

Breast cancers among very young premenopausal women (United States)

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Abstract

Objective: To assess risk factors for breast cancer among very young compared to older premenopausal women.
Methods: Between 1990 and 1992 a population-based case–control study conducted in Atlanta, GA, Seattle/Puget Sound, WA, and central NJ interviewed 3307 premenopausal women aged 20–54 years. Logistic regression models estimated adjusted relative risks (RR) and 95% confidence intervals (CI) for each of three 10-year age groups.
Results: Among the youngest age group (<35 years, n = 545), significant predictors of risk included African-American race (RR = 2.66; 95% CI 1.4–4.9) and recent use of oral contraceptives (RR = 2.26; 95% CI 1.4–3.6). Although these relationships were strongest for estrogen receptor-negative (ER–) tumors (RRs of 3.30 for race and 3.56 for recent oral contraceptive use), these associations were also apparent for young women with ER+ tumors. Delayed childbearing was a risk factor for ER+ tumors among the older premenopausal women ($p_{\text{trend}} < 0.01$), but not for women <35 years in whom early childbearing was associated with an increased risk, reflecting a short-term increase in risk immediately following a birth. Family history of early-onset breast cancer was more strongly associated with risk among women <35 years (RR = 3.22) than those 45–54 years (RR = 1.51). Risk factors for premenopausal breast cancer not significantly modified by age at diagnosis included early age at menarche, low body mass index, and heavy alcohol consumption.
Conclusion: These findings suggest the possibility that women who develop breast cancers at very young ages may be etiologically as well as clinically distinct.

Introduction

Whether breast cancer diagnosed at young ages is a disease both clinically and etiologically distinct from breast cancer diagnosed later in life has long been debated. Menopausal status was initially proposed as the natural divider for different disease etiologies [1], in large part because breast cancer incidence rates increase approximately 100-fold between age 30 and 50 years, but the rate of increase is attenuated to less than two-fold

between ages 50 and 80 years [2]. The observation of different risk factors for premenopausal and postmenopausal breast cancer provide additional support for distinct disease etiologies [3]. Risk of premenopausal breast cancer is elevated among African-American women, women with a lower body mass index, recent oral contraceptive users, those who had a recent birth, and possibly for women who do not breast feed their children [3–9]. In contrast, incidence of postmenopausal breast cancer is elevated among white women, obese women, and women with a sedentary lifestyle [3–5, 10]. Family history, early age at menarche, late age at first birth, taller height, and heavy alcohol consumption are associated with increased risk of breast cancer regardless of age at diagnosis [3–5, 11–14], although risk estimates for family

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history, early age at menarche, and late age at first birth are stronger among premenopausal women [1, 3, 11, 15].

The incidence of tumors with particularly poor prognoses is highest among women aged 35–40 years at diagnosis [16–20]. However, because only 7% of breast cancers are diagnosed among women <40 years of age [21], few epidemiologic studies have had sufficient numbers to assess the etiologic profiles of very young compared to older premenopausal women. Family history is the most extensively studied risk factor for breast cancer among very young women. A recent pooled analysis of 52 epidemiologic studies (both retrospective and prospective) that included almost 60,000 women with breast cancer and twice the number of control subjects reported a relative risk (RR) in relation to having one affected relative of 2.91 among women <35 years and a RR of 1.84 for those aged 45–49 years, compared to a RR of 1.46 for women aged 60–64 years [11]. This analysis found that women diagnosed with breast cancer at younger ages were more likely to have a relative who was also affected at a young age, and that the risk was greater the younger the relative was when diagnosed.

Both case–control and cohort studies investigating breast cancer diagnosed at young ages, most often present estimates of risk for women younger than 40–45 years, which, not surprisingly, appear similar to those for all premenopausal women [22–28]. Because many of these studies either did not report age-specific findings among the youngest women (<35 years) or did not enroll older premenopausal women (45+ years), they were unable to assess whether the relationships between risk factors and breast cancer were uniform or whether they varied across the spectrum of premenopausal age groups. It is also noteworthy that, even though very young women have a strong predilection for later stage and hormone receptor-negative tumors [16, 29], no investigation has assessed whether breast cancer risk factors were differentially associated with poor prognosis tumor types among women <35 years of age.

We undertook this study of premenopausal women using data from a large population-based case–control study in order to elucidate risk factors that may be more strongly associated with onset of disease at very young ages in comparison to older premenopausal women.

