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Premenopausal Gynecologic Surgery and Survival Among Black and White Women with Breast Cancer

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Abstract

Purpose—In the United States hysterectomies and oophorectomies are frequently performed before menopause for benign conditions. The procedures are associated with reduced breast cancer-specific mortality among White women. The relationship between premenopausal gynecologic surgery and mortality in Black women with breast cancer is unknown.

Methods—This investigation used incident invasive cases of breast cancer from Phases 1 and 2 of the Carolina Breast Cancer Study a population-based study that recruited Black and White women in North Carolina between 1993 and 2001. Premenopausal gynecologic surgery was operationalized in three categories: no surgery; hysterectomy with bilateral oophorectomy; hysterectomy with conservation of 1 ovary. Mortality was ascertained using the National Death Index, last updated in 2016. Multivariable-adjusted Cox Proportional Hazard Models were used to estimate the effect of premenopausal surgery on breast cancer-specific and all-cause mortality.

Results—Hysterectomy with bilateral oophorectomy was associated with reduced breast cancer-specific mortality (HR: 0.68; 95% CI: 0.49, 0.96). White and Black women had a similar reduction in breast cancer-specific mortality. (HR among white: 0.66; 95% CI: 0.43, 1.02), (HR among Black: 0.67; 95% CI: 0.37, 1.21).

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Conclusions—There was a similar reduction in breast cancer specific mortality following premenopausal, pre-diagnosis hysterectomy with bilateral oophorectomy across both Black and White women.

Keywords

Breast Cancer; Disparities; Hysterectomy; Oophorectomy; Survival Analysis

Introduction

Breast cancer survivors represent a growing segment of the population, with over 3 million residing in the United States as of 2014 [1]. This number is expected to grow as treatments improve and the population ages [2]. On the aggregate, survival after breast cancer diagnosis has improved over the last three decades with overall 5-year survival being greater than 95% for women diagnosed with localized disease [3]. However, Black women with breast cancer experience higher mortality and shorter survival time than White women [4–7]. Further, there is evidence that racial disparities in outcomes have also increased over time [8–10]. It is important to describe contributors to persistent racial disparities in outcomes for women with breast cancer and to identify long term prognostic indicators based on common risk factors.

Gynecologic surgeries such as hysterectomy and oophorectomy are most commonly performed in premenopausal women for non-malignant diseases such as endometriosis, uterine fibroids, and ovarian cysts [11]. Additionally, a small subset of gynecologic surgeries are performed in women who have first-degree relatives with a history of breast or ovarian cancer or who have germline mutations such as BRCA1/2; these women may undergo prophylactic hysterectomy and oophorectomy, for the primary prevention of breast and ovarian cancers [12]. Recent evidence from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System, a population-based survey of U.S. adults, indicated that 33% of Black women and 23% of white women aged 48–50 had a history of hysterectomy [13]. In nearly half of all hysterectomies bilateral oophorectomy, or removal of both ovaries is performed [14]. Additional studies have supported the observation that hysterectomy prevalence is markedly higher in Black populations compared to White populations, especially for surgeries occurring at younger ages in the premenopausal age range [15–16].

Prior studies, including one conducted in the Carolina Breast Cancer Study (CBCS), a weighted population based sample, have described a reduction in breast cancer incidence for women who had hysterectomy with bilateral oophorectomy compared to women who had not had gynecologic surgery [17–18]. Further, existing literature demonstrates that history of pre-diagnosis premenopausal hysterectomy with bilateral oophorectomy reduces the risk of breast cancer mortality for White women with breast cancer [19–20]. These findings provide evidence that there is a biological pathway mediated by pre-diagnosis premenopausal removal of the ovaries that confers some protection against both breast cancer incidence and mortality. Understanding the role of premenopausal gynecologic surgery on survival in

diverse populations of women with breast cancer could impact prognosis and racial disparities in outcomes.

The objective of the study was to evaluate effect measure modification by race between premenopausal pre-diagnosis gynecologic surgeries, including hysterectomy and oophorectomy, and breast cancer-specific mortality in a population-based sample of Black and White women with breast cancer living in the U.S. South. A secondary aim was to assess the relationship between gynecologic surgery and all-cause mortality as well as assess potential effect measure modification for both breast cancer-specific and all-cause mortality by estrogen receptor status, and a woman's family history of breast cancer.

