Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2013 March ; 22(3): 429–437. doi:10.1158/1055-9965.EPI-12-1183-T.

Hormonal and reproductive risk factors for epithelial ovarian cancer by tumor aggressiveness

Elizabeth M. Poole[1,2], **Melissa A. Merritt**[2,3,*], **Susan J. Jordan**[4,5], **Hannah P. Yang**[6], **Susan E. Hankinson**[1,2,7], **Yikung Park**[6], **Bernard Rosner**[1,2], **Penelope M. Webb**[5], **Daniel W. Cramer**[3], **Nicolas Wentzensen**[6], **Kathryn L. Terry**[3], and **Shelley S. Tworoger**[1,2]

[1]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

[3]Department of Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Boston, MA, USA

[4]School of Population Health, University of Queensland, Brisbane, Queensland, Australia

[5]Queensland Institute of Medical Research, Brisbane, Queensland, Australia

[6]Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[7]School of Public Health and Health Sciences, University of Massachusetts Amherst, Amherst, MA

Abstract

Background—Approximately half of epithelial ovarian cancers are fatal within three years; however about 35% of women survive at least ten years. In the Nurses' Health Study, New England Case-Control Study, Australian Ovarian Cancer Study, and NIH-AARP Diet and Health Study, we investigated potential differences in the associations with ovarian cancer risk factors by tumor aggressiveness, defined based on time from diagnosis until death.

Methods—We calculated relative risks (RR) and 95% confidence intervals (CI) for associations of known or suspected ovarian cancer risk factors with rapidly fatal (death within three years of diagnosis) and less aggressive tumors (all others) using Cox proportional hazards competing risks analysis (NHS, AARP) or polytomous logistic regression (NECC, AOCS). Results were combined using random effects meta-analysis.

Results—Increasing age was associated with greater risk of rapidly fatal versus less aggressive disease (OR, 5-yr increase: 1.39; 95% CI: 1.29–1.49 vs. OR: 1.09; 95% CI: 1.03–1.16, respectively; p-diff<0.0001). OC use was associated with a greater decreased risk of rapidly fatal (OR, 5-yr increase: 0.69; 95% CI: 0.58–0.82) versus less aggressive disease (OR: 0.81; 95% CI: 0.74–0.89; p-diff=0.002). Conversely, increasing parity was associated only with less aggressive disease (OR, per child: 0.87; 95% CI: 0.81–0.93).

Conclusion—In this analysis of 4,342 cases, there were clear differences in risk factors for rapidly fatal vs. less aggressive ovarian tumors.

Correspondence: Elizabeth M. Poole, PhD, Channing Laboratory, 181 Longwood Ave, 3rd Floor, Boston, MA 02115, Phone: 617-525-2202/Fax: 617-525-2008, nhlip@channing.harvard.edu.
*Present address: School of Public Health, Imperial College, London, UK

The authors have no conflicts of interest.

Impact—Differences in risk factor associations by tumor aggressiveness suggests the developmental pathways through which the tumors develop and may be important for developing primary prevention strategies for the most aggressive cancers.

Introduction

Ovarian cancer is the fifth most common cause of cancer death among women (1). In SEER data (1988–2007), 47.1% of patients died within three years of diagnosis, but ten year survival was 34.1% (2). The wide variability in ovarian cancer survival may be due, partly, to its heterogeneity, which can be characterized by differences in histology and molecular alterations (3). Recent data suggest that high grade serous carcinomas originate in the fallopian tube rather than the ovarian surface epithelium (OSE) (3). Based on these data, ovarian tumors have been classified into three developmental pathways (3). Type 1/2 tumors include low-grade serous, mucinous, endometrioid, and clear cell carcinomas that arise from the OSE or from endometriotic implants, and are characterized by mutations in *KRAS*, *BRAF*, *PTEN*, or *PIK3CA*. Type 3 tumors are high-grade serous and endometrioid tumors with mutations in *TP53*; these tumors arise in the fallopian tube and have the worst prognosis (3, 4).

