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Birth Characteristics And Risk Of Early-Onset Ovarian Cancer

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Abstract

Background: Little is known on the etiology of early-onset ovarian cancer. We conducted a population-based case-control study in California to evaluate the role of birth characteristics on the development of early-onset ovarian cancer.

Methods: Data from the California Linkage Study of Early-onset Cancers, a population-based case-control linkage study, was used. This study included 895 first primary ovarian cancer patients who were born in 1978 – 2013 and diagnosed at the age of 0-37 years and 44,750 controls frequency matched on year of birth. We utilized multivariable logistic regression analyses with the backward selection procedure to estimate odds ratios (OR) and 95% confidence intervals (CIs).

Results: In the multivariable model, compared with non-Hispanic whites, Hispanics (OR= 1.63, 95% CI: 1.36 - 1.96), and other race/ethnicity (OR= 1.51, 95% CI: 1.23 - 1.84) had increased risk of early-onset ovarian cancer. In addition, every 500-gram increase in birth weight was associated with a 10% increase in the risk of early-onset ovarian cancer. Among non-Hispanic whites, individuals with foreign-born mothers had a 55% (95% CI: 1.06 - 2.27) elevated risk of early-onset ovarian cancer than those with United States-born mothers. Having a non-private insurance type decreased risk of early-onset ovarian cancer among those 0-14 years of age (OR = 0.60, 95% CI: 0.43 - 0.83); a similar decreased risk was also observed for teratoma (OR= 0.62, 95% CI: 0.42 - 0.90).

Conclusions: Our findings support the role of race/ethnicity and birth characteristics in the etiology of early-onset ovarian cancer. Risk factors of early-onset ovarian cancer show distinct features from those of later onset.

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Introduction

Ovarian cancer is the second most common gynecologic cancer, with 21,410 estimated new cases in 2021, and the fifth leading cause of cancer death among females in the United States (US).[1] The overall incidence of ovarian cancer has been decreasing since mid-1980s to 2014, from 16.6/100,000 to 11.8/100,000;[2] however, according to the Surveillance, Epidemiology, and End Results (SEER) Program incidence data, an increased trend of pediatric ovarian cancer (< 15 years of age) has been observed since 2000.[3] Ovarian tumors are derived from one of three cell types: epithelial cells, germ cells, and stromal cells.[4] Common histologic subtypes of ovarian cancer differ by age and race/ethnicity.[2,5-7] Germ cell tumors are the dominant histologic subtype in the prepubertal age group;[8] starting from age 10 to 14 years, the incidence of epithelial cell tumors are reported to increase, and continue to increase to become the dominant subtype in adults.[9] Hispanics have the highest incidence of germ cell tumors, yet non-Hispanic whites have higher incidence of epithelial ovarian cancer than other race/ethnicity groups.[2]

Findings from previous studies suggest that prenatal and early life exposures are associated with the development of ovarian cancer in adulthood.[10,11] The Million Women's Study reported a non-linear association between birthweight and risk of ovarian cancer among women ages 50 years and older.[12] Similarly, a Danish study found that adult women (18 years or older) with lower (2.0-3.25 kilograms) and higher (3.75-5.5 kilograms) birth weights had an increased risk of epithelial ovarian cancer, especially serous ovarian cancer, than those with a birthweight of 3.26-3.75 kilograms.[10] Moreover, it has been reported that women with rapid weight gain in infancy had higher risk of ovarian cancer death at ages of 32-68 years.[11] Furthermore, prenatal events are also hypothesized to be linked with the development of germ cell tumors.[13]

There is a paucity of studies on the etiology of early-onset ovarian cancer. Of all malignant ovarian tumors, epithelial ovarian cancers constitute more than 90%, germ cell tumors and sex cord-stromal tumors consist of 2-3% and 5-6%, respectively.[4] In addition, the majority of ovarian cancers develop after 45 years.[14] Thus, studies on etiology of ovarian cancer tend to focus on epithelial ovarian tumors, and the median age of women included in the studies typically are 40 years and older.[15,16] However, distribution of histological subtype is different by age.[17,18] Over 90% of ovarian cancers diagnosed among women 40 years of age and older are epithelial cell ovarian cancer.[17] Germ cell tumors are reported to be diagnosed typically in women up to 30 years of age.[18] In addition, each histological subtype of ovarian cancer may have its own distinct causes.[19] Thus, risk factors for early-onset ovarian cancer might be different from those of ovarian cancer that occur in late adulthood.

To fill the knowledge gap, we conducted a population-based case-control study in California to evaluate the role of birth characteristics on the development of early-onset ovarian cancer.

Methods

We leveraged data from the California Linkage Study of Early-onset Cancers (CALSEC), a population-based case-control linkage study. The CALSEC linked California birth records maintained by the Center for Health Statistics and Informatics, California Department of Public Health from 1978-2013 with statewide cancer diagnosis data from the California Cancer Registry during 1988-2013.

Study population

This study included first primary ovarian cancer patients who were born in 1978–2013 and

diagnosed at the age of 0-37 years. Of the 912 first primary ovarian cancer patients, patients with missing information on residence (n = 2), maternal age (n = 1), birth weight (n = 1), birth order (n = 5), maternal birthplace (n = 2), history of stillbirth/miscarriage (n = 4), status of abnormality (n = 2) were excluded.

