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Racial/ethnic differences in ovarian cancer risk: Results from the Multiethnic Cohort Study

Danja Sarink[1], **Anna H. Wu**[2], **Loïc Le Marchand**[1], **Kami K. White**[1], **Song-Yi Park**[1], **V. Wendy Setiawan**[2], **Brenda Y. Hernandez**[1], **Lynne R. Wilkens**[1], **Melissa A. Merritt**[1]

[1]Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI

[2]Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA.

Abstract

Background: Incidence rates of epithelial ovarian cancer (EOC) vary across racial/ethnic groups, yet little is known about the impact of hormone-related EOC risk factors in non-Whites.

Methods: Among 91,625 female Multiethnic Cohort Study participants, 155 incident EOC cases were diagnosed in Whites, 93 in African Americans, 57 in Native Hawaiians, 161 in Japanese Americans, and 141 in Latinas. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between race/ethnicity and EOC risk and between hormone-related factors and EOC risk across racial/ethnic groups.

Results: Compared to Whites, African Americans and Japanese Americans had a lower multivariable adjusted EOC risk; Native Hawaiians had a suggestive higher risk. Parity and oral contraceptive (OC) use were inversely associated with EOC risk (p_{int} race/ethnicity ≥0.43); associations were strongest among Japanese Americans (e.g. ≥4 vs 0 children, HR 0.45 [CI 0.26–0.79]). Age at natural menopause and postmenopausal hormone (PMH) use were not associated with EOC risk in the overall population, but were positively associated with risk in Latinas (e.g. ≥5 years vs never PMH use, HR 2.13 [CI 1.30–3.49]).

Conclusions: We observed strong associations with EOC risk for parity and OC use in Japanese Americans and PMH use and age at natural menopause in Latinas. However, differences in EOC risk among racial/ethnic groups were not fully explained by established hormone-related risk factors.

Impact: Our study indicates there are racial/ethnic differences in EOC risk and risk factors, and could help improve prevention strategies for non-White women.

Keywords

Ovarian cancer; risk; hormone-related risk factors; cancer disparities; epidemiology

Corresponding author: Dr. Melissa A. Merritt, Cancer Epidemiology Program, University of Hawaii Cancer Center, 701 Ilalo St, Honolulu, HI 96813, USA, Phone: (808) 564-5830, Fax: (808) 586-2982, melissa.merritt@hawaii.edu.

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Data availability: For information on applications to gain access to data from the Multiethnic Cohort please see: https://www.uhcancercenter.org/for-researchers/mec-data-sharing

Background

Ovarian cancer incidence differs substantially by race/ethnicity, with the highest age-standardized rates (per 100,000 in 2010-14) in the United States (US) observed in non-Hispanic White (hereafter referred to as White) women (12.0), intermediate rates in Hispanic women (10.3), and lowest rates among African American (9.4) and Asian/Pacific Islander women (9.2) [1]. Notably, ovarian cancer incidence rates among Native Hawaiian women (11.8 per 100,000 in 2008-12) are comparable to the high rates observed for White women in the US and in Hawaii (12.0) [1, 2].

The most common type of malignant ovarian cancer is epithelial ovarian cancer (EOC) which is a heterogeneous disease with at least four major histological subtypes: serous, mucinous, endometrioid and clear cell. Many of the known EOC risk factors are related to reproduction [3–5], however few studies have evaluated EOC risk factors among non-White women [6–10]. To our knowledge five case-control studies have assessed EOC risk factors in African Americans [7–10] , and one in Latinas [7]. In addition, the largest study to date pooled data from 12 Ovarian Cancer Association Consortium (OCAC) case-control studies based in the US, Australia, and Canada (including data from refs. [7, 9]), and included 911 African American, 662 Asian/Pacific Islander, 433 Latina, and 8918 White cases [6]. Peres *et al.* [6] reported a generally similar direction of associations across racial/ethnic groups, including oral contraceptive (OC) use, although some differences were seen: family history of breast and/or ovarian cancer was most strongly associated with increased EOC risk among African Americans and Latinas; positive associations of hysterectomy and endometriosis with EOC risk were strongest in African Americans; and Asian/Pacific Islanders had the strongest decrease in EOC risk with higher parity. Limitations of the OCAC study were the retrospective design and their inability to separate Asians and Pacific Islanders. An earlier EOC case-control study included Native Hawaiian women (in addition to Japanese Americans and Whites from Hawaii), but results were not reported separately for these racial/ethnic groups [11].

We analyzed data from the Multiethnic Cohort (MEC) Study, an ethnically diverse cohort including Whites, African Americans, Native Hawaiians, Japanese Americans, and Latinas. This study of EOC risk factors provides new insights to understand the unique pathogenesis of EOC among these understudied minority groups, which could be used to inform potential avenues for prevention among racial/ethnically diverse populations.

