HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2020 January ; 29(1): 200–207. doi: 10.1158/1055-9965.EPI-19-0734.

Reproductive and hormonal factors and risk of ovarian cancer by tumor dominance: results from the Ovarian Cancer Cohort Consortium (OC3)

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Abstract

Background—Laterality of epithelial ovarian tumors may reflect the underlying carcinogenic pathways and origins of tumor cells.

Methods—We pooled data from 9 prospective studies participating in the Ovarian Cancer Cohort Consortium. Information on measures of tumor size or tumor dominance was extracted from surgical pathology reports or obtained through cancer registries. We defined dominant tumors as

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Conflicts of Interest: The authors have nothing to disclose.

those restricted to one ovary or where the dimension of one ovary was at least twice as large as the other, and non-dominant tumors as those with similar dimensions across the two ovaries or peritoneal tumors. Competing risks Cox models were used to examine whether associations with reproductive and hormonal risk factors differed by ovarian tumor dominance.

Results—Of 1,058 ovarian cancer cases with tumor dominance information, 401 were left-dominant, 363 were right-dominant, and 294 were non-dominant. Parity was more strongly inversely associated with risk of dominant than non-dominant ovarian cancer (p-heterogeneity=0.004). Ever use of oral contraceptives (OCs) was associated with lower risk of dominant tumors, but was not associated with non-dominant tumors (p-heterogeneity=0.01). Higher body mass index was associated with higher risk of left-dominant tumors, but not significantly associated with risk of right-dominant or non-dominant tumors (p-heterogeneity=0.08).

Conclusions—These data suggest that reproductive and hormonal risk factors appear to have a stronger impact on dominant tumors, which may have an ovarian or endometriosis origin.

Impact—Examining the associations of ovarian cancer risk factors by tumor dominance may help elucidate the mechanisms through which these factors influence ovarian cancer risk.

Introduction

Ovarian cancer, the most deadly gynecologic malignancy in the US women, is a highly heterogeneous disease. For example, each histotype of ovarian cancer likely originates through a different etiologic pathway, displaying a high level of heterogeneity in clinical behavior and disease progression; importantly, each histotype displays a distinct risk factor profile (1–3). Further, recent evidence suggests that different types of ovarian tumors may have distinct cellular origins, potentially representing two major carcinogenic pathways (4–6). Type 1 ovarian tumors are more likely to arise from the ovarian surface epithelium, be histologically classified as low-grade serous, endometrioid, mucinous, or clear cell subtypes, and harbor mutations in the genes of KRAS, BRAF, β-catenin and pTEN (4–6). By contrast, Type 2 tumors are more likely to be high-grade serous carcinomas with a distal fallopian tube origin and p53 mutations (4–6). Prior work suggests that tumors originating from the ovarian surface (i.e., those with Type 1 tumor characteristics) tend to present with a dominant tumor mass with tumor growth primarily confined to one ovary, whereas tumors of fallopian tube origin (i.e., those with Type 2 tumor characteristics) tend to be non-dominant resulting in bilateral tumors with a similar extent of growth or peritoneal tumors (7–11). In addition to ovarian and fallopian tube origin, emerging evidence suggests that endometrioid and clear cell ovarian cancers, which are more likely to have dominant tumor masses, may directly arise from endometriotic tissues (12). Thus, tumor dominance can be considered as an indicator for ovarian or endometriosis versus fallopian tube cancer cell of origin. While a growing body of evidence documented substantial heterogeneity in risk factor profiles by ovarian tumor characteristics including histologic subtype and aggressiveness (2,13), less is known for tumor dominance that may be an indicator of tumor developmental features such as cell of origin or tumor spread. As such, elucidating the associations with ovarian cancer risk factors by tumor dominance may provide further insights into the mechanisms through which these factors influence ovarian cancer development (14,15). We conducted the current

analysis in the Ovarian Cancer Cohort Consortium (OC3), a large-scale collaborative effort to understand etiologic heterogeneity in ovarian cancer, to examine whether the associations of ovarian cancer risk with reproductive, hormonal, anthropometric and lifestyle factors differed by ovarian tumor dominance.

Materials and Methods

Study populations

Nine prospective cohort studies (out of a total of 23 contributing studies) in the OC3 with available data on tumor dominance were included in this analysis (Table 1) (2). All OC3 participating studies had a prospective design with regular follow-up of ovarian cancer diagnoses and death, and collected key ovarian cancer risk factors (e.g., age, oral contraceptive [OC] use, parity) at baseline. Individual studies were approved by the respective institutional review board following the institution's requirement. The OC3 study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. The approaches for data pooling, harmonization and analysis, developed by OC3 Data Coordinating Center, were approved by the institutional review board of the Brigham and Women's Hospital.