For each case, 50 control subjects were randomly selected from the statewide birth records based on the same eligibility criteria. Controls were matched on year of birth and had no history of cancer diagnosis based on California Cancer Registry records at the time of linkage.

The final cohort included 895 early-onset ovarian cancer cases and 44,750 controls. The study protocol was approved by the Institutional Review Boards at the California Health and Human Services Agency, University of California, Berkeley, and Yale University.

We used the International Agency for Research on Cancer's classification system to categorize ovarian cancer.[20] This classification has been known to be the most appropriate classification system in the pediatric and young adult population.[21]As shown in Table 1, we classified ovarian cancers as epithelial ovarian cancers , sex cord-stromal tumors, germ cell tumors, other specified malignant neoplasms (including Mullerian mixed tumor, carcinosarcoma) and unspecified malignant neoplasms. Germ cell tumors, the most common group of ovarian cancer in our study population, were further specified as teratoma, dysgerminoma, and yolk sac tumor, and other subtypes, including mixed germ cell tumor.[22]

Variable of interest

We abstracted birth characteristics and parental information from birth records. Birth characteristics included child's year of birth (1978-1983, 1984-1990, 1991-2013), birthweight in

grams (<2500, 2500-2999, 3000-3499, 3500-3999, and ≥4000), race/ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Asian/Pacific Islander, Other), gestational age in weeks (22-36, 37-41, 42-44, Unknown), birth order (1st, 2nd, 3rd or higher), method of delivery (Vaginal or Cesarean section), and plurality (Singleton or Multiple). Parental information included maternal and paternal education level (High school or less, At least some college, Unknown), maternal age at delivery in years(<20, 20-24, 25-29, 30-34, ≥35), pregnancy complications (None, Yes, Unknown), history of previous cesarean section (No, Yes, Unknown), and history of miscarriage or stillbirth (Never, Ever), maternal birthplace (United States, Foreign), and mother's private insurance status (Yes, No, Unknown), and paternal age at delivery in years (<20, 20-24, 25-29, 30-34, 35-39, ≥40 years, or Unknown). Due to the small number of Asian/Pacific Islanders, we combined Asian/Pacific Islander and Other ethnicity as Other in the analyses. We also linked birth certificate with 1990 census (born before 1996), 2000 (born in 1996-2005) census data and 2008-2012 American Community Survey 5-year data (born in 2006 and later) to obtain percentage of population living below poverty and percentage of college and higher education in the census block group level. We further categorized percentage of population living below poverty in the census block group as <13%, 13-<26%, 26-<46%, ≥46%, and Unknown; and percentage of college and higher education in the census block group as 0-<35%, 35-<56%, ≥56%, and Unknown.

Statistical Methods

Categorical variables were presented using frequencies and percentages, and continuous variables were summarized by means and standard deviations. Pearson's χ^2 test for categorical variables and the Student's t-test for continuous variables were used to compare baseline characteristics across

cases and controls. To assess factors associated with risk of early-onset ovarian cancer, multivariable logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI). The initial model included birthweight, gestational age, birth order, method of delivery, plurality, maternal age at delivery, pregnancy complications, history of previous cesarean section, history of miscarriage or stillbirth, race/ethnicity, maternal and paternal education level, paternal age at birth, maternal birthplace, percentage of population living below poverty in the census block group, percentage of college and higher education in the census block group, and mother's private insurance status. After a backward selection using SAS and considering known general risk factors of reproductive cancers, the final model included race /ethnicity, birthweight in grams, maternal birthplace, percentage of college and higher education in the census block group, and mother's private insurance status. The same variables were included in the multivariable logistic regression model for both the primary and stratified analyses by race/ethnicity, age at diagnosis (children: 0-14 years, adolescent: 15-19 years, and young adults: 20-37 years), and ovarian cancer subtype. All analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) with 2 sided tests and a type I error of 5%.

Results

Of the 895 early-onset ovarian cancer patients, 548 (61.2%) were germ cell tumors and 273 (30.5%) were epithelial ovarian cancers (Figure 1). Among the subtypes of germ cell tumors, teratoma was the most frequent subtype (n = 242, 44.2%), followed by dysgerminoma (n = 128, 23.4%), and yolk sac tumor (n = 75, 8.4%). Nearly half (49.7%) of the women with early-onset ovarian cancer in our study were Hispanics.

As shown in Figure 2, germ cell tumor was the most common subtype in all three race/ethnicity

groups, with 50.6%, 67.9% and 60.4% in non-Hispanic white, Hispanic and other race/ethnicity, respectively. When further stratified by age at diagnosis, among children and adolescents, germ cell tumors consisted of more than 67% of all ovarian cancers in both non-Hispanic white and Hispanic. Among young adults, 64.1% of non-Hispanic white women had epithelial ovarian cancer; nevertheless, among Hispanic women, 44.7% and 49.7% had germ cell and epithelial ovarian cancer, respectively.

Compared with controls, cases were more likely to be Hispanics and Asian/Pacific Islanders, have higher birthweight and less-educated parents (Table 2). In addition, cases were more likely to have foreign-born mothers.

