). We asked NHS participants
about current use of analgesics “most weeks” in 1980. In 1990 (NHS) and 1989 (NHSII) and
every two or four years thereafter, participants were asked whether they used analgesics
(separately by aspirin, acetaminophen, or other NSAIDs) two or more times per week. Other
variables were defined in a similar manner as the NECC.

Identification of ovarian cancer cases—We collected information on new ovarian
cancer diagnoses on each questionnaire. For all reported cases and deaths due to ovarian
cancer identified through family members, the U.S. National Death Index,21 or the U.S.
Postal Service, we obtained medical records related to the diagnosis. A gynecologic
pathologist (J.H.) blinded to exposure status reviewed the medical records to confirm the
diagnosis, stage, histologic subtype, and invasiveness. For 215 cases in which pathology
slides were reviewed in a standardized manner by a gynecologic pathologist (JH), 98 percent
were concordant with the pathology report with respect to invasiveness and 83 percent with
respect to histology.22 If detailed pathology reports were not available, we confirmed
diagnoses and obtained information on histology, stage, and morphology through state and
federal cancer registries.

Classification of ovarian tumors: NECC, NHS and NHSII

We defined tumors as having a greater likelihood of an ovarian surface epithelium origin if
the tumor was limited to one ovary or one involved ovary exceeded the other in dimension
by at least two-fold (i.e., dominant).20 Tumors were identified as having a greater likelihood
of a tubal origin if the disease was equally distributed across the ovaries (i.e., non-
dominant). All invasive epithelial ovarian cancer (n=1,133) and primary peritoneal (n=18)
cases diagnosed between baseline and June 2008 (NHS) or 2009 (NHSII) as well as invasive
epithelial ovarian (n=1,614) and peritoneal (n=26) NECC cases diagnosed between 1992
and 2008 were evaluated for tumor dominance. After exclusions (see Statistical Methods),
969 confirmed cases were eligible for analysis in NHS/NHSII. Of these, we were able to
determine tumor dominance for 480 (50%) cases. For the remaining cases, the pathology
report did not have the information needed to determine tumor dominance for 196 (20%)
cases or we did not have a detailed pathology report available for 293 (30%) cases. Cases
with missing information on the pathology reports were more likely to have been diagnosed
earlier during follow-up, suggesting poor documentation on reports before the 1990s.
Further, cases without a detailed pathology report were more likely to have been identified
via death records through cancer registries. In the NECC, we were able to determine tumor
dominance on 1,291 (79%) of the invasive cases; undetermined tumor dominance generally
was due to missing information on the pathology report. In NHS/NHSII and NECC, cases
without tumor dominance data were similar to all potential cases on key ovarian cancer risk
factors, histology, and stage (data not shown), suggesting that there was a random loss of
information.

Statistical Analysis

Lifetime ovulatory cycles were estimated by subtracting age at menarche from age at
menopause for postmenopausal women or current age for premenopausal women and
subtracting additional time for OC use, pregnancy (one year each) and breastfeeding (NECC
only) and was categorized into quartiles using controls for NECC and the entire cohort for
NHS/NHSII. BMI was calculated as weight in kilograms divided by height in meters
squared. We modeled age, duration of breastfeeding (restricted to parous women), height
(inches) and years of PMH use as continuous variables, and intrauterine device (IUD) use,
tubal ligation, hysterectomy, endometriosis, ever PMH use, genital powder use,
acetaminophen use, aspirin use, NSAID use, family history of breast, and family history of ovarian cancer as binary variables (yes/no). Duration of OC use (never, < 5 years, ≥ 5 years), infertility (none, male, all other), BMI (<23, 23–24, 25–29, ≥30 kg/m²) and smoking status (never, past, current), and estimated lifetime number of ovulatory cycles (quartiles) were modeled categorically. Parity was modeled in two variables: ever/never and number of deliveries (continuous) when considered as the main exposure. Parity was modeled categorically (0, 1, 2, 3, 4+) as a covariate, except for the breastfeeding analysis in which a continuous parity variable was used. Endometriosis status was not available in NHS, genital powder use was not available in NHSII, and PMH analyses were restricted to postmenopausal women in NECC enrolled between 1998 and 2008 and postmenopausal NHS participants.

