Gender of Offspring and Maternal Risk of Invasive Epithelial Ovarian Cancer

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Abstract

Gender of a fetus is associated with maternal hormonal milieu and may therefore modify maternal risk of ovarian cancer following a birth. We evaluated the relation between gender of offspring and maternal risk of epithelial ovarian cancer in a large case-control study nested within a nationwide cohort. Cohort members were identified in the Swedish Fertility Register. Cases of invasive epithelial ovarian cancer were identified in the Swedish National Cancer Register from 1961 to 2001. Five controls were matched by age to each case. A total of 7,407 cases and 37,658 controls with only singleton births were included in the analysis. We fit logistic regression models to study the association between gender of offspring and ovarian cancer risk, controlling for covariates. Maternal risk of ovarian cancer was reduced with increasing numbers of male offspring and increased with number of female offspring. Compared with women who gave birth to only girls, multivariate odds ratios (95% confidence interval) of invasive epithelial ovarian cancer were 0.92 (0.87-0.98) for those who gave birth to one boy, 0.87 (0.80-0.94) for two boys, and 0.82 (0.73-0.94) for three or more boys (P value test for trend < 0.001). There was a positive but nonsignificant association with number of girls. Similar results were observed when restricting the analysis to women born before 1935. Our findings suggest that hormonal and physiologic conditions in pregnancy with male, but not with female, offspring are associated with a lowered maternal risk of invasive epithelial ovarian cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2314–20)

Introduction

Epidemiologic studies have provided consistent evidence on the protective role of increasing parity in ovarian carcinogenesis (1-10), and different mechanisms have been postulated to explain the effect of childbirth on this carcinoma (9). However, childbirth-related factors other than parity have not been extensively explored to provide further information on the potential mechanisms. Maternal hormonal milieu during normal pregnancy may differ by gender of the fetus; more notable examples include that women carrying a male fetus are exposed to lower levels of human chorionic gonadotropin (hCG) and estriol and higher levels of α-fetoprotein than those carrying a female fetus (11-13). Very few studies have examined the association between gender of offspring and maternal risk of ovarian cancer. A population-based case-control study from Delaware Valley examined the association between gender of offspring and maternal risk of ovarian cancer and found that bearing only female offspring might be associated with an increased risk (14). A population-based cohort study from Norway, on the other hand, found no association between offspring gender and maternal risk of ovarian cancer, although those with twin girls had a nonsignificant increased risk than those with singleton births (15). We have conducted a large case-control study nested within a nationwide cohort of Swedish women to better document the association between gender of offspring and maternal risk of invasive epithelial ovarian cancer.

Materials and Methods

Study Population. Members of the study cohort were identified from women who were born from 1925 and alive at the 1960 Census and listed in the Swedish Fertility Register, a nationwide population-based register including >3.4 million female resident citizens of Sweden. The Register contains information on number, gender, and dates of live births for registered women. Vital and emigration status of women in the Fertility Register is updated annually based on information obtained from a National Population Register.

We used a nested case-control sampling design to allow more efficient analyses. Ovarian cancer cases were

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ascertained by linkage with the records of the Swedish National Cancer Register, which receives reports on newly diagnosed malignant tumors from both the diagnosing physician and the confirming pathologist/cytologist since 1958 and has a near complete list of all cancer cases. Case subjects were cohort members diagnosed from 1961 to 2001 with histologically verified invasive epithelial ovarian cancer (International Classification of Diseases, seventh revision code 175.0 with pathologic anatomic diagnosis codes, such as 096 for adenocarcinoma, 196 for undifferentiated carcinoma, and 146 for squamous cell tumor; ref. 16). During the follow-up, 10,200 case subjects were diagnosed with a first invasive epithelial ovarian cancer. For each case subject, five control women were randomly selected from the eligible cohort members who had the same birth year with the index case, were alive in Sweden at least to the date of the diagnosis for the index case, and had not been previously diagnosed with ovarian cancer before this date. For both cases and controls, the highest attained educational level was obtained from a nationwide Register on Education.

