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Breast cancer risk and hysterectomy status: the Multiethnic Cohort Study

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Abstract

Objective—The main objective was to examine the association between simple hysterectomy (without bilateral oophorectomy) and breast cancer risk. Because hysterectomy prevalence varies by ethnicity, the secondary objective was to examine whether inclusion of women with hysterectomies affects the estimates of breast cancer risk by ethnicity.

Methods—The Multiethnic Cohort Study was assembled in 1993-6 and included 68,065 women from Hawaii and Los Angeles aged 45-75 years without missing information or bilateral oophorectomy. Hysterectomy status was self-reported. After 7.7 years median follow-up, 1,862 cases of invasive breast cancer were identified. Proportional hazards models were used to estimate relative risks (RR) while controlling for known risk factors.

Results—Prevalence of simple hysterectomy varied from 12 to 29% among the ethnic groups (White, African American, Native Hawaiian, Japanese American, and Latina). Overall, hysterectomy was not associated with breast cancer risk (RR=0.98). Although the RRs were nonsignificantly elevated by 15% in White women and nonsignificantly reduced by 15% in Latinas of non-US origin, the variation by ethnicity was not significant ($p_{interaction}$=0.48). The breast cancer risk associated with ethnicity was very similar when estimated with and without women with hysterectomies.

Conclusions—This study suggests that simple hysterectomy status does not alter breast cancer risk. Therefore, inclusion of women with simple hysterectomies does not substantially change estimated risk of breast cancer by ethnicity.

Keywords

Breast cancer; Hysterectomy; Ethnicity; Cohort

Introduction

It is important to investigate ways to identify women at higher risk for breast cancer as a means to understand the biology of the disease and to determine who may be most appropriate for intensified screening or preventive interventions. For example, clinical factors identified by way of routine examinations and medical history, such as bone mineral density and bilateral oophorectomy status, have been examined for their associations with breast cancer risk. In this

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regard, a few retrospective cohort studies [1,2] and case-control studies [3,4] have examined the association between simple hysterectomy (*i.e.* without bilateral oophorectomy) and breast cancer risk. The results from these studies have been inconsistent, with one showing a 30% increase in risk [1] and the others showing reductions in risk from 13% to 30% [2-4]. The crude odds ratio for hysterectomy was estimated also from data presented in a large pooled analysis examining hormone therapy use and breast cancer risk as 0.90 (95% CI=0.87-0.93) [5]. Because hysterectomy is very common and risk factors for conditions leading to hysterectomy may also increase breast cancer risk, our primary objective was to investigate this association within the prospective Multiethnic Cohort (MEC) study.

In 2002, Pike *et al.* [6] examined the incidence of breast cancer in the MEC and found that a number of ethnic differences in incidence were not explained by known breast cancer risk factors. As compared to White women, Latinas not born in the United States were at nonsignificantly reduced risk of breast cancer, whereas Native Hawaiian women were at significantly increased risk after multivariate adjustment. Women who had a simple hysterectomy before menopause were excluded from this analysis because imputation of the unknown age at menopause has the potential to bias the associations of age at menopause and hormone therapy use with breast cancer risk, and thus lead to incomplete or biased adjustment when examining whether or not these factors explained the differences in breast cancer incidence by ethnicity [7,8]. Because the prevalence rates of hysterectomy differ among ethnic groups, with African American women undergoing a hysterectomy substantially more often than White women [9-14], and because hysterectomy may be associated with breast cancer risk, inclusion of women who had a simple hysterectomy may lead to different incidence rates. Thus, a secondary objective of the present analysis was to examine ethnic differences in breast cancer risk including and excluding women with simple hysterectomies.

