Ovarian cancer risk factors by histologic subtype: An analysis from the Ovarian Cancer Cohort Consortium

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Abstract

Purpose: Understanding etiologic heterogeneity of ovarian cancer is important for improving prevention, early detection and therapeutic approaches. We evaluated 14 hormonal, reproductive, and lifestyle factors by histologic subtype in the Ovarian Cancer Cohort Consortium (OC3).

Patients and Methods: Among 1.3 million women from 21 studies, 5,584 invasive epithelial ovarian cancers were identified (3,378 serous, 606 endometrioid, 331 mucinous, 269 clear cell, 1,000 other). Using competing risks Cox proportional hazards regression stratified on study and birth year and adjusted for age, parity, and oral contraceptive use, we assessed associations for all invasive cancers and by histology. Heterogeneity was evaluated by likelihood ratio test.

Results: Most risk factors exhibited significant heterogeneity by histology. Higher parity was most strongly associated with endometrioid (RR, per birth=0.78; 95% CI=0.74-0.83) and clear cell (RR=0.68; 95%CI=0.61-0.76) carcinomas (p-het<0.0001). Similarly, age at menopause, endometriosis, and tubal ligation were only associated with endometrioid and clear cell tumors (p-het=0.009). Family history of breast cancer (p-het=0.008) had modest heterogeneity. Smoking was associated with increased risk of mucinous (RR, per 20 pack-years=1.26; 95% CI=1.08-1.46), but a decreased risk of clear cell tumors (RR=0.72; 95% CI=0.55-0.94) (p-het=0.004). Unsupervised clustering by risk factors separated endometrioid, clear cell, and low grade serous carcinomas from high grade serous and mucinous carcinomas.

Conclusion: The heterogeneous associations of risk factors with ovarian cancer subtypes emphasize the importance of conducting etiologic studies by ovarian cancer subtypes. Most established risk factors were more strongly associated with non-serous carcinomas, demonstrating challenges for risk prediction of serous cancers, the most fatal subtype.

Introduction

Ovarian cancer is the most lethal gynecologic cancer, with over 152,000 deaths world-wide each year (1). Most ovarian cancers are detected at late stage and have a poor prognosis. Screening for ovarian cancer did not reduce mortality in two large screening trials (2, 3). Understanding the etiologic heterogeneity of ovarian cancer is critical for development of new prevention strategies.

Although multiple carcinogenic mechanisms for ovarian tumorigenesis have been hypothesized, including incessant ovulation, hormonal stimulation, and chronic inflammation (4-7), the etiology of ovarian cancer is not well understood in part due to its heterogeneous nature. Disease subtypes have been categorized by putative precursor lesions, mutations, and histology (8, 9). Low-grade serous, mucinous, clear cell, and endometrioid tumors are thought to arise from inclusion cysts or implants in the ovarian surface epithelium and have *K-RAS*, *B-RAF*, or *P-TEN* mutations. High-grade serous tumors, characterized by *TP53* mutations, are thought to arise in the fallopian tube or ovarian epithelium, are more aggressive and have poorer outcomes than other types (8-10). Due to limited power, individual epidemiologic and biomarker studies usually have considered risk factor associations for all ovarian tumors together. Recently, individual cohorts and individual-level meta-analyses of primarily case-control studies have reported differential associations by subtype for menopausal hormone therapy (HT) use, oral contraceptive (OC) use, parity, smoking and body mass index (BMI) (11-17). To establish etiologic models accounting for ovarian cancer heterogeneity, there is a need for a unified prospective evaluation of multiple ovarian cancer risk factors accounting for heterogeneity. In the Ovarian Cancer Cohort Consortium (OC3) we evaluated associations of 14 key risk factors with invasive epithelial ovarian cancer risk overall and by histologic subtype based on pooled

individual-level data from 5,584 invasive ovarian cancer cases from a combined cohort of over 1.3 million women enrolled in 21 studies.

Methods

Study population

The analysis included women participating in 21 prospective cohort studies from North America, Asia, and Europe (Table 1). Prospective follow-up of ovarian cancer endpoints through questionnaires, medical records or cancer registries, as well as follow-up for death were required for participation. Minimal required information included age at study entry, OC use, and parity. All studies obtained institutional approval for cohort maintenance and 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 definitions

Full baseline cohort data (19 studies) or case-cohort datasets with weights for subcohort members (2 studies) were harmonized centrally. Exposures included: parity (ever vs. never, number of births: per 1 birth; 1, 2, 3, 4+ births), OC use (ever vs. never, duration of use: per 5 years of use; never, ≤1, >1-≤5, >5-≤10, >10 years), duration of breastfeeding (per 1 year 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), menopausal HT use (ever vs. never, duration of use: per 1 year; never, ≤5, >5 years), tubal ligation (ever vs. never), hysterectomy (ever vs. never), endometriosis (ever vs. never), first degree family history of breast cancer (ever vs. never), first degree family history of ovarian cancer (ever vs. never), BMI (per 5 kg/m^2; <20, 20-<25, 25-<30, 30-<35, ≥35 kg/m^2), height (per 0.05; <1.60, 1.60-<1.65, 1.65-1.70, ≥1.70 m), and smoking (ever vs. never, pack-years: per 20 pack-years; ≤10, >10-20, >20-35, >35 pack-years). Studies that did not collect information on a

specific risk factor were excluded from the analysis of that factor (Supplemental Table 1), leading to different samples sizes for each variable (Supplemental Table 2).

Outcome definitions

Epithelial ovarian or peritoneal cancer cases were confirmed through cancer registries or medical record review (ICD9: 183, 158; ICD10: C56). We evaluated associations of risk factors with all invasive epithelial cancers combined (n=5,584). Next, we evaluated associations with the four most common histologic types of invasive epithelial ovarian cancers (n=4,584): serous/poorly differentiated, endometrioid, mucinous, and clear cell. 1,000 cases had another histology or were missing histology information. Serous tumors were further subdivided by grade (well-, moderately-, poorly-differentiated, unknown).

Statistical methods

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. 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 endpoints (18). Follow-up time was time between study entry and date of 1) ovarian cancer diagnosis, 2) death, or 3) end of follow-up, whichever occurred first. In primary analyses, we pooled data from all cohorts, and stratified on year of birth and cohort to account for potential differences in baseline hazards by these factors. Statistical heterogeneity of associations across subtypes was assessed via a likelihood ratio test comparing a model allowing the association for the risk factor of interest to vary by histology versus one not allowing the association to vary (16). We also used random effects meta-analysis to combine cohort-specific estimates and assess

between-study heterogeneity. All models were adjusted for age at entry, number of children, and duration of OC use, unless the exposure of interest was collinear with these factors. Hysterectomy analyses were additionally adjusted for HT use. For missing data in covariates, we included a missing indicator in the model. The Sister Study was excluded from analyses of family history as all participants had a family history of breast or ovarian cancer. To evaluate our primary models sufficiently accounted for confounding, we performed a model adjusting for all exposures together (using missing indicators when needed). In 17 studies, grade was available for at least some serous cases. We conducted similar analyses among serous tumors comparing risk factors for well-, moderately-, and poorly-differentiated tumors, and unknown grade. We performed unsupervised hierarchical clustering of the four subtypes (with and without separating serous tumors by grade) using beta estimates for all exposures except for duration of breastfeeding (not significantly associated with any of the 4 subtypes) using complete linkage and uncentered correlation (Pearson's coefficient). SAS 9.1 was used to conduct the analyses and a p-value of <0.05 was considered statistically significant.

