HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2023 February 02.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2022 August 02; 31(8): 1610–1620.

doi:10.1158/1055-9965.EPI-22-0115.

Race differences in the associations between menstrual cycle characteristics and epithelial ovarian cancer

Rebecca Nash[1], **Courtney E Johnson**[1], **Holly R. Harris**[2], **Lauren C. Peres**[3], **Charlotte E Joslin**[4], **Traci N. Bethea**[5], **Elisa V. Bandera**[6], **Heather M. Ochs-Balcom**[7], **Evan R. Myers**[8], **Kristin A Guertin**[9], **Fabian Camacho**[9], **Alicia Beeghly-Fadiel**[10], **Patricia G. Moorman**[11], **Veronica Wendy Setiawan**[12], **Lynn Rosenberg**[13], **Joellen M. Schildkraut**[1], **Anna H. Wu**[12]

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta GA

[2]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

[4]Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago School of Medicine and Division of Epidemiology and Biostatistics, School of Public Health, Chicago, IL

[5]Office of Minority Health and Health Disparities Research, Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Campus, Washington, DC

[6]Cancer Epidemiology and Health Outcomes, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

[7]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo, NY

[8]Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC

[9]Department of Population Health and Prevention Sciences, University of Virginia School of Medicine, Charlottesville, VA

[10]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

[11]Department of Family Medicine and Community Health, Duke University Medical Center, Durham, NC

[12]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA

[13]Slone Epidemiology Center at Boston University, Boston, MA

Abstract

Corresponding Author: Anna H. Wu, PhD, Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, 1441 Eastlake Avenue, Rm 4443, Los Angeles, CA 90089, Phone: (323) 865–0484; annawu@usc.edu.

Conflict of Interest Statement: The authors declare no potential conflicts of interest.

Background: Menstrual cycle characteristics—including age at menarche and cycle length—have been associated with ovarian cancer risk in White women. However, the associations between menstrual cycle characteristics and ovarian cancer risk among Black women have been sparsely studied.

Methods: Using the Ovarian Cancer in Women of African Ancestry (OCWAA) Consortium that includes 1,024 Black and 2,910 White women diagnosed with epithelial ovarian cancer (EOC) and 2,325 Black and 7,549 White matched controls, we investigated associations between menstrual cycle characteristics (age at menarche, age at menstrual regularity, cycle length, and ever missing three periods) and EOC risk by race and menopausal status. Multivariable logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Black women were more likely to be <11 years at menarche than White women (controls: 9.9% vs 6.0%). Compared to ≥15 years at menarche, <11 years was associated with increased EOC risk for White (OR=1.25, 95% CI: 0.99, 1.57) but not Black women (OR=1.10, 95% CI: 0.80, 1.55). Among White women only, the association was greater for premenopausal (OR=2.20, 95% CI: 1.31, 3.68) than postmenopausal women (OR=1.06, 95% CI: 0.82, 1.38). Irregular cycle length was inversely associated with risk for White (OR=0.78, 95% CI: 0.62, 0.99) but not Black women (OR=1.06, 95% CI: 0.68, 1.66).

Conclusions: Earlier age at menarche and cycle irregularity are associated with increased EOC risk for White but not Black women.

Impact: Associations between menstrual cycle characteristics and EOC risk were not uniform by race.

INTRODUCTION

Ovarian cancer incidence is about 30% higher among White than Black women (1). Reasons for this racial disparity are not fully understood—in part due to lack of sufficient sample sizes to examine differences by race—but are likely to be multifactorial and interrelated (2). Although incidence is lower, ovarian cancer survival is poorer among Black women, even among women diagnosed with localized disease (3). Therefore, identifying factors contributing to race differences is critical to reduce disparities and improve ovarian cancer outcomes.

Factors that decrease the lifetime number of ovulatory cycles, including pregnancy, breastfeeding, and oral contraceptive use, have been established as risk-reducing for ovarian cancer (4-7). Ovulation disrupts the ovarian epithelium and promotes rapid cell division and proliferation, which increases the potential for malignant transformation (8). Earlier age at menarche, which could result in more years of ovulation, has been posited as an additional reproductive-related ovarian cancer risk factor and has been associated with an increased risk of other hormonally driven cancers, including breast and endometrial cancers (9-11). However, epidemiologic evidence for an association between age at menarche and ovarian cancer risk has been inconsistent and race differences in the association have not been adequately examined (11-15). Other menstrual cycle characteristics, including cycle irregularity, cycle length, and missing periods may also contribute to ovarian cancer risk. A large pooled analysis of 14 case–control studies found irregular menstrual cycles and

long menstrual cycles were each associated with a decreased risk of ovarian cancer (16) but, other smaller studies have found null associations or associations only for specific ovarian cancer histotypes (17,18). Cycle irregularity and missing periods may be caused by a variety of underlying factors, including endocrine disorders or uterine fibroids, and could result in fewer ovulatory cycles. One notable limitation of these previous studies is that they were all conducted in entirely or majority White populations. Although there are racial differences in the distributions of menstrual cycle characteristics (19), for example menarche has been shown to be consistently earlier in Black girls than White girls (20,21), it is not known whether there are also racial differences in the associations between menstrual cycle characteristics and ovarian cancer risk. Understanding whether associations between menstrual cycle characteristics and ovarian cancer differ by race may help inform ovarian cancer etiology and explain racial disparities.

Most epidemiologic studies of ovarian cancer lack sufficient sample sizes of Black women to investigate risk associations separately by race. Using data from the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium, we investigated the associations between four menstrual cycle characteristics—age at menarche, age at menstrual regularity, cycle length, and ever missing three periods—and risk of ovarian cancer, separately for Black and White women. The OCWAA consortium consists of harmonized data from seven well-established studies (22-28), and includes the largest number of Black women diagnosed with ovarian cancer in an epidemiologic study to date (29).

MATERIALS AND METHODS

Study population

The OCWAA consortium includes data from more than 4,000 women diagnosed with epithelial ovarian cancer (EOC), and race-, age-, and site-matched controls compiled from four case–control studies and three case–control studies that were nested within large, prospective cohorts. The OCWAA consortium has been previously described in detail (29). Briefly, data from patient questionnaires, medical records, and cancer registry records were harmonized for participants from the seven individual studies. The four case–control studies include: the African American Cancer Epidemiology Study (AACES) (22), the Cook County Case–Control Study (CCCCS) (23), the Los Angeles County Ovarian Cancer Study (LACOCS) (24), and the North Carolina Ovarian Cancer Study (NCOCS) (25). The nested case–control studies were within the Black Women's Health Study (BWHS) (26), the Multiethnic Cohort Study (MEC) (27), and the Women's Health Initiative (WHI) (28). Each study obtained informed consent from its participants. For the three cohort studies, consent was determined as follows. For MEC, receipt of a completed, mailed baseline questionnaire was considered implicit consent to participate. For BWHS, receipt of a completed baseline questionnaire was considered implicit consent to participate. Finally for WHI, participants provided written consent. The individual studies and the OCWAA Consortium were approved by the relevant Institutional Review Boards.

The analytic dataset included participants with data on any of the four menstrual cycle characteristics of interest (i.e., age at menarche, age at menstrual regularity, cycle length, or ever missed three consecutive periods) (Supplemental Table 1). Participants missing

information on all four characteristics were excluded. Approximately 84% of participants in the OCWAA consortium had information on at least one of the four menstrual cycle characteristics and were therefore included in the current analyses.

Exposure and covariate assessment

Participant race in all OCWAA studies was determined by self-report. Both Hispanic and non-Hispanic ethnicities were included, however only 2.0% of White participants and 0.5% of Black participants were of Hispanic ethnicity.

Other demographic, clinical, and medical history data were obtained by in-person or telephone interviews or mailed questionnaires. Self-reported age at menarche was collected in all seven studies. Age at menstrual regularity was collected in all studies except BWHS as either the number of months after first menstrual period before regularity (AACES, NCOCS, LACOCS) or the age at which periods became regular (MEC, CCCCS, WHI). Information on the average length of the menstrual cycle and whether subjects ever missed three consecutive periods was available in three studies only (AACES, NCOCS, and LACOCS) (Supplemental Table 1). For participants who reported months until menstrual regularity, age at menstrual regularity was calculated by adding the number of months to the self-reported age at menarche because number of months until regularity was not collected by all studies. Participants who reported never reaching menstrual regularity were excluded from age at regularity analyses. Both age variables were analyzed as 4-level categorical variables (<11, 11–12, 13–14, ≥15 years).

Additional patient characteristics included age at diagnosis for cases or at interview for controls, educational attainment (high school or less, some college, college graduate, or graduate/professional school), marital status (single, married, separated, or widowed), parity (0, 1–3, or >3 pregnancies), duration of oral contraceptive use (never, 1–5, or >5 years), body mass index (BMI, <25, 25–<30, 30–<35, or ≥35 kg/m^2), smoking status (never, former, or current), history of tubal ligation (yes or no), first degree family history of breast or ovarian cancer (yes or no), menopausal status at diagnosis (premenopausal or postmenopausal), and post-menopausal hormone use (yes or no).

