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Postoophorectomy Estrogen Use and Breast Cancer Risk

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Abstract

Objective—To estimate whether the protective effect of premenopausal bilateral oophorectomy on breast cancer risk is mitigated by estrogen therapy use after surgery.

Methods—In pooled data from 4 population-based case-control studies, we examined estrogen use after total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) and subsequent breast cancer risk. We identified postmenopausal, invasive breast cancer cases (N=10,449) ages 50–79 years from 3 state tumor registries and age-matched controls without breast cancer (N=11,787) from driver's license and Medicare lists. TAHBSO and estrogen use was queried during structured telephone interviews. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with multivariable logistic regression.

Results—Breast cancer risk comparisons were made relative to women who went through natural menopause and never used hormones. Overall, breast cancer risk increased 14% among women currently taking estrogens after TAHBSO (OR=1.14; 95% CI: 1.03, 1.28), 32% for estrogen durations <10 years (OR=1.32; 95% CI: 1.11, 1.57), and 22% for estrogen initiation within 5 years of TAHBSO (OR=1.22; 95% CI: 1.09, 1.37). Among women who underwent early TAHBSO (<40 years), 24–30% decreases in breast cancer risk were observed among both never (OR=0.70; 95% CI: 0.55–0.88) and current (OR=0.76; 0.61–0.96) estrogen users.

Conclusion—Unopposed estrogen use does not negate the reduction in breast cancer risk associated with early (<40 years) bilateral oophorectomy. However, initiating estrogen therapy after TAHBSO at ages 45 and older can increase breast cancer risk and should be considered carefully.

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Introduction

Bilateral oophorectomy is widely recognized to reduce breast cancer risk when performed before the onset of menopause (1–8). Among pre-menopausal women, risk reduction associated with oophorectomy can approach 50%, a magnitude comparable to chemoprevention with tamoxifen (9). In the United States, bilateral oophorectomy is a common elective procedure undertaken to reduce ovarian cancer risk during hysterectomy for non-malignant conditions such as uterine fibroids, prolapse and endometriosis. Between the ages of 35 and 45, approximately 11% of U.S. women undergo hysterectomy, and 40% of these surgeries include bilateral oophorectomy (10).

Removal of the ovaries in premenopausal women can result in severe menopausal symptoms including, but not limited to: vasomotor symptoms, sexual dysfunction, depression, and bone loss (11, 12). Women who undergo concurrent hysterectomy have the option of taking estrogen-only hormone therapy to mitigate some of these symptoms. However, an ongoing concern for both women and their providers is whether the use of unopposed estrogens may negate the benefit of oophorectomy for breast cancer prevention, or perhaps even increase breast cancer risk, as has been reported in some observational studies (13–16).

The Women's Health Initiative (WHI) randomized placebo-controlled trial recently reported an overall 23% decrease in breast cancer risk among postmenopausal hysterectomized women assigned to conjugated equine oestrogen compared to placebo (HR=0.77; 0.62, 0.95). However, the average age of women in the WHI was 63.6 years and >80% of participants were 10 years beyond menopause at trial enrollment (17). U.S. women undergoing hysterectomy for benign conditions are frequently younger and premenopausal (10). Whether the association between unopposed estrogens and breast cancer risk differs when therapy is initiated by premenopausal women undergoing an abrupt surgical menopause, peri-menopausal women who are seeking to ameliorate menopausal symptoms, or women who have been postmenopausal for several years is not yet clearly understood (14, 18).

To evaluate unopposed estrogen therapy after total abdominal hysterectomy with bilateral-salpingo-oophorectomy (TAHBSO) and breast cancer risk, we pooled information collected from more than 10,000 women diagnosed with invasive postmenopausal breast cancer and 10,000 population controls who participated in the Collaborative Breast Cancer Studies.

Materials and Methods

This analysis was performed using data from the Collaborative Breast Cancer Studies, a series of four population-based case-control studies of invasive breast cancer conducted continuously between 1992 and 2007 by investigators at the University of Wisconsin-Madison, the Harvard School of Public Health, and Dartmouth Medical School. Participant identification, enrollment, and data collection procedures were maintained across studies with the specific intent for future data pooling. Each study was conducted according to institutionally-approved protocols (19, 20).