Ovarian cancer risk factors associations may differ by developmental pathway. However, it is not feasible to determine developmental pathway in large-scale epidemiologic studies, primarily because determining cell of origin requires extensive sectioning of the tubes and ovaries and tumor molecular profiling only recently has become cost-effective. However, the most aggressive tumors (i.e., type 3) are likely to be quickly fatal, whereas women with less aggressive tumors (i.e., types 1/2) will have longer survival. Identifying differences in risk factor associations between the most rapidly fatal vs. less aggressive cancers could improve our understanding of ovarian carcinogenesis and better target prevention. Therefore, we conducted an analysis comparing risk factor associations between women who died within three years of diagnosis to women who survived at least three years post-diagnosis in four studies.

Methods

Study populations

Nurses' Health Study—The NHS was established in 1976 among 121,700 US female RNs, aged 30 to 55 years. Women completed an initial questionnaire about lifestyle, health behaviors, and medical history, and thereafter have completed biennial questionnaires to update exposures and disease diagnoses (5). Identification and follow-up of ovarian cancer cases has been described previously (5). At baseline, we excluded women who reported prior cancer (except non-melanoma skin cancer), previous bilateral oophorectomy, radiation-induced menopause, or who had an unknown birthdate, leaving 110,493 women for analysis. Women were censored at ovarian cancer diagnosis, death, report of any other cancer, bilateral oophorectomy, or radiation-induced menopause. This study was approved by the Institutional Review Board (IRB) of Brigham and Women's Hospital (BWH).

NIH-AARP Diet and Health Study—The AARP was established in 1995–1996 by inviting 3.5 million AARP members aged 50–71 years in six states and two metropolitan areas to complete a baseline questionnaire on diet, demographics, reproductive, and medical history (6). Identification of ovarian cancer cases has been described previously (6). We excluded study participants who used a proxy respondent, were male, reported prior cancer, bilateral oophorectomy/unknown oophorectomy status, developed borderline or non-epithelial ovarian cancer during follow-up, or had no follow-up information, leaving

153,180 women for analysis. The AARP study was approved by the National Cancer Institute's Special Studies IRB.

Australian Ovarian Cancer Study—The AOCS is an Australia-wide population-based case-control study of 1,861 ovarian cancer cases and 1,509 controls recruited in 2002–2006 (7). Controls were matched to cases on age and state of residence. Participants completed a health and lifestyle questionnaire about exposures one year prior to diagnosis (cases) or the previous 12 months (controls) (7). This analysis was limited to invasive cases (N=1,247) with known vital status. Ethics approval was received from the Human Research Ethics Committees at the Queensland Institute of Medical Research, Peter MacCallum Cancer Centre, University of Melbourne, and participating hospitals and cancer registries.

NECC—Details regarding enrollment of cases and controls in the New England Case-Control Study of ovarian cancer are described elsewhere (8). Briefly, 2,203 cases and 2,100 controls, matched to cases on age and state of residence, were interviewed in-person about exposures to known and suspected ovarian cancer risk factors that occurred at least one year before diagnosis (cases) or more than one year before the interview date (controls). This analysis was limited to 1,642 invasive cases. The study was approved by the BWH and Dartmouth Medical School IRBs.

Case definition—Invasive ovarian cancer cases were divided into two groups based on time between diagnosis and death. Rapidly fatal cases died due to ovarian cancer within three years of diagnosis, except in the NECC, where rapidly fatal cases died due to any cause within three years, as cause of death was unavailable. In the NHS, <3% of cases died due to other causes within three years. Less aggressive cases died from other causes within three years of diagnosis, died more than three years post-diagnosis, or did not die during follow-up. Cases had to have at least three years of follow-up post-diagnosis. Borderline ovarian cancers were excluded from this analysis.