Outcome assessment

Eligible cases were diagnosed with EOC, the most common type of ovarian cancer, accounting for more than 90% of all ovarian cancer cases (30). The four OCWAA case–control studies identified cases through population-based cancer registries and the case–control studies nested within cohort studies identified cases through self-report or linkage to statewide cancer registries. Each study obtained pathology data to confirm EOC diagnosis. EOC histotype was classified into seven mutually exclusive subtypes using both morphology and grade information as previously described (29,31). Specifically, cases were classified as high-grade serous, low-grade serous, endometrioid, clear cell, mucinous, carcinosarcoma, or other histotype. Cases with serous histology were classified as low-grade serous if tumor grade was 1 and as high-grade serous if tumor grade was 2 or higher. Endometrioid tumors with grades 3 or 4 (N=141 White cases, 33 Black cases) were recategorized as high-grade serous due to their biological similarity to high-grade serous tumors and the challenges

with distinguishing the two histotypes (32,33). A sensitivity analysis, excluding high grade endometrioid tumors from the high-grade serous category was performed.

Statistical Analysis

Descriptive statistics were used to summarize subject characteristics by case/control status and by race as frequency and percent for categorical variables or mean and standard deviation (SD) for continuous variables. Multivariable logistic regression was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the associations between menstrual cycle characteristics and ovarian cancer risk. Data from the seven studies was pooled and heterogeneity by study site was quantified by calculating Cochran's Q p-value. To control for study site heterogeneity, a random effect for study site was assessed in each model. If all variance components were non-zero, then the random effect for study site was included in the model. Otherwise, the model reduced to fixed effects only. Multivariable models were adjusted for age at diagnosis (continuous) and potential confounders, identified from previous literature and graphical representation of relationships between variables (i.e., directed acyclic graphs). Since menstrual cycle characteristics (especially age at menarche) occur prior to other reproductive-related ovarian cancer risk factors, multivariable models were only adjusted for height, weight (young adult), and education (as a proxy measure for socioeconomic status). All analyses were stratified by race (Black or White). Models examining the associations for age at menarche and age at menstrual regularity were also stratified by menopausal status. P-trend was calculated by considering age at menarche or age at regularity as a continuous variable (34). Statistical heterogeneity by race and menopausal status was assessed by joint Wald chi-square tests of the interaction terms.

Subgroup Analyses

EOC is a heterogeneous disease that can be further subdivided into histotypes that have distinct gene expression patterns, molecular characteristics, and clinical features (31,33,35). Therefore, we assessed race-specific associations for age at menarche and age at menstrual regularity, separately for high-grade serous tumors, the most common histotype (31). The other histotypes (low-grade serous, endometrioid, clear cell, mucinous, carcinosarcoma, and other) were grouped together because modest sample sizes precluded meaningful separate analyses. For the histotype analysis only, polytomous logistic regression was used to calculate aORs and 95% CIs. The outcomes in these models were high-grade serous or other histotypes and the reference group was all eligible controls.

Genetic disposition to being taller has been associated with increased risk of ovarian cancer (36) and age at menarche has been associated with height (37,38). Therefore, to determine whether the association between age at menarche or age at menstrual regularity and EOC risk is modified by adult height, we performed a subgroup analysis stratified by height. Cases and controls were classified as being in the upper quartile for height versus the lower three quartiles, based on heights from controls with non-missing data for age at menarche or age at menstrual regularity.

We also assessed whether associations between age at menarche or age at menstrual regularity and EOC risk differed by obesity at diagnosis/interview (as determined by BMI ≥30 kg/m^2) because overweight/obesity has been associated with anovulation and may impact menstrual cycle characteristics. Due to small numbers, 13–14 years and ≥15 years were combined into one age category for associations among premenopausal women.

Last, we repeated the analysis examining race-specific associations between age at menarche and EOC risk excluding AACES and NCOCS because these two studies have individually reported results for age at menarche among Black women (13,14) and together they account for 66% of the Black cases included in the OCWAA consortium.

The data underlying this article will be shared on reasonable request to the OCWAA Consortium.

RESULTS

A total of 3,934 cases with EOC and 9,874 matched controls were included in the analysis, with Black women accounting for 24% (1,024 cases, 2,325 controls) of the sample population. Demographic and clinical characteristics by race and case/control status are shown in Table 1. Black cases and controls were younger, had higher BMI at diagnosis/interview, lower educational attainment, and were more likely to be divorced, separated or never married than White cases and controls. Among both Black and White women separately, cases were more likely than controls to be nulliparous (among Black women: 18.3% vs 15.7% and among White women: 23.7% vs 18.4%) and to have a family history of breast or ovarian cancer (among Black women: 27.6% vs 15.6% and among White women: 20.9% vs 16.9%).

Distributions of menstrual cycle characteristics and associations with EOC are shown in Table 2. Compared to White women, Black women were more likely to be <11 years (cases: 9.9% vs 6.8%; controls: 9.9% vs 6.0%) or ≥15 years at menarche (cases: 12.2% vs 10.0%; controls: 12.3% vs 10.3%). Overall, compared with oldest age at menarche (≥15 years), youngest age at menarche (<11 years) was associated with increased risk of EOC for White (aOR=1.25, 95% CI: 0.99, 1.57) but not Black women (aOR=1.10, 95% CI: 0.80, 1.55; p-heterogeneity=0.58) (Table 2). Among Black women, there was no trend in the association between age at menarche and ovarian cancer (p-trend=0.56) but among White women, EOC risk decreased with increasing age at menarche (11–12 years: aOR=1.13, 95% CI: 0.96, 1.32; 13–14 years: aOR=1.10, 95% CI: 0.94, 1.29; p-trend=0.07). The risk pattern was observed among premenopausal White women (p-trend=0.002) but not postmenopausal women (p-trend=0.76, p-heterogeneity=0.04) and not among Black women, regardless of menopausal status (p-heterogeneity=0.85).

The associations between age at menstrual regularity and EOC followed a similar pattern as the associations between age at menarche and EOC. Overall, younger ages at menstrual regularity were associated with increased risk of EOC among White (p-trend=0.004) but not Black (p-trend=0.84) women. The trend among White women was driven by associations among premenopausal (<11 years aOR=2.17, 95% CI: 1.32, 3.57; 11–12 years:

aOR=1.61, 95% CI: 1.15, 2.26; 13–14 years aOR=1.32, 95% CI: 0.94, 1.86; p-trend<0.001) but not postmenopausal women (<11 years aOR=1.16, 95% CI: 0.88, 1.52; 11–12 years aOR=1.16, 95% CI: 0.99, 1.36; 13–14 years aOR=1.18, 95% CI: 1.01, 1.37; p-trend=0.18). No trend was observed among either premenopausal (p-trend=0.55) or postmenopausal (p-trend=0.45) Black women.

Black control women were more likely to report shorter (<25 days) menstrual cycles (7.6% vs 4.6%) but less likely to report longer cycles (31+ days: 2.5% vs 7.6%) than White control women (Table 2). However, associations between cycle length and EOC were similar by race (p-heterogeneity=0.66). Compared to cycle length 26–30 days, longer cycle length was associated with reduced EOC risk for both Black (aOR=0.60, 95% CI: 0.30, 1.22) and White (aOR=0.65, 95% CI: 0.48, 0.88) women, while shorter cycle length was not associated with risk for either Black (aOR=0.99, 95% CI: 0.68, 1.43) or White (aOR=0.90, 95% CI: 0.63, 1.27) women. Irregular menstrual cycle length was less common among Black than White control women (e.g., 5.3% vs 11.7%) and inversely associated with risk for White (aOR=0.78, 95% CI: 0.62, 0.99) but not Black women (OR=1.06, 95% CI: 0.68, 1.66). Ever missing three consecutive periods was not associated with EOC for both Black and White women (p-heterogeneity=0.71).

Subgroup Analyses

Analyses for age at menarche and age at regularity were repeated for subgroups of women to identify other potential differences in the associations. Risk patterns by EOC histotype are presented in Table 3. Associations between age at menarche and EOC did not differ consistently between high-grade serous and other histotypes for either Black (p-heterogeneity=0.98) or White (p-heterogeneity=0.24) women. Associations between age at menstrual regularity and EOC were also similar by histotype for both Black and White women. Findings by histotype were largely similar in a sensitivity analysis excluding high-grade endometrioid tumors from the high-grade serous category (Supplemental Table 2).