Overall study population

In multivariable analysis (Table 3), Hispanics (OR = 1.63, 95% CI: 1.36 - 1.96) and other race/ethnicity (OR = 1.51, 95% CI: 1.23 - 1.84) had an increased risk of ovarian cancer compared to non-Hispanic whites. Birthweight was associated with ovarian cancer risk; the OR for a 500-gram increase was 1.10 (95% CI: 1.04 - 1.17). In addition, compared with individuals whose mothers had private insurance, individuals whose mothers did not have a private insurance were associated with a decrease in the risk of early-onset ovarian cancer (OR = 0.79, 95% CI: 0.64 - 0.98).

Stratification by race/ethnicity

Among both non-Hispanic whites and Hispanics, higher birthweight was associated with increased risk of ovarian cancer. Specifically, compared with those with a birthweight of 3000-3499 grams, non-Hispanic whites with a birthweight of 3500-3999 grams and Hispanics with a birthweight of

≥4000 grams had 61% (95% CI: 1.19 - 2.17) and 47% (95% CI: 1.06 - 2.04) increased risk of ovarian cancer, respectively (Table 4). In addition, risk of ovarian cancer increased by 55% (95% CI: 1.06 - 2.27) among non-Hispanic whites with foreign-born mothers than those with US-born mothers.

Stratification by age at diagnosis

Results in adolescent and young adults, were similar (Table 5). In both age groups, being Hispanic or other ethnicity, and having higher birthweight were associated with an increased risk of ovarian cancer. Notably, among adolescents, every 500-gram increase in birthweight was associated with a 15% increase in the risk of ovarian cancer. Among girls aged 0-14 years, not having a private insurance was associated with a decreased risk of ovarian cancer (OR = 0.60, 95% CI: 0.43 - 0.83).

Stratification by ovarian cancer subtype

Impact of race/ethnicity was observed on the risk of overall germ cell tumors, as well as the two major type of germ cell tumors. Compared with non-Hispanic whites, Hispanics had a nearly one-fold increased risk of germ cell tumor (OR = 2.01, 95% CI: 1.58 - 2.55). Birthweight was associated with risk of epithelial ovarian cancer but not germ cell tumor (Table 6). Every 500-gram increase in birthweight was associated with a 14% (95% CI: 1.02 - 1.28) increase in the risk of epithelial ovarian cancer. In addition, women whose mothers did not have private insurance were at a decreased risk of germ cell tumor compared to those whose mother had private insurance (OR = 0.67, 95% CI: 0.52 - 0.86).

Discussion

To the best of our knowledge, our study is the first to evaluate associations between birth characteristics and early-onset ovarian cancer. In this large population-based study, we found that Hispanics had an increased risk of developing early-onset ovarian cancer, especially germ cell tumors. Higher birthweight was also associated with the risk of early-onset ovarian cancer. In addition, our findings also suggested that a decreased risk of early-onset ovarian cancer among women whose mothers did not have private insurance compared to those whose mothers had private insurance. These associations were not observed in all subgroup analyses, but the estimated ORs were in the same direction.

Race and ethnicity

We found that Hispanics had an increased risk of developing early-onset ovarian cancer, especially germ cell tumors. This finding is consistent with incidence of non-epithelial cell tumors by race/ethnicity or geographic region. Studies using the SEER data also found that Hispanics had a higher incidence of ovarian germ cell tumors than non-Hispanic whites.[2,23] Another study also reported that among children 0-19 years, compared with non-Hispanic whites, Hispanics had an increased risk for gonadal germ cell tumors.[24] Given that the Hispanic population has increased by 1.2 million between 2014 and 2015, which amount to approximately half of the increase in the overall US population,[25] future research is needed to elucidate further public health implications of the increased risk of early-onset ovarian cancer in Hispanics.

Our findings of increased risk of early-onset ovarian cancer among Hispanics and other race, as well as offspring of foreign-born non-Hispanic whites are in accord with reports of a possible role of genetic etiology in the pathogenesis of early-onset ovarian cancer.[26] World widely, incidence of ovarian germ cell tumors was highest in Central America and Eastern Asia, and concomitantly

high among Hispanics and Asian Pacific Islanders in the US, suggesting a possible genetic etiology.[26] Also, significant increase over time in the incidence of ovarian germ cell tumors has been observed in Western Europe compared to other parts of Europe for ages 0-19 years.[26] It has been suggested that different genetic patterns among separate geographic origins of Europeans may play a role in epithelial ovarian cancer.[27] Associations between ovarian germ cell tumors and SNPs in specific genetic locations also support the possibility of genetic etiology.[28]

Birthweight

In our study, higher birthweight was associated with the risk of early-onset ovarian cancer in the overall population. Previous studies have inconsistent findings on the association between birthweight and risk of ovarian cancer.[29,30] One study reported an overall 7% increase in risk of cancer for a birthweight increase of 1000 grams.[30] Other studies reported non-linear associations between birthweight and risk of overall ovarian cancer.[10,12] However, in a study using the data from the Nurses' Health Study, there was no association between epithelial ovarian cancer and birthweight.[29]

Birthweight has been speculated to be the outcome of fetal exposures that may impact the development of chronic diseases later in life.[31] Notably, increased risk of ovarian cancer in later life in women with higher birthweight has been attributed to abnormally high gonadotropin release during fetal development and in infancy, promoting increased estrogen secretion resulting in infant weight gain and affecting the development of ovarian cancer later in life.[10,11] Higher birthweight has also been associated with an increased number of cells at risk of developing cancer.[32] In addition, changes in the programming of the insulin-like growth factor in the fetal period may accelerate cell proliferation after birth.[33] Children with higher birthweight have increased levels of

insulin-like growth factor, which also facilitate cell proliferation responsible for tumorigenesis.[34]