Exposure definition—Analytic exposures included age, parity, oral contraceptive (OC) use, tubal ligation, family history of breast or ovarian cancer, intrauterine device (IUD) use, hysterectomy, age at menarche and natural menopause, height, body mass index (BMI), menopausal status, age at first birth, and smoking. In the NHS and NECC, we also investigated estimated lifetime number of ovulatory cycles, calculated as current age (if premenopausal) or age at natural menopause minus age at menarche, years of OC use, and parity (1 year per pregnancy). In the NHS, we analyzed type and duration of post-menopausal hormone (PMH) use. AARP did not contribute data on timing of OC use, tubal ligation, family history of ovarian cancer, or IUD use. For AARP variables that were collected in categories, the median of the category was assigned to create a "continuous" variable. As a sensitivity analysis, we also meta-analyzed study-specific results excluding the AARP when that study only had data in categories.

Statistical Methods

For the cohort studies, we used Cox proportional hazards competing risks analysis (SAS v9.2) to calculate relative risks (RR) and 95% confidence intervals (CI); for the case-control studies, odds ratios (OR) and 95% CI were calculated using polytomous logistic regression (STATA v9). For AARP, baseline exposures were analyzed; exposures were not updated until 2004, when most of the cases had already occurred. For NHS, exposures were updated whenever new data were obtained. In the NHS, NECC, and AOCS, models were adjusted for age, parity, duration of OC use, tubal ligation, duration of breastfeeding, family history of ovarian cancer, and menopausal status. The case-control studies were additionally

adjusted for matching factors. AARP analyses were adjusted for age, parity, duration of OC use, and menopausal status.

To combine RRs across studies, we used random-effects meta-analysis. P-values for heterogeneity among the studies were calculated using the Q statistic (referred to as p-het). To calculate a p-value for differences between rapidly fatal vs. less aggressive ovarian cancer, we calculated a Z-score by taking a weighted average of the differences in the betas for rapidly fatal and less aggressive disease (referred to as p-diff). Weights were the inverse of the variance of the difference in betas.

Sensitivity analyses (NHS and NECC)

Since the selection of a three-year cutoff was based on mortality trends in the NHS (data not shown), we conducted analyses using five and ten years post-diagnosis to distinguish the case groups. Also, to evaluate confounding by tumor histology or stage, we conducted analyses restricted to serous or stage III tumors. We also adjusted the RRs for stage by fitting a competing risks model with four case groups (rapidly fatal/low stage, rapidly fatal/high stage, less aggressive/low stage, less aggressive/high stage) and calculating a weighted average of the associations across stage (9). Also, although we did not have grade, treatment, and debulking information in all studies, the NECC had this information on a subset of cases, in which we adjusted for these factors. We also planned to adjust for chemotherapy, but over 85% of the cases received platinum-based therapy, indicating that potential confounding by chemotherapy was limited. Additionally, because case-control studies may not include the most aggressive cases, we compared NHS cases that were fatal within 1.5 years of diagnosis with cases that died 1.5–3 years post-diagnosis (Supplemental Tables 1–5).

Results

Compared to less aggressive cases, rapidly fatal cases were older and tended to have shorter duration of OC use (Table 1). Rapidly fatal cancers were more likely to be high stage cancers with serous histology. However, the majority of less aggressive cases were also high stage and serous histology.

We observed marked differences in the association between the two case groups for age, parity, and OC use (Table 2). Increasing age was more strongly associated with rapidly fatal disease (RR, 5-year increase: 1.39; 95% CI: 1.29–1.49) than less aggressive disease (RR: 1.09; 95% CI: 1.03–1.16; p-diff<0.0001). Similarly, the inverse association with OC use was stronger for rapidly fatal disease (RR, 5-year increase: 0.69; 95% CI: 0.58–0.82) than less aggressive disease (RR: 0.81; 95% CI: 0.74–0.89; p-diff=0.002). OC use within the last 20 years was associated with a significantly decreased risk of rapidly fatal (RR: 0.48; 95% CI: 0.38–0.61), but not less aggressive disease (RR: 0.86; 95% CI: 0.72–1.03; p-diff<0.0001). There were no differences for OC use more than 20 years ago. When recency and duration of OC use were combined, the strongest difference in association was observed for use for more than 5 years within the last 20 years (p-diff<0.0001).

