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Bilateral Oophorectomy in Relation to Risk of Postmenopausal Breast Cancer: Confounding by Nonmalignant Indications for Surgery?

Hazel B. Nichols*, Kala Visvanathan, Polly A. Newcomb, John M. Hampton, Kathleen M. Egan, Linda Titus-Ernstoff, and Amy Trentham-Dietz

* Correspondence to Hazel B. Nichols, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E6139, Baltimore, MD 21205 (e-mail: hnichols@jhsph.edu).

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Bilateral oophorectomy is often performed during hysterectomy for benign conditions and can reduce breast cancer risk by 20%–50% when performed at younger ages. Accuracy of estimating the decrease in breast cancer risk associated with bilateral oophorectomy could be affected by common conditions that lead to surgery, such as uterine fibroids or endometriosis. The authors examined the potential for confounding by nonmalignant indications for surgery on breast cancer risk estimates in a population-based case-control study of invasive breast cancer newly diagnosed in 1992–1995. Breast cancer cases ($N = 4{,}935$) aged 50–79 years were identified from Wisconsin, Massachusetts, and New Hampshire tumor registries; similarly aged controls ($N = 5{,}111$) were selected from driver's license and Medicare lists. Reproductive and medical history was obtained from structured telephone interviews. Odds ratios and 95% confidence intervals were estimated with multivariate logistic regression. Women who underwent bilateral oophorectomy with hysterectomy at age $\leq$40 years had significantly reduced odds of breast cancer (odds ratio = 0.74, 95% confidence interval: 0.60, 0.90) compared with women with intact ovaries and uterus. Effect estimates were virtually unchanged after adjustment for uterine fibroids or endometriosis history. Results indicate that breast cancer risk reductions conferred by bilateral oophorectomy are not strongly confounded by failure to account for nonmalignant indications for surgery.

breast neoplasms; case-control studies; confounding factors, epidemiology; endometriosis; hysterectomy; leiomyoma; ovariectomy

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

Few surgical procedures include the elective removal of healthy organs. Prophylactic bilateral oophorectomy (surgical removal of both ovaries) is commonly performed at the time of hysterectomy to reduce ovarian cancer risk or the need for future gynecologic surgery. Approximately half of all hysterectomies performed in the United States include bilateral oophorectomy, resulting in ovarian removal from 15% of women by age 60 years (1). While the total number of hysterectomies performed has declined during recent decades, the proportion of surgeries that include ovarian removal has continued to rise (2). Recently, increased attention has been directed at determining the risk-benefit ratio of elective oophorectomy because of reports of elevated risk of heart disease, stroke, fracture, and all-cause mortality for oophorectomized women (3–6). Accurate estimation of the long-term benefits and adverse health effects associated with bilateral oophorectomy is needed to inform risk-benefit analyses.

In addition to ovarian cancer prevention, bilateral oophorectomy can reduce breast cancer risk by 20%–50%, particularly when performed before age 40 years (7–13). Previous studies have addressed ''confounding by indication,'' or the potential for biased estimates of the association between oophorectomy and breast cancer risk based on the indication for surgery (14), by excluding surgeries performed for malignant conditions (6). However, nonmalignant conditions such as uterine fibroids or endometriosis could also confound estimates of breast cancer risk reduction conferred

by oophorectomy. For example, the prevalence of symptomatic uterine fibroids has been approximated at 30%–64% by age 50 years among US women (15, 16) and is the leading indication for hysterectomy (2). Although the etiology of fibroids is not well understood, estrogen and progesterone are contributors to fibroid development and growth, and fibroids often regress after menopause (17, 18). Increased estrogen and progesterone exposure is generally recognized as a risk factor for breast cancer (19), suggesting that the reported protective association between bilateral oophorectomy and breast cancer risk could be attenuated by failure to account for history of uterine fibroids.

The prevalence of symptomatic endometriosis is lower than that of fibroids, with estimates ranging from 2% to 10% of US women in the general population (20–22). However, endometriosis is the primary indication for 6%–20% of hysterectomies (1, 23) and has been associated with up to 3-fold increases in breast cancer risk in some studies (reviewed by Ness and Modugno (24) and by Somigliana et al. (25)), possibly because of hormonal alterations or underlying systemic inflammation. Therefore, a positive association between endometriosis and breast cancer could similarly attenuate estimates of the protective effects of oophorectomy.