Socioeconomic status

Our findings of decreased risk of early-onset ovarian cancer among women whose mothers did not have private insurance compared to those whose mothers had private insurance suggest that higher risk of early-onset ovarian cancer among women with high socioeconomic status (SES). However, given that SES is a multifactorial measure, conflicting results regarding association of SES and incidence of ovarian cancer have been reported.[35,36] A case-control study observed an increased risk of epithelial ovarian cancer among women younger than 45 years with at least 12 years of education or in high social status.[37] Among Danish women ages 30 years and older, incidence of ovarian cancer was higher in women with higher income in comparison to women with middle income; in addition, a difference in incidence of ovarian cancer of 2/100,000 person-years between women with higher education and basic education was observed.[38] However, a US study found higher education status was associated with decreased ovarian cancer risk among African-American women.[35] In addition, previous studies also found that women who scored higher in the socioeconomically deprived index score[36] or had an education level of high school or less[39] had a higher risk of being diagnosed with ovarian cancer at a more advanced stage, which suggests a potential role of lower SES on the delay of diagnosis of ovarian cancer. Further studies on the role of SES and risk of ovarian cancer are needed.

To date, our study is the most recently updated analysis of the epidemiology of early-onset ovarian cancer using a large geographic population. Strengths of our study were the large sample size, and the established temporal relationship between the potential risk factors studied and the diagnosis of ovarian cancer, owing to the design of this study. Limitations were that our sample represents a

specific geographic region, so our results may not be representative of the whole US population. Also, we could not account for potential California residents who moved out of state and afterwards got diagnosed with ovarian cancer. However, this possibility would have resulted in an increased number of cases in our study population and would not have affected the significance of our current conclusions. Since detailed clinical history such as height, body mass index, or presence of gestational diabetes and exposure information regarding ovarian cancer was largely unavailable due to the design of our study, our analysis was limited to information available from the birth certificates of study subjects. Missing data, small sample size in specific race/ethnicity and histologic subtype subgroups and unknown confounders limited our scope of analysis and limited the significance of our results.

Conclusions

Our findings support the role of race/ethnicity and birth characteristics in the etiology of early-onset ovarian cancer. Risk factors of early-onset ovarian cancer show distinct features from those of later onset, possibly due to the distinct histologic subtypes across the age at diagnosis. Knowledge of risk factors of early-onset ovarian cancer may be helpful in preventing this disease by modifying possible external factors.

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Table 1. Early-onset Ovarian Cancer Classification

	International Classification of Diseases for Oncology – 3rd edition
Epithelial ovarian cancer	8010-8231, 8246-8576, 9014-9015, 9110
Sex cord-stromal tumor	8590-8671
Germ cell tumor	8240-8245, 9060-9102
Dysgerminoma	9060
Yolk sac tumor	9071
Teratoma	9080-9084
Other	8240-8245, 9061-9070, 9072-9079, 9085-9102
Other specified	8800-9000, 9105, 9120, 9260, 9364, 9473, 9580, 9590-9975
Unspecified	8000-8005

Table 2. Characteristics of Study Population by Case/Control Status

	Case		Control		P value
	N	%	N	%	
Total	895		44,750		
Race/ethnicity					<0.01
Non-Hispanic white	263	29.4	18,118	40.5	
Non-Hispanic black	75	8.4	3,882	8.7	
Hispanic	445	49.7	18,079	40.4	
Asian/Pacific Islander	103	11.5	3,985	8.9	
Other	9	1.0	686	1.5	
Year of birth					1.00
1978-1983	305	34.1	15,250	34.1	
1984-1990	295	33.0	14,750	33.0	
1991-2013	295	33.0	14,750	33.0	
Birthweight, grams					<0.01
Median [IQR]	3370 [3010-3730]		3331[3005-3657]		
<2500	43	4.8	2,879	6.4	
2500-2999	168	18.8	7,793	17.4	
3000-3499	309	34.5	17,880	40.0	
3500-3999	289	32.3	12,405	27.7	
≥4000	86	9.6	3,793	8.5	
Gestational age, weeks					0.51
22-36	65	7.3	3,746	8.4	
37-41	653	73.0	32,346	72.3	
42-44	97	10.8	4,906	11.0	

Unknown	80	8.9	3,752	8.4	
Birth order					0.10
1st	341	38.1	18,347	41	
2nd	279	31.2	13,971	31.2	
3rd or higher	275	30.7	12,432	27.8	
Plurality					0.55
Singleton	875	97.8	43,747	97.8	
Multiple	20	2.2	1,003	2.2	
Maternal age at delivery, years					0.91
Median [IQR]	26 [22-31]		26 [22-30]		
<20	103	11.5	5,372	12.0	
20-24	256	28.6	12,671	28.3	
25-29	260	29.1	13,428	30.0	
30-34	190	21.2	9,018	20.2	
≥35	86	9.6	4,261	9.5	
Maternal educational level					<0.01
High school or less	294	32.9	13,347	29.8	
At least some college	125	14.0	7,573	16.9	
Unknown	476	53.2	23,830	53.2	
Paternal age at delivery, years					0.91
<20	35	3.9	1,899	4.2	
20-24	192	21.5	9,136	20.4	
25-29	241	26.9	12,556	28.1	
30-34	208	23.2	10,451	23.4	
35-39	117	13.1	5,524	12.3	
≥40	63	7.0	3,065	6.9	