In contrast, less aggressive disease was more strongly associated with parity. Among parous women, each birth was associated with a 13% decreased risk (95% CI: 0.81–0.93) for less aggressive disease compared to a 2% decreased risk for rapidly fatal disease (95% CI: 0.94–1.03; p-diff<0.0001). The reduction in risk for the first birth was similar between the two groups (RR: rapidly fatal: 0.82; RR: less aggressive: 0.78; p-diff=0.07). We also observed that being post-menopausal (vs. pre-menopausal) was associated with a 53% increased risk of rapidly fatal disease (95% CI: 1.24–1.89), but a non-significant decreased risk of less aggressive disease (RR: 0.88; 95% CI: 0.74–1.05; p-diff<0.0001). We observed no

differences in association by tumor aggressiveness for duration of breastfeeding, tubal ligation, family history of breast or ovarian cancers, IUD use, hysterectomy, age at first birth, age at menarche, age at menopause, height, BMI, or smoking status (Tables 2 and 3).

In the NHS and NECC, a 5-year increase in ovulatory years was associated with a greater increased risk of rapidly fatal disease (RR: 1.34; 95% CI: 1.16–1.55) than less aggressive disease (RR: 1.23; 95% CI: 1.17–1.29; p-diff=0.001). In the NHS, ever use of estrogen plus progesterone was not associated with rapidly fatal disease (RR: 0.90; 95% CI: 0.65–1.26), but was associated with an increased risk of less aggressive disease (RR: 1.39; 95% CI: 1.06–1.82; p-diff=0.04). Ever use of unopposed estrogen was associated with increased risk of both tumor types.

Discussion

We observed clear differences in the associations of ovarian cancer risk factors by tumor aggressiveness among 4,342 ovarian cancer cases. Specifically, older women and women who never used OCs were at a greater increased risk of rapidly fatal disease. By contrast, increasing parity was associated with decreased risk of less aggressive disease. Importantly, although the studies varied in design, geographic location, and timing, we generally observed highly consistent results, suggesting that the observed differences are robust.

No previous study has compared risk factors for ovarian cancer by tumor aggressiveness. In general, our findings of increased risk of fatal ovarian cancer with increasing age is consistent with SEER data showing poorer ovarian cancer survival with increasing age.(2) In addition, several groups have examined incidence of fatal ovarian cancer. Tubal ligation was associated with decreased risk of fatal ovarian cancer in the one cohort study (10), which is consistent with our findings, although four studies (11–14) of fatal disease observed no association. Additionally, a higher number of ovulatory years was associated with decreased survival in one study (13), but not in another (14). Parity and OC use generally have not been associated with ovarian cancer survival (14–17); however, among post-menopausal women, having ≥ 8 children was associated with decreased ovarian cancer mortality (18). We observed significant differences in ovarian cancer risk by tumor aggressiveness for parity and OC use, suggesting that these factors may influence a tumor's developmental pathway.

Several studies have examined differences by histologic subtype. In general no differences have been observed for OC use (19–21), although the Oxford Collaborative Group on Epidemiological studies of Ovarian Cancer reported that OC use was not associated with risk of mucinous tumors (22). However, although a pooled analysis of 10 case-control studies, including the NECC, observed no differences in association with parity (19); increasing parity was more protective for endometrioid cancers in the NHS (20) and for non-serous tumors in the AARP (21). Previous findings for parity and risk of non-serous tumors are consistent with the current study, as less aggressive tumors are more likely to be non-serous. However, that most studies reported no difference in the association with OC use by tumor histology suggests that the observed protection against more aggressive tumors is not driven through histology.

