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Characteristics related to the maternal intrauterine environment and risk of epithelial ovarian cancer

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Abstract

Purpose—In contrast to other hormonally mediated cancers such as those of the breast, prostate, and testes, almost no data are available regarding the relation of prenatal characteristics and exposures to subsequent ovarian carcinogenesis. In a population-based study of 812 women aged 35–74 years with epithelial ovarian cancer diagnosed in Washington State from 2002–2005 and 1,313 controls, we assessed the relation of such factors to disease risk.

Methods—Information was collected through in-person interviews and logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—Overall, we noted little evidence that prenatal or birth characteristics including birth weight, birth order, maternal age or *in utero* exposure to cigarette smoking were associated with risk of epithelial ovarian cancer in adulthood. Among women <55 years of age, risk was reduced among those whose weight at birth was < 5.5 pounds (OR and 95% CI= 0.54, 0.31–0.94) relative to those with birth weight 5.5–9 pounds.

Conclusions—In this study, birth weight was associated with risk of epithelial ovarian cancer only among women under 55 years of age. Prenatal influences might be expected to more substantially influence cancer risk at younger ages. Other reports examining associations of ovarian cancer risk with birth weight or other prenatal characteristics are few and have not examined risk separately according to age at diagnosis, suggesting that additional studies may prove useful.

Keywords

ovarian cancer; epidemiology; prenatal

Introduction

Characteristics such as birth weight, birth order and maternal age have been hypothesized to influence risk of hormonally-mediated cancers, perhaps serving as indicators of *in utero* exposure to hormones such as estrogen and testosterone (1,2). While the possible contribution of the intrauterine environment to risk of breast, testicular, prostate, and some other cancers has received attention in multiple studies, almost no reports have examined associations with

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ovarian cancer. Thus, in a population-based case-control study of women aged 35-74 years, we assessed the relation of prenatal and birth characteristics with risk of epithelial ovarian cancer.

Materials and Methods

The study population and methods have been described (3). Female residents of a thirteen-county area of western Washington State, 35-74 years of age, diagnosed with a primary invasive or borderline epithelial ovarian tumor from 2002 through 2005 were identified through a population-based registry that is part of the Surveillance, Epidemiology, and End Results program of the US National Cancer Institute. Of 1,058 eligible case women identified, 812 (76.7%) were interviewed; of the interviewed cases, 595 had invasive disease. Reasons for not obtaining an interview included: physician refusal (n=23); inability to locate the patient (n=10); patient refusal (n=110) and death (n=103). Among interviewed women, the large majority (73%) of those with borderline tumors had localized disease, while 85% of women with invasive tumors had regional or distant disease, according to the SEER staging system; these proportions were quite similar to the distribution among all eligible women (74 and 86%, respectively).

Controls were selected by random digit dialing (4) using stratified sampling in five-year age categories, one-year calendar intervals and two county strata in a 2:1 ratio to women with invasive epithelial ovarian cancer. For 14,561 (82.0%) of the 17,768 telephone numbers belonging to a residence, we determined whether an eligible (i.e., age- and county-eligible and, if so, with at least one ovary and no prior history of ovarian cancer) woman resided there. Of the 1,561 women identified as eligible controls, 1,313 were interviewed (84.1%). To maximize the likely accuracy of available variables as proxy measures of the prenatal environment, we excluded 40 women who had been adopted and an additional 51 women who were not singleton births, resulting in 778 cases and 1,256 controls for this analysis.

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent before participating. Information was obtained during an in-person interview. Prenatal characteristics of the study participants were recorded as described below, with the birth of the study participant designated as the index birth. Women were asked their mother's age at index birth and their mother's number of pregnancies resulting in live births prior to the index birth (henceforth referred to as birth order). In addition, women reported whether the index pregnancy had resulted in a twin or multiple birth. They were asked their birth weight in pounds and ounces; these responses were converted to grams and grouped in 500-gram categories for analysis. When the weight was unknown or could only be partially reported, participants were asked if they weighed less than 5.5 pounds, or 9 pounds or more, at birth. Maternal smoking during the index pregnancy was also recorded.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression. The analyses shown were adjusted for the frequency matching variables of age, year of diagnosis/reference date, and county of residence as well as duration of hormonal contraception and number of full-term births. Other characteristics examined as potentially confounding the associations of interest included: race/ethnicity; cigarette smoking; education; age at menarche; body weight and body mass index (BMI), assessed both at age 30 years and five years before the reference date; tubal ligation; hysterectomy; use of hormone replacement therapy; family history of breast and/or ovarian cancer; and personal history of breast cancer. Additional adjustment for these characteristics did not result in a meaningful change in odds ratio estimates. We also examined potential confounding influences of maternal age at index pregnancy, birth weight, and birth order on each of the other variables. We used polytomous

logistic regression for analyses that separated case women according to the degree of invasiveness and/or histologic type of the tumor. Tests for linear trend were done using the maximum likelihood test with the categorical variable of interest entered as a continuous term. STATA was used for analysis (version 9.2; STATA Corporation, College Station, TX).