Results

Study population

Among 1,284,586 participants (1,381,275 including full cohort size for case-cohort studies), 5,584 invasive epithelial ovarian cancers were identified during follow-up. Case numbers ranged from 1,281 for breastfeeding to 5,523 for OC use (Supplemental Table 2). There were 3,378 (73.7% of cases with known histology) serous, 606 (13.2%) endometrioid, 331 (7.2%) mucinous, and 269 (5.9%) clear cell carcinomas. Fifteen of 21 cohorts were based in North America, five in Europe, and one in Asia (Table 1); about half of the cohorts started enrollment in the 1990s. The median age at diagnosis was 67.0 years for serous, 63.0 years for endometrioid, 64.0 years for mucinous, 61.3 years for clear cell carcinomas, and 68.9 years for cases with unknown histology.

Associations of hormonal and reproductive factors

Most reproductive and hormonal risk factors, except for breastfeeding, were associated with ovarian cancer risk overall (Table 2). Parous versus nulliparous women had a reduced risk of all ovarian cancer subtypes, with significant heterogeneity by subtype (p-het=8.47×10^{-10}). The strongest risk reduction was observed for clear cell (RR: 0.35; 95% CI: 0.27-0.47) carcinomas, while serous cancers had the least risk reduction (RR: 0.81; 95% CI: 0.73-0.90). Similar patterns were observed for number of children (p-het=4.71×10^{-13}). In subtype-specific analyses, a five year increase in duration of OC use was associated with significant 14-15% lower risk of serous, endometrioid, and clear cell carcinomas, but not with mucinous tumors (p-het=0.04). Similarly, OC use >10 years was associated with a 36-49% reduction in risk for serous, endometrioid, and clear cell tumors.

A 5-year later menopause was associated with endometrioid and clear cell carcinomas (RR: 1.19; 95% CI: 1.05-1.34 and 1.37; 95% CI: 1.15-1.64, respectively), with no association for serous and mucinous carcinomas (p-het=0.009). A five-year increase in menopausal HT use was associated with an increased risk of serous (RR: 1.21; 95% CI: 1.17-1.25) and endometrioid (RR: 1.25; 95% CI: 1.15-1.36), but a reduced risk of clear cell (RR: 0.69; 95% CI: 0.52-0.92; p-het=0.00006) carcinomas. Tubal ligation was only associated with reduced risk of endometrioid (RR: 0.60; 95% CI: 0.41-0.88) and clear cell (RR: 0.35; 95% CI: 0.18-0.69; p-het=0.0005) carcinomas, while hysterectomy was associated with increased risk of serous (RR: 1.18; 95% CI: 1.07-1.29) and decreased risk of clear cell carcinomas (RR: 0.62; 95% CI: 0.41-0.96; p-het=0.005). Self-reported endometriosis was significantly associated only with endometrioid (RR: 2.32; 95% CI: 1.36-3.95) and clear cell carcinomas (RR: 2.87; 95% CI: 1.53-5.39; p-het=0.01). There was no significant heterogeneity in associations by histology for breastfeeding or age at menarche, although the latter was significantly inversely associated with clear cell carcinomas.

Associations of other risk factors

Family history of both breast and ovarian cancer and height, but not smoking or BMI were significantly associated with ovarian cancer risk overall (Table 3). A first degree family history of breast or ovarian cancer was associated with an increased risk of serous tumors (RR: 1.13; 95% CI: 1.02-1.26; p-het=0.31; RR: 1.61; 95% CI: 1.32-1.97; p-het=0.008, respectively). Family history of breast cancer was also associated with endometrioid carcinomas (RR: 1.47; 95% CI: 1.15-1.87). BMI was not significantly associated with ovarian carcinomas overall or with any subtype, although there was a borderline association with endometrioid carcinomas (RR per 5 kg/m^2: 1.07; 95% CI: 0.99-1.16). Ever smoking was associated with mucinous carcinomas only

(RR: 1.27; 95% CI: 1.01-1.59); each 20 pack-years of smoking was associated with an increased risk of mucinous and a decreased risk of clear cell carcinomas (p-het=0.002).

Associations by subtypes of serous carcinomas

Among serous tumors, moderately- and poorly differentiated carcinomas had similar associations, while associations for well-differentiated carcinomas were qualitatively different. However, the heterogeneity was not significant for most individual factors (Table 4). For example, endometriosis was significantly associated with well-differentiated carcinomas (RR: 3.77; 95% CI: 1.24-11.48), but not poorly-differentiated carcinomas (RR: 1.11; 95% CI: 0.70-1.74; p-het=0.12). Similarly, >5 years of HT use versus never was associated with a 2.9-fold higher risk of well-differentiated carcinomas, but only a 80% higher risk of poorly-differentiated carcinomas (p-het.=0.45).

Meta-analysis and heterogeneity across studies

Results for meta-analyses were similar to the pooled analyses (Supplemental Table 3). We observed little heterogeneity in associations across studies ($p<0.01$ for only 20 of 188 comparisons). Sixteen of these were for continuous variables, but the categorical associations did not show heterogeneity. Family history of ovarian cancer showed heterogeneity for all 4 subtypes across studies, likely due to the small number of exposed cases in many studies. Results were similar when including women with a history of cancer at baseline or when all exposures were included in the model (data not shown).

Integrated analysis of risk factors in ovarian cancer subtypes

Each subtype had unique patterns of risk factor associations (Figure 1). The strongest associations for most factors were observed for endometrioid and clear cell tumors. Unsupervised clustering divided the four histologic subtypes into two major groups (Figure 1A). Serous carcinomas were separate from the other three subtypes (Pearson correlation 0.18). Endometrioid and clear cell carcinomas had the most similar risk factor associations (Pearson correlation 0.70). When serous cancers were subdivided by grade (Figure 1B), they were split into two distinct groups: Well differentiated serous carcinomas clustered with endometrioid carcinomas (Pearson correlation 0.76), while moderately and poorly differentiated serous carcinomas clustered together (Pearson correlation 0.90).

Discussion

In a large pooled analysis of over 1.3 million women, we investigated 14 established or putative risk factors in ovarian cancer subtypes. Nine risk factors had significant heterogeneity across subtypes. Most reproductive and hormonal risk factors had stronger associations with endometrioid and clear cell carcinomas compared to the other types. Serous and poorly differentiated carcinomas, the most common and aggressive subtype, had modest associations only with parity, OC use, menopausal HT use, and family history of breast cancer, and stronger associations with family history of ovarian cancer.

Our analysis represents the largest comprehensive and prospective evaluation of ovarian cancer risk factors by histologic subtypes. Our results are consistent with previous reports from individual prospective studies within the OC3 (i.e., NHS/NHSII, AARP, EPIC) (15-17). However, individually these studies were underpowered to assess subtype-specific associations, particularly for rare types. Previously, other consortia, largely based on case-control studies, reported subtype-specific associations for individual risk factors (12-14, 19-21) similar to what we observed.

