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ARTICLE

Reproductive History and Oral Contraceptive Use in Relation to Risk of Triple-Negative Breast Cancer

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Background Triple-negative (ie, estrogen receptor [ER], progesterone receptor, and HER2 negative) breast cancer occurs disproportionately among African American women compared with white women and is associated with a worse prognosis than ER-positive (ER+) breast cancer. Hormonally mediated risk factors may be differentially related to risk of triple-negative and ER+ breast cancers.

Methods Using data from 155 723 women enrolled in the Women's Health Initiative, we assessed associations between reproductive and menstrual history, breastfeeding, oral contraceptive use, and subtype-specific breast cancer risk. We used Cox regression to evaluate associations with triple-negative (N = 307) and ER+ (N = 2610) breast cancers and used partial likelihood methods to test for differences in subtype-specific hazard ratios (HRs).

Results Reproductive history was differentially associated with risk of triple-negative and ER+ breast cancers. Nulliparity was associated with decreased risk of triple-negative breast cancer (HR = 0.61, 95% confidence interval [CI] = 0.37 to 0.97) but increased risk of ER+ breast cancer (HR = 1.35, 95% CI = 1.20 to 1.52). Age-adjusted absolute rates of triple-negative breast cancer were 2.71 and 1.54 per 10 000 person-years in parous and nulliparous women, respectively; by comparison, rates of ER+ breast cancer were 21.10 and 28.16 per 10 000 person-years in the same two groups. Among parous women, the number of births was positively associated with risk of triple-negative disease (HR for three births or more vs one birth = 1.46, 95% CI = 0.82 to 2.63) and inversely associated with risk of ER+ disease (HR = 0.88, 95% CI = 0.74 to 1.04). Ages at menarche and menopause were modestly associated with risk of ER+ but not triple-negative breast cancer; breastfeeding and oral contraceptive use were not associated with either subtype.

Conclusion The association between parity and breast cancer risk differs appreciably for ER+ and triple-negative breast cancers. These findings require further confirmation because the biological mechanisms underlying these differences are uncertain.

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Breast cancer is a heterogeneous disease that can be divided into distinct subtypes based on patterns of gene expression (1–3) or tumor marker staining (3–5). This biological heterogeneity translates to important clinical differences (2,4–9) and likely reflects etiologic differences (10,11). One tumor subtype that has emerged as being of particular clinical and public health significance is triple-negative breast cancer. Triple-negative breast cancers, which account for 10%–25% of invasive breast cancers (8,9,12–16), are characterized by a lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression and typically exhibit a basal-like pattern of gene expression (1,17,18). The triple-negative phenotype is associated with an aggressive pathology and poorer prognosis than the predominant ER-positive (ER+) phenotype (4,5,7–9), and there are currently no targeted therapies for the treatment of triple-negative breast cancer. If the molecular profiles of breast tumors are fixed at inception (11), distinct risk factors would be expected to contribute towards triple-negative vs ER+ breast cancers. Nevertheless, even though many studies have described risk factors for ER+ breast cancer (19–24), the etiology and risk factor profile of triple-negative tumors remain poorly understood.

Because triple-negative breast cancers are hormone receptor negative, it is plausible that established risk factors for breast cancer overall that influence disease risk through hormonal mechanisms could be differentially associated with risk of ER+ vs triple-negative tumor subtypes. There are only a few studies (13–16,25,26) that have assessed the role of potentially hormonally mediated risk factors for breast cancer overall in relation to risk of triple-negative disease in particular. These studies have been inconsistent and most have been limited by small numbers.

However, multiple studies have reported an inverse association between the number of months that a woman has spent breastfeeding and her risk of triple-negative breast cancer (13,15,25–27). Also, an increased risk of triple-negative breast cancer has been reported among parous women (relative to nulliparous women) (13–15), although an inverse association with parity has been established for ER+ disease. Two studies have reported an increased risk of triple-negative breast cancer among women who have used oral contraceptives (16,27).

Using data from the Women's Health Initiative (WHI) study, we investigated associations between menstrual and reproductive history, breastfeeding, use of oral contraceptives, and triple-negative breast cancer risk among postmenopausal women. We also assessed associations between these factors and risk of ER+ breast cancer for comparison.