Materials and methods

The MEC was designed to investigate lifestyle and dietary factors with respect to cancer outcomes in five different ethnic groups in Hawaii and Los Angeles aged 45 to 75 at baseline; details about the study have been published previously [15]. The study was approved by the institutional review boards at the University of Hawaii and the University of Southern California. The cohort was assembled between 1993 and 1996 using drivers' license records in both states, supplemented with voter registration lists in Hawaii and Health Care Financing Administration files in Los Angeles. A self-administered questionnaire was completed and returned by mail by over 215,000 people of whom 118,869 were women. Excluded from the present analysis were 6,654 women with previous self-reported or cancer registry-detected diagnoses of breast, endometrial or ovarian cancer, 8,051 women who did not belong to one of the five targeted ethnic groups (White/Caucasian, African American, Native Hawaiian, Japanese American, Latina), 11,810 women who had bilateral oophorectomy, and 4,611 women who had implausible responses on the dietary portion of the questionnaire [16]. Women (n=19,678) with missing values in the exposure or covariate variables, including extreme values for height or weight that resulted in a body mass index (BMI) outside of the 15-50 kg/m^2 range were excluded. Thus, 68,065 women were included in this analysis.

Exposure and covariate information from baseline questionnaire

The baseline questionnaire data included information about demographic factors, diet, reproductive and menstrual history, and family history of cancer. Women who reported that their menstrual periods stopped due to surgery, and responded “Yes” in response to the question “Have you ever had a hysterectomy (complete removal of the uterus)?” but did not respond, “Yes, both ovaries” to the question “Have you ever had your ovaries removed?” were classified as having had a simple hysterectomy; thus, women classified in our exposed group are women

who had a simple hysterectomy before menopause. Age at hysterectomy was determined for these women by a question inquiring how old subjects were when their menstrual periods stopped permanently. Women without simple hysterectomy (unexposed) were those who were premenopausal or experienced menopause naturally without surgery. Women with bilateral oophorectomy were excluded because of their reduced risk for breast cancer. Ethnicity was based on self report; women reporting mixed ancestry were assigned to a single group based on the priority ranking: African American, Native Hawaiian, Latina, Japanese American, and White [15]. For the present analysis, Latina women were divided into two groups: those who were born in the United States and those who were not born in the United States but were born in Mexico, Central, or South America.

Follow-up and identification of cases

Eligibility for cohort inclusion was to be 45 to 75 years of age but a few subjects (<1%) returned their questionnaires at ages 42 to 44. Thus, follow-up time was initiated at the date of return of the baseline questionnaire or the 45th birthday of the subject, whichever was last, and was accrued until the date of diagnosis of breast, endometrial or ovarian cancer, death, or the last follow-up date (31 December 2002). Incident diagnoses of cancers were identified by linkage with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the Hawaii Tumor Registry, which together cover the entire population of the two states. These registries are members of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Case ascertainment was complete to the end of 2002. Deaths were identified by linkage with the databases of the Hawaii and California vital statistics offices and the National Death Index. The primary analyses included women with invasive breast cancers as cases. The median follow-up time for women included in this analysis was 7.7 years (interquartile range: 7.2 to 8.3 years), during which time 1,862 cases of invasive cancer were identified. Information about estrogen and progesterone receptor status, stage and histology was derived from SEER registry data.

Statistical analysis

Women with a simple hysterectomy were compared to women without a simple hysterectomy with respect to breast cancer risk factors. Logistic regression modeling with hysterectomy status as the outcome was done to test if the odds of having a simple hysterectomy were different by the levels of the risk factors adjusted for age and ethnicity.

Cox proportional hazards models [17], with age in days as the time metric, were used to estimate the relative risks (RR) of breast cancer associated with having had a simple hysterectomy. Because we could not determine the menopausal status of the women with a simple hysterectomy, both pre- and postmenopausal women were included in the main analysis. All models were adjusted for ethnicity and then separate models were done for each ethnic group. All models were stratified by follow-up time (≤ 2, > 2-5, > 5 years). Additional models were adjusted for education ($\leq 12^{th}$ grade, > 12^{th} grade), age at menarche (≤ 12, 13-14, ≥ 15 years), age at first birth (never, ≤ 20, 21-30, > 30 years), number of children (0-1, 2-3, ≥ 4), duration of current estrogen with progestin use (continuous), duration of current estrogen only use (continuous), duration of past estrogen with progestin use (continuous), BMI (< 25, 25-< 30, ≥ 30 kg/m^2), alcohol consumption (none, ≤ 1, >1-< 2, ≥ 2 drinks/day), and family history of breast cancer in a mother or sister (no, yes). We found that adjustment by history of mammography screening (within two years, more than two years, never) did not change the results and thus, did not include this variable as a confounder. Their significance of cross-product terms between ethnicity and hysterectomy status were tested with a Wald test to examine whether the associations differed among the ethnic groups. The proportionality assumption of the hazards models was tested by examining the Kaplan-Meier curves and assessing the Schoenfeld residuals.

