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Original Contribution

Associations of Premenopausal Hysterectomy and Oophorectomy With Breast Cancer Among Black and White Women: The Carolina Breast Cancer Study, 1993–2001

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Black women experience higher rates of hysterectomy than other women in the United States. Although research indicates that premenopausal hysterectomy with bilateral oophorectomy decreases the risk of breast cancer in black women, it remains unclear how hysterectomy without ovary removal affects risk, whether menopausal hormone therapy use attenuates inverse associations, and whether associations vary by cancer subtype. In the population-based, case-control Carolina Breast Cancer Study of invasive breast cancer in 1,391 black (725 cases, 666 controls) and 1,727 white (939 cases, 788 controls) women in North Carolina (1993–2001), we investigated the associations of premenopausal hysterectomy and oophorectomy with breast cancer risk. Compared with no history of premenopausal surgery, bilateral oophorectomy and hysterectomy without oophorectomy were associated with lower odds of breast cancer (for bilateral oophorectomy, multivariable-adjusted odds ratios = 0.60, 95% confidence interval: 0.47, 0.77; for hysterectomy without oophorectomy, multivariable-adjusted odds ratios = 0.68, 95% confidence interval: 0.55, 0.84). Estimates did not vary by race and were similar for hormone receptor–positive and hormone receptor–negative cancers. Use of estrogen-only menopausal hormone therapy did not attenuate the associations. Premenopausal hysterectomy, even without ovary removal, may reduce the long-term risk of hormone receptor–positive and hormone receptor–negative breast cancers. Varying rates of hysterectomy are a potentially important contributor to differences in breast cancer incidence among racial/ethnic groups.

African Americans; breast cancer; case-control studies; gynecologic surgical procedures; hysterectomy; minority health and health disparities; oophorectomy; postmenopausal hormone replacement therapy

Abbreviations: CI, confidence interval; ER+, estrogen receptor–positive; ER−, estrogen receptor–negative; HR+, hormone receptor–positive; HR−, hormone receptor–negative; MHT, menopausal hormone therapy; PR+, progesterone receptor–positive; PR−, progesterone receptor–negative.

Compared with other racial/ethnic groups, black women experience higher rates of hysterectomy, or surgical removal of the uterus, particularly at younger ages (1–3). In 2004–2005, a woman's cumulative risk of hysterectomy by age 44 years was 18% (4). No nationally representative data have been published for black women in the United States, but results from studies have suggested that prevalence among black women is much greater than among white women (66%–250% greater) (1, 3).

Hysterectomy is most commonly performed to treat noncancerous conditions such as fibroids, excessive uterine bleeding, or endometriosis (5). Approximately half of hysterectomies also involve bilateral oophorectomy, or removal of both ovaries (6). Premenopausal hysterectomy with concomitant oophorectomy is associated with higher risks of stroke and higher all-cause mortality rates (7, 8). However, the surgeries may also have unintended protective effects: In some studies, premenopausal hysterectomy with oophorectomy was associated with a decreased breast cancer risk (9–11) and lower breast cancer–specific mortality rates (8, 12). Therefore, disproportionately high hysterectomy rates may be an important contributor to patterns of breast cancer incidence in black women.

Between 2002 and 2010, inpatient hysterectomy rates decreased in the United States, with estimates of the decrease as high as 40% (13, 14). Rapid declines in the use of a clinical exposure may primarily affect groups in whom prevalence was historically greatest, as demonstrated by the decline in menopausal hormone therapy use after publication of the Women's Health Initiative study results (15). Because of historically high rates of hysterectomy among black women, declining rates of surgical menopause may have the unintended consequence of disproportionately increasing the incidence of breast cancer among black women (9).

Unfortunately, the magnitude of surgery effects on cancer risk remains unclear, as do racial differences in these effects. For instance, although inverse associations between hysterectomy without oophorectomy and breast cancer risk have been reported in some studies (11, 16, 17), no association was found in others (9, 18). In addition, there have been few studies (19) in which the important clinical question of whether use of menopausal hormone therapy (MHT) might mitigate any protective effects of premenopausal surgery on breast cancer risk has been investigated. Likewise, it is important to investigate whether surgery differentially affects risks of hormone receptor–positive (HR+) and hormone receptor–negative (HR−) cancers. Racial differences in these cancer subtypes are important drivers of inequalities in rates of mortality due to breast cancer (20). Finally, these relationships have been studied among black women in few studies (8, 10).

In the present study, our objective was to assess the association between premenopausal gynecologic surgeries and risk of breast cancer in a population-representative sample of black and white women living in the US South, a region in which hysterectomy rates are particularly high (1, 13, 21). We examined whether associations differed by race, breast cancer hormone-receptor status, or use of MHT.