Methods

Study population

The design of the MEC Study has been detailed previously [12, 13]. Briefly, between 1993-6 over 215,000 men and women aged 45-75 years completed a mailed baseline questionnaire including questions on lifestyle and reproductive factors, hormone use, anthropometrics, and race/ethnicity. Participants were followed up via the Surveillance, Epidemiology, and End Results (SEER) cancer registries for Hawaii and California for diagnosis of cancer and information on tumor histology and stage was obtained. Incident invasive EOC was defined as ovarian, fallopian tube, or primary peritoneal cancer using International Classification of

Diseases for Oncology 3rd revision (ICD-O3) codes C56.9, C57.0, and C48. ICD-O3 morphology codes were used to exclude non-epithelial tumors and to define histological subtypes (Supplementary table 1). Vital status was determined by linkage to state death files and the National Death Index. The end of follow-up was defined as the date of diagnosis of incident EOC, date of death, or date of complete case and death ascertainment (December 31, 2014), whichever occurred first. From the 110,712 women from five main racial/ethnic groups in the MEC Study (White, African American, Native Hawaiian, Japanese American, and Latina) we excluded 227 participants diagnosed with EOC prior to cohort entry (identified via tumor registry or self-reported on the baseline questionnaire), 18,686 participants who self-reported a bilateral or unspecified oophorectomy at baseline, 61 participants with <1 year of follow-up, 57 participants missing extensive baseline questionnaire information (OC use, number of children, and ages at menarche and first birth), and 56 EOC cases with non-epithelial tumors, leaving 91,625 participants in our study.

Exposures and covariates

Exposures of interest were: parity (no, yes); number of children (0, 1, 2, 3, ≥4); age at menarche (<13, 13-14, ≥15 years); OC use (never, ever [≥1 month of use] and OC duration [never, <5, ≥5 years]); age at natural menopause (<45, 45-49, 50-54, ≥55 years; in postmenopausal women reporting a natural menopause); use of postmenopausal hormones (PMH) containing estrogen among postmenopausal women (never, ever and PMH duration [never, <5, ≥5 years]); body mass index (BMI; <25, 25-29, ≥30kg/m^2); diabetes (no, yes); smoking status (never, ever); and family history of breast and/or ovarian cancer in a first degree relative (no, yes). The cumulative duration of ovulatory years is a composite measure of ovarian cancer risk factors, estimating the number of natural menstrual cycles a woman experiences during her lifespan. It was calculated as the number of years between age at menarche and either age at baseline (if premenopausal) or age at natural menopause (if postmenopausal), minus the duration of OC use and time spent pregnant (number of children*0.75 years); postmenopausal women with a surgical menopause or unknown type of menopause were excluded.

Statistical analysis

We used Cox proportional hazards regression models, with the time between study entry and exit (end of follow-up) as the time scale, to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for EOC risk. Multivariable models were adjusted for important confounders that were selected *a priori*; age, menopausal status at baseline, ever OC use, and number of children; models in the full population were additionally adjusted for race/ethnicity. We tested additional adjustment for age at first birth (in parous women; <21, 21-24, ≥25 years), age at menarche (<13, 13-14, ≥15 years), age at natural menopause (among postmenopausal women reporting a natural menopause; <45, 45-49, 50-54, ≥55 years), PMH use (among postmenopausal women; no, yes), hysterectomy (no, yes, missing), BMI (<25, 25-29.9, ≥30kg/m^2), diabetes (no, yes), family history of breast and/or ovarian cancer (no, yes, missing) and, years of education (12th grade or less, vocational training or some college education, college graduate or higher). These factors did not impact the results (<10% HR change in all models) and were not included as covariates in the final models

stratified for race/ethnicity [14]. For models with race/ethnicity as the exposure we, in addition to the multivariable adjusted model adjusting for *a priori* selected covariates, calculated a fully adjusted model accounting for all EOC risk factors available in the MEC Study. Missing data in exposure variables were excluded from models. For all covariates (except family history of breast and/or ovarian cancer) less than 5% of data were missing, which were set to the largest race/ethnicity specific category. Models that included family history (8% missing data) as a covariate included a separate missing category. P values for trend were calculated using continuous variables when available. Interactions between race/ethnicity and the exposures of interest were evaluated by comparing multivariable models with and excluding multiplicative interaction terms using likelihood ratio tests. The proportional hazards assumption was assessed using Schoenfeld residuals and no violation was observed. Descriptive analyses were age-standardized [15].