All case participants had an incident diagnosis of invasive breast cancer and date of diagnosis reported to the statewide cancer registry at the study site. During 1992–2001 cases were identified in three states: Wisconsin, Massachusetts, and New Hampshire; during 2002–2007 cases were enrolled in Wisconsin only. In total, 21,713 eligible breast cancer cases were identified. Of the identified cases, physicians refused contact with 359 (1.7%), 743 (3.4%) were deceased, 624 (2.9%) could not be located and 2,794 (12.9%) refused to participate. Physician refusals indicated that an eligible participant should not be contacted to participate in a 20–30 minute telephone interview. Interviews were conducted for 17,193

(79.2%) eligible case women. Thirty-eight cases were considered to have provided unreliable information by the interviewers, leaving 17,155 case interviews available for analysis.

Population controls were identified in each state from lists of licensed drivers (<65 years) and Medicare beneficiaries (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. Of the 26,269 potential controls identified, 316 (1.2%) were deceased, 1,198 (4.6%) could not be located, and 5,446 (20.7%) refused to participate. Interviews were obtained for 19,309 (73.5%) women. Thirty-seven control interviews were considered unreliable by the interviewer, leaving 19,268 control interviews available for analysis.

All case and control participants provided information on medical history, hormone use, lifestyle and demographic factors during a structured telephone interview. Questions pertaining to postmenopausal hormone use queried information on formulation, routes of administration, age started, frequency of each episode of use, total duration, and time since last use. Study participants also reported whether they had undergone surgery to remove the uterus or ovaries, the type of surgery (hysterectomy and/or oophorectomy, including number of ovaries removed), and age at surgery. Information about personal and first-degree 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-reported date of invasive breast cancer diagnosis. For comparability, the control subjects interviewed contemporaneously with cases were assigned an individual reference date corresponding to the average time from diagnosis to interview for the case group. Reference age was defined as age at diagnosis for cases or on the reference date given to controls. Only exposures that occurred prior to the assigned reference date were included in analyses.

In three of the four pooled studies (1992–1995; 1997–2001; 2001–2004) natural menopause was defined as the absence of menses for 6 consecutive months not due to surgery, chemotherapy, radiation, or other reasons. In the most recent study (2004–2007), menopause was defined as 12 consecutive months without menses not due to surgery, chemotherapy, radiation, or other reasons. In all studies, women who reported bilateral oophorectomy before the reference date were categorized as postmenopausal. 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), to be postmenopausal if the reference age was in the highest decile for age at natural menopause among controls (>55 years of age), and otherwise to have an unknown age at menopause. Participants who had started postmenopausal hormone use before cessation of menses were categorized as postmenopausal with unknown age at menopause.

The pooled analysis was limited to women ages 50 and older (N=13,253 cases, 14,900 controls). We further excluded women who were premenopausal (N=1,352 cases, 1,462 controls) or had unknown menopausal status (N=620 cases, 661 controls), or who had a previous history of cancer (except non-melanoma skin cancer) (N=614 cases, 726 controls). Women with discordant ages at bilateral oophorectomy and hysterectomy (93 cases, 155 controls) or missing ages for both procedures (41 cases, 45 controls) were also excluded. Finally, 84 cases and 64 controls who reported bilateral oophorectomy and/or hysterectomy at the same age or older compared to the reference age were excluded. After these exclusions, 10,449 cases and 11,787 controls contributed information to our analyses.

Odds ratios (OR) and 95% confidence intervals (CI) for breast cancer were calculated using multivariable logistic regression models. The reference group was comprised of women with an intact uterus and ovaries who reported undergoing a natural menopause for estimates of breast cancer odds after TAHBSO. For estimates of breast cancer odds according to estrogen therapy use after TAHBSO, the reference group was additionally restricted to never users of hormone therapy. This allowed us to jointly assess the protective effect of early ovarian removal on breast cancer risk and potential variation according to estrogen therapy use after surgery. In sensitivity analyses, we additionally required that women in the reference group reported ages at menopause between 50–51 years (the median age of menopause among controls). Results were similar when age at menopause was and was not specified for the reference group; therefore we present results with the more expansive definition that did not specify age at menopause to maximize the sample size for the reference group.