METHODS

Study population

The Carolina Breast Cancer Study (CBCS) is a population-based, case-control study of breast cancer (22). The study was conducted in 2 phases (1993–1996 and 1996–2001). Study procedures were similar in both phases, but phase 2 included cases of in situ cancer in addition to invasive cancer. The present analysis was restricted to invasive cancer cases. Women were eligible to participate as case patients if they had an incident diagnosis of breast cancer recorded in the North Carolina Cancer Registry between the ages of 20 and 74 years during the period between 1993 and 2000 and were living in a 24-county area of central and eastern North Carolina (22). Using randomized recruitment, black case patients and young case patients (20–49 years of age) were oversampled according to predetermined sampling probabilities (22, 23). For instance, researchers recruited 100% of black case patients younger than 50 years of age but only 20% of nonblack cancer case patients who were 50 years of age or older (22).

Control patients with no history of breast cancer were selected from the same geographic area as cases. We used records from the North Carolina Division of Motor Vehicles to identify women younger than 65 years of age and from the US Health Care Financing Administration, which oversees Medicare, to identify control women 65–74 years of age. Controls were sampled to ensure approximate frequency-matching to cases by race and 5-year age group (23, 24).

Exclusions

The following were excluded from analyses: women who were unsure about whether they had undergone a premenopausal surgery or what organs were removed (for black women, $n = 15$; for white women, $n = 9$); women who stopped menstruating because of chemotherapy or radiation (for black women, $n = 9$; for white women, $n = 18$); and women who reported a premenopausal hysterectomy and use of progestin-estrogen combination MHT (for black women, $n = 5$; for white women, $n = 4$). For women without a uterus, estrogen-only MHT rather than combination therapy is indicated. The progesterone in combination therapy, which opposes the endometrial proliferative effects of estrogen, is unnecessary after hysterectomy because the risk of endometrial cancer is minimal. Therefore, women who had the co-exposure of hysterectomy and MHT combination therapy were rare, and it was not feasible to study this group. Thus, 759 black case patients and 964 white case patients were eligible to be included in the present analyses. In multivariable models, women with missing values for covariates were dropped from the model (34 black cases and 25 white cases). Therefore, the sample size for cases in the main multivariable-adjusted model was 725 black and 939 white women.

Like cases, controls were excluded from this analysis if they were unsure about whether they had undergone a premenopausal surgery or what organs were removed (for black women, $n = 9$; for white women, $n = 6$); if they had stopped menstruating because of chemotherapy or radiation (for black women, $n = 3$; for white women, $n = 2$); or if they reported a premenopausal hysterectomy and use of progestin-estrogen combination MHT (for black women, $n = 2$; for white women, $n = 2$). Thus, 704 black control women and 808 white control women were eligible to be included in the present analysis. In multivariable-adjusted models, controls with missing values for covariates were dropped from the model (38 black controls and 20 white controls). Therefore, the sample size for controls in the main multivariable-adjusted model was 666 black and 788 white women.

Data collection

Participants were interviewed in person by trained nurses using a pretested, standardized questionnaire. For 94.9% of cases (94.5% black, 95.2% white), interviews occurred within 1 year of the diagnosis date. The interview collected self-reported reproductive and menstrual histories and information on hormone therapy use, family history of cancer, alcohol consumption, occupational exposures, and sociodemographic characteristics, among other possible risk factors for breast cancer. The study was approved by the institutional review board of the University of North Carolina at Chapel Hill.

Table 1. Characteristics of Control Patients[a] by Premenopausal Gynecologic Surgery Status, Carolina Breast Cancer Study Phases 1 and 2, 1993–2001

Characteristic	All (n = 1,512)		No Surgery (n = 1,026)		Bilateral Oophorectomy (n = 190)		Hysterectomy[b] (n = 326)	
	No.	Weighted %	No.	Weighted %	No.	Weighted %	No.	Weighted %
Age, years								
20–39	192	42.7	177	52.0	5	10.1	10	11.8
40–44	240	13.5	193	14.2	17	12.2	30	10.2
45–49	332	12.1	226	11.0	37	16.3	69	15.6
50–54	164	9.6	95	7.3	29	18.3	40	17.0
55–59	159	7.4	71	4.3	31	14.0	57	19.8
60–74	425	14.8	234	11.2	71	29.0	120	25.6
Race								
Black	704	20.7	438	20.0	104	25.7	162	21.7
White	808	79.3	558	80.0	86	74.3	164	78.3
Menopausal status								
Premenopausal	701	64.5	592	76.3	0	0.0	109	37.6
Postmenopausal	811	35.5	404	23.7	190	100	217	62.4
Family history breast cancer[c]								
No	1,294	82.2	857	80.4	164	90.3	273	86.9
Yes	173	17.8	109	19.6	20	9.7	44	13.1
Missing	45		30		6		9	
Educational level[c]								
Some high school or less	279	10.0	155	8.0	48	17.9	76	16.5
High school graduate or some college	842	60.1	527	58.1	116	64.6	199	68.0
College graduate or higher	390	29.8	313	33.9	26	17.5	51	15.5
Missing	1		1		0		0	
Lifetime alcohol consumption[c]								
<12 drinks	487	25.7	285	21.7	83	42.9	119	37.7
≥12 drinks	1,024	74.3	711	78.3	107	57.1	206	62.3
Missing	1		0		0		1	
Smoking history								
Current	318	20.9	206	20.8	49	26.8	63	18.0
Former	381	31.4	246	33.1	48	24.3	87	25.9
Never	813	47.8	544	46.0	93	49.0	176	56.1
Age at menarche, years[c]								
≤11	292	17.3	191	17.5	40	17.5	61	15.9
12–13	811	52.4	545	50.7	100	59.5	166	57.7
>13	401	30.3	256	31.8	48	23.0	97	26.4
Missing	8		4		2		2	
No. of full-term pregnancies								
0	169	22.8	128	27.8	17	7.3	24	5.4
1–2	756	49.8	514	49.5	90	57.4	152	47.2
≥3	587	27.4	354	22.8	83	35.3	150	47.3