Materials and Methods

Study Population

The WHI is a longitudinal study of postmenopausal women, including multiple concurrent randomized clinical trials and an observational study. Details of the WHI study design have been published previously (28,29). Briefly, postmenopausal women aged 50–79 years were recruited from 40 clinical centers across the United States between October 1, 1993, and December 31, 1998. Women were excluded if they had a medical condition that was associated with less than 3 years of predicted survival time or were unlikely to remain in the same geographic area for at least 3 years. Additional eligibility criteria were imposed for participation in the clinical trials component of the WHI study, but women who did not meet these additional criteria or who were not interested in the clinical trials were given the option to enroll in the observational study. At the time of enrollment, all women provided written informed consent for participation and completed a baseline questionnaire. Women in the clinical trials also received a clinical breast examination and mammogram at baseline; women with baseline examinations suspicious for breast cancer or with a history of breast cancer were excluded from the clinical trials. Institutional review boards at all participating institutions approved the WHI study protocols.

Baseline information on demographic factors, medical history, family history of breast cancer, physical activity, height, weight, and mammography history were collected via self-administered questionnaires. These questionnaires were also used to collect detailed information on reproductive history, including parity, age at first birth, breastfeeding, and menstrual history. Information regarding use of oral contraceptives, postmenopausal hormone therapy (HT), and other medications was collected through structured in-person interviews.

Mammography information and medical history, including diagnosis of breast cancer, were updated on an annual (observational study) or semiannual (clinical trials) basis via mailed or telephone-administered questionnaires. Per study protocol, women in the clinical trials received clinical breast examinations and mammography annually in the case of HT trials or biennially in the case of dietary trials; these procedures were not part of the study protocol for women in the observational study, although all women (in both the observational study and clinical trials) were asked to report at each follow-up visit whether they had had a mammogram since their last visit. Breast cancer diagnoses reported by participants were verified locally by WHI physician adjudicators. Medical records and pathology reports for locally confirmed breast cancers were sent to the WHI Clinical Coordinating Center for central adjudication and coding of ER, PR, and HER2 status.

In total, 161 808 women enrolled in the WHI, 93 676 in the observational study and 68 132 in the clinical trials. After excluding 5239 women who had a history of breast cancer or mastectomy at baseline and 846 women who were without follow-up information for breast cancer diagnoses, the present analyses included 155 723 women. Over the course of a median of 7.9 years of follow-up, invasive breast cancers were identified in 5194 women. Information on ER, PR, and HER2 status was available for 4677 (90%), 4600 (89%), and 3139 (60%) of the 5194 women, respectively. Because of variability in HER2 testing practices over the study period and across institutions, we excluded 1334 ER+ case subjects with unknown HER2 status from the ER+ group to make it more comparable with the triple-negative group. Of the 3116 case subjects with complete tumor marker data, 307 (10%) were triple negative

CONTEXT AND CAVEATS

Prior knowledge

Because triple-negative breast cancers are hormone receptor–negative, unlike estrogen receptor–positive (ER+) breast cancers, it is possible that hormones and reproduction have a different influence on risk of such cancers.

Study design

Data from 307 women with triple-negative breast cancer, 2610 women with ER+ breast cancer, and 150 529 control subjects were collected from the Women's Health Initiative trials and observational study. Cox proportional hazards models were used to determine whether reproductive and menstrual history and use of oral contraceptives were associated with risk of triple-negative and/or ER+ breast cancers.

Contribution

Women without children had increased risk of ER+ breast cancer, but decreased risk of triple-negative breast cancer. However, among women who had given birth, those with more children had higher risk of triple-negative and lower risk of ER+ disease. Menstrual history was modestly associated with risk of ER+ breast cancer, but breastfeeding and use of oral contraceptives were not associated with either disease.

Implications

Childbirth appears to have opposite influences on risk of triple-negative vs ER+ breast cancer.

Limitations

The Women's Health Initiative study population was entirely of postmenopausal women, so findings may not apply to younger women. The findings should be confirmed with a larger population of women with triple-negative breast cancer, particularly because the mechanisms behind these associations are not understood.

From the Editors

and 2610 (84%) were ER+. Remaining cancers were either ER− PR+ (N = 45) or ER− PR− HER2+ (N = 154).

