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Association of fibroids, endometriosis, and gynecologic surgeries with breast cancer incidence and hormone receptor subtypes

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Abstract

Background—Fibroids and endometriosis are sex hormone-mediated and exhibit cancer-like behavior. Breast cancer may be more common in women who have had these conditions, but the literature is conflicting and does not always address factors like hysterectomy/oophorectomy status, race/ethnicity, menopause, and hormone receptor subtypes.

Methods—Data are from the Sister Study, a cohort of 50,884 U.S. women enrolled in 2003–2009 and followed through 2020. Cox proportional hazards models with time-varying exposures and covariates assessed the relationship of fibroids or endometriosis with breast cancer. Logistic regression examined the association with estrogen receptor (ER) status among cases.

Results—Fibroids (19,932 cases) were positively associated with breast cancer (fully adjusted hazard ratio [HR]: 1.07, 95% confidence interval [CI]: 1.01–1.14), notably among Black participants (HR 1.34, 95% CI: 1.07–1.69) and women who had a hysterectomy (HR: 1.18, 95% CI: 1.05–1.31). Endometriosis (3,970 cases) was not associated with breast cancer (HR: 0.99, 95% CI: 0.91–1.08). Among 4,419 breast cancer cases, fibroids were positively associated with ER+ subtypes (odds ratio [OR]: 1.34, 95% CI: 1.10–1.65), while endometriosis was negatively associated with ER+ subtypes (OR: 0.78; 95% CI: 0.61–1.01).

Conclusions—We observed a modest positive association between fibroids and breast cancer, particularly ER+ breast cancer. No relationship with endometriosis and breast cancer incidence was found.

Impact—Fibroids, even in those with a family history of breast cancer, might modify breast cancer risk stratification tools. Future studies should further assess this link and interrogate shared risk factors.

Introduction

Breast cancer is the most common cancer diagnosis and the second-most common cause of cancer mortality in women(1). The etiology is multifactorial with genetic, lifestyle, and

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environmental links (2) (3). Understanding relationships between benign and malignant conditions represents an opportunity to elucidate shared risk factors, identify novel syndromes, and refine screening recommendations. Fibroids and endometriosis are fitting benign conditions to explore given their cancer-like qualities and sex hormone mechanisms.

Fibroids are benign tumors of monoclonal origin(4,5). They exhibit chromosomal abnormalities common among other somatic growths like lipomas, hamartomas, endometrial polyps, and salivary adenomas (6) as well as meningiomas (7) and are part of a rare syndrome of hereditary leiomyomatosis and renal cell carcinoma (8). Fibroid tissue upregulates aromatase and sex hormone receptors(9). They shrink with menopause and hormone modifying fibroid treatment (10) and may be prevented with depot medroxyprogesterone acetate (11),(12).

Endometriosis is also monoclonal and exhibits behavior akin to metastasis(4). In patients with endometriosis, endometrial tissue that has migrated to a different site, as compared to endometrial tissue *in situ*, is more likely to express MYC, Cyclin D1, and GREB1, proteins implicated in breast cancer (13). Endometriosis tissue also exhibits altered expression of oncogenes and tumor suppressors (14), including WNT4 (stabilizes B-catenin and is associated with familial adenomatous polyposis syndrome) (15) and VEZT (associated with gastric cancer) (16). Furthermore, endometriosis demonstrates increased expression of sex hormone receptors (13) and aromatase (17).

A recent 2022 meta-analysis(18) found that among 16 cohort and case-control studies, women with endometriosis had an overall increased risk of breast cancer (risk ratio [RR] 1.08; 95% CI: 1.00–1.17). However, results from individual studies suggest that risk estimates may vary by age. For example, a Danish cohort of 45,790 participants found increased risk only in those over age 50(19), whereas a Finnish cohort of 49,993 participants found an increased risk among 20–40-year-olds(20). A Danish case-cohort study of 114,327 participants found decreased risk from early-onset endometriosis but increased risk from late-onset endometriosis(21).

Studies on fibroids and breast cancer tend to suggest a positive association. A few Taiwan-based studies demonstrated a positive association between fibroids and breast cancer(22,23), with one retrospective cohort of 107,357 participants reporting a HR of 1.31 (95%: 1.13–1.52) (24). Interestingly, however, they reported an inverse association between fibroids and mortality among breast cancer cases. A Korean retrospective cohort of 630,523 participants also reported a HR of 1.30 (1.20–1.41)(25). A Swedish cohort study demonstrated a positive association between fibroids and benign breast disease in premenopausal women (26). In the Black Women's Health Study, there was no relationship with breast cancer overall, but a positive association between early-onset fibroids and pre-menopausal breast cancer was observed and a possible positive relationship with estrogen receptor positive (ER+) breast cancer (27). A Mendelian randomization study on women of European descent demonstrated a positive association with breast cancer, especially ER+ breast cancer (28). Among the Sister Study cohort, it was previously reported that breast cancer was positively associated with a history of hysterectomy (29), the most common indication for which is fibroids (30).

The aim of this study is to assess the association between a history of fibroids or endometriosis and 1. incident breast cancer and 2. breast cancer hormone receptor status. Since prior studies noted differences by age and menopausal status, we examined early-onset fibroids and endometriosis, and additionally stratified by menopause status. Since fibroids and endometriosis may prompt hysterectomy and/or oophorectomy, which can in turn affect breast cancer susceptibility, we further stratify those with fibroids by surgery. Moreover, those with fibroids and hysterectomy may represent more clinically significant cases. In the case of fibroids, which are particularly common and severe in African American women (31), it is important to further examine race/ethnicity. While previous studies span multiple countries and ethnicities, each one was itself ethnically homogenous. Describing inter-disease associations can help clarify shared etiology and may improve risk calculators used for screening recommendations.

Materials and Methods

Study Population

The Sister Study is a prospective cohort designed to understand risk factors associated with breast cancer and other chronic diseases. It enrolled 50,884 women ages 35–74 years, across all US states, including Puerto Rico, during the period 2003–2009 (32). None of the women had a prior history of breast cancer themselves, but, as part of the eligibility criteria, all women had a sister (half or full) who was diagnosed with breast cancer. At enrollment, participants reported detailed medical, family, and social history, and were followed-up annually for breast cancer diagnoses, with more detailed questionnaires administered approximately every 3 years. Data are complete through October 2020 (data release 10.1).