Table continues

Exposure variables

In the present analysis, we examined history of premenopausal hysterectomy and oophorectomy. Case and control women were asked a series of questions to determine menopausal status. First, women were asked if they were "still having menstrual periods." If a woman had stopped menstruating before the diagnosis date or reference date, she was asked

Table 1. Continued

Characteristic	All (n = 1,512)		No Surgery (n = 1,026)		Bilateral Oophorectomy (n = 190)		Hysterectomy[b] (n = 326)	
	No.	Weighted %	No.	Weighted %	No.	Weighted %	No.	Weighted %
Age of first full-term pregnancy, years[c]								
Nulliparous	169	22.8	128	27.8	17	7.3	24	5.4
≤24	959	50.3	568	43.2	143	72.8	248	74.9
25–29	249	18.1	182	18.6	24	18.1	43	15.2
≥30	132	8.8	115	10.4	6	1.9	11	4.4
Missing	3		3		0		0	
Breast feeding								
Nulliparous	169	22.8	128	27.8	17	7.3	24	5.4
Parous, never	757	41.9	471	36.5	105	58.1	181	60.8
Parous, ever	586	35.3	397	35.7	68	34.6	121	33.8
Age at menstrual cessation, years[c,d]								
Premenopausal or on MHT	609	60.6	609	78.5	0	0.0	0	0.0
≤39	270	13.7	35	3.3	86	51.7	149	47.6
40–44	177	7.5	56	3.2	41	18.8	80	24.0
45–49	234	10.0	134	7.5	40	19.6	60	18.4
50–54	160	6.5	120	6.2	15	7.2	25	7.9
55–59	44	1.5	29	1.4	6	2.1	9	1.7
60–74	3	0.1	0	0.0	1	0.6	2	0.4
Missing	15		13		1		1	
Hormone replacement therapy use								
Ever	467	23.0	175	12.2	148	85.0	144	46.1
Never	1,045	77.0	821	87.8	42	15.0	182	53.9
Duration of MHT use, years[c]								
Never	1,045	77.1	821	87.8	42	15.0	182	54.2
<5	241	11.8	121	8.6	56	32.9	64	17.2
5–10	103	5.4	34	2.3	33	20.8	36	13.6
>10	121	5.8	20	1.4	59	31.3	42	15.1
Missing	2		0		0		2	
MHT type								
None MHT	1,045	77.0	821	87.8	42	15.0	182	53.9
Unopposed estrogen only	300	13.6	41	2.1	123	69.5	136	43.7
Progestin-estrogen combination	90	5.2	90	6.8	0	0.0	0	0.0
Progestin sometimes with estrogen	49	2.6	25	1.9	20	11.8	4	1.6
Progestin only	22	1.2	18	1.4	1	0.3	3	0.5
Estrogen and progestin never simultaneously	6	0.4	1	0.1	4	3.4	1	0.4

Abbreviation: MHT, menopausal hormone therapy.
[a] Restricted to black and white women. We excluded women whose surgery status or specific surgery type was unknown. We also excluded women who reported premenopausal hysterectomy and use of progestin-estrogen combination therapy.
[b] Includes hysterectomies with ovarian conservation (76.4%) and those with unilateral oophorectomy (23.6%).
[c] Women for whom data were missing were not included in the denominator.
[d] Based on menstrual cessation due to gynecologic surgery or menopause.

whether her periods had stopped "by themselves because of menopause (change of life)"; "because of an operation (removal of uterus or ovaries)"; "because of chemotherapy or radiation treatment"; or for "some other reason." Women who were still menstruating were asked whether they were taking "female hormones other than birth control pills." Self-reported hysterectomy has a high positive-predictive value (25, 26). In contrast, among women treated with bilateral oophorectomy and hysterectomy, many (36% in 1 validation study (26)) failed to report that both ovaries were also removed during surgery. In the present analysis, 4 categories of premenopausal surgery were examined: no premenopausal surgery; bilateral oophorectomy, most of which were accompanied by hysterectomy; hysterectomy with unilateral oophorectomy; and hysterectomy only, with ovaries left intact.

Statistical analysis and covariates

Univariate distributions of characteristics among controls were calculated using sampling weights. The sampling weights, defined as the inverse of the controls' sampling probabilities, allowed us to estimate prevalences in the source population from which the sample was drawn (22, 23). For instance, breast cancer is much more common among older women. Therefore, selecting controls to produce an age distribution similar to that among cases can result in a control series that is older than the general population. Incorporating weights accounts for the sampling design.

Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals for the associations between premenopausal gynecologic surgery and the risk of invasive breast cancer. To enable inference to the source population, offset terms were incorporated into each regression model. Offset terms were defined for each race-age group as the natural log of the ratio of the sampling probability of cases from that race-age group to the sampling probability of controls from that same race-age group. Incorporating these offset terms into the model accounted for the study's oversampling of black and young case patients and selection of control patients to reflect the distribution of race and age among the case patients (23). All analyses were tested for racial differences using a Wald interaction test with a liberal cutpoint of 0.20 to compensate for the low statistical power of tests for modification (27, 28).

All models were adjusted for race (unless stratified by race) and the age (in years) at which women were selected into the study modeled as a continuous variable and a quadratic term (29, 30). The quadratic term was statistically significant ($P \leq 0.05$) in preliminary analyses. Multivariable-adjusted models also included the following variables, which were identified a priori as potential confounders based on the fact that they are known risk factors for breast cancer that might may also be related to the probability of hysterectomy: educational level (some high school or less, high school graduate, or college graduate), first-degree family history of breast cancer (yes or no), age at menarche (≤11, 12–13, or >13 years), lactation history (had breastfed vs. never breastfed), a composite of parity and age at first full-term pregnancy (nulliparous; 1 child and age ≤25 years; 1 child and age >25 years; ≥2 children and age ≤25 years; and ≥2 children and age >25 years), smoking history (current, former, or never), and alcohol intake of at least 12 drinks in one's lifetime (yes or no). We did not adjust for menopausal status at the time of selection into the study. Accelerating the timing of menopause is a key mechanism by which surgery may affect breast cancer risk; therefore, menopausal status is an intermediary on the hypothesized causal pathway.

Two sets of secondary analyses were conducted. First, we examined joint associations of surgery and MHT with breast cancer risk by creating a 7-level composite variable. This variable defined combinations of surgery (no surgery, hysterectomy without oophorectomy, or oophorectomy) with use of MHT (no MHT, progestin-estrogen combination therapy, or estrogen only). As described above, surgery-MHT combinations involving progestin-estrogen therapy and hysterectomy (with or without oophorectomy) were excluded from analysis. Second, we investigated risks of HR+ cancers (estrogen receptor–positive (ER+) or progesterone receptor–positive (PR+) cancers) and HR− cancers (estrogen receptor–negative (ER−) and progesterone receptor–negative (PR−) cancers).

RESULTS

Descriptive characteristics

Using control data, we calculated weighted percentages for the population-representative distributions of selected characteristics (Table 1). Black control women appeared more likely to have had premenopausal surgeries, especially those involving bilateral oophorectomy; they represented 20.7% of the control population but 25.7% of those with a history of bilateral oophorectomy. Childbearing history was associated with premenopausal surgery: The prevalence of surgery was lower among nulliparous women, whereas women with 3 or more children or those who had their first full-term pregnancy before age 25 years were more likely to have had surgery. Women who had premenopausal surgeries were more likely to have used MHT than were women who did not have surgery (85.0% of women with bilateral oophorectomies and 46.1% of women with hysterectomies without oophorectomy versus 12.2% of women who did not undergo surgery). The majority of MHT users with surgeries used unopposed estrogen, whereas the majority of women with no surgery history used a combination of progestin and estrogen. Appendix Table 1 presents characteristics by race and case-control status.

Overall breast cancer

Premenopausal gynecologic surgery was associated with reduced odds of invasive breast cancer (Table 2). Odds ratio estimates did not vary by black/white race (Wald test for interaction, $P = 0.60$). Overall, the multivariable-adjusted odds ratios were similar for hysterectomies involving bilateral oophorectomy, unilateral oophorectomy, or conservation of both ovaries: The multivariable-adjusted odds ratios were 0.60 (95% confidence interval (CI): 0.47, 0.77), 0.74 (95% CI: 0.53, 1.03), and 0.68 (95% CI: 0.55, 0.84), respectively.

Stratification by estrogen- and progesterone-receptor status

Associations were also similar after stratification by hormone-receptor status (Table 3). For instance, the multivariable-adjusted odds ratio for the association of bilateral oophorectomy with ER+ or PR+ cancers was 0.58; the adjusted odds ratio for ER− and PR− cancers was 0.60. For hysterectomy without oophorectomy, the corresponding adjusted

Table 2. History of Gynecologic Surgery and Invasive Breast Cancer Among Study Participants, Carolina Breast Cancer Study, 1993–2001

Gynecologic Surgery	Overall[a]				Black Women				White Women			
	No. of Cases (n = 1,664)	No. of Controls (n = 1,454)	Multivariable Adjusted[b]		No. of Cases (n = 725)	No. of Controls (n = 666)	Multivariable Adjusted[b]		No. of Cases (n = 939)	No. of Controls (n = 788)	Multivariable Adjusted[b]	
			OR	95% CI			OR	95% CI			OR	95% CI
No surgery	1,236	958	1.00	Referent	505	412	1.00	Referent	731	546	1.00	Referent
Hysterectomy only	207	234	0.68	0.55, 0.84	95	113	0.65	0.48, 0.90	112	121	0.72	0.54, 0.97
Hysterectomy/ unilateral oophorectomy	77	80	0.74	0.53, 1.03	46	41	0.90	0.57, 1.42	31	39	0.59	0.36, 0.98
Bilateral oophorectomy	144	182	0.60	0.47, 0.77	79	100	0.60	0.42, 0.84	65	82	0.62	0.44, 0.89

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Wald test for interaction between race and gynecologic surgery: $P = 0.6$.