Covariates in multivariable models were selected *a priori* as factors conceptually related to both gynecologic surgery and breast cancer risk. Preliminary multivariable models were adjusted for age (5-year groups), study enrollment period (1992–1995; 1997–2001; 2001–2004; 2004–2007) and study site; final models additionally included the following covariates: age at menarche (<12 years, 12, 13, 14, unknown), age at first birth (<20 years, 20–24, 25–29, 30, unknown), parity (0–1 livebirths, 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). *P*-values < 0.05 were considered to be statistically significant. *P*-trends represent *P*-values from the Wald test for the categorical variable included as an ordinal term in regression models. All analyses were performed using SAS version 9.2 software (SAS Institute, Inc., Cary, NC).

We conducted two additional sensitivity analyses to evaluate whether the definitional change of natural menopause from 6 to 12 months of amenorrhea during 2004–2007 and whether the enrollment of participants in Wisconsin only during 2001–2007 influenced our results. In analyses restricted to participants who were defined as menopausal after 6 months amenorrhea (N=9,051 cases; 10,216 controls) and those residing in Wisconsin (N=7,310 cases; 7,892 controls), our findings were essentially unchanged compared to the overall analysis.

Results

Participant characteristics by case-control status are shown in Table 1. The average age of study participants was 63 years. In brief, case participants tended to be more highly educated, have lower parity, a positive family history of breast cancer, a BMI in the obese range, and were more likely to have used postmenopausal hormones compared to controls. Approximately 9.5% of cases and controls reported having a hysterectomy alone, and 17% of cases and 19% of controls reported undergoing total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) (Table 1).

Table 2 presents the association between gynecologic surgery and breast cancer risk. In order to directly compare breast cancer associations with hysterectomy alone versus TAHBSO, we defined a common reference group comprised of women with an intact uterus and ovaries who underwent a natural menopause. Overall, hysterectomy alone was not associated with breast cancer risk (OR=1.03; 95% CI: 0.93, 1.14) regardless of age at surgery (p-trend=0.9). Hysterectomy with removal of one ovary (OR=0.81; 95% CI: 0.70, 0.95) or both ovaries (OR=0.87; 95% CI: 0.80–0.95), was associated with 13–19% reductions in the odds of breast cancer (Table 2).

Earlier ages at TAHBSO were associated with a greater reduction in the overall odds of developing breast cancer ($p\text{-trend}<0.0001$). Effect estimates ranged from a 46% reduction in breast cancer odds for TAHBSO before age 30 ($OR=0.54$; 95% CI: 0.36, 0.82) to a 21% reduction for surgeries performed at ages 40–44 years ($OR=0.79$; 95% CI: 0.67–0.92). No reduction in breast cancer risk was observed in women who had TAHBSO at ages 45 or older. Bilateral oophorectomy without concurrent hysterectomy was reported by <1% of cases and controls and was associated with an odds ratio of 1.39 for breast cancer (95% CI: 0.97, 2.00) (Table 2).

Breast cancer risk associations for hysterectomy alone and TAHBSO according to estrogen therapy use, duration, and the interval between surgery and start of estrogen therapy are shown in Table 3. All comparisons were made relative to women with an intact uterus and ovaries who went through natural menopause and never used hormones ($N=4,442$ cases; 5,303 controls). This reference group allowed us to account for the protective effect of early ovarian removal on breast cancer risk and to assess variation according to estrogen therapy use after surgery. After multivariable adjustment, postmenopausal women who reported undergoing hysterectomy alone had a 29% increase in breast cancer odds if they reported using unopposed estrogens after surgery (95% CI: 1.11, 1.49). This increase did not appear to vary significantly based on former vs. current use, years of use, or the interval between surgery and initiation of estrogen use (Table 3).

