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History of uterine leiomyomata and incidence of breast cancer

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Abstract

Purpose—Uterine leiomyomata (UL), benign tumors of the myometrium, are influenced by sex steroid hormones. A history of UL diagnosis has been associated with a higher risk of uterine malignancies. The relation between UL and breast cancer, another hormonally-responsive cancer, has not been studied.

Methods—We investigated the association between self-reported physician-diagnosed UL and incidence of breast cancer in the Black Women's Health Study, a prospective cohort study. We followed 57,747 participants without a history of breast cancer from 1995 to 2013. UL diagnoses were reported at baseline and biennially. Breast cancer was reported on biennial questionnaires and confirmed by pathology data from medical records or cancer registries. Cox regression was used to derive incidence rate ratios (IRRs) and 95% confidence intervals (CI) and adjust for potential confounders.

Results—There were 2,276 incident cases of breast cancer (1,699 invasive, 394 *in situ*, and 183 unknown) during 879,672 person-years of follow-up. The multivariable IRR for the overall association between history of UL and breast cancer incidence was 0.99 (95% CI: 0.90-1.08), with similar results for ER+ (IRR=1.03) and ER– breast cancer (IRR=1.05). IRRs for early diagnosis of UL (before age 30) were slightly above 1.0, with IRRs of 1.14 (95% CI: 0.99-1.31) for overall breast cancer, 1.14 (95% CI: 0.93-1.40) for ER+ breast cancer, and 1.20 (95% CI: 0.89-1.61) for ER– breast cancer. IRRs for early diagnosis of UL were elevated for breast cancer diagnosed before age 40 years (IRR=1.39, 95% CI: 0.97-1.99) and premenopausal breast cancer (IRR=1.26, 95% CI: 1.01-1.58). No consistent patterns in risk were observed across estrogen receptor subtypes, and IRRs did not differ appreciably within strata of BMI, female hormone use, mammography recency, or family history of breast cancer.

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Authors' contributions

Conception and design of parent study (L.R., J.R.P., L.A.C.), obtaining of funding (L.R., L.A.C., J.R.P.), data collection, validation, and interpretation (L.A.W., L.R., L.A.C., J.R.P.), data analysis (L.A.W., R.G.R.), literature search (L.A.W.), writing of article (L.A.W.), critical revision of the article (L.A.W., R.G.R., L.R., L.A.C., J.R.P.) and final approval of manuscript (L.A.W., R.G.R., L.R., L.A.C., J.R.P.).

Competing interests

None.

Conclusions—The present study of U.S. black women suggests that a history of UL diagnosis is unrelated to the incidence of breast cancer overall. The positive associations observed for early-diagnosed UL with breast cancer before age 40 and with premenopausal breast cancer require confirmation in future studies.

Keywords

black women; uterine leiomyoma; breast carcinoma; estrogen receptor; prospective studies

Introduction

Uterine leiomyomata (UL), benign tumors of the myometrium, are influenced by sex steroid hormones: estradiol and progesterone [1]. A history of UL diagnosis has been associated with a higher risk of uterine malignancies [2-9], but it is unclear whether the association reflects an etiologic association, shared risk factors, initial misdiagnosis, or detection bias. To our knowledge, the relation between UL and breast cancer, another hormonally-responsive cancer [10-14], has not been studied. If there is a positive association, this could have important public health implications given that symptomatic UL occur in as many as 15% of white women and 35% of black women in the U.S. by age 50 years [15].

There are methodologic challenges related to the study of UL and breast cancer risk. Many cases of UL are asymptomatic and go undetected clinically. A history of UL may lead to greater contact with health providers, more frequent health care screenings, and increased detection of cancers that would otherwise go undetected. Conversely, a history of UL may be related to subsequent hysterectomy and oophorectomy, which in turn may reduce the risk of breast cancer via a reduction in exposure to estrogens. Accounting for gynecologic surgeries in the assessment of future breast cancer incidence is critical.

In a prospective cohort study of 59,000 U.S. black women, we examined the association between history of diagnosed UL and subsequent breast cancer risk overall and by estrogen receptor status and stage at diagnosis. Given that estrogens and progesterone play an important role in breast cancer etiology, we hypothesize that the association between UL and breast cancer will be stronger for ER+ breast cancer, a subtype that is more strongly associated with hormonal risk factors (e.g., age at first birth, menopausal hormone use, and body mass index) than ER– breast cancer [16, 17].

