American Journal of Epidemiology
Vol. 173, No. 1
DOI: 10.1093/aje/kwq339
Advance Access publication:
November 25, 2010

Original Contribution

Breast Cancer Risk and Ovariectomy, Hysterectomy, and Tubal Sterilization in the Women's Contraceptive and Reproductive Experiences Study

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Initially submitted March 3, 2010; accepted for publication September 2, 2010.

Removal or impairment of ovaries before menopause may affect a woman's breast cancer risk by altering her cumulative exposure to ovarian hormones. The Women's Contraceptive and Reproductive Experiences Study, a population-based, multicenter case-control study of incident invasive breast cancer, recruited women aged 35–64 years (4,490 cases and 4,611 controls) who provided data on ovariectomy, hysterectomy, and tubal sterilization during in-person interviews. Controls were frequency-matched to cases by age, race, and study site. Unconditional logistic regression analysis was used. Women who had not undergone premenopausal reproductive surgery were the referent group. Bilateral ovariectomy was associated with reduced breast cancer risk overall (odds ratio (OR) = 0.59, 95% confidence interval (CI): 0.50, 0.69) and among women <45 years of age (ORs ranged from 0.31 to 0.52), but not among those who were older at surgery. It was also associated with a reduced risk for estrogen and progesterone receptor–positive tumors (OR = 0.63, 95% CI: 0.52, 0.75) but not receptor-negative tumors. Hysterectomy with ovarian conservation (OR = 0.83, 95% CI: 0.72, 0.96) and hysterectomy with partial ovary removal (OR = 0.73, 95% CI: 0.59, 0.91) were also associated with lower risk. No association with breast cancer risk was observed with tubal sterilization only or partial ovariectomy without hysterectomy. Reproductive organ surgeries may alter ovarian hormone levels, thereby affecting breast cancer risk.

breast neoplasms; case-control studies; hysterectomy; ovariectomy; sterilization, tubal

Abbreviations: CARE, Contraceptive and Reproductive Experiences; CI, confidence interval; ER, estrogen receptor; HT, hormone therapy; OR, odds ratio; PR, progesterone receptor; RDD, random digit dialing; SEER, Surveillance, Epidemiology, and End Results.

Ovarian hormones have been implicated in the pathogenesis of breast cancer (1). Bilateral ovariectomy reduces breast cancer risk, likely because of reductions in levels of circulating ovarian hormones after removal of the ovaries (2–7). The impacts of tubal sterilization, hysterectomy with ovarian conservation, and ovariectomy with at least part of an ovary remaining on breast cancer risk are less clear. These reproductive surgeries may also affect breast cancer risk by altering hormone levels before menopause or by modifying age at menopause (8).

Epidemiologic findings on the relation between breast cancer risk and tubal sterilization are inconsistent, with some reports showing a reduction in risk after tubal sterilization (9–11) and others showing no protective effect (12–14). Some studies showed that hysterectomy with ovarian conservation lowers cancer risk (6, 9), whereas others did not support this relation (2, 5, 15). Unilateral ovariectomy alone is not generally associated with reduced breast cancer risk (2, 6). However, 1 large cohort study of Canadian women with a history of reproductive surgeries reported a reduction in risk among women who had tubal sterilization, hysterectomy with ovarian conservation, or unilateral ovariectomy (9). In these studies, it is important to determine the number of ovaries remaining after surgery and

whether the classification of women who had unilateral ovariectomy included women who had undergone a hysterectomy.

Epidemiologic data from the Women's Contraceptive and Reproductive Experiences (CARE) Study, a large, population-based case-control study of invasive breast cancer among US women, were analyzed to investigate the hypothesis that reproductive surgeries reduce breast cancer risk. Previous research on this study population has shown that breast cancer risk is associated with reproductive factors (16) and hormone therapy (HT) regimens (17) but is unrelated to oral contraceptive usage (18).