Exposure assessment

Exposure information at baseline was obtained and harmonized centrally for either the full cohort (8 studies) or a case-cohort sample with weights for subcohort members (1 study). We examined multiple putative and known ovarian cancer risk factors, including parity (nulliparous, 1 child, 2 children, 3 children, ≥4 children; per 1 child), age at first birth (<20, 20-<25, 25-<30, 30+ years; per 1 year), age at last birth (<25, 25-<30, 30-<35, 35+ years; per 1 year), years since last birth (per 1 year), duration of OC use (ever, never; never, ≤1, >1-≤5, >5-≤10, >10 years; per 5 years of use), duration of breastfeeding (per 1 year among parous women), age at menarche (≤11, 12, 13, 14, ≥15 years; per 1 year), age at natural menopause (among postmenopausal women: ≤45, >45-≤50, >50-≤55, >55 years; per 5 years), duration of postmenopausal hormone therapy (HT) use (among postmenopausal women: ever, never; never, ≤5, >5 years; per 1 year), tubal ligation (yes, no), hysterectomy (yes, no), endometriosis (yes, no), first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), BMI at baseline (<20, 20-<25, 25-<30, 30-<35, ≥35 kg/m^2; per 5 kg/m^2), BMI at age 18–20 years (<18, 18-<20, 20-<22, ≥22 kg/m^2; per 5 kg/m^2), height (<1.60, 1.60-<1.65, 1.65-<1.70, ≥1.70 m; per 0.05 m), and smoking at baseline (never, ever; never, <10, 10-<20, 20-<35, ≥35 pack-years; per 20 pack-years).

Ovarian cancer ascertainment and tumor dominance definition

Incident cases of epithelial ovarian cancer or peritoneal cancer were identified by self-report or through linkage with cancer registry. Diagnoses were confirmed, and tumor characteristics, including histology, stage, grade, and tumor size, were obtained, by review of medical or surgical pathology report or linkage with cancer registry data. Specifically, of the nine cohorts included in the current study, the Melbourne Collaborative Cohort Study, the Nurses' Health Study (NHS), NHSII, the Sister Study and the Women's Health Study

obtained ovarian cancer characteristics and tumor dominance data primarily from pathology report abstraction, supplementing with cancer registry, whereas the Netherlands Cohort Study (NCS) on Diet and Cancer and the VITamins And Lifestyle Cohort (VITAL) obtained information from cancer registry data with pathology report summaries (NCS) or full report abstraction (VITAL) to obtain additional information on tumor dominance. Data from the New York University Women's Health Study and the Swedish Mammography Cohort Study were solely based on cancer registry. For cases with a surgical pathology report available, we abstracted dimensions, area, or volume recorded for ovarian tumors identified on each side of the peritoneal cavity (left and right). For cases classified through cancer registry, we collected information regarding the extent of tumor growth on each ovary, further extracting data on tumor size on the left and right when available. We considered an ovarian cancer case as having dominant tumor mass if any of the following was met: (1) the growth of tumor was limited to one ovary, (2) a tumor mass was found on one ovary, with only tumor foci on the other ovary, or (3) the tumor dimensions, area, or volume on one side was at least twice that of the other side. A case was considered non-dominant if any of the following was met: (1) the tumor was classified as primary peritoneal cancer, (2) only tumor foci were found on both ovaries, (3) no ovaries could be identified on either side of the peritoneal cavity, or (4) the tumor dimensions, area, or volume on one side was within two times that of the other side. Cases without appropriate information to classify tumor dominance were censored at time of diagnosis.

Statistical analysis

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 by tumor dominance (right dominant, left dominant, non-dominant) (16). Person-time was counted from study entry until date of i) invasive ovarian cancer diagnosis, ii) death, or iii) end of follow-up, whichever occurred first. Given the relatively small number of available cases in individual cohorts, we pooled data and stratified on year of birth and cohort to account for potential differences in baseline hazards by these factors. Heterogeneity in the associations by tumor dominance was tested using a likelihood ratio test comparing the model allowing the association for the risk factor of interest to vary by dominance versus the one not allowing the association to vary (17). All models were adjusted for age at entry, number of children, and duration of OC use. Additional adjustment for HT use was conducted for hysterectomy analyses. For missing covariates, we included a missing indicator in the model. Primary analyses included all available invasive cases evaluating dominant versus non-dominant tumors, and secondary, hypothesis-generating analyses were conducted to assess potential differences between left and right dominant tumors. We also performed sensitivity analyses restricted to serous tumors. To address the concern that tumor dominance may reflect tumor stage or that non-dominant tumors are advanced-stage tumors that progress from early-stage, dominant tumors, we further examined the associations by tumor dominance for stage 1/2 and stage 3 ovarian cancer separately. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), with a p-value <0.05 considered statistically significant.