We carried out sensitivity analyses restricting to women who were postmenopausal at baseline (83% of participants) and restricting the outcome to serous/carcinoma not otherwise specified (NOS; hereafter referred to as serous; 74% of cases) by censoring non-serous histological subtypes. A 95% confidence interval excluding one or, for test for interaction, a two tailed $P<0.05$ was considered statistically significant. Analyses were performed using SAS 9.4.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at the University of Hawaii. The Multiethnic Cohort Study was approved by the Institutional Review Boards at the University of Hawaii and the University of Southern California.

Results

The median age at cohort entry in the overall study population was 60 years (interquartile range: 52, 67); Native Hawaiians were the youngest (54 years) and Japanese Americans the oldest (62 years; Table 1). Comparing age-standardized reproductive characteristics across five racial/ethnic groups, Native Hawaiians and Latinas had higher parity (≥50% had ≥4 children compared to ≤35% of African Americans, Whites, and Japanese Americans). Ever use of OCs was highest in Whites (50%), intermediate in African Americans (44%), and lowest in Native Hawaiians, Japanese Americans, and Latinas (≤36%). PMH use was higher in Whites and Japanese Americans (≥51% ever users) and lower in African Americans, Native Hawaiians, and Latinas (≤39% ever users). The proportion of women with an obese BMI ($\geq 30 kg/m^2$) was highest in African Americans (37%) and Native Hawaiians (32%), intermediate in Latinas (27%) and Whites (18%), and lowest in Japanese Americans (7%). The prevalence of diabetes was highest in Latinas, African Americans and Native Hawaiians (15%) and lower in Whites (6%) and Japanese Americans (9%).

During a median follow-up of 21 (interquartile range: 18, 22) years, 607 incident EOC cases were identified of which 155 occurred in Whites, 93 in African Americans, 57 in Native Hawaiians, 161 in Japanese Americans, and 141 in Latinas. Age-standardized histological subtype and stage distributions varied by racial/ethnic group (Table 2). The proportion of serous tumors was highest in Whites (78%) followed by African Americans (76%), Native

Hawaiians (73%), Latinas (69%), and Japanese Americans (67%). The proportion of endometrioid tumors was highest in Japanese Americans (15%), followed by Latinas and African Americans (11%), and was lowest in Whites (7%) and Native Hawaiians (3%). Japanese Americans had a high proportion of clear cell tumors (8% versus 3-6% in the other groups) and Native Hawaiians had a high proportion of mucinous tumors (13% versus 1-6% in other groups). Japanese Americans had the lowest frequency of distant disease (62% versus 74-78% in the other groups).

Compared to Whites, African Americans had a lower age-adjusted EOC risk (HR 0.74 [CI 0.57, 0.96]; Table 3). We observed similar risk estimates after additional adjustment for menopausal status, parity, and OC use; relative to Whites, multivariable adjusted EOC risk was lower in African Americans (HR 0.74 [CI 0.57, 0.97]) and Japanese Americans (HR 0.79 [CI 0.63, 0.99]) and was suggestively higher in Native Hawaiians (HR 1.36 [CI 0.99, 1.85]). EOC risk in Latinas did not differ from that in Whites (multivariable adjusted HR 0.96 [CI 0.76, 1.22]). Further comprehensive adjustment for all EOC risk factors in a fully adjusted model did not change these results. Associations between race/ethnicity and EOC risk were similar in analyses restricted to postmenopausal women and to serous EOC.

Table 4 shows associations between hormone-related factors and EOC risk in the overall population and for each of the racial/ethnic groups. In the overall study population, parity and OC use were inversely associated with EOC risk (parous versus nulliparous: HR 0.72 [CI 0.58, 0.89]; ≥4 children versus nulliparous: HR 0.62 [CI 0.48, 0.81]; ever versus never OC use: HR 0.77 [CI 0.63, 0.94]; ≥5 years versus never OC use: HR 0.54 [CI 0.39, 0.73]). We found no statistically significant interaction with race/ethnicity for any of the hormone-related factors (p_{int} ≥0.18). HRs for parity (versus nulliparity) ranged from 0.64 to 0.82 across racial/ethnic groups, but the association was significant only for Japanese Americans (HR 0.64 [CI 0.43, 0.94]) among whom there were additional reductions in risk with an increasing number of children (e.g., ≥4 versus 0 children: HR 0.45 [CI 0.26, 0.79]; p_{trend} <0.01). The inverse association between ever use of OCs and EOC risk was observed in most racial/ethnic groups (HRs ranged from 0.60 to 0.77) except for Whites; this association was significant only among Japanese Americans (HR 0.60 [CI 0.39, 0.93]) and stronger associations were observed with increasing duration of OC use in this group (≥5 years versus never OC use: HR 0.35 [CI 0.16, 0.78]). Age at natural menopause and PMH use were not associated with EOC risk in the overall population and there was no interaction with race/ethnicity (p_{int} ≥0.18). However, risk of EOC among Latinas increased with a later age at natural menopause (≥55 versus <45 years: HR 2.60 [CI 1.24, 5.42]). Compared to Latinas who never used PMH, ever use of PMH was positively associated with EOC risk (HR 1.46 [CI 1.02, 2.10]) and the association strengthened with a longer duration of use (≥5 years versus never: HR 2.13 [CI 1.30, 3.49]). Cumulative ovulatory years were suggestively associated with EOC risk in the overall population (tertile 3 versus 1: HR 1.27 [0.96, 1.67]; p_{trend} 0.01; p_{int} race/ethnicity 0.37), although there was a suggestive trend in Native Hawaiians (0.09) and Latinas (0.08), no significant associations were seen in any racial/ethnic group. There were no associations for age at menarche, obesity, smoking status, or diabetes with EOC risk among the overall population or in any of the racial/ethnic groups.