In the NECC, we used polytomous logistic regression (PLR) to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of each exposure with dominant and non-dominant tumors. In the NHS and NHSII analyses, participants accrued person-time from the return date of the baseline questionnaire until the date of ovarian cancer diagnosis, diagnosis of any other cancer (excluding non-melanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up. At baseline, we excluded women with no date of birth (NHS: n=165) bilateral oophorectomy (NHS: n=7,669; NHSII: n=2,229), menopause due to pelvic irradiation (NHS: n=99; NHSII: n=30), or cancer other than non-melanoma skin cancer (NHS: n=3,314; NHSII: n=1,050). We used Cox proportional hazards competing risks analysis, stratified by time period, cohort, and tumor dominance, to model the incidence rate ratio (RR) and 95% CI of epithelial ovarian cancer for each exposure. In both studies, the estimates for the exposure of interest were allowed to vary between dominant and non-dominant tumors, while estimates for covariates were constrained to a single effect estimate.

We used multivariate models adjusted for age, study center (NECC: Massachusetts, New Hampshire; NHS: NHS vs. NHSII), study phase (NECC only: 1992–1997, 1998–2002, 2003–2008), OC use, parity, tubal ligation, and family history of breast or ovarian cancer. Hysterectomy analyses also included adjustment for menopausal status (premenopausal, postmenopausal) and postmenopausal hormone use (no, past use, current use). We combined data across studies using random effects meta-analyses to calculate pooled estimates of the association and assess heterogeneity between studies. To test whether the pooled RR for dominant tumors was significantly different from the pooled RR for non-dominant tumors (p-difference), we calculated the difference in the parameter estimates for the tumor types and the associated variance (the variance for dominant tumor estimate plus the variance of the non-dominant tumor estimate minus two times the covariance of the two estimates) and estimated a p-value for heterogeneity using a normal distribution. We further evaluated histology-adjusted risk estimates by calculating a weighted average of the risk associated with serous and non-serous tumors for both dominant and non-dominant tumors using the prevalence of these histologic categories in the NECC and NHS/NHSII study populations (see supplemental methods for details). Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and Stata 9 (StataCorp, College Station, TX). All P values were based on two-sided tests and were considered statistically significant if P ≤ 0.05.

**Results**

Among the 1,771 invasive epithelial ovarian cancer cases eligible for analysis, we observed 1,089 (NECC: 766, NHS: 323) tumors with a dominant mass and 682 (NECC: 525, NHS: 157) with no dominant mass (Table 1). The dominant cases were more likely to be endometrioid (NECC: 31%, NHS: 25%), clear cell (NECC: 12%, NHS: 11%), and mucinous (NECC: 10%, NHS: 8%), while the non-dominant cases were more likely to be serous.

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About half of the dominant tumors were stage 1 and 2 cancers (NECC: 65%, NHS: 51%), while non-dominant tumors tended to be Stage 3 or 4 (NECC: 85%, NHS: 87%). In the NECC study, dominant cases were evenly distributed between low (45% grades 1/2) and high (46% grade 3), while non-dominant cases were more likely to be high grade (75%). Among serous cases in the NECC study, high-grade cases were more commonly non-dominant (61%) and low-grade cases were more frequently dominant (56%).

Several reproductive factors, including tubal ligation, parity, and endometriosis, were more strongly associated with the risk of dominant tumors compared to non-dominant tumors (Table 2). For example, tubal ligation was associated with a 40% lower risk of dominant tumors (95% CI = 0.48–0.73), but was not associated with risk of non-dominant tumors (pooled RR = 1.03, 95% CI = 0.83–1.29, p-difference = 0.0001). The difference in risk was attenuated slightly after adjustment for serous histology (p-difference = 0.02). The association between parity and cancer risk also varied by tumor dominance. The first birth was significantly associated with risk reduction for dominant (RR = 0.71, 95% CI = 0.57–0.89) and non-dominant tumors (RR = 0.75, 95% CI = 0.57–0.99; p-difference = 0.74). However, subsequent births were associated with a reduction in risk for dominant (RR, per additional birth=0.83, 95% CI = 0.73–0.94), but not for non-dominant tumors (RR = 0.93, 95% CI = 0.82–1.05; p-difference = 0.01). This difference was attenuated somewhat after adjustment for histology (p-difference = 0.16). Significant heterogeneity was observed between studies for the association between subsequent birth and dominant tumors with a more attenuated association in NHS (RR=0.89) than in NECC (RR=0.79; Supplemental table 1).

