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Timing of Menarche and First Full-Term Birth in Relation to Breast Cancer Risk

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Abstract

Ages at menarche and first birth are established risk factors for breast cancer. The interval between these ages may also affect risk, since the breast is more susceptible to carcinogenic insults during this period than during the parous period. However, few investigators have studied this relation. Using logistic regression, the authors evaluated associations between the timing of reproductive events and breast cancer risk among 4,013 cases and 4,069 controls enrolled in a multicenter, population-based US case-control study of White and African-American women (1994–1998). For White, parous premenopausal and postmenopausal women, those who had an interval of 16 years between the ages of menarche and first birth had 1.5-fold (95% confidence interval (CI): 1.0, 2.2) and 1.4-fold (95% CI: 1.1, 1.8) increased risks of breast cancer, respectively, in comparison with those who had 5 years between these ages. Adjusting for age at first birth altered these risk estimates somewhat, to odds ratios of 1.5 (95% CI: 0.8, 2.9) and 1.0 (95% CI: 0.6, 1.5), respectively. These associations were stronger for lobular and hormone-receptor-positive tumors but were absent among premenopausal African-American women. The authors conclude that the interval between age at menarche and age at first birth is associated with the risk of hormonally sensitive types of breast cancer, particularly among White women.

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Keywords

breast neoplasms; histology; menarche; menopause; pregnancy; premenopause; receptors, estrogen; receptors, progesterone

Age at menarche and age at first full-term birth are two well-established risk factors for breast cancer (1, 2). The mechanism underlying the association between these two ages and breast cancer risk is thought to be shared, at least in part, because the timing of each of these milestones contributes to the duration of time in which undifferentiated breast tissue is exposed to the potentially promotional effects of endogenous ovarian hormones produced through menstrual cycling. Specifically, an early age at menarche is thought to be associated with an increased risk of breast cancer because a higher number of lifetime ovulatory cycles, and hence greater exposure to ovarian hormones, has been shown to confer an elevated risk of breast cancer (3, 4). With respect to age at first birth, it is well known that pregnancy induces the differentiation of breast tissue, which results in a long-term reduction in breast cancer risk in both animal and human studies, particularly among women who have completed their childbearing (5, 6).

Given the susceptibility of the undifferentiated nulligravid breast to carcinogenic insults, the duration of time between age at menarche and age at first full-term birth may be independently related to breast cancer risk. However, few epidemiologic studies have evaluated this relation. Clavel-Chapelon (3) addressed this issue to some extent in the French E3N cohort by evaluating the relation between the number of menstrual cycles women had before their first full-term birth and breast cancer risk. Compared with women in the lowest quartile, women in the highest quartile of cumulative number of cycles before their first full-term birth had a 1.42-fold (95 percent confidence interval (CI): 1.20, 1.67) elevated risk of breast cancer. This risk was essentially the same when women who had used oral contraceptives were excluded from the analysis. In a combined analysis of seven case-control studies, Andrieu et al. (4, 7) found similar results. Breast cancer risk for women with 21 or more years between menarche and first childbirth was 1.45-fold higher (95 percent CI: 1.17, 1.82) than that for women with 10 years or less between these two events (4, 7). However, these studies did not evaluate differences in risk by menopausal status or race; the effect of adjusting for age at menarche and age at first birth on these associations; or the relations between risks associated with early reproductive factors and breast cancer subtype.

We analyzed data from the Women's Contraceptive and Reproductive Experiences (CARE) Study to evaluate the impact of early reproductive events, particularly the interval between ages at menarche and first birth, on risk of different types of breast cancer.

MATERIALS AND METHODS

Details of the methods used in the Women's CARE Study have been published previously (8), and the relation between established reproductive risk factors for breast cancer and the risk of different breast cancer subtypes has also been reported previously (9). Briefly, a population-based case-control study was conducted at five metropolitan sites in the United States (Atlanta, Georgia; Detroit, Michigan; Los Angeles, California; Philadelphia, Pennsylvania; and Seattle, Washington). White and African-American women aged 35–64 years with no history of in situ or invasive breast cancer who received a diagnosis of invasive breast cancer from July 1994 through April 1998 were eligible as cases. Women of other races/ethnicities were not recruited into this study. These women were ascertained by Surveillance, Epidemiology, and End Results Registry staff at four sites (Atlanta, Detroit, Los Angeles, and Seattle) and by field-center staff at one site (Philadelphia). Controls were

women with no history of breast cancer who were identified using random digit dialing and were frequency-matched to cases within strata of site, race, and age. Of the women identified, 76.5 percent of eligible cases and 78.6 percent of eligible controls participated in the study, and it included a total of 4,575 cases and 4,682 controls.