We observed no interaction between menopausal status and race/ethnicity (p_{int} 0.96). When restricting analyses to postmenopausal women (n=520 cases), we observed similar results to the overall population (Supplementary table 2). In analyses focusing on the serous histological subtype (n=447 cases), associations with hormone-related factors were generally similar to those for total EOC, with the exception of OC use where there was a significant protective association with longer duration of use in Whites (≥5 years versus never use: HR 0.50 [CI 0.26, 0.98]) (Supplementary table 3). The association for OC use with risk of serous tumors was stronger for Japanese Americans (≥5 years versus never OC use HR 0.08 [CI 0.01, 0.56]) than in analyses of total EOC. Associations observed between PMH use and total EOC among Latinas were attenuated when restricting to serous EOC (≥5 years versus never PMH use: HR 1.61 [CI 0.84, 3.06]).

Discussion

We performed a comprehensive prospective analysis and compared EOC risk in a large population of White, African American, Native Hawaiian, Japanese American, and Latina women. Risk of EOC was comparable in Whites and Latinas, but we observed suggestively higher EOC risk in Native Hawaiians and lower EOC risk in African Americans and Japanese Americans. These differences were not fully explained by hormone-related risk factors. Although we found no statistically significant interaction between race/ethnicity, selected hormone-related factors were most strongly associated with EOC risk in Japanese Americans and Latinas.

Our finding of similar EOC risk in Whites and Latinas, and lower EOC risk in African Americans and Japanese Americans than in Whites, is in agreement with US nationwide statistics [1, 16]. We observed a suggestive higher EOC risk in Native Hawaiians relative to Whites, whereas the Hawaii Tumor Registry reported similar age-adjusted incidence rates for both groups [2]. The racial/ethnic differences in EOC risk observed in our study were not fully explained by hormone-related factors. This is in line with previous studies that found that reproductive and lifestyle factors explained only a small proportion of the EOC risk differences between Whites and African Americans [7, 10] and between Whites and Latinas [7].

In the pooled OCAC study interactions with race/ethnicity were observed in associations of parity, OC use, hysterectomy, and family history of breast and ovarian cancer with EOC risk [6]. There were no statistically significant interactions between race/ethnicity and any of the hormone-related EOC risk factors that we evaluated in this study, which may be related to the modest sample size. We did however observe strong inverse associations for parity and OC use with EOC risk among Japanese Americans. This finding is consistent with strong protective associations reported for parity and OC use with EOC risk among Asian/Pacific Islanders in the OCAC study [6]. In contrast to the OCAC report and the Ovarian Cancer Cohort Consortium (OC3) in (mostly) White women [17], family history of breast/ovarian cancer was not associated with EOC risk in our overall study population or in any of the racial/ethnic groups. Hysterectomy was not associated with EOC risk in our study; OC3 similarly reported no association, but OCAC reported a positive association [6, 17]. Compared with never use of PMH, we observed that both ever-use of PMH and a longer

