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ARTICLE

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Menopausal hormone therapy use and risk of ovarian cancer by race: the ovarian cancer in women of African ancestry consortium

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BACKGROUND: Most studies examining post-menopausal menopausal hormone therapy (MHT) use and ovarian cancer risk have focused on White women and few have included Black women.

METHODS: We evaluated MHT use and ovarian cancer risk in Black ($n = 800$ cases, 1783 controls) and White women ($n = 2710$ cases, 8556 controls), using data from the Ovarian Cancer in Women of African Ancestry consortium. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of MHT use with ovarian cancer risk, examining histotype, MHT type and duration of use.

RESULTS: Long-term MHT use, ≥10 years, was associated with an increased ovarian cancer risk for White women (OR = 1.38, 95% CI: 1.22–1.57) and the association was consistent for Black women (OR = 1.20, 95%CI: 0.81–1.78, $p_{interaction} = 0.4$). For White women, the associations between long-term unopposed estrogen or estrogen plus progesterone use and ovarian cancer risk were similar; the increased risk associated with long-term MHT use was confined to high-grade serous and endometroid tumors. Based on smaller numbers for Black women, the increased ovarian cancer risk associated with long-term MHT use was apparent for unopposed estrogen use and was predominately confined to other epithelial histotypes.

CONCLUSION: The association between long-term MHT use and ovarian cancer risk was consistent for Black and White women.

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INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer-related death in US women [1]. The incidence rate of ovarian cancer is lower in Black women (5.5 per 100,000) than in White women (6.7 per 100,000) [2], but Black women have lower five-year survival (38.3% in Black women vs. 45.5% in White women) [3]. Incidence and mortality rates of ovarian cancer have been declining, but the decline has been slower in Black women than in White women [4]. Ovarian cancer is a heterogeneous disease, with histotypes differing by molecular characteristics, etiology, and distribution of incidence and survival. High-grade serous carcinoma is the most common histotype of ovarian cancer (~63% of cases), followed by endometrioid (~10%), clear cell (~10%), mucinous (~9%), and low-grade serous (~3%) [5, 6].

Estrogen regulation plays a role in the etiology and progression of ovarian cancer, but may have differential effects by histotype [7, 8]. A decreased risk of ovarian cancer has been associated with hormonal and reproductive factors, including parity (all histotypes) [9], breastfeeding (high-grade serous, endometrioid, and clear cell tumors) [10], oral contraceptive use (high-grade serous, endometrioid, and clear cell tumors) [9], and tubal ligation (endometrioid and clear cell tumors) [9, 11]. The association

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between menopausal hormone therapy (MHT) use and ovarian cancer is inconsistent and debated [12, 13]. However, recent pooled and meta-analyses reported that MHT use was associated with an approximate 30% increased risk of ovarian cancer, with increased risk confined to high-grade serous and endometrioid tumor types [9, 12, 14, 15].

The majority of studies that have examined the MHT use–ovarian cancer risk association to date have focused predominately on White women, who have a higher prevalence of MHT use than Black women [16]. Three studies investigating this association in Black women have suggested that MHT use increases ovarian cancer risk [17–19], while another reported no association [20]. However, all prior studies of Black women included less than 70 exposed cases, resulting in wide confidence intervals, and the studies were underpowered to stratify by hysterectomy status or histotype. Thus, MHT use is a potentially important risk factor for ovarian cancer that has been underexplored for Black women; the generalizability of findings from studies comprised predominately of White women is unknown. The present study evaluated type and duration of MHT use in relation to ovarian cancer risk by histotype and hysterectomy status among Black and White women, using data from the Ovarian Cancer in Women of African Ancestry (OCWAA) consortium.

METHODS

Study population

The OCWAA consortium was established to understand racial differences in risk factors for epithelial ovarian cancer. Participants in the present study are self-identified Black and White postmenopausal women from seven case-control and cohort studies whose data were harmonized in the OCWAA consortium [21]. Questionnaire, medical record, and tumor data were obtained from four case-control studies: the African American Cancer Epidemiology Study (AACES) [18], the Cook County Case-Control Study (CCCCS) [22, 23], the Los Angeles County Ovarian Cancer Study (LACOCS) [24], the North Carolina Ovarian Cancer Study (NCOCS) [25]; and in three case-control studies nested within prospective cohorts: the Black Women's Health Study (BWHS) [17], the Multiethnic Cohort Study (MEC) [26], and the Women's Health Initiative (WHI) [27]. Each cohort study constructed a nested case-control study by selecting four to six controls per case. Eligible controls were alive at the time of case diagnosis and had at least one ovary. Controls were then matched within study to the case on race, age of case diagnosis, and last questionnaire completed prior to ovarian cancer diagnosis (index date). Data for time-varying exposures and covariates were taken from the questionnaire prior to the index date. Each study obtained informed consent from participants and was approved by the relevant Institutional Review Boards.

Outcome

Eligible cases were diagnosed with epithelial ovarian cancer (International Classification of Diseases for Oncology, 3rd ed. [ICD-O-3] topography code: C56.9). Diagnosis was verified through pathology reports. Tumor histology types (i.e., histotypes) were classified, as previously described [5, 6], as serous, endometrioid, clear cell, mucinous, and other epithelial. Cases with a serous histology were classified as low-grade or high-grade. High-grade endometrioid tumors were also classified as high-grade serous, as the majority of high-grade endometrioid carcinomas are biologically similar to high-grade serous carcinomas [28]. In a sensitivity analysis, high-grade endometroid cases were excluded. Prior analyses of MHT use and ovarian cancer risk have reported associations with high-grade serous and endometroid carcinomas, but not other histotypes [9, 12, 14, 15]. Due to a limited number of cases in Black women, clear cell, mucinous, and low-grade serous tumor types were collapsed with "other epithelial" histotypes for the primary analysis.

Exposure assessment

Each study collected data from participants at the time of the cases' diagnosis (case-control studies) or from the questionnaire closest to the cases' date of diagnosis (cohort studies) on MHT use via standardized questionnaires that were either interviewer-administered or self-administered. Harmonized variables were created by comparing questionnaires between the participating studies. MHT use was classified by type (unopposed estrogen MHT, estrogen-progesterone combination MHT, or estrogen-progesterone combination MHT after unopposed estrogen use), any use (ever, never), duration of use (never, < 5, 5 to < 10, ≥ 10 years), and recency of use (never, current, recent [< 5 years since use], former [≥ 5 years since use]). We excluded post-menopausal women with missing information on MHT use (5 Black cases, 23 Black controls, 3 White cases, and 12 White controls).