Of the 4,575 cases, 2,089 women were premenopausal and 1,924 were postmenopausal. Of the 4,682 controls, 2,040 women were premenopausal and 2,029 were postmenopausal. Menopausal status was defined on the basis of self-report. For this analysis, premenopausal women were those who reported that they had not experienced menopause and were younger than 55 years of age. Postmenopausal women were those whose menstrual periods had stopped naturally, who had undergone a bilateral oophorectomy (with or without a hysterectomy), who had used menopausal hormone therapy in the past 12 months, or who were 55 years of age or older. The 562 cases and 613 controls whose menopausal status could not be defined using these definitions were excluded. All results were stratified by menopausal status, because risk factors for breast cancer are known to vary by menopausal status (10).

The study protocol was approved by an institutional review board at each study site. Written informed consent was obtained from all study subjects. All interviews were conducted in person, typically in subjects' homes, using standardized procedures. The Women's CARE Study was principally designed to assess the relation between oral contraceptive use and breast cancer risk, but self-reported information on other possible risk factors for breast cancer was also obtained. The following additional information was collected for the period before each participant's reference date: detailed reproductive history data, family history of cancer, anthropometric characteristics, use of menopausal hormone therapy, and lifetime histories of physical activity, smoking, and alcohol use. The reference date used for cases was the date of breast cancer diagnosis; for controls, it was the date on which the woman was first contacted by random digit dialing. Control identification was timed so that control reference dates would approximate the distribution of case reference dates.

The estrogen receptor (ER) and progesterone receptor (PR) status and histology of each breast cancer case were ascertained from local cancer registry data, which are based on reviews of pathology reports (except in Philadelphia, where these data were collected by staff at the field center). No statistical differences were observed in the risks associated with ER+/PR+, ER+/PR-, and ER-/PR+ breast cancer. As a result, analyses by hormone-receptor status were stratified into two groups: women with ER+ or PR+ (hormone-receptor-positive) tumors ($n = 2,371$) and women with ER-/PR- (hormone-receptor-negative) tumors ($n = 938$). For analyses by histology, cases were grouped on the basis of the *International Classification of Diseases for Oncology* (ICD-O) morphology codes assigned to their tumors; ICD-O morphology code 8500 was used to define ductal cases ($n = 3,039$), code 8520 was used to define lobular cases ($n = 244$), and code 8522 was used to define ductal-lobular cases ($n = 240$). No statistically significant differences in the risks associated with lobular and ductal-lobular cancers for the exposures of interest were observed. Accordingly, similarly to the way in which these histologic types have been treated in other epidemiologic studies, they were grouped together and defined as lobular carcinomas in all analyses (11, 12). Cases with other ICD-O morphology codes ($n = 490$) were excluded from our histology-specific analyses.

We compared cases with controls using unconditional logistic regression. We compared cases of each histologic type and each hormone-receptor profile to controls separately using multinomial polytomous logistic regression (13). All analyses were conducted using Stata SE, version 9.0 (Stata Corporation, College Station, Texas). Odds ratios and associated 95 percent confidence intervals were calculated as estimates of the relative risk. All analyses

were adjusted for age and study site because controls were frequency-matched to cases on these variables. Race was found to be a statistically significant effect modifier of the relations of both age at first full-term birth and interval between ages at menarche and first full-term birth with premenopausal breast cancer, but not with postmenopausal breast cancer. Thus, all analyses of premenopausal breast cancer were stratified by race, while those of postmenopausal breast cancer were not. Multiple variables, including oral contraceptive use, socioeconomic factors, anthropometric characteristics, family history of breast cancer, and use of menopausal hormones, were evaluated separately as potential confounders of each of the associations we evaluated. Inclusion of these factors individually in the statistical model did not alter the odds ratios of interest by more than 10 percent, so none was added to the final models (14).

We also adjusted the main effects of our three exposures of interest—age at menarche, age at first full-term birth (a pregnancy of >26 weeks' gestation), and the interval between these two ages (as categorical variables, with the categories used throughout the tables)—for each other in order to assess their relative contributions to breast cancer risk. These three exposures were also highly correlated with each other: The correlation coefficients for each combination of these three variables all had p values less than 0.0001. However, age at menarche did not confound either the association of age at first full-term birth with breast cancer risk or the association of interval between menarche and first full-term birth with breast cancer risk, so it was not included in the final statistical models. In contrast, age at first full-term birth and the interval between menarche and first full-term birth did confound the relation of each factor with breast cancer risk to some extent. Given that these two factors were highly correlated, we present results both with and without these adjustments.

RESULTS

Within each category of cases and controls, cases had distributions of educational level and household income similar to those of their respective controls (table 1). However, premenopausal African-American participants were less educated and had lower household incomes than premenopausal White participants. Among postmenopausal women, 34.0 percent of cases and 35.6 percent of controls were African-American. Of the cases, 15.7–21.2 percent had a first-degree (mother, sister, or daughter) family history of breast cancer, as compared with 6.9–13.3 percent of controls.