Supplementary analyses were done to examine the effect of hysterectomy on subgroups of breast cancer as defined by estrogen receptor (ER) status, progesterone receptor (PR) status, joint ER/PR status, stage (*in situ*, localized, advanced), and histology (infiltrating ductal carcinoma, ICD-O2 8500; lobular and mixed ductal lobular, ICD-O2 8520, 8522; mucinous, ICD-O2 8480). The interaction between hysterectomy status and history of mammography screening (within two years, more than two years, never) was also examined. Because we could not determine menopausal status in women who had a simple hysterectomy, we did a supplementary analysis restricted to women 60 years of age or older at baseline, all of whom would likely be postmenopausal, to get an indication of whether or not the effect may be modified by menopausal status.

Finally, we used Cox proportional hazards models to examine the association between ethnicity and breast cancer risk. We compared the results in all women and a subset which excluded women with simple hysterectomies. All analyses were done using SAS version 9.1.

Results

The prevalence of simple hysterectomy in cohort members with intact ovaries was 19%, but the prevalence differed by ethnicity. The prevalence was highest in African American women (*n*=3,570, 29%) and Latinas born in the US (*n*=1,774, 24%) whereas it was lowest in Japanese American women (*n*=2,331, 12%). Women in the other ethnic groups had a moderate prevalence of hysterectomy (16-18%). Compared with women without hysterectomies, women who had simple hysterectomies, on average, were older and a higher proportion had an earlier menarche, an earlier age at first birth, a greater number of children, a BMI in the overweight or obese range, 12 years of education or less, and a history of breast cancer in a first degree relative (Table 1). They were also slightly more likely to have had a mammogram and to be using estrogen only hormonal therapy at baseline.

Hysterectomy status was not associated with the risk of breast cancer overall (RR=0.98; 95% confidence interval (CI)=0.86-1.11), or in any of the ethnic groups examined (Table 2). The RR in White women was nonsignificantly elevated (1.15; 95% CI=0.89-1.47) and the RR in Latinas of non-US origin was nonsignificantly reduced (0.85; 95% CI=0.48-1.51), but the RRs did not vary significantly across the ethnic groups examined ($p_{\text{interaction}}$=0.48). We did not find an association with age at hysterectomy. The overall association was similar when the analysis was restricted to women who were 60 years of age or older at cohort entry (RR=1.05; 95% CI=0.88-1.24)) and when the analysis was done by history of mammography screening (within two years, more than two years, never; $p_{\text{interaction}}$=0.90). Furthermore, hysterectomy status was not associated with the subgroups of breast cancer defined by ER status, PR status, stage, or histology. The risk of carcinoma *in situ* also was not associated with hysterectomy status (RR=0.86; 95% CI=0.65-1.14).

With respect to our secondary objective, we observed that the risks of breast cancer according to ethnicity were very similar whether estimated with or without women with simple hysterectomies (Table 3). As compared to White women, African American women and Latinas born in the US had similar risk for breast cancer. At increased risk for breast cancer were Native Hawaiian women (including women with simple hysterectomy, RR=1.72; 95% CI=1.44-2.06) and Japanese American women (including women with simple hysterectomy, RR=1.19; 95% CI=1.04-1.35). At reduced risk for breast cancer were Latinas not born in the US, but this only reached statistical significance in the larger sample that included women with simple hysterectomies (RR=0.77; 95% CI=0.61-0.96). Because adjustment for menopausal status and age at menopause cannot be done without imputation when including women with simple hysterectomies, we investigated the confounding effect in the sample excluding these women. The change in the estimated RRs for the association between ethnicity and breast

cancer risk after adjustment for age at menopause was less extreme than -2.8% [100% × ($RR_{not\ adjusted}$-$RR_{adjusted}$)/$RR_{not\ adjusted}$] [18]. Thus, it is not likely that the risk estimates shown in Table 3 are strongly confounded by menopausal status and age at menopause.