Materials and methods

Study subjects and data collection

Brinton and colleagues [30] previously described this population-based case–control study which was con-

ducted in the metropolitan areas of Atlanta, Georgia, and Seattle/Puget Sound, Washington, and five counties of central New Jersey. Regional and governmental institutional review boards approved the study protocol. In New Jersey and Seattle the study participants included women aged 20–44 years; in Atlanta the age range was extended through 54 years of age. A rapid-reporting system identified women of these age groups who were newly diagnosed with *in-situ* or invasive breast cancer in 1990 through 1992. Hospital records of eligible patients were abstracted to document details on the clinical and pathologic characteristics of their breast cancer. Control subjects in the three geographic areas were ascertained through random-digit dialing, with a 90.5% screening response rate. Following written informed consent, participants were interviewed in person about demographic factors, reproductive and menstrual history, contraceptive behavior, use of exogenous hormones, medical and screening history, anthropometry and physical activity, adolescent diet, alcohol consumption, smoking, occupation, family history of cancer, and certain lifestyle factors. Two thousand two hundred and two (86%) eligible patients and 2009 (78%) eligible control subjects completed interviews. A comparison of respondents to non-respondents who were willing to complete an abbreviated questionnaire were similar with respect to age and race, and they reported similar distributions for variables assessed in this study [31].

Exclusions

We excluded from analysis subjects who indicated on interview that they either did not have a residential telephone ($n = 29$) or that they had a previous diagnosis of breast cancer ($n = 19$). In addition, 856 postmenopausal women (self-report of surgical menopause or natural end of menses) were excluded from analysis. After the exclusions, 1750 cases and 1557 controls remained in this investigation.

Statistical analysis

We described the relationship of age with the methods of breast cancer detection, stage at diagnosis, and hormone receptor subtypes for all breast cancer cases. We also compared the frequency of risk factors for breast cancer among cases with controls, overall and initially stratified by 5-year age groups. For brevity, we report only findings for risk factors that have previously been shown to affect overall risk of breast cancer in this study and stratified by the following age groups: <35, 35–44, and 45–54 years (the latter group includes only

patients from Atlanta). Risk factors that were not found to be associated with breast cancer in these data, such as breast feeding (ever breast fed or total years breast fed), number of abortions or miscarriages, smoking status, difficulty conceiving or maintaining pregnancy, use of an electric blanket, waist-to-hip ratio, and physical activity (at time of interview, at age 20, or at menarche) [32–37], are not presented. Lastly, we assessed whether the age-modified relationships between risk factors and breast cancer were explained by stage at diagnosis (*in-situ* compared to invasive disease) or tumor subtype (estrogen receptor (ER) and progesterone receptor (PR) status).

For bivariate analyses, Pearson's chi-square tests were used to evaluate the difference between proportions. Relative risks (RR) and their 95% confidence intervals (CIs) were used to assess the relationship between risk factors and case-control status, stratifying by age group and controlling for potential confounders. We used unadjusted and adjusted logistic regression models to obtain maximum-likelihood estimates of the odds ratio, which were used to approximate RR [38]. To test whether the relationship between each risk factor and breast cancer diagnosis was modified by age at diagnosis on a multiplicative scale, both the main effects and their interaction term were evaluated in the model and the statistical significance of the interaction term was assessed. The final models adjusted for study site (Atlanta, Seattle, New Jersey), number of mammograms within five years of diagnosis (continuous), age (continuous), race (white, black, other), age at menarche (<12, 12, 13, 14+ years), a combination variable including number of full-term births and age at first birth (no birth, one birth at age <25 years, one birth at age ≥25 years, two births first at age <25 years, etc.), family history of breast cancer in a first-degree relative (yes or no), alcohol consumption (0, <3, 3–6.9, 7–13.9, 14+ drinks each week), recent oral contraceptive use (never used or used for less than six months, within 5, 10, or 10+ years of diagnosis) and body mass index (<23, 23–26, 27+ kg/m²). All tests were two-sided, and *p*-values less than 0.05 were considered statistically significant.