Statistical analyses

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of MHT use with ovarian cancer risk by race. Race-specific ORs were stratified by histotype using polytomous regression models. P-values for heterogeneity were computed using Wald joint tests to compare the histotype-specific coefficients of each exposure. P-values for interaction between race and each exposure were assessed using likelihood ratio tests to compare regression models with and without a multiplicative term.

A test of study site heterogeneity was used to choose between common fixed effects or multi-level random effects estimators of pooled risk. Between study heterogeneity was based on the lower bound of 95% profile likelihood CI of $\tau^2 > 0$ and the I^2 statistic [29]. No site heterogeneity was detected for any main exposure; thus, data were pooled for all analyses, and results are presented using fixed effects models.

Matching bias was adjusted for by controlling for matching factors common to all studies in the regression models; additionally, results were compared with more complex and computationally intensive methods (i.e., conditional logistic regression) to handling matching and any bias was determined to be negligible [30]. All models included terms for the matching factors of study site (AACES, CCCCS, LACOCS, NCOCS, BWHS, MEC, WHI), index year (year of case diagnosis), and age at index (continuous). We constructed a directed acyclic graph to select additional covariates for adjustment in the regression models: first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), nulliparity (yes, no), education (GED or less/high school graduate, some college, college graduate, graduate/professional school), smoking status (ever, never), age at menopause (continuous), and premenopausal hysterectomy (yes, no).

Sensitivity analysis

As women who have had a premenopausal hysterectomy are often prescribed unopposed estrogen MHT, we conducted sensitivity analyses stratified by hysterectomy status. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

The present study included 800 Black ovarian cancer cases, 1783 Black controls, 2710 White cases, and 8556 White controls. Black women had a younger age at ovarian cancer diagnosis than White women (Table 1). Black women were more likely to have had a premenopausal hysterectomy than White women, while White women were more likely to be nulliparous. Black women were diagnosed with a higher proportion of endometrioid cases than White women (7.8 vs. 5.4%, respectively) and a lower proportion of clear cell cases (3.7 vs. 6.2%).

MHT use was more common in White women than in Black women (62.6 vs. 33.7% of control participants, respectively, used any MHT; Table S1). Among women who ever used MHT, White women reported longer duration of use than Black women (39.6% vs. 20.1% of controls participants, respectively, reported MHT use for ≥ 10 years). Ever use of MHT in Black women was not associated with risk of ovarian cancer overall (Table 2) or specific ovarian cancer histotypes (Table 3): high-grade serous, endometrioid, or other epithelial histotypes. However, based on larger numbers among White women, ever use was associated with an increased risk of high-grade serous ovarian cancer (OR = 1.28, 95% CI: 1.14–1.43) but inversely associated with other epithelial histotypes (OR = 0.82, 95% CI: 0.70–0.96).

MHT use for ten or more years was associated with an increased ovarian cancer risk for White women (OR = 1.38, 95% CI: 1.22–1.57,

Table 1. Characteristics of OCWAA study participants by race and case status.

	Black women		White women	
Characteristics	**Cases ($N = 800$)**	**Controls ($N = 1783$)**	**Cases ($N = 2710$)**	**Controls ($N = 8556$)**
Age at index, mean years (SD)	63 (8.8)	65 (9.9)	66 (9.1)	70 (8.8)
Age at menopause, mean years (SD)	48 (5.6)	48 (5.8)	49 (5.2)	49 (5.5)
Education, *N* (%)				
High school graduate/GED or less	342 (42.8)	633 (35.5)	583 (21.5)	1718 (20.1)
Some college	202 (25.3)	547 (30.7)	807 (29.8)	2790 (32.6)
College graduate	153 (19.1)	282 (15.8)	582 (21.5)	1401 (16.4)
Graduate/professional school	103 (12.9)	321 (18.0)	738 (27.2)	2647 (30.9)
Unknown	0	0	0	0
Body mass index, *N* (%)				
< 25.0 kg/m^2	138 (17.3)	369 (20.9)	1321 (49.1)	3647 (42.8)
25.0–29.9 kg/m^2	237 (29.8)	588 (33.3)	761 (28.3)	2806 (32.9)
30–34.9 kg/m^2	216 (27.1)	443 (25.1)	391 (14.5)	1312 (15.4)
≥ 35.0 kg/m^2	205 (25.8)	366 (20.7)	217 (8.1)	755 (8.9)
Unknown	4	17	20	36
Tubal ligation, *N* (%)				
No	557 (70.3)	1227 (70.3)	2314 (85.5)	7063 (82.7)
Yes	235 (29.7)	519 (29.7)	394 (14.6)	1479 (17.3)
Unknown	8	37	2	14
Age at menarche, *N* (%)				
8–11 years	168 (21.1)	380 (21.4)	539 (19.9)	1692 (19.8)
12–13 years	412 (51.8)	842 (47.3)	1462 (54.0)	4656 (54.5)
≥ 14 years	216 (27.1)	558 (31.4)	706 (26.1)	2196 (25.7)
Unknown	4	3	3	12
Oral contraceptive use, *N* (%)				
Never	339 (42.5)	822 (46.2)	1457 (53.8)	4974 (58.2)
Ever	458 (57.5)	956 (53.8)	1250 (46.2)	3572 (41.8)
Unknown	3	5	3	10
Premenopausal hysterectomy, *N* (%)				
No	561 (70.1)	1279 (71.7)	2141 (79.0)	7214 (84.3)
Yes	239 (29.9)	504 (28.3)	569 (21.0)	1342 (15.7)
Unknown	0	0	0	0
Nulliparous, *N* (%)				
No	681 (85.1)	1520 (85.3)	2191 (80.9)	7086 (82.8)
Yes	119 (14.9)	263 (14.8)	519 (19.2)	1470 (17.2)
Unknown	0	0	0	0
Family history of breast cancer, *N* (%)				
No	629 (78.6)	1551 (87.0)	2256 (83.3)	7357 (86.0)
Yes	171 (21.4)	232 (13.0)	454 (16.8)	1199 (14.0)
Unknown	0	0	0	0
Family history of ovarian cancer, *N* (%)				
No	750 (93.8)	1731 (97.1)	2589 (95.5)	8348 (97.6)
Yes	50 (6.3)	52 (2.9)	121 (4.5)	208 (2.4)
Unknown	0	0	0	0
Smoking status, *N* (%)				
Never	413 (51.6)	868 (48.7)	1334 (49.2)	4203 (49.1)
Ever	387 (48.4)	915 (51.3)	1376 (50.8)	4353 (50.9)
Unknown	0	0	0	0
Study site, *N* (%)				
AACES	432 (54.0)	525 (29.4)	–	–
BWHS	56 (7.0)	353 (19.8)	–	–