duration (≥5 years) of PMH use were associated with an increased EOC risk specifically among Latinas. The only previous study to evaluate associations between PMH use and EOC risk in Latinas found no association in Latinas or in other racial/ethnic groups [6].The positive association with PMH use is however consistent with the higher risk with PMH use that has been reported in a pooled analysis of 22 prospective cohort studies (based mostly on White women) in the Ovarian Cancer Cohort Consortium (OC3) [17]. Interestingly we also observed that having a later age at menopause was associated with an increased EOC risk among Latinas. To our knowledge, previous studies have not evaluated age at menopause as an EOC risk factor in Latinas specifically, but a small positive association between having a later age at menopause and EOC risk has been reported in the OC3 study [17]. It will be of interest to further investigate PMH use and age at natural menopause as EOC risk factors among Latinas. Our finding of increasing risk with a longer cumulative duration of ovulatory cycles, is in line with previous studies in Mexican women [18] and in (mostly) White women [19–21]. To our knowledge previous studies have not reported on hormone-related risk factors in relation to EOC risk in Native Hawaiians specifically. Our study highlighted a suggestive 36% increase in EOC risk among Native Hawaiians compared with Whites, and demonstrates the need for larger studies of Native Hawaiian women to further explore potential reasons for their higher EOC risk.

The strengths of our study include the prospective, ethnically diverse, population-based design of the MEC, which has been shown to be representative of its source populations [13]. To our knowledge this study is the first to evaluate the impact of hormone-related EOC risk factors in Native Hawaiians. Although the MEC is one of the largest cohorts of its kind, EOC remains a rare disease and case numbers were modest, particularly for African Americans and Native Hawaiians. We conducted a sensitivity analysis of serous EOC, the most common EOC subtype [22], and observed broadly similar findings to analyses of total EOC. Case numbers were limited to investigate racial/ethnic differences in non-serous histological subtypes, as well as premenopausal women at baseline. Another limitation was that the MEC baseline questionnaire did not collect information on breastfeeding, tubal ligation, or endometriosis therefore we could not account for these factors in our analysis. Due to multiple comparisons, some of our findings may be due to chance and should be confirmed in additional studies.

Our results suggest that differences in EOC risk among five racial/ethnic groups represented in the MEC Study were not explained by established risk factors, and differences in risk remained. Associations between hormone-related factors and EOC risk did not significantly differ across racial/ethnic groups, although parity and OC use were particularly relevant to risk in Japanese Americans and PMH use and age at menopause in Latinas. Ours is the first prospective study to contribute to a growing body of evidence on racial/ethnic differences in EOC risk factors. It is of interest to carry out additional studies in consortia of prospective studies, such as the OC3, to better understand the factors that contribute towards disparities in risk and improve prevention strategies, particularly for Native Hawaiian, Asian American, and Latina women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	Body mass index
CI	95% confidence interval
MEC	Multiethnic Cohort
EOC	Epithelial ovarian cancer
HR	Hazard ratio
ICD-O3	International Classification of Diseases for Oncology 3rd Revision
NOS	Not otherwise specified
OC	Oral contraceptive
PMH	Postmenopausal hormone
SEER	Surveillance, Epidemiology, and End Results

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Table 1.

Age-standardized distribution of hormone-related factors measured at baseline by race/ethnicity in the Multiethnic Cohort Study.

	Overall	White	African American	Native Hawaiian	Japanese American	Latina
Total number	**91,625**	**21,742**	**17,870**	**6,789**	**25,028**	**20,196**
Age at cohort entry (years)[ab]	60 (52, 67)	58 (50, 66)	61 (53, 69)	54 (48, 63)	62 (52, 69)	59 (53, 65)
Duration of follow-up (years)[b]	21 (18, 22)	21 (17, 21)	21 (14, 22)	20 (14, 21)	21 (20, 21)	21 (19, 22)
Parity (%)						
Nulliparous	12	16	12	7	14	8
Parous	87	84	87	92	86	92
1 child	11	12	15	6	12	7
2 children	23	26	20	15	32	15
3 children	20	21	17	18	24	18
≥4 children	32	24	35	53	18	50
Age at menarche (%)						
<13 years	48	49	48	54	49	46
13-14 years	38	40	36	33	38	38
≥15 years	12	11	13	11	12	14
Postmenopausal (%)	83	84	84	82	80	84
Cumulative ovulatory years (%)[c]						
Tertile 1: 4-29 years	33	36	41	34	24	38
Tertile 2: 30-34 years	34	33	32	35	34	37
Tertile 3: 35-45 years	33	32	28	31	42	25
Age at natural menopause (%)[d]						
<45 years	16	14	20	19	11	22
45-49 years	31	33	32	31	27	35
50-54 years	41	41	36	37	48	35
≥55 years	11	11	11	12	13	8
OC use (%)						
Never	55	48	51	61	61	57
Ever	41	50	44	35	36	35
<5 years	25	29	26	23	24	24
≥5 years	15	21	18	12	12	10
PMH use (%)[e]						
Never	51	41	61	59	47	56
Ever	46	57	35	38	51	39
<5 years	30	33	25	28	32	28
≥5 years	15	24	8	10	18	9
Hysterectomy - yes (%)	21	22	30	22	14	21
Body Mass Index (%)						