The aim of the study was to determine whether nonmalignant indications for surgery, such as uterine fibroids or endometriosis, confound or modify the association between bilateral oophorectomy and breast cancer risk. Therefore, we analyzed data from a population-based case-control study of invasive breast cancer among US women.

MATERIALS AND METHODS

This analysis was performed using data from the Collaborative Breast Cancer Study, a population-based case-control study of invasive breast cancer conducted in Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire. The study was conducted according to institutionally approved protocols at each study site.

Selection of cases

Eligible for this study were women residing in Wisconsin, Massachusetts, or New Hampshire aged 50–79 years with a new diagnosis of invasive breast cancer during 1992–1995 reported to each state's cancer registry. Eligibility was further limited to women with listed telephone numbers, driver's licenses verified by self-report (if younger than age 65 years), and registry-reported dates of diagnosis. A total of 6,839 eligible breast cancer cases were identified. The physician of record for each case was contacted by mail to ascertain whether there were objections to their patients' participation. Physicians refused contact with 158 (2.3%) cases, 293 (4.3%) cases were deceased, 83 (1.2%) could not be located, and 620 (9.1%) refused to participate. Therefore, 5,685 (83.1%) eligible cases were interviewed. Twenty-six interviewed cases were considered unreliable by the interviewers, leaving 5,659 case interviews available for analysis. For this analysis, we additionally excluded women with a previous history of cancer (except nonmelanoma skin cancer) ($n = 297$), who were premenopausal ($n = 267$), or had unknown menopausal status ($n = 116$). Finally, 32 records from women with discordant ages at bilateral oophorectomy and hysterectomy and 12 records of women with missing ages for both procedures were excluded. After these exclusions, 4,935 cases contributed to our analyses.

Selection of controls

Population controls were identified during 1992–1995 in each state from lists of licensed drivers (age <65 years) and Medicare beneficiaries (ages 65–79 years). Controls were randomly selected within 5-year age strata to yield an age distribution similar to the cases enrolled in each state and were required to have no personal history of breast cancer and a listed telephone number. Of the 7,655 potential controls identified, 183 (2.4%) were deceased, 124 (1.6%) could not be located, and 1,397 (18.2%) refused to participate. Interviews were obtained with 5,951 (77.7%) women. Twenty-three control interviews were considered unreliable by the interviewer. Hence, information from 5,928 controls was available for analysis. We additionally excluded controls with any other personal history of cancer (except nonmelanoma skin cancer) ($n = 310$), who were premenopausal ($n = 292$), or who had unknown menopausal status ($n = 150$). Lastly, 52 records of women with discordant ages at bilateral oophorectomy and hysterectomy and 13 records of women with missing ages for both procedures were excluded. The final analytic sample included 5,111 controls.

Data collection

Cases and controls were sent letters briefly describing the study before they were contacted by telephone by trained interviewers. The telephone interview elicited information on reproductive history, oral contraceptive and postmenopausal hormone use, lifestyle and demographic factors, and personal and family medical history. Information about personal and family history of cancer was obtained at the end of the interview to maintain interviewer blinding of case-control status.

For each case, a reference date was defined as the registry-supplied date of invasive breast cancer diagnosis. For comparability, the controls interviewed contemporaneously with cases were assigned an individual reference date corresponding to the average time from diagnosis to interview for the case group. Only exposures that occurred prior to the assigned reference date were included in analyses. Reference age was defined as age at diagnosis for cases or on the reference date for controls.

Study participants reported whether they had been diagnosed with endometriosis or uterine fibroids by a physician or had surgery to remove the uterus and/or ovaries before the reference date. Age at diagnosis for endometriosis and/or uterine fibroids, type of surgery (hysterectomy and/or oophorectomy, including number of ovaries removed), and age at surgery was asked of all participants.

A woman was categorized as postmenopausal if she reported natural menopause (defined as no menstrual periods for ≥6 months not due to surgery, chemotherapy, radiation,

or other reasons) or a bilateral oophorectomy before the reference date. Women who reported hysterectomy without bilateral oophorectomy were categorized as premenopausal if their reference age was in the first decile of age at natural menopause among controls (<42 years of age for current smokers and <43 years of age for nonsmokers), as postmenopausal if their reference age was in the highest decile for age at natural menopause among controls (>55 years of age), and otherwise as having an unknown menopausal status. Participants who had started postmenopausal hormone use before cessation of menses were categorized as postmenopausal with unknown age at menopause. Body mass index was calculated as weight (kg)/tallest adult height $(m)^2$ during the 1–2-year period prior to the reference date. Categories of body mass index were defined as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (>30 kg/m^2) (26).