Table 1. continued

	Black women		White women	
Characteristics	**Cases ($N = 800$)**	**Controls ($N = 1783$)**	**Cases ($N = 2710$)**	**Controls ($N = 8556$)**
CCCCS	24 (3.0)	35 (2.0)	129 (4.8)	205 (2.4)
LACOCS	93 (11.6)	77 (4.3)	928 (34.2)	1185 (13.9)
MEC	75 (9.4)	408 (22.9)	120 (4.4)	753 (8.8)
NCOCS	77 (9.6)	105 (5.9)	606 (22.4)	559 (6.5)
WHI	43 (5.4)	280 (15.7)	927 (34.2)	5854 (68.4)
Histotype, *N* (%)				
High-Grade Serous[a]	528 (66.0)	–	1772 (65.4)	–
Low-Grade Serous	17 (2.1)	–	59 (2.2)	–
Endometrioid	62 (7.8)	–	145 (5.4)	–
Clear Cell	29 (3.7)	–	169 (6.2)	–
Mucinous	27 (3.4)	–	93 (3.4)	–
Other Epithelial	137 (17.1)	–	472 (17.4)	–

[a]Among White high-grade serous cases, 128 (7.2%) are high-grade endometrioid. Among Black high-grade serous cases, 26 (4.9%) are high-grade endometrioid.

Table 2. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for the association between any menopausal hormone therapy use and ovarian cancer (all histotypes) by race.

	Black women[b]			White women[b]			P-int by Race[c]
	Controls	**Cases**	**OR (95% CI)**	**Controls**	**Cases**	**OR (95% CI)**	
Any menopausal hormone therapy use							
Never	1182	575	Reference	3202	1071	Reference	
Ever	601	225	1.00 (0.81, 1.24)	5354	1639	1.08 (0.97, 1.19)	0.4
Duration							
< 5 Years	346	122	0.96 (0.74, 1.24)	1768	486	0.89 (0.78, 1.02)	0.6
5 to < 10 Years	131	44	0.92 (0.62, 1.37)	1433	354	0.97 (0.84, 1.13)	0.6
≥ 10 Years	120	54	1.20 (0.81, 1.78)	2102	754	1.38 (1.22, 1.57)	0.4
Duration Trend (per 5 years)	1779	795	1.05 (0.95, 1.17)	8505	2665	1.12 (1.09, 1.16)	0.2
Recency							
Current User	82	31	0.83 (0.52, 1.33)	560	406	1.15 (0.98, 1.36)	0.04
Recent User (< 5 years)	91	40	1.23 (0.79, 1.93)	1784	589	1.18 (1.04, 1.35)	0.9
Former User (≥ 5 years)	233	111	1.00 (0.75, 1.34)	2583	559	0.99 (0.86, 1.12)	0.9

[a]ORs are based on complete case analysis, pooled across sites, and adjusted for age at index (continuous), first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), nulliparity (yes, no), education (high school graduate/GED or less, some college, college graduate, graduate/professional school), smoking status (ever, never), age at menopause (continuous), and pre-menopausal hysterectomy (yes, no).
[b]Sites included in the analysis of Black women were AACES, BWHS, CCCCS, LACOCS, MEC, NCOCS, WHI; sites included in the analysis of White women were CCCCS, LACOCS, MEC, NCOCS, WHI.
[c]*p*-value from likelihood ratio test of interaction term between exposure and race.

$p_{trend} < 0.0001$) and the association was consistent for Black women (OR = 1.20, 95% CI: 0.81–1.78, $p_{trend} = 0.4$, $p_{interaction} = 0.4$, Table 2). There was no evidence of heterogeneity between studies for Black women ($I^2 = 0.0\%$, $p_{heterogeneity} = 1.0$) or White women ($I^2 = 35.6\%$, $p_{heterogeneity} = 0.2$, Fig. 1). For White women, ten or more years of MHT use was associated with an increased risk of high-grade serous carcinoma (OR = 1.66, 95% CI: 1.43–1.92, $p_{trend} < 0.0001$) and endometroid tumors (OR = 1.38, 95% CI: 0.89–2.13, $p_{trend} = 0.009$, Table 3). For Black women, the increased risk associated with long-term use was confined to other histotypes (OR = 1.70, 95% CI: 0.97–2.99, $p_{trend} = 0.07$), with no association for high-grade serous carcinoma (OR = 1.08, 95% CI: 0.68–1.71, $p_{trend} = 0.8$) or endometroid tumors (OR = 0.53, 95% CI: 0.12–2.40, $p_{trend} = 0.8$). We interrogated this association with other epithelial histotypes further, by examining clear cell and mucinous tumors independent of other epithelial histotypes. Among Black women, ten or more years of MHT use was associated with elevated ORs for clear cell (OR = 1.93, 95% CI: 0.51–7.34, $p_{trend} = 0.02$) and mucinous tumors (OR = 2.17, 95% CI: 0.54–8.73, $p_{trend} = 0.7$), but CIs were wide and included the null as both histotypes only included three exposed cases. The association between ten or more years of MHT use and risk of other epithelial histotypes was attenuated after excluding the clear cell and mucinous tumors (OR = 1.60, 95% CI: 0.83–3.07, $p_{trend} = 0.1$), which included 14 exposed cases of other epithelial histotypes in Black women; these histotypes included six cases of carcinoma or adenocarcinoma, not otherwise specified (ICD-O-3 morphology codes: 8010 and 8140) and four cases of carcinosarcoma (8980 and 8951).

Recent MHT use, within the past 5 years, was associated with elevated ORs for both Black and White women (OR = 1.23, 95% CI:

Table 3. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for the association between any menopausal hormone therapy use and ovarian cancer by race, stratified by histotype.