Increased risk associated with endometriosis was limited to dominant tumors (p-difference = 0.0003). Endometriosis was associated with an increased risk of dominant tumors (RR = 1.58, 95% CI = 1.23–2.03), but not non-dominant tumors (RR = 0.84, 95% CI = 0.44–1.62), with little change after adjustment for histology. When we restricted the data from the Nurses’ Health Study II cohort to laparoscopically-confirmed endometriosis, we observed a stronger estimate of the pooled association between endometriosis and dominant tumors (RR=1.93, 95% CI=1.09–3.40).

IUD use appeared to be more strongly associated with risk of non-dominant versus dominant tumors, though associations were not significant. Women who reported IUD use had a lower risk of developing dominant (pooled RR = 0.83, 95% CI = 0.65–1.05), but an increased risk of developing non-dominant tumors (pooled RR=1.70, 95% CI: 0.68–4.26, p-difference = 0.02). The association between IUD use and non-dominant tumors differed significantly between studies with a two-fold increase in risk in NHS and null association in NECC (Supplemental table 1). Among participants in the NECC study enrolled when type of IUD was queried (between 1992 and 2002), 33%, 24%, and <1% used copper, plastic, and progesterone-containing IUDs, respectively, while 42% did not know the type. The distribution of IUD types did not differ between dominant and non-dominant cases (data not shown). Though we observed no significant overall differences for age at natural menopause by tumor dominance, we observed a suggestively stronger risk of non-dominant tumors with increasing age at natural menopause when we adjusted for serous histology. Compared to women who experienced menopause at < 45 years of age, women with a natural menopause after age 53 had a suggestively higher risk of non-dominant tumors (RR = 1.40, 95% CI = 0.91–2.16) than dominant tumors (RR=1.16, 95% CI=0.72–1.89; p-difference = 0.17). This difference was accentuated after adjustment for histology (p-difference = 0.01).

Other reproductive/hormonal risk factors generally had similar associations with both tumor types (Table 2). For example, OC use was associated with a reduced risk of developing both tumor types, with the greatest reduction in risk for women who used OCs for five or more
years (RR\textsubscript{Dominant} = 0.64, 95% CI = 0.35–1.18; RR\textsubscript{Non-dominant} = 0.54, 95% CI = 0.37–0.79). Likewise, breastfeeding and ovulatory years had similar associations for dominant and non-dominant tumors. We observed significant heterogeneity between studies for the PMH use associations. In NHS, women who reported ever using PMH had an increase in risk of both dominant and non-dominant tumors, while no increase in risk was observed in the NECC study (Supplemental table 1). No differences in association were noted for years of estrogen only or combination postmenopausal PMH use in either study.

Aside from age, associations for non-reproductive exposures generally did not differ between dominant and non-dominant tumors (Table 3). A five year increase in age was associated with an increased risk of both tumor types (RR\textsubscript{Dominant} = 1.37, 95% CI= 1.25–1.50; RR\textsubscript{Non-dominant} = 1.14, 95% CI = 1.01–1.28), but BMI and height were not associated with either tumor type (p-difference ≥ 0.08). Past smoking was associated with a significant 23% increase in risk of non-dominant tumors (95% CI = 1.03–1.48), but was not associated with risk of dominant tumors (pooled RR = 0.99; 95% CI = 0.85–1.15, p-difference = 0.03). Current smoking was associated with a non-significant increase in risk of both tumor types, but only in the NECC study. Analgesics and genital powder use were not significantly associated with either tumor type. Family history of ovarian cancer was more strongly associated with non-dominant tumors (RR = 2.12, 95% CI = 1.41–3.20) than dominant tumors (RR = 1.26, 95% CI = 0.71–2.24; p-difference = 0.08). However, this was attenuated after adjustment for histology (p-difference = 0.70).