Materials and Methods

Study Population

This study utilized data from women diagnosed with breast cancer who participated in Phases 1 and 2 of the Carolina Breast Cancer Study (CBCS), a weighted population-based case-control study sampling women ages 20–74 from 24 counties in North Carolina. This study was approved by the institutional review board of the University of North Carolina at Chapel Hill. Invasive breast cancer cases were identified from 1993 until 2001 using the Rapid Case Ascertainment System from the North Carolina Central Cancer Registry. CBCS oversampled Black women, and in particular, Black women under age 50 at diagnosis using a modification of randomized recruitment to obtain approximately equal numbers of Black and non-Black women [21–22]. Of all of the potentially eligible cases, 97.6% were contacted and 78.0% of contacted cases were enrolled resulting in 1,808 women with invasive cases of breast cancer being enrolled in CBCS. From this sampling scheme inverse probability of sampling weights were created to reflect the underlying source population in North Carolina [23]. Additional details on the sampling method employed in the Carolina Breast Cancer Study have been described elsewhere [24]. Cases were interviewed by trained nurse interviewers to collect self-reported information on reproductive history, family history of cancer, environmental exposures and sociodemographic characteristics. For 94.5% of women included in this study, the baseline interview was conducted within a year of their diagnosis of breast cancer.

Confirmed invasive cases of breast cancer from Phases 1 and 2 of CBCS were eligible to be included in this analysis (n=1,808). We excluded women if they identified as a race other than Black/African-American or White (n=25), if they had unknown gynecologic surgery status (n=24), or if they had radiation or chemotherapy that resulted in the cessation of menstruation (n=27). Lastly, women were excluded if they reported having a hysterectomy and also receiving estrogen and progestin combination hormone therapy because this formulation is currently contraindicated for women who have had a hysterectomy (n=9). The final analytic sample for this study included 1,723 women.

Exposure Assessment

In this study, the exposure was a 3-level indicator variable for premenopausal gynecologic surgery that occurred prior to breast cancer diagnosis and included the categories of no

gynecologic surgery, hysterectomy with bilateral oophorectomy, and hysterectomy with ovarian conservation. In study interviews, women were asked: “Are you still having menstrual periods?” If participants responded “yes” or were currently or recently pregnant they were considered premenopausal. If they responded “no” to that survey item and were also not currently or recently pregnant, they were asked “Did your periods stop because of an operation (removal of the uterus or ovaries)?” If women responded no to that item, they were categorized post-menopausal due to non-surgical causes. This was the referent level of the exposure variable. If a woman did indicate the cessation of menstruation due to surgery, she was then asked, “Was your uterus removed?” and “were one or both ovaries removed?” Women who had their uterus and both ovaries removed were categorized as having hysterectomy with bilateral oophorectomy, and women who had their uterus removed with the conservation of one or both ovaries were categorized as having hysterectomy with ovarian conservation (Figure 1). Underlying indication for gynecologic surgery was not available.

Outcome Assessment

Breast cancer-specific and all-cause mortality were the primary outcomes. Year and cause of death were determined by linkage with the National Death Index through December 31, 2016. Deaths from breast cancer were originally identified using International Classification of Disease (ICD) -9 diagnostic code 174.9. Subsequently these events were reclassified using ICD-10 code C50.9. All participants who did not have an event by December 31st 2016, were administratively censored on that date. For the breast cancer-specific mortality analyses, participants who died from causes other than breast cancer were censored. All deaths, including those from breast cancer, were included in all-cause mortality analyses.

Covariate Assessment

Models were adjusted for probable confounders of the relationship between gynecologic surgery and mortality in women with breast cancer. These confounders were determined by an assessment of previous literature in this area and categorizations were also informed by prior literature as well as CBCS convention. Body mass index (BMI: kg/m²) defined continuously as a woman’s self-reported weight 1 year prior to her breast cancer diagnosis and her measured height at the time of her interview. Parity was a composite measure to account for age and number of full-term pregnancy. Women were categorized as follows: nulliparous; one child, age at first full-term pregnancy (FTP) < 26; one child, age at FTP 26; 2 or more children, age at FTP < 26; 2 or more children, age at FTP ≥ 26. Breastfeeding was binary, having breastfed or not. Family history of breast cancer was defined as a woman self-reporting having one or more first degree relatives with a history of breast cancer. Education was a three-level variable: less than high school (referent); high school diploma and some college experience; and completion of a college degree and above. Alcohol use was a binary variable where women were categorized as never users if they had fewer than 12 lifetime drinks, and alcohol consumers if they had more than 12 lifetime drinks. Smoking history was operationalized as never smoker, former smoker or current smoked. Age at menarche was defined as a 3-level variable based on self-reported start of menses: 11 years or younger, 12 to 13 years, and 14 years or older. Women reported if they had ever used menopausal hormone therapy (MHT), and if they did, whether they used estrogen only,

combination therapy, or another formulation. Self-reported race (Black/African-American or White) was also recorded.