Participants with self-reported invasive breast cancer, ductal carcinoma *in situ* (DCIS), and lobular carcinoma *in situ* (LCIS) were considered cases. DCIS and LCIS were included as cases because they have similar risk factors with breast cancer. DCIS can develop into invasive cancer and LCIS is associated with invasive cancer at other sites (33,34). Whenever possible, pathology reports from the medical records were used to confirm diagnoses, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) status. Medical records were obtained for 82% of known cases, and self-reported data was used when the medical record was not available. Self-reported breast cancer characteristics among this cohort was previously shown to agree with medical records, with positive predictive values of 99.1% (ER+), 83.0% (ER-), 98.9% (PR+), 71.6% (PR-), 66.1% (HER2+), and 99.1% (HER2-)[35].

All participants provided written informed consent. The Sister Study was approved by the Institutional Review Board of the National Institutes of Health and conducted in accordance with recognized ethical guidelines including the US Common Rule.

Statistical Approach

Of the 50,884 participants, we excluded the following: 4 participants who withdrew; 115 who reported breast cancer prior to completing enrollment; 30 who had unclear

incident breast cancer status or timing; 231 who had a pre-baseline prophylactic bilateral mastectomy; 16 who reported having a fibroid (n=11) or endometriosis (n=5) before the age of 10; and 287 who did not contribute any follow-up information. This left 50,201 participants for analysis. We do not exclude women with a history of hysterectomy because the prevalence of pre-enrollment hysterectomy is likely be unequal in our exposed and unexposed groups and may introduce bias.

Missing covariate data at baseline were imputed using multiple imputation by chained equations with 30 imputation sets using the mice package in R(35). Although data for history of fibroids or endometriosis were nearly complete, there was moderate missingness for the age of onset of fibroids (8%) and endometriosis (7%) diagnosed prior to enrollment. Additionally, we imputed missing or "indeterminate" hormone receptor status for some cases: ER (17%), PR (19%), HER2 (31%).

Some covariables were time-dependent, changing with each survey (initial missingness <1% for each): body mass index (BMI), alcoholic drinks per week, lifetime smoking pack years, physical activity (recreational or work-related) hours per week, total years of hormone replacement therapy (HRT) as interaction with ever used (categorized as estrogen only or combined estrogen plus progestin), total years taking oral contraceptives (OCs), parity, age of first pregnancy, hysterectomy, bilateral oophorectomy. Non-time dependent covariables (<1% missing) included age of menarche, highest level of education attained, and race and ethnicity (Non-Hispanic White, Non-Hispanic Black / African American [referred to henceforth as Black], Hispanic, and Other). If follow-up questionnaire data were missing, data from the prior questionnaire were carried over.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (Cis) for the association between having a prior diagnosis of fibroids or endometriosis and incident breast cancer diagnosis. Time started at age at enrollment for the entire cohort. The diagnosis status of fibroids or endometriosis was a time-dependent binary variable that could be updated at the time of each follow-up questionnaire. In other words, a participant contributed to both unexposed and exposed person-time if they developed a fibroid or endometriosis during the study follow-up period. Since these pathologies can be treated with hysterectomy and/or oophorectomy, each analysis was followed by a separate analysis that subdivided those with fibroids based on surgical status: "bilateral oophorectomy" includes everyone with bilateral oophorectomy with or without hysterectomy but not counting those with partial/unilateral oophorectomy; "hysterectomy only" includes those with hysterectomy (partial or total) but not bilateral oophorectomy; "without surgery" indicates neither hysterectomy nor bilateral oophorectomy. Those with fibroids and partial/unilateral oophorectomy would either be categorized as "fibroids with hysterectomy only" or "fibroids without surgery". Surgical status can also change during follow-up. Nearly all women (97%, 8797/9031) who had a bilateral oophorectomy also had a hysterectomy. The referent group is no fibroids, regardless of surgical status. Fibroids and endometriosis were analyzed separately.

We stratified analyses by race/ethnicity and menopausal status (combining natural and surgical). Heterogeneity was assessed with Wald tests of the interaction between fibroids/

endometriosis and menopause as well as fibroids and race. Some participants may have had hysterectomy before they could have been diagnosed with fibroids or endometriosis. These were simply included in the analysis as people who never developed those conditions. However, we also evaluated early-onset fibroids and endometriosis, defined as diagnosis before age 35. Further, because age 35 was the minimum age of enrollment and a time point experienced by all participants, it also serves as a useful cut-point for examining early-onset diagnosis, specifically.

We also assessed the association of fibroids and endometriosis with breast cancer subtypes among cases using logistic regression. Here we report odds ratios (ORs) and 95% Cis for the association between a diagnosis of fibroids and endometriosis at any time and risk of having a breast cancer that is ER+ versus ER-, PR+ versus PR-, HER2+ versus HER2-, triple negative (ER-, PR- and HER2-) versus not.

For each analysis, age-adjusted only, partially adjusted, and fully adjusted models were used. The partially adjusted analysis included the following: alcoholic drinks per week, pack-years of smoking, BMI, exercise hours per week, race/ethnicity, education status, parity, age at first pregnancy, months breastfeeding, and age at menarche. The fully adjusted analysis additionally included variables related to endogenous or exogenous hormones that may mediate the association: oophorectomy status, years taking OCs, and HRT use. We report fully adjusted HRs and ORs in the text unless otherwise specified.

Analyses were performed in R and R studio version 2022.2.3 (available at http://www.R-project.org/ and https://rstudio.com/products/rstudio/download), using the survival (available at https://cran.r-project.org/web/packages/survival/index.html) and survminer (available at https://cran.r-project.org/web/packages/survminer/index.html) packages and graphics made with the ggplot2 (available at https://cran.r-project.org/web/packages/ggplot2/index.html) and gtsummary (available at https://cran.r-project.org/web/packages/gtsummary/index.html) packages.

Data Availability Statement:

Data used in this manuscript are available as described on the Sister Study website (The Sister Study: Collaborations and Data Requests, nih.gov) or by request via the Sister Study tracking and review system (www.sisterstudystars.org; registration required). Computing code can be requested from the corresponding author.