Unknown	39	4.4	2,119	4.7	
Paternal education level					0.02
High school or less	268	29.9	12,121	27.1	
At least some college	131	14.6	7,494	16.8	
Unknown	496	55.4	25,135	56.2	
Maternal birthplace					<0.01
United States	502	56.1	28,496	63.7	
Foreign	393	43.9	16,254	36.3	
Method of delivery					0.40
Vaginal	718	80.2	35,712	79.8	
Cesarean	177	19.8	9,038	20.2	
Pregnancy complications					0.60
None	729	81.5	36,519	81.6	
Yes	114	12.7	5,605	12.5	
Unknown	52	5.8	2,626	5.9	
History of previous cesarean section					0.43
No	792	88.5	39,450	88.2	
Yes	60	6.7	3,097	6.9	
Unknown	43	4.8	2,203	4.9	
History of miscarriage or stillbirth					0.40
Never	740	82.7	36,830	82.3	
Ever	155	17.3	7,920	17.7	
% population living below poverty in the census block group					0.34
<13%	162	18.1	8,619	19.3	
13-<26%	157	17.5	7,996	17.9	
26-<46%	168	18.8	8,447	18.9	

≥46%	176	19.7	7,749	17.3	
Unknown	232	25.9	11,939	26.7	
% of college and higher education in the census block group					<0.01
<35%	259	28.9	10,889	24.3	
35-<56%	203	22.7	10,682	23.9	
≥56%	203	22.7	11,262	25.2	
Unknown	230	25.7	11,917	26.6	
Maternal private insurance status					
Yes	188	21.0	9,113	20.4	0.56
No	184	20.6	9,483	21.2	
Unknown	523	58.4	26,154	58.4	

Abbreviation: IQR, interquartile range.

Table 3. Adjusted Odds Ratios and 95% Confidence Intervals for the Risk of Early-onset Ovarian Cancer (0-37 years), California Linkage Study of Early-Onset Cancers, 1988-2013.

	Odds Ratio	95% Confidence interval
Race/ethnicity		
Non-Hispanic white	1.00	
Hispanic	1.63	1.36 -1.96
Other	1.51	1.23 -1.84
Birthweight, grams		
<2500	0.87	0.63 -1.20
2500-2999	1.24	1.03 -1.50
3000-3499	1.00	
3500-3999	1.38	1.17 -1.62
≥4000	1.38	1.08 -1.75
Continuous (in 500 grams)	1.10	1.04 -1.17
Maternal birthplace		
United States	1.00	
Foreign	1.13	0.97 - 1.31
% of college and higher education in the census block group		
<35%	1.00	
35-<56%	0.88	0.73 - 1.06
≥56%	0.87	0.72 - 1.06
Unknown	0.90	0.74 - 1.10
Maternal private insurance status		
Yes	1.00	
No	0.79	0.64 - 0.98
Unknown	0.97	0.81 - 1.17

All variables in the table were mutually adjusted.

Table 4. Adjusted Odds Ratios and 95% Confidence Intervals for the Risk of Early-onset Ovarian Cancer (0-37 years) by Race/ethnicity

	Non-Hispanic White			Hispanic		
	Case	**Control**	**OR (95% CI)**	**Case**	**Control**	**OR (95% CI)**
Total	263	5534		445	9,263	
Birthweight, grams						
<2500	12	287	1.13 (0.61 - 2.11)	17	522	0.77 (0.46 - 1.27)
2500-2999	45	916	1.31 (0.90 - 1.91)	78	1,469	1.24 (0.94 - 1.64)
3000-3499	79	2,093	1.00	166	3,874	1.00
3500-3999	100	1,651	1.61 (1.19 - 2.17)	135	2,627	1.19 (0.94 - 1.50)
≥4000	27	587	1.22 (0.78 - 1.91)	49	771	1.47 (1.06 - 2.04)
Continuous (in 500 grams)			1.06 (0.95-1.19)			1.08 (0.98 - 1.18)
Maternal birthplace						
United States	230	5,078	1.00	176	3,612	1.00
Foreign	33	456	1.55 (1.06 - 2.27)	269	5,651	1.02 (0.84 - 1.25)
% of college and higher education in the census block group						
<35%	38	526	1.00	187	3,849	1.00
35-<56%	57	1,186	0.65 (0.43 - 1.00)	96	2,270	0.86 (0.66 - 1.10)
≥56%	83	1,616	0.68 (0.45 - 1.02)	73	1,671	0.88 (0.66 - 1.16)
Unknown	85	2,206	0.58 (0.39 - 0.88)	89	1,473	1.02 (0.77 - 1.35)
Maternal private insurance status						
Yes	65	1,040	1.00	84	1,791	1.00
No	28	469	0.91 (0.57 - 1.45)	129	3,525	0.77 (0.57 - 1.02)
Unknown	170	4,025	0.73 (0.53 - 1.01)	232	3,947	1.20 (0.92 - 1.58)

Abbreviations: CI, confidence interval; OR, odds ratio.
All variables in the table were mutually adjusted.