Statistical Analysis

Multivariable Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals [25]. Follow-up began at the date of breast cancer diagnosis and time was measured continuously in years. We conducted two main effects models, a model for breast cancer-specific mortality and another model for all-cause mortality. All models were weighted to reflect the sampling design [22]. We conducted a Wald test for interaction ($\alpha=0.2$) to evaluate the joint effect of surgery status and MHT formulation based on evidence from prior literature [19]. A more generous alpha level of 0.2 was used to compensate for the low statistical power of tests for interaction [26–27]. Two-sided tests ($\alpha=0.05$) were conducted for both the main effects and stratified models. Analyses were conducted in SAS version 9.4 (Cary, NC).

First we estimated the relationship between gynecologic surgery and breast cancer specific and all-cause mortality in the total population and then stratified by race. We then also evaluated effect measure modification between gynecologic surgery and breast cancer-specific and all-cause mortality by creating models stratified by estrogen receptor positivity and first-degree family history of breast cancer. Having one or more first-degree relatives with a history of breast cancer is a known factor for increased risk of breast cancer-specific mortality as well as being an indication for prophylactic gynecologic surgery [28–29]. Since the women in our study sample were diagnosed with breast cancer before the widespread adoption BRCA 1/2 testing, we consider self-reported first-degree history of breast cancer to be a relevant risk factor.

Results

Covariate characteristics were calculated using weighted frequencies to reflect the prevalence in the underlying source population in North Carolina (Table 1). These frequencies were weighted by the Carolina Breast Cancer Study sampling fractions to reflect the demographic distribution of women with breast cancer in the study region [21]. Age at breast cancer diagnosis ranged from 23 to 74 years with a median age of 49. Overall, 759 (21.2%) of women identified as Black. Of the 1,723 women with breast cancer, 295 women had a history of premenopausal hysterectomy with ovarian conservation, 152 had hysterectomy with bilateral oophorectomy, and 1,276 (72.6%) had no surgery. During the follow-up period, 793 women died; 447 of these deaths were breast cancer-specific.

In our data, the interaction term for gynecologic surgery and MHT use did not meet statistical significance and consequently, all models in this analysis include surgery status and hormone replacement therapy use as covariates without an interaction term. In the total study population, pre-diagnosis premenopausal hysterectomy with bilateral oophorectomy was associated with reduced breast cancer-specific mortality (HR: 0.68; 95% CI: 0.49, 0.96) in multivariable-adjusted models (Table 2). This reduction in mortality was consistent across racial groups with White and Black women having a similar reduction in breast cancer-specific mortality (HR among white: 0.66; 95% CI: 0.42, 1.02), (HR among Black: 0.67;

95% CI: 0.37,1.21), (Figure 1). For hysterectomy with ovarian conservation, there was no association with breast cancer specific mortality among White or Black women.

For all-cause mortality in the total population, there was no association between hysterectomy with bilateral oophorectomy and all-cause mortality (HR: 0.95; 95% CI 0.79,1.15) (Table 3). Additionally, no association was observed between hysterectomy with ovarian conservation and all-cause mortality (HR: 0.94, 95% CI 0.82, 1.08). However, when stratified by race, associations appeared to differ slightly for White and Black women for all-cause mortality. Among White women, there was no association between either hysterectomy with bilateral oophorectomy (HR: 1.14; 95% CI 0.92,1.41) or hysterectomy with ovarian conservation (HR: 1.11; 95% CI 0.91, 1.21) and all-cause mortality. In contrast to the results among White women, among Black women, a reduction in all-cause mortality was observed for both levels of gynecologic surgery. Black women who had hysterectomy with bilateral oophorectomy had a 32% (HR: 0.68; 95% CI 0.47, 1.00) reduced risk of mortality compared to Black women who had not had gynecologic surgery and Black women who had a hysterectomy with ovarian conservation had a 23% (HR: 0.77; 95% CI 0.59, 0.99) reduced risk of mortality compared to Black women who had not had gynecologic surgery.