		High-Grade Serous[b]		Endometrioid[b]		Other Histotypes[b,c]		Test of Heterogeneitye
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	
Black women[d]								
Any menopausal hormone therapy use								
Never	1182	394	Reference	41	Reference	140	Reference	
Ever	601	134	0.92 (0.71, 1.17)	21	1.25 (0.69, 2.27)	70	1.21 (0.87, 1.69)	0.3
Duration								
< 5 Years	346	73	0.88 (0.65, 1.19)	13	1.44 (0.73, 2.83)	36	1.10 (0.73, 1.65)	0.3
5 to < 10 Years	131	25	0.79 (0.49, 1.28)	6	1.56 (0.60, 4.08)	13	1.12 (0.60, 2.10)	0.3
≥ 10 Years	120	32	1.08 (0.68, 1.71)	2	0.53 (0.12, 2.40)	20	1.70 (0.97, 2.99)	0.2
Duration Trend (per 5 years)	1779	524	1.02 (0.90, 1.15)	62	0.96 (0.71, 1.31)	209	1.14 (0.99, 1.31)	0.3
Recency								
Current User	82	19	0.79 (0.45, 1.38)	3	0.82 (0.23, 2.97)	9	0.91 (0.42, 1.95)	1.0
Recent User (< 5 years)	91	20	0.93 (0.54, 1.60)	4	1.54 (0.48, 4.96)	16	1.90 (1.02, 3.55)	0.1
Former User (≥ 5 years)	233	75	1.00 (0.73, 1.39)	12	1.63 (0.77, 3.42)	24	0.92 (0.56, 1.51)	0.4
White women[d]								
Any menopausal hormone therapy use								
Never	3202	628	Reference	72	Reference	371	Reference	
Ever	5354	1144	1.28 (1.14, 1.43)	73	0.76 (0.54, 1.07)	422	0.82 (0.70, 0.96)	< 0.001
Duration								
< 5 Years	1768	313	0.98 (0.84, 1.15)	17	0.46 (0.27, 0.78)	156	0.84 (0.68, 1.02)	0.01
5 to < 10 Years	1433	266	1.23 (1.04, 1.46)	15	0.65 (0.37, 1.16)	73	0.60 (0.46, 0.79)	< 0.0001
≥ 10 Years	2102	532	1.66 (1.43, 1.92)	40	1.38 (0.89, 2.13)	182	0.98 (0.79, 1.20)	< 0.0001
Duration Trend (per 5 years)	8505	1739	1.17 (1.12, 1.21)	144	1.16 (1.04, 1.30)	782	1.03 (0.97, 1.08)	< 0.0001
Recency								
Current User	560	298	1.46 (1.22, 1.75)	28	0.97 (0.61, 1.56)	80	0.67 (0.51, 0.88)	< 0.0001
Recent User (< 5 years)	1784	398	1.33 (1.15, 1.55)	27	0.78 (0.49, 1.24)	164	1.02 (0.83, 1.26)	0.02
Former User (≥ 5 years)	2583	397	1.15 (0.99, 1.34)	16	0.51 (0.29, 0.91)	146	0.81 (0.65, 1.01)	0.001

[a]ORs are based on complete case analysis, pooled across sites, and adjusted for age at index (continuous), first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), nulliparity (yes, no), education (high school graduate/GED or less, some college, college graduate, graduate/professional school), smoking status (ever, never), age at menopause (continuous), and pre-menopausal hysterectomy (yes, no).
[b]Histotype specific ORs are based on polytomous regression model.
[c]Other histotypes includes clear cell, mucinous, low-grade serous, and other epithelial histotypes.
[d]Sites included in the analysis of Black women were AACES, BWHS, CCCCS, LACOCS, MEC, NCOCS, WHI; sites included in the analysis of White women were CCCCS, LACOCS, MEC, NCOCS, WHI.

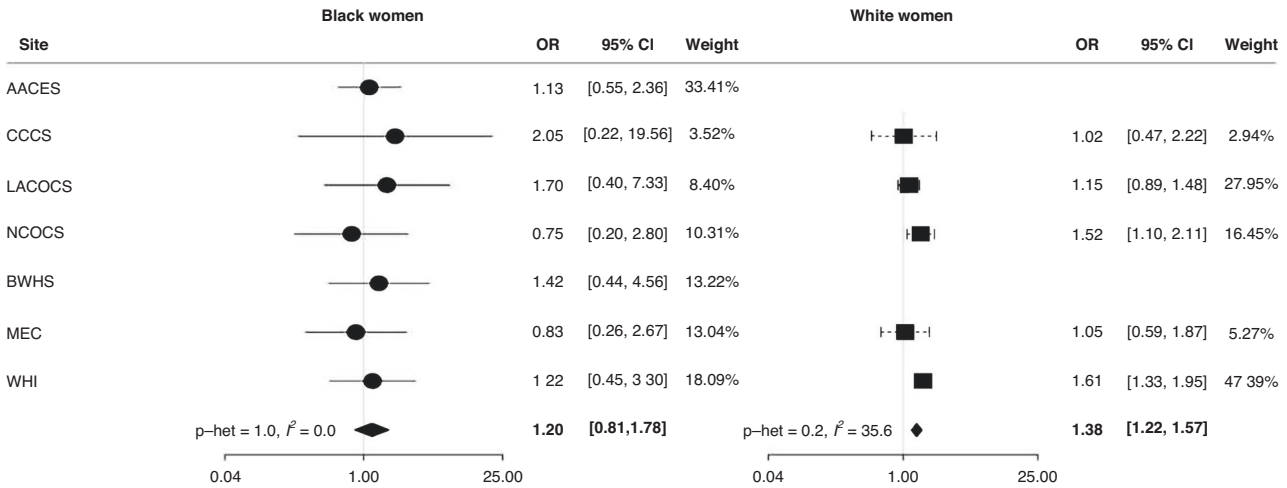

Fig. 1 Forest plot of the study-specific odds ratios (ORs)[a] and 95% confidence intervals (CIs) for the association between ≥ 10 years of menopausal hormone therapy use (compared to never use) and ovarian cancer risk by race. [a]ORs are based on complete case analysis and adjusted for age at index (continuous), first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), nulliparity (yes, no), education (high school graduate/GED or less, some college, college graduate, graduate/professional school), smoking status (ever, never), age at menopause (continuous), and pre-menopausal hysterectomy (yes, no).