In an analysis restricted to high grade serous cases in the NECC study, we observed similar associations though confidence intervals were wider due to the smaller sample size. Notably, tubal ligation remained protective for dominant tumors (RR = 0.76, 95% CI = 0.50–1.14), but not non-dominant tumors (RR = 1.01, 95% CI = 0.72–1.37), while the differences for subsequent births (RR\textsubscript{Dominant} = 0.80, 95% CI = 0.71–0.92; RR\textsubscript{Non-dominant} = 0.84, 95% CI = 0.75–0.93), endometriosis (RR\textsubscript{Dominant} = 0.72, 95% CI = 0.40–1.30; RR\textsubscript{Non-dominant} = 0.89, 95% CI = 0.57–1.39), and family history of ovarian cancer (RR\textsubscript{Dominant} = 2.71, 95% CI = 1.46–5.02; RR\textsubscript{Non-dominant} = 2.17, 95% CI = 1.24–3.80) were attenuated.

**Discussion**

Results from this study suggest that some ovarian cancer risk factors differ by tumor dominance, a surrogate for site of origin. Specifically, tubal ligation and increasing number of births among parous women were associated with a decreased risk, while endometriosis was associated with an increased risk, of developing dominant tumors (likely ovarian origin); these factors were not associated with non-dominant tumors. The association between IUD use and ovarian cancer risk appeared to vary by tumor dominance with a possible increased risk of non-dominant tumors (likely fallopian origin) but confidence bounds were wide. Regardless of the putative site of tumor origin, OC use, first birth, and breastfeeding were associated with reduced risk while estimated lifetime number of ovulatory cycles was associated with an increased risk. Non-reproductive factors generally were not associated with either tumor type, with the possible exception of family history of ovarian cancer, which was somewhat more strongly associated with non-dominant tumors before adjustment for histology. As this is the first study to evaluate ovarian cancer risk factors by tumor dominance, these results need to be validated by other studies.

Previous studies have examined epidemiologic risk factors by histologic type of ovarian cancer.\textsuperscript{13–18} Generally, the associations with serous invasive ovarian cancer reported previously were similar to the associations we observed with non-dominant tumors. For example, OC use has been inversely associated risk of serous invasive ovarian cancer,\textsuperscript{14–18, 25} particularly that of long durations.\textsuperscript{18, 25} We observed a similar inverse

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association. Furthermore, parity has been consistently associated with reduced risk of serous invasive ovarian cancer,\textsuperscript{13–18} although studies that examined first pregnancy separately from subsequent pregnancies reported a significant decrease with the first pregnancy, but no additional protection with subsequent pregnancies.\textsuperscript{14, 18} This is similar to the trend we observed between parity and risk of non-dominant tumors. For tubal ligation, most studies reported a reduction in risk for serous invasive ovarian cancer;\textsuperscript{14–18} however we observed no association between tubal ligation and non-dominant tumors, suggesting tumor dominance is not just a surrogate marker for histology, particularly since adjusting for serous histology or restricted to high-grade serous histology did not change the differential association. Smoking may be more strongly associated with mucinous tumors.\textsuperscript{14, 15, 25, 26} Our data suggested that past smoking possibly was associated more strongly with non-dominant tumors than dominant tumors, but this difference attenuated after adjustment for histology.

Ours is the first study to report risk factor associations by tumor dominance as a surrogate for cell of origin. The differences in risk that we observed between dominant and non-dominant tumors for tubal ligation, IUD use, number of births among parous women, and endometriosis, generally remained unchanged or only attenuated slightly after adjusting for serous versus non-serous histology. However, the observed difference in the association for family history of ovarian cancer was attenuated substantially by histology adjustment. This suggests that most of the observed differences by the putative cell of origin were not driven by the correlation between tumor dominance and histology. However, future studies with increased sample sizes should consider adjustment for both histology and stage.