Table 5. Adjusted Odds Ratios and 95% Confidence Intervals for the Risk of Early-onset Ovarian Cancer (0-37 years) by Age at Diagnosis

	0-14 years			15-19 years			20-37 years		
	Case	**Control**	**OR (95% CI)**	**Case**	**Control**	**OR (95% CI)**	**Case**	**Control**	**OR (95% CI)**
Total	259	12,950		238	11,900		398	19,900	
Race/ethnicity									
Non-Hispanic white	73	4,565	1.00	59	4,584	1.00	131	8,969	1.00
Hispanic	134	5,916	1.39 (0.99-1.96)	132	5,006	2.06 (1.44-2.95)	179	7,157	1.56 (1.19-2.03)
Other	52	2,469	1.32 (0.90-1.93)	47	2,310	1.64 (1.10-2.46)	88	3,774	1.55 (1.16-2.06)
Birthweight, grams									
<2500	9	840	0.54 (0.27-1.08)	13	749	1.08 (0.60-1.97)	21	1,290	0.99 (0.62-1.58)
2500-2999	40	2,281	0.87 (0.60-1.26)	45	2,045	1.40 (0.96-2.03)	83	3,467	1.45 (1.10-1.92)
3000-3499	105	5,185	1.00	75	4,802	1.00	129	7,893	1.00
3500-3999	86	3,580	1.20 (0.90-1.60)	71	3,275	1.42 (1.02-1.97)	132	5,550	1.50 (1.18-1.92)
≥4000	19	1,064	0.91 (0.55-1.49)	34	1,029	2.21 (1.46-3.34)	33	1,700	1.26 (0.86-1.86)
Continuous (in 500 grams)			1.10 (0.98-1.23)			1.15 (1.02-1.30)			1.07 (0.98-1.18)
Maternal birthplace									
United States	135	7,518	1.00	133	7,471	1.00	234	13,507	1.00
Foreign	124	5,432	1.17 (0.89-1.55)	105	4,429	0.99 (0.74-1.32)	164	6,393	1.20 (0.95-1.51)
% of college and higher education in the census block group									
<35%	84	3,670	1.00	83	3,398	1.00	92	3,821	1.00

35-<56%	68	3,449	0.87 (0.62-1.21)	65	3,220	0.96 (0.68-1.34)	70	4,013	0.82 (0.60-1.13)
≥56%	72	3,963	0.79 (0.55-1.11)	57	3,425	0.85 (0.60-1.23)	74	3,874	0.95 (0.69-1.30)
Unknown	35	1,868	0.83 (0.53-1.30)	33	1,857	0.85 (0.55-1.31)	162	8,192	0.94 (0.72-1.24)
Maternal private insurance status									
Yes	101	4,325	1.00	55	3,037	1.00	32	1,751	1.00
No	74	4,436	0.60 (0.43-0.83)	70	3,207	0.99 (0.68-1.43)	40	1,840	1.03 (0.64-1.66)
Unknown	84	4,189	0.87 (0.63-1.20)	113	5,656	1.11 (0.79-1.56)	326	16,309	1.08 (0.74-1.58)

Abbreviations: CI, confidence interval; OR, odds ratio.
All variables in the table were mutually adjusted.

Table 6. Adjusted Odds Ratios and 95% Confidence Intervals for the Risk of Early-onset Ovarian Cancer (0-37 years) by Histologic Subtype

	Epithelial ovarian cancer			Germ Cell Tumor								
				Overall			Teratoma			Dysgerminoma		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
Total	273	13,650		548	27,400		242	12,100		128	6,400	
Race/ethnicity												
Non-Hispanic white	103	5,972	1.00	133	10,618	1.00	45	4,632	1.00	41	2,498	1.00
Hispanic	113	5,101	1.26 (0.92-1.73)	302	11,508	2.01 (1.58-2.55)	133	5,160	2.76 (1.89-4.05)	80	2,656	1.70 (1.08-2.69)
Other	57	2,577	1.33 (0.94-1.88)	113	5,274	1.68 (1.29-2.19)	64	2,308	2.92 (1.95-4.37)	7	1,246	0.33 (0.15-0.75)
Birthweight, grams												
<2500	12	889	0.87 (0.47-1.61)	29	1,747	0.89 (0.60-1.31)	13	769	0.80 (0.45-1.44)	10	413	1.69 (0.84-3.42)
2500-2999	53	2,349	1.46 (1.03-2.07)	94	4,774	1.03 (0.81-1.32)	43	2,101	0.99 (0.69-1.43)	18	1,104	1.08 (0.62-1.89)
3000-3499	84	5,463	1.00	206	10,931	1.00	95	4,798	1.00	41	2,508	1.00
3500-3999	93	3,775	1.64 (1.21-2.20)	172	7,654	1.22 (0.99-1.49)	67	3,392	1.04 (0.76-1.42)	45	1,837	1.47 (0.96-2.26)
≥4000	31	1,174	1.78 (1.17-2.71)	47	2,294	1.14 (0.83-1.57)	24	1,040	1.27 (0.80-2.00)	14	538	1.59 (0.86-2.94)
Continuous (in 500 grams)			1.14 (1.02-1.28)			1.07 (0.99-1.16)			1.07 (0.95-1.20)			1.08 (0.92-1.27)
Maternal birthplace												
United States	169	9,068	1.00	284	16,996	1.00	125	7,428	1.00	70	4,038	1.00