Methods

Study population

The Black Women's Health Study (BWHS) is a large U.S. prospective cohort study of African-American women. Participants provided informed consent in 1995 by completing a 14-page health questionnaire mailed to subscribers to *Essence*, a magazine with a large readership of African-American women. Friends and relatives of early respondents and members of black professional organizations were also invited to enroll. Approximately 59,000 women aged 21-69 years at baseline from 17 states across the U.S. enrolled and provided information on demographic and lifestyle factors; reproductive history; health care

utilization; and medical conditions. They have been followed every two years through mail questionnaires. We identified deaths by reports from family members or the US Postal Service, and we searched the National Death Index periodically for BWHS nonrespondents. Retention of the baseline cohort was 80% through 2013. The institutional review board of Boston University Medical Center approved the study protocol.

Assessment of uterine leiomyomata

Participants reported diagnoses of UL (“fibroids in womb”) on the baseline (1995) and follow-up questionnaires. Age at UL diagnosis was ascertained on the baseline questionnaire, while year at UL diagnosis was ascertained on all follow-up questionnaires. We assessed the positive predictive value of self-report in a random sample of 248 UL cases. Cases were mailed supplemental surveys regarding their initial date of diagnosis, symptoms, and treatment, and were asked for permission to review their medical records. We obtained medical records from 127 of the 128 women who gave us permission and confirmed the self-report in 122 (96%). Among the 188 (76%) cases who completed the supplemental survey, 71% reported UL-related symptoms prior to being diagnosed with the condition. Over 87% reported their condition came to clinical attention because of symptoms or because a mass was palpable at the time of a routine pelvic exam. There were no appreciable differences between cases who did and did not release their medical records with respect to established risk factors for UL [18].

Assessment of breast cancer

Prevalent breast cancer cases were identified via self-report on the 1995 (baseline) questionnaire. Incident cases of breast cancer were ascertained by self-report on biennial follow-up questionnaires from 1997 through 2013 and through cancer registries in 24 states in which 95% of participants resided. Women who reported incident breast cancer were asked for written permission to review their medical records. We have obtained medical record or cancer registry data for 85.3% of self-reported cases to date, and of these, 99.4% were confirmed. Data on tumor characteristics were obtained through abstraction of medical records and cancer registry data. Due to the high confirmation rate, the present report analyzes data from all self-reported incident breast cancer cases.

Assessment of covariates

Data on breast cancer risk factors including age, age at first birth, age at menopause, menopausal status, type of menopause (natural, surgical, or medication-induced), type of gynecologic surgeries (hysterectomy, bilateral oophorectomy, unilateral oophorectomy), parity, lactation, oral contraceptive use, female hormone use (current, former, or never use; and formulation of use), current weight, vigorous physical activity, current alcohol consumption, smoking, and use of mammography were obtained at baseline and were updated on biennial follow-up questionnaires. Data on education, age at menarche, height, current weight, and weight at age 18 were obtained at baseline (1995). Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. Family history of breast cancer among first-degree relatives was ascertained on the 1995 and 1999 questionnaires.

Women who reported a hysterectomy but retained one or both ovaries were classified as premenopausal if their current age was less than the 10th percentile of age at natural menopause in the BWHS (<43 years), as postmenopausal if their age was greater than the 90th percentile of age at natural menopause in the cohort (>57 years), and as uncertain menopausal status between the ages of 43 to 56 years.

Data analysis

We excluded women with a history of breast cancer (N=731) or other cancer except nonmelanoma skin cancer (N=523) at baseline. After these exclusions, 57,747 women remained in the analytic cohort at baseline and were followed for the incidence of breast cancer. Women contributed person-years from the beginning of follow-up on March 1, 1995, until diagnosis of breast cancer, death, loss to follow-up, or end of follow-up on March 1, 2013, whichever occurred first. Cox regression models, stratified by age in one-year intervals and questionnaire cycle, were used to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) for risk of breast cancer (incidence, hormone receptor status, or stage) in relation to history of UL. In analyses confined to one subtype of breast cancer, all other subtypes were excluded. We also assessed these associations using a more stringent exposure definition—women with UL diagnosed before the age of 30 years—because there is likely to be less misclassification of UL among younger women [15].

