Title:

Offspring sex and risk of epithelial ovarian cancer: a multinational pooled analysis of 12 case-control studies

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ABSTRACT

BACKGROUND: While childbearing protects against risk of epithelial ovarian cancer (EOC), few studies have explored the impact on maternal EOC risk of sex of offspring, which may affect the maternal environment during pregnancy.

METHODS: We performed a pooled analysis among parous participants from 12 case-controls studies comprising 6,872 EOC patients and 9,101 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression for case-control associations and polytomous logistic regression for histotype-specific associations, all adjusted for potential confounders.

RESULTS: In general, no associations were found between offspring sex and EOC risk. However, compared to bearing only female offspring, bearing one or more male offspring was associated with increased risk of mucinous EOC (OR=1.45; 95%CI=1.01-2.07), which appeared to be limited to women reporting menarche before age 13 compared to later menarche (OR=1.71 vs 0.99; P-interaction=0.02). Bearing increasing numbers of male offspring was associated with greater risks of mucinous tumors (OR=1.31, 1.84, 2.31, for 1, 2 and 3 or more male offspring, respectively; trend-p = 0.005). Stratifying by hormonally-associated conditions suggested that compared to bearing all female offspring, bearing a male offspring was associated with lower risk of endometrioid cancer among women with a history of adult acne, hirsutism, or polycystic

ovary syndrome (OR=0.49, 95%CI=0.28-0.83) but with higher risk among women without any of those conditions (OR=1.64 95%CI=1.14-2.34; P-interaction=0.003).

CONCLUSION: Offspring sex influences the childbearing-EOC risk relationship for specific histotypes and conditions. These findings support the differing etiologic origins of EOC histotypes and highlight the importance of EOC histotype-specific epidemiologic studies. These findings also suggest the need to better understand how pregnancy affects EOC risk

INTRODUCTION

Ovarian cancer is the fifth most common cancer among women in developed countries and the most fatal gynecological malignancy(1). In 2018, more than 295,000 women were newly diagnosed with the disease and over 185,000 women died from it worldwide(1). More than 70% of cases are diagnosed at late stages when 5-year survival is less than 30%(2). This high fatality coupled with the lack of a screening test for early detection(3) makes it critical to understand risk factors in order to help inform prevention strategies(4).

Ever bearing children is associated with about a 30% decrease in risk of epithelial ovarian cancer (EOC) in general (5) and increasing parity increases protection (6), although the magnitudes of the relationship vary by histotype (7, 8). The exact mechanism underlying the protective effect of pregnancy remains unknown, although it is frequently attributed to ovulation suppression that accompanies pregnancy(9). However, an ovulation alone cannot explain the magnitude of the protective effect(10), suggesting that other pregnancy-associated factors may impact EOC risk. Alterations in the maternal hormonal and immune milieus may be such factors(11-13). Fetal sex potentially affects these environments during pregnancy(14-21), can impact maternal physiology(22, 23), and is associated with conditions that have long-term maternal health consequences(24, 25). Together these data support the possibility that offspring sex may impact maternal EOC risk.

Few epidemiologic studies have explored the relationship between offspring sex and EOC, and results have been inconsistent(26-30). Methodological limitations including small sample sizes overall and for specific histotypes may account for these disparate findings. EOC is a heterogeneous disease consisting of distinct histotypes exhibiting varied risk factor profiles(8) and likely having distinct etiologic pathways(31). The main aim of this study was to evaluate the associations between offspring sex and EOC in an international collaborative investigation using pooled data from 12 case-control studies participating in the Ovarian Cancer Association Consortium (OCAC). Secondarily, we wished to evaluate associations by histotype. The large sample size of the pooled analysis enabled more robust estimates of the associations between offspring sex and EOC overall and by histotype than previously reported. In addition, the pooled analysis enabled exploration of potential interactions with hormonally-associated exposures.

METHODS

Study population

OCAC was established in 2005 to promote collaborative research on epidemiologic and genetic factors associated with EOC(32). The present analysis included participant-level data for parous women from 12 OCAC case-control studies conducted in Australia, Canada, Germany, the United Kingdom, and the United States with available information on offspring sex(33-45). Characteristics of the studies are shown in Table 1. Because offspring sex was inconsistently reported for non-singleton births across studies and because non-singleton births may differentially impact EOC risk relative to singleton births, we excluded subjects with any non-singleton births (n=528) from

current analyses, resulting in 16,343 parous women with all singleton births. We then excluded women missing covariate data (n=35) and women missing offspring sex information (n=335), resulting in a total sample of 15,973 participants for data analysis (6,872 EOC patients and 9,101 controls). All participants provided informed consent and all participating institutions obtained approval from relevant ethics committees.

Study variables

Information on offspring sex for each pregnancy lasting six months or longer (full-term) was self-reported. Based on our previous work, we classified women according to the number of male offspring(26). Ever having given birth to a boy was defined as reporting at least one male offspring among all singleton full-term births. Giving birth to all boys was defined as reporting a male offspring for each full-term, singleton pregnancy. The number of boys was calculated by summing the total number of pregnancies resulting in male offspring. The number of girls was calculated by subtracting the number of boys from the total number of full-term pregnancies. The fraction of births that were boys was defined as the total number of male offspring divided by the number of full-term pregnancies.

Information on other relevant variables and potential confounders was obtained from the OCAC core dataset and included age at diagnosis (cases) or interview (controls), race, education, body mass index (BMI) at 18 years of age, recent BMI (defined as previously reported as BMI 1 year prior or 5 year prior to diagnosis/interview or at

diagnosis/interview(46)), total duration of oral contraceptive (OC) use, number of full-term pregnancies (parity), family history of ovarian or breast cancer, smoking status, and history of endometriosis, adult acne, hirsutism, polycystic ovary syndrome (PCOS), and irregular periods.

Statistical analysis

We used unconditional logistic regression to estimate odds ratios (ORs) and their 95% confidence intervals (95%CIs) for associations between bearing male offspring and EOC risk among parous women. The main multivariate model was adjusted for study site, age at reference (continuous), duration of OC use (never, less than 1 year, 1-4 years, 5-9 years, 10+ years), parity (1, 2, 3, 4, 5+ offspring) and race (white, black, Asian, other). We also considered adjustment for additional ovarian cancer risk factors including education (less than high school, high school, post-high school, college graduate, post graduate), family history of ovarian or breast cancer (yes/no), history of breastfeeding (yes/no), BMI at 18 (<18.5 / 18.5-24.9 / 25-30 / >=30 kg/m^2), recent BMI (<18.5 / 18.5-24.9 / 25-30 / >=30 kg/m^2), history of endometriosis (yes/no), history of irregular periods (yes/no), history of polycystic ovary syndrome (PCOS), adult acne, or hirsutism (yes/no), smoking history (never, ever), and age at menarche (<13 years/ >=13 years). These factors did not change the association between bearing a male offspring and EOC risk in general by more than 10% and were therefore not included in final models. Where they did alter associations by more than 10%, we present both the parsimonious model and the more adjusted model.