[b] Adjusted for age, squared age, race (when appropriate), family history of breast cancer, alcohol consumption, age at menarche, parity and age at first pregnancy composite, lactation history (ever vs. never breastfed), educational level, and smoking. Complete-case analysis was restricted to those with nonmissing values for these covariates.

odds ratios were 0.69 and 0.68, respectively. Tests for interaction by black/white race were not significant (for ER+ and PR+ cancers, Wald $P = 0.7$; for ER− and PR− cancers, Wald $P = 0.9$).

Joint associations with MHT

Table 4 lists joint associations for surgeries and hormone therapy use. Again, results did not vary significantly by race.

Table 3. History of Gynecologic Surgery and Invasive Breast Cancer by Subtype Among Study Participants, Carolina Breast Cancer Study, 1993–2001

Cancer Subtype and Gynecologic Surgery	Overall[a]				Black Women				White Women			
	No. of Cases	No. of Controls	Multivariable Adjusted[b]		No. Cases	No. Controls	Multivariable Adjusted[b]		No. Cases	No. Controls	Multivariable Adjusted[b]	
			OR	95% CI			OR	95% CI			OR	95% CI
Hormone receptor–positive cancer												
Total	1,005	1,454			370	666			635	788		
No surgery	743	958	1.00	Referent	255	412	1.00	Referent	488	546	1.00	Referent
Hysterectomy only	129	234	0.69	0.54, 0.88	50	113	0.63	0.42, 0.93	79	121	0.74	0.53, 1.02
Hysterectomy/ unilateral oophorectomy	47	80	0.71	0.48, 1.04	23	41	0.78	0.44, 1.38	24	39	0.66	0.38, 1.13
Bilateral oophorectomy	86	182	0.58	0.43, 0.77	42	100	0.57	0.38, 0.86	44	82	0.61	0.41, 0.90
Hormone receptor–negative cancer												
Total	540	1,454			302	666			238	788		
No surgery	407	958	1.00	Referent	216	412	1.00	Referent	191	546	1.00	Referent
Hysterectomy only	64	234	0.68	0.50, 0.94	38	113	0.68	0.44, 1.05	26	121	0.70	0.43, 1.14
Hysterectomy/ unilateral oophorectomy	24	80	0.74	0.45, 1.22	18	41	0.90	0.49, 1.64	6	39	0.51	0.20, 1.25
Bilateral oophorectomy	45	182	0.60	0.42, 0.87	30	100	0.61	0.38, 0.98	15	82	0.60	0.33, 1.10

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Wald test for interaction between race and gynecologic surgery: for estrogen receptor–positive and progesterone receptor–positive cancer, $P = 0.7$; for estrogen receptor–negative or progesterone receptor–negative cancer, $P = 0.9$.

[b] Adjusted for age, squared age, race (when appropriate), family history of breast cancer, alcohol consumption, age at menarche, parity and age at first pregnancy composite, lactation history (ever vs. never breastfed), educational level, and smoking. Complete-case analysis was restricted to those with nonmissing values for these covariates.

Table 4. History of Gynecologic Surgery With Hormone Therapy Use and Invasive Breast Cancer Among Study Participants, Carolina Breast Cancer Study, 1993–2001

Gynecologic Surgery and Hormone Therapy Use	Overall[a]				Black Women				White Women			
	No. of Cases (n = 1,581)	No. of Controls (n = 1,384)	Multivariable Adjusted[b]		No. of Cases (n = 714)	No. of Controls (n = 649)	Multivariable Adjusted[b]		No. of Cases (n = 867)	No. of Controls (n = 735)	Multivariable Adjusted[b]	
			OR	95% CI			OR	95% CI			OR	95% CI
No surgery												
No MHT	1,008	788	1.00	Referent	457	371	1.00	Referent	551	417	1.00	Referent
Estrogen-only MHT	39	41	0.80	0.50, 1.27	16	19	0.63	0.32, 1.27	23	22	0.93	0.50, 1.74
Progestin-estrogen MHT	129	88	1.17	0.86, 1.60	25	14	1.14	0.57, 2.29	104	74	1.12	0.79, 1.59
Hysterectomy only[c]												
No MHT	177	173	0.78	0.61, 0.99	108	105	0.79	0.58, 1.09	69	68	0.79	0.54, 1.14
Estrogen-only MHT	97	135	0.56	0.42, 0.75	32	48	0.48	0.29, 0.78	65	87	0.59	0.41, 0.86
Bilateral oophorectomy[c]												
No MHT	30	37	0.61	0.36, 1.01	25	28	0.66	0.37, 1.18	5	9	0.48	0.16, 1.48
Estrogen-only MHT	101	122	0.63	0.47, 0.84	51	64	0.58	0.38, 0.87	50	58	0.68	0.45, 1.03

Abbreviations: CI, confidence interval; MHT, menopausal hormone therapy; OR, odds ratio.