Among White and African-American premenopausal women, ages at menarche and first full-term birth were not related to breast cancer risk (table 2). The interval between age at menarche and age at first full-term birth was positively related to breast cancer risk among White premenopausal women but not among African-American premenopausal women. Specifically, White premenopausal women with 16 or more years between their ages at menarche and first birth had a 1.5-fold (95 percent CI: 1.0, 2.2) increased risk of breast cancer. The risk estimates for the interval between ages at menarche and first birth were statistically significantly different among White women as compared with African-American women ($p = 0.046$).

Among White premenopausal women, both age at first full-term birth and the interval between ages at menarche and first full-term birth were positively related to risk of ER+ or PR+ breast cancer but not to risk of ER–/PR– breast cancer (for difference between case types, $p = 0.009$ and $p = 0.022$, respectively) (table 3). There was also a suggestion that both age at first full-term birth and the interval between ages at menarche and first full-term birth were more strongly related to risk of lobular carcinoma than to risk of ductal carcinoma among White premenopausal women, but these differences were within the limits of chance (table 4). None of the three reproductive factors of interest was related to risk of breast

cancer subtypes defined by either hormone-receptor status or histology among African-American premenopausal women.

Among postmenopausal women, age at menarche was not related to breast cancer risk overall, but age at first full-term birth was positively related to risk (table 2). The interval between ages at menarche and first full-term birth was also positively related to breast cancer risk among postmenopausal women. Specifically, women with 16 years between these ages had a 1.4-fold (95 percent CI: 1.1, 1.8) increased risk of breast cancer as compared with women with <5 years between these ages. Further, both age at first full-term birth and the interval between ages at menarche and first full-term birth were more strongly related to risk of ER+ or PR+ tumors and lobular carcinomas than to risk of ER-/PR- tumors and ductal carcinomas (table 5). These differences were all statistically significant, except for the comparison between ductal and lobular carcinomas for age at first full-term birth, where the difference neared but did not reach statistical significance ($p = 0.067$). Age at menarche was also inversely related to risk of lobular carcinoma, with the observed risk estimates being statistically different from the risk estimates for ductal carcinoma ($p = 0.027$).

To explore the interrelation between age at first full-term birth and the interval between ages at menarche and first full-term birth, we evaluated how adjusting our analyses of these variables for each other altered the associations we observed (table 6). Among White premenopausal women, the elevations in risk associated with age at first full-term birth largely disappeared when risk estimates were adjusted for the interval between ages at menarche and first full-term birth. In contrast, adjusting for age at first full-term birth did not appreciably alter the risks for the interval between ages at menarche and first birth among White premenopausal women. Among postmenopausal women, adjusting for this interval did not substantially change the risks associated with age at first birth for breast cancer overall or for hormone-receptor-positive breast cancer. Adjusting for age at first full-term birth did substantially attenuate the associations of interval between ages at menarche and first birth with breast cancer risk overall and hormone-receptor-positive tumors, but much less so for lobular carcinoma. However, after adjustment for age at first birth, the risk estimates associated with lobular carcinoma were no longer statistically significant.

DISCUSSION

Certain limitations of our study should be considered when interpreting the results. As in all studies of this type, reliance on participants' recall of exposures to potential risk factors resulted in at least some recall bias. This recall was nondifferential, and thus it biased our results toward the null; it may also have had a greater impact on our risk estimates for postmenopausal women than on our risk estimates for premenopausal women, given that postmenopausal women had to recall events that occurred many more years in the past. Some degree of misclassification of menopausal status was probably also present, given that menopausal status was defined on the basis of self-report and age. Another limitation is that we did not perform independent or centralized pathology reviews of the tumors, instead relying on the diagnoses made by numerous pathologists across each of the study sites; misclassification of tumor histology and ER/PR status may have resulted in some instances. Additionally, we were able to interview only 79.1 percent of eligible White cases, 80.7 percent of eligible White controls, 72.2 percent of eligible African-American cases, and 75.1 percent of eligible African-American controls. Our results could be biased if the women we were unable to interview differed from those who participated with regard to the exposures relevant to this analysis.

Similarly to previous investigators, we observed that a longer duration between age at menarche and age at first full-term birth was associated with an elevated risk of breast cancer, except among premenopausal African-American women. The elevations in risk observed were largely confined to women with hormone-receptor-positive and lobular tumors. This is not surprising if the mechanism underlying the association between the duration of this time period and breast cancer risk is hormonal, because both hormone-receptor-positive tumors and lobular tumors may be more hormonally sensitive. (In a large case series of 4,140 lobular cases and 45,169 ductal cases of all ages from the Baylor College of Medicine, 93 percent of lobular carcinomas were ER+ and 67 percent were PR+, while 81 percent of ductal carcinomas were ER+ and 60 percent were PR+ (15).) Although investigators in prior studies have also shown that the interval between age at menarche and age at first full-term birth is associated with breast cancer, they did not adjust their risk estimates for other early reproductive events (3, 4, 7).