Random effects meta-analyses across study sites of all cancer histotypes showed no evidence of heterogeneity (I^2=0.0%; p-het=0.57 Figure 1). Consequently, all analyses were performed using the pooled dataset adjusted for study site. We performed polytomous logistic regression to evaluate associations between bearing male offspring and EOC risk by the main histotypes (high-grade serous, mucinous, endometrioid, clear cell). We further stratified analyses by number of full-term births to separate associations with offspring sex from those with parity. We also explored models containing terms for total number of male and total number of female offspring and models containing terms for total number of full-term pregnancies and fraction of boys.

To identify potential interactions between offspring sex and hormonally-associated exposures for EOC in general and by specific histotypes, we performed stratified analyses by history of endometriosis (associated with excess estrogens(47) or reduced progesterone(48)), history of acne or hirsutism or PCOS (associated with excess androgens(49-51)), age at menarche less than 13 (which is associated with excess estrogens and increased ovulations(52-54)), recent BMI greater than or equal to 30 kg/m^2 (which is associated with hormonal imbalances(55, 56)), history of irregular periods (associated with hormonal dysregulation(57)), history of ever using oral contraceptives (associated with altered hormonal milieu(58-60)), and history of ever smoking cigarettes (associated with anti-estrogenic effects(61)). Interactions and linear trends were assessed with Wald statistics. Stata/SE version 15.1 (StataCorp, College

Station, TX) was used to conduct all analyses. All tests were two-sided with significance level of 5%.

RESULTS

Among parous controls, the study-specific frequency of never bearing a male offspring ranged from 17% to 31%, whereas among parous cases it ranged from 19% to 36% (Table 1). Compared to controls, women with EOC were less likely to have used OCs, had more than one child, attained a college education, reported a history of acne, hirsutism, or PCOS, and reported a history of irregular periods. Case women were more likely to have higher recent BMI, reported histories of endometriosis, and family histories of breast or ovarian cancer (Table 2).

Compared to bearing all females, ever having borne a male was not associated with EOC overall (OR=1.05; 95%CI=0.96-1.14; Table 3); however, bearing a male offspring was associated with increased risk of mucinous histotype (OR=1.25; 95%CI=1.02-1.54). This association strengthened when we further adjusted for hormonally-associated conditions (endometriosis, irregular periods, acne or PCOS or hirsutism, smoking, history of early menarche and recent BMI; OR=1.45; 95%CI=1.01-2.07). Similarly, giving birth only to boys was not associated with EOC risk overall, whereas compared to giving birth to at least one girl, bearing all male offspring was associated with increased risk of mucinous tumors (OR=1.29; 95%CI=1.07-1.55). The association was slightly strengthened when further adjusted for hormonally-associated conditions (OR=1.35;

95%CI=0.99-1.84). Increasing number of male offspring was associated with increasing risk of mucinous ovarian cancer in both the most parsimonious model (OR=1.16, 1.56, 1.55, for 1, 2 and 3 or more male offspring compared to all female offspring, respectively; trend-p = 0.006) and in a model additionally controlling for hormonally-associated conditions (OR=1.31, 1.84, 2.31, for 1, 2 and 3 or more male offspring, respectively; trend-p = 0.005). There were no associations between increasing number of male offspring and EOC risk overall or for any other histotypes.

In models including separate quantitative terms for total number of male offspring and total number of female offspring, each additional offspring was associated with about an 8% decrease in EOC risk overall regardless of whether the offspring was male (OR=0.93; 95%CI=0.90-0.96) or female (OR=0.92; 95%CI=0.89-0.95) (Table 3). While the point estimates for high-grade serous, clear cell, and endometrioid subtypes were similar for both male and female offspring, for the mucinous histotype, each additional female offspring was associated with a 12% decrease in risk (OR=0.88; 95%CI=0.81-0.96) whereas each male offspring was not associated with risk (OR=1.03; 95%CI=0.95-1.11). The results from models controlling for total number of full-term births also showed that a 25% increase in the fraction of births that were boys was associated with a 9% increase in risk of mucinous EOC (OR=1.09; 95%CI=1.03-1.16). Fraction of male births was not associated with risk of the other subtypes.

Stratifying by number of offspring (Table 3) yielded similar patterns of risk associated with increasing male offspring for the mucinous histotype. Among women with exactly one full-term birth, bearing a male offspring was associated with a 22% increased risk of mucinous cancer compared to bearing a female offspring. Among women with exactly two births, compared to bearing all female offspring, bearing exactly one male offspring was associated with a 16% increased risk of mucinous tumors, whereas bearing two male offspring was associated with a 58% increased risk (P-trend=0.01).

For mucinous histotype, we further observed interactions with age at menarche (Table 4). Compared to never giving birth to a boy, ever bearing a male offspring was associated with an increased risk of mucinous cancer among women with menarche before age 13 (OR=1.71, 95%CI=1.23-2.38) but no increased risk associated with menarche at a later age (OR=0.99, 95%CI=0.76-1.30; P-interaction=0.02). Results were similar when we examined interactions between menarche and giving birth to all boys (OR=1.55 for early menarche versus OR=1.08 for later menarche; P-interaction=0.08). Among women with menarche prior to age 13, increasing number of male offspring was associated with increasing risk of mucinous tumor (ORs for bearing 1, 2, 3+ male offspring: 1.54, 2.34, 2.24 compared to no male offspring; P-trend =0.002). Among women with later menarche no trend was observed (ORs for bearing 1, 2, 3+ male offspring: 0.94, 1.16, 1.20; P-trend=0.32; P-interaction=0.10). Consistent with this observation, each 25% increase in fraction of male offspring was associated with a significant 18% increase in mucinous cancer among women with earlier menarche but no increase in women with later menarche (P-interaction=0.01). We also observed an

interaction between age at menarche and bearing female offspring, with each female offspring associated with a significant 21% reduced risk of mucinous tumors among women with earlier menarche but little or no association among women with later menarche (OR=0.79 versus 0.94 for each female offspring in women with and without early menarche, respectively; P-interaction=0.02). There was no interaction between age at menarche and bearing male offspring (OR=1.04 versus 1.01 for each male offspring in women with and without early menarche, respectively; P-interaction=0.51).

