Research Article

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Exogenous Hormone Use and Endometrial Cancer in U.S. Black Women

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Abstract

Background: Although endometrial cancer risk differs among white and black women, few data on its associations with exogenous hormone use in the latter group are available. Studies have reported lower endometrial cancer risk among users of oral contraceptives (OCs), but higher risk among users of estrogen-only female menopausal hormones (FMHs). Evidence for the risk among estrogen plus progestin FMHs users is equivocal.

Methods: We followed 47,555 Black Women's Health Study participants with an intact uterus from 1995 through 2013. Data on exogenous hormone use, covariates, and endometrial cancer were obtained biennially. Self-reported incident cases of endometrial cancer were confirmed by medical records or cancer registries whenever possible. We estimated incidence rate ratios (IRRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression.

Results: We observed 300 endometrial cancer cases during 689,546 person-years of follow-up. Compared with never use, ≥10 years' duration of OC use was associated with lower risk (multivariable IRR = 0.45, 95% CI, 0.27–0.74), but risk was higher among current users of estrogen-only (IRR = 3.78, 95% CI, 1.69–8.43) and estrogen plus progestin FMH (IRR = 1.55, 95% CI, 0.78–3.11). Risk was not increased among former users of estrogen-only (IRR = 0.87, 95% CI, 0.44–1.72) or estrogen plus progestin FMH (IRR = 0.63, 95% CI, 0.36–1.09).

Conclusions: Current use of estrogen-only and estrogen plus progestin FMH was associated with increased risk of endometrial cancer. Risk appeared lower among former users of estrogen plus progestin FMH. Long-term OC use was associated with reduced risk.

Impact: Our results are generally consistent with those among white women. *Cancer Epidemiol Biomarkers Prev; 27(5); 558–65. ©2018 AACR.*

Introduction

The risk of endometrial cancer, which has the highest incidence among gynecologic cancers and the fourth highest incidence among women in the United States (1), is thought to depend primarily upon exposure of the endometrium to estrogens and progesterone (2). Estrogens, which spur the proliferation of endometrial tissue, are associated with increased risk (2). Conversely, progesterone blocks the activity of estrogens and is associated with decreased risk (2).

Most epidemiologic studies have found an inverse association between the use of oral contraceptives (OCs) and endometrial cancer (3–13), although one reported a positive association (14). Stronger inverse associations have been reported for longer durations of use (4–9, 13), which may continue at least 20 years after cessation (9, 11). The association of OC use with endometrial cancer does not appear to vary according to the potency of estrogen or progestins used (10, 13). The association between various formulations of female menopausal hormones (FMHs) and endometrial cancer has been extensively studied (reviewed in ref. 15). Use of estrogen-only FMH has been consistently associated with increased endometrial cancer risk (16–23). Relative risks range from 2.0 to 10.0 for long-term use (generally ≥5 or ≥10 years; refs. 18–20, 22). Progestins were added to FMH formulations to reduce the risk of endometrial cancer. The earliest formulations of these drugs administered estrogens and progestins sequentially, with progestins taken for 1–3 weeks every month. Studies of sequential FMHs have been inconsistent, with reports of increased risk (18, 19, 22–25) or no association with endometrial cancer (20). Most studies have found that FMH formulations in which progestins are taken continuously decrease risk (4, 16, 20, 22–27), but one observed a positive association (19).

To our knowledge, no studies of endometrial cancer and FMH have reported race-specific estimates. Because black women have a higher prevalence of obesity and obesity may modify the association between FMH and endometrial cancer (16, 17, 20, 21, 23), it is of interest to examine association of FMH with risk of endometrial cancer in this population. To contribute to the body of evidence regarding use of exogenous hormones and risk of endometrial cancer in black women, we evaluated these relationships in the Black Women's Health Study (BWHS), a U.S.-based prospective cohort study.

Materials and Methods

Data source

The BWHS is a cohort study that has followed 59,001 self-identified black women since its inception in 1995 (28). Women

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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ages 21–69 were identified from a list of *Essence* magazine subscribers, black professional organizations, and friends and relatives of study participants and enrolled via mailed questionnaires. At baseline, participants provided data on demographic factors, reproductive history, health history tobacco and alcohol use, anthropometric measurements and other factors. Participants completed follow-up questionnaires every two years to update outcome, exposure, and covariate data. As of 2013, follow-up is complete for approximately 87% of potential person-years. All participants provided written informed consent, and the study protocol was approved by the Boston University Institutional Review Board.