Our analyses suggest that the risk associated with this interval may be largely influenced by age at first full-term birth among postmenopausal women, because after adjustment for age at first full-term birth, the association of this period of time with breast cancer risk disappears, for the most part. However, among White premenopausal women, this interval appears to be an independent risk factor for breast cancer, since neither adjustment for age at menarche nor adjustment for age at first full-term birth attenuated this risk estimate. It is unclear what explains this difference. For White premenopausal women, this finding may be related to the biologic differences between premenopausal and postmenopausal breast cancer, where this interval may be a particularly important risk period for premenopausal disease. It is also unclear why these reproductive factors are related to breast cancer risk among White premenopausal women but not African-American premenopausal women. When interpreting this result, however, it is notable that the distributions of age at first birth varied substantially by race. Specifically, 34.0 percent of premenopausal African-American controls in this study had their first full-term birth before age 20 years, as compared with only 11.5 percent of premenopausal White controls. Thus, compared with White women as a whole, African-Americans experienced the long-term protection against breast cancer conferred by parity at much younger ages, and thus the interval between ages at menarche and first full-term birth may have had less of an influence on breast cancer risk within this population.

In this study, associations with later age at first full-term birth were also largely restricted to elevations in risk of hormonally sensitive tumors, including hormone-receptor-positive and lobular tumors, except among premenopausal African-American women, for whom age at first full-term birth was not related to risk of any breast cancer type. Only two studies have evaluated this relation, and neither observed that a late age at first full-term birth was related to risk of lobular carcinoma (9, 16). Further studies are needed to further clarify this potential association.

Although our results regarding age at first full-term birth and the interval between ages at menarche and first full-term birth are generally consistent with previous results, our findings with respect to age at menarche are not. Epidemiologic studies of both premenopausal and postmenopausal women have consistently found that breast cancer risk is reduced 5–20 percent for each year that menarche is delayed (1, 17), but here we found that an older age at menarche was not associated with a reduced risk of breast cancer. The reason for this inconsistency is unclear, although, in our study, older age at menarche appeared to reduce risk of lobular carcinoma among postmenopausal women.

In summary, we hypothesized that the duration between age at menarche and age at first full-term birth was an independent risk factor for breast cancer because of the evidence that

this is a period when breast tissue is largely undifferentiated and thus particularly susceptible to carcinogens (5, 6). We found that this duration was an independent risk factor for hormonally sensitive types of breast cancer, particularly among White premenopausal women. Few studies have assessed this potential risk factor for breast cancer, and further work is needed to characterize its associations with different types of breast cancer in different populations. Age at first full-term birth also appears to be an early reproductive event that affects risk of hormonally sensitive breast cancers among White premenopausal women and postmenopausal women, but this was not apparent in this study among African-American premenopausal women.

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Abbreviations

CARE	Contraceptive and Reproductive Experiences
CI	confidence interval
ER	estrogen receptor
ICD-O	<i>International Classification of Diseases for Oncology</i>
PR	progesterone receptor

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Demographic characteristics of premenopausal and postmenopausal breast cancer cases and controls, Women's Contraceptive and Reproductive Experiences (CARE) Study, 1994–1998

TABLE 1

Characteristic	Premenopausal women						Postmenopausal women					
	Whites			African Americans								
	Cases (n = 1,358)	Controls (n = 1,357)		Cases (n = 731)	Controls (n = 683)		Cases (n = 1,924)	Controls (n = 2,029)		Cases (n = 1,924)	Controls (n = 2,029)	
	No.	%		No.	%		No.	%		No.	%	
Age (years)												
35–39	441	32.5	422	31.1	212	29.0	194	28.4	9	0.5	22	1.1
40–44	411	30.3	443	32.6	232	31.7	237	34.7	30	1.6	50	2.5
45–49	350	25.8	354	26.1	190	26.0	179	26.2	96	5.0	149	7.3
50–54	156	11.5	138	10.2	97	13.3	73	10.7	338	17.6	360	17.7
55–59	N/A*		N/A		N/A		N/A		735	38.2	767	37.8
60–64	N/A		N/A		N/A		N/A		716	37.2	681	33.6
Race												
White	1,358	100.0	1,357	100.0	0	0.0	0	0.0	1,269	66.0	1,307	64.4
African-American	0	0.0	0	0.0	731	100.0	683	100.0	655	34.0	722	35.6
Study site												
Atlanta, Georgia	230	16.9	213	15.7	144	19.7	142	20.8	360	18.7	389	19.2
Detroit, Michigan	199	14.7	216	15.9	129	17.6	138	20.2	483	25.1	452	22.3
Los Angeles, California	336	24.7	336	24.8	261	35.7	244	35.7	269	14.0	327	16.1
Philadelphia, Pennsylvania	164	12.1	181	13.3	172	23.5	136	19.9	304	15.8	349	17.2
Seattle, Washington	429	31.6	411	30.3	25	3.4	23	3.4	508	26.4	512	25.2
Education												
Less than high school	46	3.4	39	2.9	74	10.1	67	9.8	239	12.4	286	14.1
High school graduation	304	22.4	313	23.1	220	30.1	189	27.7	652	33.9	679	33.5
Attended technical school	438	32.3	411	30.3	272	37.2	276	40.4	571	29.7	585	28.8
Attended college	570	42.0	594	43.8	165	22.6	151	22.1	462	24.0	479	23.6
Annual household income												
<\$10,000	48	3.6	30	2.3	136	19.0	99	14.8	201	11.0	223	11.4