Statistical analysis

Odds ratios and 95% confidence intervals for breast cancer were calculated by using multivariate logistic regression models. *P*-trends were obtained by including categorical variables in regression models. Initial multivariate models were adjusted a priori for age (5-year groups) and state of residence; final models additionally included the following covariates: age (years) at menarche (<12, 12, 13, ≥14, unknown), oral contraceptive use (never, <1 year, 1–4.9 years, ≥5 years, unknown), age (years) at first birth (<20, 20–24, 25–29, ≥30, unknown), parity (livebirths) (0–1, 2–3, ≥4, unknown), postmenopausal hormone use (never, estrogen only, estrogen + progestin only, combination of estrogen and estrogen + progestin, other/unknown), first-degree family history of breast cancer (yes, no, unknown), mammography screening (yes, no, unknown), and body mass index (underweight, normal, overweight, obese, unknown). Analyses stratified according to gynecologic surgery status (none vs. bilateral oophorectomy with hysterectomy) additionally adjusted for age (years) at menopause (<45, 45–49, 50–54, ≥55, unknown). Effect modification was evaluated by including cross-product interaction terms in logistic models and measuring the change in the log-likelihood using chi-squared tests. *P* values ≤0.05 were considered statistically significant.

In these data, we were unable to determine whether uterine fibroids or endometriosis was diagnosed before versus at the time of hysterectomy when the same age was reported for both. To evaluate the sensitivity of our estimates to asymptomatic fibroids or endometriosis that may have been diagnosed at the time of surgery, we additionally calculated odds ratios for breast cancer excluding hysterectomies performed at the same age at diagnosis of these conditions. All analyses were performed using SAS version 9.2 software (SAS Institute, Inc., Cary, North Carolina).

Reliability substudy

A sequential sample of study participants was reinterviewed to evaluate the reliability of participant responses to the study questionnaire. After an average of 3.5 months (range, 2–6), 195 controls completed a second interview. Cohen's kappa was used to evaluate reliability for categorical variables including surgery to remove the uterus and/or ovaries and physician diagnosis of fibroids or endometriosis. Among controls interviewed a second time, reproducibility of the uterine and ovarian removal questions was extremely high. Cohen's κ was 0.94 for both uterine (yes/no; 95% confidence interval (CI): 0.90, 0.99) and ovarian (0, 1, or 2 ovaries; 95% CI: 0.88, 0.99) removal. The reproducibility of responses to questions regarding physician diagnosis of fibroids and of endometriosis was also good ($\kappa = 0.71$, 95% CI: 0.59, 0.83 and $\kappa = 0.79$, 95% CI: 0.59, 0.99, respectively).

RESULTS

The mean ages were 66.2 years (standard deviation, 7.4) for cases and 65.0 years (standard deviation, 7.5) for controls. Approximately 60% of cases and controls were Wisconsin residents; 30% lived in Massachusetts and 10% in New Hampshire. Table 1 displays odds ratios and 95% confidence intervals for breast cancer according to gynecologic surgery status and select breast cancer risk factors. Bilateral oophorectomy with hysterectomy was the most frequently reported gynecologic surgery (17.9% of cases, 18.8% of controls), followed by hysterectomy alone (9.6% of cases, 9.3% of controls). Overall, previous history of gynecologic surgery was not associated with breast cancer risk. Hysterectomy alone was not associated with breast cancer risk for younger (age ≤40 years) or older (age >40) women compared with women with an intact uterus and ovaries. However, bilateral oophorectomy with hysterectomy at age ≤40 years was associated with a 26% reduction in breast cancer risk (odds ratio (OR) = 0.74, 95% CI: 0.60, 0.90). No reduction in breast cancer odds was observed for women who underwent a bilateral oophorectomy with hysterectomy after age 40 years (OR = 1.00, 95% CI: 0.88, 1.14).