There was no evidence of effect measure modification of the association between hysterectomy with ovarian conservation and breast cancer specific mortality according to Estrogen Receptor (ER) status (Table 2). There was evidence of effect measure modification by first-degree family history. Among women without a family history of breast cancer who had hysterectomy with bilateral oophorectomy there was instability in the estimated hazard ratio (HR: 0.90; 95% CI 0.63, 1.29) (Table 2) for breast cancer specific mortality. However, among women with a family history of breast cancer, there was a substantial reduction in both breast cancer-specific and all-cause mortality among women with hysterectomy with bilateral oophorectomy compared to women who did not have surgery (Tables 2 and 3).

Discussion

In this weighted population-based study, a reduction in breast cancer-specific mortality was seen in women who had a hysterectomy with bilateral oophorectomy and was observed consistently in both Black and White self-defined racial groups. This result was robust even after controlling for several confounders, contributing to the body of literature that supports including premenopausal pre-diagnosis gynecologic surgery as a prognostic factor for outcomes among women with breast cancer. Given the high prevalence of hysterectomy with bilateral oophorectomy for common gynecologic conditions among Black women compared to White women, it is possible that this exposure plays a role in population level patterns of breast cancer survival [13]. Within a population-based study of privately insured women, hysterectomy rates among women ages 18 to 64 decreased 39% between 2000 and 2014 and oophorectomy rates decreased 19% during the same timeframe [30]. This population-level change in the exposure prevalence of a protective factor that has a greater prevalence in Black women may be consequential for racial disparities in breast cancer outcomes in future years.

In addition to conferring protection for breast cancer specific mortality, a prior study found a reduction in all-cause mortality in women with breast cancer who had pre-diagnosis hysterectomy with bilateral oophorectomy, only for women who had survived at least five years [20]. In our study using a weighted population based sample, for all-cause mortality, there was evidence of a protective effect for both levels of gynecologic surgery for Black women but not for White women. Given the protective effect observed in Black women but not in White women for all-cause mortality and different distributions of causes of death, there may exist additional pathways for other causes of death, however we were unable to directly address this in our data.

In contrast to previous literature which primarily focused on the effect of hysterectomy with bilateral oophorectomy, the effect of hysterectomy with ovarian conservation on mortality in women with breast cancer had not been thoroughly investigated [20]. Previous studies conducted in Australia demonstrated a reduction in breast cancer-specific mortality for women who have had their uteri removed but have one or both ovaries intact but demonstrated no effect on all-cause mortality [31–32]. Our study found no evidence of an association between hysterectomy with ovarian conservation for breast cancer specific mortality.

Our analysis revealed evidence of potential effect measure modification by first-degree family history of breast cancer. When conducting the analysis only amongst women who did not have a family history of breast cancer, the hazard ratio for breast cancer-specific mortality for women with hysterectomy with bilateral oophorectomy compared to women who had not had surgery became null. The instability of the estimate once women with family history are removed may suggest that the overall protective relationship observed between hysterectomy and bilateral oophorectomy and breast cancer-specific mortality could be driven by the small subset of women with positive family history who benefit the most, due to having a higher baseline risk of breast cancer mortality. Previous literature has demonstrated a reduction in breast cancer specific and all-cause mortality for BRCA1/2 mutation carriers who had a prophylactic oophorectomy [33–34]. We consider our finding in line with this prior research and applicable to women who made decisions about gynecologic surgery before the advent of genetic testing, who may have only had family history information to rely on to guide the decision-making process. Our results reinforce existing guidelines that only recommend prophylactic procedures in women with germline mutations that put them at increased risk for breast and ovarian cancers [12].

The study population used for this investigation allowed for the evaluation of both pre-diagnosis premenopausal hysterectomy with ovarian conservation as well as hysterectomy with bilateral oophorectomy on survival among women with breast cancer. Additionally, lengthy follow-up permitted the evaluation of long term outcomes for women with breast cancer with the median survival time being 18 years. Further, this study was conducted in a population-based sample of women with breast cancer that included a substantial number of Black women and women diagnosed with breast cancer before the age of 50. The depth of the covariate data in CBCS allowed for the control of many important potential confounders of the relationship between gynecologic surgery and survival in women with breast cancer. Some limitations should also be considered. Despite the population-based sampling, our