A covariate was included in multivariable analyses if the literature supported its role as a risk factor for breast cancer and if this risk factor was associated with UL in the BWHS cohort at baseline. Multivariable models were adjusted for age at menarche (continuous), BMI (<25, 25-29, ≥30 kg/m²), family history of breast cancer (mother or sister), education at baseline (<12, 13-15, 16, ≥17 years), parity (0, 1, 2, ≥3 births), age at first birth (<20, 20-24, 25-29, ≥30 years), years since last birth (continuous, centered on the sample median = 10 years), menopausal status (postmenopausal, premenopausal, uncertain), cause of menopause (natural menopause, bilateral oophorectomy), age at menopause (continuous), menopausal female hormone use (never, estrogen only current, estrogen only former, progesterone only current, progesterone only former, estrogen and progesterone current, estrogen and progesterone former), vigorous activity at baseline (none, 1-4, ≥5 hours/week), current smoking status (yes vs. no), and current alcohol consumption (none, <1, 1-7, and ≥14 drinks per week). Duration of oral contraceptive use was omitted from our final models because it was not associated with UL at baseline and made little difference in the main association. Values for time-varying variables – e.g., parity, age at first birth, years since last birth, BMI, smoking, alcohol, menopausal status, mammography, and female hormone use – were reassigned every two years using data reported at the start of the questionnaire cycle. Secondary analyses were performed in which we used the baseline values of all covariates only and in which we lagged exposure by varying amounts of time (e.g., 4, 6, and 8 years) to allow for a longer induction period among more recently-diagnosed UL cases. For example, when lagging exposure by 6 years, we considered a woman as having a “positive UL history” only if her UL diagnosis was at least 6 years ago.

Subgroup analyses were also conducted in which we stratified the data by current age, BMI, family history of breast cancer, menopausal status, female hormone use, and recency of

mammography. To examine whether associations were modified by other variables, a cross-product term between UL and the potential effect modifier was included in the multivariable model. Two-sided p-values for tests of interaction were obtained from a likelihood ratio test with the degrees of freedom equal to the difference in the number of parameters between the null and alternative models. Departures from the proportional hazards assumption (i.e., a constant IRR across time) were tested by the likelihood ratio test comparing models with and without interaction terms for age and calendar time with the main exposure variables.

Results

Baseline characteristics of the study participants according to history of UL are shown in Table 1. A history of UL was positively associated with age at baseline, years since last birth, education, postmenopausal status, and female hormone use, and inversely associated with age at menarche and current smoking. There was little difference between UL groups by BMI, BMI at age 18, vigorous exercise, total years of oral contraceptive use, family history of breast cancer, or recency of mammogram and physician visits.

There were 2,276 incident cases of invasive breast cancer during 879,672 person-years of follow-up (Table 2), including 1,132 cases of ER+ breast cancer and 532 cases of ER– breast cancer. There were 1,699 (75%) invasive cases, 394 (17%) *in situ* cases, and 183 (8%) of unknown localization. Among invasive breast cancer cases with data on stage at diagnosis, 713 (37%) were stage 1 and 826 (43%) were stage 2, 3, or 4 at diagnosis. Among women with a history of UL, 52% of breast cancer cases were diagnosed 10 years since UL diagnosis; that percentage was 96% among women with an early diagnosis of UL (before age 30).

The multivariable IRR for the overall association between history of UL and breast cancer incidence was 0.99 (95% CI: 0.90-1.08), with similar results for ER+ (IRR=1.03) and ER– breast cancer (IRR=1.05). IRRs for early diagnosis of UL (before age 30) were all slightly above 1.0, with IRRs of 1.14 (95% CI: 0.99-1.31) for overall breast cancer, 1.14 (95% CI: 0.93-1.40) for ER+ breast cancer, and 1.20 (95% CI: 0.89-1.61) for ER– breast cancer.