No other interactions between hormonal-associated exposures and EOC were observed, except for self-reported history of acne or hirsutism or PCOS and risk of endometrioid cancer (Table 5). Compared to bearing all female offspring, bearing at least one male offspring was associated with reduced risk of endometrioid cancer among women with a history of any of those conditions (OR=0.49, 95%CI=0.28-0.83), but an increased risk among women with no history of any of those conditions (OR=1.64 95%CI=1.14-2.34; P-interaction=0.003). Results were similar when we examined the interaction between reported history of acne/hirsutism/PCOS and number of male offspring (ORs for bearing 1, 2 or 3+ male offspring: 0.47, 0.52, 0.47 versus 1.69, 1.59. 0.78, for women with and without this history, respectively, P-interaction=0.007). An interaction was also observed between reported history of those androgenic conditions and bearing female offspring, with each female offspring associated with reduced endometrioid cancer risk in women with no reported history compared to those with such a history (OR=0.80 vs 1.02 for each female offspring in women without and with a history, respectively; P-interaction 0.03). There appeared to be no interaction between

a history of those androgenic conditions and bearing male offspring (OR=0.82 vs 0.87 for each male offspring in women without and with a history, respectively; P-interaction=0.44).

DISCUSSION

In this pooled analysis of data from 6,872 parous women with EOC and 9,101 parous controls, sex of offspring was not associated with maternal EOC risk overall. However, bearing male offspring was associated with less protection against mucinous cancers. When examining the per-pregnancy association, offspring sex was not associated with EOC risk overall or for high-grade serous, clear cell, and endometrioid histotypes, but was associated with risk of mucinous tumors. In particular, bearing female offspring was associated with decreased risk of mucinous tumors among parous women, whereas bearing male offspring appeared to have no relation to that histotype. We observed no interactions between offspring sex and hormonally-associated exposures, except among women with mucinous tumors and menarche prior to age 13 and among women with endometrioid tumors and a history of acne, hirsutism, or PCOS. Among women with menarche before age 13, bearing male children was associated with higher risk of mucinous cancer than in women with later menarche. Among women with a history of acne, hirsutism, or PCOS, bearing male children was associated with lower risk of endometrioid cancer than in women without those conditions.

Five studies have reported the association between offspring sex and ovarian cancer risk(26-30), including two studies included in this pooled analysis (HOPE and AUS). In the HOPE Study, conducted in western Pennsylvania, USA from 2003-2008, compared to bearing all female offspring, bearing any male offspring was associated with lower risk of EOC (OR=0.92) and bearing all male offspring was associated with even lower risk (OR=0.86)(30). A earlier population-based study of 511 cases and 1136 controls conducted in eastern Pennsylvania, USA from 1994-1998 by the same group reported similar findings – relative to all female offspring, bearing all male offspring was associated with decreased EOC risk (OR=0.80)(26). These findings were supported by a nested case-control study within the population-based Swedish Fertility Register that included 7,407 women diagnosed with EOC between 1961 and 2001 and 37,658 controls(27): compared to bearing all female offspring, bearing a male child was associated with reduced EOC risk in a dose-response fashion (ORs: 0.92, 0.87, 0.82, for 1, 2 or 3+ boys, compared to all girls)(27). In contrast, the Australia-wide population-based study (AUS) conducted between 2002 and 2005 and included in this pooled analysis reported no association between offspring sex and EOC for parous women in general but a 2-fold increased risk of the mucinous histotype associated with bearing only male offspring(29). Notably, excluding AUS data from the current analysis did not appreciably affect the observed association with mucinous tumors. A population-based cohort study of 5,092 EOC cases in the Norwegian national registry also reported no EOC-offspring sex association in general(28). However, that study reported an increased risk of endometrioid tumors among women who gave birth only to

girls compared to those who gave birth only to boys (incidence ratio 1.35 based on 475 cases).

Although there are histotype differences in the magnitude of the protective effect, greater parity has consistently been associated with reduced EOC risk(7, 8), especially among non-mucinous disease; however, the mechanism underlying this association remains unknown. Two theories have dominated the literature: suppressed ovulation(9) and lowered gonadotropin levels(62). Pregnancy, regardless of fetal sex, should equally affect ovulation and gonadotropin secretion; thus, our results suggest the possibility of additional mechanisms. Reducing inflammation(12) and altering circulating steroid hormones(11) have been postulated. During pregnancy, both maternal hormonal and immune milieus differ by fetal sex. Carriage of a male fetus is associated with lower maternal levels of estradiol and hCG(14, 15, 18) and higher maternal levels of progesterone(16) and testosterone(19). While the role of hCG in EOC etiology is unclear, progesterone is believed to protect against EOC while estrogens and androgens may increase risk(11) in a histotype-specific way(20, 21). Whether the observed maternal hormonal differences by fetal sex are large enough to matter in the context of the high hormonal levels of pregnancy is unknown. Women carrying male fetuses also exhibit more proinflammatory/proangiogenic immune milieus than women carrying female fetuses(17). Pregnancy outcomes also vary by offspring sex, with preterm birth, higher birth weight, and gestational diabetes associated with males(63-65), and increased risk of maternal hypertensive disorders and asthma flares associated with females(66, 67). Genetic and metabolic profiles of the placenta also

452 vary by fetal sex(68), and both hormones and cells derived from the fetoplacental unit
453 persist in maternal circulation for years after pregnancy ends(69). Moreover, male-origin
454 microchimerism, which arises predominantly but not exclusively from fetal cells acquired
455 during pregnancy(70) and persists for decades after pregnancy(71), has recently been
456 associated with reduced rates of ovarian cancer(72). Fetal sex also influences maternal
457 physiology(22, 23), and pregnancy conditions that differ by fetal sex, such as pre-
458 eclampsia and gestational diabetes, may impact future maternal health outcomes(24,
459 25). Together, these observations suggest that fetal sex-based differences can have
460 long-term health consequences and support a potential link between offspring sex and
461 EOC risk.
462
463 Despite this apparent biologic plausibility, the results of this study did not show any
464 overall relationship between offspring sex and EOC risk. However, we did observe
465 relationships with offspring sex for the mucinous histotype in general and specifically for
466 women with menarche prior to age 13. We further observed an association for
467 endometrioid tumors in relation to maternal androgenic conditions.
468
469 It is now accepted that while pregnancy protects against EOC in general, the protection
470 varies by histotype. In the Ovarian Cancer Cohort Consortium (OCCC), ever bearing
471 offspring provided a 31% decrease in risk in general, with a greatest protection seen for
472 the clear cell histotype (RR=0.35, 95%CI:0.27-0.47) and the least protection observed in
473 the serous histotype (RR=0.81, 95%CI=0.73-0.90) (8). The Million Women Study also
474 reported a differing protective effect against EOC associated with every bearing

offspring based on histotype, with the greatest effect seen among clear cell cases and the least seen among serous cases (7). Both studies also report histotype differences based on the number of offspring. Given these differences in protective effect of pregnancy by hisotype, it is possible that the relationship between offspring sex and EOC could also vary by histotype.