Results

Participants were followed for a median of 11.6 years (range 0.1 to 15.3). Of the 50,201 eligible participants, 19,932 (40%) were diagnosed with fibroids and 8,951 (18%) were diagnosed with endometriosis by the end of follow-up (Table 1), while 4,419 participants developed breast cancer by the end of follow up. For fibroids, 14,719 (81%) were diagnosed pre-baseline and 4,230 (21%) were diagnosed before the age of 35. For endometriosis, 7,119 (86%) were diagnosed pre-baseline and 3,970 (44%) were diagnosed before the age of 35. The mean age of diagnosis for fibroids was 43.4 years old and endometriosis was 38.0 years old (Supplemental Figure 1).

Baseline characteristics sometimes differed between those with fibroids, endometriosis, and no pathology (Table 1). Nulliparity was more frequently reported by those participants with fibroids (19%, 3,828/19,932) or endometriosis (24%, 2,180/8,951) than participants with neither condition (16%, 4,374/26,547). Participants with fibroids or endometriosis more frequently reported hysterectomies and/or bilateral oophorectomies. For those without either diagnosis, 9.8% (6,929/26,547) had only hysterectomies and 8.4% (9,031/26,547) had bilateral oophorectomies. For those with fibroids, 20% (3,913/19,932) and 28% (5,537/19,932) had the procedures, respectively, and for endometriosis, 20% (1,763/8,951) and 39% (3,472/8,951). Participants with fibroids and endometriosis reported more use of HRT. Those with fibroids or endometriosis more often reported a BMI consistent with obesity. No large differences by race were apparent for endometriosis, but fibroids were more common in Black participants (64%, 2,886/4,521) than non-Black participants (37%, 17,046/45,680) in this cohort.

After imputation, among those with both fibroids and hysterectomy, 89% (9,921/11,118) of fibroids were reported as diagnosed prior to hysterectomy. For endometriosis, 88% (5,176/5,878) were reported prior to hysterectomy.

Fibroids were associated with a higher rate of incident breast cancer (fully adjusted HR: 1.07, 95% CI: 1.01–1.14) (Figure 1). For endometriosis, there was no evidence of an association with breast cancer (HR: 0.99, 95% CI: 0.91–1.08). Both models met the proportional hazards assumption (Schoenfeld tests $p>0.05$).

In analyses where women with fibroids are separated by their hysterectomy and oophorectomy status, the referent group is no diagnosed fibroids, with or without gynecological surgery (Figure 1). The positive association between fibroids and breast cancer was most evident among participants who also had a hysterectomy only (HR: 1.17, 95% CI: 1.05–1.31). In contrast, fibroids were not associated with increased breast cancer rates among participants who underwent bilateral oophorectomy regardless of hysterectomy status (HR: 0.99, 95% CI: 0.90–1.10). Endometriosis was not associated with breast cancer among participants with a hysterectomy or neither gynecological surgery, but endometriosis with bilateral oophorectomy was associated with lower breast cancer incidence (HR: 0.88, 95% CI: 0.77–1.00).

Since fibroids are more common and often more severe among Black participants, we stratified by race and ethnicity, separating non-Hispanic Black women from everyone else (“non-Black”) (Table 2). Among Black participants, the hazard ratio between fibroids and breast cancer was higher (HR 1.34, 95% CI: 1.07–1.69) than that observed among non-Black participants (HR 1.07, 95% CI: 1.00–1.15; p-for-heterogeneity=0.08).

This association between fibroids and breast cancer was similar for pre- and post-menopausal person-time (p-for-heterogeneity = 0.51) (Table 3). The association between endometriosis and breast cancer continued to be null in models stratified by menopause status, also without significant heterogeneity (p-value = 0.38) (Figure 1, Table 3).

When examining fibroids and endometriosis diagnosed before the age of 35, most associations were near null, even when stratifying by surgical status and menopausal status

(Supplemental Table 1–2). There was a possible positive association between fibroids with hysterectomy and breast cancer among post-menopausal participants (HR=1.20, 95% CI: 0.96–1.50).

Among breast cancer cases, those with fibroids were more likely to have ER+ (versus ER-) disease (OR: 1.34, 95% CI: 1.10–1.65), whereas those with endometriosis were less likely to be ER+ (OR=0.78; 95% CI: 0.61–1.01) (Figure 2). Fibroids were inversely associated with triple negative breast cancer (versus non-triple negative; OR=0.64; 95% CI: 0.49–0.83), whereas endometriosis was non-significantly associated with triple negative breast cancer (OR=1.11; 95% CI: 0.80–1.53) (Figure 2).

These associations potentially differed with regards to race/ethnicity (Supplemental Figure 2; Supplemental Tables 3-7). For example, among Black participants, fibroids were positively associated with HER2+ breast cancer (fully adjusted OR 1.80; 95% CI 0.80–4.04), but not associated with ER+ breast cancer (OR 1.04; 95% CI 0.55–1.97).

Discussion

This study investigated the association between previously diagnosed fibroids or endometriosis and incident breast cancer in the Sister Study, a cohort of 50,884 U.S. participants. Emphasis was placed on the intersection of these uterine pathologies with surgeries often used as treatment (hysterectomy and oophorectomy), race/ethnicity, menopausal status, and age of diagnosis. Finally, we examined the association of these pathologies with ER, PR, HER2, and triple negative subtypes of breast cancer.

History of fibroids was positively associated with incident breast cancer, with a HR of 1.07 of developing breast cancer. While this is statistically significant, it is a clinically modest effect size. As outlined in the introduction, most studies suggest a positive relationship with fibroids and breast cancer, but some are conflicting. Among those that report hazard ratios, a Taiwanese cohort with 107,357 participants reported a HR of 1.31 (95%: 1.13–1.52)(24), and South Korean cohort with 630,523 participants reported an HR of 1.30 (1.20–1.41). In this cohort, we showed that the hazard ratio was larger among Black women 1.34 (1.07 to 1.69), compared to non-Black women, and among women who had a hysterectomy without bilateral oophorectomy 1.17 (95% CI: 1.07–1.31). Contrary to our finding, the Black Women's Health Study reported no association between fibroids and breast cancer, but a positive association between early-onset fibroids and pre-menopausal breast cancer(27). Fibroids here were positively associated with ER+ breast cancer subtypes and negatively associated with triple negative breast cancer.