Traditionally, ovarian tumors were thought to arise from the ovarian surface epithelium, but several lines of evidence suggest that some ovarian cancers arise from the fallopian tubes. First, the fimbria is the predominant site of early lesions discovered in asymptomatic $BRCA$ + women. Second, a TIC can be detected in approximately half of serous and some endometrioid ovarian tumors. Finally, $p53$ sequencing shows genetic identity between TICs and primary ovarian tumors.\textsuperscript{7}

A method of detailed sectioning of the fallopian tubes has been developed to identify fimbrial involvement, but this approach is labor intensive and not applicable to cases identified after surgery.\textsuperscript{27} Therefore, more practical methods of identifying the cell of origin for use in epidemiologic studies must be considered. In a series of 124 invasive serous and endometrioid tumors, Roh and colleagues reported that, 73\% of non-dominant tumors had fimbrial involvement and 42\% had a TIC, suggesting that these tumors may have had a fimbrial origin.\textsuperscript{20} Conversely, relatively few dominant tumors had fimbrial involvement (42\%) or a TIC (5\%), suggesting they are of ovarian origin.\textsuperscript{20} These findings imply that measurements available from pathology reports can be used to categorize cases by likely site of origin in epidemiologic studies. Though histology and grade may be an alternative approach to classifying tumors by cell of origin, this approach is prone to misclassification as well since some tumors classified by histology and grade, such as high-grade serous, are hypothesized to arise from either the ovary or fallopian tube.\textsuperscript{9, 28} Furthermore, grade taken from pathology reports is often inconsistent due to variability by grading method and individual pathologists.\textsuperscript{29} Ultimately, epidemiologic studies need to consider multiple metrics on which to stratify tumors to better understand the role of tumor heterogeneity in disease development and risk factor associations.

Thus, we used dominance as a surrogate for site of origin to classify 1,771 cases in the NECC study and NHS/NHSII cohort studies. Differences in risk of dominant vs. non-dominant ovarian cancer risk by parity, tubal ligation, IUD use, and endometriosis provide novel insight into the development of these tumors. Parity is a well-established ovarian
cancer risk factor. Our data suggest that any pregnancy was protective regardless of tumor type after adjustment for histology; however, the protective effect of subsequent pregnancies was restricted to tumors likely arising from the ovary, suggesting that the mechanism of protection for the first pregnancy is different than for subsequent pregnancies. Clearance of premalignant cells has been cited as the reason for pregnancy-associated risk reduction of ovarian cancer; this mechanism could be important for tumors deriving from either the fallopian tube or ovarian epithelium. Other pregnancy-associated changes attributed to the first pregnancy that could reduce ovarian cancer risk include changes in the hormonal or immunologic milieu as well as ovulation suppression. It is not clear why subsequent pregnancies may only influence risk of ovarian-derived tumors. However, biologic data suggest that progesterone, which is increased during pregnancy, may promote involution of endometrial hyperplasia (EIN) to a benign histology, and studies in which progestins have been used to treat endometriosis, EIN, or well-differentiated endometrioid carcinoma have reported significant regression of these diseases. It is possible that similar mechanisms may apply to the development of ovarian-derived tumors, although this should be explored in future studies. Furthermore, some evidence supports that retrograde menstruation or endometriosis is associated with an increased risk of endometrioid and clear cell ovarian tumors, consistent with our results that endometriosis was associated with an increased risk of dominant tumors. Progesterone exposure from multiple pregnancies may be important in reducing risk among women with endometriosis; however we did not have enough power to assess a possible interaction.

Tubal ligation is another well-established risk factor for ovarian cancer. Blockage of potential carcinogens such as talcum powder or retrograde menstruation from reaching the ovarian surface has been proposed as the mechanism for this inverse association. Our data suggest that tubal ligation protects against tumors likely arising from the ovary, but not the fallopian tubes. If tubal ligation blocks the transport of endometrial cells through the genital tract, which are hypothesized to implant on ovarian surface and possibly develop into endometrioid ovarian cancer, then this could explain why tubal ligation is more likely to reduce the risk of dominant tumors. However, the inverse association between tubal ligation and dominant tumors persisted in analyses adjusted for serous histology and restricted to high-grade serous tumors, suggesting that histology and grade cannot completely account for the finding. This differential association requires further exploration.