The factors most strongly inversely related to developing rapidly fatal cancer in our study, i.e. long duration of OC use and fewer lifetime ovulatory cycles, suggest that the effects of ovulation, such as wound healing or chronic inflammation, may drive an ovarian tumor towards an aggressive phenotype. However, it is unclear why increasing parity was associated only with decreased risk of less aggressive cancers. Compared to long-term OC use, each birth involves a shorter interruption of ovulation; thus parity may be acting

through another mechanism. A Finnish cohort of grand multiparous women (≥ 5 births) was at decreased risk of ovarian cancer compared to the general Finnish population, but there was no evidence of decreasing risk with increasing parity (23), suggesting that each pregnancy does not have the same effect on ovarian cancer risk. Further, in a pooled analysis of eight case-control studies, including the NECC, a history of multiple births (among parous women) was associated with decreased risk of non-mucinous ovarian cancers (24). Given that progesterone levels increase during pregnancy, and are higher in multiple pregnancies (25, 26), these findings suggest a potential role for progesterone in preventing less aggressive ovarian cancers.

A limitation of this study was that we could not account for grade or treatment, except in a subset of women. Treatment, especially cytoreductive surgery, is an important determinant of survival (27). It is possible that our categorization of cases is a proxy for treatment or that our results are confounded by treatment. However, in the NECC, we examined chemotherapy and debulking status among patients with this information (N=607). We observed no difference in chemotherapy regimens between rapidly fatal and less aggressive tumors (data not shown), suggesting that tumor aggressiveness is not a proxy for chemotherapy. Further, we observed that adjusting for debulking status had little impact on the observed differences by case group (Supplemental Table 5). We also observed no differences in analyses limited to stage III or serous tumors, suggesting that tumor characteristics are not important confounders. Similarly, when we adjusted for tumor grade in the NECC (Supplemental Table 6), our results were largely unchanged, suggesting that our observations were not driven through differences in tumor grade between the two case groups.

Additionally, case-control studies may not include the most aggressive cases due to delays in recruitment. To address this, we compared NHS women who died within 1.5 vs. 1.5–3 years post-diagnosis (Supplemental Table 4). We observed no differences between the two groups, except for PMH use. Also, AARP lacked information on several exposures, including PMH type, limiting our sample size for some analyses. However, when AARP was excluded, we had 1,168 rapidly fatal and 2,519 less aggressive cases, ensuring adequate power for all analyses. In addition, for some variables, such as parity and duration of OC use, the AARP study collected data in categories; we applied the median of each category to make “continuous’ variables. To evaluate whether this difference in the way data were collected impacted heterogeneity across studies, we also conducted a sensitivity analysis excluding the AARP for these variables (Supplemental Table 7); in general, the associations were similar when we included or excluded AARP, but heterogeneity across studies was reduced.

The ideal classification of tumors in this study would have been to combine histology, grade, cell of origin (fallopian tube vs. ovary), and mutational profile to determine each tumor’s carcinogenic pathway. However, this is not feasible in large-scale epidemiologic studies, in which tumor tissue is limited, grade is not commonly reported, and tumor mutational status is often unknown. In a recent study in three Danish cohorts, in which carcinogenic pathway was determined using histology, grade, and mutational status, type 3 tumors had a median survival of about 2.5 years vs. 6 years for type 1/2 (4), suggesting that classifying tumors by time to death may be a useful proxy for carcinogenic pathway. However, even if our system is not a good proxy for carcinogenic pathway, we observed clear differences between tumors classified by time to death, an endpoint that is crucial to ovarian cancer patients. Our observation of differences between the two groups demonstrates that pre-diagnostic exposures can have important impacts on ovarian cancer survival, possibly by driving the tumor’s carcinogenic pathway. Although increasing parity and OC use cannot be recommended on a population level for ovarian cancer prevention, if

we can identify modifiable factors that prevent the most aggressive cases, then we will gain insight into ovarian cancer biology and improve prevention. Thus, this study provides proof of principle that there are differences in risk by ovarian tumor aggressiveness. Future research should apply this classification system to other potential risk factors.

The strengths of this study include its large sample size and detailed information on ovarian cancer risk factors. Additionally, our sensitivity analyses demonstrate the robustness of our results. Our findings that the associations with age and OC use are stronger for rapidly fatal tumors suggest biological differences independent of histologic subtype. This has important implications for ovarian cancer prevention because OCs are not prescribed in post-menopausal women and the protective effect of OC use lessens after cessation (22); thus, there is no known effective prevention strategy among older women, who have the highest incidence of aggressive disease.