Results

Diagnostic stage and tumor subtypes among cases

In this study, 265 (15%) of the premenopausal cases were aged 20–34 years, 1214 (69%) were aged 35–44 years, and 271 (16%) were aged 45–54 years at the time of diagnosis. Younger women were less likely to be diagnosed with early-stage and favorable prognosis

tumor subtypes than older women (Table 1). Eleven percent of women aged <35 years, 15% aged 35–44 years, and 21% aged 45–54 years were diagnosed with non-invasive tumors. The larger proportion of *in-situ* tumor diagnoses with older age paralleled more frequent mammography use prior to diagnosis as well as a larger percentage of cancers that were detected by mammography (data not shown). Of cases in the youngest to oldest age groups, 21%, 57%, and 82% had at least one mammogram prior to diagnosis and 5% (<35 years), 23% (35–44 years), and 34% (45–54 years) of tumors within these age groups were detected by mammography. The age-dependent increase in the diagnosis of non-invasive tumors was evident only among cases who ever had a mammogram, for whom *in-situ* tumors were diagnosed in 15% of women aged <35 years, 17% aged 35–44 years, and 22% aged 45–54 years. Of cases who never had a mammogram, 10% were diagnosed with *in-situ* tumors in all age groups.

Compared to cases diagnosed at an older age, younger cases were also more likely to be diagnosed with hormone receptor-negative tumor subtypes. ER and PR status was highly correlated ($\rho=0.93$, $p < 0.01$). Approximately 60% of women <35 years had either an ER- or PR- tumor compared with 40% of women in the oldest age group. The larger proportion of hormone receptor-negative tumors in the younger age groups was evident among white women only. Approximately 50% of tumors diagnosed among African-American women in each age group were hormone receptor-negative in all age groups. Within strata defined by stage at diagnosis, approximately 40% of all tumors were ER- regardless of stage. Thus, adjustment for stage at diagnosis did not change the relationship between age and hormone receptor status.

Case-control analysis of risk factors

We found that the relationship with breast cancer risk depended strongly on the woman's age at diagnosis for each of the following risk factors: race, oral contraceptive use, and age at first full-term pregnancy ($p_{\text{interaction}} < 0.05$ for each of these age * risk factor combinations) (Table 2). Within the youngest age group, significant predictors of breast cancer risk included African-American race (RR = 2.66; 95% CI 1.4–4.9) and oral contraceptive use for a minimum of six months (RR = 2.03; 95% CI 1.3–3.1). Among women 35+ years, the estimates for risk of breast cancer for African-American women were only modestly elevated. Risk of breast cancer associated with ever use of oral contraceptives diminished with increasing age with RRs of 1.13 for women 35–44 years, and 0.73 for women aged

Table 1. Tumor detection, stage, and hormone receptor subtype among 1750 premenopausal women with breast cancer

	Age <35 years (n = 265)		Age 35–44 years (n = 1214)		Age 45–54 years (n = 271)	
	No.	Percentage	No.	Percentage	No.	Percentage
Stage						
<i>In-situ</i>	28	11	178	15	55	21
Local	130	50	574	48	131	49
Regional/distant	100	39	443	37	82	31
Missing	7		19		3	
Method of detection						
BSE or accidental ^a	211	80	760	63	131	49
Clinical breast examination	24	9	98	8	34	13
Mammography	12	5	279	23	91	34
Other ^b	16	6	63	5	13	5
Missing	2		14		2	
Estrogen receptor (ER) status						
ER–	105	46	353	37	52	27
ER+	121	54	604	63	144	73
Missing	39		257		75	
Progesterone receptor (PR) status						
PR–	110	50	328	35	64	33
PR+	111	50	603	65	130	67
Missing	44		283		77	
Combination ER/PR status						
ER+/PR+	87	40	509	55	114	59
ER+/PR–	29	13	79	8	27	14
ER–/PR+	23	10	93	10	15	8
ER–/PR–	81	37	249	27	37	19
Missing	45		284		78	

^a Accidental self-discovery or accidental discovery by partner.

^b Other modes of detection include presentation with signs or symptoms such as pain, swelling, dimpling, or discovery during treatment for other medical problems.

Note: Pearson's chi-square test for homogeneity significant for all comparisons ($p < 0.05$).

45–54 years. Furthermore, among women <35 years, risk of breast cancer associated with oral contraceptive use was strongest for those who used oral contraceptives within five years prior to diagnosis (RR = 2.26) and, although also elevated, was weaker for women who used oral contraceptives 5–10 years (RR = 1.87) or 10+ years (RR = 1.44) prior to diagnosis ($p_{\text{trend}} < 0.01$).