Women reporting a history of uterine cancer ($n = 258$), cervical cancer ($n = 82$), or hysterectomy ($n = 10{,}659$), and those from whom no follow-up questionnaire has been received ($n = 447$) were excluded from this analysis. The analytic sample comprised the remaining 47,555 women who were followed for incident endometrial cancer from 1995 through 2013.

Outcome ascertainment

A total of 354 potential cases were identified by self-report of new diagnoses of "uterine cancer" on biennial follow-up questionnaires from 1997 through 2013 or through state cancer registries in 24 states where 95% of participants lived. Eighteen women subsequently reported that they had a condition other than uterine cancer when contacted for permission to release medical records, 18 were disconfirmed by medical record, 231 were confirmed as either endometrial cancer ($n = 213$) or uterine sarcoma ($n = 18$), and records could not be obtained for 87. Because of the high confirmation rate, we included the 87 unverified cases in the analysis. After uterine sarcomas were excluded, 300 cases of endometrial cancer were available for study. International Classification of Diseases for Oncology (ICD-O) codes were available to allow 188 of the confirmed cases to be classified by histological type; 136 (72%) were classified as type I (ICD-O codes 8010, 8020, 8140, 8210, 8255, 8260, 8262, 8263, 8380, 8382, 8383, 8440, 8480, 8481, 8570), and 51 as other histologic types (ICD-O codes 8041, 8050, 8070, 8071, 8072, 8310, 8323, 8441, 8460, 8461, 8560, 8950, 8951, 8980).

Exposure ascertainment

At baseline, women were asked if they had ever used OCs and the duration of use for each age between 13 and "45 or more." Choices included <6, 6–9, or ≥10 months. On subsequent questionnaires, they indicated if they had used OCs since the previous questionnaire, as well as the duration of use during that time period (choose <6, 6–11, 12–17, or ≥18 months in 1997, 1999, and 2001; fill in number of months in 2003, 2005, 2007, 2009, 2011, and 2013).

In 1995, women reported whether or not they had ever used replacement female hormones for menopause, when they last took them (current user, <1, 1–2, ≥3 years ago), how many years they took them (<1, 1, 2, 3–4, 5–6, 7–9, 10–14, ≥15 years) and the name and type of hormone used most recently. Women who reported progestin use were asked about their pattern of use (used continuously, 2–3 weeks each month, <2 weeks each month, other pattern of use). Follow-up questionnaires asked whether they had used estrogen replacement therapy since the last questionnaire, the duration of use during that period (choose <6, 6–11, 12–17, or ≥18 months in 1997, 1999, and 2001; fill in number of months in 2003, 2005, 2007, 2009, 2011, and 2013), and the name and type of hormone used most recently. Data on pattern of progestin use among estrogen plus progestin FMH users was not collected after the baseline questionnaire. Use of estrogen vaginal cream was not considered exposure to estrogen-only FMH.

Covariates

Women reported their age at menarche, education level, and weight at age 18 on the baseline questionnaire in 1995. Data on height and current weight [with which we computed body mass index (BMI)] and physician-diagnosed diabetes, age at first birth, parity, gynecologic surgeries (hysterectomy, bilateral oophorectomy, unilateral oophorectomy), and menopausal status were collected at baseline and updated on subsequent biennial follow-up questionnaires. Menopause was defined as the absence of menstrual periods within the last 12 months. We classified women whose menopausal status was unknown according to the distribution of age at natural menopause in the BWHS. They were classified as premenopausal if their current age was below the 10th percentile (43 years), postmenopausal if their current age was greater than the 90th percentile (56 years), and unknown status if current age was 43–56 years (29). Data on vigorous exercise (hours/week) were collected on every questionnaire except 2003 and 2005. Marital status was reported in 1995, 1997, 1999, and 2003.

Data analysis

We calculated person-time from baseline until the first occurrence of one the following events: diagnosis of endometrial cancer, diagnosis of nonepithelial uterine cancer, hysterectomy, loss-to-follow-up, or the end of follow-up (2013). Age- and questionnaire cycle-stratified Cox proportional hazards regression models (30) were used to estimate crude and adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for all categories of exposure compared with the reference category. Because data on the timing of progestin use in estrogen plus progestin FMH user was available only at baseline, this variable was analyzed as a time-invariant Cox model using baseline data. The Andersen–Gill data structure (31) was used to update time-varying covariates for all other exposures. Missing values were imputed by carrying forward the last observation. Departures from proportional hazards were assessed by comparing models with and without interaction terms between exposures and each of the time scales (age and questionnaire cycle) using the likelihood ratio test.