Discussion

As compared to other studies, we neither found an increased [1] nor a decreased [2-4] risk of breast cancer in relation to simple hysterectomy status. In agreement with other studies, we did not find an association with age at surgery [1-3,5]. Given these null findings, inclusion of women with hysterectomy in the analysis of the association between ethnicity and breast cancer risk did not materially change the conclusions about this association despite large variation in hysterectomy prevalence by ethnic group.

The balance of several phenomena, including measurement error and biological mechanisms that may be weak or counteract one another, could have resulted in the null association that was estimated between hysterectomy and breast cancer risk in this study. A biological mechanism that could increase risk is that conditions leading to hysterectomy may share a hormonal etiology with breast cancer. Indications for hysterectomy include leiomyomas (uterine fibroids), endometriosis, uterine prolapse, and menstrual disorders [12,19-21]. Risk factors for some of these conditions are also known breast cancer risk factors: early age at menarche, low parity, BMI, and low physical activity [10,22-29]. There are exceptions. Alcohol intake and BMI decrease the risk for endometriosis [30-32] but increase the risk for postmenopausal breast cancer. Parity and early age at first birth increase the risk of prolapse [33-35] but decrease the risk of breast cancer. Further, the conditions themselves should be associated with breast cancer but studies of endometriosis show no overall association [1, 36-39] or a slightly increased risk [40] and the one study of hysterectomy for leiomyomas reported only a slight increased risk [1].

Another biological mechanism, but which could reduce the risk associated with hysterectomy, is that simple hysterectomy seems to reduce blood flow to the ovaries [41] and consequently, lessens the production of estrogens and hastens menopause. Simple hysterectomy is associated with changes in ovarian histology [42], differential expression of menopausal symptoms [43-45], and increases in follicle-stimulating hormone [46]. Women with a simple hysterectomy have an average age at menopause as determined by follicle-stimulating hormone levels > 40 IU/L that is 3.7 years younger than women who have a natural menopause [47]. Given that each year of earlier age at menopause reduces breast cancer risk by 2 to 3% [5, 48], 3.7 years earlier would translate into a risk reduction of 7% to 11%. The reduction in risk could be larger because hysterectomy may have effects on hormone levels even after menopause; levels of testosterone and estrone are slightly lower in women who had a simple hysterectomy than women who had a natural menopause [49].

The null association that was estimated between hysterectomy and breast cancer risk could also be influenced by the possibility that women may have taken pharmacological treatments for the indications for which they had a hysterectomy prior to having the surgery and these treatments could have affected breast cancer risk. For example, treatments given for leiomyomas and endometriosis, two of the main indications for hysterectomy, may include danazol (an androgenic medication), oral contraceptives, and gonatropin releasing hormone agonists [50-52].

Finally, possible measurement error in hysterectomy status could influence the association that was estimated as null. Although one study showed excellent concordance between hospital records and self-reported hysterectomy and oophorectomy [53], other studies have shown less concordance between self-report and information from physicians [54], hospital records [55],

a second self-report up to ten years later [59], or a second self-report within a short period of time [56,57]. The study with excellent concordance was among nurses, who are likely more medically informed than the general population [53]. Because bilateral oophorectomy reduces breast cancer risk (in the current study, relative to women having natural menopause, RR=0.81; 95% CI=0.69-0.94), if women with bilateral oophorectomy were included in the simple hysterectomy group, the risk associated with hysterectomy would be biased toward a reduction in risk. This bias may be more apparent in studies using self-report than in studies using medical records. Although slightly reduced risks were observed in two case-control studies using self-reported data [3,4], reduced risks were also observed in one of the two retrospective studies using medical records [2]. Conversely, women who were premenopausal at the time of entry into the cohort study could subsequently have had a simple hysterectomy in the follow-up time. The person-years incorrectly classified should be minimal, however, because few women were premenopausal at baseline and those women who were premenopausal were over 45 years of age.

The balance of these biological mechanisms and potential biases could be different among different populations such that some studies estimate an increased risk, some estimate a decreased risk, and some show no risk difference with hysterectomy. On the other hand, no real association may exist between hysterectomy and breast cancer risk.