Nulliparous women and those with a recent birth (2–7 years as opposed to 8+ years) were at somewhat elevated risk. This was generally true for all age groups. The pattern of association for the remaining two birth-related risk factors, age at first birth and number of full-term births, varied according to age at diagnosis. Among women <35 years, we found no trend of increased risk with advancing maternal age but rather a surprisingly strong risk associated with having had a first child at the ages of 20–24 years (RR = 2.49). We explored confounding of this relationship by interval since last birth. Among participants <35 years who were aged 20–24 years at first birth (n = 91), 59% of cases compared to 40% of controls had a child within 2–

7 years of diagnosis, when risk associated with a recent birth was the highest (RRs of 1.51 for a 2–4 year and 1.74 for a 5–7 year interval since last birth). In contrast, among the women who first gave birth prior to 20 years of age, only 46% of cases and 36% of controls had a child within 2–7 years of diagnosis. Nonetheless, in multivariate models restricted to parous women we found the relationship between age at first birth and breast cancer unchanged after controlling for interval since last birth, number of births, and the other variables specified in Table 2.

On the contrary, later age at first birth was significantly related to risk of breast cancer among women in the older age groups at the time of diagnosis (35–54 years) ($p_{\text{trend}} = 0.03$, model restricted to parous women and adjusted for interval since last birth and number of births). Late childbearing (30+ vs <20 years at first birth) was associated with RRs of 2.42 for women aged 45–54 years and 1.35 for women aged 35–44 years at diagnosis. Although fewer full-term births was related to breast cancer risk among parous women

aged 35–44 years even after adjusting for the effects of age at first birth, no pattern emerged for the relationship between number of full-term births and risk of breast cancer in either the younger or older age groups.

Effects of a positive first-degree family history of breast cancer did not initially appear to display marked differences across the three age categories. However, an assessment of the effects of a family history of breast cancer was complicated by the fact that such histories were truncated in the younger age groups. We did find that risk associated with having had a mother with an early breast cancer diagnosis (<50 years) was more pronounced among women <35 years (RR = 3.22) and those aged 35–44 years (RR = 3.37) than women aged 45–54 years (RR = 1.51). The relationship was even more marked among women <30 years (n = 125) for whom having a mother diagnosed with breast cancer before her fiftieth birthday (eight cases and two controls) was associated with a RR of 6.63 (0.9–50.5).

Breast cancer risk among women 20–54 years was associated positively with heavy alcohol consumption (14+ vs 0 drinks/week, RR = 2.06; 95%CI 1.4–3.1), lower body mass index (<23 vs 27+ kg/m², RR = 1.25; 95% CI 1.0–1.5), young age at menarche (<12 vs 14+ years, RR = 1.31; 95% CI 1.0–1.6), and a previous breast biopsy (RR = 1.41; 95% CI 1.1–1.8). Among women <35 years the risk associated with alcohol consumption was slightly reduced (RR for 14+ drinks/week = 1.71) and that with body mass index (RR for <23 kg/m² = 1.51) and a previous breast biopsy slightly stronger (RR = 2.25). Although based on small numbers, it is noteworthy that young age at menarche (<12 vs 14+ years) was associated with nearly a 10-fold risk of breast cancer (RR = 9.58; 95% CI 1.8–50.6) among women <30 years.

Risk factor profiles for each of the three age groups summarized in Table 2 were similar when stratified by study site and after controlling for number of mammograms in the 5 years prior to breast cancer diagnosis, the latter of which was associated in women aged 20–54 years with a RR of 1.16 (1.1–1.2) for each additional mammogram.

For risk factors whose association with breast cancer depended on age at diagnosis (that is, a significant interaction of the risk factor with age at diagnosis), we assessed whether these relationships were explained by the predilection of younger women to be diagnosed with either later stage or poor prognosis tumor subtypes. Thus we stratified our findings by hormone receptor status and stage. As shown in Table 3, African-American compared to white women were at significantly higher risk of ER– breast cancer. Among women <35 years, African-American race was associated with

a 3.3-fold increased risk of ER– breast cancer and a 2.5-fold increased risk of ER+ breast cancer. Similarly, oral contraceptive use was a stronger risk factor among very young women with ER– tumors (RR = 3.06) than those with ER+ tumors (RR = 1.61). Although there was no apparent trend with later maternal age at first birth among women <35 years, later age at first birth (30+ vs <20 years) was a risk factor for ER+ tumors among the women aged 35–54 years (RR = 1.97, 95% CI 1.4–2.8) ($p_{\text{trend}} < 0.01$ among parous women). Because ER and PR status were highly correlated, we found similar results to those presented in Table 3 when stratifying either by PR status or by combination ER/PR status (positive–positive compared to negative–negative).