[a] Wald test for interaction between race and gynecologic surgery with MHT: $P = 0.8$.

[b] Adjusted for age, squared age, race (when appropriate), family history of breast cancer, alcohol consumption, age at menarche, parity and age at first pregnancy composite, lactation history (ever vs. never breastfed), educational level, and smoking. Complete-case analysis was restricted to those with nonmissing values for these covariates.

[c] Those who reported using progestin-estrogen MHT were excluded because of the small sample size.

Pronounced inverse associations were observed for surgery with and without use of estrogen-only MHT. The multivariable-adjusted odds ratios for hysterectomy only and bilateral oophorectomy with estrogen-only MHT were 0.56 (95% CI: 0.42, 0.75) and 0.63 (95% CI: 0.47, 0.84), respectively. There was also the suggestion of an inverse association among those women who reported bilateral oophorectomy without MHT (odds ratio = 0.61, 95% CI: 0.36, 1.01). There was a less pronounced inverse association among those women who reported hysterectomy only with no MHT use (odds ratio = 0.78, 95% CI: 0.61, 0.99). In contrast, combination progestin-estrogen MHT in the absence of surgery showed a weakly elevated association with breast cancer risk (odds ratio = 1.17, 95% CI: 0.86, 1.60). The remaining group, estrogen-only MHT use in the absence of surgery, had relatively imprecise estimates and there was no strong association with cancer risk.

Stratifying by HR+ versus HR− cancers did not substantially alter the joint associations of surgery and MHT (data not shown). For both HR+ and HR− cancers, inverse associations were observed for 1) hysterectomy only with estrogen-only MHT use and 2) bilateral oophorectomy with estrogen-only MHT use. Moreover, as with overall cancer, although results were relatively imprecise, hysterectomy-only with no MHT use and bilateral oophorectomy with no MHT use showed suggestions of inverse associations with both HR+ and HR− cancers.

DISCUSSION

In a population-representative sample of women from North Carolina with high rates of premenopausal surgery, we found inverse associations between premenopausal gynecologic surgery and the risk of breast cancer. These associations were similar for both black and white women. Additionally, we found no evidence that use of estrogen-only MHT attenuated these inverse associations. Finally, in our sample, the protective associations appeared to be of similar magnitude for HR+ and HR− breast cancers.

It is especially important to investigate this question among black women because their premenopausal hysterectomy rates have historically been high (1–3). In the only study besides ours in which whites and blacks were compared, investigators observed that black women experienced a 35% greater prevalence of hysterectomy without oophorectomy (44.6% vs. 33.4%) and a 20% greater prevalence of bilateral oophorectomy (23.8% vs. 19.8%) than did white women (11). Further, among control women in our study who had ceased menstruating, nearly half (47%) of nonmenstruating black women had ceased menstruating before 40 years of age versus only one-third (31%) of white women. This low age at menstrual cessation reflects the high rates of premenopausal gynecologic surgery among black women in the US South (1). For instance, the prevalence of premenopausal hysterectomy among women aged 21–69 years in the Black Women's Health Study in 1995 was 20.5% (9). The prevalence among black women in our sample was greater (25.3%).

In the United States, the relatively high rates of hysterectomy among black women are partially due to the greater prevalence and severity of uterine fibroids, the most common indication for hysterectomy (5). Also, most black women live in the South (31), where hysterectomy rates are up to 2.5 times as common as in other parts of the United States (1). However, racial disparities persist even when controlling for fibroids prevalence, geography, and other hysterectomy risk factors (1, 3).

Additionally, this research is of importance because gynecologic surgery rates are decreasing (32). The historically greater prevalence of premenopausal gynecologic surgeries among US black women may have contributed to the historically lower overall incidence of breast cancer in this population. Therefore, the decline in the rate of premenopausal gynecologic surgeries (13) may be a novel contributor to rising rates of breast cancer among black women. In 2012, the incidence of invasive breast cancer converged for US black and white women (132.2 and 131.9 per 100,000 women, respectively) as the incidence declined among white women and rose among black women (33). Rising breast cancer incidence among black women could contribute to widening racial disparities in breast cancer mortality rates (34).

Our study is one of the first in which researchers examined how specific formulations of MHT may interact with gynecologic surgery to influence breast cancer risk. In most previous studies of the associations of hysterectomy and oophorectomy with breast cancer risk, investigators adjusted for hormone therapy use without specifically examining the joint effects (9, 11, 16, 17, 35). In a study in which MHT use was examined, Nichols et al. (19) found that use of unopposed estrogen after 45 years of age somewhat attenuated the protective effects of premenopausal oophorectomy on postmenopausal breast cancer. Our results may differ from those of Nichols et al. because in our population, the majority of premenopausal oophorectomies were performed before age 40 years, and estrogen use likely commenced before age 45 years.