Time-varying variables were defined similarly for OCs and FMH. Ever use was defined as a report on the current or any prior questionnaire. An ever user was classified as a current user if she reported any use since the last questionnaire, otherwise she was classified as a former user. Recency and duration of use were determined at baseline and updated whenever a woman reported use since the prior questionnaire.

For OCs, duration of use was categorized as (0, 1–4, 5–9, and ≥10 years). Recency of use was categorized as (never user, current user, 1–9, 10–19, 20–29, ≥30 years since last use). We also cross-tabulated recency and duration of use in categories, comparing never users to each combination of duration (1–4, ≥5 years) and recency (1–9, 10–19, ≥20 years). For FMH, duration was categorized as (0, 1–4, ≥5 years) and recency as (never user, current user, 1–9, ≥10 years).

To control for confounding, we adjusted for the following known or suspected risk factors for endometrial cancer: age at

menarche (<11, 11, 12–13, ≥14 years), parity (parous, nulliparous), smoking status (never, former, current), vigorous physical activity (0, 1–4, ≥5 hours/week), and BMI (<25, 25–29, 30–34, 35–39, ≥40 kg/m^2). Models were mutually adjusted for OC use (never, former, current) and use of estrogen-only and estrogen plus progestin FMH (never, former, current), when appropriate. In analyses of OC use, we additionally adjusted for menopausal status (premenopausal, postmenopausal, unknown status). We further examined potential confounding by BMI at age 18, history of infertility, income, and marital status. Inclusion of these variables did not change effect estimates appreciably (<10%), and they were omitted them from the final models.

Young women are at low risk for endometrial cancer and unlikely to use FMH for menopause. We therefore restricted the analysis of FMH use to women who were (i) 40 years or older, (ii) had known menopausal status, and (iii) did not report current use of OCs. Each type of FMH (estrogen-only, estrogen plus progestin, and progestin-only) was analyzed separately, restricted to person-years contributed by women who used only that one type, compared with women who did not report any FMH use (estrogen-only, estrogen plus progestin, progestin-only, or unknown type). Few women (2,159 women, 17,099 person-years, 3 cases) switched from one FMH type to another, so we did not perform separate analyses in these women.

Obesity is strongly associated with endometrial cancer, can affect steroid hormone levels through the action of aromatase, and has been found to modify the associations of exogenous hormone use with endometrial cancer. We therefore repeated our analyses stratified by obesity (BMI ≥30 vs. <30 kg/m^2).

Separate analyses were performed to investigate the association of type I and other histologic types endometrial cancers with exogenous hormone use, censoring all other incident cases that could not be classified at the time of diagnosis. In secondary analyses, we restricted case group to confirmed cases, censoring unconfirmed incident cases at the time of diagnosis, and repeated analyses censoring all prior cancers.

All analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc.).

Results

We identified 300 endometrial cancer cases during 689,546 person-years of follow up. Mean length of follow-up was 14.5 years. Compared with never users of oral contraceptives, ever users at baseline were younger, more likely to be married, parous, and premenopausal (Table 1).

Table 1. Age-standardized baseline characteristics[a] of 47,555 participants in the Black Women's Health Study

	Oral contraceptive use	
	Ever	Never
Age, mean (SD)	36.6 (116.5)	39.2 (170.8)
Education, %		
<High school	1.8	4.3
High school	13.5	17.0
College	24.4	22.8
Graduate	21.9	21.4
Marital status, %		
Single	37.2	48.7
Married/living together	39.1	29.3
Separated/divorced/widowed	22.8	20.9
Age at menarche	12.3 (20.8)	12.3 (22.0)
History of infertility, %	10.0	9.8
Parous, %	63.4	50.3
Postmenopausal, %	8.2	22.0
BMI (kg/m^2)	29.0 (93.1)	30.5 (109.8)
Vigorous physical activity, hours/week, %		
1–4	53.0	47.5
≥5	13.3	12.2
Ever use of estrogen-only FMH, %[b]	2.6	3.4
Ever use of estrogen+progestin FMH, %[b]	8.7	9.0
Ever use of progestin-only female hormones, %[b]	1.6	1.1

[a]Values are means (SD) or percentages and are standardized to the age distribution of the study population.
[b]Among women age ≥40 years and not taking oral contraceptives.