It is not likely that fibroids are directly causing breast cancer. More plausibly, other factors are driving both simultaneously, likely those involving estrogen exposure. High serum estrogen levels are documented for both diseases, and several estrogenic risk factors are common between the two diseases, including obesity, alcohol use, early menarche, and nulliparity (2,9),(36). The multivariable models reported here account for these risk factors, suggesting that other environmental or genetic risks may drive the link between fibroids and breast cancer. For instance, di-(2-ethylhexyl)-phthalate has been associated with both

fibroids and breast cancer (37), suggesting that sex hormone disrupting chemicals could contribute to both diseases. Our findings that fibroids are associated with a higher odds ratio of ER+ and PR+ subtypes, and oophorectomy removes the association between fibroids and breast cancer, further support similar estrogenic etiology. Because Sister Study participants all have a full- or half-sister with a history of breast cancer, our results suggest the positive association between history of fibroids and breast cancer is also present in in those with a known family history of breast cancer.

Mutagenic compounds may also be implicated, since 50% of fibroids have chromosomal abnormalities (9). Mediator complex subunit 12 (MED12) represents an interesting link. Inactivation of MED12 modulates CDK8 and upregulates TGF-B, and 50–80% of fibroids have point mutations in MED12 (9,38). MED12 mutations have also been associated with fibroadenoma, phyllodes tumors, more aggressive prostate and ovarian cancer, and chronic lymphocytic leukemia (38–40).

Among those with fibroids, those with only hysterectomy had a marginally elevated hazard ratio for breast cancer incidence. Hysterectomy is a historically common treatment of fibroids, with 75% of patients with fibroids electing to treat with hysterectomy, despite increasing availability of other treatment modalities (30). Fibroids treated with hysterectomy may represent a more severe subset of fibroids that are larger, more numerous, or more symptomatic. The association was also higher among Black women, who experience a higher prevalence of fibroids on average as well as more burdensome fibroids in terms of number and size(41). The marginally increased incidence rates among Black women and women who had hysterectomies potentially points to a dose-dependent relationship between fibroid severity and breast cancer. Studies that use ultrasound to precisely measure fibroid size would be best suited to corroborate this.

In addition to fibroids, Black women are also disproportionately affected by breast cancer (41). As a group, they have lower incidence but higher mortality from breast cancer, with a discrepancy thought to be largely explained by the fact that Black women are more likely to have early-onset, aggressive (high-grade), and difficult to treat (triple negative) forms of breast cancer (42). However, even within subtypes, Black women experience higher mortality (43). Differing from the rest of the cohort, Black women with both fibroids and breast cancer were not more likely to have ER+ or PR+ subtypes. This suggests that non-sex-hormonal exposures may be more relevant disease mechanisms for this subgroup. Possible candidates include factors strongly influenced by structural racism, such as diet, housing, stress, and exposure to pollution and other toxins (44).

Additionally, vitamin D deficiency is associated with both fibroids and breast cancer (45,46), via two potential mechanisms: its anti-estrogen/progesterone properties and its ability to promote differentiation and apoptosis (46,47). Among the Sister Study cohort, it was previously reported that serum vitamin D levels as well as self-reported supplementation were associated with a lower breast cancer incidence, (48) with a weakly negative association observed among Black women (49).

There was a near null but trending positive association between fibroids diagnosed before age 35 and breast cancer. While early-onset fibroids does not represent a strong risk, this does not invalidate the overall association, since 79% of fibroids in our cohort were diagnosed over the age of 35.

Endometriosis was not associated with breast cancer in this cohort, even when stratifying by race/ethnicity, menopause status, or separately considering early-onset endometriosis. This is conflicting with a recent meta-analysis demonstrating a positive association.(18) However, among cases, endometriosis was more strongly associated with ER- and PR- subtypes (relative to ER+/PR+). This may be due to endometriosis-induced ovarian damage. Twenty eight percent of ovarian endometriosis was bilateral in one case series (50), and women with endometriosis have lower circulating levels of estradiol and progesterone (51).

For both fibroids and endometriosis, bilateral oophorectomy was associated with a reduced hazard of breast cancer. For fibroids, the increased risk was largely ameliorated. These results seem to represent the protective effect of oophorectomy on breast cancer risk, which is consistent with previous findings from this cohort(29).

A strength of this study was the inclusion of many potential confounders in the regression models and the ability to stratify by factors that might help explain the true mechanisms behind the observed associations. Participants in this study must have full- or half-sisters with a history of breast cancer. This unique study sample may mean that our results are not fully generalizable to the general US population or other demographic groups. However, several previous studies that did not enrich for breast cancer family history have also demonstrated a positive association. Beyond the potential lack of generalizability, another limitation of our study is that history of fibroids was self-reported, which omits asymptomatic fibroids that can only be detected on imaging. Similar concerns are present for self-reported endometriosis, which is typically only diagnosed surgically.