Statistical Analyses

We used Cox regression to assess associations between menstrual history (ages at menarche and menopause), reproductive history (parity and age at first birth), lifetime duration of breastfeeding, oral contraceptive use (lifetime duration of use and age at first use), and subtype-specific breast cancer risk. Proportional hazards assumptions for all models were verified by testing for a nonzero slope of the scaled Schoenfeld residuals on ranked failure times and on the log of analysis time. Age at menopause was defined as either the age at which a participant experienced her last menstrual period, received a bilateral oophorectomy, or initiated use of menopausal HT, whichever came first.

Separate regression models were constructed for the two outcomes of interest (ie, triple-negative and ER+ breast cancer). In all models, the time axis was defined as the time since random assignment in the case of clinical trials and time since study enrollment in the case of the observational study. Women diagnosed with in situ breast cancer or with an invasive breast cancer other than the model-specific outcome were censored at the time of diagnosis. We also compared hazard ratios (HRs) with 95% confidence intervals (CIs) for women with triple-negative and ER+ breast cancers by using competing risks partial likelihood methods (30). *P* values for comparisons were based on two-sided tests. Analyses were performed using STATA SE version 10.1 (StataCorp, College Station, TX).

Analyses were adjusted for age at study enrollment or random assignment (in 5-year intervals) and study arm through stratification of the baseline hazards. We also adjusted for the following baseline characteristics associated with overall breast cancer risk: race (non-Hispanic white, Hispanic, African American, or other), educational level (high school or less, vocational or training school, some college or associate's degree, or college graduate), family history of breast cancer in first-degree relatives (yes, no), body mass index (in quartiles), HT use (never use, exclusive use of estrogen-only HT, ever use of combined estrogen–progestin HT), smoking history (never, ever), history of mammography within the 2 years before baseline (yes, no), and mammography during follow-up (time-varying covariate, yes vs no mammogram since last study visit). Exposures of interest were mutually adjusted for each other, with the exception that we adjusted for parity (1, 2, or 3 or more births), age at first birth (<20, 20–29, or ≥30 years), and breastfeeding (never, 1–6, 7–12, or >12 months) only in analyses restricted to parous women.

Results

Our study included 2610 women with ER+ breast cancer, 307 women with triple-negative breast cancer, and 150 529 control subjects whose demographic and tumor characteristics are provided (Table 1). The women with triple-negative breast cancer were younger, more likely to have a family history of breast cancer, and had a higher grade and larger tumor size than the women with ER+ breast cancer. Women with triple-negative cancer were also more likely to be African American. Age-adjusted incidence rates of triple-negative breast cancer were 2.44 and 4.57 cancers per 10 000 person-years among non-Hispanic white and African American women, and rates for ER+ disease were 23.30 and 14.15 cancers per 10 000 person-years for the same two groups, respectively.

Aspects of menstrual and reproductive history emerged as being differentially associated with risk of ER+ and triple-negative breast cancers (Table 2). Age at menarche was modestly inversely associated and age at menopause was modestly positively associated with risk of ER+ breast cancer; these associations were not evident for triple-negative breast cancer. More considerable differences were noted in associations between reproductive history and risk of ER+ vs triple-negative breast cancer. Compared with parous women, nulliparous women had an increased risk of ER+ breast cancer (HR = 1.35, 95% CI = 1.20 to 1.52) but a decreased risk of triple-negative breast cancer (HR = 0.61, 95% CI = 0.37 to 0.97; $P_{\text{competing risks}} = .02$). Age-adjusted incidence rates for ER+ breast cancer were 28.16 and 21.10 cancers per 10 000 person-years in nulliparous and parous women, respectively. In comparison, age-adjusted incidence of triple-negative disease was 1.54 and 2.71 cancers per 10 000 person-years in the same two groups. History of pregnancy losses was not associated with risk of either subtype (results not shown). Among parous women, the number of births was inversely associated with ER+ breast cancer (HR = 0.88, 95% CI = 0.74 to 1.04) but positively associated with triple-negative breast cancer risk (HR for three births or more vs one birth = 1.46, 95% CI = 0.82 to 2.63), and age at first birth was positively associated with risk of ER+ cancers but not triple-negative disease; however, differences between subtype-specific associations were not statistically significant. Lifetime duration of breastfeeding was not associated with risk of either subtype.