To minimize the possible effect of multiple birth pregnancies on the relation between gender of offspring and ovarian cancer risk, we excluded 147 cases and 735 matched controls as well as 790 additional control subjects who had ever had such pregnancies. Among the 59,528 women (10,053 cases and 49,475 controls) without a multiple birth pregnancy, we further excluded 13,178 nulliparous women (2,534 cases and 10,644 controls) and 1,285 parous women (112 cases and 1,173 controls) who had missing information on gender of any offspring. Thus, a total of 45,065 women (7,407 cases and 37,658 controls) were available for this analysis. For both cases and controls, only live births before the index case's date of diagnosis were included in the analyses.

Statistical Analyses. We conducted unconditional logistic regression analyses to estimate odds ratio (OR; relative risk) of invasive epithelial ovarian cancer and its 95% confidence interval (95% CI), controlling for potential confounding variables. Variables included in the analyses were gender of offspring, attained age (age at diagnosis for cases or age at identification for controls), age at first childbirth, parity, attained educational level by age 40, and area of residence at age 40. Age at diagnosis and age at first childbirth were adjusted for as continuous variables in the models, whereas parity, educational level, and area of residence were adjusted for as categorical indicator variables. We presented OR estimates for categories of numbers of boys and girls (1, 2, 3, or more) using all girls (no boy) or all boys (no girl) as reference group. We tested for linear trend in OR estimates by treating number of boys and number of girls as ordinal variables. For uniparous, biparous, and triparous women, the effect of bearing a boy on the risk of invasive epithelial ovarian cancer was evaluated for each birth order using bearing a girl as the reference. The effect of fetal gender was further analyzed for uniparous, biparous, and triparous women together using bearing two girls in biparous women as the reference.

Information on use of oral contraceptives was unavailable in the registry data. To minimize the potential confounding effect, if any, of oral contraceptives on the association between gender of offspring and invasive epithelial ovarian cancer risk, we conducted further analyses among women who were born before 1935 because oral contraceptive use was limited in the older cohort (17). Statistical Analysis System procedures (SAS 8.0, SAS Institute) were used to conduct the analyses.

Results

Characteristics of the study subjects are shown in Table 1. Compared with control women, case women were more likely to be uniparous, reside in rural area, and bear only girls.

Table 2 displays, by birth order and among all children, the distribution of offspring gender for the cases and controls. Case women were more likely to give birth to a girl for the first to fourth children than the controls. The sex ratio (number of boys/number of girls) of all children was 1.03 for cases and 1.07 for controls.

Table 3 presents multivariate ORs of maternal ovarian cancer associated with numbers of boys and numbers of girls. The risk decreased with increasing numbers of boys: compared with women who gave birth to only girls, the ORs (95% CI) were 0.92 (0.87-0.98) for those who gave birth to one boy, 0.87 (0.80-0.94) for two boys, and 0.82 (0.73-0.94) for three or more boys (P value test for trend < 0.001). In contrast, there was a positive association between number of girls and maternal risk of ovarian cancer: multivariate ORs (95% CI) were 1.00 (0.94-1.06) for one girl, 1.03 (0.95-1.11) for two girls, and 1.13 (0.99-1.28) for three or more girls compared with women with only boys (P value test for trend = 0.16). Restricting the analysis to the 21,932 women (3,585 cases

Table 1. Characteristics of the study subjects (n = 45,065)

Variables	Cases (n = 7,407), n (%)	Controls (n = 37,658), n (%)
Age at diagnosis or enrollment (y)		
17-29	148 (2.0)	868 (2.3)
30-39	741 (10.0)	3,974 (10.6)
40-49	2,003 (27.0)	10,177 (27.0)
50-59	2,594 (35.0)	13,054 (34.7)
60+	1,921 (26.0)	9,585 (25.4)
Parity		
1	2,071 (28.0)	8,653 (23.0)
2	3,313 (44.7)	16,498 (43.8)
3	1,418 (19.1)	8,430 (22.4)
4 or more	605 (8.2)	4,077 (10.8)
Age at 1st childbirth (y)		
14-19	1,350 (18.2)	6,490 (17.2)
20-24	3,158 (42.6)	16,179 (43.0)
25-29	2,011 (27.2)	10,557 (28.0)
30-34	673 (9.1)	3,365 (9.0)
35+	215 (2.9)	1,067 (2.8)
Education level (y)		
<9	3,652 (49.3)	18,086 (48.0)
≥9	3,503 (47.3)	18,536 (49.2)
Missing information	252 (3.4)	1,036 (2.8)
Area of residence		
Urban	3,985 (53.8)	20,775 (55.2)
Rural	3,422 (46.2)	16,883 (44.8)
Gender of offspring		
All girls	2,007 (27.1)	8,836 (23.5)
All boys	2,103 (28.4)	10,007 (26.6)
Mixed boys and girls	3,297 (44.5)	18,815 (50.0)