Associations between age at menarche and EOC were not different by height overall for Black (p-heterogeneity=0.43) or White (p-heterogeneity=0.99) women. However, differences by height were observed among premenopausal Black women (p-heterogeneity=0.02, Table 4). Among premenopausal Black women in the upper quartile for height, compared to ≥15 years at menarche, ages <11, 11–12, and 13–14 years were associated with increased risk of EOC with aORs of 2.94 (95% CI: 1.04, 8.37), 1.60 (95% CI: 0.70, 3.64), and 2.53 (95% CI: 1.09, 5.87), respectively (p-trend=0.40) (Table 4). In contrast, among premenopausal Black women in the lower three quartiles for height, earlier ages at menarche were not associated with EOC risk (<11 years aOR=0.66, 95% CI: 0.30, 1.45; 11–12 years aOR=0.89, 95% CI: 0.47, 2.12; 13–14 years aOR=0.59, 95% CI: 0.30, 1.18). Associations between age at menstrual regularity and EOC also differed by height for premenopausal Black women (p-heterogeneity=0.03). Associations were more pronounced among women in the upper quartile for height (<11 years aOR=1.62, 95% CI: 0.48, 5.52; 11–12 years aOR=1.21, 95% CI: 0.52, 2.81; 13–14 years aOR=3.31, 95% CI: 1.39, 7.92) than among women in the lower three quartiles for height (<11 years aOR=0.73, 95% CI: 0.31, 1.68; 11–12 years aOR=1.08, 95% CI: 0.56, 2.07; 13–14 years aOR=0.85, 95% CI:

0.41, 1.74) however, associations did not follow a monotonic trend for either group. EOC risk patterns among White women did not differ by height (Supplemental Table 3).

Results stratified by BMI are shown in Supplemental Table 4. Among both White and Black women, overall trends for age at menarche were similar by BMI category, however the association for age at menarche <11 years, compared to ≥13 years, were of greater magnitude among premenopausal White women with BMI ≥30 kg/m^2 (aOR = 2.43, 95% CI: 1.10, 5.36) than among premenopausal White women with BMI <30 kg/m^2 (aOR=1.59, 95% CI: 0.98, 2.57). Overall trends for age at regularity were also similar by BMI category for both White and Black women but the association for <11 years among premenopausal White women was of greater magnitude for women with BMI ≥30 kg/m^2 (aOR=3.07, 95% CI: 1.29, 7.38) than among women with BMI <30 kg/m^2 (aOR=1.68, 95% CI: 1.02, 2.76).

Last, we repeated the main analyses for age at menarche excluding AACES and NCOCS from the pooled dataset (Supplemental Table 5). Results among White women were similar to the primary analyses but results among Black women differed. With 35% of the Black cases and 60% of the Black controls remaining after exclusion, compared to ≥15 years, younger ages at menarche were associated with an increased risk of EOC among Black women overall (p-trend=0.06); the trend was driven by associations among premenopausal women (p-trend=0.04) but not postmenopausal women (p-trend=0.27). For example, ages at menarche of <11, 11–12, and 13–14 years, compared to ≥15 years, were associated with increased risk of EOC among premenopausal Black women with aORs of 2.94 (95% CI: 0.88, 9.76), 2.24 (95% CI: 0.80, 6.33), and 1.68 (95% CI: 0.56, 4.98), respectively.

DISCUSSION

In this large study, associations between menstrual cycle characteristics and risk of EOC were not uniform among Black and White women. Near null associations between age at menarche and EOC were observed among Black women regardless of menopausal status. In contrast, younger ages at menarche were associated with an increased risk of EOC among premenopausal White women; this trend was not observed among postmenopausal White women. Associations between earlier age at menstrual regularity and risk of EOC were similarly observed among premenopausal White but not Black women. In addition, irregular cycle length was associated with reduced risk for White but not Black women. In contrast, associations between longer menstrual cycle length (≥31 days) and ever missing 3 consecutive periods were similar for Black and White women, although estimates for these two factors were less precise because the sample of Black women was only about one-third that of White women.

Prior investigations of the association between age at menarche and ovarian cancer risk have mostly found older ages at menarche to be associated with reduced ovarian cancer risk (11,14,15,39,40), which is supported by our findings among White women. These previous reports rarely examined associations in non-White populations or by menopausal status. A large 2013 meta-analysis consisting of 27 observational studies (22 case-control, 5 cohort studies) found a 15% decrease in ovarian cancer risk comparing the oldest with the youngest age at menarche category, in both case-control (RR=0.84, 95% CI: 0.75, 0.97) and cohort

(RR=0.89, 95% CI: 0.76, 1.03) studies (15). A more recent pooled analysis of eight cohort studies (none of which were included in the 2013 meta-analysis (15)) consisting mostly of US and European White women found a small decrease in ovarian cancer risk (RR=0.98, 95% CI: 0.95, 1.01) with each additional year delay in the age at menarche (11). Race was not considered in the pooled analysis of cohort studies (11) and the meta-analysis only examined associations separately for Asians, Americans, and Europeans (15). Two studies (AACES and NCOCS), included in the OCWAA consortium, have provided information on age at menarche and risk of ovarian cancer in Black women (13,14). In the AACES study, menarche at ages 12–13 years (compared to younger than 12 years) was associated with increased EOC risk (OR=1.3, 95% CI: 1.0, 1.8) among postmenopausal Black women, but this association was not found in premenopausal women (13). After excluding AACES and NCOCS, which accounted for two-thirds of the Black cases in OCWAA, we observed an increase in EOC risk for youngest ages at menarche among premenopausal Black women, which is in contrast to the results observed among all women in OCWAA.

Literature on associations between other menstrual cycle characteristics and EOC is more limited. A pooled analysis of more than 13,000 ovarian cancer cases from 14 case–control studies (including NCOCS and LACOCS), as part of the Ovarian Cancer Association Consortium (OCAC), found a decrease in EOC risk associated with both irregular and long (>35 days) menstrual cycles (16). The analyses were adjusted for race, but race-specific associations were not estimated. Smaller case–control studies conducted in majority White populations have also found inverse associations for longer or irregular menstrual cycles (17,18). In contrast, a prospective analysis using the Child Health and Development Studies (CHDS) cohort established during 1959–1966 and followed through 2011 via linkage to the California Cancer Registry, found elevated ovarian cancer risk with irregular menstrual cycles, after adjustment for race and ethnicity, oral contraceptive use, parity, and other factors (41). In addition, older age at menarche was associated with increased risk of ovarian cancer in the CHDS cohort, also inconsistent with our results and results reported in the meta-analysis (15) and pooled cohort analysis (11).

Age at menarche is influenced by several factors, including body weight and height, which likely reflect the contribution of a myriad additional and complex factors such as overall nutrition and health status (38,42-45). Some studies have shown that over the last several decades, age at menarche has decreased, while adult height has increased (46,47). Taller height has been associated with earlier menarche in multiethnic populations (38). However, in a large study of mainly European whites, women with earlier menarche ultimately reached a shorter adult height (37). Our subgroup analyses did not show significant differences by height among White women, however, among premenopausal Black women there was a non-linear increase in EOC for earlier ages at menarche among women in the highest quartile of height. Differences by BMI were not significant for either race group, although associations for the youngest age at menarche were of greater magnitude among premenopausal White women with BMI ≥30 kg/m^2 than among premenopausal White women with BMI <30 kg/m^2.

Histotype differences in the associations between menstrual cycle characteristics and risk of ovarian cancer have been explored in a few previous studies. In the 2013 meta-analysis,

age at menarche was not associated with risk of invasive serous ovarian cancer but this was based on only two studies (15). In an OCAC pooled analysis, both irregular cycles and long cycles (>35 days) were associated with decreased risk of high grade serous EOC (16). In a pooled analysis that included 1.3 million women in the Ovarian Cancer Cohort Consortium (OC3), differences in associations between reproductive characteristics—including age at menarche—and risk of ovarian cancer were observed. Oldest age at menarche (≥15 years), compared to youngest age (≤11 years), was associated with reduced risk of clear cell (RR=0.55, 95% CI: 0.34, 0.90) but not endometrioid (RR=0.98, 95% CI: 0.73, 1.31) or mucinous (RR=1.13, 95% CI: 0.76, 1.66) tumors (40). Our subgroup analysis did not find meaningful differences in the race-specific associations by histotype, however, data were sparse and we were unable to examine histotypes other than high grade serous. Investigating histotype differences in race-specific associations is an important area of future inquiry.

The association between earlier age at menarche and increased ovarian cancer risk may be partly explained by the incessant ovulation hypothesis, which suggests there is a positive association between frequency of ovulation and ovarian cancer risk, because earlier menarcheal age results in an increase in the lifetime number of ovulations (48). In addition, early menarche is associated with a more rapid onset of ovulatory cycles and a tendency to sustain higher levels of circulating estrogens (49). Although a role of sex steroid hormones in the etiology of ovarian cancer is biologically compelling, the mechanism for ovarian carcinogenesis has not been well characterized. Exogenous hormones, administered as menopausal hormone therapy, have been associated with an increased risk of ovarian cancer (50), while those administered earlier in life, as oral contraceptives, have been associated with a reduced risk of ovarian cancer (4). Evidence for the role of endogenous hormones is conflicting and limited by small sample sizes or non-representative patient populations (e.g., pregnant women) (51-54).