In conclusion, we observed clear differences in risk for rapidly fatal vs. less aggressive disease by age, parity, OC use, and PMH use, even when accounting for tumor characteristics. These findings have important implications for preventing the most aggressive forms of ovarian cancer. Future research should validate our classification system against the carcinogenic pathway. Additional studies should evaluate modifiable risk factors, including diet and physical activity, by tumor aggressiveness; identification of population-level modifiable risk factors for rapidly fatal ovarian cancer could have dramatic effects on the incidence of this fatal disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The NECC study thanks Allison Vitonis, Cameron Fraer and Mary De Pari. The NHS investigators thank the following state cancer registries: 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, and WY. The AOCS gratefully acknowledges the Australian Ovarian Cancer Study Group.

Sources of financial support:

NHS: National Cancer Institute grants P01 CA87969 and R03 CA143928. Dr. Poole is supported by National Cancer Institute grant T32 CA009001.

AARP: Drs. Yang, Park, and Wentzensen are supported by the Intramural Research Program of the National Institutes of Health.

AOCS: US Army Medical Research and Materiel Command DAMD17-01-1-0729, the Cancer Councils of New South Wales, Queensland, South Australia, Tasmania, and Victoria, the Cancer Foundation of Western Australia and grants No. 199600 and 400413 from the National Health and Medical Research Council of Australia. Drs. Jordan and Webb are supported by fellowships from the National Health and Medical Research Council of Australia.

NECC: National Cancer Institute grants R01 CA54419, P50 CA105009, and Department of Defense grant W81XWH-10-1-0280. Dr. Merritt is supported by National Cancer Institute grant R25 CA098566.

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Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 March 01.

Table 1

Characteristics of the study populations by tumor aggressiveness

	AARP[a]		AOCS[a]		NECC[a]		NHS[a]	
	Rapidly fatal[b] (n=240)	**Less aggressive[b] (n=415)**	**Rapidly fatal[b] (n=447)**	**Less aggressive[b] (n=800)**	**Rapidly fatal[b] (n=361)**	**Less aggressive[b] (n=1281)**	**Rapidly fatal[b] (n=360)**	**Less aggressive[b] (n=438)**
Means (SD)								
Age	63.3 (5.0)	62.2 (5.5)	62.2 (10.1)	58.4 (11.0)	57.3 (10.2)	53.7 (11.3)	62.8 (9.8)	61.0 (10.1)
Years of OC use	NA		4.3 (6.1)	4.8 (6.1)	1.7 (3.2)	2.4 (4.1)	1.0 (2.6)	1.6 (3.0)
Years of breastfeeding(parous only)	NA		0.9 (0.9)	0.9 (1.0)	0.5 (1.1)	0.5 (0.9)	0.3 (0.6)	0.4 (0.7)
BMI	27.2 (6.2)	26.2 (5.5)	26.9 (5.8)	27.0 (5.7)	26.6 (6.2)	26.4 (6.2)	25.7 (5.6)	26.0 (5.1)
Percentages								
Parous	83	80	84	82	77	69	89	89
Tubal ligation	NA		24	22	15	13	11	11
Hysterectomy	23	30	22	26	8	10	23	21
Family history of breast cancer	15	12	15	16	17	17	11	13
Family history of ovarian cancer	NA		4	5	5	5	4	5
Smoking status								
Former smoker	36	36	25	26	36	37	37	40
Current smoker	10	13	15	30	19	16	18	15
Stage								
I/II	0	11	8	38	11	45	9	41
III/IV	66	55	92	62	74	42	86	56
Unknown	34	34	1	0	16	12	4	2
Tumor histology								
Serous	54	54	73	62	76	46	73	59
Mucinous	3	5	1	4	2	7	6	6
Endometrioid	5	12	3	15	9	23	9	21
Clear cell	3	4	6	8	8	17	3	5
Other histologies	17	13	18	12	5	5	6	5
Unknown	18	12	0	0	1	2	4	3

[a]Abbreviations used: AARP: NIH-AARP Diet and Health Study; AOCS: Australian Ovarian Cancer Study; NECC: New England Case-Control Study; NHS; Nurses' Health Study

[b] Rapidly fatal: Death due to ovarian cancer within 3 years of diagnosis (NECC: death due to any cause within 3 years). Less aggressive: Case did not die of ovarian cancer within 3 years.