Foreign	104	4,582	1.10 (0.82-1.46)	264	10,404	1.19 (0.98-1.43)	117	4,672	1.08 (0.82-1.42)	58	2,362	1.14 (0.75-1.72)
% of college and higher education in the census block group												
<35%	60	2,759	1.00	178	7,273	1.00	74	3,219	1.00	50	1,764	1.00
35-<56%	49	2,811	0.86 (0.58-1.27)	136	7,035	0.89 (0.70-1.11)	65	3,062	1.02 (0.73-1.44)	24	1,711	0.57 (0.34-0.94)
≥56%	58	2,785	1.05 (0.72-1.54)	131	7,605	0.84 (0.66-1.07)	55	3,411	0.85 (0.58-1.23)	32	1,708	0.80 (0.49-1.29)
Unknown	106	5,295	0.99 (0.70-1.40)	103	5,487	0.88 (0.67-1.15)	48	2,408	1.04 (0.70-1.56)	22	1,217	0.71 (0.41-1.23)
Maternal private insurance status												
Yes	30	1,552	1.00	146	6,783	1.00	67	2,982	1.00	28	1,404	1.00
No	34	1,643	1.03 (0.62-1.70)	131	7,072	0.67 (0.52-0.86)	55	3,096	0.62 (0.42-0.90)	31	1,542	0.76 (0.44-1.30)
Unknown	209	10,455	1.04 (0.70-1.57)	271	13,545	0.93 (0.75-1.16)	120	6,022	0.86 (0.62-1.20)	69	3,454	0.99 (0.62-1.58)

Abbreviations: CI, confidence interval; OR, odds ratio.
All variables in the table were mutually adjusted.

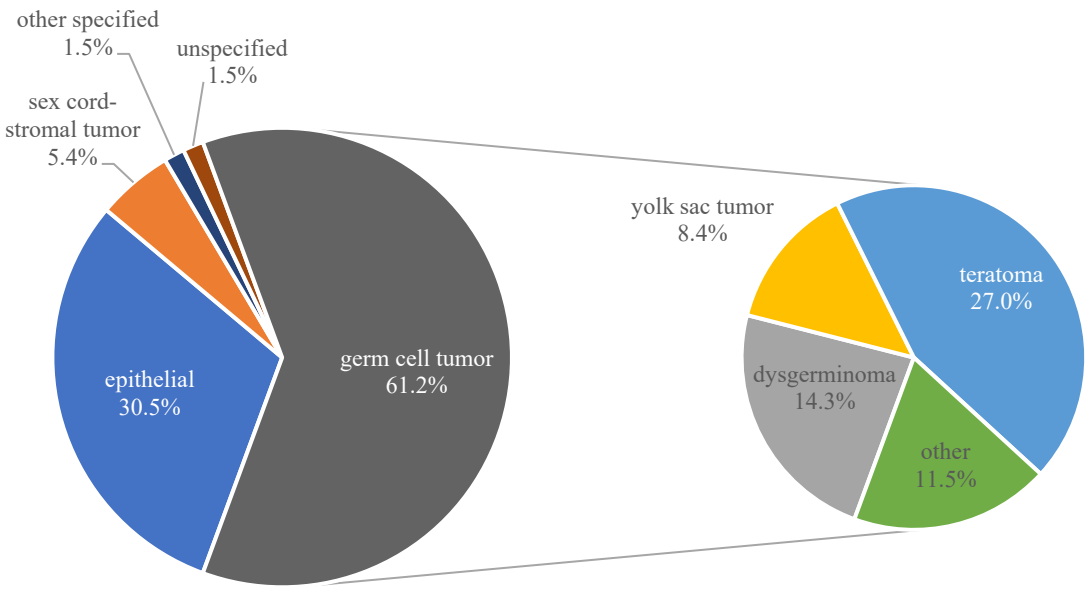

Figure 1. Distribution of early-onset ovarian cancer (0-37 years) by histologic subtype, California Linkage Study of Early-onset Cancers, 1988-2013.