In some previous studies of ovarian cancer, reproductive factors, including pregnancies and oral contraceptive use and duration, were more strongly associated with premenopausal than postmenopausal ovarian cancer risk (13,39,55). These and other reproductive-related exposures, including age at menarche, have occurred in the more distant past for postmenopausal than premenopausal women. Difficulty with recall, resulting in differential misclassification by age, may have contributed to our weaker findings in postmenopausal women. However, differences in associations with ovarian cancer risk by menopausal status may also represent specific periods of susceptibility. The lifetime number of ovulatory cycles is influenced by many factors, including age at menopause. Therefore, associations among premenopausal women may reflect a greater lifetime number of ovulatory cycles in women who are still ovulating. A better understanding of the underlying reasons contributing to effect modification by menopausal status is needed.

Biological reasons for the largely null association between age at menarche and risk of EOC among Black women, regardless of menopausal status, are unclear. One potential mechanism is obesity-related anovulation, which may reduce ovarian cancer risk by decreasing the lifetime number of ovulations. Among premenopausal women with EOC in our study, only 32% of White but 78% of Black cases were overweight or obese. A lower proportion of overweight/obesity observed among Black cases (59%) after excluding

AACES and NCOCS could partly explain the inverse association among premenopausal Black women after the restriction, similar to the association observed among premenopausal White women. Although obesity has been associated with an increased risk of ovarian cancer in previous studies, the association may differ by menopausal status, age at menarche, race, and histotype (56,57). Subgroup analyses in a 2012 meta-analysis that included 47 epidemiologic studies found a small increased risk of ovarian cancer with higher BMI for all women (relative risk (RR) per 5 kg/m^2 increase in BMI=1.05, standard error (SE)=0.011); risk was slightly higher for premenopausal women (RR=1.12, SE=0.024), weaker for women with younger (<13 years) ages at menarche (RR=1.05, SE=0.015) and largely null for non-White women (RR=0.98, SE=0.059) (56). Unpublished OCWAA consortium results showed BMI ≥30 kg/m^2 was associated with an overall increased risk of EOC for Black but not White women and no association for high grade serous EOC for either race group (58). The Black cases in our analysis were more likely to be premenopausal at diagnosis, but also more likely to have younger ages at menarche. Stratifying by BMI in our analysis did not explain null results among Black women. An additional consideration may be race differences in age at menopause, which combined with age at menarche, parity, oral contraceptive use, and breastfeeding duration, determine the lifetime number of ovulatory cycles. These data are not yet harmonized for OCWAA, and previous reports of race differences in timing of menopause have been mixed (59-62). Disentangling the complex interactions between these factors is beyond the scope of the current study but is an important area of future research.

There are some limitations to our current study, most notable is the potential for misclassification of the exposure. Menstrual cycle characteristics were ascertained by patient self-report, which is subject to misclassification and potentially differential by, case/control status or age. Exposure information for the four case–control studies was collected several decades after menarche for most women, and around the time of cancer diagnosis for cases. Recall may also be differential with respect to age and menopausal status because the length of time since onset of menarche and other menstrual cycle characteristics is longer for postmenopausal women. Due to small sample sizes, we were unable to examine associations separately for histotypes other than high-grade serous, potentially masking heterogeneity in associations by tumor histotype. Despite these limitations, OCWAA is a rich resource with sufficient sample size to examine ovarian cancer risk factors by race. This study is the largest to investigate race differences in the association between menstrual cycle characteristics and ovarian cancer risk but the sample size of Black cases and controls was only about one-third the sample size of White cases and controls.

In conclusion, we observed differences in the associations between certain menstrual cycle characteristics (i.e., age at menarche, age at menstrual regularity, and irregular menstrual cycles) and risk of EOC by race. Earlier ages at menarche and menstrual regularity were associated with an increased risk of EOC for premenopausal White women but not Black women. As age at menarche among girls decreases, this warrants further attention. Recent estimates from the National Health Statistics Report showed 14% of Black girls but only 9% of White girls had reached menarche by 10 years of age (63). We also found irregular cycles reduced risk for White but not Black women, while long menstrual cycles appeared

to reduce risk for both race groups. Future studies should examine EOC risk factors by race and investigate reasons for these disparities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Pathology data were obtained from the following state cancer registries (AZ, CA, CO, CT, DE, DC, FL, GA, IL, IN, KY, LA, MD, MA, MI, NJ, NY, NC, OK, PA, SC, TN, TX, VA), and results reported do not necessarily represent their views. The IRBs of participating institutions and cancer registries have approved these studies, as required.

Financial Support

The Ovarian Cancer in Women of African Ancestry (OCWAA) Consortium is supported by the US National Cancer Institute (R01-CA207260, to J.M. Schildkraut and L. Rosenberg and K01-CA212056, to T.N. Bethea). AACES was funded by NCI (R01-CA142081, to J.M. Schildkraut); BWHS is funded by NIH (R01-CA058420, UM1-CA164974, and U01-CA164974, to L. Rosenberg); CCCS was funded by NIH/NCI (R01-CA61093, to K. Rosenblatt); LACOCS was funded by NCI (R01-CA17054, to M. Pike, R01-CA58598, to M. Goodman and A.H. Wu, and Cancer Center Core grant P30-CA014089, to B. Henderson and A.H. Wu) and by the California Cancer Research Program (2II0200, to A.H. Wu); and NCOCS was funded by NCI (R01-CA076016, to J.M. Schildkraut). The WHI program is funded by the National Heart, Lung, and Blood Institute through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. Additional grants to support WHI inclusion in OCWAA include UM1-CA173642-05 (to Anderson), NHLBI-CSB-WH-2016-01-CM, and NHLBI-75N92021D00002. R Nash is additionally supported by an award from the US National Cancer Institute (F31CA268737).

REFERENCES

1. Peres LC, Schildkraut JM. Racial/ethnic disparities in ovarian cancer research. Adv Cancer Res 2020;146:1–21. [PubMed: 32241384]
2. Peres LC, Bethea TN, Camacho TF, Bandera EV, Beeghly-Fadiel A, Chyn DL, et al. Racial Differences in Population Attributable Risk for Epithelial Ovarian Cancer in the OCWAA Consortium. J Natl Cancer Inst 2021;113(6):710–8. [PubMed: 33252629]
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7–30. [PubMed: 31912902]
4. Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371(9609):303–14. [PubMed: 18294997]
5. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. Am J Epidemiol 1992;136(10):1184–203. [PubMed: 1476141]
6. Gaitskell K, Green J, Pirie K, Barnes I, Hermon C, Reeves GK, et al. Histological subtypes of ovarian cancer associated with parity and breastfeeding in the prospective Million Women Study. Int J Cancer 2018;142(2):281–9. [PubMed: 28929490]
7. Li DP, Du C, Zhang ZM, Li GX, Yu ZF, Wang X, et al. Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. Asian Pac J Cancer Prev 2014;15(12):4829–37. [PubMed: 24998548]
8. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 1998;90(23):1774–86. [PubMed: 9839517]
9. Collaborative Group on Hormonal Factors in Breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13(11):1141–51. [PubMed: 23084519]