Table 2. Gender distribution of the offspring by birth order

Gender of offspring	Cases		Controls	
	Boy (*n*)/girl (*n*)	% Boy	Boy (*n*)/girl (*n*)	% Boy
Birth order				
1st child	3,773/3,634	50.9	19,467/18,191	51.7
2nd child	2,678/2,694	49.9	15,315/14,192	51.9
3rd child	1,057/997	51.5	6,766/6,237	52.0
4th child	312/302	50.8	2,181/2,083	51.2
5th child	91/77	54.2	709/653	52.1
6th and above	44/41	51.8	433/405	51.7
All children	7,955/7,745	50.7	44,871/41,761	51.8

and 18,347 controls, all parities) born before 1935, when oral contraceptive use was unlikely, we found a similar inverse association for boys (P value from test for trend = 0.004) and a stronger positive association for girls (P value test for trend = 0.006; Table 3).

We examined further the effect of offspring gender on ovarian cancer risk, separately for each birth order, among uniparous, biparous, and triparous women (Table 4). There was a consistent reduction in risk associated with having a boy rather than having a girl at each birth order for each group. For example, among triparous women in the full cohort, multivariate ORs (95% CI) associated with having a boy were 0.95 (0.85-1.06) for the first birth, 0.89 (0.80-1.00) for the second birth, and 0.94 (0.84-1.06) for the third birth. Risk reduction was also observed with distinct pattern of offspring gender, with male offspring (boy/boy for biparous women and all boys for triparous women) associated with the lowest risk and female offspring (girl/girl or all girls) having the highest risk.

Among women born before 1935, the pattern of risk reduction at each birth was similar (Table 4). Graphically, for this older cohort, using the middle category of biparous women with only girls as the reference, Fig. 1 summarizes the effect of offspring gender on maternal risk of invasive epithelial ovarian cancer among uniparous, biparous, and triparous women. Compared with biparous women who had only girls, multivariate ORs (95% CI) were 1.11 (0.95-1.28) for uniparous women with one girl, 1.04 (0.90-1.21) for uniparous women with one boy, 0.87 (0.76-1.00) for biparous women with one boy and one girl, 0.84 (0.71-0.98) with two boys, 0.87 (0.67-1.11) for triparous women with three girls, 0.67 (0.56-0.81) for two girls and one boy, 0.66 (0.55-0.79) for two boys and one girl, and 0.63 (0.49-0.80) for three boys (Fig. 1).

Discussion

Our results show a dose-response relationship between increasing number of male offspring and reduced maternal risk of invasive epithelial ovarian cancer. In contrast, mothers with only female offspring were at a higher risk of ovarian cancer than those with at least one male offspring. These data agreed with the study from Delaware Valley and the findings on twin girls in the Norwegian study (14, 15).

Table 3. Number of boys and girls among ovarian cancer cases and control subjects and the associated OR with 95% CI