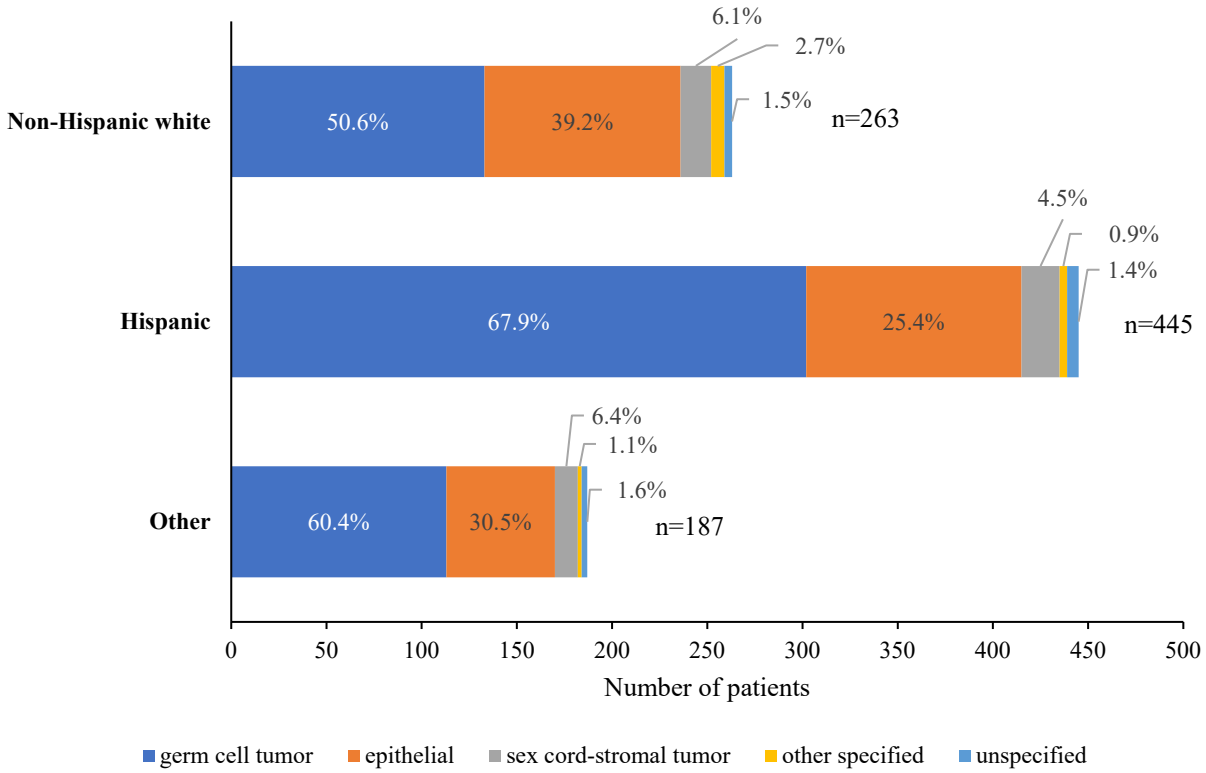

Figure 2. Distribution of early-onset ovarian cancer (0-37 years) by race/ethnicity and histologic subtype, California Linkage Study of Early-onset Cancers, 1988-2013.

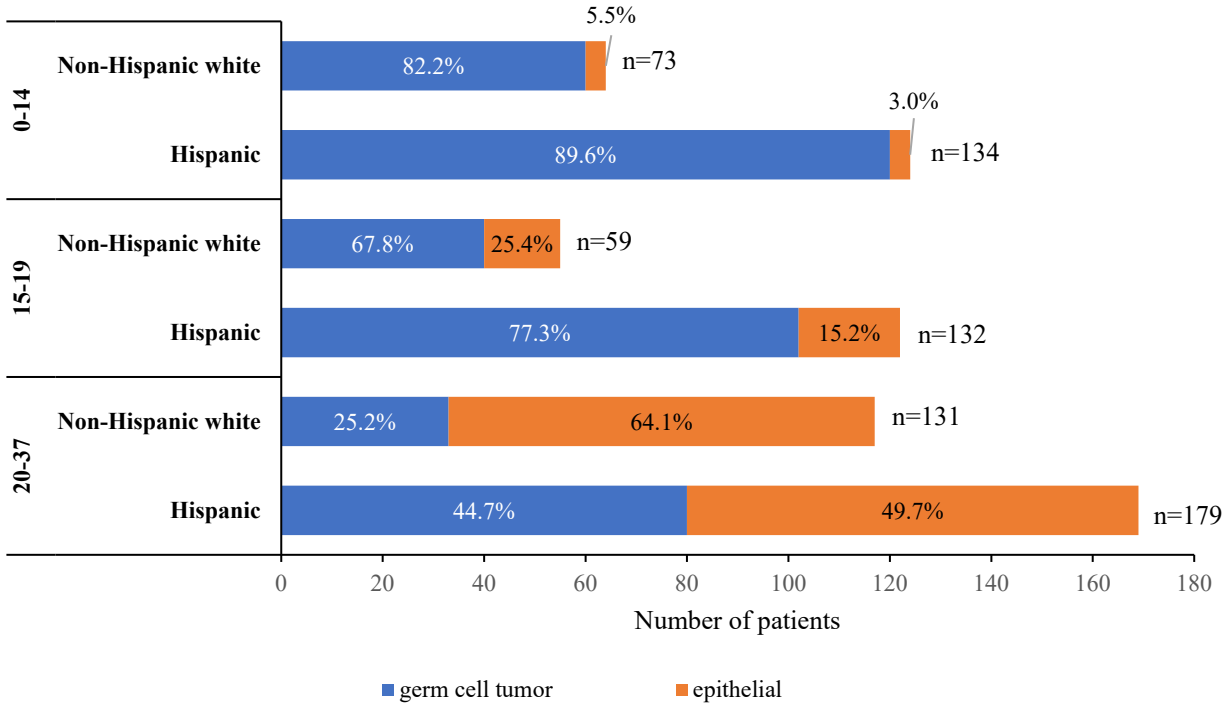

Figure 3. Distribution of early-onset ovarian cancer (0-37 years) by race/ethnicity, histologic subtype, and age at diagnosis, California Linkage Study of Early-onset Cancers, 1988-2013.