Compared to the reference group, ever use of estrogen therapy after TAHBSO was associated with a 9% increase in breast cancer odds ($OR=1.09$; 0.99, 1.19) that was not statistically significant. This increase appeared driven by a 14% increase in breast cancer odds among current estrogen users ($OR=1.14$; 95% CI: 1.03, 1.28); former use of estrogen was not associated with breast cancer risk ($OR=0.95$; 95% CI: 0.80, 1.12). Among current estrogen users, breast cancer odds were increased 32% among those who had used estrogen therapy for 0.5–9.9 years ($OR=1.32$; 1.11, 1.57); longer durations of use were not associated with statistically significant increases in breast cancer risk ($OR=1.09$; 95% CI: 0.92, 1.29 for 10–19.9 years and $OR=1.00$; 95% CI: 0.82, 1.23 for 20 years). Estrogen use that was initiated within 5 years of TAHBSO was associated with a 22% increase in breast cancer odds compared to the referent group ($OR=1.22$; 95% CI: 1.09, 1.37), while a 54% reduction was observed among women who started estrogen use 5 years after TAHBSO ($OR=0.46$; 95% CI: 0.30, 0.71; Table 3). However, on average, women who started using estrogen 5 years after oophorectomy were younger (40–41 years) than women who started using estrogens closer to surgery (45–46 years).

Table 4 displays odds ratios for breast cancer according to ages at surgery and diagnosis for never and current estrogen users. Among women who never used hormones, TAHBSO before age 40 was associated with a 30% decrease in breast cancer odds ($OR=0.70$; 95% CI: 0.55, 0.88), and TAHBSO at ages 40–44 was associated with a 36% decrease in breast cancer odds ($OR=0.64$; 95% CI: 0.49, 0.84) compared to the reference group. No significant associations between TAHBSO at older ages and breast cancer were observed in women who never used postmenopausal hormones (Table 4).

Overall increases in breast cancer risk were observed among women who reported currently using unopposed estrogens and having TAHBSO surgery at older ages. However, among current estrogen users, TAHBSO at the youngest ages (<40 years) remained associated with an overall decrease (24%) in breast cancer odds ($OR=0.76$; 95% CI: 0.61, 0.96). Odds ratios ranged from 1.19 for surgeries at 40–44 years (95% CI: 0.96, 1.48) to 1.26 for surgeries at ages 50 and older (95% CI: 1.05, 1.52) (Table 4).

Discussion

Our findings provide detailed estimates of the association between estrogen therapy and breast cancer risk for women who have undergone hysterectomy with concomitant bilateral oophorectomy (TAHBSO). Among women who reported TAHBSO before age 40, estrogen use did not negate the usual reduction in breast cancer risk conferred by early removal of the ovaries. Among women who initiated estrogen after TAHBSO at older ages, no reduction in breast cancer risk was observed. Instead, current use of unopposed estrogens was associated with a 14% increase in breast cancer odds.

Our findings confirm previous reports of 25–50% reductions in breast cancer risk associated with bilateral oophorectomy, with greater magnitudes of risk reduction for surgeries performed at earlier ages and no apparent benefit after age 45 (1–8). In contrast to some prior studies (5, 7, 8, 13, 21), we did not observe an association between hysterectomy alone and breast cancer risk, irrespective of age at surgery. We did observe a 29% increase in breast cancer odds associated with using unopposed estrogens after hysterectomy alone.

Few studies of the relation between unopposed estrogen use and breast cancer risk have reported estimates specific to hysterectomized women who underwent concurrent oophorectomy (16, 22). In the Women's Health Initiative (WHI) randomized trial, 76 incident breast cancers developed among women who had undergone bilateral oophorectomy (33 assigned to estrogen, 43 to placebo); estrogen use was associated with an estimated 14% reduction in breast cancer risk (HR=0.86; 95% CI: 0.55, 1.36) (22). In the Nurses' Health Study, 366 incident breast cancers were investigated among women who had undergone bilateral oophorectomy: 55 among never hormone users and 311 among current estrogen users. The authors reported a 71% increase in breast cancer risk associated with long-term (> 20 years) estrogen therapy use (95% CI: 1.16, 2.53) (16). Among *BRCA1/2* carriers, breast cancer risk reduction estimates associated with bilateral oophorectomy were similar among 50 women who used estrogen therapy (HR=0.44; 95% CI: 0.12, 1.61) and 50 women who did not (HR=0.59; 95% CI: 0.14, 2.52) over an average 3.6 year follow-up (23). These disparate findings may be due, in part, to younger ages at bilateral oophorectomy among *BRCA1/2* mutation carriers and differences in the timing of estrogen therapy relative to menopause between observational population-based studies and the WHI randomized trial.