In stratum-specific analyses among women with early diagnosis of UL, IRRs were elevated for breast cancer diagnosed before age 40 years (IRR=1.39, 95% CI: 0.97-1.99) and for premenopausal breast cancer (IRR=1.26, 95% CI: 1.01-1.58) (Table 3). Associations did not differ appreciably within strata of mammography recency (Table 3), BMI, female hormone use, or family history of breast cancer (data not shown). There were no consistent patterns in associations between early UL diagnosis and breast cancer across estrogen receptor subtypes (Table 3).

Table 4 presents data by stage at breast cancer diagnosis. There was no evidence that women with a history of UL were more likely to have breast cancer diagnosed at earlier stages. Among women with a history of early UL diagnosis (age <30), there was no difference among invasive cases by stage at diagnosis (stage <2: IRR=1.16 vs. stage 2: IRR=1.16); the IRR among *in situ* cases was 1.04.

The results from analyses in which we lagged exposure by 4, 6, or 8 years were generally consistent with the results from the primary analysis (data not shown). When we repeated our analyses using baseline exposure, the results were similar to those in which UL diagnoses were updated over time (data not shown).

Discussion

In this prospective investigation of UL and risk of breast cancer, there was no association overall, but some evidence of a positive association between UL diagnosed before age 30 and early-onset breast cancer risk. There were no consistent patterns in these associations by estrogen receptor status. There are no previous studies with which to compare our results.

Self-reported UL was confirmed in 96% of BWHS participants in a validation study. Nevertheless, because participants were not systematically screened for UL, under-ascertainment of UL was likely, particularly among women with asymptomatic disease. This concern is partly addressed by our examination of associations in younger women, among whom UL are less likely to be missed [15]. Detection bias could have explained the positive association observed with early onset UL and breast cancer because women with an early diagnosis of UL may have been more likely to receive regular gynecologic exams to monitor UL recurrence. However, the vast majority of breast cancer cases among women with early-diagnosed UL occurred 10 years or more after the diagnosis of UL, when detection bias associated with care for UL might have been less likely. Furthermore, there was no evidence that a history of UL was associated with a higher incidence of breast cancer diagnosed at earlier stages, thereby ruling out detection bias as a likely explanation of our findings.

Strengths of our study include the high accuracy of self-reported breast cancer (99%), as documented in our validation study. Data on tumor characteristics were obtained from cancer registry and pathology reports. While classification of ER+ and ER– tumors may have been slightly inconsistent because of the range of pathology labs and changes in classification over time, misclassification was unlikely to have been differential with respect to UL history. Because the majority of UL diagnoses in the BWHS were symptomatic, our definition of UL is likely to reflect clinically-significant UL (e.g., causing menorrhagia).

The BWHS collected data on a wide range of risk factors, making it possible to account for many potential confounding factors in multivariable analyses, including gynecologic surgeries and recency of mammographic screening. Overall participation in the BWHS is high and nonrespondents are similar to respondents with respect to important baseline characteristics, suggesting a lack of differential loss to follow-up. Although the BWHS is a convenience sample of women with higher levels of education than the general population, prevalence estimates of UL diagnoses were generally similar to those found in other studies, suggesting that the results may generalize to other black women [18].

An association between tumors of the uterus and the breast via hormonal pathways is biologically plausible [14]. Pathologies of the uterus and breast—including endometrial cancer, endometriosis, UL, and breast cancer—are associated with sex steroid hormones [14]. In particular, estradiol (in synergy with 5alpha-dihydrotestosterone-bezoate) has

growth-promoting effects on mammary epithelial ducts and alveoli [19]. Likewise, smooth muscle cells in UL exhibit increased expression of steroid hormone receptors, growth factors, and growth factor receptors, most of which are regulated by estrogen [20-22], and concentrations of estrogens are higher in leiomyoma tissue than adjacent myometrium. GnRH agonists create a temporary hypoestrogenic state by reducing biologically-active gonadotropin secretions of the pituitary gland, and these effects are associated with a marked reduction in UL size [23]. Progesterone, also a sex steroid hormone, is pro-proliferative in normal mammary tissue, and progesterone promotes UL growth by increasing cellular proliferation, hypertrophy, and deposition of extracellular matrix [14]. Given evidence that UL are hormone-responsive tumors, the same hormonal milieu that contributed to UL may increase susceptibility to ER+ breast cancer, a subtype that is more strongly associated with hormonal risk factors than are ER- tumors [16, 17]. Reasons for a possible association with ER- breast cancer are unclear.