The relationship between fibroids and breast cancer may reflect common risk factors. The higher odds of ER+ subtypes indicates that some of these shared risk factors involve sex hormone mechanisms. This includes reproductive factors such as parity and exogenous hormone use, but also suggests other factors like vitamin D or endocrine-disrupting exposures. Fibroids diagnoses may prove to be a useful variable to include in risk calculations that guide breast cancer screening recommendations. Large prospective cohort studies should replicate these findings, and a meta-analysis of existing studies should be performed to better characterize the association, with careful consideration of surgical status, race/ethnicity, and other factors. Further studies that use imaging to detect asymptomatic fibroids and measure fibroid severity may help quantify this risk more precisely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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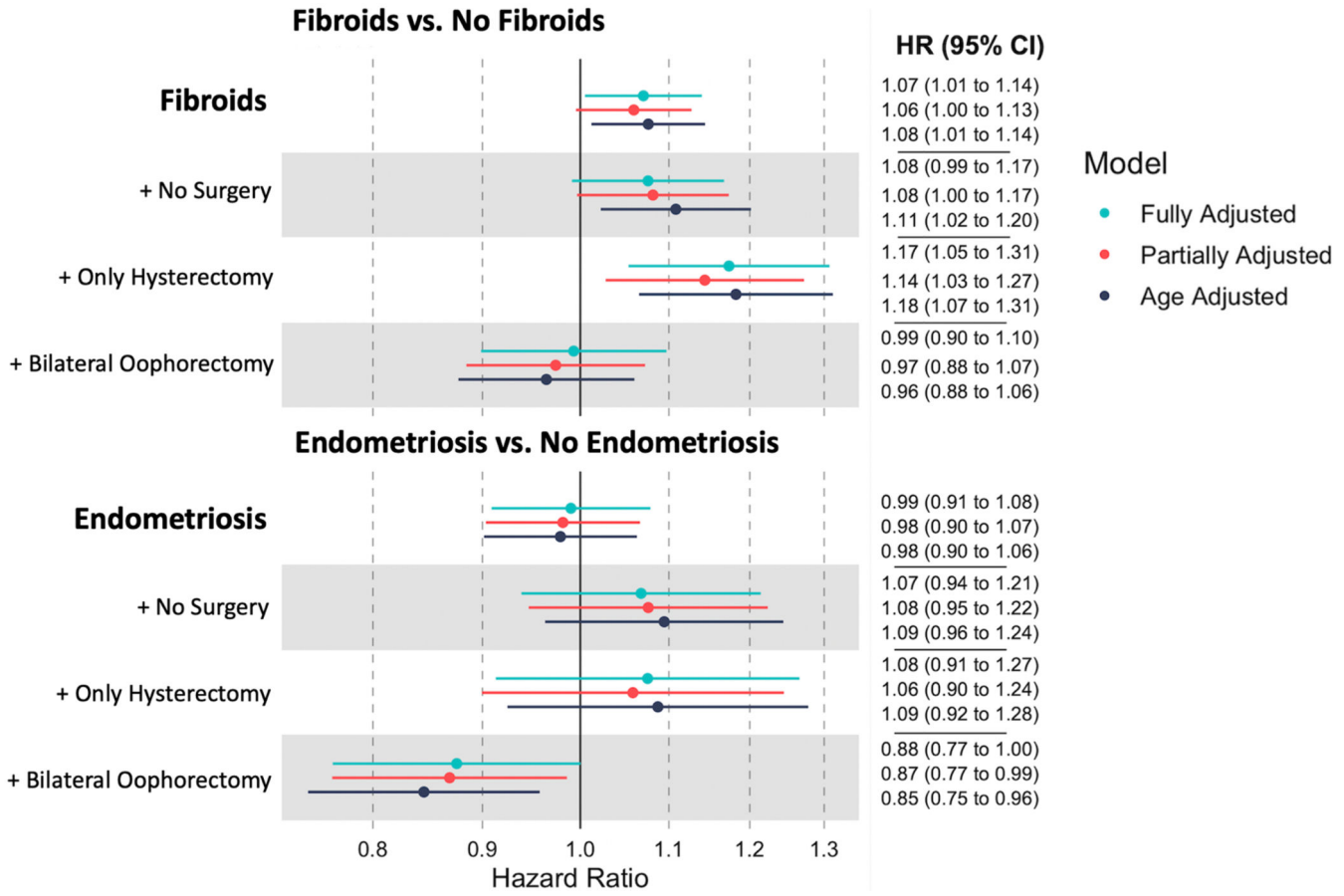

Figure 1:

Association of fibroids and endometriosis with breast cancer with and without hysterectomy and oophorectomy

Results from Cox proportional hazards model assessing the relationship between history of fibroids or endometriosis and incident breast cancer. Further analysis includes fibroids plus surgical history, either bilateral oophorectomy (regardless of hysterectomy status) and hysterectomy without oophorectomy. The referent group is no fibroids (or no endometriosis), regardless of surgical history. Age adjusted, partially adjusted, and fully adjusted models are included