10. Gong TT, Wang YL, Ma XX. Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. Sci Rep 2015;5:14051. [PubMed: 26360785]
11. Fuhrman BJ, Moore SC, Byrne C, Makhoul I, Kitahara CM, Berrington de Gonzalez A, et al. Association of the Age at Menarche with Site-Specific Cancer Risks in Pooled Data from Nine Cohorts. Cancer Res 2021;81(8):2246–55. [PubMed: 33820799]
12. Braem MG, Onland-Moret NC, van den Brandt PA, Goldbohm RA, Peeters PH, Kruitwagen RF, et al. Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. Am J Epidemiol 2010;172(10):1181–9. [PubMed: 20861144]
13. Moorman PG, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, et al. Reproductive factors and ovarian cancer risk in African-American women. Ann Epidemiol 2016;26(9):654–62. [PubMed: 27528178]
14. Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM. Ovarian cancer risk factors in African-American and white women. Am J Epidemiol 2009;170(5):598–606. [PubMed: 19605513]
15. Gong TT, Wu QJ, Vogtmann E, Lin B, Wang YL. Age at menarche and risk of ovarian cancer: a meta-analysis of epidemiological studies. Int J Cancer 2013;132(12):2894–900. [PubMed: 23175139]
16. Harris HR, Babic A, Webb PM, Nagle CM, Jordan SJ, Risch HA, et al. Polycystic Ovary Syndrome, Oligomenorrhea, and Risk of Ovarian Cancer Histotypes: Evidence from the Ovarian Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2018;27(2):174–82. [PubMed: 29141849]
17. Harris HR, Titus LJ, Cramer DW, Terry KL. Long and irregular menstrual cycles, polycystic ovary syndrome, and ovarian cancer risk in a population-based case-control study. Int J Cancer 2017;140(2):285–91. [PubMed: 27667654]
18. Titus-Ernstoff L, Perez K, Cramer DW, Harlow BL, Baron JA, Greenberg ER. Menstrual and reproductive factors in relation to ovarian cancer risk. Br J Cancer 2001;84(5):714–21. [PubMed: 11237375]
19. John EM, Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of seven U.S. case-control studies. Epithelial ovarian cancer in black women. Collaborative Ovarian Cancer Group. J Natl Cancer Inst 1993;85(2):142–7. [PubMed: 8418303]
20. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, et al. Age at menarche and racial comparisons in US girls. Pediatrics 2003;111(1):110–3. [PubMed: 12509562]
21. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics 2002;110(4):e43. [PubMed: 12359816]
22. Schildkraut JM, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, et al. A multi-center population-based case-control study of ovarian cancer in African-American women: the African American Cancer Epidemiology Study (AACES). BMC Cancer 2014;14:688. [PubMed: 25242549]
23. Peterson CE, Rauscher GH, Johnson TP, Kirschner CV, Freels S, Barrett RE, et al. The effect of neighborhood disadvantage on the racial disparity in ovarian cancer-specific survival in a large hospital-based study in cook county, illinois. Front Public Health 2015;3:8. [PubMed: 25657992]
24. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer 2009;124(6):1409–15. [PubMed: 19065661]
25. Schildkraut JM, Moorman PG, Halabi S, Calingaert B, Marks JR, Berchuck A. Analgesic drug use and risk of ovarian cancer. Epidemiology 2006;17(1):104–7. [PubMed: 16357602]
26. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. J Am Med Womens Assoc (1972) 1995;50(2):56–8. [PubMed: 7722208]
27. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 2000;151(4):346–57. [PubMed: 10695593]

28. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, et al. The Women's Health Initiative recruitment methods and results. Ann Epidemiol 2003;13(9 Suppl):S18–77. [PubMed: 14575939]
29. Schildkraut JM, Peres LC, Bethea TN, Camacho F, Chyn D, Cloyd EK, et al. Ovarian Cancer in Women of African Ancestry (OCWAA) consortium: a resource of harmonized data from eight epidemiologic studies of African American and white women. Cancer Causes Control 2019;30(9):967–78. [PubMed: 31236792]
30. American Cancer Society. Cancer Facts & Figures 2018 Special Section: Ovarian Cancer. Atlanta: American Cancer Society; 2018.
31. Peres LC, Cushing-Haugen KL, Kobel M, Harris HR, Berchuck A, Rossing MA, et al. Invasive Epithelial Ovarian Cancer Survival by Histotype and Disease Stage. J Natl Cancer Inst 2019;111(1):60–8. [PubMed: 29718305]
32. Gilks CB, Prat J. Ovarian carcinoma pathology and genetics: recent advances. Hum Pathol 2009;40(9):1213–23. [PubMed: 19552940]
33. Kurman RJ, Carcangiu ML, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs. Lyon, France: International Agency for Research on Cancer; 2014.
34. Liu H, Merck Research Labs. Cochran-Armitage Trend Test Using SAS. PharmaSUG conference: 2007.
35. Marquez RT, Baggerly KA, Patterson AP, Liu J, Broaddus R, Frumovitz M, et al. Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon. Clin Cancer Res 2005;11(17):6116–26. [PubMed: 16144910]
36. Dixon-Suen SC, Nagle CM, Thrift AP, Pharoah PDP, Ewing A, Pearce CL, et al. Adult height is associated with increased risk of ovarian cancer: a Mendelian randomisation study. Br J Cancer 2018;118(8):1123–9. [PubMed: 29555990]
37. Onland-Moret NC, Peeters PH, van Gils CH, Clavel-Chapelon F, Key T, Tjonneland A, et al. Age at menarche in relation to adult height: the EPIC study. Am J Epidemiol 2005;162(7):623–32. [PubMed: 16107566]
38. Koprowski C, Ross RK, Mack WJ, Henderson BE, Bernstein L. Diet, body size and menarche in a multiethnic cohort. Br J Cancer 1999;79(11-12):1907–11. [PubMed: 10206312]
39. Moorman PG, Calingaert B, Palmieri RT, Iversen ES, Bentley RC, Halabi S, et al. Hormonal risk factors for ovarian cancer in premenopausal and postmenopausal women. Am J Epidemiol 2008;167(9):1059–69. [PubMed: 18303003]
40. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. J Clin Oncol 2016;34(24):2888–98. [PubMed: 27325851]
41. Cirillo PM, Wang ET, Cedars MI, Chen LM, Cohn BA. Irregular menses predicts ovarian cancer: Prospective evidence from the Child Health and Development Studies. Int J Cancer 2016;139(5):1009–17. [PubMed: 27082375]
42. Bratke H, Bruserud IS, Brannsether B, Assmus J, Bjerknes R, Roelants M, et al. Timing of menarche in Norwegian girls: associations with body mass index, waist circumference and skinfold thickness. BMC Pediatr 2017;17(1):138. [PubMed: 28587648]
43. Meyer F, Moisan J, Marcoux D, Bouchard C. Dietary and physical determinants of menarche. Epidemiology 1990;1(5):377–81. [PubMed: 2078613]
44. Maclure M, Travis LB, Willett W, MacMahon B. A prospective cohort study of nutrient intake and age at menarche. Am J Clin Nutr 1991;54(4):649–56. [PubMed: 1897472]
45. Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. Am J Epidemiol 1993;138(4):217–24. [PubMed: 8356963]
46. Anderson SE, Dallal GE, Must A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart. Pediatrics 2003;111(4 Pt 1):844–50. [PubMed: 12671122]
47. Nichols HB, Trentham-Dietz A, Hampton JM, Titus-Ernstoff L, Egan KM, Willett WC, et al. From menarche to menopause: trends among US Women born from 1912 to 1969. Am J Epidemiol 2006;164(10):1003–11. [PubMed: 16928728]

48. Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? Lancet 1971;2(7716):163. [PubMed: 4104488]
49. Vihko R, Apter D. Endocrine characteristics of adolescent menstrual cycles: impact of early menarche. J Steroid Biochem 1984;20(1):231–6. [PubMed: 6231419]
50. Collaborative Group On Epidemiological Studies Of Ovarian C, Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, et al. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet 2015;385(9980):1835–42. [PubMed: 25684585]
51. Gharwan H, Bunch KP, Annunziata CM. The role of reproductive hormones in epithelial ovarian carcinogenesis. Endocr Relat Cancer 2015;22(6):R339–63. [PubMed: 26373571]
52. Helzlsouer KJ, Alberg AJ, Gordon GB, Longcope C, Bush TL, Hoffman SC, et al. Serum gonadotropins and steroid hormones and the development of ovarian cancer. JAMA 1995;274(24):1926–30. [PubMed: 8568986]
53. Lukanova A, Lundin E, Akhmedkhanov A, Micheli A, Rinaldi S, Zeleniuch-Jacquotte A, et al. Circulating levels of sex steroid hormones and risk of ovarian cancer. Int J Cancer 2003;104(5):636–42. [PubMed: 12594820]
54. Schock H, Surcel HM, Zeleniuch-Jacquotte A, Grankvist K, Lakso HA, Fortner RT, et al. Early pregnancy sex steroids and maternal risk of epithelial ovarian cancer. Endocr Relat Cancer 2014;21(6):831–44. [PubMed: 25270324]
55. Tung KH, Wilkens LR, Wu AH, McDuffie K, Nomura AM, Kolonel LN, et al. Effect of anovulation factors on pre- and postmenopausal ovarian cancer risk: revisiting the incessant ovulation hypothesis. Am J Epidemiol 2005;161(4):321–9. [PubMed: 15692075]
56. Collaborative Group on Epidemiological Studies of Ovarian C. Ovarian cancer and body size: individual participant meta-analysis including 25,157 women with ovarian cancer from 47 epidemiological studies. PLoS Med 2012;9(4):e1001200. [PubMed: 22606070]
57. Olsen CM, Nagle CM, Whiteman DC, Ness R, Pearce CL, Pike MC, et al. Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium. Endocr Relat Cancer 2013;20(2):251–62. [PubMed: 23404857]
58. Bandera EV, Camacho F, Chyn D, Cloyd EK, Bethea TN, Beeghly-Fadiel A, Joslin CE, Myers E, Moorman PG, Ochs-Balcom HM, Harris HR, Peres LC, Setiawan VW, Wu AH, Rosenberg L, Schildkraut JM. Racial disparities in body mass index and ovarian cancer risk in the OCWAA Consortium [abstract]. In: Proceedings of the Twelfth AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved; 2019 Sep 20-23; San Francisco, CA. Philadelphia (PA): AACR; Cancer Epidemiol Biomarkers Prev 2020;29(6 Suppl_2):Abstract nr C070.
59. McKnight KK, Wellons MF, Sites CK, Roth DL, Szychowski JM, Halanych JH, et al. Racial and regional differences in age at menopause in the United States: findings from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Am J Obstet Gynecol 2011;205(4):353 e1–8.
60. Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997;145(2):124–33. [PubMed: 9006309]
61. Gold EB. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin North Am 2011;38(3):425–40. [PubMed: 21961711]
62. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001;153(9):865–74. [PubMed: 11323317]
63. Martinez GM. Trends and Patterns in Menarche in the United States: 1995 through 2013-2017. Natl Health Stat Report 2020(146):1–12.