Thus, while our histotype-specific observations are plausible, the underlying biologic reasons for these observations are unclear. Mucinous EOC is a relatively infrequent histotype, representing some 5-20% of cases(73); however, epidemiologic evidence supports a substantially different risk-factor profile than that of the other histotypes(74). Notably, apart from pregnancy, the relationships between hormonal exposures and mucinous tumors are less pronounced or perhaps nonexistent compared to other histotypes(74), suggesting that alteration in the hormonal milieu may not account for our mucinous-disease findings in general and among women with menarche prior to age 13. In addition to higher endogenous estrogen exposure, earlier age at menarche is associated with earlier and more prolonged ovulation(52, 53). That observation, however, cannot explain the mucinous-specific association because increasing lifetime ovulations are associated with increased ovarian cancer risk overall(75-77). Moreover, histotype-specific results show no relationship between lifetime ovulations and the mucinous subtype(77). Similarly, it is unclear why the relationship between offspring sex and endometrioid tumors should vary based on history of androgenic conditions, as endometrioid tumors are more closely associated with estrogenic exposures(78-80) and possibly higher circulating androgen levels in the post-menopause(20).

Regardless of the underlying biology, our findings underscore the need to further understand the mechanisms whereby pregnancy impacts EOC risk. Moreover, they reflect the heterogeneous etiologic nature of ovarian cancer(81), which is no longer believed to be a single disease but a group of diseases with separate etiologic origins. EOC histotypes exhibit differing clinical behavior and are believed to have different or differentially evolved cells of origin leading to distinct carcinogenic pathways(82). Epidemiologic studies further support the multifactorial origin of EOC, with most well-established risk factors exhibiting substantial heterogeneity by histotype(8, 74). Our results lend further population-based support to the distinct etiology of EOC histotypes, and in particular for that of mucinous tumors compared to the others(8, 74).

A strength of the present study is the use of participant-level data from 12 population-based case-control studies spanning three continents. The large sample size resulted in increased statistical power to examine histotype-specific associations, which individual studies could not adequately do. In addition, pooling data from population-based case-control studies with detailed lifestyle, reproductive, and medical history data enabled us to control for potential confounders and to stratify by hormonally-associated exposures, which the population-based registry studies were unable to do. The included studies were all population-based, and the majority of studies used in-person interviews to obtain data on offspring sex and other exposures, increasing the generalizability of findings. Study-specific data were carefully cleaned, harmonized, and entered into a single dataset, further increasing confidence in the quality of the data and

allowing us to adjust for a single set of standard confounders. Finally, all available OCAC studies with information on offspring sex were included, thus mitigating the possibility of publication bias.

Despite these strengths, some limitations should be considered. First, data were self-reported; thus, potential confounding variables could be influenced by case/control status, which could distort our findings. Moreover, due to missing data, we were not able to assess relationships between offspring sex and some factors that may influence ovarian cancer risk, such as age at first pregnancy. We also can not eliminate the possibility of unknown confounders influencing results. Selection bias is also a concern as controls participating in these studies may differ from cases by factors related to offspring sex or EOC risk, including unknown factors that could not be accounted for in the analyses. Validation in prospective cohorts is needed to address these concerns. Because our study population was predominately white, we could not evaluate the impact of offspring sex in non-white women and how it may differ across race. Finally, we cannot eliminate the possibility that our findings are due to chance.

In conclusion, offspring sex appears to affect differentially EOC risk based on histotype and, possibly, in combination with other host factors. Our findings support the distinct etiologic pathways among EOC histotypes and suggest that current etiologic models of EOC may be incomplete. Our findings also suggest the need to better understand how pregnancy affects EOC risk. Confirmation of these findings in prospective cohorts is

543 needed to improve our understanding of EOC etiology, thereby paving the way for new
544 avenues of prevention research for this highly fatal disease.
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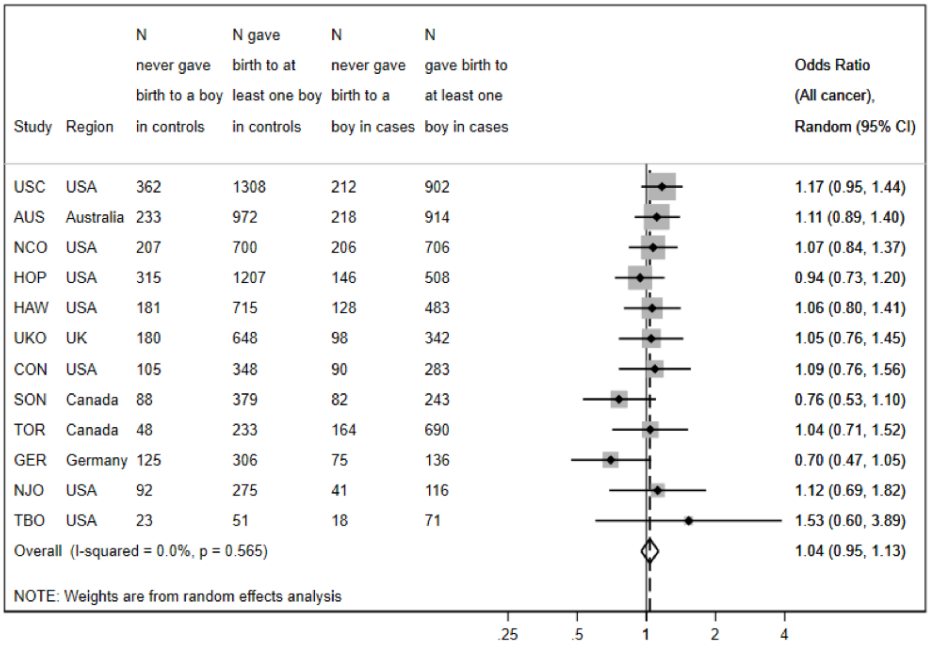
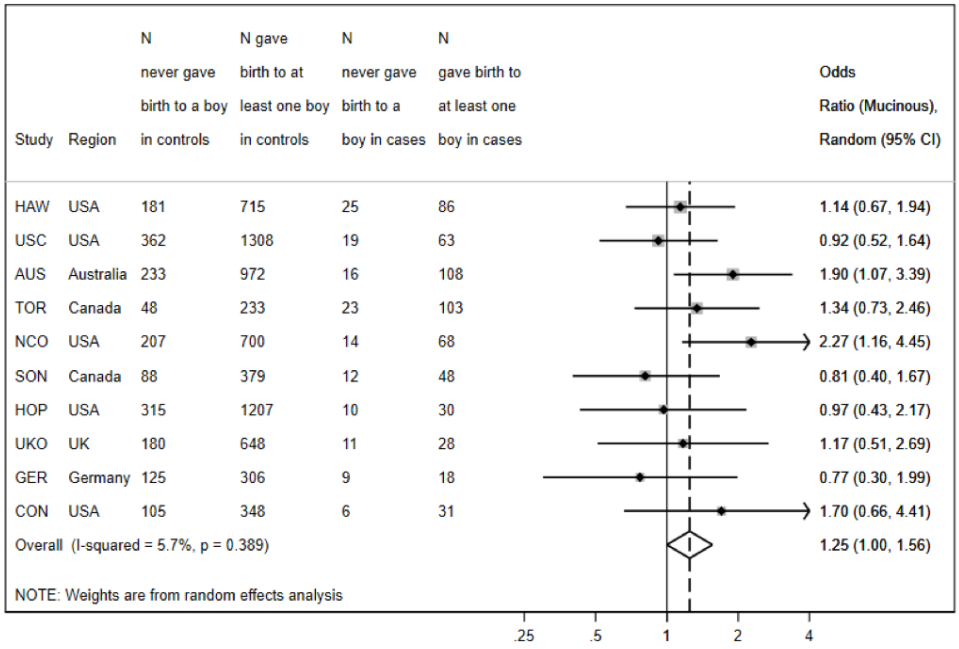
Figure 1: Association Between Offspring Sex and Epithelial Ovarian Cancer (EOC) among Participants in 12 Population-Based, Case-Control Studies in Australia, Europe, and North America from 1989-2010.