Models of ovarian carcinogenesis have separated epithelial tumors into major pathways with distinct cells of origin, carcinogenic pathways and histology with different clinical behavior (8, 10). An integrated evaluation of ovarian cancer risk factors by subtypes is important to understand factors that drive these etiologic pathways on the population level. Each subtype had a qualitatively unique pattern of associations, and serous carcinomas were clearly separated from endometrioid, clear cell, and mucinous carcinomas. While endometrioid and clear cell carcinomas had qualitatively similar associations for 9 risk factors, they differed in associations

related to HT use (which went in opposite directions), family history of breast cancer (associated with endometrioid only), as well as age at menarche, hysterectomy, and smoking (associated with clear cell only). Every reproductive/hormonal factor was significantly associated with clear cell tumors, except breastfeeding.

Our results suggest that currently hypothesized, unifying mechanisms, such as incessant ovulation (4), do not apply equally to ovarian cancers. Several variables that determine a woman's lifetime number of ovulations had significant heterogeneity across subtypes. Only parity and height were associated with all subtypes, suggesting a common biologic effect (22). Notably, mucinous tumors were not associated with any ovulation-related factors except parity, suggesting a more distinct etiology.

Ovarian cancer subtypes share some risk factors with other cancer sites. The inverse association between smoking and clear cell ovarian carcinomas is similar to that for endometrial cancer (23). Mucinous ovarian cancers share histologic appearance and an association with smoking with colorectal cancers (24). Serous ovarian cancers had weaker associations with most hormonal and reproductive factors compared to non-serous cancers (with the exception of OC use), similar to associations for hormone receptor negative breast cancers (25). These similarities of risk factor associations across cancers mirror molecular data showing that tumor subtypes from different organs may be more similar to each other on the molecular level compared to other subtypes at the same site (e.g., high-grade serous ovarian cancer and basal-like breast cancer) (26).

While the subtype-specific associations observed in our study strongly corroborate the etiologic heterogeneity of ovarian cancers, a purely histology-based classification of endpoints may have limitations (27). Histologic evaluation is subjective and pathology practice changes over time,

which could affect subtype distributions by location and year of diagnosis. We observed the most heterogeneity between studies for mucinous tumors, possibly related to temporal and geographic differences in defining mucinous tumors. However, overall, we did not observe significant differences in subtype proportions across studies or over time (data not shown). Unsupervised clustering demonstrated that well-differentiated serous carcinomas are distinct from higher grade serous carcinomas, and group with endometrioid carcinomas. This is important etiologically and further supports differentiating these two groups of serous carcinomas, as proposed in models based on somatic mutations (REF). However, in population-based studies, grade reported on pathology reports may not be reliable and low-grade serous carcinomas account for only about 5% of all serous cancers (28), limiting potential misclassification when considering associations for all serous carcinomas together (29). Analyses by tumor aggressiveness and tumor dominance have also shown differences in risk factor associations, indicating that there may be important biological heterogeneity beyond histological subtypes (30, 31). Further, additional molecular subgroups have been described within high-grade serous ovarian cancers (32, 33), but thus far, based on small studies, these subtypes have shown only limited heterogeneity in risk factor associations (34).

In summary, we conducted the largest integrated prospective analysis of ovarian cancer risk factors to date. Most factors showed heterogeneity across histologic subtypes and each subtype had unique patterns of risk factor associations. Our results have important implications with respect to etiology and prevention of ovarian cancers. Oral contraceptives continue to be an important preventive factor for most types of ovarian cancer. Few other risk factors for ovarian cancer are modifiable and those that are, like smoking and obesity, did not show clear associations with serous carcinomas, the most common and fatal subtype. The substantial

heterogeneity of individual risk factor associations across ovarian cancer subtypes supports that subtypes are indeed different diseases and underscores the importance of evaluating risk factors and biomarkers by ovarian cancer subtypes. Our work has implications for the development of risk prediction models, which generally consider ovarian cancer as a whole (35): due to weaker associations observed for high grade serous carcinomas, prediction of the clinically most important subtype may perform worse than for other types, underscoring the importance of finding better risk markers for serous carcinomas. Evaluation of subtype-specific risk factor associations is important for better understanding of ovarian cancer etiology and for targeted development of novel prevention approaches; these analyses require pooling of data across many studies in consortia.

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Figure legend:

Figure 1: Unsupervised hierarchical clustering of ovarian cancer histologic subtypes by their associations with risk factors

Unsupervised hierarchical clustering of the (A) four subtypes and (B) including the serous subtype subdivided into well- moderately- and poorly differentiated carcinomas using the beta estimates, complete linkage, and an uncentered correlation similarity metric. The categories used in the cluster analysis were ever vs. never parous, ever vs. never OC use, ever vs. never tubal ligation, ever vs. never endometriosis, age at menarche >15 years vs. <=11 years, age at menopause <40 years vs. 50-55 years, ever vs. never menopausal HT use, ever vs. never hysterectomy, family history of breast cancer (yes vs. no), family history of ovarian cancer (yes vs. no), BMI >35 vs. 20-25, height (per 5cm increase) and ever vs. never smoking. The color scale shows the range of beta values for each exposure.