Characteristic	Premenopausal women						Postmenopausal women					
	Whites			African Americans								
	Cases (n = 1,358)	No.	%	Controls (n = 1,357)	No.	%	Cases (n = 731)	No.	%	Controls (n = 683)	No.	%
\$10,000–\$19,999	78	5.9	64	4.8	76	10.6	108	16.2	238	13.0	253	12.9
\$20,000–\$34,999	215	16.2	212	16.0	163	22.8	164	24.6	396	21.6	440	22.4
\$35,000–\$49,999	232	17.5	231	17.4	141	19.7	119	17.8	339	18.5	332	16.9
\$50,000	756	56.9	791	59.6	199	27.8	177	26.5	656	35.8	716	36.5
First-degree family history of breast cancer												
No	1,080	82.4	1,175	90.1	578	84.3	590	93.1	1,431	78.8	1,657	86.7
Yes	230	17.6	129	9.9	108	15.7	44	6.9	384	21.2	254	13.3

* N/A, not applicable.

TABLE 2

Odds ratios for breast cancer associated with age at menarche, age at first full-term birth, and the interval between these two ages, by menopausal status, Women's Contraceptive and Reproductive Experiences (CARE) Study, 1994–1998

Premenopausal women																	Postmenopausal women					
Whites																	African Americans					
		Controls (n = 1,357)		Cases (n = 1,358)		OR ^{†,‡}		95% CI [†]		Controls (n = 683)		Cases (n = 731)		OR [‡]		95% CI						
		No.	%	No.	%					No.	%	No.	%			No.	%					
Age (years) at menarche																						
<12		734	54.1	749	55.3	1.0	Referent	374	54.8	435	59.6	1.0	Referent	1,048	51.7	1,022	53.1					
13–14		512	37.8	510	37	1.0	0.8, 1.1	245	35.9	230	31.5	0.8	0.6, 1.0	772	38.1	724	37.6					
15		110	8.1	95	7.0	0.9	0.6, 1.1	64	9.4	65	8.9	0.9	0.6, 1.3	207	10.2	177	9.2					
<i>p</i> value [§]		0.388																				
Age (years) at first full-term birth																						
19		155	11.5	118	8.7	1.0	Referent	232	34.0	267	36.6	1.0	Referent	601	29.6	493	25.6					
20–24		288	21.3	296	21.8	1.3	1.0, 1.8	210	30.8	186	25.5	0.8	1.3, 1.0	776	38.3	708	36.8					
25–29		295	21.8	278	20.5	1.2	0.9, 1.6	77	11.3	106	14.5	1.2	0.9, 1.7	277	13.7	319	16.6					
30		274	20.3	263	19.4	1.3	0.9, 1.7	61	8.9	55	7.5	0.8	0.5, 1.2	122	6.0	134	7.0					
Nulliparous		340	25.1	403	29.7	1.5	1.2, 2.0*	102	15.0	115	15.8	1.0	0.7, 1.4	251	12.4	270	14.0					
<i>p</i> value		0.021																				
Interval (years) between age at menarche and age at first full-term birth																						
<5		75	5.6	48	3.5	1.0	Referent	149	21.8	271	23.6	1.0	Referent	339	16.8	271	14.1					
6–10		276	20.5	269	19.9	1.5	1.0, 2.2*	246	36.1	231	31.9	0.8	0.6, 1.1	809	40.0	735	38.3					
11–15		306	22.7	295	21.8	1.5	1.0, 2.2	99	14.5	129	17.8	1.2	0.8, 1.6	438	21.7	439	22.9					
16		352	26.1	339	25.0	1.5	1.0, 2.2*	86	12.6	79	10.9	0.8	0.5, 1.2	186	9.2	204	10.6					
Nulliparous		340	25.2	403	29.8	1.8	1.2, 2.7*	102	15.0	115	15.9	1.0	0.7, 1.4	251	12.4	270	1.1					
<i>p</i> value		0.046																				

* *p* < 0.05.