	Overall	White	African American	Native Hawaiian	Japanese American	Latina
Total number	**91,625**	**21,742**	**17,870**	**6,789**	**25,028**	**20,196**
<25 kg/m^2	45	53	24	32	68	32
25-29.9 kg/m^2	31	28	35	32	24	39
≥30 kg/m^2	22	18	37	32	7	27
Diabetes - yes (%)	11	6	15	15	9	15
Ever smoker (%)	43	55	53	54	32	33
Family history of breast or ovarian cancer (%)	14	16	15	18	13	12

[a] Not age-standardized

[b] Values are median (P25, P75)

[c] Among 63,107 women with available information. Calculated as years between ages at menarche and natural menopause (if postmenopausal) or baseline (if premenopausal), minus the duration of pregnancies and OC use

[d] among 51,164 postmenopausal women who reported a natural menopause

[e] among 75,768 postmenopausal women. Percentages may not add up to 100% due to missing data.

Table 2.

Age-standardized distribution of EOC case characteristics by race/ethnicity.

	Overall	White	African American	Native Hawaiian	Japanese American	Latina
Number of EOC cases	**607**	**155**	**93**	**57**	**161**	**141**
Age at diagnosis (years)[ab]	71 (64, 78)	70 (63, 77)	72 (63, 78)	68 (63, 74)	72 (64, 79)	69 (65, 75)
Duration of follow-up (years)[bc]	10 (5, 15)	9 (4, 15)	9 (5, 14)	11 (4, 15)	9 (5, 14)	9 (4, 15)
Histological subtype (%)						
Serous[d]	74	78	76	73	67	69
Endometrioid	9	7	11	3	15	11
Clear cell	6	4	3	4	8	6
Mucinous	5	3	1	13	6	6
Carcinosarcoma & other	7	8	8	7	4	8
Disease stage[e] (%)						
Localized & regional	24	21	19	21	38	21
Distant	73	78	76	77	62	74

[a] Not age-standardized

[b] Values are median (P25, P75)

[c] Time between cohort entry and diagnosis

[d] combined serous and carcinoma not otherwise specified histological subtype.

[e] 3% missing data in overall population (0-6% in racial/ethnic groups). Percentages may not add up to 100% due to missing data. Abbreviations: EOC: epithelial ovarian cancer.

Table 3.

Associations (HR and 95% CI) between race/ethnicity and EOC risk in the overall study population, as well as restricting to postmenopausal women at baseline and to serous EOC.

	n	n cases	Age-adjusted	Multivariable adjusted[a]	Fully adjusted[ab]
Total EOC					
White (ref.)	21,742	155	1.00	1.00	1.00
African American	17,870	93	0.74 (0.57, 0.96)	0.74 (0.57, 0.97)	0.77 (0.59, 1.01)
Native Hawaiian	6,789	57	1.30 (0.96, 1.76)	1.36 (0.99, 1.85)	1.34 (0.98, 1.84)
Japanese American	25,028	161	0.83 (0.66, 1.03)	0.79 (0.63, 0.99)	0.79 (0.63, 1.00)
Latina	20,196	141	0.93 (0.74, 1.17)	0.96 (0.76, 1.22)	1.02 (0.80, 1.30)
Postmenopausal women					
White (ref.)	17,590	132	1.00	1.00	1.00
African American	15,350	83	0.74 (0.57, 0.98)	0.75 (0.57, 0.99)	0.78 (0.58, 1.04)
Native Hawaiian	4,932	45	1.31 (0.94, 1.84)	1.37 (0.97, 1.93)	1.36 (0.96, 1.93)
Japanese American	20,471	138	0.82 (0.65, 1.04)	0.79 (0.62, 1.00)	0.79 (0.61, 1.01)
Latina	17,425	122	0.90 (0.70, 1.15)	0.93 (0.72, 1.20)	1.00 (0.77, 1.30)
Serous EOC[c]					
White (ref.)	21,742	122	1.00	1.00	1.00
African American	17,870	71	0.70 (0.52, 0.94)	0.70 (0.52, 0.94)	0.75 (0.55, 1.03)
Native Hawaiian	6,789	42	1.25 (0.88, 1.78)	1.27 (0.89, 1.82)	1.30 (0.90, 1.87)
Japanese American	25,028	113	0.72 (0.56, 0.93)	0.69 (0.53, 0.89)	0.67 (0.51, 0.87)
Latina	20,196	99	0.83 (0.63, 1.08)	0.83 (0.63, 1.10)	0.89 (0.67, 1.18)