Results

Compared to women who did not develop ovarian cancer during follow-up, those later diagnosed with ovarian cancer were older and more likely to be postmenopausal, but were less likely to have ever used OC, be parous or have tubal ligation at baseline (Table 2). Compared to ovarian cancer patients with non-dominant tumors, those with a dominant tumor mass were less likely to be parous and, among those who were parous, had fewer children. In addition, women with a dominant tumor mass were less likely to have ever smoked, have ever used OC, or have tubal ligation, hysterectomy and unilateral oophorectomy than those with non-dominant tumors. Further, compared with women with right-dominant tumors, women with left-dominant tumors were less likely to be parous or have used OC.

Of 1,058 incident ovarian cancer cases identified during follow-up with tumor dominance information, 764 (72.2%) were classified as dominant tumors, with 401 (37.9%) having a dominant tumor mass on the left and 363 (34.3%) on the right (Table 3). There were higher proportions of serous, stage 3, or poorly differentiated tumors among non-dominant cases, whereas non-serous, stage 1/2, and well or moderately differentiated tumors were more common in dominant cases. When comparing tumor characteristics by laterality of tumor dominance, there were more serous tumors in right-dominant tumors and more clear cell subtype in left-dominant tumors; other tumor characteristics were similar.

When evaluating reproductive factors with ovarian cancer risk by tumor dominance, parity, tubal ligation, and endometriosis appeared more strongly associated with risk of dominant versus non-dominant ovarian cancer (Table 4). The HR (95% CI) for each additional child was 0.85 (0.81, 0.89) for dominant tumors compared to 0.97 (0.90, 1.04) for non-dominant tumors (p-heterogeneity=0.004). The association with parity was more inverse for left-dominant tumors (HR: 0.81; 95% CI: 0.76, 0.87) than for right-dominant tumors (HR: 0.90; 95% CI: 0.84, 0.96; Supplemental Table 1). Although the difference was not statistically significant (p-heterogeneity=0.07), tubal ligation was associated with a suggestively lower risk of dominant tumors (HR: 0.74; 95%: 0.56, 0.99) but a non-significant higher risk of non-dominant tumors (HR: 1.13; 95% CI: 0.80, 1.60); the inverse association with tubal ligation was similar for left and right dominant tumors. Similarly, despite a lack of statistically significant heterogeneity, there was a suggestion of a stronger positive association of endometriosis with dominant tumors (HR: 1.70; 95% CI: 1.00, 3.00) than non-dominant tumors (HR: 1.12; 95% CI: 0.40, 3.15).

When examining the associations with exogenous hormonal factors, the association with OC use differed significantly by tumor dominance (Table 5). Ever OC use was associated with significantly lower risk of dominant ovarian tumors (HR: 0.70; 95% CI: 0.59, 0.83), while no association was observed for non-dominant tumors (HR: 1.05; 95% CI: 0.80, 1.39; p-heterogeneity=0.01). Further, the reduced ovarian cancer risk among ever versus never OC users was significantly lower for left dominant tumors (HR: 0.59; 95% CI: 0.47, 0.76) and suggestively lower for right dominant tumors (HR: 0.83; 95% CI: 0.65, 1.06; Supplemental Table 2). In addition, while no heterogeneity was observed when comparing all dominant versus non-dominant tumors (p-heterogeneity=0.76), current BMI was associated with a

significantly increased risk of left-dominant ovarian cancer (HR for every 5-unit increase in BMI: 1.14, 95% CI: 1.04, 1.26), with no association for right-dominant or non-dominant tumors (p-heterogeneity=0.08). However, we did not observe clear differences by tumor dominance in the associations with postmenopausal HT, family history, anthropometric factors, or smoking. Postmenopausal HT, family history of ovarian cancer, and height were positively associated with ovarian cancer risk regardless of tumor dominance (p-heterogeneity>0.30).