A.



B.



Footnote: Results presented according to study site and overall and are adjusted for age at diagnosis/reference date (continous), race (Black, White, Asian, Other), duration of oral contraceptive use (never, less than 1 years, 1-4 years, 5-9 years, and more than 10 years) and number of full-term pregnancies (1, 2, 3, 4, 5+).
Association for (a) EOC in general and for (b) the mucinous histotype.

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Table 1. Characteristics of the 12 Ovarian Cancer Case-Control Studies from the Ovarian Cancer Association Consortium, Conducted in Australia, Europe, and North America Between 1989 and 2010

							Response Rate %				Controls, n(%)		All cancer, n(%)			Mucinous, n(%)		
Study	Region	Study Name	Study Period	Study Type	Method of Data Collection	Matching Variables	Cases	Controls	Total number of parous women[2]	Age (years), mean (SD)	Never gave birth to a boy	Ever gave birth to a boy	Never gave birth to a boy	Ever gave birth to a boy	Adjusted OR (95% CI) model[3]	Never gave birth to a boy	Ever gave birth to a boy	Adjusted OR (95% CI) model[3]
AUS	Australia	Australian Ovarian Cancer Study	2002-2005	Population-based	Self-administered questionnaire	Age (5-year categories)	84	47	2337	57.9 (11.1)	233 (19.3)	972 (80.7)	218 (19.3)	914 (80.7)	1.11 (0.89, 1.40)	16 (12.9)	108 (87.1)	1.90 (1.07, 3.39)
CON	USA	Connecticut Ovarian Cancer Study	1998-2003	Population-based	In-person interview	Age (3 age groups: 35-49 years, 50-64 years, and 65-79 years)	69	61	826	55.70 (10.96)	105 (23.2)	348 (76.8)	90 (24.1)	283 (75.9)	1.09 (0.76, 1.56)	6 (16.2)	31 (83.8)	1.70 (0.66, 4.41)
GER	Germany	Germany Ovarian Cancer Study	1993-1996	Population-based	Self-administered questionnaire	Age and study region	58	51	642	56.3 (10.6)	125 (29.0)	306 (71.0)	75 (35.6)	136 (64.5)	0.70 (0.47, 1.05)	9 (33.3)	18 (66.7)	0.77 (0.30, 1.99)
HAW	USA	Hawaii Ovarian Cancer Case-Control Study	1993-2008	Population-based	In-person interview	Age (5-year categories, race/ethnicity)	78	80	1507	56.5 (13.9)	181 (20.2)	715 (79.8)	128 (21.0)	483 (79.0)	1.06 (0.80, 1.41)	25 (22.5)	86 (77.5)	1.14 (0.67, 1.94)
HOP	USA	Hormones and Ovarian Cancer Prediction Study	2003-2008	Population-based	In-person interview	Age (5-year categories), Race, Telephone prefix	71	68	2176	59.4 (12.4)	315 (20.7)	1207 (79.3)	146 (22.3)	508 (77.7)	0.94 (0.73, 1.20)	10 (25.0)	30 (75.0)	0.97 (0.43, 2.17)
NCO	USA	North Carolina Ovarian Cancer Study	1999-2008	Population-based	In-person interview	Age (5-year categories, race/ethnicity)	67	60	1819	56.5 (11.0)	207 (22.8)	700 (77.2)	206 (22.6)	706 (77.4)	1.07. (0.84, 1.37)	14 (17.1)	68 (82.9)	2.27 (1.16, 4.45)
NJO	USA	New Jersey Ovarian Cancer Study	2002-2008	Population-based	In-person interview	No matching	47	40	524	62.4 (11.1)	92 (25.1)	275 (74.9)	41 (26.1)	116 (73.9)	1.12 (0.69, 1.82)	2 (40.0)	3. (60.0)	-
SON	Canada	Southern Ontario Ovarian Cancer Study	1989-1993	Population-based	In-person interview	Age (3 age groups: 35-49 years, 50-64 years, and 65-79 years)	71	65	792	56.7 (11.7)	88 (18.8)	379 (81.2)	82 (25.2)	243 (74.8)	0.76 (0.53, 1.10)	12 (20.0)	48 (80.0)	0.81 (0.40, 1.67)
TBO	USA	Tampa Bay Ovarian Cancer Study	2000-present	Population-based	In-person interview	Age (5-year categories, race)	68	60	163	61.3 (10.2)	23 (31.1)	51 (68.9)	18 (20.2)	71 (79.8)	1.53 (0.60, 3.89)	0 (0.0)	1 (100.0)	-
TOR[1]	Canada	Familial Ovarian Tumour Study (FOTS) AND Health Watch (HW)	FOTS: 1995-1999 and 2000-2003; HW: 1995-	Population-based	In-person interview	Age (5-year categories)	50	80	1135	57.3 (12.2)	48 (17.1)	233 (82.9)	164 (19.2)	690 (80.8)	1.04 (0.71, 1.52)	23 (18.3)	103 (81.7)	1.34 (0.73, 2.46)
UKO	UK	United Kingdom Ovarian cancer Population Study	2006-2010	Hospital- based	In-person interview	No matching	86	97	1268	63.5 (8.0)	180 (21.7)	648 (78.3)	98 (22.3)	342 (77.7)	1.05 (0.76, 1.45)	11 (28.2)	28 (71.8)	1.17 (0.51, 2.69)
USC	USA	Los Angeles County Case-Control Studies of Ovarian Cancer	1993-2009	Population-based	In-person interview	Age (5-year categories, race/ethnicity)	73	73	2784	56.9 (11.2)	362 (21.7)	1308 (78.3)	212 (19.0)	902 (81.0)	1.17 (0.95, 1.44)	19 (23.2)	63 (76.8)	0.92 (0.52, 1.64)
Pooled	-	-	-						15973	58.0 (11.6)	1959 (21.5)	7142 (78.5)	1478 (21.5)	5394 (78.5)	1.04 (0.95, 1.13)	147 (20.0)	587 (80.0)	1.25 (1.00, 1.56)

[1] Although TOR controls were limited to relatives and in-laws, it should not affect the exposure of interest, offspring sex. Thus, cases and controls from TOR can all be included in the currect analysis.