As in other studies [12,21,58], we found that the prevalence of simple hysterectomy differed by ethnicity; it was relatively high in African American women and low in Japanese American women. This difference in prevalence could be due to ethnic differences in the incidence and severity of uterine pathologies, prevalence of early treatment to prevent hysterectomy, or medical practice [12,59]. We had been concerned that if hysterectomy was associated with breast cancer risk and also associated with ethnicity, then the exclusion of women with simple hysterectomies would affect the association between ethnicity and breast cancer risk. Their exclusion, however, did not substantially change the association and supports the generalizability of this observation. Furthermore, the association was remarkably similar to results presented previously for the MEC [6] despite two to three years additional follow-up and a sample with premenopausal women, women with a simple hysterectomy and naturally postmenopausal women as compared to using a sample with naturally postmenopausal women and women with bilateral oophorectomy.

Although we did not have specific data to disentangle the effects of differing age at menopause, indication for hysterectomy, or possible misreporting of hysterectomy and oophorectomy status, this study and others have not shown an increased risk of breast cancer associated with simple hysterectomy. Despite the considerable variation in hysterectomy prevalence by ethnicity, because of the lack of association between hysterectomy and breast cancer risk, exclusion of women with simple hysterectomies did not substantially change the observed differences in breast cancer risk by ethnicity.

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Table 1

Baseline characteristics of the women in the Multiethnic Cohort, by hysterectomy status

Characteristic	No simple hysterectomy[a]		Simple hysterectomy		p^b
	n	(%)	*n*	(%)	
Age (years)					
< 60	30327	(54.9)	6004	(47.0)	
≥ 60	24953	(45.1)	6781	(53.0)	<0.0001
Ethnicity					
White	14289	(25.8)	3207	(25.1)	
African American	8604	(15.6)	3570	(27.9)	
Native Hawaiian	4233	(7.7)	830	(6.5)	
Japanese American	16912	(30.6)	2331	(18.2)	
Latina - US born	5692	(10.3)	1774	(13.9)	
Latina - not US born	5550	(10.0)	1073	(8.4)	<0.0001
Age at menopause or hysterectomy (years)					
Premenopausal	13248	(24.0)	-		
< 45	6620	(12.0)	9761	(76.3)	
45-49	13312	(24.1)	2202	(17.2)	
≥ 50	22100	(40.0)	822	(6.4)	-
Age at menarche (years)					
≤ 12	26948	(48.7)	6798	(53.2)	
13-14	21561	(39.0)	4680	(36.6)	
≥ 15	6771	(12.2)	1307	(10.2)	<0.0001
Age at first birth (years)					
Never	7193	(13.0)	1306	(10.2)	
≤ 20	14193	(25.7)	5021	(39.3)	
21-30	29434	(53.2)	6027	(47.1)	
≥ 30	4460	(8.1)	431	(3.4)	<0.0001
Number of children					
0	7193	(13.0)	1306	(10.2)	
1	6272	(11.3)	1299	(10.2)	
2-3	25141	(45.5)	5512	(43.1)	

Characteristic	No simple hysterectomy[a]		Simple hysterectomy		
	n	(%)	*n*	(%)	*p*[b]
≥ 4	16674	(30.2)	4668	(36.5)	<0.0001
BMI (kg/m^2)					
< 25	29490	(53.3)	5569	(43.6)	
25-< 30	16012	(29.0)	4306	(33.7)	
≥ 30	9778	(17.7)	2910	(22.8)	<0.0001
Current estrogen and progestin use					
No	45701	(82.7)	12478	(97.6)	
Yes	9579	(17.3)	307	(2.4)	<0.0001
Current estrogen use					
No	52807	(95.5)	8369	(65.5)	
Yes	2473	(4.5)	4416	(34.5)	<0.0001
Past estrogen and progestin use					
No	51497	(93.2)	11831	(92.5)	
Yes	3783	(6.8)	954	(7.5)	<0.0001
Alcohol intake (drinks/day)					
Never	41869	(75.7)	9734	(76.1)	
< 1	8275	(15.0)	1922	(15.0)	
1-< 2	2678	(4.8)	629	(4.9)	
≥ 2	2458	(4.4)	500	(3.9)	0.0003
Education (years)					
≤ 12	23357	(42.3)	5957	(46.6)	
> 12	31923	(57.7)	6828	(53.4)	<0.0001
Family history[c]					
No	49452	(89.5)	11244	(87.9)	
Yes	5828	(10.5)	1541	(12.1)	0.0006
Previous mammography					
Never	7153	(12.9)	1044	(8.2)	
> 2 years ago	6020	(10.9)	1347	(10.5)	
Within 2 years	42107	(76.2)	10394	(81.3)	<0.0001