Table 2 presents the association between benign gynecologic conditions (i.e., uterine fibroids and endometriosis) and gynecologic surgery status among controls. After adjustment for potential confounders, women who reported a diagnosis of uterine fibroids had 6 times the odds of having a bilateral oophorectomy with hysterectomy compared with women without a diagnosis of fibroids (OR = 6.04, 95% CI: 4.85, 7.52). A positive history of endometriosis (compared with no endometriosis) increased the odds of bilateral oophorectomy with hysterectomy approximately 10-fold (OR = 9.95, 95% CI: 6.60, 14.99).

Table 3 displays odds ratios (and 95% confidence intervals) for breast cancer according to history of uterine fibroids or endometriosis in the full study population and stratified by hysterectomy status. In the full study population, a positive history of uterine fibroids was associated with a 13% increase in the odds of invasive breast cancer (95% CI: 1.01, 1.26) with no apparent pattern according to age at fibroids diagnosis. A history of endometriosis was not associated with breast cancer risk overall or when examined by age at diagnosis.

Table 1. Odds Ratios and 95% Confidence Intervals for Invasive Breast Cancer According to Gynecologic Surgery and Select Risk Factors for US Women, 1992–1995

Characteristic	Cases (N = 4,935)		Controls (N = 5,111)		OR[a]	95% CI	OR[b]	95% CI
	No.	%	No.	%				
Gynecologic surgery								
None	3,181	64.5	3,271	64.0	1		1	
Hysterectomy alone (uterus only)	476	9.6	474	9.3	1.03	0.89, 1.18	1.06	0.92, 1.23
At age ≤40 years	167	3.4	174	3.4	1.02	0.82, 1.27	1.04	0.83, 1.30
At age >40 years	301	6.1	290	5.7	1.04	0.88, 1.23	1.07	0.90, 1.28
Hysterectomy with unilateral oophorectomy	178	3.6	183	3.6	0.98	0.79, 1.21	0.98	0.79, 1.23
Bilateral oophorectomy with hysterectomy	885	17.9	961	18.8	0.95	0.86, 1.06	0.93	0.83, 1.05
At age ≤40 years	194	3.9	270	5.3	0.75	0.62, 0.91	0.74	0.60, 0.90
At age >40 years	691	14.0	691	13.5	1.03	0.92, 1.16	1.00	0.88, 1.14
Unilateral oophorectomy (without hysterectomy)	139	2.8	131	2.6	1.07	0.84, 1.37	1.05	0.82, 1.35
Bilateral oophorectomy (without hysterectomy)	32	0.6	29	0.6	1.07	0.65, 1.78	1.06	0.63, 1.77
Unknown	44	0.9	62	1.2				
Oral contraceptive use								
Never	3,741	75.8	3,788	74.1	1		1	
Ever, months of use	1,136	23.0	1,286	25.2	1.06	0.96, 1.18	1.09	0.98, 1.22
1–11	334	6.8	360	7.0	1.11	0.94, 1.31	1.11	0.94, 1.31
12–59	365	7.4	426	8.3	1.04	0.89, 1.22	1.06	0.91, 1.25
≥60	407	8.2	459	9.0	1.08	0.93, 1.25	1.12	0.96, 1.31
Unknown	58	1.2	37	0.7				
Parity								

Table continues

In analyses restricted to women who reported having a bilateral oophorectomy with hysterectomy, a uterine fibroids diagnosis was associated with a 32% increase in breast cancer odds (95% CI: 1.08, 1.61), with a positive trend according to age at fibroids diagnosis (P-trend = 0.002). Among women with an intact uterus and ovaries, there was little evidence of an overall association between fibroids history and breast cancer risk (OR = 1.14, 95% CI: 0.94, 1.37). No statistically significant associations between endometriosis history and breast cancer risk were observed for women who either reported bilateral oophorectomy with hysterectomy or had an intact uterus and ovaries. A diagnosis of endometriosis before age 35 years was associated with a positive, borderline significant increase in breast cancer odds (OR = 1.83, 95% CI: 0.95, 3.51) for women with an intact uterus and ovaries (Table 3).

To address our a priori hypothesis of confounding of the association between bilateral oophorectomy with hysterectomy and invasive breast cancer by the indication for hysterectomy, we included uterine fibroids and/or endometriosis diagnosis as covariates in our multivariate logistic regression models. The overall association between bilateral oophorectomy with hysterectomy at age ≤40 years and breast cancer risk (OR = 0.74, 95% CI: 0.60, 0.90; Table 1) was virtually unchanged after additional adjustment for endometriosis (OR = 0.74, 95% CI: 0.60, 0.91) or fibroids (OR = 0.72, 95% CI: 0.58, 0.88) diagnosis.