Table 1.

Demographic and clinical characteristics of the Ovarian Cancer in Women of African Ancestry (OCWAA) Consortium study population by race and case/control status

	Black (N = 3349)		White (N = 10459)	
	Cases (N = 1024)	Controls (N = 2325)	Cases (N = 2910)	Controls (N = 7549)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Overall				
Age at diagnosis/interview (years)	58 (11.4)	58 (13.2)	62 (11.9)	65 (12.6)
BMI at diagnosis/interview (kg/m^2)	32 (8.0)	30 (7.3)	26 (6.0)	26 (5.8)
BMI at age 18 (kg/m^2)	22 (4.6)	22 (4.4)	21 (3.2)	21 (3.1)
Height at diagnosis/interview (m)	1.64 (0.1)	1.64 (0.1)	1.63 (0.1)	1.63 (0.1)
Premenopausal (N=2678)				
Age at diagnosis/interview (years)	45 (7.0)	43 (7.7)	45 (6.6)	44 (7.2)
BMI at age 18 (kg/m^2)	24 (5.5)	23 (5.3)	22 (4.1)	21 (3.6)
Height at diagnosis/interview (m)	1.65 (0.1)	1.65 (0.1)	1.64 (0.1)	1.65 (0.1)
Postmenopausal (N=11130)				
Age at diagnosis/interview (years)	63 (8.7)	64 (9.7)	66 (9.1)	69 (9.0)
BMI at diagnosis/interview (kg/m^2)	22 (4.2)	21 (3.9)	21 (2.9)	21 (3.0)
Height at diagnosis/interview (m)	1.64 (0.1)	1.64 (0.1)	1.63 (0.1)	1.63 (0.1)
	N (%)	N (%)	N (%)	N (%)
Demographic Characteristics				
Study Site				
AACES	558 (54.5)	746 (32.1)	--	--
BWHS	90 (8.8)	586 (25.2)	--	--
CCCCS	43 (4.2)	79 (3.4)	232 (8.0)	413 (5.5)
LACOCS	127 (12.4)	145 (6.2)	1176 (40.4)	1805 (23.9)
MEC	80 (7.8)	453 (19.5)	141 (4.9)	829 (11.0)
NCOCS	108 (10.6)	181 (7.8)	791 (27.2)	847 (11.2)
WHI	18 (1.8)	135 (5.8)	570 (19.6)	3655 (48.4)
Education				
High school, GED or less	415 (40.5)	769 (33.1)	623 (21.4)	1454 (19.3)
Some college	265 (25.9)	700 (30.1)	797 (27.4)	2168 (28.7)
College graduate	201 (19.6)	454 (19.5)	688 (23.6)	1472 (19.5)
Graduate or professional school	143 (14.0)	402 (17.3)	802 (27.6)	2455 (32.5)
Marital Status				
Single	164 (17.3)	383 (17.3)	166 (6.8)	363 (5.2)
Married or living with partner	360 (37.9)	917 (41.3)	1551 (63.3)	4348 (62.8)
Divorced or separated	249 (26.2)	569 (25.6)	338 (13.8)	941 (13.6)
Widowed	178 (18.7)	350 (15.8)	394 (16.1)	1269 (18.3)
Unknown	73 (−)	106 (−)	431 (−)	628 (−)
Clinical Characteristics *				

	Black (N = 3349)		White (N = 10459)	
	Cases (N = 1024)	Controls (N = 2325)	Cases (N = 2910)	Controls (N = 7549)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BMI				
Normal weight (<25 kg/m^2)	182 (17.8)	524 (22.6)	1515 (52.4)	3737 (49.7)
Overweight (25–<30 kg/m^2)	298 (29.2)	749 (32.3)	766 (26.5)	2267 (30.2)
Obese (30–<35 kg/m^2)	269 (26.3)	538 (23.2)	383 (13.2)	946 (12.6)
Very obese (35+ kg/m^2)	273 (26.7)	506 (21.8)	228 (7.9)	570 (7.6)
Unknown	2 (−)	8 (−)	18 (−)	29 (−)
Height **				
Upper Quartile (≥1.68 m)	408 (39.8)	811 (34.9)	881 (30.3)	2088 (27.7)
Below Upper Quartile (<1.68 m)	616 (60.2)	1514 (65.1)	2029 (69.7)	5461 (72.3)
Smoking Status				
Never	544 (53.2)	1219 (52.7)	1455 (50.3)	3771 (50.3)
Former	343 (33.5)	673 (29.1)	1151 (39.8)	3034 (40.5)
Current	136 (13.3)	422 (18.2)	289 (10.0)	692 (9.2)
Unknown	1 (−)	11 (−)	15 (−)	52 (−)
Menopausal Status				
Premenopausal	262 (25.6)	680 (29.3)	566 (19.5)	1170 (15.5)
Postmenopausal	762 (74.4)	1645 (70.8)	2344 (80.6)	6379 (84.5)
Medical History				
Family History of Breast or Ovarian Cancer				
Yes	262 (27.6)	347 (15.6)	593 (20.9)	1215 (16.9)
No	688 (72.4)	1872 (84.4)	2239 (79.1)	5996 (83.2)
Unknown	74 (−)	106 (−)	78 (−)	338 (−)
Parity ***				
0 pregnancies	187 (18.3)	363 (15.7)	690 (23.7)	1382 (18.4)
0−3 pregnancies	401 (39.2)	1034 (44.6)	1259 (43.3)	3056 (40.7)
3+ pregnancies	435 (42.5)	920 (39.7)	958 (33.0)	3075 (40.9)
Unknown	1 (−)	8 (−)	3 (−)	36 (−)
Oral Contraceptive Use				
Never	385 (38.2)	876 (38.2)	1352 (47.0)	3793 (50.5)
<5 years	367 (36.4)	744 (32.4)	905 (31.5)	1834 (24.4)
5+ years	257 (25.5)	675 (29.4)	619 (21.5)	1884 (25.1)
Unknown	15 (−)	30 (−)	34 (−)	38 (−)
Tubal Ligation				
Yes	307 (30.3)	715 (31.6)	432 (14.9)	1336 (17.7)
No	707 (69.7)	1549 (68.4)	2476 (85.1)	6202 (82.3)
Unknonwn	10 (−)	61 (−)	2 (−)	11 (−)
Post-Menopausal Hormone				
Yes	234 (23.0)	587 (25.6)	1474 (50.8)	4045 (53.7)
No	783 (77.0)	1710 (74.4)	1429 (49.2)	3484 (46.3)

	Black (N = 3349)		White (N = 10459)	
	Cases (N = 1024)	Controls (N = 2325)	Cases (N = 2910)	Controls (N = 7549)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Unknown	7 (−)	28 (−)	7 (−)	20 (−)

*Assessed at diagnosis (cases) or at time of interview (controls)

**Quartiles for height were determined based on heights from controls with non-missing data for age at menarche or age at regularity

***Defined as delivery at 24 weeks gestation or later

Table 2.

Associations between menstrual cycle characteristics and epithelial ovarian cancer among women in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium by race and menopausal status