Characteristic	No simple hysterectomy[a]		Simple hysterectomy		p^b
	n	(%)	*n*	(%)	

[a] Premenopausal women and postmenopausal women who had natural menopause

[b] *p*-value from logistic regression adjusted for age (continuous) and ethnicity. Age is adjusted for ethnicity only and ethnicity is adjusted for age only

[c] Family history of breast cancer in mother or a sister

Table 2

Multivariate adjusted relative risks (RR) of breast cancer according to hysterectomy status, by ethnicity

Ethnicity	Simple hysterectomy	Cases	Age adjusted RR	Age adjusted (95% CI)	Fully adjusted[a] RR	Fully adjusted[a] (95% CI)
White	No	390	1.0		1.0	
	Yes	101	1.07	(0.86-1.33)	1.15	(0.89-1.47)
African American	No	232	1.0		1.0	
	Yes	88	0.90	(0.70-1.15)	0.90	(0.69-1.16)
Native Hawaiian	No	153	1.0		1.0	
	Yes	29	0.85	(0.57-1.27)	0.89	(0.58-1.35)
Japanese American	No	527	1.0		1.0	
	Yes	69	0.92	(0.71-1.18)	0.89	(0.67-1.19)
Latina - US born	No	126	1.0		1.0	
	Yes	43	1.05	(0.74-1.48)	1.10	(0.76-1.60)
Latina - not US born	No	90	1.0		1.0	
	Yes	14	0.80	(0.46-1.41)	0.85	(0.48-1.51)
Overall[b]	No	1518	1.0		1.0	
	Yes	344	0.93	(0.83-1.05)	0.98	(0.86-1.11)
Overall, by age at hysterectomy	No	1518	1.0		1.0	
	Yes, at <45 years of age	250	0.90	(0.78-1.03)	0.94	(0.81-1.09)
	Yes, at 45-49 years of age	69	1.05	(0.82-1.33)	1.10	(0.86-1.41)
	Yes, at 50+ years of age	25	0.99	(0.66-1.47)	1.03	(0.69-1.54)

[a] Adjusted for age, BMI, family history in a mother or sister, education, alcohol consumption, age at menarche, age at first birth, number of children, duration of current estrogen with progestin use, duration of current estrogen only use, and duration of past estrogen with progestin use. For analyses including all women, additionally adjusted for ethnicity

[b] $p_{\text{interaction}}$ =0.48 between hysterectomy (no, yes) and ethnicity when added to this model

Table 3

Multivariate adjusted relative risks (RR) of breast cancer according to ethnicity, comparing different groups defined by menopausal and hysterectomy status

	All women[a]			Excluding women with simple hysterectomy		
Ethnicity	**Cases**	**RR[b]**	**(95% CI)**	**Cases**	**RR[b]**	**(95% CI)**
White	491	1.0		390	1.0	
African American	320	1.01	(0.86-1.16)	232	1.07	(0.90-1.27)
Native Hawaiian	182	1.72	(1.44-2.06)	153	1.80	(1.48-2.20)
Japanese American	596	1.19	(1.04-1.35)	527	1.25	(1.08-1.44)
Latina - US born	169	0.92	(0.77-1.10)	125	0.94	(0.76-1.16)
Latina - not US born	104	0.77	(0.61-0.96)	90	0.83	(0.65-1.06)

[a] Premenopausal women, women with natural menopause, and women with simple hysterectomy

[b] Adjusted for age, BMI, family history in a mother or sister, education, alcohol consumption, age at menarche, age at first birth, number of children, duration of current estrogen with progestin use, duration of current estrogen only use, and duration of past estrogen with progestin use