Results

The majority of cases (89.2%) and controls (90.0%) were non-Hispanic whites. Cases were less likely than controls to have given birth, used hormonal contraception, or to have had a tubal ligation, and family history of ovarian cancer was more commonly reported among cases (data not shown).

Sufficient information to allow assessment of birth weight within 500-gram categories was reported by 579 cases (74.4%) and 930 controls (74.0%). For most of the remaining women, the collected data allowed us to assign birth weight within categories of <5.5, 5.5-9, or >9 pounds (Table 1). Whether or not women with more broadly estimated birth weights were included in the analysis, we observed little evidence that this characteristic was associated with risk in the overall study population. Also, we noted no association with mother's age at index birth, number of births prior to the index birth, or smoking during the index pregnancy.

Because we hypothesized that prenatal influences might more substantially influence cancer risk at younger ages, we conducted subanalyses to separately assess risk in women <55 years of age (the approximate midpoint of the age distribution of cases) and women 55 years or older. Among women <55 years, risk of epithelial ovarian cancer was reduced by nearly 50% among women who weighed <5.5 pounds at birth (Table 2). Also, in this age group, a trend of increasing risk with increasing birth weight was observed, both in an analysis limited to women whose birth weight could be placed within a 500-gram category (p trend= 0.03) and when the analysis also included women whose birth weight was estimated in one of three broader categories (p trend= 0.01). The relative risks among women with birth weight <5.5 pounds, relative to 5.5-9 pounds, were 0.29 (95% CI 0.09-0.97) and 0.69 (CI 0.37-1.30) among women aged 35-44 years and 45-54 years, respectively (data not shown). Risk did not vary according to mother's age at index birth, birth order, or maternal smoking during pregnancy. Among women $\geq$ 55 years, we noted no association with any of the prenatal or birth characteristics studied (Table 3).

In most cases, additional adjustment of our analyses for other prenatal characteristics had no appreciable impact on the results. Among women under 55 years, adjustment of birth order by maternal age slightly increased the strength of association (e.g., risk among women who were the third or subsequent births= 1.42, 95% CI 0.88-2.28; p trend=0.17); however, wide confidence bounds suggest this may reflect a chance effect.

The reduction in risk among younger women with birth weight <5.5 pounds was evident for both borderline and invasive ovarian tumors (ORs and 95% CIs for weight <5.5 pounds relative to 5.5-<9 pounds among women <55 were 0.46, 0.20-1.06, and 0.59, 0.31-1.11, respectively). While our ability to examine risks among histologic subtypes was limited by small numbers, we observed no clear differences in the association with birth weight or other prenatal characteristics according to tumor histology (serous, mucinous, endometrioid, clear cell, or other epithelial), whether in analyses that included all women, or separately examined women less than 55 years and 55 years of age or older, or further stratified tumors according to the degree of invasiveness (data not shown).

Discussion

Differences in characteristics of cases and controls who did or did not choose to participate might influence the results of this study, as might errors in recall of prenatal and birth characteristics. Little information is available regarding the accuracy of self-reported birth weight or other prenatal exposures. In one study (5), recall of birth weight by study subjects was fairly similar to that reported by their mothers (Spearman correlation coefficient =0.77). Some evidence suggests that the accuracy of recalled birth weight may be greater in younger women (6). While we have no external means of validating recalled birth weight in the current study, a greater proportion of younger than older women (among both cases and controls) were able to provide sufficient information in answer to an open-ended question to allow an examination of birth weight within 500-gram categories, while larger proportions of older cases and controls could only be grouped according to three pre-supplied broad categories of birth weight.