The interval between menopause and start of estrogen therapy is emerging as an important factor in determining the risks and benefits of hormone use for breast cancer incidence (18). In the WHI, the protective effect of estrogen therapy appeared more strongly among women who started estrogen therapy further from menopause (HR=0.65; 0.48–0.89) versus within 5 years of menopause (HR=0.89; 0.66, 1.20); although the difference between these estimates was not statistically significant (17). In the Million Women Study screening cohort, increased risk of breast cancer associated with current use of estrogen therapy was restricted to women who initiated hormone use within 5 years of menopause (HR=1.43; 95% CI: 1.36, 1.49 for intervals <5 years versus HR=1.05; 95% CI: 0.89, 1.23 for ≥ 5 years) (14). In our data, we observed a 58% decrease in breast cancer odds among women who initiated estrogen therapy ≥ 5 years after TAHBSO compared to women who underwent a natural menopause and never used hormones. It is possible that unopposed estrogen therapy given in a post-menopausal state of relative estrogen deprivation induces apoptosis and exhibits anti-tumor effects (24, 25). However, only 29 cases and 86 controls reported initiating estrogen therapy ≥ 5 years after TAHBSO making it an unusual occurrence.

Conversely, estrogen use among perimenopausal women, or postmenopausal women with recent exposure to ovarian-produced estrogens, could instead contribute to breast cancer

growth, particularly among estrogen-receptor positive tumors. Among women who initiated estrogen therapy within 5 years of TAHBSO, we observed a 22% increase in breast cancer risk. This increase was limited to the first 10 years of use. The relation of estrogen therapy to breast cancer risk may be dependent on the presence of initiated cells as well as the estrogen environment surrounding tumor cells (26). For example, close to menopause, estrogen therapy may have a greater effect on the promotion of initiated breast cancer cells by prolonging a relatively estrogen-rich environment; the increased risk may not continue beyond 10 years due to an absence or depletion of transformed cells. Growth of tumor cells that arise in a low estrogen environment after menopause may be inhibited by the introduction of exogenous estrogen (24, 25). This potential dynamic, however, does not explain the increased risk of breast cancer with long durations of estrogen therapy observed in other observational studies(13–16).

The case-control design and large sample size of the pooled studies allowed us to estimate breast cancer odds specifically among women who reported TAHBSO and to examine variation according to age at surgery and estrogen therapy use. Despite the large sample and extensive covariate information available in these data, some limitations should be considered in the interpretation of our results. The number of cases and controls was small for some analyses. In our report, we have used the abbreviation, TAHBSO (total abdominal hysterectomy bilateral salpingo-oophorectomy), to reflect surgeries where the uterus and both ovaries were removed simultaneously. Based on information from the study interview, we are unable to confirm whether these procedures were performed vaginally or abdominally, nor whether the fallopian tubes were removed. However, based on clinical practice at the time, the majority of surgeries were likely to be abdominal and to include salpingectomy (27).

Exposure status was self-reported by case and control participants, introducing the potential for recall bias. In a subset of these data (19) and other studies (28–33), self-reported postmenopausal hormone use has been shown to be a reliable and valid measure for use in epidemiological studies. In our data, self-reported hysterectomy and oophorectomy status had high reliability ($\kappa = 0.98$; 95% CI: 0.95, 1.00) among a sequential sample of 195 control participants who were re-interviewed (34). Although validation data are unavailable for the studies analyzed here, 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 TAHBSO status for cases, and 84% among controls (2). Validity of self-reported hysterectomy status was also high in the Nurses' Health Study; among 69 women who reported TAHBSO, medical record confirmation was obtained for 66 (95.7%) (35). However, among 49 women enrolled in the Breast Cancer Screening Program the percent agreement was only 74% between medical record review and self-reported bilateral oophorectomy status (36).

Breast cancer risk associations with unopposed estrogen use may be attenuated in analyses that do not restrict to ER+/PR+ cancers (16); we were unable to assess hormone receptor status in these data. The protective effect of TAHBSO for breast cancer risk may also vary according to hormone receptor subtypes. In the Women's Contraceptive and Reproductive Experiences Study, bilateral oophorectomy was more strongly associated with reduced risk of ER+/PR+ breast cancer (OR=0.55; 95% CI: 0.45, 0.68) compared to ER-/PR- tumors (OR=0.82; 95% CI:0.63, 1.07) (8). In our study, all breast cancer cases were postmenopausal and 50 years of age, suggesting that the majority of tumors were likely to be hormone receptor positive (37).