Table 2

Associations between known ovarian cancer risk factors and risk of rapidly fatal vs. less aggressive ovarian tumors[a]

	Rapidly fatal ovarian cancer[b]					Less aggressive ovarian cancer[b]					
Exposure	**AARP N=240 RR**	**AOCS N=447 OR**	**NECC N=361 OR**	**NHS N=360 RR**	**meta-analysis RR (95% CI)**	**AARP N=415 RR**	**AOCS N=800 OR**	**NECC N=1281 OR**	**NHS N=438 RR**	**meta-analysis RR (95% CI)**	**p-diff between outcomes[c]**
Age[d]	1.32	NA[d]	NA[d]	1.42	**1.39** (1.29–1.49)	1.06	NA[d]	NA[d]	1.11	**1.09** (1.03–1.16))	**<0.0001**
Parity											
Ever vs. Never	0.96	0.73	1.06	0.57	**0.82** (0.62–1.08)	1.01	0.64	0.71	0.86	**0.78** (0.65–0.95)	0.07
Number of children[e]	0.96	1.02	0.93	1.02	**0.98** (0.94–1.03)	0.90	0.99	0.80	0.91	**0.87** (0.81–0.93)	**<0.0001**
Duration of breastfeeding[f]	NA	0.78	0.85	0.72	**0.80** (0.73–0.87)	NA	0.80	0.82	0.93	**0.84** (0.78–0.90)	0.45
Oral contraceptive use											
Ever vs. Never	0.86	0.79	0.50	0.70	**0.69** (0.55–0.88)	0.75	1.05	0.68	1.06	**0.86**[g] (0.68–1.09)	**0.0003**
Duration of OC use[d]	0.83	0.76	0.55	0.65	**0.69**[g] (0.58–0.82)	0.82	0.80	0.74	0.96	**0.81** (0.74–0.89)	**0.002**
Time since last OC use											
Never use	NA	ref.	ref.	ref.	**1.00** (ref.)	NA	ref.	ref.	ref.	**1.00** (ref.)	
≤20 years		0.48	0.40	0.57	**0.48** (0.38–0.61)		0.81	0.85	0.90	**0.86** (0.72–1.03)	**<0.0001**
>20 years		0.83	0.86	0.77	**0.82** (0.70–0.96)		0.89	0.90	1.14	**0.97** (0.83–1.13)	0.10
OC Duration combined with time since last use											
Never use	NA	ref.	ref.	ref.	**1.00** (ref.)	NA	ref.	ref.	ref.	**1.00** (ref.)	
Use for < 5 years less than 20 years ago		0.34	0.32	0.78	**0.46** (0.24–0.86)		0.93	0.65	1.02	**0.83** (0.61–1.11)	**0.001**
Use for < 5 years 20+ years ago		0.81	0.83	0.76	**0.80** (0.67–0.95)		0.93	0.88	1.11	**0.95** (0.83–1.08)	0.10
Use for 5+ years less than 20 years ago		0.47	0.22	0.30	**0.31** (0.19–0.51)		0.72	0.49	0.74	**0.60** (0.45–0.81)	**<0.0001**
Use for 5+ years 20+ years ago		0.81	0.46	0.51	**0.58** (0.40–0.85)		0.78	0.47	1.04	**0.72**[g] (0.44–1.15)	0.45
Tubal ligation (ever vs. never)	NA	0.86	0.87	0.80	**0.85** (0.71–1.01)	NA	0.76	0.70	0.76	**0.73** (0.64–0.84)	0.15
Family history of ovarian cancer (yes vs. no)	NA	1.38	1.83	1.31	**1.50** (1.07–2.10)	NA	1.94	1.98	1.62	**1.85** (1.44–2.37)	0.28
Family history of breast cancer (yes vs. no)	1.27	1.72	1.30	1.12	**1.29** (1.08–1.53)	1.01	1.72	1.21	1.30	**1.23** (1.04–1.44)	0.68