Further stratification of the age-specific relationships between risk factors and breast cancer by tumor stage (*in-situ* vs invasive) generally did not alter our findings. Among women 35+ years, we did see a somewhat stronger relationship between nulliparity (vs age at first birth <20 years) and *in-situ* tumors (RR = 2.04; 95% CI 1.2–3.6) than for invasive tumors (RR = 1.30; 95% CI 1.0–1.8). Nulliparity as opposed to a young maternal age (<20 years) was similarly associated with both non-invasive and invasive tumors among women <35 years (RR = 1.4).

Discussion

Breast cancer diagnosed at very young ages (<35 years) is well recognized as clinically different than breast cancers diagnosed at older ages [29]. Our findings further suggest the possibility that breast cancers diagnosed at very young ages may also be etiologically distinct. Specifically, African-American race, oral contraceptive use, and young age at first birth were differentially associated with breast cancer risk among women <35 years compared to those aged 35–54 years. As previously reported by others [6, 39, 40] we found that the risk of breast cancer associated with African-American race (RR = 2.66) and recent use of oral contraceptives (RR = 2.26) diminished with increasing age. Rather than being a true age effect, we attribute the positive association of young age at first birth found only among women <35 years to confounding by a transient increase in risk associated with a recent birth, as seen in other studies [7, 8, 28]. Adjustment for interval since last birth did not alter the estimate of risk associated with an early age at first birth because of the homogeneity in birth patterns among women <35 years, of whom the vast majority had a child within 7 years of diagnosis.

We found that these age-dependent relationships were explained, at least in part, by the high proportion of

Table 2. Risk factors for breast cancer stratified by age at diagnosis among premenopausal women

Risk factors	Age <35 years				Age 35-44 years				Age 45-54 years ^a			
	Cases (n = 265)	Controls (n = 280)	RR	95% CI	Cases (n = 1214)	Controls (n = 1033)	RR	95% CI	Cases (n = 271)	Controls (n = 244)	RR	95% CI
Race^b												
White	187	224	1.0	Ref.	998	816	1.0	Ref.	223	198	1.0	Ref.
African-American	60	33	2.66	1.4-4.9	156	140	1.16	0.9-1.6	46	40	1.66	1.0-2.9
Other	18	23	1.40	0.7-3.0	60	77	0.84	0.6-1.2	2	6	0.23	0.0-1.3
Use of oral contraceptives for more than 6 months ^b												
No	59	94	1.0	Ref.	293	288	1.0	Ref.	89	70	1.0	Ref.
Yes	206	186	2.03	1.3-3.1	921	745	1.13	0.9-1.4	182	174	0.73	0.5-1.1
Recency of use (years prior to diagnosis)												
Within 5	136	119	2.26	1.4-3.6	155	121	1.31	1.0-1.8	1	9	0.08	0.0-0.7
5 to 9	41	40	1.87	1.0-3.5	145	116	1.17	0.8-1.6	13	10	0.96	0.4-2.5
10+	29	27	1.44	0.7-2.9	621	508	1.09	0.9-1.4	168	155	0.76	0.5-1.2
Age at first birth (years) ^{b,c}												
<20	28	33	1.0	Ref.	145	155	1.0	Ref.	39	44	1.0	Ref.
20-24	54	37	2.49	1.2-5.3	257	262	1.00	0.7-1.3	89	96	0.92	0.5-1.6
25-29	53	65	1.21	0.6-2.5	288	233	1.17	0.9-1.6	58	51	1.06	0.6-2.0
30+	22	27	1.06	0.4-2.6	255	186	1.35	1.0-1.9	37	13	2.42	1.1-5.6
Nulliparous	108	118	1.46	0.7-2.9	269	197	1.46	1.1-2.0	48	40	1.02	0.5-2.0
Interval since last birth (years) ^c												
Nulliparous	108	118	1.22	0.6-2.6	269	197	1.38	1.1-1.8	48	40	0.99	0.6-1.7
0-1	49	79	0.88	0.4-1.9	89	93	1.05	0.7-1.5				
2-4	56	42	1.51	0.7-3.4	158	142	1.17	0.9-1.5	5	4	1.29	0.3-5.7
5-7	31	22	1.74	0.7-4.3	176	140	1.26	1.0-1.6	12	8	2.71	1.0-7.7
8+	21	19	1.0	Ref.	520	457	1.0	Ref.	205	190	1.0	Ref.
Full-term births ^c												
0	108	118	1.0	Ref.	269	197	1.0	Ref.	48	40	1.0	Ref.
1	59	60	0.95	0.6-1.6	243	198	0.79	0.6-1.0	42	41	0.96	0.5-1.9
2	69	73	0.96	0.6-1.6	460	369	0.86	0.7-1.1	91	77	1.20	0.7-2.1
3+	29	29	1.03	0.5-2.0	242	269	0.65	0.5-0.9	90	86	0.99	0.6-1.8
Family history of breast cancer												
None	233	265	1.0	Ref.	1038	964	1.0	Ref.	228	231	1.0	Ref.
Any	32	15	2.72	1.3-5.7	176	69	1.99	1.5-2.7	43	13	2.78	1.4-5.5
Sister	5	0			29	12	1.76	0.9-3.6	12	2	7.47	1.5-36.3
Mother	28	15	2.50	1.2-5.3	156	61	2.03	1.5-2.8	34	11	2.46	1.2-5.2
Mother's age at breast cancer diagnosis (years)												
<50	16	8	3.22	1.2-8.9	54	16	3.37	1.8-6.3	6	3	1.51	0.3-6.6
50+	11	7	1.69	0.6-5.1	99	44	1.63	1.1-2.4	28	8	2.81	1.2-6.6