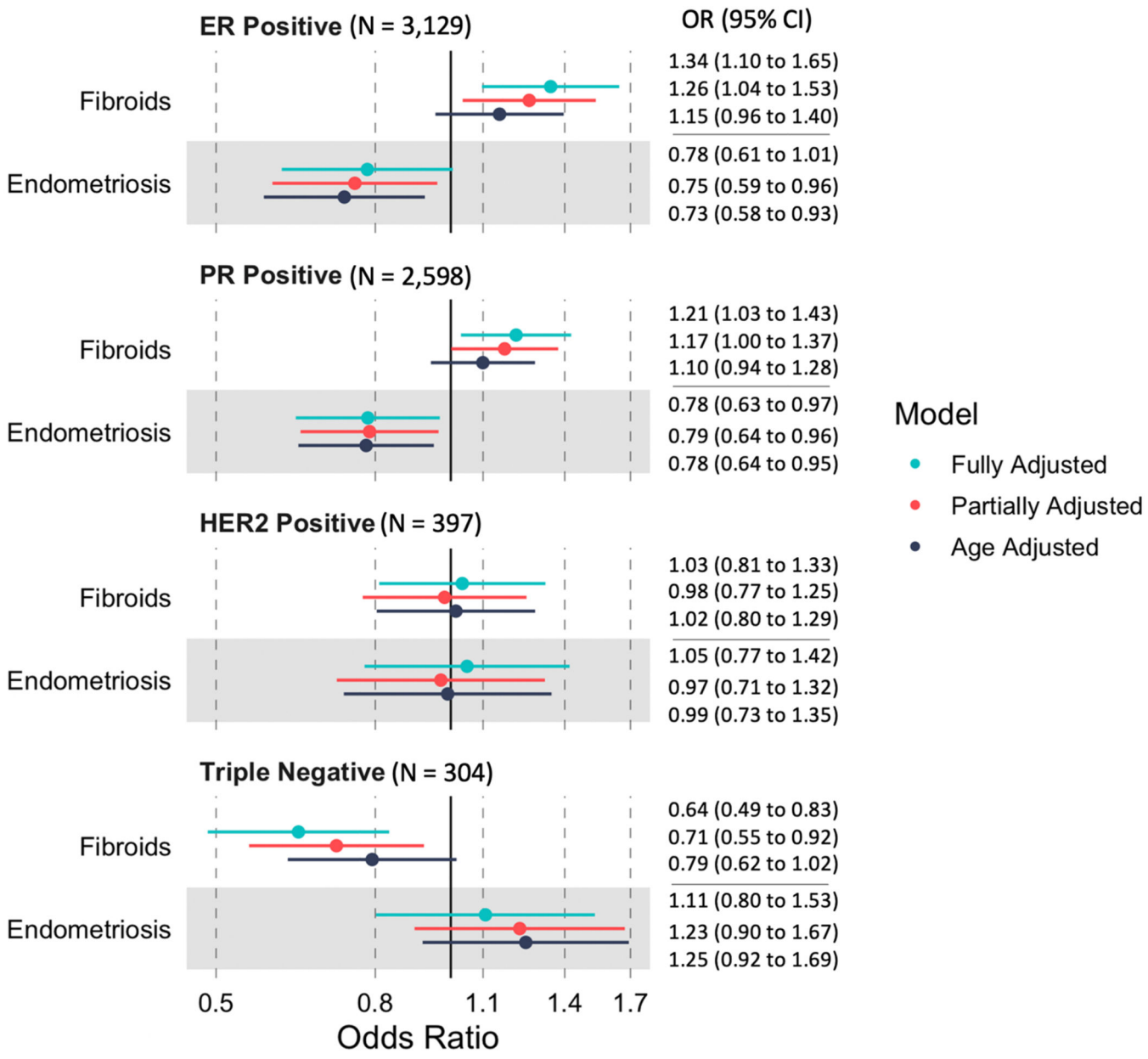

Figure 2:

Association of fibroids and endometriosis with hormone receptor subtypes among 4,419 breast cancer cases

Results from logistic regression model among breast cancer cases assessing the relationship between history of fibroids or endometriosis and breast cancer subtype (ER+ versus ER-, PR+ versus PR-, HER2+ versus HER2- and triple-negative vs. non-triple-negative). The referent group is no fibroids (or no endometriosis), regardless of surgical history. Age adjusted, partially adjusted, and fully adjusted models are included

Table 1

Baseline (2003–2009) characteristics of Sister Study participants (n=50,201) according to their fibroid and endometriosis status at the end of follow-up (up to September 2020)

		Fibroid and Endometriosis Status at End of Follow-up				
Baseline Characteristics[3]	**All Participants**	**Neither diagnosis**	**Fibroids**	**Fibroids diagnosed < 35 years**	**Endometriosis**	**Endometriosis diagnosed < 35 years**
	N = 50,201	**N = 26,547 (52.8%)**	**N = 19,932[1] (39.7%)**	**N = 4,230[1] (8.4%)**	**N = 8,951[1] (17.8%)**	**N = 3,970[1] (7.9%)**
Age at Baseline	56 (9)	55 (9)	56 (9)	56 (9)	56 (9)	54 (8)
Race						
Non-Hispanic White	42,038 (84%)	22,996 (87%)	15,773 (79%)	2,891 (68%)	7,547 (84%)	3,316 (84%)
Non-Hispanic Black/ African American	4,521 (9.0%)	1,465 (5.5%)	2,886 (14%)	1,050 (25%)	741 (8.3%)	375 (9.4%)
Hispanic	2,315 (4.6%)	1,366 (5.1%)	779 (3.9%)	171 (4.0%)	381 (4.3%)	152 (3.8%)
Other	1,327 (2.6%)	720 (2.7%)	494 (2.5%)	118 (2.8%)	282 (3.2%)	127 (3.2%)
Education						
High School	7,683 (15%)	4,284 (16%)	2,781 (14%)	617 (15%)	1,345 (15%)	553 (14%)
Some College	16,930 (34%)	8,606 (32%)	6,956 (35%)	1,559 (37%)	3,314 (37%)	1,538 (39%)
Undergraduate Degree	13,556 (27%)	7,418 (28%)	5,208 (26%)	1,035 (24%)	2,223 (25%)	998 (25%)
Graduate Degree	12,032 (24%)	6,239 (24%)	4,987 (25%)	1,019 (24%)	2,069 (23%)	881 (22%)
Body mass index (BMI) at Baseline (kg/m^2)						
<18.5	519 (1.0%)	320 (1.2%)	171 (0.9%)	25 (0.6%)	73 (0.8%)	32 (0.8%)
18.5–25	19,801 (39%)	11,170 (42%)	7,135 (36%)	1,340 (32%)	3,300 (37%)	1,548 (39%)
25–30	15,971 (32%)	8,334 (31%)	6,439 (32%)	1,396 (33%)	2,910 (33%)	1,261 (32%)
>30	13,910 (28%)	6,723 (25%)	6,187 (31%)	1,469 (35%)	2,668 (30%)	1,129 (28%)
Physical Activity Including Work						
<10 hours/week	18,901 (38%)	9,907 (37%)	7,620 (38%)	1,610 (38%)	3,285 (37%)	1,471 (37%)
10–20 hours/week	20,738 (41%)	11,083 (42%)	8,126 (41%)	1,652 (39%)	3,655 (41%)	1,616 (41%)
20–30 hours/week	8,403 (17%)	4,406 (17%)	3,345 (17%)	779 (18%)	1,583 (18%)	691 (17%)
>30 hours/week	2,159 (4.3%)	1,151 (4.3%)	841 (4.2%)	189 (4.5%)	428 (4.8%)	192 (4.8%)
Alcohol						
Non-Drinking	9,538 (19%)	4,939 (19%)	3,885 (19%)	965 (23%)	1,804 (20%)	815 (21%)
<7 drinks/week	33,874 (67%)	17,831 (67%)	13,509 (68%)	2,807 (66%)	6,019 (67%)	2,688 (68%)
7+ drinks/week	6,789 (14%)	3,777 (14%)	2,538 (13%)	458 (11%)	1,128 (13%)	467 (12%)
Smoking (pack-years)						
Never	28,338 (56%)	14,910 (56%)	11,417 (57%)	2,383 (56%)	4,905 (55%)	2,170 (55%)
<15 pack-years	13,687 (27%)	7,173 (27%)	5,478 (27%)	1,106 (26%)	2,502 (28%)	1,087 (27%)