Analyses of lifetime duration of oral contraceptive use indicated no association with risk of ER+ or triple-negative breast cancer, with the exception of a modestly reduced risk of ER+ disease among women who had used oral contraceptives for at least 10 years (HR = 0.80, 95% CI = 0.68 to 0.94) (Table 3). There was no evidence of a difference in subtype-specific HR estimates ($P_{\text{competing risks}} = .49$). Results were similar when stratified into broad age categories (50–59 years vs 60–79 years, data not shown). We also found no association between the age at which a woman initiated oral contraceptive use and risk of either subtype; however, these analyses were limited in power because the vast majority of women using oral contraceptives initiated use at or after age 25.

Discussion

The results from this analysis are consistent with prior studies in suggesting that reproductive factors play a different role in relation to risk of triple-negative breast cancer vs ER+ breast cancer (13–15). Specifically, we found that nulliparity was associated with a 39% lower risk of triple-negative breast cancer but a 35% higher risk of ER+ disease in postmenopausal women. Among parous women, we found that having multiple children was associated with greater risk of triple-negative breast cancer but with lesser risk of ER+ breast cancer. Although associations with other risk factors were comparable across subtypes, differences in associations with parity are consistent with existing literature and with hypothesized etiologic distinctions between ER+ and triple-negative tumors.

Table 1. Distribution of demographic and tumor characteristics among case subjects with breast cancer and control subjects*

Characteristic	Control subjects, n (%)	Case subjects, n (%)	
		ER+	Triple negative
Stage			
Localized	N/A	1910 (74)	213 (71)
Regional or distant		664 (26)	89 (29)
Unknown		36	5
Tumor grade			
Well differentiated	N/A	772 (32)	15 (5)
Moderately differentiated		1097 (46)	55 (19)
Poorly differentiated or anaplastic		509 (21)	221 (76)
Unknown		232	16
Tumor size, mm			
<10	N/A	733 (31)	49 (18)
10–19		1007 (43)	123 (44)
20–39		494 (21)	77 (28)
≥40		117 (5)	30 (11)
Unknown		260	28
Age at random assignment or enrollment, y			
50–59	50400 (34)	746 (29)	122 (40)
60–69	67505 (45)	1250 (48)	125 (41)
70–79	32624 (22)	614 (24)	60 (20)
Race and/or ethnicity			
Non-Hispanic white	124008 (86)	2317 (92)	241 (81)
Hispanic or Latina	6084 (4)	53 (2)	8 (3)
African American	13675 (10)	149 (6)	50 (17)
Other or unknown	6762	91	8
Education			
≤High school diploma or GED	33928 (23)	483 (19)	75 (25)
Vocational or training school	15347 (10)	232 (9)	30 (10)
Some college or associate's degree	41508 (28)	696 (27)	78 (26)
≥College graduate	58622 (39)	1177 (45)	118 (39)
Missing	1124	22	6
Breast cancer family history			
No	116663 (82)	1901 (77)	207 (72)
Yes	25648 (18)	574 (23)	81 (28)
Unknown	8218	135	19
Menopausal hormone therapy use			
Never use	56534 (38)	841 (32)	114 (37)
Exclusive use of unopposed estrogen	47871 (32)	727 (28)	106 (35)
Ever use of combined estrogen–progestin	46101 (31)	1042 (40)	87 (28)
Unknown	23	0	0
Smoking history			
Never	75933 (51)	1227 (48)	158 (52)
Ever	72648 (49)	1350 (52)	147 (48)
Unknown	1948	33	2
BMI at baseline, kg/m^2			
<23.75	37377 (25)	596 (23)	66 (22)
23.75–26.89	37318 (25)	650 (25)	71 (23)
26.90–31.04	37326 (25)	648 (25)	80 (26)
≥31.05	37207 (25)	698 (27)	89 (29)
Unknown	1301	18	1

* GED = General Educational Development; BMI = body mass index; ER+ = estrogen receptor–positive with known HER2 status; triple negative = ER−, PR−, and HER2−.

In the largest comparative study of triple-negative and other breast cancer subtypes to date, which included 335 triple-negative patients, Ma et al. (27) reported a decreased risk of ER+ breast cancer (odds ratio = 0.55) among women who had at least four pregnancies compared with nulligravid women but found no association with risk of triple-negative breast cancer (odds ratio = 1.00). Smaller studies that included 78–187 triple-negative patients have also reported no association between parity or age at first birth and triple-negative breast cancer risk (16,25,26), although others have found an increased risk of triple-negative disease in multiparous women (13–15).