Table 3. Risk factors for breast cancer stratified by age at diagnosis and estrogen receptor status

Risk factors	Age <35 years						Age ≥35 years					
	ER+			ER−			ER+			ER−		
	Cases ^a	RR	95% CI									
Race												
White	88	1.0	Ref.	69	1.0	Ref.	641	1.0	Ref.	299	1.0	Ref.
African-American	26	2.48	1.2–5.3	28	3.30	1.4–7.5	77	0.95	0.7–1.3	91	2.04	1.4–2.9
Other	7	0.94	0.3–2.6	8	2.01	0.7–5.6	30	0.77	0.5–1.2	15	0.74	0.4–1.4
Use of oral contraceptives for more than 6 months												
No	32	1.0	Ref.	18	1.0	Ref.	197	1.0	Ref.	93	1.0	Ref.
Yes	89	1.61	0.9–2.8	87	3.06	1.6–5.9	551	1.02	0.8–1.3	312	1.21	0.9–1.6
Recency of oral contraceptive use (years prior to diagnosis)												
<5	56	1.66	0.9–3.0	57	3.56	1.8–7.1	82	1.15	0.8–1.7	50	1.36	0.9–2.1
5–9	18	1.57	0.7–3.4	18	2.58	1.1–6.3	72	1.00	0.7–1.4	51	1.45	0.9–2.2
10+	15	1.49	0.6–3.5	12	1.99	0.7–5.5	397	1.00	0.8–1.3	211	1.14	0.8–1.5
Age at first birth (years)^b												
<20	14	1.0	Ref.	13	1.0	Ref.	75	1.0	Ref.	65	1.0	Ref.
20–24	28	2.52	1.0–6.2	19	1.82	0.6–5.2	168	1.14	0.8–1.6	105	0.91	0.6–1.3
25–29	23	0.94	0.4–2.3	22	1.27	0.5–3.3	177	1.41	1.0–2.0	83	0.87	0.6–1.3
30+	9	0.83	0.3–2.5	11	1.21	0.4–3.9	171	1.97	1.4–2.8	70	1.11	0.7–1.7
Nulliparous	47	1.19	0.5–2.7	40	1.18	0.5–2.9	157	1.59	1.1–2.3	82	1.07	0.7–1.6

^a Number of cases in each stratum. Number of controls in each stratum is summarized in Table 2.

^b Not adjusted for any of the other birth-related variables (full-term births or interval since last birth).