Oral contraceptives

After adjustment for potential confounders, the IRR comparing ever with never use of OCs was 0.86 (95% CI, 0.63–1.18; Table 2). IRRs for former and current use compared with never OC use were 0.87 (95% CI, 0.64–1.20) and 0.69 (95% CI, 0.40–1.20), respectively. IRRs for 1–9, 10–19, 20–29, and ≥30 years since last use compared with never use were 0.69 (95% CI, 0.44–1.08), 0.85 (95% CI, 0.54–1.32), 0.98, (95% CI, 0.66–1.45) and 0.89, (95% CI, 0.62–1.28), respectively (P_{trend} = 0.43). There was an inverse relation between duration of OC use and endometrial cancer risk. IRRs for 1–4, 5–9 and ≥10 years of use vs. never use 0.98 (95% CI, 0.71–1.35), 0.74 (95% CI, 0.48–1.13) and 0.45 (95% CI, 0.27–0.74), respectively (P_{trend} = 0.0002). The inverse association between OC use and endometrial cancer risk among women who used OCs ≥5 years compared with never users changed little for up to 20 years since last use. The IRRs for <10, 10–19, and ≥20 years since last use in such women were 0.45 (95% CI, 0.26–0.76), 0.51 (95% CI, 0.26–0.99), and 0.80 (95% CI, 0.51–1.25), respectively. There was little evidence for an association among women who used OCs for <5 years in any recency category.

The association between oral contraceptive use and endometrial cancer was confined to non-obese women (Table 3). The IRRs for current use compared with never use were 0.44 (95% CI, 0.18–1.07 and 0.98 (95% CI, 0.48–2.01) for non-obese and obese women, respectively. Compared with never users, the IRRs for former users were 0.70 (95% CI, 0.42–1.16) and 1.05 (95% CI, 0.60–1.59) among non-obese and obese women, respectively. The IRR for ≥10 years of use compared with never use was 0.19 (95% CI, 0.07–0.47) among non-obese women and 0.77 (95% CI, 0.42–1.41) among obese women.

We did not observe clear evidence of differences in the association of OC use with histologic subtypes of endometrial cancer (Supplementary Table S1). When analyses were restricted to confirmed endometrial cancer cases, the IRR for <5 years of OC use and discontinuation within the last 10 years (IRR = 0.54, 95% CI, 0.28–1.06) was similar to ≥5 years of OC use with the same recency (IRR = 0.55, 95% CI, 0.29–1.05; Supplementary Table S2). In contrast, the IRR for <5 years of OC use and discontinuation within the last 10 years (IRR = 1.00, 95% CI, 0.52–1.95) was closer to the null than for ≥5 years of OC use and discontinuation within the last 10 years (IRR = 0.38, 95% CI, 0.15–0.98) in the main analysis. Estimates did not change substantially when nonendometrial cancers were censored (Supplementary Table S3).

Female menopausal hormones

The IRR for current use of estrogen-only FMH compared with never use of any FMH was 3.78 (95% CI, 1.69–8.43) (Table 4). There was little difference in the IRRs by duration of use 1–4

Table 2. Association of endometrial cancer with oral contraceptive use, 1995–2013

				Age adjusted[a]		Multivariable adjusted[b]	
Exposure	**Cases**	**Person-years**	**Rate[c]**	**IRR**	**95% CI**	**IRR**	**95% CI**
OC use							
Never	57	79,594	71.6	1.00	Referent	1.00	Referent
Ever	243	609,906	39.8	0.72	0.53–0.98	0.86	0.63–1.18
Former	221	489,406	45.2	0.74	0.54–1.00	0.87	0.64–1.20
Years since last use[d]							
1–9	40	174,341	22.9	0.52	0.34–0.80	0.69	0.44–1.08
10–19	38	134,455	28.3	0.72	0.46–1.13	0.85	0.54–1.32
20–29	58	105,042	55.2	0.85	0.58–1.26	0.98	0.66–1.45
≥30	77	62,163	123.9	0.79	0.55–1.14	0.89	0.62–1.28
Current	22	120,500	18.3	0.61	0.36–1.03	0.69	0.40–1.20
Duration (years)							
1–4	165	325,167	50.7	0.84	0.61–1.15	0.98	0.71–1.35
5–9	42	142,583	29.5	0.59	0.39–0.90	0.74	0.48–1.13
≥10	24	122,339	19.6	0.37	0.22–0.60	0.45	0.27–0.74
				P_{trend}	<0.0001	P_{trend}	0.0002
Recency (years) × Duration (years)[e]							
<10, <5	36	118,125	30.5	0.74	0.48–1.14	0.91	0.58–1.45
<10, ≥5	22	168,133	13.1	0.34	0.20–0.58	0.45	0.26–0.76
10–19, <5	27	76,367	35.4	0.96	0.59–1.58	1.09	0.66–1.80
10–19, ≥5	11	58,087	18.9	0.41	0.21–0.80	0.51	0.26–0.99
≥20, <5	102	129,808	78.6	0.85	0.60–1.18	0.95	0.68–1.34
≥20, ≥5	33	37,397	88.2	0.69	0.45–1.08	0.80	0.51–1.25