0.79–1.93 and OR = 1.18, 95% CI: 1.04–1.35, respectively), while MHT use that ended five or more years prior to diagnosis or index date had near null associations (OR = 1.00, 95% CI: 0.75–1.34 and OR = 0.99, 95% CI: 0.86–1.12, respectively, Table 2). However, associations with recency of MHT use appeared to be due to longer duration of use (Table S2). Ten or more years of MHT use was associated with an increased ovarian cancer risk among current/recent MHT users and former MHT users for White women (OR = 1.41, 95% CI: 1.21–1.64 and OR = 1.47, 95% CI: 1.22–1.78, respectively) and the associations were consistent for Black women (OR = 1.36, 95% CI: 0.78–2.37 and OR = 1.19, 95% CI: 0.61–2.32, respectively).

The associations between ten or more years of unopposed estrogen use and ovarian cancer risk were similar to the associations with ten or more years of any MHT, although stronger in magnitude, for both Black women (OR = 1.44, 95% CI: 0.92–2.25, $p_{trend} = 0.05$) and White women (OR = 1.61, 95% CI: 1.36–1.92, $p_{trend} < 0.0001$, Table 4). In White women, the association between ten or more years of estrogen plus progesterone use and ovarian cancer risk was similar to the association for ten or more years of unopposed estrogen use (OR = 1.33, 95% CI: 1.12–1.58, $p_{trend} = 0.0008$). In Black women, no association between estrogen plus progesterone use and ovarian cancer risk was found, but data were sparse.

Among women who reported MHT use, 91% of Black women and 95% of White women with a hysterectomy used unopposed estrogens, compared to 48% of Black women and 53% of White women without a hysterectomy. When we examined the associations by hysterectomy status (Tables 5, 6), results were attenuated in women without a hysterectomy. In Black women, ten or more years of MHT use was associated with an elevated OR for women with a hysterectomy (OR = 1.40, 95% CI: 0.83–2.36, $p_{trend} = 0.4$, Table 5), but the OR was not elevated among women without a hysterectomy (OR = 0.93, 95% CI: 0.48–1.79, $p_{trend} = 0.8$). In White women, ten or more years of MHT use was associated with an increased ovarian cancer risk for women with a hysterectomy (OR = 1.75, 95% CI: 1.30–2.37, $p_{trend} < 0.0001$, Table 6), but this association was attenuated among women without a hysterectomy (OR = 1.31, 95% CI: 1.14–1.52, $p_{trend} < 0.0001$). Results were similar when we examined unopposed estrogen use only (Tables S3, S4). Results were also similar when we excluded high-grade endometroid cases from the analyses (Tables S5, S6).

DISCUSSION

The OCWAA consortium leveraged seven U.S. studies of post-menopausal women to examine the MHT use-ovarian cancer association by race, accounting for histotype and hysterectomy status. Use of MHT for 10 or more years was associated with a 20–38% increased ovarian cancer risk, which was consistent for Black and White women.

This study extends prior knowledge with a more comprehensive examination of the MHT–ovarian cancer risk association in U.S. Black women. The similarity of the associations for duration of use and ovarian cancer risk for Black and White women suggests that the extensive prior literature on this topic, which has been primarily conducted in populations of White women, may extend to Black women. The majority of epidemiologic studies have reported that unopposed estrogen use increases ovarian cancer risk [12, 14, 15], but the association with estrogen plus progesterone use is less clear. One recent pooled analysis suggested that estrogen plus progesterone use increased ovarian cancer risk [12], while another pooled study found no associations with ovarian cancer risk [31]. In the current study, unopposed estrogen use was associated with an increased ovarian cancer risk in both Black and White women. Estrogen plus progesterone use was associated with an increased ovarian cancer risk in White women, but estrogen plus progesterone use was too infrequent for informative analysis among the Black women. Similar to the results from our study, most prior studies have noted that an increased risk of ovarian cancer associated with MHT use is primarily seen in long-term users (defined by most studies as ≥ 5 years of use) [9, 12, 32, 33], providing some reassurance about little to no increased ovarian cancer risk for women who use MHTs for short durations. Further, the association between short duration of MHT use and ovarian cancer is susceptible to reverse causation [13], which is less likely an explanation for an association between longer term MHT use and ovarian cancer as we see in the current study.

Recent pooled and meta-analyses that have examined ovarian cancer histotypes have reported that MHT use was associated with an increased risk of serous and endometrioid tumor histotypes [9, 12, 14, 15]. No association—or an inverse association—has been reported between MHT use and clear cell, mucinous, and other epithelial histotypes. Our results among White women were consistent with the prior reports: Ten or more years of MHT use was associated with a 38–66% increased risk of high-grade serous

Table 4. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for the association between types of menopausal hormone therapy use and ovarian cancer by race, stratified by histotype.