MATERIALS AND METHODS

The Women's CARE Study was designed to evaluate risk factors for invasive breast cancer among both black and white women aged 35–64 years. Field centers participating in this study were in Atlanta, Georgia; Detroit, Michigan; Los Angeles, California; Philadelphia, Pennsylvania; and Seattle, Washington. The Centers for Disease Control and Prevention served as the data-coordinating center. Study protocols were approved by institutional review boards at participating institutions, in accordance with assurances filed with and approved by the US Department of Health and Human Services. All women provided written informed consent before study participation. A detailed description of the study methods was published previously (19).

Case group

Case patients were US-born, English-speaking women residing in the study locations who received a diagnosis of histologically confirmed invasive breast cancer between July 1994 and April 1998. Surveillance, Epidemiology, and End Results (SEER) cancer registries were used to identify cases at SEER field centers. In Philadelphia, field staff abstracted medical records at hospitals in the study area to identify cases. Eligible cases had no previous diagnosis of invasive or in situ breast cancer. Younger cases were oversampled according to a random sampling scheme that yielded approximately equal age strata; black cases were oversampled relative to white cases to maximize their numbers in the study. Of the 5,982 eligible cases, 4,575 (76.5%) were interviewed.

Control group

Control participants were US-born, English-speaking women who had never had a diagnosis of invasive or in situ breast cancer. Random digit dialing (RDD) methods were used to identify potential participants in each geographic region covered by case-identification protocols. Controls selected randomly from eligible women in households that had been screened were frequency-matched to cases by 5-year age group, race, and field center. Approximately 82% of residential households called by RDD were successfully screened. Of the 5,956 potentially eligible controls, 4,682 (78.6%) were interviewed.

Data collection

Trained female interviewers administered in-person structured questionnaires on demographic and lifestyle factors, contraceptive history, use of hormone therapy, menstrual history, pregnancy history, and medical history, including cancer and mammogram history and family history of breast cancer. Women were asked whether they had undergone surgery that partially or totally removed one or both ovaries. Each ovarian surgery was recorded, with women reporting the number or fraction of ovaries removed and the month and year of the procedure(s). Ovarian surgeries were considered partial if some ovarian tissue remained and bilateral if both ovaries were removed either simultaneously or sequentially. Women were also asked whether they had undergone a hysterectomy or tubal sterilization and the approximate month and year of the procedure(s). All self-reports of these surgeries were recorded on a life-events calendar created during in-person interviews. During the interview, information was collected only up to a reference date, which was the date of a case's diagnosis or the date a control's household was first contacted during the RDD process. To ascertain exogenous hormone exposures, a mixture of recall and recognition techniques was used (structured questionnaire, response cards, color pictures of hormone preparations, and life-events calendar) (20, 21).

Receptor status

When available at each study center, pathology records were used to record the estrogen receptor (ER) and progesterone receptor (PR) status of cases. SEER registries routinely collect these laboratory results as recorded in the medical records. Both ER and PR status were available for 3,771 cases (82.4%). Reasons for missing ER/PR status data included the test not being carried out (ER: 153 cases, PR: 238 cases), tests ordered but results not available (ER: 171 cases, PR: 179 cases), and incomplete medical records (unknown whether tests were ordered and not recorded or not ordered at all) (ER: 252 cases, PR: 319 cases). Cases with ER/PR status classified as borderline were excluded when analyses focused on ER/PR status (ER: 30 cases, PR: 44 cases).

Assessment of reproductive surgeries

The term ''reproductive surgeries,'' used in a generic sense, refers to ovariectomy (bilateral or with at least part of an ovary remaining), hysterectomy, and tubal sterilization. Only surgeries that occurred before menopause were considered. Age at reproductive surgery was determined by subtracting the date of birth from the month and year of reproductive surgery. If the surgery was performed in the birth month, women with a day of birth before the 15th of the month were considered to have increased a year in age before the surgery. For bilateral ovariectomy, the calculation was based on the date of the surgery that resulted in no ovaries remaining. Duration since reproductive surgery was determined by subtracting the month and year of the reproductive surgery from the reference date. For 19 women

Table 1. Percentage of Control Participants Reporting Premenopausal Reproductive Surgery by Selected Covariates in the Women's Contraceptive and Reproductive Experiences Study, 1994–1998