[a] Cox proportional hazards models adjusted for baseline age (continuous) and menopausal status (pre-/peri- [ref.], postmenopausal), use of OCs (never [ref.], ever), and number of children (0 [ref.], 1, 2, 3, ≥4)

[b] Models additionally adjusted for age at menarche (<13 [ref.], 13-14, ≥15years), age at natural menopause (if postmenopausal; <44 [ref.], 45-49, 50-54, ≥55years, surgical or unknown type of menopause), duration of PMH use (if postmenopausal; never [ref.], <5, ≥5years), duration of OC use (never [ref.], <5, ≥5years), hysterectomy (no [ref.], yes), family history of breast and/or ovarian cancer (no [ref.], yes, missing), diabetes (no [ref.], yes) and smoking status (never [ref.], ever).

[c] serous/carcinoma not otherwise specified histological subtype. Abbreviations: 95% CI: 95% confidence interval; EOC: epithelial ovarian cancer; HR: hazard ratio.

Table 4.

Associations (HR and 95% CI)[a] between hormone-related factors and EOC risk by race/ethnicity.

	Overall[b]	White	African American	Native Hawaiian	Japanese American	Latina	P_{int}[c]
Number of cases/total number	607/91,625	155/21,742	93/17,870	57/6,789	161/25,028	141/20,196	
Parity							
Nulliparous (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Parous	0.72 (0.58, 0.89)	0.70 (0.47, 1.03)	0.82 (0.46, 1.45)	0.77 (0.33, 1.84)	0.64 (0.43, 0.94)	0.82 (0.47, 1.44)	0.89[d]
1 child	0.82 (0.61, 1.12)	1.01 (0.60, 1.71)	0.54 (0.23, 1.25)	0.43 (0.09, 2.16)	0.85 (0.49, 1.46)	0.96 (0.43, 2.11)	
2 children	0.78 (0.60, 1.01)	0.67 (0.41, 1.07)	0.93 (0.46, 1.84)	0.84 (0.29, 2.39)	0.72 (0.46, 1.12)	1.00 (0.51, 1.96)	
3 children	0.74 (0.56, 0.97)	0.55 (0.33, 0.94)	1.20 (0.61, 2.36)	0.83 (0.30, 2.27)	0.59 (0.36, 0.96)	1.00 (0.53, 1.91)	
≥4 children	0.62 (0.48, 0.81)	0.69 (0.43, 1.12)	0.66 (0.34, 1.27)	0.80 (0.32, 1.96)	0.45 (0.26, 0.79)	0.71 (0.40, 1.28)	0.43[e]
p_{trend} number of children (incl. 0)	<0.01	0.08	0.64	0.78	<0.01	0.02	
p_{trend} number of children (excl. 0)	0.01	0.34	0.92	0.49	0.03	0.01	
Age at menarche							
<13 years (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
13-14 years	0.83 (0.70, 0.99)	0.98 (0.70, 1.39)	0.72 (0.45, 1.15)	0.86 (0.48, 1.55)	0.74 (0.52, 1.05)	0.84 (0.59, 1.21)	
≥15 years	1.01 (0.79, 1.29)	1.50 (0.95, 2.39)	0.81 (0.42, 1.56)	0.92 (0.39, 2.21)	0.98 (0.62, 1.55)	0.80 (0.48, 1.35)	0.89
Age at natural menopause[f]							
<45 years (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
45-49 years	1.04 (0.75, 1.44)	0.96 (0.52, 1.76)	1.56 (0.60, 4.03)	0.72 (0.22, 2.36)	0.91 (0.47, 1.74)	1.03 (0.53, 1.99)	
50-54 years	1.10 (0.80, 1.51)	0.83 (0.46, 1.52)	1.88 (0.75, 4.69)	1.66 (0.61, 4.56)	0.84 (0.45, 1.55)	1.16 (0.61, 2.20)	
≥55 years	1.25 (0.84, 1.86)	1.00 (0.47, 2.16)	0.76 (0.19, 3.09)	0.67 (0.13, 3.54)	0.99 (0.47, 2.07)	2.60 (1.24, 5.42)	0.18
Cumulative ovulatory years[g]							
Tertile 1 (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Tertile 2	1.06 (0.81, 1.38)	1.18 (0.72, 1.94)	1.04 (0.48, 2.23)	2.14 (0.84, 5.46)	0.74 (0.44, 1.23)	0.98 (0.55, 1.74)	
Tertile 3	1.27 (0.96, 1.67)	1.25 (0.73, 2.13)	1.39 (0.63, 3.04)	2.57 (0.95, 6.96)	0.80 (0.48, 1.33)	1.64 (0.93, 2.91)	0.37
P_{trend}	0.01	0.25	0.31	0.09	0.64	0.08	
OC use							
Never (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	