We observed a suggested positive association between bilateral oophorectomy without hysterectomy and breast cancer risk, although this finding was not statistically significant.

One potential explanation for this finding is that our statistical adjustment for first-degree family history of breast cancer was unable to protect against residual confounding according to very strong family histories of breast and ovarian cancer (38). Women with known *BRCA1/2* gene mutations are counseled to consider bilateral oophorectomy after age 35 or completion of childbearing (although some women elect to undergo surgery at younger ages) for ovarian and breast cancer prevention (www.nccn.org).

The present findings are reassuring to younger women who undergo oophorectomy and elect to use estrogen therapy and are concerned about future breast cancer risk. Our results suggest a precautionary approach for women undergoing TAHBSO at older ages; benefits of estrogen therapy should be weighed against the possibility of increased breast cancer risk.

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Table 1

Participant Characteristics According to Invasive Breast Cancer Case and Control Status

Characteristic	Cases		Controls	
Total N, %	10,449	100.0	11,787	100.0
Age				
Mean years, SD	63.5	6.7	63.1	6.6
Study enrollment years; n, %				
1992–1995	4,914	47.0	5,065	43.0
1997–2001	3,108	29.7	4,003	34.0
2001–2004	1,029	9.8	1,148	9.7
2004–2007	1,398	13.4	1,571	13.3
Study site; n, %				
Wisconsin	7,310	70.0	7,892	67.0
Massachusetts	2,332	22.3	2,952	25.0
New Hampshire	807	7.7	943	8.0
Education n, %				
High school diploma or less	6,028	57.7	6,937	58.9
Some college	2,292	21.9	2,717	23.1
College degree or higher	2,000	19.1	1,991	16.9
Missing	129	1.2	142	1.2
Parity				
Mean number of live births, SD *	3.2	1.6	3.4	1.8
Body mass index n, %				
Underweight (less than 18.5 kg/m ²)	144	1.4	225	1.9
Normal (18.5–24.9 kg/m ²)	4,064	38.9	4,885	41.4
Overweight (25–29.9 kg/m ²)	3,464	33.2	3,938	33.4
Obese (30 kg/m ² or more)	2,456	23.5	2,378	20.2
Missing	321	3.1	361	3.1
Cigarette smoking n, %				
Never	5,024	48.1	5,719	48.5
Former	3,530	33.8	3,784	32.1
Current	1,770	16.9	2,158	18.3
Missing	125	1.2	126	1.1
First-degree family history of breast cancer n, %				
Yes	2,236	21.4	1,733	14.7
Missing	261	2.5	281	2.4
Regular mammography screening				
Yes				
Missing				

Characteristic	Cases		Controls	
Postmenopausal hormone therapy n, %				
None	5,986	57.3	7,182	60.9
Estrogen only	2,034	19.5	2,392	20.3
Estrogen plus progestin only	1,709	16.4	1,502	12.7
Multiple or other formulations	541	5.2	530	4.5
Missing	179	1.7	181	1.5
Gynecologic surgery n, %				
None	6,916	66.2	7,503	63.7
Hysterectomy alone	991	9.5	1,106	9.4
Bilateral oophorectomy with hysterectomy	1,780	17	2,222	18.9
Other	650	6.2	809	6.9
Missing	112	1.1	147	1.2

SD, standard deviation.

* Among parous women only: n=9,128 cases, 10,550 controls.