Covariates	No. of Control Participants	Tubal Sterilization, %	Ovariectomy, %	Hysterectomy, %
Age, years[a]				
35–39	663	22.5	10.6	6.0
40–44	830	31.3	14.9	14.8
45–49	850	35.1	20.5	25.8
50–54	809	34.5	26.3	35.5
55–59	780	27.2	25.6	41.9
60–64	679	15.6	29.2	42.6
Chi-square *P* value[b]		<0.001	<0.001	<0.001
Race				
White	2,972	22.5	19.8	24.8
Black	1,639	38.7	23.8	33.4
Chi-square *P* value[b]		<0.001	<0.01	<0.001
Study site				
Atlanta, Georgia	882	29.0	21.2	31.9
Detroit, Michigan	767	29.7	22.6	28.6
Los Angeles, California	1,236	25.7	21.8	27.2
Philadelphia, Pennsylvania	725	37.7	20.3	23.0
Seattle, Washington	1,001	22.9	20.3	28.2
Chi-square *P* value[b]		<0.001	0.74	<0.01
Age at menarche, years				
<11	446	32.3	27.4	34.1
11–13	3,232	28.3	20.8	26.9
≥14	933	26.4	19.8	28.4
Chi-square *P* value[b]		0.07	<0.01	<0.01

Table continues

who reported having 2 tubal sterilizations, only the first procedure was used for analysis.

Menopausal status is difficult to determine in epidemiologic studies for women who have natural menopause and undergo a gradual transition into menopause and also for women who have undergone a hysterectomy with ovarian conservation (22). We considered a woman postmenopausal if she had not had a menstrual period for 12 months and had not used HT during that time (natural menopause), if she reported a bilateral ovariectomy that halted her menstrual periods (surgical menopause), or if menstrual periods stopped because of irradiation or chemotherapy at least 12 months before the reference date. Determination of menopausal status was not possible for women who had had a hysterectomy and no bilateral ovariectomy resulting in immediate cessation of menstrual periods or had had a hysterectomy within 12 months of their last menstrual period. Determination was also not possible for those who began HT while still menstruating or within 12 months of their last menstrual period. Women who had undergone reproductive surgery, including those with hysterectomy without bilateral ovariectomy, while still menstruating were considered premenopausal at the time of surgery. In analyses by age, comparisons for the age groups 40–44 and ≥45 years were restricted to women whose reference age was the same as or older than that of the age group of interest. Because the reference age of all women in the study was ≥35 years, restriction for younger age groups was unnecessary.

Statistical analyses

Information on reproductive surgery was not provided for 20 cases and 22 controls. Information on pregnancy history or age at menarche was insufficient for 13 cases and 12 controls. Duration of HT was unknown for 4 cases and 4 controls, and educational status was unknown for 1 case. In addition, it was not possible to determine for 80 women whether bilateral ovariectomy performed after age 45 years resulted in menopause or occurred after natural menopause. After participants with missing information or unclear menopausal status were excluded, 4,490 cases (1,591 black women and 2,899 white women) and 4,611 controls (1,639 black women and 2,972 white women) were included in the analyses. Chi-square tests were

Table 1. Continued

Covariates	No. of Control Participants	Tubal Sterilization, %	Ovariectomy, %	Hysterectomy, %
No. of term pregnancies				
0	800	4.3	21.5	21.0
1	711	21.8	21.7	24.5
2	1,335	30.9	21.8	27.7
≥3	1,765	39.8	20.5	32.5
Chi-square *P* value[b]		<0.001	0.82	<0.001
Family history of breast cancer[c]				
Yes	443	28.4	23.0	30.5
No	3,992	28.3	20.8	27.4
Unknown or adopted	176	27.8	25.6	33.0
Chi-square *P* value[b]		0.99	0.20	0.12
Educational status				
Some high school or less	438	35.6	28.8	38.6
High school graduate	1,325	32.5	23.5	30.0
Some college or technical school	1,476	28.9	23.2	32.7
College graduate or higher	1,372	21.1	14.5	17.1
Chi-square *P* value[b]		<0.001	<0.001	<0.001
Duration of hormone therapy use				
Never	2,817	28.5	11.8	13.7
0–6 months	375	37.1	24.0	33.6
>6 months to <5 years	660	30.5	31.4	44.6
≥5 years	759	12.2	46.1	63.1
Chi-square *P* value[b]		<0.001	<0.001	<0.001

[a] Age at first contact for interview.
[b] Comparing prevalence of reproductive surgery across covariate categories.
[c] History of breast cancer in mother, sister, or daughter.

conducted to determine whether the distribution of women having a reproductive surgery of interest differed within categories of covariates.