[a]Age-adjusted model stratified by age and study period.
[b]Multivariable model stratified by age and study period and adjusted for age at menarche, parity, menopausal status, estrogen-only FMH use, estrogen plus progestin FMH use, smoking, BMI, and vigorous physical activity.
[c]Crude rate per 100,000 person-years.
[d]Years since last use [P_{trend} = 0.03 (age- and period adjusted), 0.43 (multivariable adjusted)].
[e]Cross-tabulated recency and duration of use.

(IRR = 1.25, 95% CI, 0.70–2.23, based on 13 cases) and ≥5 years (IRR = 1.90, 95% CI, 0.59–6.09, based on 3 cases). No elevation was observed for former users (IRR = 0.87, 95% CI, 0.44–1.72).

The IRR for ever users of estrogen plus progestin FMH relative to never users was IRR = 0.82, (95% CI, 0.53–1.28; Table 4). However, among current users, the comparable IRR was 1.55 (95% CI, 0.78–3.11). In analyses of baseline data on the pattern of progestin use, risk was higher among users of sequential estrogen plus progestin FMH taking progestins <2 weeks/month (IRR = 1.29; 95% CI, 0.70–2.39) and lower among continuous users of progestin (IRR = 0.74, 95% CI, 0.36–1.50) compared with women who never used any FMH.

The IRRs comparing ever use of progestin-only FMH to never use was 1.51 (95% CI, 0.73–3.09, based on 8 cases; Table 4).

While ever use compared with never use of estrogen-only FMH was associated with increased endometrial cancer risk among non-obese women (IRR = 3.05; 95% CI, 1.44–6.46, 10 cases), this was not the case among obese women (IRR = 0.99; 95% CI, 0.44–2.24, 7 cases; Table 5). However, risk was similarly increased among non-obese and obese current users (IRR = 5.05; 95% CI,

Table 3. Association of endometrial cancer with oral contraceptive use, stratified by obesity status 1995–2013

	Non-obese (BMI < 30 kg/m^2)				Obese (BMI ≥ 30 kg/m^2)			
	Cases	**Rate[a]**	**IRR[b]**	**95% CI**	**Cases**	**Rate[a]**	**IRR[b]**	**95% CI**
OC use								
Never	23	49.4	1.00	Referent	33	103.5	1.00	Referent
Ever	96	25.2	0.68	0.41–1.13	145	64.8	1.05	0.69–1.58
Former	88	29.7	0.70	0.42–1.16	131	69.5	1.05	0.69–1.59
Years since last use								
1–9	15	13.3	0.47	0.23–0.97	25	41.6	0.96	0.54–1.72
10–19	18	22.2	0.71	0.36–1.41	20	38.3	0.97	0.53–1.78
20–29	28	46.3	0.94	0.51–1.72	30	68.8	1.03	0.61–1.76
≥30	23	67.9	0.64	0.34–1.18	52	189.1	1.12	0.70–1.78
Current	8	9.5	0.44	0.18–1.07	14	39.8	0.98	0.48–2.01
Duration (years)								
1–4	68	34.5	0.86	0.51–1.43	95	76.3	1.11	0.73–1.70
5–9	17	18.7	0.55	0.28–1.07	25	49.6	0.95	0.55–1.65
≥10	6	7.5	0.19	0.07–0.47	18	43.7	0.77	0.42–1.41

[a]Crude rate per 100,000 person-years.
[b]Multivariable model stratified by age and study period and adjusted for age at menarche, parity, menopausal status, estrogen-only FMH use, estrogen plus progestin FMH use, smoking, body mass index, (continuous), and vigorous physical activity.