study had low power to assess additional causes of death. A prior study found increased risk of all-cause mortality among obese women older than age 40 who had hysterectomy with bilateral oophorectomy but did not observe this relationship in younger or non-obese women [35]. Given small cell sizes among women with hysterectomy with bilateral oophorectomy we were unable to evaluate this relationship in our study. Additionally, ER status had approximately 10% missing data which may have influenced those stratified analyses. Since the exposure was self-reported gynecologic surgery history, there may exist a degree of exposure misclassification. Women who reported only having one ovary removed may have actually had both and we were unable to clinically verify [36]. However, misclassification in this direction would likely make the effect of hysterectomy with bilateral oophorectomy appear more conservative. Further, we were not able to evaluate reason for gynecologic surgery, whether it was a prophylactic procedure or was done to treat an underlying benign gynecologic condition. Finally, we did not account for differences in treatment received for breast cancer, which is also a predictor of survival.

In summary, we extended previous work showing that premenopausal hysterectomy with bilateral oophorectomy is a prognostic factor for breast cancer specific-mortality and confirms the existence of this relationship among Black women. This confirmation is important given that Black women, particularly those residing in the US South historically have had higher rates of hysterectomy and higher rates of breast-cancer specific mortality than White women. A comprehensive understanding of cancer survivors' risk profiles, including the interplay between family history, estrogen receptor status, and gynecologic surgery status can help inform clinical decision making.

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Figure 1.
Displaying how women's surgical status was categorized

Table 1-

Descriptive characteristics of women diagnosed with breast cancer in the Carolina Breast Cancer study, phases 1 and 2, 1993–2001

	All		No Surgery		Hysterectomy with Ovarian Conservation		Hysterectomy with Bilateral Oophorectomy	
	Count	Weighted ^a %	Count	Weighted ^a %	Count	Weighted ^a %	Count	Weighted ^a %
TOTAL N	1,723		1,276	72.6	295	18.0	152	9.4
Person Years	20,459		15,103		3,454		1,902	
Median Age at Diagnosis	49		47		53		57	
Race								
White	964	78.8	748	79.9	148	76.9	68	74.2
Black	759	21.2	528	20.1	147	23.1	84	25.8
Education								
<High School degree	317	16.1	207	13.8	77	25.4	33	16.1
High School and Some College	927	54.8	664	52.6	174	59.1	89	64.4
College Degree or more	479	29.1	405	33.8	44	15.5	30	19.5
Median BMI (kg/m²)	27.0		26.6		27.9		27.5	
Age at Menarche (years)								
11	391	20.5	270	18.6	82	27.3	39	22.0
12–13	951	56.8	724	58.4	147	52.4	80	53.1
>13	379	22.6	282	23.0	66	20.3	31	24.0
Missing	2	0.1	0		0		2	0.9
Receptor Subtype								
ER Positive	915	59.6	672	59.4	162	60.7	81	59.5
ER Negative	692	33.9	521	34.3	113	32.9	58	32.9
Missing	116	6.5	83	6.3	20	6.4	13	7.6
Alcohol Use								
Ever	1183	67.3	890	68.1	187	63.8	106	68.4
Never	539	32.5	385	31.7	108	36.2	46	31.6
Missing	1	0.1	1	0.2	0		0	
Smoking								
Never	901	49	692	51	137	43.9	72	43.8
Former	446	30.1	326	30.3	75	28.3	45	31.7
Current	376	20.9	258	18.7	83	27.8	35	24.5
Menopausal Hormone Therapy								
Never User	1,256	61.3	1,040	70.8	183	47.5	33	14.9
Estrogen Only	249	18.7	41	4.1	102	48.1	106	75.1

	All		No Surgery		Hysterectomy with Ovarian Conservation		Hysterectomy with Bilateral Oophorectomy	
	Count	Weighted ^a %	Count	Weighted ^a %	Count	Weighted ^a %	Count	Weighted ^a %
Estrogen and Progestin Combination	134	13.2	134	18.2	0	0	0	0
Other Formulations	84	2.28	61	2.33	10	1.48	13	3.34
Family History								
Positive Family History of Breast Cancer	283	17.3	195	15.9	64	23.4	24	16.6
No Family History of Breast Cancer	1390	79.9	1046	81.5	221	73.1	123	80.5
Missing	50	2.8	35	2.6	10	3.5	5	2.9

^aWeights were constructed to account for the non-random sampling of cases in the CBCS study population of central North Carolina.