In contrast to prior studies, we found no association between breastfeeding and risk of triple-negative breast cancer. Five previous studies, conducted in diverse settings, have noted a statistically significantly lower risk of triple-negative breast cancer in parous women who have ever breastfed a child (15), or who breastfed

Table 2. Relationship between menstrual and reproductive history and risk of estrogen receptor-positive (ER+) and triple-negative breast cancer

	Control subjects, n (%)	Case subjects*				Competing risks analysis,§ *P*
		ER+		Triple negative		
		n (%)	HR (95% CI)	n (%)	HR (95% CI)	
Age at menarche,† y						
<12	32 816 (21)	618 (24)	1.0 (ref)	79 (26)	1.0 (ref)	.608
12–13	82 463 (56)	1406 (54)	0.87 (0.79 to 0.97)	160 (52)	0.88 (0.65 to 1.19)	
≥14	34 660 (23)	572 (22)	0.89 (0.79 to 1.00)	67 (22)	0.96 (0.67 to 1.39)	
Unknown	590	14		1		
P_{trend}			.066		.837	
Age at menopause,† y						
<35	8400 (6)	100 (4)	0.79 (0.63 to 0.98)	19 (6)	0.91 (0.52 to 1.57)	.603
35–44	34 500 (24)	95 (20)	0.85 (0.76 to 0.96)	60 (20)	0.76 (0.54 to1.06)	
45–54	84 509 (59)	1544 (61)	1.0 (ref)	183 (62)	1.0 (ref)	
≥55	16 920 (12)	378 (15)	1.13 (1.00 to 1.27)	31 (11)	1.02 (0.68 to 1.52)	
Unknown	6200	93		14		
P_{trend}			<0.001		0.237	
Parity†						
Nulliparous	17 509 (11)	380 (15)	1.35 (1.20 to 1.52)	23 (8)	0.61 (0.37 to 0.97)	.020
≥1 full-term pregnancy	132 064 (89)	2210 (85)	1.0 (ref)	283 (92)	1.0 (ref)	
Unknown	956	20		1		
Parous women						
Parity‡						
1	13 151 (10)	248 (11)	1.0 (ref)	20 (7)	1.0 (ref)	.541
2	37 355 (28)	683 (31)	0.97 (0.81 to 1.15)	90 (32)	1.71 (0.96 to 3.07)	
≥3	81 558 (62)	1,279 (58)	0.88 (0.74 to 1.04)	173 (61)	1.46 (0.82 to 2.63)	
P_{trend}			0.060		0.631	
Age at first birth,‡ y						
<20	19 365 (16)	258 (13)	1.0 (ref)	43 (18)	1.0 (ref)	.677
20–29	87 961 (74)	1,481 (74)	1.03 (0.88 to 1.20)	184 (76)	1.26 (0.82 to 1.94)	
≥30	10 861 (9)	255 (13)	1.36 (1.10 to 1.67)	16 (7)	1.05 (0.53 to 2.06)	
Unknown	13 877	216		40		
P_{trend}			0.005		0.693	
Duration of breastfeeding,‡ mo						
Never breastfed	54 797 (42)	905 (41)	1.0 (ref)	23 (45)	1.0 (ref)	.744
1–6	38 351 (29)	644 (29)	1.00 (0.89 to 1.12)	88 (32)	0.92 (0.66 to 1.27)	
7–12	16 414 (13)	284 (13)	0.97 (0.83 to 1.13)	22 (8)	0.67 (0.41 to 1.10)	
>12	20 928 (16)	353 (16)	0.98 (0.85 to 1.13)	43 (16)	0.81 (0.53 to 1.26)	
Unknown	1574	24		7		
P_{trend}			0.685		0.168	

* ER+ = estrogen receptor–positive with known HER2 status; triple negative = ER−, PR−, and HER2−; HR = hazard ratio.

† Adjusted for age, study arm, race, education level, family history of breast cancer, body mass index, hormone therapy use, smoking history, history of mammography (at baseline), mammography during follow-up, age at menarche, age at menopause, nulliparity, and oral contraceptive use.

‡ Adjusted for age, study arm, race, education level, family history of breast cancer, body mass index, hormone therapy use, smoking history, history of mammography (at baseline), mammography during follow-up, age at menarche, age at menopause, oral contraceptive use, parity, age at first birth, and breastfeeding.