To address potential effect modification of the association between bilateral hysterectomy with oophorectomy and postmenopausal breast cancer risk according to fibroids and endometriosis history, we first conducted analyses stratified by these conditions and then assessed the statistical significance of interaction terms included in logistic regression models. Among women who had never been diagnosed with endometriosis or fibroids, the protective effect of bilateral oophorectomy with hysterectomy at age ≤40 years compared with no surgery was similar to that observed in the full study population (OR = 0.73, 95% CI: 0.55, 0.97). Among women who reported being diagnosed with uterine fibroids, bilateral oophorectomy with hysterectomy was not significantly associated with breast cancer risk, either overall (OR = 1.18, 95% CI: 0.89, 1.56) or for women who

Table 1. Continued

Characteristic	Cases (N = 4,935)		Controls (N = 5,111)		OR[a]	95% CI	OR[b]	95% CI
	No.	%	No.	%				
Nulliparous	572	11.6	533	10.4	1		1	
1	521	10.6	440	8.6	1.07	0.90, 1.28	1.07	0.89, 1.27
2–3	2,207	44.7	2,244	43.9	0.92	0.81, 1.06	0.92	0.80, 1.05
≥4	1,592	32.3	1,878	36.7	0.80	0.70, 0.92	0.77	0.67, 0.89
Unknown	43	0.9	16	0.3				
Postmenopausal hormone use								
Never	3,486	70.6	3,714	72.7	1		1	
Estrogen only	899	18.2	909	17.8	1.08	0.98, 1.20	1.20	1.08, 1.34
Estrogen + progestin only	290	5.9	266	5.2	1.41	1.18, 1.69	1.58	1.32, 1.90
Estrogen and estrogen + progestin	126	2.6	111	2.2	1.38	1.06, 1.80	1.56	1.19, 2.04
Other/unknown	134	2.7	111	2.2				
Family history of breast cancer								
No	3,759	76.2	4,331	84.7	1		1	
Yes	1,074	21.8	702	13.7	1.74	1.03, 1.88	1.80	1.62, 2.01
Unknown	102	2.1	78	1.5				
Body mass index, kg/m^2								
Underweight (<18.5)	76	1.5	103	2.0	0.80	0.59, 1.09	0.78	0.57, 1.06
Normal weight (18.5–24.9)	1,964	39.8	2,294	44.9	1		1	
Overweight (25.0–29.9)	1,588	32.2	1,610	31.5	1.14	1.04, 1.25	1.18	1.08, 1.30
Obese (≥30)	1,080	21.9	884	17.3	1.45	1.30, 1.61	1.55	1.38, 1.73
Unknown	227	4.6	220	4.3				

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

[a] Odds ratios were adjusted for age and US state.

[b] Odds ratios were adjusted for age, US state, age at menarche, duration of oral contraceptive use, parity, age at first birth, postmenopausal hormone use, body mass index, mammography screening, and family history of breast cancer.

reported having surgery at age ≤40 years (OR = 0.96, 95% CI: 0.63, 1.47) compared with no surgery. The P value for interaction between uterine fibroids diagnosis and hysterectomy status was 0.4.

Sample sizes were insufficient in the strata of women with endometriosis to perform full multivariate adjustment; odds ratio estimates for invasive breast cancer in these strata were exploratory and were adjusted for age and state only. Among women with endometriosis, bilateral oophorectomy with hysterectomy was associated with reduced risk of breast cancer when performed at age ≤40 years (OR = 0.42, 95% CI: 0.21, 0.87) compared with no surgery. The test for interaction between endometriosis diagnosis and hysterectomy status was statistically significant (P-interaction = 0.03) (Table 4).