The mechanisms of prenatal influences on cancer risk are not well understood, but may involve *in utero* hormonal influences or an altered number of cells at risk for later carcinogenesis (2). Some studies of breast and testicular cancer suggest an increased risk among firstborn individuals, possibly reflecting higher bioavailable estrogen due to less sex-hormone binding globulin in nulliparous women (1,2,7). Higher birth weight may reflect maternal obesity, which may be associated with a relatively estrogenic *in utero* environment; or birth weight may serve as a proxy of other aspects of fetal growth, gestation length, or other pregnancy hormone levels such as insulin-like growth factors (1). Reduced fetal growth has been associated with a number of ovarian alterations later in life, including a reduced ovarian fraction of primordial follicles and anovulation in late adolescence (8,9). In one study (10), mean ovarian volume was reduced by 38% among adolescent girls who were born small for gestational age relative to similarly-aged girls who were not. Also, in a related study (11), girls born small for gestational age had lower average birth weights than girls who were not (mean weights of 2416 and 3301 grams in the two groups, respectively), and exhibited a serum hormonal profile indicative of ovarian hyporesponsiveness to follicle stimulating hormone. It is possible that some of these alterations may have relevance to ovarian cancer risk: e.g., reduced ovarian volume may indicate a lesser number of epithelial cells at risk, or ovarian hormone production may be reduced in ovaries with a smaller stromal compartment.

Almost no epidemiologic evidence exists to support or refute the hypothesis that prenatal factors may be involved in ovarian carcinogenesis. Similar to the current study, no association with maternal smoking was noted in a case-control study conducted in Hawaii (12). In a retrospective cohort analysis of 5,585 women that employed medical-records-based assessments of birth weight and weight at one year of age (13), no association of birth weight with risk of fatal ovarian cancer was observed, while women in the highest category of weight at one year of age were at increased risk (>24 lbs; standardized mortality ratio= 3.6, CI: 1.7, 6.5). In a cohort of 5,346 Swedish women (of whom 89 developed ovarian cancer), birth characteristics standardized for gestational age were examined, with no associations with ovarian cancer risk seen for birth weight, birth length, or head circumference; no data regarding differences in ovarian cancer risk by age at diagnosis were presented (14).

While we observed no clear association of birth weight with ovarian cancer risk overall, among women under 55 years of age, risk was reduced among women with low birth weight. Prenatal influences on ovarian cancer risk might operate more strongly among women who develop this disease at a younger age, as such a pattern has been observed in studies of birth weight and risk of breast cancer (1). Our results may also, to some extent, reflect improved accuracy of recalled birth weight among younger women. Other studies examining this potential association are few and have not examined risk separately according to age at cancer diagnosis.

The limited extent of published data, coupled with the findings of our study, suggest that additional studies of prenatal factors and ovarian cancer risk may prove useful.

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Table 1
Risk of epithelial ovarian cancer according to prenatal and birth characteristics among women aged 35-74 years

	Cases (n= 778)		Controls (n=1256)		OR ²	95% CI
	n	% ¹	n	% ¹		
Birth weight (g)						
<2500	70	12.1	123	13.2	0.87	0.61-1.24
2500-2999	124	21.4	218	23.4	0.85	0.64-1.14
3000-3499	210	36.3	328	35.3	1.00	Ref
3500-3999	116	20.0	171	18.4	1.02	0.75-1.39
≥4000	59	10.2	90	9.7	0.97	0.66-1.42
missing	199	(25.6)	326	(26.0)		<i>p trend=0.30</i>
Birth weight (lbs)						
<5.5	60	7.9	110	9.0	0.89	0.63-1.24
5.5- <9.0	640	84.5	1028	84.2	1.00	Ref
≥9.0	57	7.5	83	6.8	1.06	0.74-1.53
missing	21	(2.7)	35	(2.8)		<i>p trend=0.44</i>
Mother's age at index birth (yrs)						
<20	64	8.3	113	9.0	0.89	0.62-1.28
20-24	222	28.7	340	27.2	1.00	Ref
25-29	219	28.3	378	30.2	0.88	0.69-1.12
30-34	159	20.6	270	21.6	0.88	0.67-1.15
≥ 35	109	14.1	149	11.9	1.07	0.78-1.45
missing	5	(0.6)	6	(0.5)		<i>p trend=0.85</i>
Births prior to index birth						
0	269	34.8	486	38.8	1.00	Ref
1	227	29.4	360	28.8	1.06	0.84-1.34
2	135	17.5	203	16.2	1.18	0.90-1.55
≥3	142	18.4	203	16.2	1.21	0.92-1.59
missing	5	(0.6)	4	(0.3)		<i>p trend=0.12</i>
Maternal smoking						
no	516	72.7	846	72.9	1.00	Ref
yes	194	27.3	314	27.1	0.97	0.78-1.21
missing	68	(8.7)	96	(7.6)		

¹ Percentages in parentheses are based on 778 cases and 1256 controls; all others are based on cases and controls with known data for the relevant variable.

² Adjusted for age, reference year, county, number of full-term births, and duration of hormonal contraception.