In conclusion, the present study of U.S. black women suggests that the diagnosis of UL is unrelated to the incidence of breast cancer overall, but that there may be a positive association between a history of early-diagnosed UL and breast cancer in young women. The positive associations observed for early-diagnosed UL with breast cancer before age 40 and with premenopausal breast cancer require confirmation in future studies.

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Abbreviations

BMI	body mass index
BWHS	Black Women's Health Study
CI	confidence interval
ER	estrogen receptor
IRR	incidence rate ratio

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Table 1

Characteristics of 57,747 participants in the Black Women's Health Study according to history of uterine leiomyomata at baseline, 1995^a

	No UL	Uterine leiomyomata (UL)	
		UL diagnosed at any age	UL diagnosed before age 30 years
Number of participants	39,209	18,538	5,651
Age at baseline, yrs (mean)	36.1	44.5	39.8
Age at menarche, yrs (mean)	12.4	12.1	12.0
Parity, births (mean)	1.5	1.3	1.2
Age at first birth, yrs (mean) ^b	22.2	22.3	22.4
Time since last birth, yrs (mean) ^b	15.0	15.6	14.0
Vigorous exercise, hrs/wk (mean)	2.0	2.0	2.1
BMI at age 18, kg/m ² (mean) ^c	21.5	21.5	21.6
Current BMI, kg/m ² (mean)	28.0	28.2	28.1
Education, yrs (mean)	14.6	14.8	14.9
Oral contraceptive use, yrs (mean)	3.8	3.9	3.7
Postmenopausal, %	16	19	16
Female hormone use, %	12	20	19
Family history of breast cancer, %	7	6	6
Current smoker, %	17	15	15
Alcohol consumption 1 drink/day, %	6	5	5
Mammogram <1 yr ago, %	27	30	25
Physician visit <1 yr ago, %	86	91	90

^a Means and percentages standardized to age distribution of cohort in 1995. All characteristics assessed in 1995.

^b Restricted to 37,113 participants who were parous at baseline.

^c Restricted to 56,702 participants who reported their weight at age 18.

Table 2History of UL and risk of breast cancer, overall and by hormone receptor status^c

	Person-years	Cases	IRR (95% CI) ^a	IRR (95% CI) ^b
History of UL, any age				
No	501,989	1,120	1.00 (Ref.)	1.00 (Ref.)
Yes	377,683	1,156	1.00 (0.91-1.08)	0.99 (0.90-1.08)
<i>ER+ cases</i>				
No UL	496,772	532	1.00 (Ref.)	1.00 (Ref.)
UL at any age	373,330	600	1.04 (0.92-1.18)	1.03 (0.90-1.17)
<i>ER- cases</i>				
No UL	493,654	260	1.00 (Ref.)	1.00 (Ref.)
UL at any age	370,313	272	1.04 (0.87-1.24)	1.05 (0.87-1.27)
History of UL, age<30 years				
No	501,989	1,120	1.00 (Ref.)	1.00 (Ref.)
Yes	90,733	276	1.17 (1.03-1.34)	1.14 (0.99-1.31)
<i>ER+ cases</i>				
No UL	496,772	532	1.00 (Ref.)	1.00 (Ref.)
UL at age<30	89,616	140	1.20 (0.99-1.46)	1.14 (0.93-1.40)
<i>ER- cases</i>				
No UL	493,654	260	1.00 (Ref.)	1.00 (Ref.)
UL at age<30	88,839	64	1.23 (0.93-1.62)	1.20 (0.89-1.61)

^a Adjusted for age.^b Adjusted for age, questionnaire cycle, menopausal status, cause of menopause, age at menopause, parity, age at first birth, years since last birth, BMI, age at menarche, female hormone use (recency and formulation), smoking, alcohol consumption, family history of breast cancer, education, and vigorous exercise.^c There were 612 cases (284 exposed and 328 unexposed) with missing data on hormone receptor status.