Unconditional logistic regression modeling (23) was used to calculate odds ratios and corresponding 95% confidence intervals to examine the association between reproductive surgeries, including age at surgery, and breast cancer risk. The referent group for analyses comprised women who had not experienced a reproductive organ surgery before menopause. For women with tubal sterilization, the calendar year of surgery was also examined. For each analysis, risk associated with reproductive surgeries was assessed in 2 models. The first included age, race, and study site. The second additionally adjusted for age at menarche, family history of breast cancer in mother, sisters, or daughters, number of full-term pregnancies, educational status, and duration of HT use. Other potential confounding factors, including number of screening mammograms, age at first term pregnancy, and treatment for infertility, increased or decreased the risk estimates presented here <5%.

RESULTS

Reproductive surgeries were reported by 47.9% of cases and 52.9% of controls. On average, women were aged 32.0 years at tubal sterilization, 36.1 years at ovariectomy (bilateral or with at least part of an ovary remaining), and 38.8 years at hysterectomy. Prevalence of reproductive surgeries varied across levels of covariates among controls (Table 1). Black women and women <11 years of age at menarche were more likely to report having reproductive surgery before menopause. Parous women were more likely to report having had tubal sterilization or hysterectomy.

Tubal sterilization was unrelated to breast cancer risk among women with no other premenopausal reproductive surgery (Table 2). Among the 1,820 women who had tubal sterilization alone, neither age at sterilization nor calendar year of tubal sterilization was associated with breast cancer risk. Risk did not vary by parity or years since tubal sterilization (data not shown). However, women who had had tubal sterilization and hysterectomy, ovariectomy, or both

Table 2. Relation of Breast Cancer Risk to Tubal Sterilization Before Menopause in the Women's Contraceptive and Reproductive Experiences Study, 1994–1998

Exposure Variable	No. of Case Patients	No. of Control Participants	Adjusted Odds Ratio[a]	95% Confidence Interval
Tubal sterilization and another reproductive surgery				
No reproductive surgery	2,339	2,174	1.00	Referent
No tubal sterilization, but other reproductive surgery[b]	925	1,133	0.74	0.66, 0.83
Tubal sterilization	1,226	1,304	0.93	0.84, 1.03
Plus hysterectomy or ovariectomy	326	385	0.83	0.70, 0.99
Alone	900	919	0.97	0.86, 1.09
Age at tubal sterilization, years[c]				
<28	178	199	0.90	0.72, 1.12
28–31	203	208	0.99	0.80, 1.22
32–35	244	240	1.01	0.83, 1.22
≥36	275	272	0.97	0.81, 1.16
Calendar year of tubal sterilization[c]				
<1975	212	226	0.90	0.73, 1.10
1975–1979	216	223	0.92	0.75, 1.13
1980–1984	213	194	1.09	0.88, 1.34
≥1985	259	276	0.98	0.81, 1.18

[a] Adjusted for age (continuous), race (white or black), study site (Atlanta, Detroit, Los Angeles, Philadelphia, or Seattle), age at menarche (continuous), first-degree family history of breast cancer (yes, no, or unknown/adopted), number of term pregnancies (0, 1, 2, or ≥3), educational status (some high school or less, high school graduate, some college or technical school, or college graduate or higher), and duration of hormone therapy use (never, 0–6 months, >6 months to <5 years, or ≥5 years).

[b] Includes women with hysterectomy and/or ovariectomy.

[c] Restricted to women who had a tubal sterilization without hysterectomy or ovariectomy.

were at lower breast cancer risk (odds ratio (OR) = 0.83, 95% confidence interval (CI): 0.70, 0.99) than were women who had not had any reproductive surgery.