		All Histotypes		High-Grade Serous[b]		Endometrioid[b]		Other Histotypes[b,c]		Test of Heterogeneity[e]
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	
Black women[d]										
Unopposed estrogen use										
Never (Any hormone)	1182	575	Reference	394	Reference	41	Reference	140	Reference	
Ever (estrogen only)	380	160	1.07 (0.83, 1.37)	97	0.99 (0.74, 1.32)	12	1.00 (0.48, 2.10)	51	1.39 (0.94, 2.04)	0.3
Duration										
< 5 Years	233	83	0.92 (0.68, 1.24)	47	0.79 (0.55, 1.14)	7	1.00 (0.42, 2.41)	29	1.30 (0.82, 2.05)	0.2
5 to < 10 Years	66	27	1.16 (0.69, 1.96)	20	1.27 (0.71, 2.26)	2	1.08 (0.23, 5.06)	5	0.89 (0.33, 2.34)	0.8
≥ 10 Years	79	46	1.44 (0.92, 2.25)	27	1.30 (0.77, 2.17)	2	0.66 (0.14, 3.04)	17	2.14 (1.14, 4.02)	0.2
Duration Trend (per 5 years)	1560	731	1.12 (1.00, 1.26)	488	1.10 (0.97, 1.26)	52	0.94 (0.64, 1.39)	191	1.20 (1.02, 1.41)	0.4
Estrogen plus Progesterone Use										
Never (any hormone)	1182	575	Reference	394	Reference	41	Reference	140	Reference	
Ever (E + P)	270	62	0.81 (0.58, 1.13)	35	0.71 (0.47, 1.07)	8	1.36 (0.57, 3.22)	19	0.94 (0.55, 1.62)	0.3
Duration										
< 5 Years	163	38	0.89 (0.59, 1.34)	25	0.92 (0.57, 1.48)	4	1.37 (0.45, 4.16)	9	0.78 (0.37, 1.61)	0.7
5 to < 10 Years	71	17	0.74 (0.41, 1.36)	7	0.47 (0.20, 1.08)	3	1.49 (0.38, 5.79)	7	1.23 (0.52, 2.87)	0.1
≥ 10 Years	33	5	0.64 (0.24, 1.72)	2	0.34 (0.08, 1.49)	1	2.01 (0.23, 17.63)	2	0.87 (0.19, 3.94)	0.3
Duration Trend (per 5 years)	1449	635	0.88 (0.69, 1.12)	428	0.67 (0.46, 0.98)	49	1.27 (0.81, 1.98)	158	1.04 (0.74, 1.45)	0.06
E + P after E Use										
No	1182	575	Reference	394	Reference	41	Reference	140	Reference	
Yes	40	8	0.87 (0.38, 1.97)	6	0.95 (0.37, 2.43)	0	–	2	0.86 (0.19, 3.83)	–
White women[d]										
Unopposed Estrogen Use										
Never	3202	1071	Reference	628	Reference	72	Reference	371	Reference	
Ever	3335	992	1.16 (1.03, 1.30)	706	1.39 (1.21, 1.59)	44	0.87 (0.57, 1.34)	242	0.84 (0.69, 1.02)	< 0.0001
Duration										
< 5 Years	1724	398	0.99 (0.86, 1.14)	282	1.18 (1.00, 1.39)	13	0.56 (0.30, 1.02)	103	0.76 (0.60, 0.97)	0.0008
5 to < 10 Years	597	161	1.12 (0.91, 1.38)	121	1.41 (1.12, 1.78)	8	0.94 (0.43, 2.05)	32	0.68 (0.46, 1.00)	0.003
≥ 10 Years	986	409	1.61 (1.36, 1.92)	286	1.90 (1.56, 2.31)	23	1.98 (1.09, 3.58)	100	1.15 (0.87, 1.52)	0.005
Duration Trend (per 5 years)	6509	2039	1.15 (1.11, 1.20)	1317	1.18 (1.13, 1.23)	116	1.23 (1.07, 1.41)	606	1.08 (1.01, 1.15)	0.03
Estrogen plus Progesterone Use										
Never	3202	1071	Reference	628	Reference	72	Reference	371	Reference	
Ever	3552	949	1.09 (0.98, 1.22)	674	1.31 (1.15, 1.50)	39	0.72 (0.48, 1.10)	236	0.80 (0.67, 0.96)	< 0.0001
Duration										
< 5 Years	1541	377	0.98 (0.85, 1.14)	261	1.15 (0.97, 1.36)	11	0.42 (0.22, 0.82)	105	0.82 (0.65, 1.04)	0.002
5 to < 10 Years	1178	283	1.08 (0.92, 1.27)	205	1.31 (1.09, 1.57)	12	0.77 (0.41, 1.47)	66	0.76 (0.57, 1.00)	0.002
≥ 10 Years	813	272	1.33 (1.12, 1.58)	195	1.63 (1.34, 1.98)	15	1.37 (0.75, 2.49)	62	0.85 (0.64, 1.15)	0.0004
Duration Trend (per 5 years)	6734	2003	1.09 (1.04, 1.15)	1,289	1.17 (1.10, 1.24)	110	1.12 (0.91, 1.36)	604	0.92 (0.84, 1.01)	< 0.0001
E + P after E Use										
No	3202	1071	Reference	628	Reference	72	Reference	371	Reference	
Yes	718	197	1.37 (1.12, 1.66)	135	1.56 (1.24, 1.95)	5	0.70 (0.27, 1.80)	57	1.16 (0.85, 1.59)	0.09

[a]ORs are based on complete case analysis, pooled across sites, and adjusted for age at index (continuous), first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), nulliparity (yes, no), education (high school graduate/GED or less, some college, college graduate, graduate/professional school), smoking status (ever, never), age at menopause (continuous), and pre-menopausal hysterectomy (yes, no).
[b]Histotype specific ORs are based on polytomous regression model.
[c]Other histotypes includes clear cell, mucinous, low-grade serous, and other epithelial histotypes.
[d]Sites included in the analysis of Black women were AACES, BWHS, CCCCS, LACOCS, MEC, NCOCS, WHI; sites included in the analysis of White women were CCCCS, LACOCS, MEC, NCOCS, WHI.
[e]p-values from Wald joint tests comparing the histotype-specific coefficients of each exposure.

Table 5. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for the association between any menopausal hormone therapy use and ovarian cancer, stratified by histotype and hysterectomy status, for Black women.