[a]Adjusted for age, parity, duration of breastfeeding, duration of oral contraceptive use, tubal ligation, family history of ovarian cancer, and menopausal status. AARP models adjusted for age, parity, duration of OC use, and menopausal status.

[b] Rapidly fatal: Death due to ovarian cancer within 3 years of diagnosis (NECC: death due to any cause within 3 years). Less aggressive: Case did not die of ovarian cancer within 3 years.

[c] P-value for a Z-score calculated by taking a weighted average of the differences in the betas for rapidly fatal and less aggressive disease. Weights were the inverse of the variance of the difference in betas.

[d] Per 5 year increase; results are not shown for case-control studies because age was a matching factor.

[e] Per 1 child increase among parous women

[f] Per 1 year increase among parous women

[g] P-hetergeneity between studies <0.01

Table 3

Associations between potential ovarian cancer risk factors and risk of rapidly fatal vs. less aggressive ovarian cancer[a]

	rapidly fatal	less aggressive	
Exposure	**RR[b] (95% CI)**	**RR[b] (95% CI)**	**p-diff between outcomes**
IUD use (ever vs. never)	**0.86** (0.70–1.05)	**0.95** (0.83–1.10)	0.44
Hysterectomy (yes vs. no)	**1.00** (0.86–1.16)	**1.15** (0.99–1.34)	0.06
Age at menarche			
<12	**0.99** (0.82–1.18)	**1.05** (0.91–1.21)	0.50
12	**0.91** (0.63–1.31)	**1.01** (0.89–1.15)	0.19
13	**1.00** (ref.)	**1.00** (ref.)	
14	**1.04** (0.85–1.28)	**0.96** (0.82–1.13)	0.63
15+	**0.95** (0.76–1.18)	**0.77** (0.63–0.94)	0.18
Age at natural menopause (per 5 year increase)	**1.11** (1.00–1.24)	**1.02** (0.92–1.13)	0.14
Height (per 5 cm increase)	**1.01** (0.96–1.06)	**1.00** (0.96–1.03)	0.81
BMI			
<20	**1.11** (0.88–1.39)	**0.97** (0.80–1.17)	0.30
20–<22	**0.80** (0.66–0.97)	**0.96** (0.77–1.20)	0.11
22–<25	**1.00** (ref.)	**1.00** (ref.)	
25–<27	**0.91** (0.75–1.09)	**0.99** (0.86–1.14)	0.47
27–<30	**0.89** (0.74–1.07)	**0.92** (0.78–1.07)	0.54
30–<35	**0.96** (0.79–1.16)	**1.07** (0.92–1.23)	0.55
35+	**1.19** (0.78–1.81)	**1.01** (0.74–1.37)	0.35
Menopausal status (Post vs. pre/unknown)	**1.53** (1.24–1.89)	**0.88** (0.74–1.05)	**<0.0001**
Age at first birth (per 5 year increase)	**0.87**[c] (0.70–1.06)	**0.92** (0.83–1.02)	0.59
Smoking status			
Former vs. never	**0.97** (0.85–1.10)	**1.00** (0.89–1.12)	0.62
Current vs. never	**1.21** (0.84–1.75)	**1.12** (0.94–1.33)	0.16

[a]Adjusted for age, parity, duration of breastfeeding, duration of oral contraceptive use, tubal ligation, family history of ovarian cancer, and menopausal status. AARP models adjusted for age, parity, duration of OC use, and menopausal status.

[b]RR and 95% CI from meta-analysis;

** AARP did not contribute data to the IUD use analysis.

C P-hetergeneity between studies <0.01