Bilateral ovariectomy before 45 years of age reduced the risk of breast cancer, and risk estimates declined significantly as age at ovariectomy decreased (Table 3). Bilateral ovariectomy was protective if it had been performed ≥10 years previously, with an approximately 60% breast cancer risk reduction experienced by women whose bilateral ovariectomy had occurred at least 20 years earlier (OR = 0.40, 95% CI: 0.29, 0.55).

Hysterectomy with at least part of 1 ovary remaining (OR = 0.73, 95% CI: 0.59, 0.91) and hysterectomy with no ovariectomy (OR = 0.83, 95% CI: 0.72, 0.96) were associated with reduced breast cancer risk; ovariectomy with at least part of 1 ovary remaining but no hysterectomy did not reduce risk. Women whose duration since hysterectomy in the absence of bilateral ovariectomy was 10–19 years or ≥20 years experienced a moderate risk reduction (for ≥20 years: OR = 0.77, 95% CI: 0.63, 0.94). However, longer duration since partial ovariectomy with or without hysterectomy was not associated with reduced risk (Table 3).

Risk estimates for tubal sterilization, hysterectomy without ovariectomy, and partial ovariectomy with or without hysterectomy did not vary by ER/PR status. However, bilateral ovariectomy was associated with breast cancer risk reduction among women with ER-positive (ER+)/PR-positive (PR+) breast cancer (OR = 0.56, 95% CI: 0.45, 0.69), but not ER-negative (ER−)/PR-negative (PR−) breast cancer (OR = 0.82, 95% CI: 0.63, 1.08). This difference was substantive (ER+/PR+ cases versus ER−/PR− cases: OR = 0.68, 95% CI: 0.50, 0.92) (Table 4). Associations with breast cancer risk did not significantly differ between white women and black women for any of the reproductive surgeries analyzed. For example, bilateral ovariectomy was protective among both white women (OR = 0.55, 95% CI: 0.44, 0.68) and black women (OR = 0.68, 95% CI: 0.52, 0.89) (interaction of ORs = 1.25, 95% CI: 0.89, 1.75).

DISCUSSION

Factors that affect cumulative exposure to ovarian hormones have repeatedly been associated with breast cancer

Table 3. Relation of Breast Cancer Risk to Reproductive Surgery Before Menopause in the Women's Contraceptive and Reproductive Experiences Study, 1994–1998

Exposure Variable	No. of Case Patients	No. of Control Participants	Adjusted Odds Ratio[a]	95% Confidence Interval
Type of reproductive surgery				
No reproductive surgery	2,339	2,174	1.00	Referent
Bilateral ovariectomy	349	527	0.59	0.50, 0.69
Partial ovariectomy[b] without hysterectomy	227	228	0.94	0.77, 1.14
Partial ovariectomy[b] with hysterectomy	185	224	0.73	0.59, 0.91
Hysterectomy only	490	539	0.83	0.72, 0.96
Tubal sterilization only	900	919	0.96	0.85, 1.08
Duration since bilateral ovariectomy, years				
<10	159	179	0.84	0.67, 1.07
10–19	126	218	0.48	0.38, 0.61
≥20	64	130	0.40	0.29, 0.55
Age at bilateral ovariectomy, years				
<30	21	58	0.31	0.19, 0.51
30–34	28	56	0.44	0.28, 0.71
35–39	62	120	0.47	0.34, 0.65
40–44	86	144	0.52	0.39, 0.69
≥45	152	149	0.93	0.72, 1.18
Duration since hysterectomy without bilateral ovariectomy, years				
<10	183	206	0.86	0.69, 1.06
10–19	256	286	0.80	0.66, 0.96
≥20	236	271	0.77	0.63, 0.94
Duration since partial ovariectomy with or without hysterectomy, years				
<10	93	112	0.78	0.59, 1.04
10–19	160	165	0.91	0.72, 1.14
≥20	159	175	0.82	0.65, 1.03

[a] Adjusted for age (continuous), race (white or black), study site (Atlanta, Detroit, Los Angeles, Philadelphia, or Seattle), age at menarche (continuous), first-degree family history of breast cancer (yes, no, or unknown/adopted), number of term pregnancies (0, 1, 2, or ≥3), educational status (some high school or less, high school graduate, some college or technical school, or college graduate or higher), and duration of hormone therapy use (never, 0–6 months, >6 months to <5 years, or ≥5 years).