In sensitivity analyses, we examined associations with risk of serous ovarian cancer by tumor dominance. Among the reproductive factors, the association between parity and serous ovarian cancer by tumor dominance was similar to the primary analysis (Supplemental Table 3). The HR for each additional child was statistically significant for dominant tumors (HR: 0.92; 95% CI: 0.86, 0.98), but not for non-dominant tumors (HR: 0.99; 95% CI: 0.92, 1.07; p-heterogeneity=0.15). In analyses of hormonal factors, family history, anthropometric factors, and smoking, associations were largely similar to those in the primary analysis (Supplemental Table 4). Finally, when examining the associations by stage 1/2 and stage 3 separately, we observed similar differences by tumor dominance for parity, tubal ligation and OC use (Supplemental Table 5), although the differences were less statistically significant due to reduced sample size within each stratum.

Discussion

In this pooled analysis of 9 prospective cohort studies, we observed that several reproductive and hormonal factors, including parity, OC use, tubal ligation, and endometriosis, were differentially associated with ovarian cancer risk by tumor dominance, with suggestively stronger relationships with dominant versus non-dominant ovarian tumors. However, the associations with other reproductive factors, hormonal factors, anthropometric measures, family history and smoking did not vary substantially between dominant and non-dominant tumors. Intriguingly, OC use and current BMI showed a different association with left-dominant and right-dominant ovarian tumors.

Our results were consistent with a prior study in NHS, NHSII, and New England Case-Control Study, which reported stronger associations of parity, tubal ligation and endometriosis with dominant tumors than with non-dominant tumors (14). Taken together, these findings suggest that parity, tubal ligation and endometriosis are more likely to influence ovarian tumors originating from ovarian surface epithelial cells. Indeed, higher parity leads to a lower number of ovulatory cycles, which reduces the possibility of neoplastic progression on the ovarian surface epithelium resulting from ovulation-induced wounds (18,19). On the other hand, the elevated progesterone levels during pregnancy may confer potential protection against ovarian carcinogenesis by suppressing proliferation and inducing apoptosis of ovarian epithelial cells (20). Interestingly, we also observed that OC use was more strongly inversely associated with dominant versus non-dominant ovarian cancer risk, which was not noted in the prior study (14). The differential impact of OC use on ovarian cancer tumor dominance may be explained by similar mechanisms as proposed for parity, although the reasons for the stronger inverse association for left- versus right-dominant tumors require further study.

It is hypothesized that the mechanism through which endometriosis increases ovarian cancer risk is possibly due to the reflux and implantation of endometrial fragments onto the ovarian surface during menstruation, which leads to inflammation and malignant transformation (21,22). Similarly, tubal ligation may be protective for ovarian cancer by blocking the retrograde passage of endometrial tissues through the fallopian tubes and preventing subsequent potential carcinogenesis on the ovarian surface (23,24). These mechanisms point to the suggestively stronger associations of endometriosis and tubal ligation with dominant ovarian tumors, which may have an ovarian surface epithelium origin. However, although endometriosis and ovarian endometrioma have been suggested to have left lateral predisposition (25,26), the observed association between endometriosis and risk of dominant ovarian cancer was suggestively stronger for right- (HR: 1.97) versus left-dominant tumors (HR: 1.55). Nevertheless, it should be noted that the analyses of endometriosis and tubal ligation were based on a smaller number of cases, and the observed differences, which did not reach statistical significance, could be due to chance. It is unclear why the associations with current BMI also differed by laterality of dominant ovarian tumors, with a positive association only observed for left dominant cancers. A recent study suggests that adiposity during early life was more strongly associated with ovarian cancer risk, particularly non-serous ovarian cancer, compared to adiposity during adulthood (27). More research is needed to confirm whether the association between early life adiposity and ovarian cancer risk is also primarily driven by left dominant tumors. Further, there is some evidence suggesting that BMI has a stronger positive association with distal colon cancer than proximal colon cancer (28), suggesting that the hormonal impact of adiposity may have different impact across tissue types/locations. Future investigation should replicate these analyses in independent data sets and evaluate potential underlying mechanisms.

Of note, tumor dominance was highly correlated with other tumor characteristics, with non-dominant tumors more likely to be serous, high-grade, and poorly differentiated. Despite this, we observed that the majority of both dominant and non-dominant cases had a serous subtype (n= 357 dominant serous tumors versus 235 non-dominant serous tumors); similarly, there was a distribution of dominant and non-dominant tumors within both low-stage and high-stage tumors. We conducted sensitivity analyses restricted to serous tumors or stratified by tumor stage. Interestingly, we observed similar differences in risk factor associations by tumor dominance in serous tumors, as well as in both low-stage tumors and in high-stage tumors, suggesting that tumor dominance provides additional insight that pre-diagnosis risk factors can influence tumor developmental pathways. Here our results suggest that reproductive factors may be particularly relevant to tumor spread within the peritoneal cavity and may be more important for tumors likely to be of ovarian or endometriosis origin, beyond serous histotype and tumor stage (12). However, even with the large sample size through consortia efforts, we cannot exclude that the differential associations by tumor dominance in non-serous ovarian cancer may be partly due to the stronger associations of certain risk factors with non-serous subtypes. For example, we and others have previously shown that endometriosis was more strongly associated with risk of endometrioid and clear cell ovarian cancer (2,22). Given that about 95% of endometrioid and clear cell tumors were classified as dominant, it is possible that the positive association between endometriosis and dominant ovarian cancer may be largely explained by histotype. Future studies are needed to

elucidate whether the observed differences by tumor dominance are independent of histotype and other tumor characteristics.