Table 2
Risk of epithelial ovarian cancer according to prenatal and birth characteristics, among women < 55 years of age

	Cases (n=380)		Controls (n=505)		OR ²	95% CI
	n	% ¹	n	% ¹		
Birth weight (g)						
<2500	26	8.9	52	13.0	0.58	0.33-1.02
2500-2999	68	23.4	105	26.3	0.79	0.52-1.20
3000-3499	104	35.7	136	34.1	1.00	Ref
3500-3999	60	20.6	70	17.5	1.01	0.64-1.60
≥4000	33	11.3	36	9.0	1.15	0.65-2.02
missing	89	(23.4)	106	(21.0)		<i>p trend=0.03</i>
Birth weight (lbs)						
<5.5	22	6.0	50	10.0	0.54	0.31-0.94
5.5- <9.0	314	85.6	417	83.7	1.00	Ref
≥9.0	31	8.4	31	6.2	1.39	0.80-2.39
missing	13	(3.4)	7	(1.4)		<i>p trend=0.01</i>
Mother's age at index birth (yrs)						
<20	35	9.2	53	10.5	0.85	0.50-1.42
20-24	109	28.7	132	26.2	1.00	Ref
25-29	108	28.4	150	29.8	0.82	0.57-1.20
30-34	72	18.9	106	21.0	0.76	0.50-1.14
≥35	56	14.7	63	12.5	0.99	0.62-1.58
missing	0	(0.0)	1	(0.2)		<i>p trend=0.76</i>
Births prior to index birth						
0	108	28.5	154	30.6	1.00	Ref
1	121	31.9	152	30.2	1.18	0.82-1.69
2	71	18.7	97	19.3	1.10	0.73-1.66
≥3	79	20.8	100	19.9	1.21	0.81-1.82
missing	1	(0.3)	2	(0.4)		<i>p trend=0.42</i>
Maternal smoking						
no	239	67.3	313	67.2	1.00	Ref
yes	116	32.7	153	32.8	1.02	0.75-1.39
missing	25	(6.6)	39	(7.7)		

¹ Percentages in parentheses are based on 380 cases and 505 controls; all others are based on cases and controls with known data for the relevant variable.

² Adjusted for age, reference year, county, number of full-term births, and duration of hormonal contraception.

Table 3
Risk of epithelial ovarian cancer according to prenatal and birth characteristics, among women ≥ 55 years of age

	Cases (n=398)		Controls (n=751)		OR ²	95% CI
	n	% ¹	n	% ¹		
Birth weight (g)						
<2500	44	15.3	71	13.4	1.17	0.74-1.86
2500-2999	56	19.4	113	21.3	0.91	0.60-1.37
3000-3499	106	36.8	192	36.2	1.00	Ref
3500-3999	56	19.4	101	19.0	1.04	0.68-1.58
≥ 4000	26	9.0	54	10.2	0.81	0.47-1.40
missing	110	(27.6)	220	(29.3)		<i>p trend=0.51</i>
Birth weight (lbs)						
<5.5	38	9.7	60	8.3	1.24	0.80-1.93
5.5- <9.0	326	83.6	611	84.5	1.00	Ref
≥ 9.0	26	6.7	52	7.2	0.85	0.52-1.41
missing	8	(2.0)	28	(3.7)		<i>p trend=0.23</i>
Mother's age at index birth (yrs)						
<20	29	7.4	60	8.0	0.89	0.53-1.50
20-24	113	28.8	208	27.9	1.00	Ref
25-29	111	28.2	228	30.6	0.93	0.67-1.30
30-34	87	22.1	164	22.0	1.02	0.72-1.46
≥ 35	53	13.5	86	11.5	1.16	0.76-1.77
missing	5	(1.3)	5	(0.7)		<i>p trend=0.41</i>
Births prior to index birth						
0	161	40.9	332	44.3	1.00	Ref
1	106	26.9	208	27.8	1.03	0.76-1.41
2	64	16.2	106	14.2	1.32	0.91-1.92
≥ 3	63	16.0	103	13.8	1.25	0.86-1.82
missing	4	(1.0)	2	(0.3)		<i>p trend=0.12</i>
Maternal smoking						
no	277	78.0	533	76.8	1.00	Ref
yes	78	22.0	161	23.2	0.93	0.68-1.28
missing	43	(10.8)	57	(7.6)		

¹ Percentages in parentheses are based on 398 cases and 751 controls; all others are based on cases and controls with known data for the relevant variable.

² Adjusted for age, reference year, county, number of full-term births, and duration of hormonal contraception.