[b] Not bilateral; includes women with an unknown number of ovaries removed.

risk. Late age at natural menopause, for example, is an important reproductive risk factor for breast cancer (24, 25). Bilateral ovariectomy also reduces breast cancer risk, presumably by artificially lowering a woman's age at menopause and by causing an immediate halt to the production of ovarian hormones (2–6). The present study supports the role of lifetime exposure to ovarian hormones as a predictor of breast cancer risk. Women who underwent bilateral ovariectomy at earlier ages experienced successively reduced risks, with an approximate 69% risk reduction among women with bilateral ovariectomy before 30 years of age. Odds ratios for bilateral ovariectomy after 45 years of age approached unity, likely because these ages coincided with ages at natural menopause, resulting in similar exposure to ovarian hormones for women who had surgical menopause and for those who had natural menopause. These findings are consistent with other studies that reported a protective effect of bilateral ovariectomy performed before, but not after, 50 years of age (2–4).

Table 4. Relation of Breast Cancer Risk to Reproductive Surgery by Estrogen Receptor/Progesterone Receptor Status in the Women's Contraceptive and Reproductive Experiences Study, 1994–1998

Type of reproductive surgery	No. of Controls	Cases[a] vs. Controls			ER+/PR+ Cases[a] vs. Controls			ER−/PR− Cases[a] vs. Controls			ER+/PR+ Cases[a] vs. ER−/PR− Cases[a]	
		No. of Cases	OR[b]	95% CI	No. of Cases	OR[b]	95% CI	No. of Cases	OR[b]	95% CI	OR[b]	95% CI
No reproductive surgery	2,174	1,668	1.00	Referent	1,143	1.00	Referent	525	1.00	Referent	1.00	Referent
Bilateral ovariectomy	527	257	0.63	0.52, 0.75	163	0.55	0.45, 0.68	94	0.82	0.63, 1.07	0.67	0.49, 0.92
Partial ovariectomy[c] with hysterectomy	224	128	0.75	0.60, 0.96	81	0.71	0.54, 0.93	47	0.88	0.62, 1.23	0.81	0.55, 1.19
Partial ovariectomy[c] without hysterectomy	228	149	0.87	0.70, 1.09	101	0.89	0.69, 1.14	48	0.84	0.60, 1.16	1.06	0.74, 1.53
Hysterectomy, no ovariectomy	539	330	0.81	0.69, 0.95	216	0.77	0.64, 0.93	114	0.91	0.72, 1.15	0.85	0.65, 1.11
Tubal sterilization only	919	630	0.98	0.86, 1.11	388	0.98	0.84, 1.13	242	0.97	0.81, 1.17	1.00	0.82, 1.23

Abbreviations: CI, confidence interval; ER−, estrogen receptor-negative; ER+, estrogen receptor-positive; OR, odds ratio; PR−, progesterone receptor-negative; PR+, progesterone receptor-positive.

[a] Number of cases excludes women with estrogen receptor/progesterone receptor status that was unknown, borderline, not determined, or unavailable.

[b] Adjusted for age (continuous), race (white or black), study site (Atlanta, Detroit, Los Angeles, Philadelphia, or Seattle), age at menarche (years, continuous), first-degree family history of breast cancer (yes, no, or unknown/adopted), number of term pregnancies (0, 1, 2, or ≥3), educational status (some high school or less, high school graduate, some college or technical school, or college graduate or higher), and duration of hormone therapy use (never, 0–6 months, >6 months to <5 years, or ≥5 years).

[c] Not bilateral; includes women with an unknown number of ovaries removed.

