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Gender of Offspring and Risk of Ovarian Cancer: the HOPE Study

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Abstract

Objective—To examine the association between gender of offspring and epithelial ovarian cancer (EOC).

Methods—We compared gender of offspring between 664 incident EOC cases and 1531 controls participating in a population-based study conducted in Pennsylvania, Ohio, and New York from 2003-2008. Multivariable unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) adjusting for potential confounders.

Results—Bearing a male offspring was associated with an 8% lower EOC risk; bearing all boys was associated with an 11% lower risk. Compared to bearing all girls, bearing all boys was associated with a 14% decrease risk. Increasing number of male offspring increased the protective effect (adjusted-OR: 0.92, 0.91, 0.84, for 1, 2, and 3+ boys compared to all girls). Results where similar when limiting cases to invasive disease and to the high-grade serous histotype.

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Conclusion—Fetal sex, which influences maternal hormonal milieu, may impact EOC risk.

Keywords

Epithelial Ovarian Cancer; case-control study; gender of offspring

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy[1]. Bearing children has consistently been shown to protect against the disease[2]. Although the exact mechanism of this protective effect is unknown, it is generally attributed to suppressed ovulation throughout the pregnancy[3]; however, anovulation alone cannot explain the magnitude of the protective effect[4], suggesting that other pregnancy-associated factors may impact EOC risk. One such factor is fetal sex, which may influence the maternal hormonal milieu[5-7] thereby affecting EOC risk. There are few epidemiologic studies of the relationship between gender of offspring and EOC risk, and the results have been inconsistent[8-11].

We used data from a large, case-control study of EOC to assess the association between gender of offspring and EOC.

Methods

Subjects

The Hormone and Ovarian cancer PrEdiction (HOPE) study is a population-based case-control study conducted in the contiguous region of western Pennsylvania, eastern Ohio, and western New York. Details of eligibility criteria for the population and recruitment methods have been published previously[12]. Briefly, cases were women diagnosed with incident epithelial ovarian, peritoneal, or fallopian tube cancer between February 2003 and November 2008. Controls were identified using random digit dialing and frequency matched to cases by 5-year age groups and 3-digit telephone prefix. A total of 902 cases and 1802 controls participated in the study. The study was approved by the University of Pittsburgh Institutional Review Board.

Data Collection an Exposure Assessment

Two-hour, in-person interviews were conducted by trained interviewers to obtain information on reproductive, medical, and demographic data from birth until a reference date. The reference date was calculated as 9 months before diagnosis for cases or interviews for controls to ensure that exposures occurred before ovarian cancer diagnosis in cases and within a similar time frame for cases and controls. A life events calendar with milestones such as marriages, births, and deaths was used to aid recall. For each pregnancy, a woman was asked the outcome, including live or still birth. For each live or still birth, the woman was asked if it was a single birth followed by “Was it a boy or girl?”

Statistical Analyses

Analyses were limited to 1531 controls and 664 cases who reported all singleton, full-term (live or still birth) births and gender of offspring for each birth. Differences in demographic factors between cases and controls were estimated using chi-square and t-tests, as appropriate. Unconditional logistic regression analyses were conducted to estimate odds ratio (OR) 95% confidence intervals (CIs) for the association of gender of offspring and EOC risk. Linear trends were assessed with Wald tests. In the multivariable models, we controlled for age, race, education level, duration of oral contraception use, and number of full-term births. Sensitivity analyses with models including age at first birth, duration of breastfeeding, tubal ligation, and hysterectomy showed no change in results; these variables were excluded from the final models. Because *BRCA* mutation carriage may skew offspring gender ratios[13] and because it is associated with EOC risk, we performed all analyses limiting to women without a reported family history of breast or ovarian cancers, using family history as a surrogate for BRCA carriage status. These analyses showed no changes in results.

Stata/SE version 15.1 (StataCorp) was used to conduct the analyses. Two-sided P-values less than 0.05 were considered significant.

Results

Characteristics of the 1531 controls and 664 cases are summarized in Table 1. Compared to the controls, cases were older and less likely to be white, highly educated, use oral contraceptives, have had a tubal ligation, and breastfed. They were more likely have had a hysterectomy, use talc, and report a family history of breast or ovarian cancer.

The association between gender of offspring and EOC risk is presented in Table 2. Ever bearing a male offspring was associated with an 8% lower EOC risk (adjusted-OR:0.92; 95%CI:0.75-1.24); bearing all boys was associated with a somewhat greater protective effect (adjusted-OR:0.89; 95%CI:0,70-1.13). Compared to giving birth to girls only, giving birth to boys only was associated with a 14% decrease in EOC risk (adjusted-OR:0.86; 95%CI: 0.65-1.15). Increasing number of male offspring appeared to increase the protective effect (adjusted-OR: 0.92, 0.91, 0.84, for 1, 2, and 3 or more boys compared to all girl offspring).