§ *P* values are from two-sided tests that compared adjusted hazard ratios for the two breast cancer subtypes by competing risks partial likelihood methods.

for a cumulative duration of at least 4 (13), 6 (25,27), or 12 months (26) ($P < .05$). Most of these studies have included premenopausal and postmenopausal women, without stratification by menopausal status. Although the one study conducted only in postmenopausal women (25) indicated a 50% lower risk of triple-negative breast cancer in parous women who breastfed for at least 6 months compared with parous women who never breastfed, another study (27) that stratified analyses by attained age indicated that breastfeeding was more strongly associated with triple-negative breast cancer among women aged 35–44 years than among women aged 45–64 years. This latter finding is consistent with other studies that did not stratify by tumor marker expression (31) because it suggests that associations between breastfeeding and breast cancer risk are most pronounced in premenopausal women. Thus, it is possible that we observed no association between breastfeeding and risk of triple-negative or ER+ breast cancers because of the older age and postmenopausal status of the study population.

The age range of this study population may also explain why we found no association between use of oral contraceptives and risk of triple-negative breast cancer, as was previously suggested (16,27). Dolle et al. reported a 4.7-fold increased risk of triple-negative breast cancer in women who were younger than 40 years and used oral contraceptives for 6 years or more. In the same age group, they reported a 6.4-fold increased risk of triple-negative breast cancer among women who initiated use of oral contraceptives before age 18 compared with those who had never used them; however, use of oral contraceptives was not associated with risk in

Table 3. Relationship between oral contraceptive use and risk of estrogen receptor–positive (ER+) and triple-negative breast cancer*

	Control subjects, n (%)	Case subjects				Competing risks analysis,‡ *P*
		ER+		Triple negative		
		n (%)	HR (95% CI)†	n (%)	HR (95% CI)†	
Lifetime duration of use of oral contraceptives, y						
Overall						
Never used	87861 (58)	1562 (60)	1.0 (ref)	171 (56)	1.0 (ref)	.492
<5	34628 (23)	580 (22)	0.97 (0.87 to 1.08)	65 (21)	0.84 (0.65 to 1.18)	
5–9	14209 (9)	261 (10)	1.04 (0.89 to 1.20)	40 (13)	1.30 (0.88 to 1.93)	
≥10	13780 (9)	207 (8)	0.80 (0.68 to 0.94)	31 (10)	1.11 (0.72 to 1.70)	
Unknown	51	0		0		
P_{trend}			0.049		0.383	
Age at first use of oral contraceptives, y						
Overall						
Never used	87861 (58)	1562 (60)	1.0 (ref)	171 (56)	1.0 (ref)	.752
≥25	45783 (30)	800 (31)	0.94 (0.85 to 1.03)	88 (29)	0.98 (0.73 to 1.32)	
20–24	15148 (10)	223 (9)	0.97 (0.81 to 1.15)	46 (15)	1.12 (0.72 to 1.76)	
<20	1623 (1)	21 (1)	1.08 (0.67 to 1.72)	2 (1)	0.62 (0.15 to 2.60)	
Unknown	114	4		0		

* ER+ = estrogen receptor-positive with known HER2 status; triple-negative = ER−, PR−, and HER2−; HR = hazard ratio.

† Adjusted for age, study arm, race, education level, family history of breast cancer, body mass index, hormone therapy use, smoking history, history of mammography (at baseline), mammography during follow-up, age at menarche, age at menopause, and nulliparity.

‡ *P* values are from two-sided tests that compared adjusted hazard ratios for the two breast cancer subtypes by competing risks partial likelihood methods.

the upper age range of that study population (41–45 years) (16). Recently, Ma et al. (27) reported an increased risk of triple-negative breast cancer associated with use of oral contraceptives but only among women aged 45–64 years who first used oral contraceptives before age 18. Our study included women aged 50–79 years and included no women with triple-negative cancers who had used oral contraceptives before age 18. Thus, although our findings suggest no association between use of oral contraceptives and triple-negative breast cancer, inferences based on these results should be restricted to postmenopausal women who initiated use of oral contraceptives at a relatively older age.