A protective effect of hysterectomy on breast cancer risk was observed previously in some studies (6, 9, 12) but not in a recent prospective study (15). The latter study cited unpublished results from the Collaborative Group on Hormonal Factors in Breast Cancer (26), which estimated an approximate 10% breast cancer risk reduction due to the effect of hysterectomy (OR = 0.90, 95% CI: 0.87, 0.93). Hysterectomy with ovarian conservation in premenopausal women was associated with premature ovarian failure in some (27–34) but not all (35–39) studies. A decrease in ovarian blood supply has been observed immediately after hysterectomy (34), and it has been suggested that this phenomenon is a mechanism by which both tubal sterilization and hysterectomy may protect against ovarian cancer (40). Some (29–33) but not all (35–40) studies using concentrations of follicle-stimulating hormone as a clinical marker of ovarian function have reported high concentrations of this hormone, which indicates a decline in ovarian function (41), in women who had hysterectomy with ovarian conservation. Other findings for women who had hysterectomy with ovarian conservation included an increase in complaints about climacteric symptoms (42), bone loss (43), and increased risk of hypertension (44), which may also indicate hormonal sequelae after hysterectomy. Our data indicate that hysterectomy in the absence of bilateral ovariectomy is associated with a moderate reduction in breast cancer risk after >10 years.

A prior report from this Women's CARE Study population found that continuous combined HT use was associated with increased breast cancer risk among current HT users (17). Another Women's CARE Study report indicated that the association with HT use was limited to invasive lobular breast carcinoma (45). The effect of HT use on breast cancer risk, as well as its possible interaction with ovariectomy and hysterectomy, indicates that studies investigating the effects of hysterectomy, partial ovariectomy, or HT use on breast cancer risk should account for all 3 of these potential risk factors in their analyses. Among studies investigating hysterectomy with ovarian conservation and premature ovarian failure, none considered HT use in their analyses. Several studies excluded hysterectomized women with a history of HT use (27, 30, 35, 36, 38).

One study (9) examined the effect of tubal sterilization as the only reproductive surgery. Results showed a reduction in breast cancer risk among all women and among those who had tubal sterilization at 15–34 years of age. Studies that have examined the impact of tubal sterilization with no consideration of other reproductive surgeries have provided inconsistent results (10–14). Tubal sterilization techniques have varied over time, and there is speculation that disparate procedures may have differential effects on blood flow and tissue damage and thus hormone levels and ovarian function (46). Studies assessing risk in relation to calendar year of tubal sterilization have also been inconsistent (11, 13, 14). When we considered tubal sterilization irrespective of other reproductive surgeries, a protective effect was observed for tubal sterilization before age 28 years (OR = 0.79, 95% CI: 0.66, 0.96) and before calendar year 1980 (OR = 0.84, 95% CI: 0.74, 0.96). However, it is likely that the cumulative impact of other reproductive surgeries dominated this effect, because among women having only tubal sterilization, breast cancer risk was not reduced within any age grouping (Table 2), calendar-year grouping (Table 2), or duration since tubal sterilization (data not shown).

A previous Women's CARE Study report found multiparity and early age at first birth to be associated with reduced risk of ER+/PR+ tumors but not ER−/PR− tumors (16). ER/PR status mediated the associations between breast cancer and reproductive and lifestyle risk factors in a case-control study of Vietnamese and Chinese women eligible for a clinical trial of ovariectomy and tamoxifen as breast cancer treatment (47). However, neither report considered ER/PR status as a possible mediator in the protective effect of bilateral ovariectomy. In the current analysis, bilateral ovariectomy was associated with reduced risk of ER+/PR+ tumors but not ER−/PR− tumors, although the direction was the same. The finding that the protective effect of bilateral ovariectomy, which terminates exposure to ovarian hormones, is limited to receptor-positive tumors is consistent with the proposal that ER+ and PR+ breast cancers are influenced by exposure to estrogen and progesterone, whereas ER− and PR− breast cancers are not (48).

Among this study's strengths are the study size, population-based sampling, geographic diversity, and inclusion of both black and white women. The large number of women who underwent reproductive surgery in each subsample provides sufficient statistical power to detect moderate associations.

A potential limitation of case-control studies is that selection bias or recall bias may influence results. Here, RDD screening rates and interview completion rates were acceptably high (76.5% of eligible cases; 78.6% of eligible controls at households successfully screened), falling within ranges reported in the literature (19). Recall bias was minimized by assessing reproductive and contraceptive histories in conjunction with completion of a calendar of life events to facilitate recall.