Table 2

Crude and Multivariable Adjusted Breast Cancer-Specific Mortality Hazard Ratios by Race, Estrogen Receptor Status, and Family History Status

			No Surgery	Hysterectomy with Ovarian Conservation		Hysterectomy with Bilateral Oophorectomy	
	Person-Years	Deaths	HR	Crude HR	Adjusted HR	Crude HR	Adjusted HR
Combined Population ^a	25,242	447	1	0.91 (0.76,1.10)	0.90 (0.72,1.12)	0.64 (0.48,0.84)	0.68 (0.49,0.96)
Race ^b							
White	15,153	208	1	0.90 (0.72,1.13)	0.91 (0.68,1.20)	0.61 (0.42,0.87)	0.66 (0.43,1.02)
Black	10,089	239	1	0.84 (0.61,1.16)	0.84 (0.59,1.20)	0.60 (0.38,0.95)	0.67 (0.37,1.21)
Estrogen Receptor Status ^a							
ER+	13,893	190	1	0.99 (0.78,1.26)	1.01 (0.75,1.36)	0.81 (0.57,1.16)	0.82 (0.53,1.27)
ER–	9,732	196	1	0.88 (0.65,1.20)	0.90 (0.64,1.27)	0.46 (0.27,0.79)	0.59 (0.32,1.12)
Family History ^c							
Positive Family History	4,143	70	1	1.08 (0.74,1.58)	0.77 (0.45,1.29)	0.17 (0.05,0.58)	0.11 (0.03,0.36)
No Family History	20,369	368	1	0.90 (0.73,1.12)	0.88 (0.69,1.12)	0.73 (0.54,1.98)	0.90 (0.63,1.29)

^a Adjusted for Race, Body Mass Index, education level, age at menarche, parity, breastfeeding history, family history of breast cancer, alcohol use, smoking status, menopausal hormone therapy use and formulation.

^b Adjusted for Body Mass Index, education level, age at menarche, parity, breastfeeding history, family history of breast cancer, alcohol use, smoking status, menopausal hormone therapy use and formulation.

^c Adjusted for Race, Body Mass Index, education level, age at menarche, parity, breastfeeding history, alcohol use, smoking status, menopausal hormone therapy use and formulation.

Table 3

Crude and Multivariable Adjusted All-Cause Mortality Hazard Ratios by Race, Estrogen Receptor Status, and Family History Status

			No Surgery	Hysterectomy with Ovarian Conservation		Hysterectomy with Bilateral Oophorectomy	
	Person-Years	Deaths	HR	Crude HR	Adjusted HR	Crude HR	Adjusted HR
Combined Population ^a	25,242	793	1	1.10 (1.98,1.23)	0.94 (0.82,1.08)	1.13 (0.97,1.31)	0.95 (0.79,1.15)
Race ^b							
White	15,153	412	1	1.15 (1.00,1.31)	1.11 (0.91,1.26)	1.22(1.03,1.45)	1.14(0.92,1.41)
Black	10,089	424	1	0.92 (0.73,1.16)	0.77 (0.59,0.99)	0.83 (0.61,1.12)	0.68 (0.47,1.00)
Estrogen Receptor Status ^a							
ER+	13,893	457	1	0.98 (0.85,1.14)	0.77 (0.64,0.93)	1.31 (1.09,1.57)	0.99 (0.79,1.25)
ER–	9,732	314	1	1.27 (1.04,1.56)	1.16 (0.91,1.46)	1.08 (0.82,1.43)	1.07 (0.75,1.53)
Family History ^c							
Positive Family History	4,143	136	1	1.28 (1.01,1.62)	0.83 (0.61,1.14)	0.60 (0.38,0.94)	0.39 (0.23,0.65)
No Family History	20,369	674	1	1.10 (0.96,1.26)	0.95 (0.82,1.11)	1.24 (1.06,1.46)	1.10 (0.90,1.34)

^a Adjusted for Race, Body Mass Index, education level, age at menarche, parity, breastfeeding history, family history of breast cancer, alcohol use, smoking status, menopausal hormone therapy use and formulation.

^b Adjusted for Body Mass Index, education level, age at menarche, parity, breastfeeding history, family history of breast cancer, alcohol use, smoking status, menopausal hormone therapy use and formulation.

^c Adjusted for Race, Body Mass Index, education level, age at menarche, parity, breastfeeding history, alcohol use, smoking status, menopausal hormone therapy use and formulation.