[†] OR, odds ratio; CI, confidence interval.

[‡]All odds ratios were adjusted for age and study site. The odds ratios for postmenopausal women were also adjusted for race.

[§]*p* value for difference between White and African-American premenopausal women.

TABLE 3

Odds ratios for breast cancer associated with age at menarche, age at first full-term birth, and the interval between these two ages among premenopausal White and African-American women, by estrogen receptor (ER) and progesterone receptor (PR) status, Women's Contraceptive and Reproductive Experiences (CARE) Study, 1994–1998

	Premenopausal White women						Premenopausal African-American women					
	ER+ or PR+ (n = 855)			ER-/PR- (n = 329)			ER+ or PR+ (n = 335)			ER-/PR- (n = 231)		
	No.	OR	95% CI†	No.	OR	95% CI	No.	OR‡	95% CI	No.	OR‡	95% CI
Age (years) at menarche												
<12	474	1.0	Referent	175	1.0	Referent	197	1.0	Referent	139	1.0	Referent
13–14	321	1.0	0.8, 1.2	127	1.0	0.8, 1.3	112	0.9	0.7, 1.5	67	0.7	0.5, 1.0
16	57	0.8	0.6, 1.2	26	1.0	0.6, 1.6	26	0.8	0.5, 1.3	25	1.1	0.6, 1.8
<i>p</i> [§] for ER+ or PR+ tumors												0.317
<i>p</i> for ER-/PR-tumors												0.793
												0.221
Age (years) at first full-term birth												
19	64	1.0	Referent	35	1.0	Referent	115	1.0	Referent	92	1.0	Referent
20–24	183	1.5	1.1, 2.1*	66	1.0	0.6, 1.5	82	0.8	0.6, 1.1	53	0.6	0.4, 0.9*
25–29	163	1.3	0.9, 1.9	83	1.2	0.8, 1.8	52	1.4	0.9, 2.1	35	1.1	0.7, 1.8
30	164	1.4	1.0, 2.0*	66	1.0	0.6, 1.6	30	1.0	0.6, 1.6	17	0.7	0.4, 1.2
Nulliparous	281	2.0	1.4, 2.8*	79	1.0	0.6, 1.5	56	1.2	0.8, 1.7	33	0.8	0.5, 1.2
<i>p</i> for ER+ or PR+ tumors												0.698
<i>p</i> for ER-/PR-tumors												0.022
												0.548
Interval (years) between age at menarche and age at first full-term birth												
5	24	1.0	Referent	16	1.0	Referent	81	1.0	Referent	50	1.0	Referent
6–10	159	1.7	1.0, 2.9*	62	1.1	0.6, 2.0	98	0.7	0.5, 1.0	82	1.0	0.7, 1.5
11–15	184	1.8	1.1, 3.0*	82	1.2	0.7, 2.3	57	1.0	0.7, 1.6	41	1.2	0.8, 2.0
16	203	1.7	1.1, 2.8*	90	1.2	0.6, 2.1	42	0.9	0.5, 1.4	24	0.8	0.5, 1.4
Nulliparous	281	2.5	1.5, 4.1*	79	1.1	0.6, 1.9	56	1.0	0.7, 1.6	33	0.9	0.5, 1.5
<i>p</i> for ER+ or PR+ tumors												0.534
<i>p</i> for ER-/PR-tumors												0.040
												0.740

* $p < 0.05$.

[†] OR, odds ratio; CI, confidence interval.

[‡] All odds ratios were adjusted for age and study site.

[§] p value for difference between premenopausal White and African-American women.

Odds ratios for breast cancer associated with age at menarche, age at first full-term birth, and the interval between these two ages among premenopausal White and African-American women, by histologic type, Women's Contraceptive and Reproductive Experiences (CARE) Study, 1994–1998