Table 4. Association of female menopausal hormone use with endometrial cancer among women age ≥40 years, 1995–2013[a]

				Age adjusted[b]		Multivariable adjusted[c]	
Exposure	**Cases**	**Person-years**	**Rate[d]**	**IRR**	**95% CI**	**IRR**	**95% CI**
Estrogen-only FMH use[e]							
Never[f]	155	277,471	55.9	1.00	Referent	1.00	Referent
Ever	16	12,130	131.9	1.28	0.76–2.17	1.32	0.78–2.23
Former	9	8,882	101.3	0.86	0.44–1.70	0.87	0.44–1.72
Years since last use							
1–9	5	6,230	80.3	0.71	0.29–1.73	0.73	0.30–1.80
≥10	4	2,637	151.7	1.19	0.43–3.26	1.15	0.42–3.17
Current	7	3,248	215.5	3.45	1.56–7.65	3.78	1.69–8.43
Duration (years)							
1–4	13	10,668	121.9	1.22	0.68–2.16	1.25	0.70–2.23
≥5	3	1,271	236.0	1.85	0.58–5.89	1.90	0.59–6.09
Estrogen + progestin FMH use[g]							
Never[f]	155	277,471	55.9	1.00	Referent	1.00	Referent
Ever	25	28.602	87.4	0.71	0.46–1.11	0.82	0.53–1.28
Former	15	17,790	84.3	0.55	0.32–0.96	0.63	0.36–1.09
Years since last use							
1–9	9	13,586	66.2	0.46	0.23–0.92	0.53	0.27–1.06
≥10	6	4,180	143.5	0.79	0.34–1.83	0.86	0.37–2.01
Current	10	10,812	92.5	1.29	0.65–2.56	1.55	0.78–3.11
Duration							
1–4	16	20,356	78.6	0.71	0.42–1.20	0.79	0.47–1.35
≥5	9	7,304	123.2	0.81	0.41–1.61	0.99	0.49–1.98
Pattern of progestin use[g]							
Never used FMH[f]	177	186,113	95.1	1.00	Referent	1.00	Referent
<2 wk/mo.	11	7,836	140.4	1.14	0.62–2.11	1.29	0.70–2.39
2–3 wk/mo.	0	5,080	0.0	0.00	—	0.00	—
Continuous	8	9,442	84.7	0.64	0.31–1.31	0.74	0.36–1.50
Other	1	1,390	71.9	0.62	0.09–4.44	0.63	0.09–4.49
Progestin-only FMH use[e,g]							
Never[f]	155	277,471	55.9	1.00	Referent	1.00	Referent
Ever	8	7,366	108.6	1.74	0.85–3.56	1.51	0.73–3.09

[a]Analysis restricted to women ≥40 years of age, not taking oral contraceptives, with known menopause status, and not reporting use of multiple FMH types.
[b]Age-adjusted model stratified by age and study period.
[c]Multivariable model stratified by age and study period and adjusted for age at menarche, parity, menopausal status, oral contraceptive use, smoking, BMI, and vigorous physical activity.
[d]Crude rate per 100,000 person-years.
[e]Additionally adjusted for estrogen plus progestin FMH use.
[f]Never reported any FMH use.
[g]Additionally adjusted for estrogen-only FMH use.

1.42–18.03 and IRR = 5.16; 95% CI, 1.51–17.58, respectively, 4 cases in each group). The IRRs for ever use of estrogen plus progestin FMH were 1.00 (95% CI, 0.47–2.10) and 0.62 (95% CI, 0.33–1.19) among non-obese and obese women, respectively.

There was little evidence that the associations of FMH use with endometrial varied according to histologic subtypes (Supplementary Table S4).

Compared with the primary analysis, the association between progestin-only FMH use and endometrial cancer was attenuated when restricted to confirmed cancer cases (Supplementary Table S5). Associations of other variables with endometrial cancer were comparable between the main analysis and the analysis restricted to confirmed cases and when all nonendometrial cancers were censored (Supplementary Table S6).

Discussion

In this prospective cohort study of U.S. black women, long-term OC use was associated with reduced endometrial cancer risk in a dose-response manner. Current use of estrogen-only FMH was associated with increased risk, while former use was not appreciably associated with risk. Our results for estrogen plus progestin FMH suggested increased risk among current users but decreased risk among former users, although we had little data on pattern of progestin use and numbers of users were small.