Another unique aspect of our analyses was the evaluation of the effects of surgery on risks of different breast cancer subtypes. We found no evidence that bilateral oophorectomy or hysterectomy without oophorectomy affected risk of breast cancer differentially by hormone-receptor status. In 1 other study, investigators also found no differences in the associations of surgery with ER+/PR+ versus ER−/PR− breast cancers (35). However, our results differ from findings from the Black Women's Health Study and the Women's Contraceptive and Reproductive Experiences (Women's CARE) case-control study (9, 11). Results from these studies indicated that premenopausal bilateral oophorectomy was more strongly associated with a decreased risk of ER+/PR+ cancers versus ER−/PR− cancers. In the Black Women's Health Study, the multivariable-adjusted hazard ratios for bilateral oophorectomy in women younger than 40 years of age were 0.67 (95% CI: 0.39, 1.15) for ER+ breast cancer and 1.00 (95% CI: 0.53, 1.15) for ER− breast cancer (9). In the Women's Contraceptive and Reproductive Experiences Study, investigators found a multivariable-adjusted odds ratio for bilateral oophorectomy and ER+/PR+ breast cancer of 0.55 (95% CI: 0.45, 0.68) versus a suggestively protective odds ratio of 0.82 (95% CI: 0.63, 1.07) for ER−/PR− breast cancer (11).

A surprising finding was the inverse association of breast cancer risk with hysterectomy only and no MHT use. Hysterectomy without oophorectomy among younger women (i.e., <45 years of age) has been associated with a decreased breast cancer risk in some studies (11, 16, 17), whereas there was no association in others (9, 18). Although the inverse association we observed could be attributable to exposure misclassification bias (the hysterectomy–no MHT subgroup may include women who inaccurately reported hysterectomy only instead of hysterectomy with bilateral oophorectomy (26)), there is biological evidence that suggests that hysterectomy without oophorectomy may alter breast cancer risk. Studies have demonstrated earlier ovarian failure among premenopausal women who have hysterectomy without oophorectomy (5), possibly because of altered circulatory functioning in conserved ovaries after hysterectomy.

The present study was limited by several factors. As discussed above, exposure assessment relied on self-reported data, which may have biased the hysterectomy-only results downward. Additionally, we did not have information on clinical indication for the surgery, which is a potential confounder. However, previous research has suggested that indication is not a cause of appreciable confounding bias when examining the association between premenopausal surgery and breast cancer risk (10). Finally, our analysis of cancer subtypes resulted in some imprecise estimates, and we did not examine the full intrinsic subtype profile. Surgery may be more strongly associated with etiologic intrinsic subtypes than hormone receptor status. A larger study is needed to evaluate relationships for more finely resolved etiologic subtypes.

This work has unique strengths. With our population-based sample of white and black women, we had the unique ability to examine how racial differences in hysterectomy rates may affect racial inequalities in breast cancer risk. Additionally, because the Carolina Breast Cancer Study is conducted in the US South, the region in which the majority (55%) of black Americans live (31) and in which hysterectomy rates are the highest (36), we were able to make inferences to a target population highly affected by the exposure. Moreover, in this analysis, we comprehensively studied gynecologic premenopausal surgery and breast cancer risk, stratifying by type of surgery and use of MHT and examining associations by cancer subtypes. Another major strength is that the population-based design allowed us to better document the racial differences in surgery rates, including the higher prevalence of premenopausal bilateral oophorectomy among black women in this population. Finally, the CBCS Study used a rapid case ascertainment system to contact and interview 95% of breast cancer case patients within 12 months of diagnosis, limiting potential selection bias from differential mortality rates from those with and without gynecologic surgery.

In summary, this research adds further evidence that premenopausal hysterectomy and oophorectomy may reduce the long-term risk of breast cancer. Further, the higher prevalence of premenopausal surgery among black women indicates that these surgeries could be an important contributor to race-specific trends in breast cancer incidence. Historically higher rates of premenopausal hysterectomy and oophorectomy may have transiently lowered breast cancer rates among black women. As hysterectomy rates decline, breast cancer incidence may increase among older black women and in the US South, a trend that has been observed in recent surveillance (34, 37). Monitoring the long-term effects of changing clinical practice in gynecologic surgery may inform strategies to mitigate the growing breast cancer burden among US black women.