TABLE 4

	Premenopausal White women						Premenopausal African-American women					
	Ductal carcinoma (n = 1,048)			Lobular carcinoma (n = 152)			Ductal carcinoma (n = 567)			Lobular carcinoma (n = 61)		
	No.	OR [†] , #	95% CI [†]	No.	OR [‡]	95% CI	No.	OR [‡]	95% CI	No.	OR [‡]	95% CI
Age (years) at menarche												
12	582	1.0	Referent	86	1.0	Referent	374	1.0	Referent	37	1.0	Referent
13–14	389	1.0	0.7, 1	59	1.0	0.7, 1.4	245	0.8	0.7, 1.1	23	1.0	0.6, 1.7
16	74	0.9	0.6, 1.2	7	0.6	0.6, 1.3	64	0.8	0.3, 1.3	1	0.2	0.6, 1.2
<i>p</i> § for ductal carcinoma												0.215
<i>p</i> for lobular carcinoma												0.638
Age (years) at first full-term birth												0.456
19	102	1.0	Referent	10	1.0	Referent	207	1.0	Referent	24	1.0	Referent
20–24	222	1.1	0.8, 1.6	31	1.7	0.8, 3.5	150	0.8	0.6, 1.1	16	0.7	0.4, 1.4
25–29	207	1.0	0.8, 1.4	35	2.1	1.0, 4.3	81	1.2	0.8, 1.7	10	1.4	0.6, 3.1
30	210	1.1	0.8, 1.5	28	1.7	0.8, 3.6	41	0.7	0.5, 1.2	4	0.7	0.2, 2.0
Nulliparous	307	1.3	1.0, 1.8	48	2.3	1.1, 4.6*	86	0.9	0.7, 1.3	7	0.8	0.3, 1.9
<i>p</i> for ductal carcinoma												0.935
<i>p</i> for lobular carcinoma												0.107
Interval (years) between age at menarche and age at first full-term birth												0.235
5	43	1.0	Referent	4	1.0	Referent	131	1.0	Referent	19	1.0	Referent
6–10	212	1.3	0.9, 2.0	26	1.7	0.6, 4.9	184	0.8	0.6, 1.1	18	0.6	0.3, 1.1
11–15	212	1.2	0.8, 1.8	36	2.2	0.8, 6.4	99	1.1	0.8, 1.6	11	0.9	0.4, 2.0
16	271	1.3	0.9, 2.0	38	2.0	0.7, 5.9	61	0.8	0.5, 1.2	6	0.6	0.2, 1.5
Nulliparous	307	1.5	1.0, 2.3*	48	2.5	0.9, 7.3	86	0.9	0.6, 1.4	7	0.6	0.3, 1.6
<i>p</i> for ductal carcinoma												0.708
<i>p</i> for lobular carcinoma												0.104
												0.197

* *p* < 0.05.

[†]OR, odds ratio; CI, confidence interval.

[‡]All odds ratios were adjusted for age and study site.

[§]*p* value for difference between premenopausal White and African-American women.

Odds ratios for breast cancer associated with age at menarche, age at first full-term birth, and the interval between these two ages among postmenopausal women, by estrogen receptor (ER)/progesterone receptor (PR) status and histologic type, Women's Contraceptive and Reproductive Experiences (CARE) Study, 1994–1998

TABLE 5

	ER/PR status				<i>p</i> for difference between case types	Histologic type				
	ER+ or PR+ (<i>n</i> = 1,181)		ER-/PR- (<i>n</i> = 378)			Ductal carcinoma (<i>n</i> = 1,424)		Lobular carcinoma (<i>n</i> = 271)		
	No	OR [†] , 95% CI [‡]	No.	OR [‡] , 95% CI		No.	OR [‡] , 95% CI	No.	OR [‡] , 95% CI	
Age (years) at menarche										
12	627	1.0	Referent	197	1.0	Referent	738	1.0	Referent	
13–14	449	0.9	0.8, 1.1	144	1.0	0.8, 1.3	539	1.0	0.8, 1.1	0.7 0.5, 1.0 *
15	104	0.9	0.7, 1.1	37	0.9	0.6, 1.4	146	1.0	0.8, 1.2	0.837 0.6 0.3, 0.9 *
Age (years) at first full-term birth										
19	255	1.0	Referent	119	1.0	Referent	372	1.0	Referent	
20–24	446	1.2	1.0, 1.5 *	148	1.1	0.8, 1.4	524	1.1	0.9, 1.3	1.0 1.4 1.0, 2.0
25–29	213	1.6	1.3, 2.1 *	57	1.1	0.8, 1.6	232	1.4	1.1, 1.7 *	2.1 1.4, 3.2 *
30	77	1.4	1.0, 1.9 *	28	1.2	0.8, 2.0	100	1.3	1.0, 1.8	1.5 0.8, 2.8
Nulliparous	190	1.8	1.4, 2.3 *	26	0.5	0.3, 0.8 *	196	1.3	1.0, 1.6 *	46 2.2 1.4, 3.3 *
Interval (years) between age at menarche and age at first full-term birth										
5	128	1.0	Referent	72	1.0	Referent	217	1.0	Referent	
6–10	451	1.4	1.1, 1.8 *	156	1.0	0.7, 1.4	539	1.0	0.9, 1.3	1.9 1.2, 3.1 *
11–15	282	1.5	1.2, 2.0 *	82	1.0	0.7, 1.5	321	1.2	0.9, 1.5	71 2.4 1.4, 4.0 *
16	127	1.7	1.2, 2.3 *	40	1.1	0.7, 1.7	148	1.3	1.4, 4.7	32 2.6 1.4, 4.7 *
Nulliparous	190	2.0	1.5, 2.7 *	26	0.5	0.3, 0.8 *	196	1.3	3.0, 1.7	46 3.0 1.7, 5.2 *
										0.017

* *p* < 0.05.