According to the unopposed estrogen hypothesis (2), endometrial cancer risk is principally determined by the mitotic rate of endometrial cells, which is increased by estrogens in the absence of progesterone. Therefore, the use of exogenous estrogens and progestins is likely to influence endometrial cancer risk.

Virtually every study of OC use and endometrial cancer risk has found an inverse association (3–13). A recent meta-analysis of 36 studies with 27,276 endometrial cancer cases found a summary OR of 0.69 (95% CI, 0.66–0.73) for the association of ever versus never OC use (32). This was lower, although not incompatible, with our result of 0.86 (95% CI, 0.63–1.17). Likewise, our finding of reduced risk with increasing lifetime duration of use was comparable with the meta-analysis of OCs with RRs of 0.81 (95% CI, 0.76–0.86), 0.64 (95% CI, 0.59–0.69), 0.52 (95% CI, 0.47–0.58), and 0.32 (95% CI, 0.28–0.38) for 1–4, 5–9, 10–14, and ≥15 years of use (32). It is likely, therefore, that our higher estimate of risk among ever users was attributable, in part, to the relatively low proportion of long-duration OC users in our study. We found only two studies, a pooled analysis of 11 U.S. studies

Table 5. Association of female menopausal hormone use with endometrial cancer among women age ≥40 years, stratified by obesity status, 1995–2013[a]

	Non-obese (BMI < 30 kg/m^2)				Obese (BMI ≥ 30 kg/m^2)			
	Cases	Rate[b]	IRR[c]	95% CI	Cases	Rate[b]	IRR[c]	95% CI
Estrogen-only FMH use[d]								
Never[e]	32	65.4	1.00	Referent	71	188.4	1.00	Referent
Ever	10	173.7	3.05	1.44–6.46	7	172.9	0.99	0.44–2.24
Former	6	156.8	2.50	1.01–6.17	3	99.2	0.50	0.15–1.63
Current	4	207.3	5.05	1.42–18.03	4	389.9	5.16	1.51–17.58
Estrogen + progestin FMH use[f]								
Never[e]	32	65.4	1.00	Referent	71	188.4	1.00	Referent
Ever	11	63.6	1.00	0.47–2.10	12	121.1	0.62	0.33–1.19
Former	5	51.4	0.73	0.27–1.94	10	156.0	0.65	0.33–1.30
Current	6	79.5	1.65	0.55–4.93	2	57.2	0.48	0.09–2.47

[a]Analysis restricted to women ≥40 years of age, not taking oral contraceptives, with known menopause status, and not reporting use of multiple FMH types.
[b]Multivariable model stratified by age and study period and adjusted for age at menarche, parity, menopausal status, oral contraceptive use, smoking, body mass index (continuous), and vigorous physical activity.
[c]Crude rate per 100,000 person-years.
[d]Additionally adjusted for estrogen plus progestin FMH use.
[e]Never reported any FMH use.
[f]Additionally adjusted for estrogen-only FMH use.

(4 case–control and 7 cohort, 516 black cases; ref. 5) and a case–control study from South Africa (12) (524 total black cases) that examined the association of OC use and endometrial cancer among black women. The results of both studies were comparable with findings among white women.

The majority of studies have found that users of estrogen-only FMH have a higher risk of endometrial cancer compared with never users of FMH (16–23). In our study, current users had over 3.75 times the risk of never FMH users, although former users were not at increased risk. Most previous studies have found increasing risk with increasing duration of use (18–20, 22, 23), although one small study did not (17). Prior studies have reported relative risks ranging from 2 to 10 among long-term users (18–20, 22). Our estimates were consistent with increased risk with long-term use, although they were based on few cases and imprecisely estimated.

The association of estrogen plus progestin FMH is complicated by different formulations and patterns of progestin use in these drugs (15). Sequential formulations, where estrogens are taken alone for a portion of a given month and progestins are taken for the remainder of the month, may increase risk (18, 19, 22–25), although one study observed no association (20). In contrast, most (4, 16, 20, 22–27) but not all (18, 19) studies have found that continuous combined estrogen plus progestin FMHs decrease risk. Our analysis of the baseline data on patterns of progestin use in FMH was consistent with this, although our estimates were imprecise. In our time-varying analysis, risk was lower among former users of estrogen plus progestin FMH compared with never users of FMH, but higher among current users. This may be attributable to random variation due to estimation based on a small number of cases. In addition, it is difficult to compare our time-varying estrogen plus progestin FMH results with previous studies without knowing which types (sequential vs. continuous) were being used by our current and former users after baseline.