This study is strengthened by the relatively large sample size including data from 10 prospective studies, each with abstracted data on tumor size and laterality using a standardized abstraction procedure. Further, the use of harmonized exposure data reduced the potential for misclassification. However, this study was still limited by a relatively low number of cases, in part because tumor data were not available on a large proportion of cases, usually because a pathology report was not available or size information about the tumor was not listed in the report. This also precluded an analysis examining associations by tumor dominance within histotypes other than serous, the most common subtype. As discussed above, given that we previously showed associations of reproductive factors, in particular, varied by histotypes (2), we cannot fully clarify whether the observed differences in the associations were due to dominance or histotype.

In summary, we found that reproductive and hormonal factors were more strongly associated with dominant tumors, suggesting that progesterone exposure may be particularly relevant for tumors of ovarian origin. Further, the intriguing, albeit suggestive, differences in association between dominant tumors on the left versus right side for OC use and BMI, should be explored in future studies. Additional research should also examine other ways to leverage pathology report data and assess key metrics of tumor heterogeneity to better elucidate etiologic mechanisms underlying ovarian cancer development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by Department of Defense Ovarian Cancer Research Program grant W81XWH-12-1-0561 (SST). Additional research funding and support included: NCI Intramural Research Program; VicHealth and Cancer Council Victoria, and Australian National Health and Medical Research Council grants 209057, 396414, and 1074383 (Melbourne Collaborative Cohort Study); UM1 CA186107, P01 CA87969 (Nurses' Health Study); UM1 CA176726 (Nurses' Health Study II); UM1 CA182934, P30 CA016087 and P30 ES000260 (NYU Women's Health Study); NIEHS Intramural Research Program (Sisters Study, Project Z01-ES044005 to DPS); Swedish Cancer Foundation (Swedish Mammography Cohort); K05CA154337 from the National Cancer Institute (NCI) and Office of Dietary Supplements (VITamins And Lifestyle Cohort); CA047988, HL043851, HL080467, HL099355, and CA182913 (Women's Health Study).

The authors acknowledge the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, as the home of the Nurses' Health Study. The Nurses' Health Study would like to thank the following state cancer registries for their assistance: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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Table 1.

Characteristics of included cohorts participating in the Ovarian Cancer Cohort Consortium

Study	Location	Baseline	Cohort size	Median age (yrs)	Median follow-up (yrs)	All invasive cases	Cases with tumor dominance data[3]
Melbourne Collaborative Cohort Study	Australia	1990–1994	20,836	55	16	95	70
Nurses' Health Study 1980[1]	US	1980–1982	86,624	46	16	359	114
Nurses' Health Study 1996[1]	US	1996–1998	67,519	62	14	444	166
Nurses' Health Study II	US	1989–1990	111,875	35	20	237	154
Netherlands Cohort Study on diet and cancer[2]	Netherlands	1986	2,755	62	17	446	258
New York University Women's Health Study	US	1985–1991	14,274	49	24	122	57
Sister Study	US	2003–2009	39,195	55	5	39	32
Swedish Mammography Cohort Study	Sweden	1997	34,425	60	14	161	34
VITamins And Lifestyle Cohort	US	2000–2002	28,331	60	10	130	103
Women's Health Study	US	1993–1996	33,548	53	17	204	70

[1]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.

[2]This cohort was included as a case-cohort design, reflecting a total cohort population of 62,573 women. Appropriate weights for subcohort selection were applied in all analyses.

[3]The percent of cases with missing tumor dominance data ranged from 17.9% in Sister Study to 78.9% in Swedish Mammography Cohort Study

Table 2.