Table 3
History of UL diagnosed before age 30 and risk of breast cancer, by estrogen receptor subtype and selected variables

Variable	All breast cancer subtypes				ER+ breast cancer ^b				ER- breast cancer ^b			
	Person-years	Cases	IRR (95% CI) ^a		Person-years	Cases	IRR (95% CI) ^a		Person-years	Cases	IRR (95% CI) ^a	
<i>Age < 40 yrs</i>												
No UL	217,622	198	1.00 (Ref.)		215,809	81	1.00 (Ref.)		214,886	53	1.00 (Ref.)	
UL at age<30	25,287	37	1.39 (0.97-1.99)		24,987	17	1.47 (0.85-2.53)		24,836	8	1.19 (0.56-2.54)	
<i>Age 40 yrs</i>												
No UL	284,367	922	1.00 (Ref.)		280,963	451	1.00 (Ref.)		278,768	207	1.00 (Ref.)	
UL at age<30	65,446	239	1.11 (0.95-1.30)		64,629	123	1.10 (0.88-1.37)		64,004	56	1.20 (0.87-1.65)	
<i>Premenopausal</i>												
No UL	351,509	521	1.00 (Ref.)		348,176	234	1.00 (Ref.)		346,382	131	1.00 (Ref.)	
UL at age<30	44,073	95	1.26 (1.01-1.58)		43,570	42	1.12 (0.79-1.59)		43,315	24	1.37 (0.88, 2.15)	
<i>Postmenopausal</i>												
No UL	120,162	480	1.00 (Ref.)		118,694	245	1.00 (Ref.)		117,558	99	1.00 (Ref.)	
UL at age<30	30,852	122	1.07 (0.86-1.34)		30,485	69	1.12 (0.83-1.52)		30,184	25	1.02 (0.62-1.68)	
<i>Recent Mammogram</i>												
No UL	247,866	746	1.00 (Ref.)		244,959	377	1.00 (Ref.)		242,983	165	1.00 (Ref.)	
UL at age<30	57,338	209	1.17 (0.99-1.38)		56,560	111	1.12 (0.88-1.42)		56,031	48	1.27 (0.89-1.81)	
<i>No Recent Mammogram</i>												
No UL	183,748	204	1.00 (Ref.)		182,260	82	1.00 (Ref.)		181,438	51	1.00 (Ref.)	
UL at age<30	23,431	36	1.15 (0.79-1.67)		23,227	18	1.53 (0.88-2.67)		23,038	6	0.70 (0.28-1.72)	

^a Adjusted for age, questionnaire cycle, menopausal status, cause of menopause, age at menopause, parity, age at first birth, years since last birth, BMI, age at menarche, female hormone use (recency and formulation), smoking, alcohol consumption, family history of breast cancer, education, and vigorous exercise.

^b There were 612 cases (284 exposed and 328 unexposed) with missing data on hormone receptor status.

Table 4History of UL and risk of breast cancer, by stage at breast cancer diagnosis^b

	Person-years	Cases	IRR (95% CI) ^a
History of UL, any age			
<i>In situ breast cancer</i>			
No UL	491,368	184	1.00 (Ref.)
UL at any age	368,295	210	1.02 (0.82-1.27)
<i>Stage 1 breast cancer</i>			
No UL	491,561	337	1.00 (Ref.)
UL at any age	368,513	376	0.99 (0.84-1.16)
<i>Stage 2, 3 or 4 breast cancer</i>			
No UL	491,665	430	1.00 (Ref.)
UL at any age	368,519	396	0.97 (0.83-1.12)
History of UL, age<30 years			
<i>In situ breast cancer</i>			
No UL	491,368	184	1.00 (Ref.)
UL at age<30	88,302	45	1.04 (0.72-1.49)
<i>Stage 1 breast cancer</i>			
No UL	491,561	337	1.00 (Ref.)
UL at age<30	88,350	87	1.16 (0.90-1.50)
<i>Stage 2, 3, or 4 breast cancer</i>			
No UL	491,665	430	1.00 (Ref.)
UL at age<30	88,377	105	1.16 (0.92-1.47)

^a Adjusted for age, questionnaire cycle, menopausal status, cause of menopause, age at menopause, parity, age at first birth, years since last birth, BMI, age at menarche, female hormone use (recency and formulation), smoking, alcohol consumption, family history of breast cancer, education, and vigorous exercise.

^b There were 160 invasive cases (80 exposed and 80 unexposed) with missing data on stage at diagnosis.