		Fibroid and Endometriosis Status at End of Follow-up				
Baseline Characteristics[3]	**All Participants**	**Neither diagnosis**	**Fibroids**	**Fibroids diagnosed < 35 years**	**Endometriosis**	**Endometriosis diagnosed < 35 years**
	N = 50,201	**N = 26,547 (52.8%)**	**N = 19,932[1] (39.7%)**	**N = 4,230[1] (8.4%)**	**N = 8,951[1] (17.8%)**	**N = 3,970[1] (7.9%)**
15–30 pack-years	4,890 (9.7%)	2,635 (9.9%)	1,863 (9.3%)	430 (10%)	927 (10%)	426 (11%)
>30 pack-years	3,286 (6.5%)	1,829 (6.9%)	1,174 (5.9%)	311 (7.4%)	617 (6.9%)	287 (7.2%)
Parity						
No children	9,079 (18%)	4,374 (16%)	3,828 (19%)	811 (19%)	2,180 (24%)	1,018 (26%)
1 child	7,261 (14%)	3,539 (13%)	3,059 (15%)	791 (19%)	1,547 (17%)	780 (20%)
2 children	18,450 (37%)	9,882 (37%)	7,242 (36%)	1,483 (35%)	3,107 (35%)	1,388 (35%)
3+ children	15,411 (31%)	8,752 (33%)	5,803 (29%)	1,145 (27%)	2,117 (24%)	784 (20%)
Age at First Pregnancy						
Never Pregnant	7,762 (15%)	3,941 (15%)	3,059 (15%)	637 (15%)	1,762 (20%)	851 (21%)
<20 years old	9,536 (19%)	4,629 (17%)	4,217 (21%)	1,064 (25%)	1,751 (20%)	741 (19%)
20–24 years old	17,466 (35%)	9,117 (34%)	7,187 (36%)	1,470 (35%)	2,950 (33%)	1,213 (31%)
25–29 years old	9,349 (19%)	5,300 (20%)	3,425 (17%)	590 (14%)	1,433 (16%)	610 (15%)
30+ years old	6,088 (12%)	3,560 (13%)	2,044 (10%)	469 (11%)	1,055 (12%)	555 (14%)
Breastfeeding						
Never	21,596 (43%)	10,756 (41%)	9,026 (45%)	2,021 (48%)	4,416 (49%)	1,930 (49%)
<1 year	16,407 (33%)	8,556 (32%)	6,628 (33%)	1,393 (33%)	2,927 (33%)	1,323 (33%)
1–2 years	6,503 (13%)	3,768 (14%)	2,343 (12%)	436 (10%)	929 (10%)	415 (10%)
>2 years	5,695 (11%)	3,467 (13%)	1,935 (9.7%)	380 (9.0%)	679 (7.6%)	302 (7.6%)
Age of Menarche						
<12 years old	10,254 (20%)	4,847 (18%)	4,606 (23%)	1,123 (27%)	2,093 (23%)	965 (24%)
12–14 years old	28,194 (56%)	15,027 (57%)	11,109 (56%)	2,304 (54%)	4,874 (54%)	2,124 (54%)
>14 years old	11,753 (23%)	6,673 (25%)	4,217 (21%)	803 (19%)	1,984 (22%)	881 (22%)
Years taking oral contraceptives						
Never	8,015 (16%)	4,399 (17%)	3,113 (16%)	648 (15%)	1,190 (13%)	465 (12%)
0–2 years	7,948 (16%)	3,916 (15%)	3,415 (17%)	763 (18%)	1,559 (17%)	696 (18%)
2–10 years	21,556 (43%)	11,291 (43%)	8,604 (43%)	1,901 (45%)	3,959 (44%)	1,882 (47%)
10+ years	12,682 (25%)	6,941 (26%)	4,800 (24%)	918 (22%)	2,243 (25%)	927 (23%)
Hormone Replacement Therapy						
None	28,056 (56%)	16,404 (62%)	10,044 (50%)	2,038 (48%)	3,832 (43%)	1,728 (44%)
Estrogen and Progestin	12,388 (25%)	7,016 (26%)	4,442 (22%)	833 (20%)	1,982 (22%)	863 (22%)
Estrogen Only	9,757 (19%)	3,127 (12%)	5,446 (27%)	1,359 (32%)	3,137 (35%)	1,379 (35%)

		Fibroid and Endometriosis Status at End of Follow-up				
Baseline Characteristics[3]	**All Participants**	**Neither diagnosis**	**Fibroids**	**Fibroids diagnosed < 35 years**	**Endometriosis**	**Endometriosis diagnosed < 35 years**
	N = 50,201	**N = 26,547 (52.8%)**	**N = 19,932[1] (39.7%)**	**N = 4,230[1] (8.4%)**	**N = 8,951[1] (17.8%)**	**N = 3,970[1] (7.9%)**
Surgery[2]						
No Surgery	34,241 (68%)	21,940 (83%)	10,482 (53%)	1,765 (42%)	3,716 (42%)	1,685 (42%)
Hysterectomy Only	6,929 (14%)	2,374 (8.9%)	3,913 (20%)	1,259 (30%)	1,763 (20%)	865 (22%)
Bilateral Oophorectomy Only	234 (0.5%)	141 (0.5%)	78 (0.4%)	13 (0.3%)	36 (0.4%)	10 (0.3%)
Both	8,797 (18%)	2,092 (7.9%)	5,459 (27%)	1,193 (28%)	3,436 (38%)	2,092 (7.9%)

[1] Those subjects who have both fibroids and endometriosis contribute to the statistics of both the fibroids and endometriosis columns.

[2] "Hysterectomy Only" indicates hysterectomy but not bilateral oophorectomy; "bilateral oophorectomy" indicates bilateral oophorectomy with or without hysterectomy; "no surgery" indicates neither hysterectomy nor bilateral oophorectomy. Partial/unilateral oophorectomies would either be classified under "no surgery" or "hysterectomy only".