Reproductive and hormonal risk factors at baseline by ovarian cancer status and tumor dominance in OC3[1]

	Non-cases	Ovarian cancer cases				
		All cases	Non-dominant tumor mass	Dominant tumor mass		
				All	Left-dominant	Right-dominant
N	435,291	1058	294	764	401	363
Age	49.9 (12.7)	55.9 (11.3)	55.8 (11.8)	55.9 (11.1)	55.8 (11.5)	55.9 (10.8)
Height (meters)	1.6 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
BMI at age 18 (kg/m^2)	21.2 (3.1)	21.3 (2.9)	21.4 (3.2)	21.3 (2.8)	21.2 (2.8)	21.4 (2.9)
Current BMI (kg/m^2)	25.4 (5.2)	25.8 (5.0)	26.1 (5.8)	25.7 (4.7)	26.0 (4.9)	25.3 (4.5)
Ever smoker, %	45.8	45.2	52.4	42.4	41.0	43.9
Age at menarche (yrs)	12.6 (1.5)	12.8 (1.6)	12.7 (1.5)	12.9 (1.7)	12.9 (1.7)	12.9 (1.7)
Ever OC use, %	65.6	45.6	53.8	42.4	39.5	45.5
Duration of OC use (yrs)[2]	4.8 (4.7)	4.9 (4.9)	4.8 (5.2)	5.0 (4.7)	4.7 (4.4)	5.3 (4.9)
Parous, %	84.3	78.4	85.8	75.5	72.3	79.0
Parity[3]	2.7 (1.4)	2.8 (1.5)	3.0 (1.4)	2.7 (1.5)	2.7 (1.5)	2.8 (1.5)
Age at first birth[3]	25.0 (4.2)	25.4 (4.2)	25.1 (4.0)	25.6 (4.3)	25.8 (4.4)	25.3 (4.1)
Age at last birth[3]	30.3 (4.7)	30.7 (4.7)	31.2 (4.8)	30.3 (4.6)	30.3 (4.6)	30.3 (4.6)
Breastfeeding (months)[3]	10.5 (13.5)	9.3 (12.8)	9.1 (13.0)	9.4 (12.6)	8.4 (11.8)	10.4 (13.4)
Postmenopausal status, %	46.7	71.7	70.0	71.5	69.9	73.2
Age at menopause[4]	49.9 (4.2)	50.1 (3.8)	50.4 (3.6)	50.0 (3.9)	49.9 (4.0)	50.1 (3.8)
Duration HT use (years)[4]	3.3 (5.2)	2.9 (5.3)	4.4 (6.6)	2.4 (4.6)	2.2 (4.6)	2.5 (4.7)
Hysterectomy, %	12.3	13.0	15.1	12.2	11.9	12.5
Unilateral oophorectomy, %	3.9	3.5	4.4	3.1	3.7	2.5
Tubal ligation, %	16.9	9.7	15.5	7.5	7.2	7.7
Endometriosis, %[5]	4.1	6.2	6.2	6.2	5.8	6.7
Family history of breast cancer, %	17.6	14.3	16.9	13.2	12.3	14.2
Family history of ovarian cancer, %	2.4	3.3	4.5	2.9	3.0	2.7

[1] Values are mean (SD) unless otherwise indicated

[2] Among ever users

[3] Among parous women

[4] Among postmenopausal women

[5] Endometriosis data were only available in the Nurses' Health Study II, Sister Study, Swedish Mammography Cohort Study, and Women's Health Study (n=218,402 non-cases, 65 non-dominant cases, 121 left dominant cases, and 104 right dominant cases)

Table 3.

Ovarian tumor dominance by tumor characteristics in OC3

	All cases	Non-dominant tumor mass	Dominant tumor mass		
			All	Left-dominant	Right-dominant
Total N	1058	294	764	401	363
Histology					
N (%)	896 (100)	261 (100)	635 (100)	333 (100)	302 (100)
Serous, n (%)	592 (66.1)	235 (90.0)	357 (56.2)	179 (53.8)	178 (58.9)
Endometrioid, n (%)	123 (13.7)	6 (2.3)	117 (18.4)	60 (18.0)	57 (18.9)
Mucinous, n (%)	76 (8.5)	8 (3.1)	68 (10.7)	35 (10.5)	33 (10.9)
Clear cell, n (%)	72 (8.0)	3 (1.1)	69 (10.9)	47 (14.4)	22 (7.3)
Poorly differentiated, n (%)	33 (3.7)	9 (3.4)	24 (3.8)	12 (3.6)	12 (4.0)
Stage					
N (%)	819 (100)	201 (100)	618 (100)	324 (100)	294 (100)
1 (Localized), n (%)	216 (26.4)	5 (2.5)	211 (34.1)	118 (36.4)	93 (31.6)
2 (Regional), n (%)	214 (26.1)	28 (13.9)	186 (30.1)	96 (29.6)	90 (30.6)
3 (Distant), n (%)	389 (47.5)	168 (83.6)	221 (35.8)	110 (34.0)	111 (37.8)
Grade					
N (%)	751 (100)	154 (100)	597 (100)	311 (100)	286 (100)
Well-differentiated, n (%)	94 (12.5)	10 (6.5)	84 (14.1)	44 (14.2)	40 (14.0)
Moderately differentiated, n (%)	168 (22.4)	30 (19.5)	138 (23.1)	77 (24.8)	61 (21.3)
Poorly differentiated, n (%)	443 (59.0)	104 (67.5)	339 (56.8)	173 (55.6)	166 (58.0)
Undifferentiated, n (%)	46 (6.1)	10 (6.5)	36 (6.0)	17 (5.5)	19 (6.6)