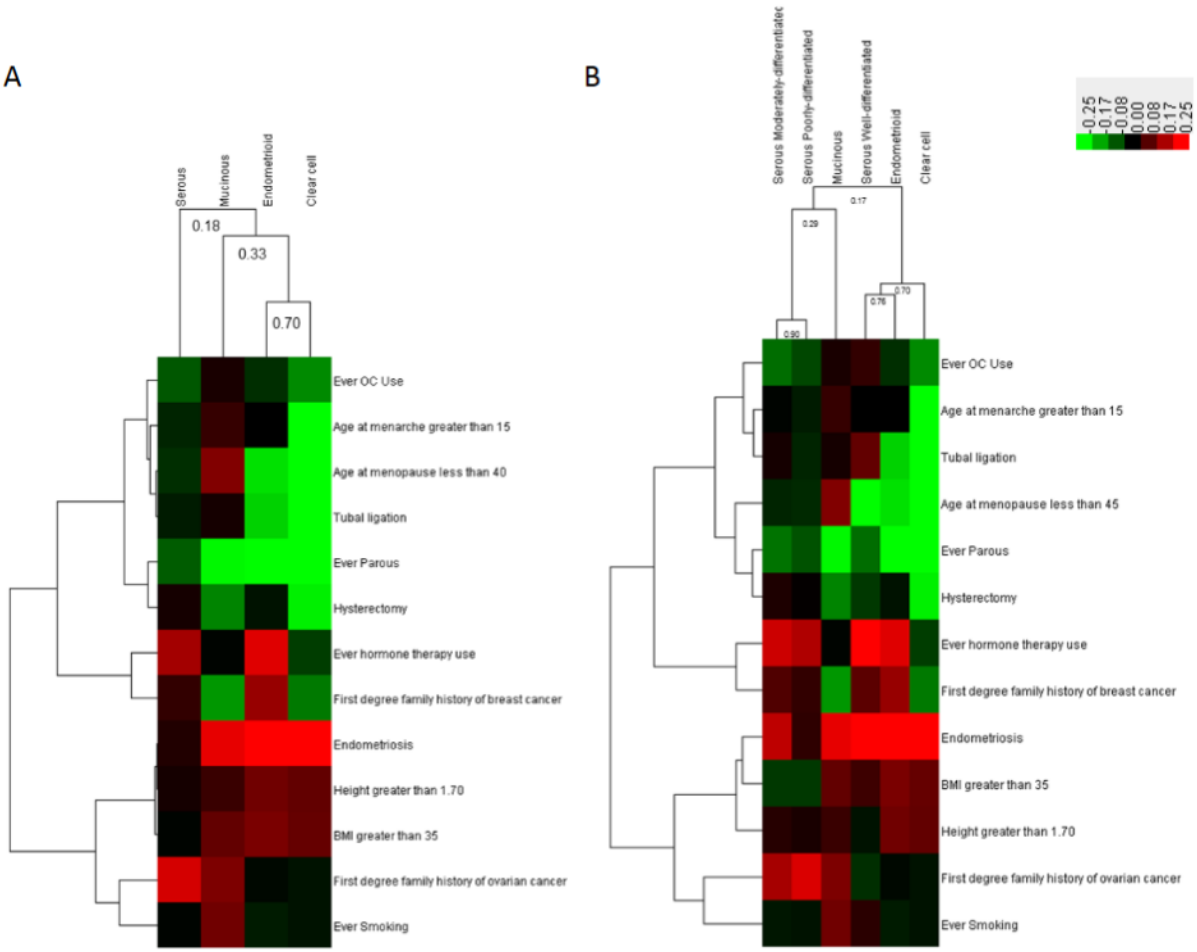

Table 1: Characteristics of cohorts participating in the Ovarian Cancer Cohort Consortium

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
NIH-AARP Diet and Health Study	AARP	U.S.	1995-1997	153,069	62	11	2006	703
Breast Cancer Detection Demonstration Project Follow-up Study	BCDDP	U.S.	1987-1989	36,212	61	9	1999	159
Breakthrough Generations Study	BGS	UK	2001-2014	101,869	48	6	2014	75
Canadian Study of Diet, Lifestyle, and Health	CSDLH	Canada	1991-1999	2,745[b]	58	16	2010	90
Campaign against Cancer and Stroke	CLUEII	U.S.	1989	12,382	46	22	2012	82
Cancer Prevention Study II Nutrition Cohort	CPSII-NC	U.S.	1992-1993	65,884	62	15	2009	533
California Teachers Study	CTS	U.S.	1995-1999	43,778	50	15	2010	185
European Prospective Investigation into Cancer and Nutrition Study	EPIC	Europe	1992-2000	263,796	51	13	2010	671
Iowa Women's Health Study	IWHS	U.S.	1986	30,537	61	23	2010	263
Multiethnic/Minority Cohort Study[c]	MEC	U.S.	1993-1998	16,474	57	11	2011	75
Nurses' Health Study 1980[d]	NHS80	U.S.	1980-1982	86,608	46	16	1998	351
Nurses' Health Study 1996[d]	NHS96	U.S.	1996-1998	67,530	62	14	2010	417
Nurses' Health Study II	NHSII	U.S.	1989-1990	111,800	35	20	2011	215
New York University Women's Health Study	NYU	U.S.	1984-1991	12,427	49	24	2012	129
Netherlands Cohort Study on diet and cancer	NLCS	Netherlands	1986	2,757[b]	62	17	2003	448
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	PLCO	U.S.	1993-2002	60,191	62	12	2009	358
Singapore Chinese Health Study	SCHS	Singapore	1993-1999	31,939	56	14	2011	95
Sister Study	SS	U.S.	2003-2009	39,195	55	5	2012	39
Swedish Mammography Cohort Study	SMC	Sweden	1997	34,427	60	14	2011	161
VITamins And Lifestyle Cohort	VITAL	U.S.	2000-2002	28,331	60	10	2011	130
Women's Lifestyle and Health	WLHS	Sweden	1991-1992	49,087	40	21	2012	201
Women's Health Study	WHS	U.S.	1993-1996	33,548	53	18	2012	204

[a]After exclusions for baseline cancers and women with bilateral oophorectomy

[b]These cohorts were included as a case-cohort design, reflecting a total cohort population of 39,618 women for the CSDLH and 62,573 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 hormonal and reproductive factors with invasive epithelial ovarian cancer overall and by subtypes in the Ovarian Cancer Cohort Consortium

Exposure	All invasive N=5584 RR (95% CI)	Serous N=3378 RR (95% CI)	Endometrioid N=606 RR (95% CI)	Mucinous N=331 RR (95% CI)	Clear cell N=269 RR (95% CI)	p-heterogeneity (between histologic types)[b]
Parity						
Ever/never	0.69 (0.64-0.74)	0.81 (0.73-0.90)	0.48 (0.39-0.58)	0.56 (0.42-0.74)	0.35 (0.27-0.47)	**8.47E-10**
Number of children, per 1 child	0.90 (0.89-0.92)	0.93 (0.92-0.95)	0.78 (0.74-0.83)	0.91 (0.84-0.99)	0.68 (0.61-0.76)	**1.09E-14**
Number of children						
0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
1	0.82 (0.43-0.91)	0.86 (0.75-1.00)	0.78 (0.60-1.03)	0.59 (0.38-0.92)	0.67 (0.46-0.98)	
2	0.74 (0.68-0.81)	0.87 (0.78-0.97)	0.49 (0.39-0.62)	0.61 (0.44-0.86)	0.38 (0.27-0.53)	**4.71E-13**
3	0.67 (0.62-0.74)	0.82 (0.73-0.92)	0.41 (0.32-0.54)	0.52 (0.36-0.74)	0.29 (0.19-0.43)	
4+	0.58 (0.53-0.64)	0.72 (0.63-0.81)	0.34 (0.25-0.45)	0.55 (0.38-0.80)	0.14 (0.08-0.25)	
Oral contraceptive use						
Ever/never	0.84 (0.79-0.89)	0.82 (0.76-0.89)	0.89 (0.73-1.07)	1.02 (0.80-1.31)	0.72 (0.55-0.94)	0.25
Duration of use, per 5 year increase	0.87 (0.84-0.90)	0.85 (0.81-0.89)	0.86 (0.77-0.95)	1.54 (0.93-1.19)	0.86 (0.74-1.00)	**0.04**
Duration of use, years						
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
≤1	0.98 (0.87-1.05)	0.99 (0.88-1.12)	1.01 (0.76-1.35)	0.98 (0.66-1.45)	0.68 (0.42-1.09)	
>1-≤5	0.86 (0.78-0.92)	0.85 (0.77-0.95)	0.82 (0.64-1.05)	0.84 (0.58-1.21)	0.88 (0.62-1.24)	0.35
>5-≤10	0.77 (0.67-0.84)	0.72 (0.64-0.83)	0.85 (0.64-1.13)	0.91 (0.61-1.37)	0.80 (0.54-1.20)	
>10	0.67 (0.58-0.75)	0.64 (0.54-0.74)	0.64 (0.44-0.93)	1.18 (0.77-1.81)	0.51 (0.29-0.87)	
Duration of breastfeeding, per 1 year[c]	0.96 (0.89-1.03)	0.94 (0.86-1.03)	0.85 (0.69-1.05)	0.88 (0.63-1.23)	1.03 (0.81-1.33)	0.64
Age at menarche						
Per 1 year increase	0.99 (0.97-1.00)	0.99 (0.97-1.02)	1.00 (0.94-1.05)	1.00 (0.93-1.07)	0.92 (0.85-0.99)	0.31
Age in years						
≤11	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
12	0.92 (0.84-1.00)	0.95 (0.85-1.05)	1.02 (0.80-1.31)	1.15 (0.81-1.65)	0.78 (0.54-1.12)	
13	0.94 (0.87-1.02)	0.99 (0.90-1.09)	0.97 (0.79-1.22)	1.06 (0.76-1.48)	0.79 (0.56-1.11)	0.66
14	0.93 (0.85-1.03)	0.99 (0.88-1.12)	0.84 (0.62-1.13)	0.97 (0.64-1.47)	0.80 (0.52-1.23)	
≥15	0.88 (0.80-0.97)	0.92 (0.81-1.05)	0.98 (0.73-1.31)	1.13 (0.76-1.66)	0.55 (0.34-0.90)	
Age at menopause[d]						
Per 5 year increase	1.06 (1.02-1.10)	1.05 (1.01-1.10)	1.19 (1.05-1.34)	0.95 (0.81-1.11)	1.37 (1.15-1.64)	**0.009**
Age in years						
≤40	0.89 (0.77-1.03)	0.87 (0.73-1.04)	0.59 (0.34-1.00)	1.31 (0.78-2.20)	0.15 (0.03-0.71)	
>40-≤45	0.80 (0.70-0.91)	0.85 (0.73-1.00)	0.76 (0.51-1.14)	0.77 (0.44-1.33)	0.43 (0.20-0.94)	
>45-≤50	0.93 (0.86-1.00)	0.96 (0.87-1.06)	0.86 (0.67-1.09)	0.95 (0.68-1.31)	0.95 (0.64-1.39)	0.11
>50-≤55	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
>55	1.02 (0.89-1.17)	1.01 (0.85-1.21)	1.19 (0.78-1.80)	0.91 (0.49-1.68)	1.03 (0.50-2.09)	