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(Appendix follows)

Appendix Table 1. Characteristics of Case and Control Patients by Race[a], Carolina Breast Cancer Study Phases 1 and 2, 1993–2001

Characteristic	Black Cases (*n* = 759)		White Cases (*n* = 964)		Black Controls (*n* = 704)		White Controls (*n* = 808)	
	No.	%[b]	No.	%[b]	No.	%[b]	No.	%[b]
Premenopausal surgery								
No surgery	528	69.6	748	77.6	438	62.2	558	69.1
Bilateral oophorectomy	84	11.1	68	7.1	104	14.8	86	10.6
Hysterectomy/unilateral oophorectomy	46	6.1	33	3.4	42	6.0	40	5.0
Hysterectomy only	101	13.3	115	11.9	120	17.0	124	15.3
Age, years								
20–39	130	17.1	151	15.7	102	14.5	90	11.1
40–44	105	13.8	166	17.2	107	15.2	133	16.5
45–49	143	18.8	231	24.0	153	21.7	179	22.2
50–54	83	10.9	83	8.6	76	10.8	88	10.9
55–59	88	11.6	84	8.7	81	11.5	78	9.7
60–74	210	27.7	249	25.8	185	26.3	240	29.7
Menopausal status								
Premenopausal	339	44.7	513	53.2	333	47.3	368	45.5
Postmenopausal	420	55.3	451	46.8	371	52.7	440	54.5
Family history of breast cancer								
No	616	84.2	774	82.3	597	88.6	697	87.9
Yes	116	15.8	167	17.7	77	11.4	96	12.1
Missing	27		23		30		15	
Educational level[c]								
Some high school or less	226	29.8	91	9.4	199	28.3	80	9.9
High school graduate or some college	401	52.8	526	54.6	377	53.6	465	57.5
College graduate or higher	132	17.4	347	36.0	127	18.1	263	32.5
Missing	0		0		1		0	
Lifetime alcohol consumption[c]								
<12 drinks	284	37.4	255	26.5	270	38.4	217	26.9
≥12 drinks	475	62.6	708	73.5	433	61.6	591	73.1
Missing	0		1		1		0	
Smoking history								
Current	165	21.7	211	21.9	145	20.6	173	21.4
Former	169	22.3	277	28.7	142	20.2	239	29.6
Never	425	56.0	476	49.4	417	59.2	396	49.0
Age at menarche, years[c]								
≤11	191	25.2	199	20.7	163	23.3	129	16.1
12–13	391	51.6	560	58.2	339	48.4	472	58.8
>13	176	23.2	204	21.2	199	28.4	202	25.2
Missing	1		1		3		5	
No. of full-term pregnancies								
0	109	14.4	152	15.8	78	11.1	91	11.3
1–2	293	38.6	544	56.4	299	42.5	457	56.6
≥3	357	47.0	268	27.8	327	46.4	260	32.2

Table continues

Appendix Table 1. Continued

Characteristic	Black Cases (n = 759)		White Cases (n = 964)		Black Controls (n = 704)		White Controls (n = 808)	
	No.	%[b]	No.	%[b]	No.	%[b]	No.	%[b]
Age at first full-term pregnancy, years[c]								
Nulliparous	109	14.5	152	15.8	78	11.1	91	11.3
≤24	520	69.1	479	49.7	503	71.8	456	56.4
25–29	78	10.4	211	21.9	72	10.3	177	21.9
≥30	46	6.1	122	12.7	48	6.8	84	10.4
Missing	6		0		3		0	
Breast feeding								
Nulliparous	109	14.4	152	15.8	78	11.1	91	11.3
Parous, never	431	56.8	432	44.8	377	53.6	380	47.0
Parous, ever	219	28.9	380	39.4	249	35.4	337	41.7
Age at menstrual cessation, years[c,d]								
Premenopausal or on MHT	286	38.2	450	46.9	272	39.1	337	42.0
≤39	133	17.8	104	10.8	150	21.6	120	15.0
40–44	79	10.6	100	10.4	80	11.5	97	12.1
45–49	114	15.2	160	16.7	99	14.2	135	16.8
50–54	101	13.5	117	12.2	71	10.2	89	11.1
55–59	30	4.0	25	2.6	22	3.2	22	2.7
60–74	5	0.7	4	0.4	1	0.1	2	0.2
Missing	11		4		9		6	
MHT use								
Ever	144	19.0	323	33.5	165	23.4	302	37.4
Never	615	81.0	641	66.5	539	76.6	506	62.6
Duration of MHT use, years[c]								
Never	615	81.2	641	66.9	539	76.7	506	62.7
<5	87	11.5	157	16.4	97	13.8	144	17.8
5–10	38	5.0	85	8.9	36	5.1	67	8.3
>10	17	2.2	75	7.8	31	4.4	90	11.2
Missing	2		6		1		1	
MHT type								
None	615	81.0	641	66.5	539	76.6	506	62.6
Unopposed estrogen only	104	13.7	145	15.0	131	18.6	169	20.9
Progestin-estrogen combination	28	3.7	106	11.0	15	2.1	75	9.3
Progestin sometimes with estrogen	7	0.9	41	4.3	10	1.4	39	4.8
Progestin only	4	0.5	21	2.2	9	1.3	13	1.6
Estrogen and progestin never simultaneously	1	0.1	10	1.0	0	0	6	0.7

Abbreviation: MHT, menopausal hormone therapy.

[a] Restricted to black and white women. We excluded women whose surgery status or specific surgery type was unknown. We also excluded women who reported premenopausal hysterectomy and use of progestin-estrogen combination therapy.

[b] Percentages are not weighted.

[c] Women for whom data were missing were not included in the denominator.

[d] Based on menstrual cessation due to gynecologic surgery or menopause.