Stratified analyses by number of full-term births provided additional support for reduced risk associated with male offspring. Compared to women bearing only girls, among women with exactly one full-term birth as well as among women with exactly two full-term births, bearing a male offspring was consistently associated with reduced risk (Table 2).

Results were similar when limiting cases to invasive disease and to the high-grade serous histotype, the most common EOC subtype (Table 2). Small number of cases of the other main histotypes precluded meaningful analyses.

Discussion

We investigated the association between gender of offspring and EOC risk. In general, bearing male offspring was associated with reduced EOC risk. Although our findings failed

to reach statistical significance, the consistent protective effect of a male offspring and the increasing protective effect with greater number of male offspring found herein lend support to the hypothesis that the influence of fetal sex on the maternal hormonal milieu during pregnancy may impact EOC risk.

Four studies have investigated the association between offspring gender and ovarian cancer risk[8-11]. Our previous population-based study conducted in eastern Pennsylvania reported findings similar to the current study – bearing male offspring was associated with a non-significant decrease in EOC risk[8]. Notably, the point estimate for bearing all boys compared to all girls was 0.84, which is similar to what we report herein (0.86). A nested case-control study in Sweden supported these findings reporting that bearing a male child was significantly associated with reduced EOC risk, and increasing number of male offspring was associated with increasing protection (adjusted ORs: 0.92, 0.87, 0.82, for 1, 2 or 3+ boys, compared to all girls)[9]. Again, the magnitude of the point estimates were similar to what we found (0,92, 0.91, 0.84, respectively). In contrast, a population-based study in Australia reported no association between offspring gender and EOC in general but a 2-fold increase risk of the mucinous histotype associated with bearing only male offspring[11]. A cohort study in Norway reported no EOC-offspring gender association in general, but an increased risk of endometrioid tumors among women who gave birth to girls only[10]. Although our sample size was limited for examining mucinous and endometroid subtypes, we found bearing male offspring was associated with reduced risk of high-grade serous EOC, the most common and fatal subtype. Prior studies did not separate low from high-grade serous EOC, which are now believed to have distinct etiologies and be different disease[14]. This may explain, in part, the disparate findings between prior work and what we report herein.

Pregnancy has consistently been shown to protect against EOC[2]. Although the exact mechanism for this association remains unknown, an altered maternal hormonal milieu may play a role[15]. During pregnancy, maternal hormone concentrations may differ by fetal sex. Carriage of a male fetus is associated with lower maternal levels of estradiol and hCG[5, 6] and higher maternal levels of progesterone[7]. While the role of hCG in EOC etiology is unclear, progesterone is believed to protect against EOC while estrogens may increase risk[15]. Thus, it is biologically plausible that bearing male offspring can impact EOC risk differently than bearing female offspring.

A strength of this study is its population-basis and collection of data through standardized, structured, in-person interviews administered by trained personnel, ensuring consistent and high-quality exposure measurements. The major weakness is sample size, which enabled us to detect a minimum OR of only 0.75 (80% power, alpha=0.05). A greater sample size is needed to determine whether the actual estimate is more in the range of what we and others have reported (0.84-0.86). In addition, a larger sample size would enable us to explore histotype-specific associations, as EOC is now believed to be several etiologically-distinct diseases[16]. Another weakness is that this data set did not have *BRCA* or other germline mutation status recorded. Emerging data suggest that among *BRCA* mutation carriers, gender is skewed towards female offspring[13]. Thus, carriage of a *BRCA* mutation may confound the relationship between offspring gender and EOC risk. However, we controlled

for family history of breast or ovarian cancer (a surrogate for *BRCA* status) in our analyses. Moreover, we found similar associations between offspring gender and EOC when limiting analyses to women without a family history of breast or ovarian cancers.

In summary, we report that bearing male offspring may be associated with a decreased risk of EOC compared to bearing female offspring. Although our results were not statistically significant, the consistency of findings in our analyses, the similarity of our estimates to previous studies, and the biologic plausibility of the association support our conclusions. As no one study may be powered to address the question adequately, pooled analyses of existing studies to examine the EOC-offspring gender association are warranted. The larger sample size will enable histotype-specific analyses, which could shed light on disease etiology and pave the way for new avenues of prevention research for this often-fatal disease.

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Highlights

- Pregnancy protects against ovarian cancer and hormones impact risk for the disease
- During pregnancy, hormone levels vary based on fetal sex
- Results imply that bearing male offspring reduces risk more than female offspring

Table 1.