No. girls	No. boys				Adjusted OR*,† (95% CI)	Birth year <1935, adjusted OR*,‡ (95% CI)
	0	1	2	3+		
0						
Cases	—	998	797	212	1.00 (reference)	1.00 (reference)
Control	—	3,929	3,697	1,210		
1						
Cases	1,037	1,696	517	141	1.00 (0.94-1.06)	1.06 (0.97-1.15)
Control	4,222	8,617	3,071	855		
2						
Cases	825	537	146	52	1.03 (0.95-1.11)	1.11 (0.99-1.25)
Control	4,190	3,354	1,060	323		
3+						
Cases	241	139	48	21	1.13 (0.99-1.28)	1.33 (1.10-1.59)
Control	1,595	944	376	215		
Adjusted OR*,† (95% CI)	1.00 (reference)	0.92 (0.87-0.98)	0.87 (0.80-0.94)	0.82 (0.73-0.94)		
Birth year <1935, adjusted OR*,‡ (95% CI)	1.00 (reference)	0.90 (0.82-0.98)	0.84 (0.75-0.94)	0.85 (0.70-1.01)		

*Data are adjusted for age at diagnosis or enrollment, age at first childbirth, parity, education level closest to age 40, and area of residence closest to age 40.
† P value from test for trend was <0.001 for number of boys and 0.16 for number of girls.
‡ P value from test for trend was 0.004 for number of boys and 0.006 for number of girls.

Table 4. Relation between gender of offspring and maternal risk of ovarian cancer in uniparous, biparous, triparous, and all women

Gender of offspring	Cases/controls	Crude OR (95% CI)	Adjusted OR* (95% CI)	Birth year <1935, adjusted OR* (95% CI)
Among uniparous women (n = 10,724)				
Boy	1,058/4,478	0.97 (0.89-1.07)	0.97 (0.88-1.07)	0.94 (0.82-1.08)
Girl	1,013/4,175	1.00 (reference)	1.00 (reference)	1.00 (reference)
Among biparous women (n = 19,811)				
1st child				
Boy	1,680/8,522	0.96 (0.89-1.04)	0.96 (0.89-1.04)	0.92 (0.82-1.02)
Girl	1,633/7,976	1.00 (reference)	1.00 (reference)	1.00 (reference)
2nd child				
Boy	1,664/8,489	0.95 (0.88-1.03)	0.96(0.89-1.03)	0.92 (0.82-1.03)
Girl	1,649/8,009	1.00 (reference)	1.00 (reference)	1.00 (reference)
1st child/2nd child				
Boy/boy	826/4,200	0.91 (0.82-1.02)	0.91 (0.82-1.02)	0.84 (0.71-0.98)
Boy/girl	854/4,322	0.92 (0.82-1.02)	0.91 (0.82-1.01)	0.87 (0.74-1.02)
Girl/boy	838/4,289	0.91 (0.82-1.01)	0.90 (0.81-1.01)	0.87 (0.75-1.02)
Girl/girl	795/3,687	1.00 (reference)	1.00 (reference)	1.00 (reference)
Among triparous women (n = 9,848)				
1st child				
Boy	722/4,403	0.95 (0.85-1.06)	0.95 (0.85-1.06)	0.93 (0.79-1.10)
Girl	696/4,027	1.00 (reference)	1.00 (reference)	1.00 (reference)
2nd child				
Boy	703/4,423	0.89 (0.80-0.99)	0.89 (0.80-1.00)	0.83 (0.70-0.98)
Girl	715/4,007	1.00 (reference)	1.00 (reference)	1.00 (reference)
3rd child				
Boy	727/4,431	0.95 (0.85-1.06)	0.94 (0.84-1.06)	0.98 (0.83-1.16)
Girl	691/3,999	1.00 (reference)	1.00 (reference)	1.00 (reference)
Three boys	196/1,276	0.81 (0.65-1.01)	0.81 (0.65-1.00)	0.72 (0.52-0.98)
Two boys and one girl	526/3,249	0.86 (0.71-1.03)	0.85 (0.71-1.02)	0.76 (0.58-0.98)
One boy and two girls	512/2,931	0.93 (0.77-1.11)	0.92 (0.76-1.10)	0.77 (0.59-1.01)
Three girls	184/974	1.00 (reference)	1.00 (reference)	1.00 (reference)
All women (n = 45,065)				
All boys	2,103/10,007	0.93 (0.87-0.99)	0.93 (0.87-0.99)	0.88 (0.80-0.97)
Mixed boys and girls	3,297/18,815	0.77 (0.73-0.82)	0.89 (0.83-0.95)	0.89 (0.80-0.98)
All girls	2,007/8,836	1.00 (reference)	1.00 (reference)	1.00 (reference)

*Data are adjusted for age at diagnosis or enrollment, age at first childbirth, education level closest to age 40, and area of residence closest to age 40. For biparous and triparous women, data are further adjusted for age at last birth with the previous covariates. For all women, data are further adjusted for parity.