We additionally performed sensitivity analyses that excluded hysterectomies performed at the same age as fibroids or endometriosis diagnosis to avoid incidental findings during surgery. In analyses that excluded hysterectomies performed at the same age as fibroids diagnosis, the estimate for breast cancer risk associated with bilateral oophorectomy with hysterectomy at age ≤40 years (compared with no surgery) was similar to that observed in the full study population but was not statistically significant (OR = 0.70, 95% CI: 0.35, 1.39). In analyses that excluded hysterectomies performed at the same age as endometriosis diagnosis, the odds ratio for breast cancer associated with bilateral oophorectomy with hysterectomy at age ≤40 years (compared with no surgery) was 0.24 (95% CI: 0.09, 0.67) (Table 4).

DISCUSSION

Results from this study provide reassurance that previously reported (7–13) estimates of breast cancer risk reductions conferred by bilateral oophorectomy with hysterectomy are unlikely to be strongly confounded by nonmalignant indications for surgery such as uterine fibroids or endometriosis. Valid estimates of the magnitude of breast cancer risk reduction conferred by oophorectomy are necessary for the current debate regarding the risk-benefit ratio for this often-elective procedure (3, 6). Our data suggest potential effect modification of the association between bilateral oophorectomy with hysterectomy and breast cancer risk according to

Table 2. Odds Ratios and 95% Confidence Intervals for Bilateral Oophorectomy With Hysterectomy According to Benign Gynecologic Conditions Among US Controls, 1992–1995

Characteristic	Bilateral Oophorectomy With Hysterectomy (N = 961)		Intact Uterus and Ovaries (N = 3,271)		OR[a]	95% CI	OR[b]	95% CI
	No.	%	No.	%				
Uterine fibroids								
No	601	62.5	2,999	91.7	1		1	
Yes	353	36.7	244	7.5	7.37	6.11, 8.88	6.04	4.85, 7.52
Unknown	7	0.7	28	0.9				
Endometriosis								
No	810	84.3	3,212	98.2	1		1	
Yes	142	14.8	44	1.3	12.83	9.03, 18.23	9.95	6.60, 14.99
Unknown	9	0.9	15	0.5				

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

[a] Odds ratios were adjusted for age and US state.

[b] Odds ratios were adjusted for age, US state, age at menarche, duration of oral contraceptive use, parity, age at first birth, postmenopausal hormone use, body mass index, mammography screening, and family history of breast cancer.

endometriosis history. Among women who reported having endometriosis, surgery at age $\leq$40 years (vs. no surgery) was associated with a 58% reduction in breast cancer odds compared with a 27% reduction observed among women without endometriosis. However, analyses of women with endometriosis were limited by small samples that were insufficient for full multivariate adjustment; we therefore remain cautious in our interpretation until these findings can be replicated elsewhere.

To our knowledge, uterine fibroids and endometriosis diagnoses have not been formally evaluated as potential confounders or effect modifiers of the association between bilateral oophorectomy with hysterectomy and breast cancer risk. However, the possibility of confounding by these benign conditions has been suggested relative to breast cancer risk associations for hysterectomy alone (11) and hysterectomy with bilateral oophorectomy (12). Evidence in support of potential confounding comes from reports that 50%–60% of hysterectomies performed in the United States list uterine fibroids or endometriosis as the primary indication (1, 2, 27), combined with estimates of increased breast cancer risk associated with fibroids and endometriosis in some studies (24, 28–30). In Swedish registry data from 1965 and 1983, hysterectomy (without oophorectomy) indicated by uterine myoma was associated with a 30% increase in the standardized mortality ratio for breast cancer (95% CI: 1.0, 1.7) (28). Two earlier studies showed either small increases (standardized incidence ratio = 1.7; $P < 0.01$) (29) in breast cancer risk or no association with uterine fibroids (31). In our analysis, a diagnosis of uterine fibroids was associated with a 13% increase in breast cancer odds overall, with a significant positive trend between increasing age at fibroids diagnosis and breast cancer risk for women who reported undergoing bilateral oophorectomy with hysterectomy.

Endometriosis has been associated with up to 3-fold increases in breast cancer risk in some (30), but not all (32), previous studies (reviewed by Ness and Modugno (24) and by Somigliana et al. (25)). We observed no significant associations between endometriosis diagnosis and breast cancer risk in the overall study population or according to hysterectomy status, although an increased breast cancer risk (OR = 1.83, 95% CI: 0.95, 3.51) was suggested for women who had not had surgery and were diagnosed with endometriosis at the earliest ages. Our exploratory finding of a 58% reduction in breast cancer odds for women with endometriosis who underwent bilateral oophorectomy with hysterectomy at age $\leq$40 years compared with those with an intact uterus and ovaries could suggest an additional benefit conferred by early interruption of an inflammatory process that may ultimately contribute to breast cancer risk.