Hormone therapy use[d]						
Ever/never	1.36 (1.28-1.46)	1.41 (1.30-1.53)	1.67 (1.36-2.05)	1.00 (0.75-1.34)	0.90 (0.64-1.28)	**0.004**
Duration of use, per 5 year increase	1.20 (1.16-1.23)	1.21 (1.17-1.25)	1.25 (1.15-1.36)	1.09 (0.94-1.26)	0.69 (0.52-0.92)	**0.00006**
Duration of use, years						
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
≤5 years	1.17 (1.07-1.27)	1.22 (1.09-1.36)	1.46 (1.11-1.91)	1.13 (0.78-1.63)	0.94 (0.61-1.44)	**0.0005**
>5 years	1.60 (1.47-1.74)	1.75 (1.58-1.94)	1.90 (1.44-2.51)	1.06 (0.69-1.65)	0.51 (0.27-0.96)	
Tubal ligation, ever/never	0.82 (0.73-0.93)	0.91 (0.79-1.06)	0.60 (0.41-0.88)	1.01 (0.60-1.71)	0.35 (0.18-0.69)	**0.005**
Hysterectomy[e]**,** ever/never	1.11 (1.03-1.19)	1.18 (1.07-1.29)	1.14 (0.91-1.43)	0.83 (0.59-1.15)	0.62 (0.41-0.96)	**0.005**
Endometriosis, ever/never	1.35 (1.07-1.71)	1.03 (0.74-1.46)	2.32 (1.36-3.95)	1.62 (0.58-4.51)	2.87 (1.53-5.39)	**0.01**

[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 histologic subtype to a model forcing the association to be the same across subtypes.

[c]Parous women only.

[d]Postmenopausal women only.

[e]Additionally adjusted for duration of hormone therapy use.

Table 3: Associations[a] of family history, demographic and lifestyle factors with invasive epithelial ovarian cancer overall and by subtypes in the Ovarian Cancer Cohort Consortium

Exposure	All invasive N=5584 RR (95% CI)	Serous N=3378 RR (95% CI)	Endometrioid N=606 RR (95% CI)	Mucinous N=331 RR (95% CI)	Clear cell N=269 RR (95% CI)	p-diff (between histologic types)[b]
First degree family history of breast cancer, ever/never	1.09 (1.00-1.19)	1.13 (1.02-1.26)	1.47 (1.15-1.87)	0.73 (0.47-1.13)	0.75 (0.46-1.22)	**0.008**
First degree family history of ovarian cancer, ever/never	1.48 (1.26-1.75)	1.61 (1.32-1.97)	0.97 (0.52-1.82)	1.33 (0.59-3.00)	0.96 (0.36-2.57)	0.31
Body mass index						
Per 5 kg/m^2	1.01 (0.98-1.04)	0.97 (0.93-1.01)	1.07 (0.99-1.16)	1.08 (0.96-1.20)	1.04 (0.92-1.17)	0.06
In kg/m^2						
<20	1.02 (0.91-1.13)	1.06 (0.92-1.21)	0.85 (0.60-1.19)	1.36 (0.90-2.04)	0.96 (0.60-1.53)	
20-<25	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
25-<30	0.97 (0.91-1.03)	0.91 (0.84-0.99)	0.97 (0.80-1.18)	1.42 (1.10-1.83)	1.21 (0.91-1.61)	0.10
30-<35	0.99 (0.90-1.08)	0.92 (0.82-1.04)	1.09 (0.83-1.43)	1.23 (0.83-1.82)	0.97 (0.62-1.51)	
≥35	1.09 (0.97-1.24)	0.97 (0.83-1.14)	1.26 (0.88-1.80)	1.24 (0.69-2.21)	1.23 (0.70-2.15)	
Height						
Per 0.5m	1.06 (1.04-1.08)	1.06 (1.03-1.09)	1.06 (1.00-1.13)	1.04 (0.95-1.13)	1.08 (0.98-1.19)	0.94
In meters						
<1.60	0.89 (0.83-0.96)	0.86 (0.78-0.95)	1.03 (0.82-1.29)	0.87 (0.64-1.18)	0.92 (0.65-1.30)	
1.60-<1.65	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
1.65-<1.70	1.02 (0.95-1.10)	1.04 (0.95-1.14)	0.93 (0.74-1.17)	0.83 (0.61-1.13)	0.97 (0.70-1.36)	0.27
≥1.70	1.12 (1.03-1.21)	1.06 (0.96-1.17)	1.27 (1.01-1.60)	1.12 (0.82-1.52)	1.24 (0.88-1.73)	
Smoking						
Ever/never	0.99 (0.94-1.05)	0.99 (0.92-1.06)	0.93 (0.79-1.09)	1.27 (1.01-1.59)	0.95 (0.74-1.21)	0.14
Per 20 pack-years	0.98 (0.94-1.02)	1.01 (0.96-1.06)	0.92 (0.80-1.06)	1.20 (1.04-1.39)	0.68 (0.53-0.89)	**0.002**
In pack-years						
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
≤10	1.07 (0.97-1.17)	1.07 (0.96-1.21)	1.02 (0.78-1.32)	1.14 (0.78-1.68)	0.95 (0.64-1.40)	
>10-20	1.02 (0.90-1.15)	1.04 (0.89-1.21)	0.72 (0.49-1.07)	1.40 (0.89-2.20)	0.88 (0.52-1.48)	0.09
>20-35	0.96 (0.85-1.08)	0.99 (0.85-1.15)	0.92 (0.65-1.30)	1.16 (0.72-1.88)	0.44 (0.22-0.91)	
>35	0.99 (0.88-1.12)	1.08 (0.93-1.24)	0.85 (0.57-1.26)	1.60 (1.02-2.51)	0.42 (0.18-0.94)	

[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 a pooled analysis 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 histologic subtype to a model forcing the association to be the same across subtypes.