Characteristics of HOPE Study Participants, 2003-2008

	Controls (N=1531)	Cases (N=664)	P-Value
Age, years, mean (SD)	57.37 (12.38)	60.20 (12.24)	<0.0001
Race			0.004
White	1490 (97.32)	630 (94.88)	
Non-White	41 (2.68)	34 (5.12)	
Education			<0.001
Less than High School	74 (4.83)	69 (10.39)	
High School	476 (31.09)	241 (36.30)	
Post High School Training	485 (31.68)	183 (27.56)	
College Graduate	300 (19.60)	97 (14.61)	
Postgraduate	196 (12.80)	74 (11.14)	
Duration of Oral Contraceptive Use, years			<0.001
0	439 (28.67)	260 (39.16)	
<1	237 (15.48)	120 (18.07)	
1-4	416 (27.17)	152 (22.89)	
5-9	260 (16.98)	91 (13.70)	
10+	179 (11.69)	41 (6.17)	
Number of Full Births			0.224
1	225 (14.70)	116 (17.47)	
2	576 (37.62)	249 (37.50)	
3+	730 (47.68)	299 (45.03)	
Tubal Ligation			<0.001
No	957 (62.51)	476 (71.69)	
Yes	574 (37.49)	188 (28.31)	
Hysterectomy			0.002
No	1252 (81.78)	505 (76.05)	
Yes	279 (18.22)	159 (23.95)	
Talc Use			0.001
No	1028 (67.15)	395 (59.49)	
Yes	503 (32.85)	269 (40.51)	
Family History of Breast or Ovarian Cancer *			0.038
No	1265 (82.73)	523 (79.00)	
Yes	264 (17.27)	139 (21.00)	
Duration of breastfeeding (years)			<0.001
0	665 (43.46)	368 (55.51)	
<1	488 (31.90)	188 (28.36)	
1 or more s	377 (24.64)	107 (16.14)	

* 2 missing in controls and 2 missing in cases

** among women with at least 1 live birth

Table 2.

Association between gender of offspring and risk of epithelial ovarian cancer: The HOPE Study, 2003-2008

		All Cancer		Invasive		HGSOC	
	Controls	Cases	Adjusted OR*	Cases	Adjusted OR*	Cases	Adjusted OR*
	N(%)	N(%)	95% CI	N(%)	95% CI	N(%)	95% CI
Gave birth to a boy							
Never	316 (20.64)	150 (22.59)	ref	126 (21.95)	ref	76 (22.16)	ref
Ever	1215 (79.36)	514 (77.41)	0.92 (0.72, 1.16)	448 (78.05)	0.93 (0.73, 1.20)	267 (77.84)	0.89 (0.65, 1.21)
All Boys							
No	1199 (78.31)	525 (79.07)	ref	458 (79.79)	ref	277 (80.76)	ref
Yes	332 (21.69)	139 (20.93)	0.89 (0.70, 1.13)	119 (20.21)	0.85 (0.66, 1.10)	66 (19.24)	0.83 (0.61, 1.13)
Gender of offspring							
All girls	316 (20.64)	150 (22.59)	ref	116 (20.21)	ref	66 (19.24)	ref
All boys	332 (21.69)	139 (20.93)	0.86 (0.65, 1.15)	126 (21.95)	0.85 (0.63, 1.15)	76 (22.16)	0.80 (0.55, 1.17)
Mixed	883 (57.67)	375 (56.48)	0.95 (0.74, 1.24)	332 (57.84)	0.99 (0.76, 1.31)	201 (58.60)	0.95 (0.68, 1.32)
Number of boys							
No boy	316 (20.64)	150 (22.59)	ref	126 (21.95)	ref	76 (22.16)	ref
1 boy	602 (39.32)	261 (39.31)	0.92 (0.72, 1.19)	227 (39.55)	0.94 (0.72, 1.23)	141 (41.11)	0.96 (0.70, 1.33)
2 boys	403 (26.32)	171 (25.75)	0.91 (0.68, 1.22)	150 (26.13)	0.93 (0.68, 1.26)	79 (23.03)	0.76 (0.52, 1.11)
3 or more boys	210 (13.72)	82 (12.35)	0.84 (0.56, 1.25)	71 (12.37)	0.82 (0.54, 1.25)	47 (13.70)	0.79 (0.48, 1.30)
P for trend			0.41		0.36		0.24
Among women with one birth†							
No boy	117 (52.00)	65 (56.03)	ref	51 (53.13)	ref	31 (51.67)	ref
1 boy	108 (48.00)	51 (43.97)	0.85 (0.53, 1.36)	45 (46.88)	0.95 (0.58, 1.56)	29 (48.33)	1.04 (0.57, 1.88)
Among women with two births†							
No boy	139 (24.13)	66 (26.51)	ref	58 (26.98)	ref	35 (29.91)	ref
1 boy	300 (52.08)	124 (49.80)	0.84 (0.58, 1.22)	108 (50.23)	0.84 (0.57, 1.23)	60 (51.28)	0.78 (0.49, 1.26)
2 boys	137 (23.78)	59 (23.69)	0.88 (0.57, 1.36)	49 (22.79)	0.84 (0.53, 1.32)	22 (18.80)	0.62 (0.34, 1.12)
P for trend			0.56		0.44		0.12

*Adjusted for age, race, education, duration of OC use, number of full-term births; further adjusting for duration of breast feeding, tubal ligation and hysterectomy did not change the results (data not shown)

†Not adjusted for number of full-term pregnancies in the analysis by number of births.