The questionnaire in this study did not ascertain whether physician-diagnosed endometriosis included laparoscopic or imaging confirmation (33); as such, our categorization is likely subject to some misclassification of exposure. However, despite very small numbers, the strong breast cancer risk reduction associated with bilateral oophorectomy with hysterectomy at earlier ages among women diagnosed with endometriosis was still apparent in sensitivity analyses that excluded women who reported the same age for both hysterectomy and endometriosis diagnosis (where endometriosis may have been an incidental finding rather than the indication for surgery).

Limitations to our analysis should be considered when interpreting these findings. Gynecologic surgery information and previous physician diagnosis of fibroids or endometriosis were obtained by participant self-report. A 1988 validation study of 128 breast cancer cases and 154 controls enrolled in the Breast Cancer Detection and Demonstration Project reported 90% agreement between medical reports and self-reported bilateral oophorectomy with hysterectomy status for cases, and 84% among controls (7). Validity of self-reported hysterectomy status was also high in the Nurses' Health Study; among 69 women who reported bilateral oophorectomy with hysterectomy, medical record confirmation was obtained for 66 (95.7%) (34). More recently, 74%

Table 3. Odds Ratios and 95% Confidence Intervals for Invasive Breast Cancer According to Benign Gynecologic Conditions, Age at Diagnosis, and Gynecologic Surgery Status of US Women, 1992–1995

Characteristic	Full Study Population				Bilateral Oophorectomy With Hysterectomy[a]				Intact Uterus and Ovaries[a]			
	Cases (n = 4,935)	Controls (n = 5,111)	OR[b]	95% CI	Cases (n = 885)	Controls (n = 961)	OR[b]	95% CI	Cases (n = 3,181)	Controls (n = 3,271)	OR[b]	95% CI
Uterine fibroids												
No	3,964	4,170	1		495	601	1		2,868	2,999	1	
Yes	845	835	1.13	1.01, 1.26	378	353	1.32	1.08, 1.61	254	244	1.14	0.94, 1.37
Diagnosed at age <35 years	158	170	1.14	0.91, 1.44	46	66	0.97	0.64, 1.47	61	56	1.26	0.86, 1.83
Diagnosed at ages 35–44 years	311	314	1.16	0.98, 1.38	129	121	1.44	1.07, 1.93	79	67	1.19	0.85, 1.67
Diagnosed at age ≥45 years	349	331	1.08	0.91, 1.27	198	161	1.39	1.06, 1.81	97	109	1.00	0.75, 1.33
P-trend				0.08				0.002				0.5
Endometriosis												
No	4,642	4,789	1		782	810	1		3,088	3,212	1	
Yes	198	228	0.99	0.80, 1.21	95	142	0.82	0.60, 1.10	54	44	1.23	0.81, 1.85
Diagnosed at age <35 years	81	85	1.14	0.83, 1.57	30	53	0.76	0.46, 1.23	26	15	1.83	0.95, 3.51
Diagnosed at ages 35–44 years	66	78	1.00	0.71, 1.41	37	45	1.07	0.66, 1.74	16	16	0.97	0.48, 1.98
Diagnosed at age ≥45 years	48	59	0.83	0.56, 1.22	27	41	0.69	0.41, 1.15	11	11	0.98	0.42, 2.29
P-trend				0.5				0.2				0.6

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

[a] The total numbers of cases and controls with bilateral oophorectomy with hysterectomy and intact uterus and ovaries do not equal the full study population because women with removal of the uterus alone, uterus plus 1 ovary, 1 ovary alone, or 2 ovaries alone were excluded.

[b] Odds ratios were adjusted for age, US state, age at menarche, duration of oral contraceptive use, parity, age at first birth, age at menopause, postmenopausal hormone use, body mass index, mammography screening, and family history of breast cancer.