	Black				White				Race p-het
	Cases N (%)	Controls N (%)	aOR (95 % CI)	p-value for Q statistic	Cases N (%)	Controls N (%)	aOR (95 % CI)	p-value for Q statistic	
Age at Menarche									
Overall									
<11 years	101 (9.9)	231 (9.9)	1.10 (0.80, 1.55)	0.34	198 (6.8)	450 (6.0)	1.25 (0.99, 1.57)	0.34	0.58
11-12 years	416 (40.7)	978 (42.1)	1.17 (0.91, 1.51)	0.16	1206 (41.5)	3077 (40.8)	1.13 (0.96, 1.32)	0.09	
13-14 years	380 (37.2)	830 (35.7)	1.19 (0.92, 1.53)	0.18	1213 (41.7)	3241 (43.0)	1.10 (0.94, 1.29)	0.15	
15+ years	125 (12.2)	286 (12.3)	Reference		292 (10.0)	776 (10.3)	Reference		
P-trend			0.56				0.07		
Menopause p-het			0.85				0.04		
Premenopausal									
<11 years	33 (12.6)	77 (11.3)	1.18 (0.63, 2.18)	0.28	51 (9.0)	69 (5.9)	2.20 (1.31, 3.68)	0.24	0.39
11-12 years	119 (45.4)	314 (46.2)	1.13 (0.69, 1.84)	0.64	255 (45.1)	479 (40.9)	1.58 (1.07, 2.33)	0.08	
13-14 years	78 (29.8)	212 (31.2)	1.11 (0.66, 1.87)	0.53	219 (38.7)	495 (42.3)	1.37 (0.93, 2.03)	0.17	
15+ years	32 (12.2)	77 (11.3)	Reference		41 (7.2)	127 (10.9)	Reference		
P-trend			0.63				0.002		
Postmenopausal									
<11 years	68 (9.0)	154 (9.4)	1.09 (0.73, 1.62)	0.95	147 (6.3)	381 (6.0)	1.06 (0.82, 1.38)	0.61	0.66
11-12 years	297 (39.1)	664 (40.4)	1.22 (0.91, 1.65)	0.09	951 (40.6)	2598 (40.8)	1.04 (0.87, 1.24)	0.18	
13-14 years	302 (39.7)	618 (37.6)	1.24 (0.92, 1.68)	0.57	994 (42.4)	2746 (43.1)	1.05 (0.88, 1.25)	0.27	
15+ years	93 (12.2)	209 (12.7)	Reference		251 (10.7)	649 (10.2)	Reference		
P-trend			0.66				0.76		
Age at Regularity									
Overall (N=12073)									
<11 years	72 (8.3)	147 (9.0)	0.96 (0.67, 1.39)	0.3	165 (6.0)	292 (4.3)	1.34 (1.06, 1.70)	0.29	0.19
11-12 years	336 (38.8)	599 (36.5)	1.23 (0.95, 1.59)	0.13	1045 (38.1)	2275 (33.3)	1.23 (1.07, 1.42)	0.02	
13-14 years	331 (38.2)	596 (36.3)	1.26 (0.97, 1.63)	0.09	1139 (41.6)	2910 (42.6)	1.19 (1.04, 1.37)	0.15	
15+ years	127 (14.7)	299 (18.2)	Reference		392 (14.3)	1348 (19.8)	Reference		

	Black				White				Race p-het
	Cases N (%)	Controls N (%)	aOR (95 % CI)	p-value for Q statistic	Cases N (%)	Controls N (%)	aOR (95 % CI)	p-value for Q statistic	
P-trend			0.84				0.004		
Menopause p-het			0.51				0.09		
Premenopausal (N=2327)									
<11 years	22 (10.1)	49 (11.7)	0.94 (0.47, 1.85)	0.23	45 (8.2)	61 (5.3)	2.17 (1.32, 3.57)	0.17	0.04
11-12 years	92 (42.4)	186 (44.4)	1.12 (0.67, 1.87)	0.49	236 (43.0)	424 (37.1)	1.61 (1.15, 2.26)	0.03	
13-14 years	71 (32.7)	113 (27.0)	1.52 (0.89, 2.61)	0.38	207 (37.7)	474 (41.5)	1.32 (0.94, 1.86)	0.43	
15+ years	32 (14.8)	71 (17.0)	Reference		61 (11.1)	183 (16.0)	Reference		
P-trend			0.55				<0.001		
Postmenopausal (N=9746)									
<11 years	50 (7.7)	98 (8.0)	1.00 (0.65, 1.55)	0.89	120 (5.5)	231 (4.1)	1.16 (0.88, 1.52)	0.47	0.58
11-12 years	244 (37.6)	413 (33.8)	1.33 (0.98, 1.80)	0.05	809 (36.9)	1851 (32.6)	1.16 (0.99, 1.36)	0.18	
13-14 years	260 (40.1)	483 (39.5)	1.25 (0.93, 1.68)	0.21	932 (42.5)	2436 (42.9)	1.18 (1.01, 1.37)	0.35	
15+ years	95 (14.6)	228 (18.7)	Reference		331 (15.1)	1165 (20.5)	Reference		
P-trend			0.45				0.18		
Cycle Length									
Overall (N=5048)									
≤ 25 days	53 (7.3)	75 (7.6)	0.99 (0.68, 1.43)	0.85	57 (4.1)	88 (4.6)	0.90 (0.63, 1.27)	<0.01	0.66
26–30 days	623 (85.8)	836 (84.6)	Reference		1156 (82.2)	1468 (76.1)	Reference		
31+ days	12 (1.7)	25 (2.5)	0.60 (0.30, 1.22)	0.35	68 (4.8)	146 (7.6)	0.65 (0.48, 0.88)	0.84	
Irregular	38 (5.2)	52 (5.3)	1.06 (0.68, 1.66)	0.45	125 (8.9)	226 (11.7)	0.78 (0.62, 0.99)	0.07	
Ever Missed 3 Consecutive Periods *									
Overall (N=5270)									
No	616 (88.6)	868 (86.9)	Reference		1327 (87.0)	1730 (84.4)	Reference		0.71
Yes	79 (11.4)	131 (13.1)	0.92 (0.68, 1.25)	0.72	198 (13.0)	321 (15.7)	0.80 (0.21, 3.04)	0.14	

All models adjusted for site, age, education, young adult weight, and height

*Random effect for study site included in overall model and model within White women.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2023 February 02.

Table 3.

Associations between menstrual cycle characteristics and epithelial ovarian cancer among women in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium by race, menopausal status and histotype

	Black						White					
	Controls	HGS Cases	Other Histotype Cases	HGS	Other Histotype	hist. p-het	Controls	HGS Cases	Other Histotype Cases	HGS	Other Histotype	hist. p-het
	N (%)	N (%)	N (%)	aOR (95 % CI)	aOR (95 % CI)		N (%)	N (%)	N (%)	aOR (95 % CI)	aOR (95 % CI)	
Age at Menarche												
Overall												
<11 years	231 (9.9)	62 (9.6)	39 (10.5)	1.09 (0.74, 1.62)	1.15 (071, 1.84)	0.98	450 (6.0)	113 (6.4)	85 (7.5)	1.29 (0.98, 1.71)	1.18 (0.86, 1.62)	0.24
11-12 years	978 (42.1)	248 (38.2)	168 (45.0)	1.12 (0.83, 1.51)	1.26 (0.88, 1.82)		3077 (40.8)	730 (41.1)	476 (42.1)	1.20 (0.99, 1.46)	1.03 (0.82, 1.28)	
13-14 years	830 (35.7)	259 (39.9)	121 (32.4)	1.26 (0.94, 1.70)	1.05 (0.72, 1.53)		3241 (43.0)	764 (43.0)	449 (39.7)	1.20 (0.99, 1.45)	0.96 (0.77, 1.20)	
15+ years	286 (12.3)	80 (12.3)	45 (12.1)	Reference	Reference		776 (10.3)	170 (9.6)	122 (10.8)	Reference	Reference	
P-trend				0.92	0.21					0.11	0.23	
Meno. p-het				0.87	0.90					0.05	0.09	
Premenopausal												
<11 years	77 (11.3)	18 (12.6)	15 (12.6)	1.16 (0.54, 2.50)	1.18 (0.52, 2.70)	0.99	69 (5.9)	22 (8.6)	29 (9.3)	2.58 (1.26, 5.30)	1.97 (1.06, 3.66)	0.38
11-12 years	314 (46.2)	62 (43.4)	57 (47.9)	1.09 (0.59, 2.01)	1.19 (0.61, 2.29)		479 (40.9)	116 (45.5)	139 (44.7)	1.89 (1.07, 3.32)	1.39 (0.86, 2.23)	
13-14 years	212 (31.2)	45 (31.5)	33 (27.7)	1.18 (0.62, 2.24)	1.05 (0.52, 2.12)		495 (42.3)	101 (39.6)	118 (37.9)	1.66 (0.94, 2.93)	1.19 (0.74, 1.93)	
15+ years	77 (11.3)	18 (12.6)	14 (11.8)	Reference	Reference		127 (10.9)	16 (6.3)	25 (8.0)	Reference	Reference	
P-trend				0.87	0.56					0.01	0.02	
Postmenopausal												
<11 years	154 (9.4)	44 (8.7)	24 (9.5)	1.06 (0.67, 1.68)	1.15 (0.64, 2.07)	0.97	381 (6.0)	91 (6.0)	56 (6.8)	1.11 (0.82, 1.51)	0.99 (0.68, 1.43)	0.23
11-12 years	664 (40.4)	186 (36.8)	111 (43.7)	1.16 (0.82, 1.64)	1.33 (0.86, 2.07)		2598 (40.8)	614 (40.3)	337 (41.1)	1.11 (0.90, 1.37)	0.93 (0.73, 1.20)	
13-14 years	618 (37.6)	214 (42.3)	88 (34.7)	1.32 (0.94, 1.86)	1.09 (0.69, 1.71)		2746 (43.1)	663 (43.6)	331 (40.3)	1.15 (0.93, 1.41)	0.90 (0.70, 1.16)	
15+ years	209 (12.7)	62 (12.3)	31 (12.2)	Reference	Reference		649 (10.2)	154 (10.1)	97 (11.8)	Reference	Reference	
P-trend				0.87	0.25					0.68	0.99	
Age at Regularity												
Overall												
<11 years	147 (9.0)	44 (8.0)	28 (8.9)	0.92 (0.60, 1.42)	1.04 (0.61, 1.75)	0.77	292 (4.3)	92 (5.5)	73 (6.8)	1.31 (0.98, 1.74)	1.39 (1.01, 1.92)	0.83
11-12 years	599 (36.5)	196 (35.5)	140 (44.6)	1.12 (0.82, 1.52)	1.42 (0.98, 2.06)		2275 (33.3)	630 (37.7)	415 (38.9)	1.25 (1.06, 1.49)	1.20 (0.98, 1.48)	