Table 4. Associations[a] of risk factors with among serous ovarian carcinomas by grade in the Ovarian Cancer Cohort Consortium

Exposure	Well-differentiated[b]	Moderately-differentiated	Poorly-differentiated	Unknown grade	p-het.[c]
Parity					
Ever/never	0.78 (0.47-1.29)	0.77 (0.60-0.99)	0.83 (0.72-0.96)	0.88 (0.71-1.09)	0.87
Number of children, per 1 child	0.89 (0.80-1.00)	0.90 (0.85-0.95)	0.94 (0.91-0.96)	0.96 (0.93-1.01)	0.20
Number of children					
0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
1	0.84 (0.41-1.73)	0.90 (0.64-1.27)	0.85 (0.69-1.05)	0.94 (0.70-1.26)	
2	0.88 (0.50-1.55)	0.86 (0.65-1.13)	0.89 (0.76-1.05)	0.89 (0.70-1.13)	0.42
3	0.88 (0.50-1.54)	0.68 (0.51-0.91)	0.87 (0.74-1.03)	0.86 (0.67-1.10)	
4+	0.45 (0.22-0.91)	0.68 (0.50-0.92)	0.69 (0.58-0.82)	0.89 (0.69-1.14)	
Oral contraceptive use					
Ever/never	1.11 (0.72-1.72)	0.80 (0.65-0.98)	0.85 (0.76-0.95)	0.77 (0.66-0.90)	0.36
Duration of use, per 5 year increase	0.79 (0.62-1.00)	0.82 (0.73-0.92)	0.90 (0.84-0.96)	0.77 (0.69-0.87)	0.09
Categorical duration of use (years)					
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
≤1	1.80 (0.98-3.30)	0.90 (0.63-1.29)	1.01 (0.84-1.20)	0.96 (0.74-1.24)	
>1-≤5	1.12 (0.65-1.94)	0.95 (0.72-1.25)	0.86 (0.74-1.00)	0.85 (0.68-1.06)	0.25
>5-≤10	0.94 (0.48-1.83)	0.82 (0.60-1.13)	0.77 (0.65-0.92)	0.59 (0.44-0.79)	
>10	0.56 (0.22-1.42)	0.45 (0.28-0.73)	0.76 (0.61-0.94)	0.49 (0.34-0.71)	
Duration of breastfeeding, per 1 year[d]	1.06 (0.68-1.66)	0.93 (0.75-1.15)	0.95 (0.83-1.08)	0.89 (0.74-1.08)	0.86
Age at menarche (years)					
Per 1 year increase	1.01 (0.91-1.11)	1.00 (0.94-1.06)	1.01 (0.98-1.04)	0.95 (0.91-1.00)	0.21
Categorical					
≤11	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
12	1.26 (0.70-2.28)	0.86 (0.64-1.14)	1.06 (0.91-1.23)	0.86 (0.69-1.06)	
13	1.37 (0.83-2.28)	0.94 (0.73-1.20)	1.10 (0.96-1.26)	0.76 (0.62-0.92)	0.22
14	1.20 (0.62-2.34)	0.86 (0.62-1.18)	1.16 (0.97-1.38)	0.83 (0.65-1.05)	
≥15	1.00 (0.49-2.05)	0.99 (0.72-1.36)	0.94 (0.78-1.14)	0.80 (0.62-1.02)	
Age at menopause (years)					
Per 5 year increase	1.54 (1.23-1.91)	1.04 (0.93-1.16)	1.03 (0.97-1.10)	1.05 (0.95-1.16)	0.06
Categorical					
≤45	0.20 (0.07-0.56)	0.92 (0.66-1.28)	0.91 (0.77-1.09)	0.89 (0.69-1.17)	
>45-≤50	0.49 (0.29-0.84)	1.21 (0.94-1.56)	0.96 (0.83-1.10)	0.98 (0.80-1.21)	**0.02**
>50-≤55	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
>55	0.41 (0.13-1.32)	1.16 (0.73-1.84)	0.97 (0.75-1.24)	1.23 (0.87-1.73)	
HT use[e]					
Ever/never	1.80 (1.15-2.83)	1.57 (1.27-1.95)	1.49 (1.33-1.67)	1.23 (1.04-1.45)	0.15
Duration of use, per 5 year increase	1.35 (1.18-1.53)	1.26 (1.17-1.36)	1.21 (1.16-1.26)	1.20 (1.12-1.29)	0.54