Table 4. Odds Ratios and 95% Confidence Intervals for Invasive Breast Cancer According to Gynecologic Surgery, Uterine Fibroids, and Endometriosis History of US Women, 1992–1995

	No. of Cases	No. of Controls	OR[a]	95% CI				
No uterine fibroids or endometriosis								
Intact uterus and ovaries	2,819	2,952	1					
Bilateral oophorectomy with hysterectomy	429	499	0.86	0.73, 1.01				
At age ≤40 years	97	137	0.73	0.55, 0.97				
At age >40 years	332	362	0.90	0.76, 1.08				
					Bilateral Oophorectomy With Hysterectomy ≥1 Year After Fibroids Diagnosed			
	No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[a]	95% CI
Uterine fibroids (only)[b]								
Intact uterus and ovaries	245	239	1		245	239	1	
Bilateral oophorectomy with hysterectomy	345	307	1.18	0.89, 1.56	119	115	1.14	0.77, 1.69
At age ≤40 years	63	71	0.96	0.63, 1.47	18	28	0.70	0.35, 1.39
At age >40 years	282	236	1.25	0.93, 1.68	101	87	1.31	0.86, 2.00
					Bilateral Oophorectomy With Hysterectomy ≥1 Year After Endometriosis Diagnosed			
	No. of Cases	No. of Controls	OR[d]	95% CI	No. of Cases	No. of Controls	OR[d]	95% CI
Endometriosis (only)[c]								
Intact uterus and ovaries	44	40	1		44	40	1	
Bilateral oophorectomy with hysterectomy	63	98	0.62	0.36, 1.08	33	43	0.68	0.36, 1.30
At age ≤40 years	18	41	0.42	0.21, 0.87	6	21	0.24	0.09, 0.67
At age >40 years	45	57	0.78	0.42, 1.42	27	22	1.14	0.54, 2.37

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

[a] Odds ratios were adjusted for age, US state, age at menarche, duration of oral contraceptive use, age at first birth, parity, postmenopausal hormone use, body mass index, mammography screening, and family history of breast cancer.

[b] *P* value for interaction between uterine fibroids diagnosis (yes/no) and hysterectomy status (none/bilateral oophorectomy with hysterectomy) = 0.4.

[c] *P* value for interaction between endometriosis diagnosis (yes/no) and hysterectomy status (none/bilateral oophorectomy with hysterectomy) = 0.03.

[d] Odds ratios were adjusted for age and US state; sample sizes were insufficient for full multivariate adjustment.

agreement between medical record review and self-reported bilateral oophorectomy status was observed among 49 women enrolled in the Breast Cancer Screening Program (35).

Our study interview had high reliability of self-reported gynecologic surgery status; however, we were unable to assess the validity of participant recall. Women who undergo hysterectomy may be asymptomatic for benign gynecologic conditions but receive a diagnosis at surgery. To address this issue, we performed sensitivity analyses to examine associations stratified by fibroids and endometriosis history where the benign condition was known to precede hysterectomy. We also relied on the assumption that a prior diagnosis of uterine fibroids or endometriosis contributed to the decision to undergo bilateral oophorectomy with hysterectomy as nonmalignant indications. This assumption is supported by national estimates that uterine fibroids are the leading indication (40%) for hysterectomy among US women, and that endometriosis is the primary indication in 10%–20% of surgeries (1, 2, 27).

These data were collected from a large, population-based study of breast cancer with standardized data collection instruments and extensive information on reproductive and hormonal covariates. The analyses address a key factor in accurately estimating the long-term health benefits and risk conferred by bilateral oophorectomy with hysterectomy, which is a current and important issue to large numbers of US women. Results from this study did not support our a priori hypothesis that the association between bilateral oophorectomy and breast cancer risk would be confounded by nonmalignant indications for surgery such as uterine fibroids or endometriosis. Our findings provide additional confidence that effect estimates for the association between bilateral oophorectomy with hysterectomy and breast

cancer risk are not meaningfully altered in studies unable to account for history of these benign conditions.

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Author affiliations: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Hazel B. Nichols, Kala Visvanathan); Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland (Kala Visvanathan); Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington (Polly A. Newcomb); University of Wisconsin-Madison Paul P. Carbone Comprehensive Cancer Center, Madison, Wisconsin (John M. Hampton); Department of Oncologic Sciences, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida (Kathleen M. Egan); Department of Epidemiology and Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida (Kathleen M. Egan); Department of Community and Family Medicine, Dartmouth Medical School, Lebanon, New Hampshire (Linda Titus-Ernstoff); and Department of Population Health Sciences, University of Wisconsin, Madison, Wisconsin (Amy Trentham-Dietz).

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