	Black						White					
	Controls	HGS Cases	Other Histotype Cases	HGS	Other Histotype	hist. p-het	Controls	HGS Cases	Other Histotype Cases	HGS	Other Histotype	hist. p-het
	N (%)	N (%)	N (%)	aOR (95 % CI)	aOR (95 % CI)		N (%)	N (%)	N (%)	aOR (95 % CI)	aOR (95 % CI)	
13-14 years	596 (36.3)	230 (41.7)	101 (32.2)	1.33 (0.98, 1.80)	1.12 (0.76, 1.64)		2910 (42.6)	713 (42.6)	426 (39.9)	1.24 (1.05, 1.47)	1.12 (0.92, 1.38)	
15+ years	299 (18.2)	82 (14.9)	45 (14.3)	Reference	Reference		1348 (19.8)	238 (14.2)	154 (14.4)	Reference	Reference	
P-trend				0.53	0.21					0.03	0.02	
Meno. p-het				0.38	0.61					0.15	0.26	
Premenopausal												
<11 years	49 (11.7)	11 (9.5)	11 (10.9)	0.74 (0.31, 1.75)	1.24 (0.49, 3.11)	0.26	61 (5.3)	18 (7.3)	27 (8.9)	2.20 (1.10, 4.37)	2.17 (1.20, 3.91)	0.62
11-12 years	186 (44.4)	45 (38.8)	47 (46.5)	0.86 (0.46, 1.61)	1.55 (0.76, 3.17)		424 (37.1)	107 (43.3)	129 (42.7)	1.79 (1.11, 2.88)	1.50 (0.99, 2.27)	
13-14 years	113 (27.0)	40 (34.5)	31 (30.7)	1.33 (0.70, 2.56)	1.82 (0.86, 3.88)		474 (41.5)	97 (39.3)	110 (36.4)	1.52 (0.94, 2.45)	1.20 (0.79, 1.82)	
15+ years	71 (17.0)	20 (17.2)	12 (11.9)	Reference	Reference		183 (16.0)	25 (10.1)	36 (11.9)	Reference	Reference	
P-trend				0.21	0.74					0.01	0.004	
Postmenopausal												
<11 years	98 (8.0)	33 (7.6)	17 (8.0)	1.00 (0.60, 1.66)	1.02 (0.53, 1.95)	0.82	231 (4.1)	74 (5.2)	46 (6.0)	1.15 (0.83, 1.57)	1.17 (0.79, 1.72)	0.78
11-12 years	413 (33.8)	151 (34.6)	93 (43.7)	1.26 (0.88, 1.79)	1.47 (0.94, 2.28)		1851 (32.6)	523 (36.7)	286 (37.3)	1.18 (0.98, 1.42)	1.12 (0.88, 1.42)	
13-14 years	483 (39.5)	190 (43.6)	70 (32.9)	1.39 (0.99, 1.96)	0.99 (0.63, 1.55)		2436 (42.9)	616 (43.2)	316 (41.3)	1.21 (1.01, 1.45)	1.11 (0.88, 1.40)	
15+ years	228 (18.7)	62 (14.2)	33 (15.5)	Reference	Reference		1165 (20.5)	213 (14.9)	118 (15.4)	Reference	Reference	
P-trend				0.93	0.15					0.26	0.35	

All models are adjusted for site, age, education, young adult weight, and height

Table 4.

Association between menstrual cycle and epithelial ovarian cancer among Black women in the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium by menopausal status and height

	Upper Quartile of Height *			Lower Three Quartiles of Height *			
	Black Cases N (%)	Black Controls N (%)	aOR (95 % CI)	Black Cases N (%)	Black Controls N (%)	aOR (95 % CI)	p-het for height
Overall							
<11 years	35 (8.6)	61 (7.5)	1.37 (0.77, 2.42)	66 (10.7)	170 (11.2)	1.05 (0.69, 1.59)	0.43
11-12 years	154 (37.8)	337 (41.6)	1.08 (0.72, 1.62)	262 (42.6)	641 (42.3)	1.24 (0.89, 1.71)	
13-14 years	166 (40.8)	300 (37.0)	1.27 (0.84, 1.90)	214 (34.8)	530 (35.0)	1.14 (0.82, 1.60)	
15+ years	52 (12.8)	113 (13.9)	Reference	73 (11.9)	173 (11.4)	Reference	
P-trend			0.55			0.73	
Menopause p-het			0.19			0.13	
Premenopausal							
<11 years	14 (11.9)	25 (8.9)	2.94 (1.04, 8.37)	19 (13.2)	52 (13.1)	0.66 (0.30, 1.45)	0.02
11-12 years	49 (41.5)	135 (47.9)	1.60 (0.70, 3.64)	70 (48.6)	179 (45.0)	0.89 (0.47, 1.69)	
13-14 years	45 (38.1)	83 (29.4)	2.53 (1.09, 5.87)	33 (22.9)	129 (32.4)	0.59 (0.30, 1.18)	
15+ years	10 (8.5)	39 (13.8)	Reference	22 (15.3)	38 (9.6)	Reference	
P-trend			0.40			0.89	
Postmenopausal							
<11 years	21 (7.3)	36 (6.8)	1.00 (0.49, 2.05)	47 (10.0)	118 (10.6)	1.22 (0.74, 1.99)	0.53
11-12 years	105 (36.3)	202 (38.2)	0.95 (0.59, 1.55)	192 (40.8)	462 (41.4)	1.44 (0.98, 2.12)	
13-14 years	121 (41.9)	217 (41.0)	1.02 (0.63, 1.65)	181 (38.4)	401 (35.9)	1.45 (0.99, 2.14)	
15+ years	42 (14.5)	74 (14.0)	Reference	51 (10.8)	135 (12.1)	Reference	
P-trend			0.83			0.45	
Age at Regularity							
Overall							
<11 years	22 (6.4)	36 (6.8)	1.08 (0.56, 2.07)	50 (9.6)	111 (10.0)	0.94 (0.60, 1.47)	0.41
11-12 years	123 (35.8)	191 (36.0)	1.18 (0.77, 1.80)	213 (40.8)	408 (36.8)	1.26 (0.91, 1.75)	
13-14 years	146 (42.4)	194 (36.5)	1.49 (0.99, 2.26)	185 (35.4)	402 (36.2)	1.14 (0.82, 1.59)	
15+ years	53 (15.4)	110 (20.7)	Reference	74 (14.2)	189 (17.0)	Reference	

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2023 February 02.

	Upper Quartile of Height *			Lower Three Quartiles of Height *			
	Black Cases N (%)	Black Controls N (%)	aOR (95 % CI)	Black Cases N (%)	Black Controls N (%)	aOR (95 % CI)	p-het for height
P-trend			0.99			0.67	
Menopause p-het			0.06			0.67	
Premenopausal							
<11 years	7 (7.4)	13 (7.9)	1.62 (0.48, 5.52)	15 (12.3)	36 (14.1)	0.73 (0.31, 1.68)	0.03
11-12 years	34 (35.8)	76 (46.3)	1.21 (0.52, 2.81)	58 (47.5)	110 (43.1)	1.08 (0.56, 2.07)	
13-14 years	42 (44.2)	42 (25.6)	3.31 (1.39, 7.92)	29 (23.8)	71 (27.8)	0.85 (0.41, 1.74)	
15+ years	12 (12.6)	33 (20.1)	Reference	20 (16.4)	38 (14.9)	Reference	
P-trend			0.55			0.82	
Postmenopausal							
<11 years	15 (6.0)	23 (6.3)	1.03 (0.47, 2.29)	35 (8.8)	75 (8.8)	1.04 (0.61, 1.77)	0.99
11-12 years	89 (35.7)	115 (31.3)	1.29 (0.78, 2.14)	155 (38.8)	298 (34.9)	1.38 (0.94, 2.03)	
13-14 years	104 (41.8)	152 (41.4)	1.22 (0.75, 1.99)	156 (39.0)	331 (38.7)	1.30 (0.88, 1.90)	
15+ years	41 (16.5)	77 (21.0)	Reference	54 (13.5)	151 (17.7)	Reference	
P-trend			0.57			0.51	

All models adjusted for site, age, education, and young adult weight

* Upper quartile cutpoint is 1.68 m