[2] Excludes women with non-singleton births (n=528), missing core data (n=35), and missing offspring sex data (n=335)

[3] Adjusted for age at diagnosis/reference date (continous), race (Black, White, Asian, Other), duration of oral contraceptive use (never, less than 1 years, 1-4 years, 5-9 years, and more than 10 years) and number of full-term pregnancies (1, 2, 3, 4, 5+)

Table 2. Characteristics of Participants in the Ovarian Cancer Association Consortium (Australia, Europe, and North America), 1989-2010[1]

	Controls (N=9101) n (%)	Cases (N=6872) n (%)	P-Value
Age, years, mean (SD)	57.5 (11.8)	58.6 (11.3)	<0.0001
Race			0.42
White	7544 (83.0)	5633 (82.2)	
Black	331 (3.6)	269 (3.9)	
Asian	331 (3.6)	276 (4.0)	
Other	880 (9.7)	677 (9.9)	
Education			<0.001
Less than High School	1233 (15.5)	1336 (22.4)	
High School	2530 (31.9)	1958 (32.9)	
Post High School Training	1964 (24.8)	1419 (23.8)	
College Graduate	1194 (15.1)	710 (11.9)	
Post graduate	1011 (12.7)	535 (9.0)	
Body Mass Index (BMI) at 18, kg/m^2			0.064
<18.5	1246 (16.3)	792 (15.4)	
18.5-24.9	5689 (74.3)	3788 (73.8)	
25-29.9	551 (7.2)	429 (8.4)	
≥30	168 (2.2)	121 (2.4)	
Recent Body Mass Index (BMI), kg/m^2			
<18.5	108 (1.67)	68 (1.50)	0.006
18.5-24.9	2874 (44.43)	1906 (42.07)	
25-29.9	1975 (30.53)	1370 (30.24)	
≥30	1512 (23.37)	1187 (26.2)	
Duration of Oral Contraceptive Use, years			<0.001
0	3031 (33.7)	2917 (43.0)	
<1	1203 (13.4)	1070 (15.8)	
1-4	1986 (22.1)	1277 (18.8)	
5-9	1466 (16.3)	894 (13.2)	
10+	1316 (14.6)	619 (9.1)	
Number of Full Term Pregnancies			<0.001
1	1493 (16.4)	1356 (19.7)	
2	3659 (40.2)	2632 (38.3)	
3	2282 (25.1)	1664 (24.2)	
4	1010 (11.1)	726 (10.5)	
5+	657 (7.2)	494 (7.2)	
Endometriosis			<0.001
No	8381 (94.5)	6180 (92.5)	
Yes	485 (5.5)	501 (7.5)	
Smoking Status			0.33
Never Smoker	4426 (54.7)	3206 (53.4)	

Former Smoker	1171 (14.5)	902 (15.0)	
Current Smoker	2501 (30.9)	1894 (31.6)	
Acne or Hirsutism or Polycystic ovary syndrome (PCOS)			0.004
No	3906 (77.1)	2831 (79.7)	
Yes	1157 (22.9)	720 (20.3)	
Irregular periods			0.001
No	5692 (81.3)	4079 (83.6)	
Yes	1308 (18.7)	798 (16.4)	
Age at Menarche			
<13 years	4068 (44.96)	2972 (43.51)	0.069
≥13 years	4981 (55.04)	3859 (56.49)	
Family History of Breast or Ovarian Cancer in first-relative			<0.001
No	7516 (85.4)	4846 (80.7)	
Yes	1285 (14.6)	1156 (19.3)	

[1] Missing data are as follows: race 15 controls, 17 cases; education 1169 controls, 914 cases; BMI at 18 1447 controls, 1742 cases; recent BMI 2632 controls, 2341 cases; duration of oral contraceptive use 99 controls, 95 cases; endometriosis 235 controls, 191 cases; smoking 1003 controls, 870 cases; acne or hirsutism or PCOS 4038 controls, 3321 cases; irregular period 2101 controls, 1995 cases; age at menarche 52 controls, 41 cases; family history of breast or ovarian

table 3

Table 3: Adjusted Pooled Odds Ratios for the Association Between Offspring Sex and Epithelial Ovarian Cancer Among Parous Women with Only Singleton Births in the Ovarian Cancer Association Consortium (Australia, Europe, and North America), 1989-2010