As in previous reports (7,8,13,32), we found race and/or ethnicity to be a major factor associated with triple-negative breast cancer: the triple-negative subtype accounted for 22% of breast cancers in African American women compared with 9% in women of other races and/or ethnicities. This difference is consistent with another analysis within the WHI cohort (33), which reported that African American women with breast cancer are more likely to have poorly differentiated hormone receptor-negative disease than non-Hispanic white women. That analysis found that differences in breast cancer incidence rates between African American and non-Hispanic white women were not fully explained by differences in the distribution of established breast cancer risk factors. Based on the present analysis, one possibility is that differences in risk factor distributions do not explain differences in incidence rates between these groups because risk factors for the triple-negative subtype (which disproportionately occurs in African American women) differ from those for ER+ disease. Although small numbers prevented us from assessing subtype-specific associations by race and/or ethnicity, we found that the prevalence of late age at first birth was lower among African Americans with breast cancer (7.5%) than among non-Hispanic whites with breast cancer (11.8%). The prevalence of nulliparity, however, was slightly higher among African Americans with breast cancer (14.7% vs 13.6% in non-Hispanic whites).

In addition to the differences between the women with ER+ and triple-negative breast cancers that were observed here, heterogeneity within each of these groups of case subjects is also plausible. Previous studies have indicated clinical and, to a lesser extent, epidemiological differences between women who have triple-negative tumors that express basal markers (ie, basal-like cancers) and those who have triple-negative tumors that do not express basal markers (ie, normal-like cancers) (3–5,13,14). Differences in risk factor associations for ER+ breast cancer according to PR and/or HER2 status have been suggested (13–15,19,20,26,27). Heterogeneity within ER+ and triple-negative subtypes could influence subtype-specific associations and comparisons between subtypes. However, heterogeneity within these groups of case subjects is assumed to be less pronounced than the differences between subtypes.

There are limitations to consider in interpreting these results. Approximately 40% of case subjects had unknown HER2 status and, therefore, did not contribute to either case group. Case subjects with missing HER2 data were similar to other case subjects with regard to all exposures and covariates. In sensitivity analyses, we used multiple imputation to explore the potential impact of censoring these observations at diagnosis and found almost no difference from the results presented here. Additionally, some misclassification of case groups may have resulted from the use of tumor marker data from multiple laboratories across WHI clinical centers because testing practices can vary; however, testing results were reviewed centrally to minimize differences in classification across institutions. Misclassification of exposure status is also plausible because most exposures considered here occurred many years

before study enrollment or random assignment; although errors in recall are likely, the prospective design of the WHI makes differential recall by case status unlikely. Lastly, as previously mentioned, these results may not be generalizable to younger women because the WHI was restricted to postmenopausal women.

There are several important strengths to this analysis, including its large size, prospective design, and completeness of follow-up and exposure information. To date, few studies have examined risk factors for triple-negative breast cancer, and many of these have been underpowered (N = 78 to N = 335 women with triple-negative disease). This analysis thus contributes to a sparse literature and provides further support for the distinct epidemiology of triple-negative breast cancers.

It has been hypothesized that risk of ER+ breast cancer is positively associated with a woman's cumulative lifetime exposure to endogenous ovarian hormones (34); thus, aspects of reproductive and menstrual history could influence risk by affecting the number of ovulatory cycles a woman experiences over her lifetime. If hormonal mechanisms predominate in the relationships between reproductive factors and breast cancer risk, it is not surprising that our results suggest that nulliparity or low parity, late age at first birth, early menarche, and late menopause are associated with risk of ER+ breast cancer. Because triple-negative breast cancers are hormone receptor negative, it seems plausible that risk factors operating through hormonal mechanisms would be less important in the etiology of triple-negative than ER+ breast cancers. Nevertheless, it remains unclear why nulliparity (or low parity) would be associated with a decreased risk of triple-negative breast cancer. It is also unclear why the difference between ER+ and triple-negative subtypes would be limited to associations with parity and age at first birth and not extend to differences in associations with other aspects of reproductive history, such as duration of breastfeeding, which also influence a woman's cumulative lifetime exposure to endogenous estrogens.

Given the poor prognosis associated with triple-negative breast cancer, it remains important to identify the factors that influence a woman's risk of developing this subtype of disease and to further characterize if and how such factors differ from risk factors for the more predominant ER+ breast cancer subtype that has a better prognosis.

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