		All Histotypes		High-Grade Serous[b]		Endometrioid[b]		Other Histotypes[b,c]		Test of Heterogeneity[e]
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	
Black women with a hysterectomy[d]										
Any Menopausal Hormone Therapy Use										
Never	278	124	Reference	86	Reference	13	Reference	25	Reference	
Ever	226	115	1.21 (0.85, 1.73)	63	0.98 (0.65, 1.48)	10	1.23 (0.49, 3.09)	42	2.31 (1.31, 4.08)	0.03
Duration										
< 5 Years	107	54	1.18 (0.77, 1.81)	26	0.90 (0.53, 1.52)	8	2.08 (0.76, 5.67)	20	2.20 (1.13, 4.27)	0.04
5 to < 10 Years	53	19	1.04 (0.55, 1.96)	13	0.96 (0.47, 1.96)	1	0.79 (0.09, 6.79)	5	1.42 (0.48, 4.19)	0.8
≥ 10 Years	65	40	1.40 (0.83, 2.36)	22	1.08 (0.59, 1.99)	1	0.28 (0.03, 2.49)	17	3.22 (1.51, 6.89)	0.01
Duration Trend (per 5 years)	503	237	1.06 (0.93, 1.22)	147	1.01 (0.86, 1.19)	23	0.74 (0.45, 1.20)	67	1.26 (1.05, 1.52)	0.03
Recency										
Current User	42	19	0.84 (0.42, 1.66)	13	0.79 (0.37, 1.69)	0	–	6	1.29 (0.43, 3.82)	–
Recent User (< 5 years)	31	23	1.79 (0.88, 3.65)	11	1.28 (0.56, 2.90)	2	–	10	3.99 (1.48, 10.72)	–
Former User (≥ 5 years)	80	46	0.90 (0.55, 1.49)	27	0.83 (0.47, 1.46)	7	–	12	1.17 (0.51, 2.66)	–
Black women without a hysterectomy[d]										
Any Menopausal Hormone Therapy Use										
Never	904	451	Reference	308	Reference	28	Reference	115	Reference	
Ever	374	110	0.87 (0.66, 1.14)	71	0.88 (0.64, 1.21)	11	1.29 (0.59, 2.81)	28	0.75 (0.48, 1.19)	0.5
Duration										
< 5 Years	239	68	0.85 (0.62, 1.17)	47	0.92 (0.63, 1.33)	5	1.04 (0.38, 2.84)	16	0.68 (0.39, 1.19)	0.6
5 to < 10 Years	78	25	0.87 (0.51, 1.46)	12	0.64 (0.33, 1.25)	5	2.11 (0.68, 6.50)	8	0.99 (0.45, 2.19)	0.2
≥ 10 Years	55	14	0.93 (0.48, 1.79)	10	1.03 (0.48, 2.19)	1	1.40 (0.17, 11.58)	3	0.61 (0.18, 2.08)	0.7
Duration Trend (per 5 years)	1276	558	1.02 (0.87, 1.20)	377	1.01 (0.83, 1.23)	39	1.32 (0.88, 1.98)	142	0.94 (0.70, 1.25)	0.4
Recency										
Current User	40	12	0.74 (0.36, 1.52)	6	0.64 (0.25, 1.61)	3	1.80 (0.43, 7.54)	3	0.54 (0.16, 1.90)	0.4
Recent User (< 5 years)	60	17	0.92 (0.50, 1.71)	9	0.76 (0.35, 1.65)	2	1.24 (0.24, 6.39)	6	1.03 (0.41, 2.59)	0.8
Former User (≥ 5 years)	153	65	1.03 (0.72, 1.47)	48	1.13 (0.76, 1.69)	5	1.46 (0.51, 4.18)	12	0.73 (0.38, 1.41)	0.4

[a]ORs are based on complete case analysis, pooled across sites, and adjusted for age at index (continuous), first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), nulliparity (yes, no), education (high school graduate/GED or less, some college, college graduate, graduate/professional school), smoking status (ever, never), and age at menopause (continuous).
[b]Histotype specific ORs are based on polytomous regression model.
[c]Other histotypes includes clear cell, mucinous, low-grade serous, and other epithelial histotypes.
[d]Sites included in the analysis of Black women were AACES, BWHS, CCCCS, LACOCS, MEC, NCOCS, WHI.
[e]p-values from Wald joint tests comparing the histotype-specific coefficients of each exposure.

Table 6. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) for the association between any menopausal hormone therapy use and ovarian cancer, stratified by histotype and hysterectomy status, for White women.

		All Histotypes		High-Grade Serous[b]		Endometrioid[b]		Other Histotypes[b,c]		Test of Heterogeneity[e]
	Controls	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	Cases	OR (95% CI)	
White women with a hysterectomy[d]										
Any Menopausal Hormone Therapy Use										
Never	275	113	Reference	68	Reference	6	Reference	39	Reference	
Ever	1065	456	1.43 (1.09, 1.89)	318	1.69 (1.22, 2.33)	24	1.96 (0.75, 5.15)	114	1.13 (0.74, 1.71)	0.2
Duration										
< 5 Years	249	75	0.97 (0.67, 1.40)	43	0.94 (0.61, 1.47)	5	1.50 (0.44, 5.13)	27	1.04 (0.60, 1.79)	0.8
5 to < 10 Years	211	73	1.33 (0.90, 1.96)	52	1.60 (1.03, 2.49)	4	1.72 (0.45, 6.54)	17	1.00 (0.53, 1.89)	0.4
≥ 10 Years	593	295	1.75 (1.30, 2.37)	214	2.17 (1.53, 3.07)	15	2.56 (0.89, 7.36)	66	1.22 (0.77, 1.94)	0.07
Duration Trend (per 5 years)	1328	556	1.17 (1.10, 1.24)	377	1.23 (1.15, 1.31)	30	1.14 (0.94, 1.39)	149	1.07 (0.98, 1.17)	0.02
Recency										
Current User	140	144	1.47 (1.02, 2.12)	103	1.91 (1.26, 2.88)	12	2.34 (0.79, 6.89)	29	0.87 (0.50, 1.53)	0.03
Recent User (< 5 years)	355	167	1.75 (1.25, 2.46)	113	2.03 (1.38, 2.98)	6	1.65 (0.50, 5.47)	48	1.59 (0.96, 2.61)	0.7
Former User (≥ 5 years)	450	120	1.14 (0.79, 1.64)	87	1.35 (0.89, 2.05)	6	2.12 (0.60, 7.48)	27	0.81 (0.45, 1.45)	0.2
White women without a hysterectomy[d]										
Any Menopausal Hormone Therapy Use										
Never	2927	958	Reference	560	Reference	66	Reference	332	Reference	
Ever	4287	1182	1.03 (0.92, 1.14)	826	1.22 (1.08, 1.39)	49	0.64 (0.44, 0.94)	307	0.78 (0.66, 0.92)	< 0.0001
Duration										
< 5 Years	1519	411	0.89 (0.77, 1.02)	270	1.00 (0.85, 1.19)	12	0.36 (0.19, 0.68)	129	0.81 (0.65, 1.00)	0.003
5 to < 10 Years	1222	281	0.93 (0.79, 1.10)	214	1.20 (1.00, 1.44)	11	0.55 (0.29, 1.06)	56	0.56 (0.41, 0.75)	< 0.0001
≥ 10 Years	1509	459	1.31 (1.14, 1.52)	318	1.54 (1.30, 1.81)	25	1.28 (0.77, 2.11)	116	0.96 (0.76, 1.21)	0.002
Duration Trend (per 5 years)	7177	2109	1.10 (1.06, 1.15)	1362	1.14 (1.09, 1.19)	114	1.17 (1.02, 1.35)	633	1.01 (0.94, 1.08)	0.004
Recency										
Current User	420	262	1.10 (0.91, 1.32)	195	1.40 (1.14, 1.73)	16	0.79 (0.45, 1.41)	51	0.63 (0.46, 0.88)	< 0.001
Recent User (< 5 years)	1429	422	1.09 (0.94, 1.26)	285	1.22 (1.03, 1.44)	21	0.73 (0.44, 1.21)	116	0.91 (0.72, 1.15)	0.03
Former User (≥ 5 years)	2133	439	0.98 (0.85, 1.13)	310	1.14 (0.97, 1.35)	10	0.38 (0.19, 0.76)	119	0.83 (0.65, 1.05)	0.001