	Controls	All Cancers			HGSOC			Mucinous			Clear cell			Endometriod		
	N(%)	Cases, n (%)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)	Cases, n (%)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)	Cases, n (%)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)	Cases, n (%)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)	Cases, n (%)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Gave birth to a boy																
Never	1959 (21.5)	1478 (21.5)	ref	ref	548 (20.4)	ref	ref	147 (20.0)	ref	ref	88 (23.7)	ref	ref	181 (23.4)	ref	ref
Ever	7142 (78.5)	5394 (78.5)	1.05 (0.96, 1.14)	1.06 (0.93, 1.21)	2135 (79.6)	1.06 (0.94, 1.20)	1.03 (0.87, 1.22)	587 (80.0)	**1.25 (1.02, 1.54)**	**1.45 (1.01, 2.07)**	283 (76.3)	1.14 (0.87, 1.49)	1.06 (0.70, 1.61)	593 (76.6)	1.03. (0.85, 1.25)	1.06 (0.78, 1.44)
Gave birth to all boys																
No	7077 (77.8)	5257 (76.5)	ref	ref	2133 (79.5)	ref	ref	521 (71.0)	ref	ref	269 (72.5)	ref	ref	589 (76.1)	ref	ref
Yes	2024 (22.2)	1615 (23.5)	0.99 (0.91, 1.08)	1.02 (0.90, 1.16)	550 (20.5)	0.91 (0.81, 1.02)	0.96 (0.82, 1.13)	213 (29.0)	**1.29 (1.07, 1.55)**	**1.35 (0.99, 1.84)**	102 (27.5)	1.02 (0.79, 1.31)	0.90 (0.60, 1.35)	185 (23.9)	0.93 (0.77, 1.13)	0.80 (0.58, 1.10)
Number of boys																
No boy	1959 (21.5)	1478 (21.5)	ref	ref	548 (20.4)	ref	ref	147 (20.0)	ref	ref	88 (23.7)	ref	ref	181 (23.4)	ref	ref
1 boy	3826 (42.0)	2910 (42.3)	1.04 (0.95, 1.13)	1.05 (0.92, 1.20)	1130 (42.1)	1.08 (0.95, 1.22)	1.04 (0.87, 1.24)	309 (42.1)	1.16 (0.93, 1.44)	1.31 (0.90, 1.91)	186 (50.1)	1.20 (0.91, 1.57)	1.19 (0.78, 1.82)	339 (43.8)	1.03. (0.84, 1.26)	1.07 (0.78, 1.48)
2 boys	2244 (24.7)	1723 (25.1)	1.09 (0.98, 1.21)	1.12 (0.96, 1.31)	683 (25.5)	1.05 (0.90, 1.22)	1.05 (0.86, 1.29)	193 (26.3)	1.56 (1.20, 2.02)	1.84 (1.18, 2.87)	74 (20.0)	1.00 (0.70, 1.42)	0.70 (0.39, 1.24)	195 (25.2)	1.10 (0.86, 1.41)	1.11 (0.75, 1.64)
3 or more boys	1072 (11.8)	761 (11.1)	0.99 (0.86, 1.15)	0.93 (0.75, 1.16)	322 (12.0)	0.95 (0.77, 1.16)	0.86 (0.65, 1.13)	85 (11.6)	1.55 (1.08, 2.23)	2.31 (1.24, 4.29)	23 (6.2)	0.75 (0.43, 1.31)	0.75 (0.34, 1.67)	59 (7.6)	0.68 (0.47, 1.00)	0.54 (0.29, 1.02)
P for Trend			0.90	0.65		0.56	0.32		**0.006**	**0.005**		0.24	0.28		0.08	0.07
Continuous[3]																
number of boys	9101 (100.0)	6872 (100.0)	0.93 (0.90, 0.96)	0.91 0.87, 0.96)	2683 (100.0)	0.95 (0.91, 0.99)	0.93 (0.87, 0.99)	734 (100.0)	1.03 (0.95, 1.11)	1.02 (0.88, 1.17)	371 (100.0)	0.70 (0.62, 0.80)	0.73 (0.60, 0.88)	774 (100.0)	0.81. (0.74, 0.88)	0.80 (0.70, 0.91)
number of girls	9101 (100.0)	6872 (100.0)	0.92 (0.89, 0.95)	0.91 (0.87, 0.96)	2683 (100.0)	0.96 (0.92, 1.00)	0.95 (0.90, 1.02)	734 (100.0)	0.88 (0.81, 0.96)	0.80 (0.69, 0.94)	371 (100.0)	0.73 (0.64, 0.82)	0.81 (0.67, 0.98)	774 (100.0)	0.85. (0.78, 0.92)	0.88 (0.77, 1.00)
Fraction of births that were boys, per 25% increase[4]	9101 (100.0)	6872 (100.0)	1.01 (0.99, 1.04)	1.01 (0.98, 1.05)	2683 (100.0)	1.00 (0.96, 1.03)	1.00 (0.95, 1.04)	734 (100.0)	**1.09 (1.03, 1.16)**	**1.13 (1.03, 1.24)**	371 (100.0)	1.01 (0.94, 1.09)	0.98 (0.87, 1.09)	774 (100.0)	1.00 (0.95, 1.06)	0.97 (0.89, 1.06)

		Stratified by number of birth episodes[5]													
Among with exactly 1 birth															
Girl	742 (49.7)	651 (48.0)	ref	ref	230 (52.0)	ref	ref	71 (42.8)	ref	ref	45 (43.7)	ref	ref	75 (43.4)	ref	ref
Boy	751 (50.3)	705 (52.0)	1.02 (0.88, 1.20)	1.11 (0.87, 1.41)	212 (48.0)	0.96 (0.76, 1.20)	1.06 (0.77, 1.47)	95 (57.2)	1.22 (0.86, 1.72)	1.31 (0.73, 2.34)	58 (56.3)	1.22 (0.80, 1.86)	1.58 (0.79, 3.15)	98 (56.6)	1.27 (0.91, 1.78)	0.98 (0.56, 1.69)
Among women with exactly 2 births															
No boy	873 (23.9)	558 (21.2)	ref	ref	217 (21.4)	ref	ref	56 (19.4)	ref	ref	29 (19.5)	ref	ref	76 (24.4)	ref	ref
1 boy	1924 (52.6)	1423 (54.1)	1.14 (1.00, 1.30)	1.02 (0.84, 1.25)	564 (55.6)	1.20 (1.00, 1.44)	1.01 (0.78, 1.30)	146 (50.7)	1.16 (0.83, 1.61)	1.27 (0.71, 2.25)	87 (58.4)	1.30 (0.84, 2.01)	1.00 (0.52, 1.90)	166 (53.4)	0.99. (0.74, 1.33)	1.12 (0.69, 1.81)
2 boys	862 (23.6)	651 (24.7)	1.15 (0.99, 1.35)	1.12 (0.89, 1.40)	233 (23.0)	1.07 (0.86, 1.33)	1.01 (0.75, 1.36)	86 (29.9)	1.58 (1.10, 2.28)	1.89 (1.02, 3.52)	33 (22.1)	1.15 (0.69, 1.93)	0.61 (0.27, 1.42)	69 (22.2)	0.92 (0.65, 1.32)	0.92 (0.51, 1.64)
P for trend			0.07	0.35		0.56	0.95		**0.01**	**0.04**		0.59	0.26		0.66	0.77
Among women with exactly 3 births															
No boy	262 (11.5)	209 (12.6)	ref	ref	79 (11.4)	ref	ref	15 (9.3)	ref	ref	12 (15.6)	ref	ref	24 (13.7)	ref	ref
1 boy	822 (36.0)	562 (33.8)	0.86 (0.69, 1.08)	0.91 (0.66, 1.27)	250 (36.1)	1.02 (0.75, 1.37)	1.06 (0.69, 1.62)	53 (32.9)	1.21 (0.65, 2.26)	2.08 (0.59, 7.35)	28 (36.4)	0.71 (0.35, 1.42)	0.82 (0.27, 2.51)	54 (30.9)	0.72 (0.42, 1.22)	0.76 (0.32, 1.73)
2 boys	874 (38.3)	682 (41.0)	0.97 (0.78, 1.20)	0.97 (0.70, 1.34)	277 (40.0)	1.03 (0.77, 1.39)	1.10 (0.72, 1.66)	68 (42.2)	1.52 (0.83, 2.81)	2.33 (0.67, 8.09)	27 (35.1)	0.66 (0.33, 1.34)	0.54 (0.17, 1.71)	82 (46.9)	1.00 (0.60, 1.65)	0.97 (0.44, 2.15)
3 boys	324 (14.2)	211 (12.7)	0.82 (0.63, 1.06)	0.79 (0.54, 1.18)	87 (12.6)	0.89 (0.62, 1.29)	0.92 (0.55, 1.52)	25 (15.5)	1.44 (0.72, 2.89)	2.59 (0.66, 10.10)	10 (13.0)	0.63 (0.26, 1.50)	0.55 (0.13, 2.22)	15 (8.6)	0.43 (0.21, 0.88)	0.33 (0.10, 1.13)
P for trend			0.23	0.31		0.57	0.78		0.22	0.16		0.28	0.31		0.05	0.11

[1] Adjusted for study sites, age at diagnosis/reference date (continous), race (Black, White, Asian, Other), duration of oral contraceptive use (never, less than 1 years, 1-4 years, 5-9 years, and more than 10 years) and number of full-term pregnancies (1, 2, 3, 4, 5+); Two hundrad twenty three women with missing data in race or oral contraceptive use were excluded from the analysis.