Categorical duration of use (years)					
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
≤5	1.33 (0.71-2.48)	1.26 (0.94-1.69)	1.27 (1.09-1.48)	1.12 (0.90-1.41)	0.42
>5	2.91 (1.72-4.92)	2.10 (1.60-2.76)	1.80 (1.56-2.07)	1.57 (1.27-1.95)	
Tubal ligation, ever/never	1.25 (0.66-2.36)	1.05 (0.71-1.57)	0.92 (0.76-1.11)	0.62 (0.43-0.88)	0.10
Hysterectomy, ever/never[f]	0.87 (0.53-1.42)	1.08 (0.86-1.35)	1.01 (0.89-1.15)	1.03 (0.86-1.24)	0.88
Endometriosis, yes/no	3.77 (1.24-11.48)	1.54 (0.72-3.30)	1.11 (0.70-1.74)	0.57 (0.18-1.80)	0.12
First degree family history of breast cancer, yes/no	1.23 (0.71-2.15)	1.20 (0.91-1.58)	1.12 (0.97-1.30)	0.96 (0.76-1.21)	0.58
First degree family history of ovarian cancer, yes/no	0.90 (0.22-3.70)	1.46 (0.83-2.54)	1.63 (1.25-2.13)	1.64 (1.08-2.47)	0.82
Body mass index (kg/m^2)					
Per 5 kg/m^2	0.92 (0.74-1.14)	0.99 (0.90-1.08)	0.92 (0.87-0.97)	1.05 (0.97-1.13)	**0.03**
Categorical					
<20	1.33 (0.67-2.62)	0.78 (0.51-1.19)	1.15 (0.95-1.39)	1.11 (0.83-1.49)	
20-<25	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
25-<30	1.02 (0.65-1.59)	1.08 (0.88-1.33)	0.84 (0.74-0.94)	0.89 (0.75-1.05)	0.22
30-<35	0.85 (0.44-1.66)	0.98 (0.73-1.32)	0.85 (0.72-1.00)	1.04 (0.83-1.32)	
≥35	1.15 (0.51-2.59)	0.88 (0.56-1.39)	0.88 (0.70-1.10)	1.25 (0.92-1.70)	
Height (meters)					
Per 0.5m	1.05 (0.93-1.18)	1.06 (0.99-1.14)	1.07 (1.03-1.11)	1.03 (0.97-1.08)	0.72
Categorical					
<1.60	0.83 (0.49-1.39)	0.92 (0.72-1.17)	0.82 (0.72-0.95)	1.00 (0.82-1.21)	
1.60-<1.65	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	0.70
1.65-<1.70	1.21 (0.75-1.95)	1.03 (0.81-1.30)	1.03 (0.91-1.18)	1.15 (0.95-1.39)	
≥1.70	0.96 (0.55-1.69)	1.08 (0.83-1.41)	1.06 (0.92-1.22)	0.96 (0.77-1.20)	
Smoking					
Ever/never	1.10 (0.85-1.41)	0.95 (0.84-1.07)	0.96 (0.90-1.03)	1.04 (0.95-1.15)	0.38
Continuous pack-years, per 20 pack-years	0.87 (0.59-1.26)	1.00 (0.87-1.15)	0.98 (0.92-1.05)	1.07 (0.97-1.18)	0.44
Categorical pack-years					
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	
≤20	1.20 (0.70-2.08)	1.00 (0.76-1.32)	1.08 (0.94-1.24)	1.10 (0.88-1.36)	0.91
>20	0.72 (0.34-1.52)	0.97 (0.71-1.31)	1.03 (0.89-1.21)	1.09 (0.87-1.38)	

[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. Excluding 5 cohorts with no information on grade for any ovarian cancer cases.

[b]Number of cases ranges from 28 (breastfeeding)-121 (OC use) for well-differentiated, 113 (Endometriosis)-496 (OC use) for moderately-differentiated, 338 (breastfeeding)-1637 (OC use) for poorly-differentiated, and 141 (endometriosis)-773 (OC use) for unknown grade.

[c]Assessed using a likelihood ratio test comparing a Cox proportional hazards competing risks model allowing the association to vary by grade to a model forcing the association to be the same across grades.

[d]Parous women only.
[e]Postmenopausal women only.
[f]Additionally adjusted for duration of hormone therapy use.

Supplemental Table 1. Studies[a] in the Ovarian Cancer Cohort Consortium contributing to each exposure analysis

Variable	Studies
Ever/never parous:	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS**
Number of children (continuous or categorical):	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SMC, SS, VITAL, WHS, WLHS**
Ever/never OC use: Duration of OC use (continuous or categorical):	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS**
Duration of breastfeeding (continuous): Age at menarche (continuous or categorical):	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS**
Age at menopause (continuous and categorical):	~~**BGS, CTS, EPIC, NHS, NHSII, SS, WLHS**~~
Ever use of HT	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS**
Duration of HT use (continuous and categorical):	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS**
Tubal ligation:	~~**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS**~~
Hysterectomy:	**AARP, BCDDP, BGS, CPSII-NC, CSDLH, EPIC, IWHS, MEC, NHS, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS**
Endometriosis:	**CPSII-NC, CTS, EPIC, MEC, NHS, NHSII, NLCS, NYU, PLCO, SMC, SS, VITAL, WHS**
Family history of breast cancer:	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS**
Family history of ovarian cancer:	**BGS, CTS, IWHS, NHSII, PLCO, SS**
BMI (continuous and categorical):	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, VITAL, WHS**
Height (continuous and categorical):	**AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, VITAL, WHS**
Ever/never smoker:	AARP, BCDDP, BGS, CLUEII, CPSII-NC, CTS, IWHS, MEC, NHS, NHSII, NLCS, PLCO, SCHS, SS, VITAL, WHS
Pack-years of smoking (continuous and categorical):	~~AARP, BCDDP, BGS, CLUE, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS~~ BCDDP, BGS, CPSII-NC, CSDLH, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS
[a]Study abbreviations can be found in Table 1	AARP, BCDDP, BGS, CLUE, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS AARP, BCDDP, BGS, CLUEII, CPSII-NC, CSDLH, CTS, EPIC, IWHS, MEC, NHS, NHSII, NLCS, NYU, PLCO, SCHS, SMC, SS, VITAL, WHS, WLHS

Supplemental Table 2. Number of invasive epithelial ovarian cancer cases overall and by histologic subtype for each exposure

Case numbers for each exposure	Serous	Endometrioid	Mucinous	Clear cell	All Invasive
Parity					
Ever/never	3300	598	318	254	5429
Number of children (continuous or categorical)	3268	587	303	241	5351
Oral contraceptive use					
Ever/never	3347	604	326	265	5523
Duration of use (continuous or categorical)	3287	587	318	263	5418
Duration of breastfeeding	831	157	70	63	1281
Age at menarche (continuous or categorical)	3331	602	327	266	5489
Age at menopause (postmenopausal only; continuous or categorical**)**	2162	345	207	132	3494
HT use (postmenopausal only)					
Ever/never	2682	411	238	157	4319
Duration of use (continuous or categorical)	2394	347	216	138	3802
Tubal ligation	2387	435	213	193	3914
Hysterectomy	3146	550	301	230	5486
Endometriosis	900	169	73	86	1503
First degree family history of breast cancer	3291	589	316	262	5383
First degree family history of ovarian cancer	2634	459	238	205	4332
Body mass index (continuous or categorical)	3234	578	319	262	5354
Height (continuous or categorical)	3277	592	322	267	5433
Smoking					
Ever/never	3335	605	328	268	5514
Pack-years(continuous or categorical)	2257	416	223	191	4690

Supplemental Table 3. Associations[a] of risk factors with ovarian cancer subtypes based on meta-analysis pooling the results of individual studies in the Ovarian Cancer Cohort Consortium