	Overall[b]	White	African American	Native Hawaiian	Japanese American	Latina	P_{int}[c]
Ever	0.77 (0.63, 0.94)	1.13 (0.78, 1.66)	0.77 (0.46, 1.30)	0.62 (0.33, 1.17)	0.60 (0.39, 0.93)	0.69 (0.46, 1.04)	0.67[h]
Ever <5 years	0.91 (0.73, 1.13)	1.43 (0.96, 2.14)	0.88 (0.49, 1.56)	0.76 (0.39, 1.50)	0.75 (0.47, 1.18)	0.71 (0.45, 1.13)	
Ever ≥5 years	0.54 (0.39, 0.73)	0.66 (0.38, 1.14)	0.66 (0.32, 1.35)	0.38 (0.13, 1.11)	0.35 (0.16, 0.78)	0.65 (0.34, 1.25)	0.63[i]
PMH use[j]							
Never (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Ever	1.08 (0.91, 1.29)	0.92 (0.65, 1.31)	0.82 (0.51, 1.30)	0.92 (0.50, 1.69)	1.21 (0.86, 1.70)	1.46 (1.02, 2.10)	0.25[h]
Ever <5 years	1.05 (0.86, 1.29)	0.82 (0.54, 1.26)	0.85 (0.51, 1.42)	0.97 (0.50, 1.87)	1.30 (0.88, 1.91)	1.31 (0.87, 1.98)	
Ever ≥5 years	1.16 (0.91, 1.48)	1.04 (0.68, 1.59)	0.59 (0.24, 1.48)	0.83 (0.29, 2.40)	1.11 (0.70, 1.76)	2.13 (1.30, 3.49)	0.18[i]
Hysterectomy[k]							
No (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Yes	1.02 (0.83, 1.25)	1.09 (0.73, 1.62)	1.16 (0.74, 1.83)	1.13 (0.60, 2.13)	0.77 (0.48, 1.24)	1.00 (0.67, 1.52)	0.73
BMI							
<25 kg/m^2 (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
25-29.9 kg/m^2	0.77 (0.63, 0.94)	0.83 (0.56, 1.21)	0.81 (0.46, 1.43)	0.48 (0.24, 0.95)	0.87 (0.59, 1.27)	0.75 (0.50, 1.13)	
≥30 kg/m^2	1.12 (0.90, 1.39)	1.12 (0.74, 1.70)	1.37 (0.81, 2.29)	0.76 (0.42, 1.40)	1.03 (0.54, 1.97)	1.10 (0.73, 1.66)	0.94
p_{trend}	0.16	0.23	0.52	0.64	0.82	0.40	
Diabetes							
No (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Yes	1.12 (0.86, 1.45)	0.98 (0.46, 2.10)	1.38 (0.80, 2.39)	1.70 (0.87, 3.30)	0.72 (0.38, 1.36)	1.16 (0.72, 1.85)	0.40
Smoking status							
Never (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Ever	1.07 (0.90,1.26)	1.08 (0.79, 1.49)	0.86 (0.57, 1.30)	0.77 (0.45, 1.29)	1.20 (0.86, 1.68)	1.25 (0.88, 1.77)	0.42
Family history of breast and/or ovarian cancer							
No (ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Yes	1.19 (0.96, 1.48)	1.08 (0.71, 1.65)	1.08 (0.62, 1.90)	0.82 (0.38, 1.73)	1.36 (0.90, 2.05)	1.48 (0.95, 2.31)	0.63

[a] Cox proportional hazards models adjusted for baseline age (continuous), menopausal status (pre-/peri- [ref.], postmenopausal), use of OCs (never [ref.], ever), and number of children (0 [ref.], 1, 2, 3, ≥4)

[b] Models in the full cohort additionally adjusted for race/ethnicity (White [ref.], African American, Native Hawaiian, Japanese American, Latina)

[c] $P_{interaction}$ comparing models without to models with interaction terms for the exposure and race/ethnicity variables using log-likelihood ratio tests

[d] parity (no, yes)

[e] number of children (0, 1, 2, 3, =>4)

[f] among 51,164 postmenopausal women with a natural menopause

[g] among 63,107 women with available information

[h] never vs ever use

[i] duration of use (never, <5, ≥5 years)

[j] among 75,768 postmenopausal women

[k] additionally adjusted for ever PMH use (if postmenopausal; never [ref], ever). Abbreviations: 95% CI: 95% confidence interval, BMI: body mass index, EOC: epithelial ovarian cancer; HR: hazard ratio, OC: oral contraceptive, PMH: postmenopausal hormone therapy.