Note: RRs and 95% CIs estimated using maximum-likelihood methods adjusted for study site, number of mammograms within 5 years prior to diagnosis, age at diagnosis/interview, race, recent oral contraceptive use, a combination variable for age at birth and number of full-term births, family history of breast cancer, alcohol consumption, age at menarche, and body mass index.

hormone receptor-negative tumors in younger women. Although the relationships of race and oral contraceptive use were strongest for ER− tumors (RRs of 3.30 for race and 3.06 for oral contraceptive use), they were not entirely due to the predilection for young women to develop ER− tumors [29]. Race and oral contraceptive use were also associated, although to a lesser extent, with ER+ tumors (RRs of 2.48 and 1.61, respectively). Other case-control studies of both premenopausal and postmenopausal women report only modest associations of race and oral contraceptive use with ER− tumors (RR ~ 1.2–1.3) and no association with ER+ tumors [41, 42], similar to the estimates that we report among women 35+ years of age. Several studies have demonstrated that the excess risk of ER− compared to ER+ tumors for African-American women is strongest in the youngest age groups and declines with increasing age [39, 43], suggesting that the more modest results of earlier studies including women from a wider age range may be more similar to our findings for race if they were restricted to younger or premenopausal women.

Although there was no clear relationship among the women <35 years, delayed childbearing was a risk factor for ER+ tumors among the older women in this study. Our findings among women aged 35–54 years are

consistent with previous reports of increased risk of ER+ tumors with delayed childbearing for both premenopausal and postmenopausal women [44–47], one of which estimated that every 10-year delay in childbearing was associated with a 50% increase in risk of ER+ tumors [44]. We were unable to untangle whether this relationship persisted among women <35 years because of the particularly close intermingling of age at first birth and interval since last birth in this age group.

Recently investigators have suggested that estrogen and progesterone receptor status define up to four types of breast cancer (ER+PR+, ER+PR−, ER−PR+, ER−PR−) [39, 48]. We found that the age-stratified relationships between breast cancer risk factors and progesterone receptor status were generally similar to that which was observed in the estrogen receptor analyses. Consequently, we only presented risk factor profiles by estrogen receptor status. However, our findings are limited by lack of quality control in determining ER and PR status, for which analysis was conducted at several laboratories that used different methods.

Women with breast cancer diagnosed at a very young age frequently have a dominant family history of disease [11]. Population-based estimates for mutations in the

BRCA1/BRCA2 genes are higher among women diagnosed ≤ 35 years (11–15%) compared to those diagnosed 36–45 years (4–5%) and among women with at least one first-degree relative with breast cancer [49, 50]. Accordingly, we found that women diagnosed < 45 years whose mother was diagnosed with early breast cancer (< 50 years) were at twice the risk ($RR \sim 3.3$) as those whose mothers were diagnosed at older ages (45–54 years, $RR = 1.51$); although based on small numbers, risk among women < 30 years was the highest with a RR of 6.63. Because of a truncation in years of exposure in the youngest age group, we did not observe an age-dependent relationship for women with a first degree relative with breast cancer ($RR = 2.19$ for all subjects).

Young age at menarche (< 12 vs $14+$ years) was associated with a 30% increased risk of breast cancer for all subjects, yet the small subset of women < 30 years were at a much higher risk ($RR = 9.58$). This finding is not inconsistent with those of other studies reporting a stronger association with age at menarche among women diagnosed at earlier ages [1, 15]; however, it may also reflect better recall among young women, or may be a chance effect.

We found the relationship of alcohol consumption, body mass, and a previous breast biopsy with breast cancer risk varied only slightly across age strata, all of which have been documented in the literature as associated with premenopausal breast cancer [4, 14, 33, 51].

The lower number of diagnoses of non-invasive cancers among the youngest women in this and other studies [19] was attributable to age-related patterns of mammography use. As expected [52], we observed increased use of mammography according to increasing age. Because the relationship between age and stage of disease was explained by screening, it was not surprising that stratification of risk factor profiles by stage at diagnosis generally did not further explain the age-related associations. The modestly higher risk of non-invasive tumors among nulliparous women in this study has already been discussed in detail [53].

This investigation is one of the first large studies to address whether breast cancer diagnosed at very young ages is etiologically distinct from that of older premenopausal women. The strengths of the present study include a population-based sample of cases and controls, over 500 of which were under 35 years of age. Our findings, in particular those related to oral contraceptive use, do not appear to be susceptible to a surveillance bias, as the estimates were similar after adjustment for mammography use prior to diagnosis. Given the poor clinical prognosis of breast cancer diagnosed at young ages, identifying young women at highest risk deserves further investigation from new prospective studies [54]

or using existing data from other large case-control and cohort studies [24–27, 40, 55].

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