Exposure	Serous	Endometrioid	Mucinous	Clear cell
Parity				
Ever/never	0.80 (0.73-0.89)	0.44 (0.36-0.55)	0.45 (0.31-0.64)	0.32 (0.24-0.43)
Number of children, per 1 child	0.94 (0.92-0.96)	0.78 (0.72-0.84)	0.84 (0.75-0.95)[b]	0.65 (0.57-0.73)
Number of children				
0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1	0.87 (0.74-1.02)	0.79 (0.58-1.07)	0.83 (0.48-1.45)	0.57 (0.36-0.91)
2	0.87 (0.77-0.97)	0.47 (0.37-0.59)	0.52 (0.33-0.82)	0.41 (0.27-0.63)
3	0.80 (0.71-0.90)	0.41 (0.32-0.54)	0.53 (0.34-0.80)	0.32 (0.19-0.52)
4+	0.72 (0.63-0.83)	0.33 (0.24-0.46)	0.60 (0.39-0.91)	0.31 (0.14-0.67)
Oral contraceptive use				
Ever/never	0.82 (0.75-0.89)	0.88 (0.73-1.05)	1.04 (0.81-1.34)	0.74 (0.54-1.01)
Duration of use, per 5 year increase	0.84 (0.78-0.90)	0.89 (0.77-1.02)	1.19 (0.99-1.43)	0.96 (0.82-1.12)
Duration of use, years				
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≤1	1.01 (0.88-1.16)	1.15 (0.86-1.55)	1.22 (0.77-1.91)	1.24 (0.74-2.06)
>1-≤5	0.88 (0.78-0.99)	0.95 (0.74-1.23)	1.15 (0.77-1.71)	1.25 (0.78-2.01)
>5-≤10	0.76 (0.65-0.89)	0.90 (0.67-1.21)	1.28 (0.84-1.95)	1.06 (0.67-1.68)
>10	0.67 (0.57-0.79)	0.75 (0.97-1.16)	1.67 (1.06-2.64)	0.73 (0.36-1.45)
Duration of breastfeeding, per 1 year[c]	1.01 (0.87-1.18)[b]	0.93 (0.78-1.11)	0.94 (0.68-1.31)	1.13 (0.93-1.36)
Age at menarche				
Per 1 year increase	0.99 (0.96-1.02)	1.00 (0.95-1.05)	1.00 (0.94-1.07)	0.94 (0.87-1.02)
Age in years				
≤11	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
12	0.90 (0.75-1.08)	0.97 (0.74-1.27)	1.13 (0.75-1.70)	0.81 (0.54-1.22)
13	0.99 (0.88-1.10)	1.00 (0.75-1.33)	1.05 (0.74-1.49)	0.84 (0.47-1.49)
14	0.97 (0.85-1.12)	0.88 (0.63-1.23)	1.05 (0.65-1.68)	0.77 (0.46-1.27)
≥15	0.91 (0.79-1.05)	1.02 (0.73-1.42)	1.37 (0.87-2.17)	0.80 (0.46-1.40)
Age at menopause				
Per 5 year increase	1.05 (1.00-1.10)	1.44 (1.08-1.93)[b]	1.04 (0.80-1.37)[b]	1.96 (1.37-2.81)[b]
Age in years				
≤40	1.02 (0.82-1.27)	0.79 (0.45-1.40)	2.02 (0.67-6.04)	0.64 (0.14-2.89)
>40-≤45	0.88 (0.75-1.04)	1.03 (0.64-1.66)	1.10 (0.54-2.25)	0.95 (0.37-2.48)
>45-≤50	0.96 (0.86-1.06)	0.86 (0.65-1.13)	0.96 (0.68-1.35)	1.06 (0.69-1.63)
>50-≤55	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>55	1.05 (0.88-1.25)	1.35 (0.88-2.08)	1.66 (0.83-3.34)	1.93 (0.88-4.23)
HT use[d]				
Ever/never	1.40 (1.27-1.55)	1.81 (1.41-2.32)	1.04 (0.77-1.41)	0.90 (0.57-1.42)
Duration of use, per 5 year increase	1.22 (1.15-1.29)	1.33 (1.17-1.51)	1.08 (0.86-1.36)	0.69 (0.49-0.98)[b]

Duration of use, years				
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≤5	1.24 (1.11-1.38)	1.71 (1.20-2.43)	1.27 (0.87-1.85)	1.06 (0.63-1.75)
>5	1.75 (1.55-1.98)	2.32 (1.59-3.38)	1.43 (0.89-2.30)	0.83 (0.55-1.25)
Tubal ligation, ever/never	0.97 (0.81-1.16)	0.79 (0.53-1.18)	1.43 (0.80-2.56)	0.63 (0.27-1.46)
Hysterectomy, ever/never[e]	1.18 (0.79-1.76)[b]	1.21 (0.64-2.30)[b]	1.09 (0.61-1.95)[b]	0.95 (0.55-1.63)
Endometriosis, yes/no	1.14 (0.81-1.61)	2.84 (1.56-5.18)	5.06 (1.51-16.9)	3.43 (1.52-7.75)
First degree family history of breast cancer, yes/no	1.19 (1.02-1.39)	1.56 (1.22-1.99)	1.04 (0.67-1.61)	1.29 (0.78-2.13)
First degree family history of ovarian cancer, yes/no	1.16 (0.43-3.18)[b]	0.29 (0.01-5.89)[b]	0.01 (0.00-1.13)[b]	0.02 (0.00-1.68)[b]
Body mass index				
Per 5 kg/m^2	0.97 (0.93-1.01)	1.03 (0.92-1.15)[b]	1.08 (0.97-1.20)	0.95 (0.80-1.14)[b]
In kg/m^2				
<20	1.08 (0.94-1.24)	1.18 (0.83-1.67)	1.97 (1.28-3.02)	1.50 (0.92-2.44)
20-<25	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
25-<30	0.93 (0.84-1.03)	1.00 (0.82-1.23)	1.44 (1.11-1.87)	1.37 (1.01-1.84)
30-<35	0.94 (0.83-1.06)	1.28 (0.97-1.70)	1.86 (1.22-2.86)	1.77 (1.04-3.00)
≥35	1.07 (0.84-1.35)	1.73 (1.20-2.50)	2.18 (1.09-4.36)	2.26 (1.19-4.29)
Height				
Per 0.5m	1.06 (1.03-1.10)	1.06 (0.99-1.13)	1.08 (0.96-1.19)[b]	1.08 (0.98-1.17)
In meters				
<1.60	0.87 (0.79-0.96)	1.05 (0.83-1.32)	0.98 (0.71-1.34)	1.02 (0.71-1.46)
1.60-<1.65	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1.65-<1.70	1.05 (0.94-1.19)	1.00 (0.79-1.27)	1.02 (0.73-1.41)	1.02 (0.67-1.58)
≥1.70	1.06 (0.96-1.17)	1.28 (1.01-1.63)	1.23 (0.88-1.71)	1.23 (0.85-1.78)
Smoking				
Ever/never	1.02 (0.92-1.12)	0.95 (0.80-1.12)	1.25 (0.99-1.57)	0.92 (0.70-1.21)
Continuous pack-years, per 20 pack-years	1.03 (0.97-1.10)	0.98 (0.84-1.15)	1.21 (1.04-1.40)	0.79 (0.59-1.05)
Categorical pack-years				
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≤10	1.12 (0.99-1.27)	1.21 (0.91-1.59)	1.29 (0.86-1.93)	1.04 (0.67-1.63)
>10-20	1.09 (0.92-1.28)	0.91 (0.61-1.37)	1.62 (0.96-2.72)	1.25 (0.66-2.37)
>20-35	1.08 (0.87-1.32)	1.12 (0.77-1.63)	1.53 (0.89-2.61)	0.94 (0.42-2.11)
>35	1.13 (0.94-1.35)	1.20 (0.78-1.85)	2.13 (1.27-3.55)	0.98 (0.40-2.40)

[a]Stratified on birth year, 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).
[b]Meta-analysis p-heterogeneity across studies <0.01 using the q-statistic from a random-effects meta-analysis. [c]Parous women only.
[d]Postmenopausal women only. eAdditionally adjusted for duration of hormone therapy use.