Table 2
Odds Ratios and 95% Confidence Intervals for Invasive Breast Cancer According to Gynecologic Surgery

Characteristic	Cases (n=10,449)		Controls (n=11,787)		OR (95% CI)*	OR (95% CI)†
	n	%	n	%		
Any gynecologic surgery						
Reference group: No surgery, natural menopause	6,622	63.4%	7,311	62.0%	1	1
Hysterectomy alone	991	9.5%	1,106	9.4%	0.96 (0.88, 1.06)	1.03 (0.93, 1.14)
Hysterectomy with unilateral oophorectomy	321	3.1%	444	3.8%	0.78 (0.67, 0.90)	0.81 (0.70, 0.95)
Total abdominal hysterectomy with bilateral salpingo-oophorectomy	1,780	17.0%	2,222	18.9%	0.88 (0.82, 0.95)	0.87 (0.80, 0.95)
Unilateral oophorectomy	259	2.5%	311	2.6%	0.91 (0.77, 1.08)	0.87 (0.73, 1.03)
Bilateral oophorectomy	70	0.7%	54	0.5%	1.42 (0.77, 1.08)	1.39 (0.97, 2.00)
Unknown	112	1.1%	147	1.2%		
Hysterectomy alone						
Reference group: No surgery, natural menopause	6,622	63.4%	7,311	62.0%	1	1
Hysterectomy alone younger than 30 years	36	0.3%	54	0.5%	0.74 (0.48, 1.13)	0.81 (0.52, 1.25)
Hysterectomy alone 30–34 years	152	1.5%	150	1.3%	1.12 (0.89, 1.41)	1.23 (0.97, 1.56)
Hysterectomy alone 35–39 years	227	2.2%	264	2.2%	0.94 (0.79, 1.13)	1.00 (0.83, 1.21)
Hysterectomy alone 40–44 years	223	2.1%	270	2.3%	0.89 (0.74, 1.07)	0.95 (0.78, 1.14)
Hysterectomy alone 45–49 years	145	1.4%	151	1.3%	1.02 (0.81, 1.29)	1.10 (0.87, 1.40)
Hysterectomy alone 50 years or older	208	2.0%	217	1.8%	1.01 (0.83, 1.22)	1.06 (0.87, 1.29)
P-trend					0.9	0.9
Total abdominal hysterectomy with bilateral salpingo-oophorectomy						
Reference group: No surgery, natural menopause	6,622	63.4%	7,311	62.0%	1	1
TAHBSO younger than 30 years	35	0.3%	72	0.6%	0.54 (0.36, 0.81)	0.54 (0.36, 0.82)
TAHBSO 30–34 years	103	1.0%	167	1.4%	0.70 (0.55, 0.90)	0.70 (0.54, 0.90)
TAHBSO 35–39 years	183	1.8%	314	2.7%	0.65 (0.54, 0.78)	0.64 (0.53, 0.78)
TAHBSO 40–44 years	342	3.3%	464	3.9%	0.82 (0.71, 0.94)	0.79 (0.67, 0.92)
TAHBSO 45–49 years	521	5.0%	586	5.0%	0.99 (0.87, 1.12)	0.96 (0.84, 1.11)
TAHBSO 50 years or older	596	5.7%	619	5.3%	1.04 (0.93, 1.18)	1.03 (0.90, 1.17)
P-trend					<0.001	<0.001

OR, odds ratio; CI, confidence interval; TAHBSO, total abdominal hysterectomy with bilateral salpingo oophorectomy.

* Odds ratios adjusted for age, study enrollment years, and study site.

[†] Odds ratios adjusted for age, study enrollment years, study site, age at menarche, age at first birth, parity, postmenopausal hormone use, body mass index, education, mammography screening, and family history of breast cancer.

Table 3
Odds Ratios and 95% Confidence Intervals for Invasive Breast Cancer According to Gynecologic Surgery and Estrogen Use