[a]ORs are based on complete case analysis, pooled across sites, and adjusted for age at index (continuous), first degree family history of breast cancer (yes, no), first degree family history of ovarian cancer (yes, no), nulliparity (yes, no), education (high school graduate/GED or less, some college, college graduate, graduate/professional school), smoking status (ever, never), and age at menopause (continuous).
[b]Histotype specific ORs are based on polytomous regression model.
[c]Other histotypes includes clear cell, mucinous, low-grade serous, and other epithelial histotypes.
[d]Sites included in the analysis of White women were CCCCS, LACOCS, MEC, NCOCS, WHI.
[e]p-values from Wald joint tests comparing the histotype-specific coefficients of each exposure.

and endometrioid tumors, but there was no association with other epithelial histotypes. However, our results among Black women were the opposite: Ten or more years of MHT use was associated with a 70% increased risk of other epithelial histotypes, but there was little to no association with high-grade serous or endometrioid tumors. We further assessed this association by examining clear cell and mucinous tumors independent of other epithelial histotypes. Although the sample sizes were limited, the ORs remained elevated for clear cell tumors, mucinous tumors, and all other epithelial histotypes.

Following the results from the WHI randomized controlled trial [34, 35], which reported MHT use was associated with an increased risk of breast cancer and cardiovascular disease, MHT use decreased in all racial/ethnic groups [16]. Although indications for MHT use, including hysterectomy and vasomotor symptoms associated with menopause, are more common in Black women than White women [36–40], use of MHT remains about twice as high among White women as compared to Black women [16]. In our study's control participants, 63% of White women reported MHT use compared to 34% of Black women. The lower prevalence of MHT use in Black women makes examining the MHT use–ovarian cancer association challenging in individual studies. Three studies (AACES, NCOCS, and BWHS, which are all included in OCWAA), previously reported that MHT use is associated with an increased ovarian cancer risk in Black women [17–19], but power was limited. Additionally, these prior studies were unable to examine potential differences in the MHT use–ovarian cancer association by race, as they were either underpowered to stratify by race [19] or included only Black women [17, 18]. MEC was able to stratify by race and reported no association between MHT use and ovarian cancer for White or Black women [20]. However, the study included only 132 White and 83 Black post-menopausal ovarian cancer cases.

Cellular studies support the hypothesis that estrogens influence ovarian cancer risk [8]. Estrogen binds to estrogen receptor-α, which leads to activation of estrogen-responsive genes including proto-oncogenes. In turn, these genes signal cellular proliferation and differentiation [8, 41]. Independent of estrogen receptor pathways, metabolic activation of estrogens can result in formation of free radicals and mutagenic DNA adducts, leading to mutations and subsequent neoplastic transformation of proliferating cells [8, 42, 43]. Epidemiologic studies have consistently shown that surrogates for a lower lifetime endogenous estrogen exposure (i.e., parity, breastfeeding, tubal ligation, and oral contraceptive use) are associated with a decreased ovarian cancer risk [9–11]. However, studies of endogenous circulating sex steroid hormones have reported null associations between estrogen metabolites and risk of ovarian cancer when not evaluated by subtype [44–46]. Recent studies have shown an association between estrogen metabolites and an increased risk of non-serous ovarian cancer, both among MHT users [7] and non-users [47]. This is in contrast to the current study and prior literature, which suggests that exogenous unopposed estrogen use increases the risk of serous and some non-serous histotypes of ovarian cancer.

Limitations of the present study include potential inaccuracies in exposure capture and recall bias. MHT use in the included studies was all self-reported and may not have been reported accurately compared to pharmaceutical records. However, in a study from Sweden with prescription drug linkage, longer duration MHT use was also associated with increased ovarian cancer risk [48], but there was no assessment of specific MHT formulations. Recall bias was not a concern for the cases and controls nested within prospective cohort studies (BWHS, MEC, WHI), but recall bias may be a concern for case-control studies, particularly those conducted following the report of results on associations of MHT with increased risk of some disease outcomes in 2002 from the WHI hormone trials [34, 35]. However, as shown in the forest plot, our results are consistent between the cohort and case-control studies.

Strengths of our study include the larger number of Black women than in previous studies. The OCWAA consortium provided greater statistical power than any prior study to examine the association between MHT use and ovarian cancer risk for Black women, allowing examination by histotype and hysterectomy status. However, the number of Black women in these stratified analyses was still often small. The OCWAA consortium harmonized the covariates across the included studies, which has an advantage over a meta-analytic type of approach by allowing for uniform adjustment for potential confounders. Our approach allowed for examination of study heterogeneity and racial differences in associations.

In conclusion, long-term use of MHTs, particularly unopposed estrogen use, was associated with an increased ovarian cancer risk in the OCWAA consortium for White women and the association was consistent for Black women. Further research is needed to assess estrogen plus progesterone use in Black women, specific MHT formulations (e.g., bioidentical estrogens vs. animal-derived estrogens), and associations with ovarian cancer histotypes. Since the OCWAA consortium was designed to examine racial differences in ovarian cancer risk factors between Black and White women, this study was unable to examine the association between MHT use and ovarian cancer for additional underrepresented racial/ethnic populations. Studies of MHT and ovarian cancer are needed for such populations.

DATA AVAILABILITY

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

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Conceptualization: JMS, LR, CEJ, LCP, JLP. Data curation: CEJ, EVB, TNB, ABF, HRH, PGM, EM, HMO, VWS, AHW, LR, JMS. Formal Analysis: CEJ, TFC, WR. Funding acquisition: JMS, LR. Methodology: JMS, LR, CEJ, LCP, MEB, JLP. Critical revision and interpterion: All authors. Writing – original draft: JLP, LR. Writing – critical revision & editing: All authors. Approval of final manuscript: All authors.

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Each study obtained informed consent from its participants; the individual studies and the OCWAA Consortium were approved by the relevant Institutional Review Boards.

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