The preponderance of endometrioid tumors in the dominant tumor category also may explain the increased risk of this tumor subtype for women with endometriosis and decreased risk for IUD users. In prior studies, endometriosis has been observed to increase risk for endometrioid ovarian cancer and IUD use to decrease risk of endometrial cancer, which is histologically similar to endometrioid ovarian cancer. Interestingly, we observed a non-significant elevation in risk of non-dominant ovarian tumors with non-hormonal IUD use. IUDs generate a local inflammatory reaction that is spermicidal and creates a hostile environment for implantation. In women using a copper IUD, the concentration of copper ions is equally elevated in tubal and uterine fluid, suggesting the physiologic effects of the IUD extend to the fallopian tubes. Several prospective studies have reported that elevated inflammatory markers are associated with an increased risk of ovarian cancer. Interestingly, Ali-Fehmi and colleagues observed that tumors likely to be of fallopian origin were more likely to express inflammatory markers including COX1, COX2, iNOS, and Glut1, suggesting that inflammation may be particularly relevant to cancer originating in the fallopian tube. However, we did not observe an association between anti-inflammatory medication and non-dominant tumors; although the questions about analgesic use were asked differently across the studies. Most prospective studies do not support a role of these medications in ovarian cancer development.
The use of tumor dominance is an easily accessible method of classifying tumors into likely site of origin, but is likely to misclassify some tumors as it is a surrogate marker of cell of origin. In the Roh study, 28% of the non-dominant tumors did not have fimbrial involvement and 60% had no evidence of a TIC.\(^{20}\) Therefore, some non-dominant cases in our study likely are of ovarian origin. It is probable that there is less misclassification in the dominant tumors as only 5% had a TIC in the Roh study. However, despite this, we observed interesting differences between these two tumor types in this large case population drawn from two different study designs that are suggestive of novel developmental pathways.

Use of complementary study designs (cohort and case-control) allowed us to capitalize on the strengths and mitigate the limitations of each design. Since NECC cases were identified after diagnosis, cases with the most aggressive disease were less likely to be enrolled, and reported exposures may have been influenced by the presence of disease, though cases were asked to recall exposures one year prior to diagnosis to minimize this potential bias. These limitations are balanced by the prospective data collection in the NHS/NHSII, which has complete case ascertainment as well as exposure assessment before cancer diagnosis, including laparoscopically-confirmed endometriosis in NHSII. In contrast, the NHS/NHSII are limited by a small sample size that could lead to false negative findings due to limited power. However, the large sample size in the NECC provides sufficient power to evaluate promising but non-significant findings in the NHS/NHSII cohorts. Exposures were harmonized where possible but some differences remained, including lack of endometriosis data in the NHS and differences in analgesic reporting. Study-specific associations varied significantly for several exposures, most notably for IUD use, PMH use, genital powder use, and current smoking. However, the consistency of study-specific associations for tubal ligation, endometriosis, and family history should also be appreciated.

In summary, our understanding of ovarian cancer is rapidly changing; understanding risk factor profiles for potentially independent carcinogenic pathways (e.g., putative cell of origin as the ovary versus the fallopian tube) is needed to better understand the etiology of this disease. In turn, this may lead to targeted prevention strategies and possibly the development of more effective therapies.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


Novelty statement

Recent evidence suggests that some ovarian cancers arise from ovary while others arise from the fallopian tube, but whether risk factors vary by site of origin is unknown. We classified cases based on tumor measurements as a proxy for cell of origin and found that some risk factors differed between groups. Understanding risk factor profiles for potentially independent carcinogenic pathways is needed to better understand the etiology of this disease.
Table 1

<table>
<thead>
<tr>
<th></th>
<th>NECC Dominant n=766</th>
<th>NECC Non-dominant n=525</th>
<th>NHS and NHSII Dominant n=323</th>
<th>NHS and NHSII Non-dominant n=157</th>
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<td><strong>Age at diagnosis, mean (sd)</strong></td>
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<tr>
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<td>43</td>
<td>72</td>
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<tr>
<td>Endometrioid, %</td>
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<td>9</td>
<td>25</td>
<td>8</td>
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<tr>
<td>Clear Cell, %</td>
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<td>2</td>
<td>11</td>
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</tr>
<tr>
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<tr>
<td><strong>Grade</strong></td>
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<tr>
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<td>--</td>
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<tr>
<td>3, %</td>
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</tr>
<tr>
<td>Missing/unknown, %</td>
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<td>5</td>
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<tr>
<td><strong>Stage</strong></td>
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<td>3 / 4, %</td>
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<td>87</td>
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<td>Unknown, %</td>
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<td>1</td>
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</table>

* Poorly differentiated tumors are included in serous category for NHS cohorts and undifferentiated tumors are included in other/unknown for NECC