Table 4.

Associations of reproductive factors with ovarian cancer risk by tumor dominance

	Hazard ratio (95% confidence interval)[1]		
Risk factors	**Dominant**	**Non-dominant**	**P-het[2]**
Parity			
Nulliparous	1.00 (ref)	1.00 (ref)	
1 child	0.78 (0.61, 1.02)	0.80 (0.48, 1.34)	
2 children	0.60 (0.48, 0.74)	0.83 (0.56, 1.24)	
3 children	0.53 (0.43, 0.67)	0.92 (0.61, 1.37)	
≥4 children	0.44 (0.34, 0.55)	0.80 (0.52, 1.21)	
Per 1 child	0.85 (0.81, 0.89)	0.97 (0.90, 1.04)	0.004
Tubal ligation			
No	1.00 (ref)	1.00 (ref)	
Yes	0.74 (0.56, 0.99)	1.13 (0.80, 1.60)	0.07
Hysterectomy[3]			
No	1.00 (ref)	1.00 (ref)	
Yes	0.76 (0.60, 0.95)	0.80 (0.58, 1.10)	0.79
Endometriosis			
No	1.00 (ref)	1.00 (ref)	
Yes	1.74 (1.00, 3.00)	1.12 (0.40, 3.15)	0.45
Age at menarche (yrs)			
≤11	1.00 (ref)	1.00 (ref)	
12	0.90 (0.72, 1.13)	0.94 (0.67, 1.31)	
13	0.95 (0.76, 1.18)	0.98 (0.71, 1.35)	
14	1.06 (0.83, 1.35)	0.84 (0.56, 1.27)	
≥15	0.92 (0.71, 1.20)	0.85 (0.55, 1.32)	
Per 1 year	1.00 (0.96, 1.05)	0.98 (0.91, 1.05)	0.58
Age at menopause (yrs)			
≤40	0.72 (0.40, 1.31)	0.20 (0.03, 1.50)	
>40–45	0.77 (0.55, 1.10)	0.70 (0.39, 1.27)	
>45–50	0.95 (0.76, 1.18)	0.93 (0.66, 1.32)	
>50–55	1.00 (ref)	1.00 (ref)	
>55	1.21 (0.80, 1.83)	0.99 (0.49, 1.97)	
Per 5 years	1.15 (1.03, 1.30)	1.22 (0.99, 1.48)	0.68
Age at first birth (yrs)			
<20	1.08 (0.75, 1.57)	0.74 (0.38, 1.44)	
20–<25	1.00 (ref)	1.00 (ref)	
25–<30	1.18 (0.98, 1.43)	0.69 (0.52, 0.92)	
≥30	0.93 (0.71, 1.21)	0.72 (0.48, 1.09)	
Per 1 year	1.00 (0.98, 1.02)	0.98 (0.95, 1.01)	0.28
Age at last birth (yrs)			

	Hazard ratio (95% confidence interval)[1]		
Risk factors	**Dominant**	**Non-dominant**	**P-het[2]**
<25	0.98 (0.61, 1.59)	0.72 (0.36, 1.42)	
25–<30	1.00 (ref)	1.00 (ref)	
30–<35	1.02 (0.76, 1.38)	0.85 (0.59, 1.23)	
≥35	0.81 (0.55, 1.19)	1.18 (0.77, 1.81)	
Per 1 year	0.98 (0.95, 1.01)	1.02 (0.98, 1.05)	0.11
Years since last birth			
Per 1-year	1.02 (0.99, 1.05)	0.98 (0.95, 1.02)	0.09
Breastfeeding			
Per 1-year	0.95 (0.81, 1.11)	1.06 (0.89, 1.26)	0.32

[1] Stratified by cohort and adjusted for age, parity and duration of oral contraceptive use

[2] P-heterogeneity comparing hazard ratios for all dominant tumors versus non-dominant tumors

[3] Additionally adjusted for HT use

Table 5.