Characteristic	Hysterectomy Alone			Total Abdominal Hysterectomy With Bilateral Salpingo-oophorectomy		
	Cases	Controls	OR(95% CI)*	OR(95% CI)*	Cases	Controls
Reference group: No surgery, natural menopause, no hormone use	4,422	5,303	1	1	4,422	5,303
Unopposed estrogen use						
Never	483	559	1.00 (0.88, 1.30)	1.05 (0.92, 1.19)	540	708
Ever	420	461	1.13 (0.98, 1.26)	1.29 (1.11, 1.49)	1,034	1,278
Former	115	111	1.18 (0.90, 1.54)	1.30 (0.99, 1.70)	274	344
Current	305	350	1.11 (0.95, 1.31)	1.28 (1.09, 1.51)	760	934
CURRENT ESTROGEN USERS:						
Duration of estrogen use						
0.5–9.9 years	129	160	1.05 (0.82, 1.33)	1.19 (0.94, 1.52)	287	318
10–19.9 years	116	123	1.20 (0.92, 1.55)	1.36 (1.05, 1.78)	287	376
20 years or more	60	67	1.09 (0.77, 1.56)	1.26 (0.88, 1.81)	186	240
Interval between surgery and hormone use						
Less than 5 years	128	146	1.09 (0.85, 1.39)	1.28 (1.00, 1.63)	699	807
5 years or more	170	195	1.14 (0.92, 1.41)	1.28 (1.04, 1.53)	53	118
5 years or more before surgery	8	16	0.59 (0.25, 1.38)	0.64 (0.27, 1.52)	24	32
5 years or more after surgery	162	179	1.19 (0.95, 1.48)	1.35 (1.08, 1.68)	29	86

OR, odds ratio; CI, confidence interval.

* Odds ratios adjusted for age, study enrollment years, and study site.

[†] Odds ratios adjusted for age, study enrollment years, study site, age at menarche, age at first birth, parity, body mass index, education, mammography screening, and family history of breast cancer.

Table 4

Odds Ratios and 95% Confidence Intervals ^{*},[†] for Invasive Breast Cancer According to Age at Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy and Age at Breast Cancer Diagnosis and Stratified by Unopposed Estrogen Use

	NEVER HORMONE USERS			
	Age at Breast Cancer Diagnosis			
	50–59	60–69	70–80	All ages
Age at TAHBSO				
Younger than 40	0.56 (0.32, 0.99)	0.74 (0.54, 1.03)	0.71 (0.46, 1.10)	0.70 (0.55, 0.88)
(cases/controls)	17/44	62/100	36/51	115/195
40–44	0.56 (0.30, 1.03)	0.61 (0.42, 0.88)	0.81 (0.47, 1.40)	0.64 (0.49, 0.84)
(cases/controls)	15/38	43/84	24/31	82/153
45–49	0.93 (0.55, 1.56)	1.08 (0.80, 1.46)	1.08 (0.80, 1.46)	1.05 (0.83, 1.32)
(cases/controls)	25/36	84/95	34/30	143/161
50 or older	1.42 (0.81, 2.49)	1.23 (0.93, 1.62)	1.00 (0.70, 1.42)	1.17 (0.95, 1.44)
(cases/controls)	26/25	108/106	66/68	200/199
All ages	0.81 (0.61, 1.07)	0.93 (0.79, 1.09)	0.90 (0.71, 1.13)	0.90 (0.79, 1.01)
(cases/controls)	83/143	297/385	160/180	540/708
	CURRENT ESTROGEN USERS			
	Age at Breast Cancer Diagnosis			
	50–59	60–69	70–80	All ages
Age at TAHBSO				
Younger than 40	0.69 (0.49, 0.97)	0.79 (0.56, 1.11)	1.24 (0.51, 3.04)	0.76 (0.61, 0.96)
(cases/controls)	52/115	57/92	10/10	119/217
40–44	1.27 (0.91, 1.74)	1.11 (0.81, 1.51)	1.38 (0.62, 3.09)	1.19 (0.96, 1.48)
(cases/controls)	72/88	80/90	14/11	166/189
45–49	1.38 (1.07, 1.78)	1.09 (0.82, 1.45)	0.79 (0.41, 1.52)	1.20 (1.00, 1.44)
(cases/controls)	129/139	90/110	16/23	235/272
50 or older	1.34 (0.99, 1.81)	1.39 (1.08, 1.81)	0.77 (0.47, 1.25)	1.26 (1.05, 1.52)
(cases/controls)	87/96	124/119	29/41	240/256
All ages	1.17 (1.00, 1.38)	1.11 (0.95, 1.29)	0.91 (0.65, 1.26)	1.11 (0.99, 1.24)
(cases/controls)	340/438	351/411	69/85	760/934

TAHBSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.

^{*} Odds ratios adjusted for age, study enrollment years, state, age at menarche, age at first birth, parity, mammography screening, body mass index, education and family history of breast cancer.

[†] Reference group is 4,422 cases and 5,303 controls who reported no gynecologic surgery, natural menopause, and never used hormones.