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### Table 2


<table>
<thead>
<tr>
<th>Exposure</th>
<th>Multivariate adjusted</th>
<th></th>
<th>Multivariate and histology adjusted</th>
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<tr>
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<td>p-diff</td>
<td>RR 95% CI</td>
<td>p-diff</td>
</tr>
<tr>
<td></td>
<td>Dominant</td>
<td>Non-dominant</td>
<td>Dominant</td>
<td>Non-dominant</td>
</tr>
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<td>Age at menarche</td>
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<td>&lt; 12 years</td>
<td>1.05 (0.86–1.27)</td>
<td>1.18 (0.94–1.50)</td>
<td>1.03 (0.84–1.25)</td>
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<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
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<td>1.07 (0.85–1.34)</td>
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<td>1.11 (0.82–1.49)</td>
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<td>0.77 (0.54–1.09)</td>
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<td>0.97 (0.92–1.01)</td>
<td>0.93 (0.88–0.99)</td>
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<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
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<td>&lt; 5 years</td>
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<td>0.90 (0.73–1.12)</td>
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<tr>
<td>≥5</td>
<td>0.64 ‡</td>
<td>0.54 (0.37–0.79)</td>
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<td>0.62 ‡</td>
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<td>IUD use</td>
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<td>1.70 ‡</td>
<td>0.02</td>
<td>0.86 (0.67–1.10)</td>
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<td>Tubal ligation</td>
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<td>1.03 (0.83–1.29)</td>
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<td>0.63 (0.51–0.78)</td>
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<td>Hysterectomy</td>
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<td>0.94 (0.70–1.26)</td>
<td>0.29</td>
<td>0.79 (0.62–1.00)</td>
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<td>Parity</td>
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<tr>
<td>First birth §</td>
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<td>0.75 (0.57–0.99)</td>
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<td>0.78 (0.62–0.99)</td>
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<tr>
<td>Subsequent births §</td>
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<td>0.01</td>
<td>0.84 ‡</td>
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<tr>
<td>Breastfeeding (per year) §</td>
<td>0.79 (0.72–0.88)</td>
<td>0.87 (0.72–1.05)</td>
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<td>0.80 (0.72–0.88)</td>
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<tr>
<td>Infertility (female only) §</td>
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<td>1.15 ‡</td>
<td>0.22</td>
<td>1.23 ‡</td>
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<td>1.00 (ref.)</td>
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<td>1.73 (0.43–1.50)</td>
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<td>1.02 (0.72–1.43)</td>
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<td>1.73 (0.36–1.33)</td>
<td>0.58</td>
<td>0.93 (0.67–1.30)</td>
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<tr>
<td>Exposure</td>
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<td></td>
<td></td>
<td>Multivariate and histology adjusted†</td>
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<td>--------------------------------</td>
<td>------------------------</td>
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<td>--------------------------------------</td>
</tr>
<tr>
<td></td>
<td>RR  95% CI</td>
<td>RR  95% CI</td>
<td>p-diff</td>
<td>RR  95% CI</td>
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<tr>
<td>&gt;53</td>
<td>1.16 (0.72–1.89)</td>
<td>1.40 (0.91–2.16)</td>
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<td>1.13 (0.67–1.92)</td>
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<tr>
<td>continuous</td>
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<td>1.02 (0.99–1.04)</td>
<td>0.25</td>
<td>1.01 (0.96–1.07)</td>
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<tr>
<td>Post-menopausal hormone use‡</td>
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<tr>
<td>Ever estrogen only</td>
<td>1.76 (1.29–2.41)</td>
<td>1.50 (0.97–2.30)</td>
<td>0.54</td>
<td>1.83 (1.33–2.51)</td>
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<tr>
<td>Ever estrogen + progesterone</td>
<td>1.52 (1.07–2.16)</td>
<td>2.27 (1.47–3.52)</td>
<td>0.15</td>
<td>1.54 (1.08–2.19)</td>
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<tr>
<td>Years of estrogen use</td>
<td>1.06 (1.03–1.11)</td>
<td>1.04 (0.99–1.10)</td>
<td>0.52</td>
<td>1.07 (1.03–1.11)</td>
</tr>
<tr>
<td>Years of estrogen + progesterone use</td>
<td>1.02 (0.97–1.08)</td>
<td>1.07 (1.01–1.13)</td>
<td>0.26</td>
<td>1.02 (0.97–1.08)</td>
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<td>Ovulatory cycles</td>
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<tr>
<td>quartile 1</td>
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<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
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<td>quartile 2</td>
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<td>1.96 (1.41–2.73)</td>
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<td>1.79 (1.16–2.78)</td>
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<td>quartile 3</td>
<td>2.62 (1.96–3.50)</td>
<td>2.98 (2.16–4.11)</td>
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<td>2.61 (1.48–4.58)</td>
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<td>quartile 4</td>
<td>3.39 (2.60–4.43)</td>
<td>3.54 (2.56–4.89)</td>
<td>0.70</td>
<td>3.25 (2.12–5.00)</td>
</tr>
</tbody>
</table>