[†] OR, odds ratio; CI, confidence interval.

[‡] All odds ratios were adjusted for age, study site, and race (White or African-American).

Odds ratios for breast cancer associated with age at first full-term birth and the interval between ages at menarche and first full-term birth after each of these factors was adjusted for the other, by estrogen receptor (ER)/progesterone receptor (PR) status and histologic type, Women's Contraceptive and Reproductive Experiences (CARE) Study, 1994–1998

TABLE 6

		White premenopausal women			Postmenopausal women		
		Baseline model [†]	Adjusted model [‡]	OR	95% CI	Baseline model [†]	Adjusted model [‡]
		OR [§]	95% CI [§]	OR	95% CI	OR	95% CI
Age (years) at first full-term birth							
All cases							
19	1.0	Referent	1.0	Referent	1.0	Referent	1.0
20–24	1.3	1.0, 1.8	1.2	0.8, 1.7	1.1	0.9, 1.3	1.1
25–29	1.2	0.9, 1.6	1.0	0.6, 1.7	1.4	1.1, 1.7*	1.5
30	1.2	0.9, 1.7	1.0	0.6, 1.8	1.3	1.0, 1.8*	1.5
ER+ or PR+							
19	1.0	Referent	1.0	Referent	1.0	Referent	1.0
20–24	1.5	1.1, 2.1*	1.2	0.8, 1.9	1.2	1.0, 1.5*	1.1
25–29	1.3	0.6, 1.9	1.1	0.6, 1.9	1.6	1.3, 2.1*	1.6
30	1.4	1.0, 2.0*	1.2	0.6, 2.3	1.4	1.0, 1.9*	1.4
Lobular carcinoma							
19	1.0	Referent	1.0	Referent	1.0	Referent	1.0
20–24	1.7	0.8, 3.5	1.4	0.6, 3.6	1.4	1.0, 2.0	1.1
25–29	2.1	1.0, 4.3	1.7	0.5, 5.2	2.1	1.4, 3.2*	1.5
30	1.7	0.8, 3.6	1.4	0.4, 5.3	1.5	0.8, 2.8	1.0
Interval (years) between age at menarche and age at first full-term birth							
All cases							
19	1.0	Referent	1.0	Referent	1.0	Referent	1.0
20–24	1.5	1.0, 2.2*	1.4	0.9, 2.2	1.1	0.9, 1.4	1.1
25–29	1.5	1.0, 2.2	1.4	0.8, 2.4	1.3	1.0, 1.6*	1.0
30	1.5	1.0, 2.2*	1.5	0.8, 2.9	1.4	1.1, 1.8*	1.0
ER+ or PR+							
19	1.0	Referent	1.0	Referent	1.0	Referent	1.0
20–24	1.5	1.0, 2.2*	1.4	0.9, 2.2	1.1	0.9, 1.4	1.1
25–29	1.5	1.0, 2.2	1.4	0.8, 2.4	1.3	1.0, 1.6*	1.0
30	1.5	1.0, 2.2*	1.5	0.8, 2.9	1.4	1.1, 1.8*	1.0

White premenopausal women				Postmenopausal women			
Baseline model [†]		Adjusted model [‡]		Baseline model [†]		Adjusted model [‡]	
OR [§]	95% CI [§]	OR	95% CI	OR	95% CI	OR	95% CI
19	1.0	Referent	1.0	Referent	1.0	Referent	1.0
20–24	1.7	1.0, 2.9 *	1.5	0.8, 2.7	1.4	1.1, 1.8 *	1.3
25–29	1.8	1.1, 3.0 *	1.6	0.8, 3.2	1.5	1.2, 2.0 *	1.2
30	1.7	1.1, 2.8 *	1.5	0.7, 3.4	1.7	1.2, 2.3 *	1.2
Lobular carcinoma							
19	1.0	Referent	1.0	Referent	1.0	Referent	1.0
20–24	1.7	0.6, 4.9	1.3	0.4, 4.5	1.9	1.2, 3.1 *	1.8
25–29	2.2	0.3, 5.9	1.4	0.3, 5.9	2.4	1.4, 4.0 *	1.9
30	2.0	0.7, 5.9	1.5	0.3, 7.3	2.6	1.4, 4.7 *	2.3

* $p < 0.05$.

[†] Adjusted for age at diagnosis, study site, and race (White or African-American).

[‡] Adjusted for baseline covariates and the other factor (interval between ages at menarche and first birth (top) or age at first full-term birth (bottom)).

[§] OR, odds ratio; CI, confidence interval.