Strengths of our study include the population-based nature of the study, the largest sample size thus far on this study question, and the histologically verified cases. A potential limitation is the lack of information on family history of ovarian cancer and oral contraceptive use. However, sex ratio is unlikely to be associated with mutations in BRCA1 and BRCA2 (18-20) and with use of oral contraceptives (21). Thus, the association between gender of offspring and ovarian cancer is unlikely to be confounded by these factors. Furthermore, separate analyses were conducted among women born before 1935 among which use of oral contraceptive has been very limited.

The protective role of pregnancy on the development of ovarian cancer can be explained by several biological mechanisms (9). Physiologic conditions related to

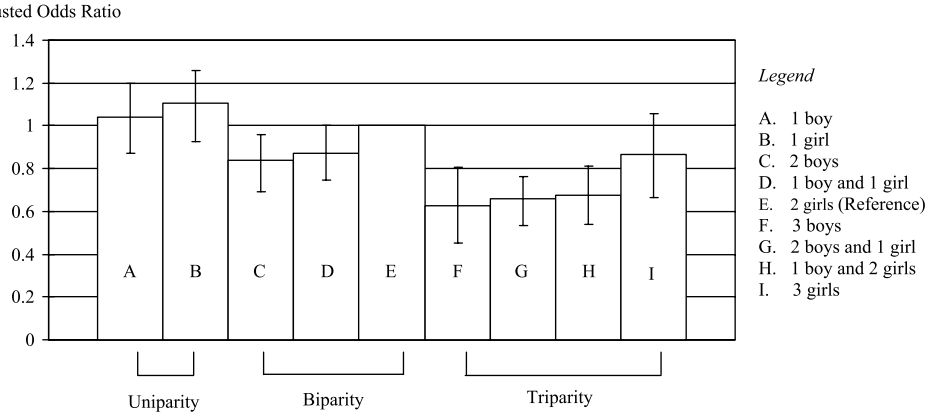

Figure 1. Relation between gender of offspring and maternal risk of ovarian cancer in uniparous, biparous, and triparous women born before 1935 (3,219 cases and 15,810 controls for the three parities). Data are adjusted for age at diagnosis or enrollment, age at first childbirth, education level closest to age 40, and area of residence closest to age 40.

ovulatory trauma (22) and gonadotropin stimulation (23), both among the most recognized etiologic hypotheses on ovarian cancer, are inhibited by childbearing (24). Moreover, it has been suggested that pregnancy confers additional protection through clearance effects on premalignant epithelial ovarian cells (3) and that hormonal changes during pregnancy may be responsible for this mechanism (25-28).

Pregnancies with male or female offspring should have equivalent benefits from anovulation and suppressed secretion of gonadotropins. We explored potential differences in hormones that may underlie the observed difference in maternal ovarian cancer risk between bearing male and female offspring. Table 5 summarizes—from a review of epidemiologic and experimental studies—the association between hormone levels and ovarian cancer risk as well as hormonal differences during pregnancy associated with fetal gender. Estradiol, estrone, and their metabolites stimulate proliferation of malignant and normal ovarian cell lines (29, 30). A role for estrogen in increasing ovarian cancer risk is supported by epidemiologic evidence on long-term use of unopposed estrogen (31). However, no association was found between circulating estrogen levels and ovarian cancer risk (32, 33).

Because pregnancy increases the production of estrogen but plays a protective role in the risk, additional hormones are likely to be involved in the etiology of ovarian cancer (25). Potential candidates include androgens; results from animal studies indicate that testosterone can act as a stimulus in epithelial proliferation of ovary and lead to adenomas in the ovarian parenchyma and papillomas on the surface (34). In humans, circulating androstenedione was found to be positively associated with ovarian cancer risk (32). Several experimental studies indicate a protective effect for progesterone on ovarian carcinogenesis through apoptotic mechanisms (35-37).