It was not possible to compare reported reproductive surgeries with medical records. Self-reporting of hysterectomy and tubal sterilization was shown to be reliable and valid in an Australian study (49). A validation study of self-reported hysterectomy and ovariectomy in a group setting in Washington State reported high accuracy for hysterectomy but not for ovariectomy (22). The accuracy of self-reporting for ovariectomy is a potential limitation in our study, especially when reproductive surgeries were performed concurrently. This may have been a particular problem for self-reporting of the number of ovaries remaining after all reproductive surgeries. It is possible that women may not always know the extent of a hysterectomy operation (i.e., unilateral, partial, or bilaterateral ovariectomy performed in addition to a hysterectomy). Of women classified as having had a hysterectomy and partial ovariectomy in our study, 128 reported having both ovaries intact after all ovarian surgeries. Excluding these women from analyses did not alter our results. It is unclear whether previous studies assessing the relation between breast cancer risk and unilateral ovariectomy (2, 5, 6, 9, 12) included only women with 1 total ovary removed, excluding those with partial ovariectomy. An additional potential limitation is that we did not collect data on indications for reproductive surgeries. Hysterectomy rates have considerable geographic, patient-related, and physician-related variation (50). This may help explain discrepant findings in studies investigating hysterectomy and breast cancer risk. Another potential limitation is our inability to control for age at menopause among women having a hysterectomy before natural menopause; for these women, age at menopause is unknown.

ER/PR status was not available for all cases. A previous study conducted within SEER registries (51) reported a frequency of 18% unknown ER/PR status and 5% not carried out, which is comparable to the 17.6% frequency of unknown receptor status in our study. The Women's CARE Study cases with no ER/PR status were more likely to be multiparous, have earlier first births, and have breastfed for shorter periods of time; however, it is unlikely that information on ER/PR status for these women would have altered findings (16). An additional limitation was that we used ER/PR status as reported in the pathology report. It is possible that the cutoff for positive receptor status and assay quality varied between laboratories. A recent Women's CARE Study publication, which compared ER/PR status obtained from SEER registries to that obtained from a single expert laboratory (for Los Angeles and Detroit cases), showed that registry results for ER+/PR+ and ER−/PR− tumors are reasonably reliable and that risk estimates for tumors classified using the SEER results and using the expert laboratory classification differed minimally for standard reproductive breast cancer risk factors (52).

In summary, our findings support the association between bilateral ovariectomy and lower breast cancer risk. Hysterectomy with or without partial ovary removal was also protective. Breast cancer risk was not reduced among women who had only tubal sterilization or partial ovariectomy without hysterectomy. Because reproductive surgeries can alter ovarian hormone production, such alterations are likely to mediate the association between these surgeries and breast cancer risk.

ACKNOWLEDGMENTS

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Center, Springfield, Massachusetts (Ronald T. Burkman); Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington (Kathleen E. Malone); Cancer Centers Branch, National Cancer Institute, Bethesda, Maryland (Linda K. Weiss); and Contraceptive and Reproductive Health Branch, Center for Population Research, National Institute of Child Health and Human Development, Bethesda, Maryland (Robert Spirtas).

Data collection for the Women's CARE Study was supported by the National Institute of Child Health and Human Development, with additional support from the National Cancer Institute, through contracts with Emory University (N01-HD-2-3168), the Fred Hutchinson Cancer Research Center (N01-HD-2-3166), the Karmanos Cancer Institute at Wayne State University (N01-HD-3-3174), the University of Pennsylvania (N01-HD-3-3176), and the University of Southern California (N01-HD-3-3175); and through an intraagency agreement with the Centers for Disease Control and Prevention (Y01-HD-7022). Support for use of Surveillance, Epidemiology, and End Results cancer registries for case identification was obtained through contracts N01-PC-67006 (Atlanta), N01-CN-65064 (Detroit), N01-PC-67010 (Los Angeles), and N01-CN-0532 (Seattle). The collection of cancer incidence data in California used in this publication (University of Southern California, Los Angeles County portion of this study) was also supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by the California Health and Safety Code, Section 103885.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the California Department of Health Services.

Conflict of interest: none declared.

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