*Analyses adjusted for age (years), OC use (never, <5 years, 5+ years), parity (0, 1, 2, 3, 4+ births), tubal ligation (yes, no), family history of breast or ovarian cancer (yes, no), study phase (1992–1997, 1998–2002, 2003–2008) and center (MA, NH) for NECC; NHS/NHSII analyses were stratified by time period and cohort

‡Adjusted for all the covariates indicated above as well as histology (serous, non-serous)

†p-het between studies <0.05

§The risk associated with birth of the first child is modeled as parous (ever/never) adjusted for number of children while the risk associated with subsequent births is modeled as continuous parity adjusted for ever being parous. The association between breastfeeding and risk was restricted to parous women.

¶Among NHS post-menopausal participants.
### Table 3


<table>
<thead>
<tr>
<th>Exposure</th>
<th>Multivariate adjusted</th>
<th>Multivariate and histology adjusted</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Dominant RR 95% CI</td>
<td>Non-dominant RR 95% CI</td>
</tr>
<tr>
<td>Age, per 5 years</td>
<td>1.37 (1.25–1.50)</td>
<td>1.14 (1.01–1.28)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td></td>
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</tr>
<tr>
<td>&lt;23 kg/m²‡</td>
<td>1.00 (ref.)</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>23–24</td>
<td>1.04 (0.85–1.26)</td>
<td>1.06 (0.60–1.90)</td>
</tr>
<tr>
<td>25–29</td>
<td>0.99 (0.83–1.18)</td>
<td>0.84 (0.54–1.31)</td>
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<tr>
<td>&gt;30</td>
<td>1.21 (1.00–1.46)</td>
<td>1.08 (0.71–1.64)</td>
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<tr>
<td>Height, inches</td>
<td>1.03 (0.96–1.11)</td>
<td>1.01 (0.98–1.05)</td>
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<td>Smoking</td>
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<td>Never</td>
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<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Past smoker</td>
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<td>1.23 (1.03–1.48)</td>
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<td>Current smoker</td>
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<td>1.24 (0.81–1.90)</td>
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<td>Aspirin use §</td>
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<td>1.17 (0.96–1.42)</td>
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<td>Other NSAID use §</td>
<td>0.90 (0.76–1.06)</td>
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<td>Genital powder use **</td>
<td>1.16‡ (0.75–1.80)</td>
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<tr>
<td>Family history of breast cancer</td>
<td>1.28 (1.06–1.54)</td>
<td>1.06 (0.76–1.49)</td>
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<tr>
<td>Family history of ovarian cancer</td>
<td>1.26 (0.71–2.24)</td>
<td>2.12 (1.41–3.20)</td>
</tr>
</tbody>
</table>

*Analyses adjusted for age (years), OC use (never, <5 years, 5+ years), parity (0, 1, 2, 3, 4+ births), tubal ligation (yes, no), family history of breast or ovarian cancer (yes, no), study phase (1992–1997, 1998–2002, 2003–2008) and center (MA, NH) for NECC; NHS/NHSII analyses were stratified by time period and cohort

†Adjusted for all the covariates indicated above as well as histology (serous, non-serous)

‡p-het between studies <0.05

§In the NHS, aspirin use was not queried until 1980; acetaminophen and other NSAIDs were not queried until 1990.

**Powder use on genital area at least once per week. Does not include NHSII participants.