[3] Characteristics are based on status at baseline, while fibroids and endometriosis refer to status at end of follow-up

Mean (SD) or Count (percentage)

Data represented here is the average of all 30 imputed data sets

Table 2

Association of fibroids with breast cancer, stratified by race/ethnicity

			Age Adjusted	Partially Adjusted	Fully Adjusted
	Person-Years	**Breast Cancer Events**	**HR (95% CI)[1]**	**HR (95% CI)[1]**	**HR (95% CI)[1]**
non-Black women (includes non-Hispanic White women, Hispanic women, and other non-Black women)					
Fibroids					
No Fibroids	29,501	2,609	Ref	Ref	Ref
Fibroids	15,018	1,439	1.05 (0.99 to 1.12)	1.04 (0.98 to 1.11)	1.07 (1.00 to 1.15)
Fibroids +/− Surgery					
No Fibroids	29,501	2,609	Ref	Ref	Ref
Fibroids Without Surgery	6,861	658	1.09 (1.00 to 1.19)	1.07 (0.98 to 1.16)	1.06 (0.97 to 1.16)
Fibroids With Hysterectomy Only	3,080	333	1.16 (1.04 to 1.31)	1.13 (1.01 to 1.27)	1.17 (1.04 to 1.31)
Fibroids With Bilateral Oophorectomy	5,078	448	0.94 (0.85 to 1.04)	0.95 (0.86 to 1.05)	0.97 (0.87 to 1.08)
Non-Hispanic Black / African American women					
Fibroids					
No Fibroids	1,561	121	Ref	Ref	Ref
Fibroids	2,420	250	1.30 (1.04 to 1.62)	1.31 (1.05 to 1.64)	1.34 (1.07 to 1.69)
Fibroids +/− Surgery					
No Fibroids	1,561	121	Ref	Ref	Ref
Fibroids Without Surgery	1,037	103	1.31 (1.01 to 1.71)	1.32 (1.01 to 1.73)	1.34 (1.02 to 1.75)
Fibroids With Hysterectomy Only	708	77	1.35 (1.01 to 1.80)	1.34 (1.00 to 1.80)	1.37 (1.02 to 1.85)
Fibroids With Bilateral Oophorectomy	675	70	1.23 (0.91 to 1.66)	1.26 (0.92 to 1.71)	1.24 (0.90 to 1.71)
Wald Test for Heterogeneity of association between fibroids and breast cancer by race/ethnicity					
p-value			0.12	0.10	0.08

[1] HR = Hazard Ratio, CI = Confidence Interval

Table 3

Association of fibroids or endometriosis with breast cancer, stratified by menopause-time

	Person-Years	Breast Cancer Events	Age Adjusted HR (95% CI)	Partially Adjusted HR (95% CI)	Fully Adjusted HR (95% CI)
Pre-Menopausal Person-Time					
Fibroids					
No Fibroids	11,309	890	Ref	Ref	Ref
Fibroids	5,242	464	1.07 (0.96 to 1.20)	1.07 (0.95 to 1.20)	1.09 (0.97 to 1.23)
Fibroids +/− Surgery					
No Fibroids	11,309	890	Ref	Ref	Ref
Fibroids Without Hysterectomy	3,328	297	1.09 (0.95 to 1.24)	1.08 (0.95 to 1.24)	1.09 (0.95 to 1.24)
Fibroids With Hysterectomy	1,914	167	1.04 (0.88 to 1.23)	1.04 (0.87 to 1.23)	1.07 (0.90 to 1.28)
Endometriosis					
No Endometriosis	14,469	1,170	Ref	Ref	Ref
Endometriosis	2,082	184	1.08 (0.92 to 1.26)	1.07 (0.91 to 1.25)	1.09 (0.93 to 1.28)
Endometriosis +/− Surgery					
No Endometriosis	14,469	1,170	Ref	Ref	Ref
Endometriosis Without Hysterectomy	1,238	110	1.10 (0.91 to 1.34)	1.09 (0.90 to 1.33)	1.09 (0.89 to 1.32)
Endometriosis With Hysterectomy	845	74	1.04 (0.83 to 1.32)	1.03 (0.82 to 1.31)	1.08 (0.85 to 1.37)
Post-Menopausal Person-Time					
Fibroids					
No Fibroids	19,753	1,840	Ref	Ref	Ref
Fibroids	12,196	1,225	1.08 (1.00 to 1.16)	1.06 (0.98 to 1.14)	1.09 (1.01 to 1.18)
Fibroids +/− Surgery					
No Fibroids	19,753	1,840	Ref	Ref	Ref
Fibroids Without Surgery	4,597	464	1.10 (0.99 to 1.21)	1.07 (0.97 to 1.19)	1.07 (0.96 to 1.18)
Fibroids With Hysterectomy Only	2,246	273	1.22 (1.07 to 1.38)	1.19 (1.05 to 1.36)	1.24 (1.08 to 1.41)
Fibroids With Bilateral Oophorectomy	5,352	488	1.00 (0.91 to 1.11)	0.98 (0.88 to 1.08)	0.99 (0.89 to 1.10)
Endometriosis					
No Endometriosis	26,536	2,580	Ref	Ref	Ref
Endometriosis	5,413	485	0.97 (0.88 to 1.06)	0.95 (0.86 to 1.05)	0.98 (0.88 to 1.09)
Endometriosis +/− Surgery					
No Endometriosis	26,536	2,580	Ref	Ref	Ref
Endometriosis Without Surgery	1,430	142	1.07 (0.91 to 1.27)	1.05 (0.89 to 1.25)	1.04 (0.88 to 1.23)
Endometriosis With Hysterectomy Only	843	92	1.06 (0.86 to 1.31)	1.05 (0.86 to 1.30)	1.08 (0.87 to 1.33)

	Person-Years	Breast Cancer Events	Age Adjusted HR (95% CI)	Partially Adjusted HR (95% CI)	Fully Adjusted HR (95% CI)
Endometriosis With Bilateral Oophorectomy	3,140	251	0.88 (0.78 to 1.01)	0.87 (0.76 to 0.99)	0.87 (0.76 to 1.00)
Heterogeneity testing with Wald test (p-value) for association between fibroids or endometriosis and breast cancer by menopausal status					
Fibroids			0.91	0.83	0.51
Endometriosis			0.23	0.23	0.38