[2] Further adjsuted for endometriosis (yes, no), smoking (ever, never), acne or hirsutism or PCOS (yes, no), irrgular periods (yes, no), recent BMI (<18.5, 18.5-24.9, 24.9-30, ≥30), and age at menarche (<13 years, ≥13 years).

[3] Models did not adjust for total number of full term pregnancies

[4] Models adjust for total number of full term pregnancies as a continous variable

[5] Adjusted for study sites, age at diagnosis/reference date (continous), race (Black, White, Asian, Other) and duration of oral contraceptive use (never, less than 1 years, 1-4 years, 5-9 years, and more than 10 years)

Table 4: Adjusted Pooled Odds Ratios for the Association Between Offspring Sex and Mucinous Epithelial Ovarian Cancer Stratified by History of Estrogenic Conditions Among Parous Women with Only Singleton Births in the Ovarian Cancer Association Consortium (Australia, Europe, and North America), 1989-2010[1]

	Age at Menarche <13 years			Age at Menarche ≥13 years		
	Controls N(%)	Cases N(%)	Adjusted OR (95% CI)	Controls N(%)	Cases N(%)	Adjusted OR (95% CI)
Gave birth to a boy						
Never	916 (22.52)	56 (18.24)	ref	1032 (20.72)	91 (21.46)	ref
Ever	3152 (77.48)	251 (81.76)	1.71 (1.23, 2.38)	3949 (79.28)	333 (78.54)	0.99 (0.76, 1.30)
P for interaction			**0.02**			
Gave birth to all boys						
Not all boys	3124 (76.79)	205 (66.78)	ref	3913 (78.56)	314 (74.06)	ref
All boys	944 (23.21)	102 (33.22)	1.55 (1.18, 2.04)	1068 (21.44)	110 (25.94)	1.08 (0.83, 1.40)
P for interaction			0.08			
No. of boys						
No boy	916 (22.52)	56 (18.24)	ref	1032 (20.72)	91 (21.46)	ref
1 boy	1663 (40.88)	132 (43.00)	1.54 (1.09, 2.18)	2137 (42.90)	176 (41.51)	0.94 (0.71, 1.24)
2 boys	1010 (24.83)	86 (28.01)	2.34 (1.55, 3.53)	1222 (24.53)	105 (24.76)	1.16 (0.82, 1.63)
3 or more boys	479 (11.77)	33 (10.75)	2.24 (1.27, 3.98)	590 (11.85)	52 (12.26)	1.20 (0.75, 1.93)
P for trend			**0.002**			0.32
P for interaction			0.10			
Number of boys[2]	1919 (100.00)	132 (100.00)	1.04 (0.92, 1.18)	4981 (100.00)	424 (100.00)	1.01 (0.90, 1.12)
P for interaction			0.51			
Number of girls[2]	1919 (100.00)	132 (100.00)	0.79 (0.69, 0.91)	4981 (100.00)	424 (100.00)	0.94 (0.84, 1.05)
P for interaction			**0.02**			
Fraction of births that were boys, 25% increase[3]	1919 (100.00)	132 (100.00)	1.18 (1.09, 1.28)	4981 (100.00)	424 (100.00)	1.03 (0.95, 1.11)

P for interaction	**0.01**

[1] Adjusted for study sites, age at diagnosis/reference date (continous), race (Black, White, Asian, Other), duration of oral contraceptive use (never, less than 1 years, 1-4 years, 5-9 years, and more than 10 years) and number of full-term pregnancies (1, 2, 3, 4, 5+)

[2] Adjsuted for each other

[3] Models adjust for total number of full term pregnancies as a continous variable

Table 5: Adjusted Pooled Odds Ratios for the Association Between Offspring Sex and Endometrioid Epithelial Ovarian Cancer Stratified by History of Androgenic Conditions Among Parous Women with Only Singleton Births in the Ovarian Cancer Association Consortium (Australia, Europe, and North America), 1989-2010[1]

	History of Acne or Hirsutism or PCOS			No history of Acne or Hirsutism or PCOS		
	Controls N(%)	Cases N(%)	Adjusted OR (95% CI)	Controls N(%)	Cases N(%)	Adjusted OR (95% CI)
Gave birth to a boy						
Never	253 (21.9)	28 (34.1)	ref	832 (21.3)	48 (18.8)	ref
Ever	904 (78.1)	54 (65.9)	0.49 (0.28, 0.83)	3074 (78.7)	207 (81.2)	1.64 (1.14, 2.34)
P for interaction			**0.003**			
Gave birth to all boys						
Not all boys	894 (77.3)	65 (79.3)	ref	3075 (78.7)	197 (77.3)	ref
All boys	263 (22.7)	17 (20.7)	0.88 (0.49, 1.59)	831 (21.3)	58 (22.7)	0.93 (0.67, 1.28)
P for interaction			0.56			
No. of boys						
No boy	253 (21.9)	28 (34.1)	ref	832 (21.3)	48 (18.8)	ref
1 boy	492 (42.5)	27 (32.9)	0.47 (0.27, 0.85)	1606 (41.1)	127 (49.8)	1.69 (1.18, 2.44)
2 boys	275 (23.8)	18 (22.0)	0.52 (0.26, 1.06)	1004 (25.7)	64 (25.1)	1.59 (1.02, 2.49)
3 or more boys	137 (11.8)	9 (11.0)	0.47 (0.16, 1.67)	464 (11.9)	16 (6.3)	0.78 (0.39, 1.56)
P for trend			0.21			0.47
P for interaction			**0.007**			
Number of boys[2]	1157 (100.0)	82 (100.0)	0.77 (0.60, 0.99)	3906 (100.0)	255 (100.0)	0.82 (0.71, 0.95)
P for interaction			0.44			
Number of girls[2]	1157 (100.0)	82 (100.0)	1.02 (0.81, 1.30)	3906 (100.0)	255 (100.0)	0.80 (0.69, 0.93)
P for interaction			**0.03**			
Fraction of births that were boys, 25% increase[3]	1157 (100.0)	82 (100.0)	0.85 (0.72, 1.00)	3906 (100.0)	255 (100.0)	1.06 (0.96, 1.15)
P for interaction			**0.03**			

[1] Adjusted for study sites, age at diagnosis/reference date (continous), race (Black, White, Asian, Other), duration of oral contraceptive use (never, less than 1 years, 1-4 years, 5-9 years, and more than 10 years) and number of full-term pregnancies (1, 2, 3, 4, 5+)

[2] Adjsuted for each other

[3] Models adjust for total number of full term pregnancies as a continous variable