Epidemiologic investigation on oral contraceptives provides indirect evidence on the protective potential of progesterone against ovarian cancer. Women who used oral contraceptives containing high-potency progesterone are at a lower risk of ovarian cancer than those using oral contraceptives of low progesterone potency (38). Information is limited on the relation of hCG with ovarian cancer. hCG is elevated during the early period of pregnancy, functions in continued production of progesterone, and regulates the secretion of testosterone by the fetal testes (39). *In vitro* studies showed that medium containing hCG significantly inhibits growth of benign, borderline, and malignant epithelial cell lines of the ovary (40). Tumorigenic effects of insulin-like growth factor-I (IGF-I) in breast, prostate, and colon cancers have been supported by experimental and epidemiologic studies (41). Higher levels of IGF-I have been found to be associated with ovarian cancer risk, particularly among younger women (42). The first column of Table 5 summarizes the above observations.

Maternal and fetal hormone concentrations during normal pregnancy may differ by gender of the fetus. Women carrying a male fetus have lower levels of hCG (11, 43-46) and estriol (12) than those carrying a female fetus. Findings on testosterone have been less consistent: levels in maternal and cord serum at term were not shown to be significantly different by offspring gender in some studies (43, 47), whereas higher maternal and amniotic fluid levels in male bearers were found in others (48, 49). Progesterone levels in maternal and fetal blood tend to be higher in male bearers than female bearers, although the difference was not significant (43, 50). Studies that measured 17-hydroxyprogesterone, a metabolite of progesterone, have found significantly higher blood levels in males than in female newborns (51), particularly among the full-term deliveries (52). Whereas IGF-I plays an important role in fetal growth and development and has a strong positive association with birth weight of newborns (53, 54), gender difference in maternal and fetal levels of IGF-I has not been consistently observed (55, 56). However, in a study that adjusted for maternal factors and ponderal index, higher levels of IGF-I were found in cord blood of female offspring (56). The second column of Table 5 summarizes these findings.

Thus, if these hormones are involved in the pathway for the association between bearing male offspring and ovarian cancer risk, the expected association between hormone and ovarian cancer risk would be null or inverse for estrogen, positive or null for testosterone, inverse or null for progesterone, positive for chorionic gonadotropin, and inverse or null for IGF-I (the third column of Table 5). Our findings on offspring gender agree with expected associations for progesterone and IGF-I.

In addition to differences in pregnancy-related hormones, male bearers have higher serum levels of α-fetoprotein than female bearers (13, 57, 58). However,

Table 5. Associations between pregnancy-related hormones, offspring gender, and ovarian cancer risk

Pregnancy-related hormones and proteins	(1) Possible association between hormone and ovarian cancer risk	(2) Possible association between bearing male offspring and hormone*	(3) Predicted association between bearing male offspring and maternal ovarian cancer risk†	Agreement between the present findings and the predicted association‡
Estrogen	↑/−	↓	−/↓	Partial agreement
Androgens	↑	↑/−	↑/−	Disagreement
Progesterone	↓	↑/−	−/↓	Partial agreement
hCG	↓	↓	↑	Disagreement
IGF-I	↑	−/↓	−/↓	Partial agreement
α-Fetoprotein	0	↑	0	Undetermined

NOTE: ↑, positive association; ↓, inverse association; −, null association; 0, no information.
*Compared with bearing female offspring.
† Predicted associations, based on the possible associations in (1) and (2), between bearing male offspring and ovarian cancer risk.
‡ Agreement or disagreement between the predicted and our observed associations between bearing male offspring and maternal ovarian cancer risk.

there is currently no information on whether α-fetoprotein levels can modify ovarian cancer risk in adult women.

In conclusion, we found that women with male offspring were at a lower risk of invasive epithelial ovarian cancer than those with only female offspring. Further investigations into the effect of progesterone, IGF-I, and α-fetoprotein on ovarian cancer risk are warranted, if the protective effect of bearing male offspring against ovarian cancer is mediated by hormonal and proteomic milieu above and beyond pregnancy-derived benefits of anovulation and gonadotropin suppression.

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