Associations of exogenous hormonal factors, family history, anthropometric factors, and smoking with ovarian cancer risk by tumor dominance

	Hazard ratio (95% confidence interval)[1]		
Risk factors	**Dominant**	**Non-dominant**	**P-het[2]**
OC use			
Never	1.00 (ref)	1.00 (ref)	
Ever	0.70 (0.59, 0.83)	1.05 (0.80, 1.39)	0.01
Duration of OC use (yrs)			
Never	1.00 (ref)	1.00 (ref)	
≤1	0.78 (0.58, 1.05)	1.12 (0.75, 1.69)	
>1–5	0.69 (0.55, 0.88)	1.09 (0.77, 1.54)	
>5–10	0.70 (0.54, 0.90)	0.75 (0.48, 1.16)	
>10	0.64 (0.45, 0.90)	0.95 (0.59, 1.55)	
Per 5 years	0.85 (0.76, 0.95)	0.95 (0.80, 1.12)	0.25
Postmenopausal HT use			
Never	1.00 (ref)	1.00 (ref)	
Ever	1.46 (1.18, 1.82)	1.19 (0.87, 1.61)	0.30
Duration of postmenopausal HT use (yrs)			
Never	1.00 (ref)	1.00 (ref)	
≤5	1.26 (0.97, 1.64)	1.10 (0.75, 1.61)	
>5	1.48 (1.13, 1.94)	1.63 (1.15, 2.31)	
Per 1 year	1.03 (1.01, 1.05)	1.04 (1.02, 1.07)	0.34
Family history of breast cancer			
No	1.00 (ref)	1.00 (ref)	
Yes	1.06 (0.83, 1.36)	1.24 (0.87, 1.78)	0.49
Family history of ovarian cancer			
No	1.00 (ref)	1.00 (ref)	
Yes	1.71 (1.07, 2.75)	1.89 (1.05, 3.39)	0.80
BMI (kg/m^2)			
<20	0.95 (0.70, 1.30)	1.33 (0.85, 2.06)	
20–<25	1.00 (ref)	1.00 (ref)	
25–<30	1.16 (0.98, 1.38)	1.22 (0.93, 1.61)	
30–<35	1.13 (0.88, 1.45)	1.04 (0.69, 1.57)	
≥35	1.13 (0.79, 1.61)	1.62 (1.03, 2.57)	
Per 5 kg/m^2	1.05 (0.98, 1.14)	1.08 (0.95, 1.22)	0.76
BMI at 18 (kg/m^2)			
<18	0.91 (0.65, 1.28)	1.12 (0.69, 1.80)	
18–<20	1.00 (ref)	1.00 (ref)	
20–<22	1.01 (0.80, 1.27)	1.02 (0.72, 1.43)	
≥22	1.03 (0.82, 1.30)	1.13 (0.80, 1.58)	

Risk factors	Hazard ratio (95% confidence interval)[1]		P-het[2]
	Dominant	Non-dominant	
Per 5 kg/m^2	1.02 (0.89, 1.16)	1.07 (0.87, 1.32)	0.67
Height (m)			
<1.60	0.86 (0.70, 1.07)	0.61 (0.42, 0.89)	
1.60–<1.65	1.00 (ref)	1.00 (ref)	
1.65–<1.70	0.93 (0.77, 1.13)	1.36 (1.02, 1.82)	
≥1.70	1.12 (0.91, 1.37)	0.97 (0.69, 1.37)	
Per 0.05 m	1.08 (1.02, 1.14)	1.11 (1.02, 1.20)	0.58
Smoking			
Never	1.00 (ref)	1.00 (ref)	
Ever	0.94 (0.82, 1.09)	1.24 (0.98, 1.56)	0.06
Pack-years			
Never	1.00 (ref)	1.00 (ref)	
<10	0.94 (0.77, 1.14)	1.53 (1.15, 2.04)	
10–<20	1.02 (0.79, 1.31)	0.94 (0.61, 1.46)	
20–<35	0.80 (0.60, 1.07)	0.88 (0.56, 1.37)	
≥35	1.02 (0.76, 1.37)	1.30 (0.87, 1.94)	
Per 20 pack-yrs	0.98 (0.88, 1.09)	1.04 (0.90, 1.19)	0.56

BMI, body mass index; HT, hormone therapy; OC, oral contraceptive.

[1]Stratified by cohort and adjusted for age, parity and duration of oral contraceptive use

[2]P-heterogeneity comparing hazard ratios for all dominant tumors versus non-dominant tumors