Our data suggest that women who used progestin-only FMH were at increased risk of endometrial cancer. Progestin-only FMH are a standard treatment for endometrial hyperplasia (33). Lacey and colleagues found that, accounting for treatment, women seeking biopsy and diagnosed with any type of endometrial hyperplasia had four times the risk of endometrial cancer compared with those diagnosed with disordered proliferative endometrium, with RR ranging from 2.0 to 14.2 depending on presence of atypia (34). Women with atypical hyperplasia remained at substantially increased risk after 5 years. Although we lack data on this condition, our results are consistent with progestin-only FMH use being a marker for endometrial hyperplasia and thus the association with endometrial cancer may be due to confounding by indication.

Obesity has been reported to modify the associations of endometrial cancer with both oral contraceptives and FMH. Oral contraceptives have been found to be less protective in obese women (10, 35) although a large meta-analysis reported no modification (32). The positive association between estrogen-only FMH and endometrial cancer has likewise been reported reduced in obese women (16, 17, 20), while the inverse association with estrogen plus progestin FMH has been reported to be strongest among obese women (15, 16, 23). Obesity could alter the association of endometrial cancer with exogenous hormones because of differences in volume of distribution or pharmacokinetics (36). It has also been suggested that there is a threshold above which increased concentrations of estrogen do not further increase the growth of endometrial tissue (2), which could reduce the impact of exogenous estrogens in obese women. Our results were consistent with a reduction of the protective effect of oral contraceptives in obese women and a protective effect of estrogen plus progestin FMH restricted to obese women. The strength of association between current use of estrogen only FMH and endometrial cancer was similar among obese and non-obese women.

We did not find compelling evidence for differences of associations of histologic subtypes of endometrial cancer with exogenous hormone use. The small numbers of cancers not classified as type I in our study limited our power to detect any potential differences in these associations, and combining these types may not be appropriate. Recent studies of risk factors for histologic subtypes have found little evidence of differences in associations with OC use between type I and II tumors (37) or FMH with type I, or II cancers (38).

Our study had a number of strengths. We analyzed data from a large prospective cohort study of self-identified black women. To the best of our knowledge, this is the first report of the association between FMH use and endometrial cancer incidence specifically in black women. We controlled for a large

number of potential confounders, including anthropometric and reproductive factors.

There were several notable limitations. Foremost among them were the low prevalence of FMH use among women with an intact uterus and the high prevalence of short duration OC use, which resulted in limited power. Our OC analysis did not take into account changes that have occurred in these formulations over time. Hormone dosages have decreased over time, and a sequential formula which was associated with increased risk of endometrial cancer was used until 1979. However, prior studies have not found a large influence of dose on the overall effect of OC use and endometrial cancer (10, 13). Of greater concern are the limited data on the type of estrogen plus progestin FMH that were used. If sequential and continuous formulations had differing associations with endometrial cancer, it is likely to have attenuated our results to a degree which would depend on the mixture of sequential and continuous use in our study.

Our data are based on self-report. Thus, we would expect some degree of misclassification of exposure. As our data were collected prospectively, misclassification was most likely random. In the case of dichotomous exposures and in the extreme categories of polytomous categorical variables, we expect an attenuation of our results. We also included unconfirmed cases in our analysis, which may have resulted in misclassification of outcome. The inclusion of conditions whose associations with the exposures in this study differ from those of endometrial cancer in the case group could result in a differential bias whose direction would depend on the nature of those differences. However, estimated associations were generally similar to the results presented when we restricted analysis to confirmed cases. BWHS participants may differ from the U.S. black population as a whole in ways that could influence our results. This could limit generalizability of our findings to all black women.

We found that associations between use of exogenous hormones and endometrial cancer in black women are generally similar to what has been reported previously in white women. However, due to the low prevalence of FMH use and lack of data on the pattern of progestin use in estrogen plus progestin FMH users in our study, our finding on FMH use and endometrial cancer require confirmation in other studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T.R. Sponholtz, L.A. Wise
Development of methodology: L.A. Wise
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.R. Palmer, L.A. Rosenberg
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.R. Sponholtz, J.R. Palmer, E.E. Hatch, A.-C. Lucile, L.A. Wise
Writing, review, and/or revision of the manuscript: T.R. Sponholtz, J.R. Palmer, L.A. Rosenberg, E.E. Hatch, A.-C. Lucile, L.A. Wise
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.A. Wise
Study supervision: E.E. Hatch, L.A. Wise

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