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ESTROGEN RECEPTOR POSITIVE TUMORS: DO REPRODUCTIVE FACTORS EXPLAIN DIFFERENCES IN INCIDENCE BETWEEN BLACK AND WHITE WOMEN?

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Abstract

Purpose—The incidence of estrogen receptor positive (ER+) breast cancer is higher among white women relative to black women. In two large prospective cohorts, the Black Women's Health Study (BWHS) and the Nurses' Health Study II (NHSII), we investigated whether reproductive factors explain the difference.

Methods—During 1,582,083 person-years of follow-up of 140,914 women observed from 1995-2007, 327 ER+ breast cancers were identified among black women in BWHS and NHSII and 1179 among white women in NHSII. Cox proportional hazards regression models, stratified by race and pooled, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of race, parity, age at first birth, and lactation in relation to risk of ER+ cancer with adjustment for age and other breast cancer risk factors.

Results—Age at first birth differed markedly in the two groups, with 66% of parous black women having their first child before age 25 as compared with 36% of white women. Each additional year of age at first birth was associated with a 4% increased risk of ER+ breast cancer among both racial groups. Relative to nulliparous women, parous women were at decreased risk of ER+ breast cancer (HR 0.59, 95% CI: 0.20, 1.77), in black women and (HR 0.63, 95% CI: 0.45, 0.87) in white women. The HR for the association of black race with ER+ cancer was 0.67 (95% CI: 0.53, 0.84) in a model that adjusted for age only, 0.77 (95% CI: 0.61, 0.99) in a model that controlled for parity, age at first birth, and other reproductive/hormonal factors, and 0.83 (95% CI: 0.70, 0.98) in a model that additionally controlled for other breast cancer risk factors such as alcohol consumption and use of hormone supplements. Similar associations were seen among premenopausal women and in an analysis restricted to ER+PR+ tumors.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Conclusions—Reproductive factors explained some of the higher incidence of ER+ tumors among white women as compared to black women.

Keywords

breast carcinoma; race; estrogen receptor; reproductive factors; incidence; black; African-American

Background

The incidence of estrogen receptor (ER) positive and negative tumors varies by race in the United States (1). Non-Hispanic white women (hereafter referred to as white women) have the highest incidence rates of ER positive tumors, while non-Hispanic black women (black women) have the highest incidence of ER negative tumors (2-4). Reproductive factors such as age at first birth, parity, and age at menarche have been consistently associated with breast cancer risk (5-7). Reproductive factors have been more strongly associated with estrogen receptor positive breast cancer than other subtypes (8-10). In a 2006 meta-analysis of 10 published studies, Ma et al. found that parity was inversely associated with ER+/PR+ breast cancer but not associated with risk of ER-/PR- breast cancer. Older age at menarche was associated with decreased risk of both ER+/PR+ and ER-/PR- breast cancer, though the reduction was significantly greater for ER+/PR+ tumors (9). Research in the Nurses' Health Study found that first pregnancy was associated with a one-time increased risk for breast cancer but only among ER-/PR- tumors (10). In the Black Women's Health Study, parity was associated with a reduced risk of ER+/PR+ breast cancer but with an increased risk of ER-/PR- cancer while late age at first birth was associated with both subtypes. Lactation was not associated with risk of ER+ tumors, but did reduce risk of ER-/PR- tumors by nearly 20% (8).

Several studies have examined reproductive factors with respect to risk of breast cancer among black and white women, although not by hormone receptor status. Ursin et al. (2004) found that lactation and increasing number of full-term pregnancies were inversely associated with breast cancer risk in black and white women (11). Research from the Carolina Breast Cancer Study found that women who lactated were 20-30% less likely to develop breast cancer than those who did not (12). Consistently across each of these studies researchers found different reproductive patterns for black and white women. White women have fewer children, have an older age at first birth, and are more likely to have breastfed as compared to black women in the United States (13, 14).

Most studies that have examined breast cancer risk factors by hormone receptor status have found similar associations for ER+/PR+ and ER+/PR- tumors, suggesting that ER status is the more important phenotype. For example, Colditz et al. 2004 found that parity and age at each birth, as summarized in the birth index, had very similar associations across ER+ tumors regardless of PR status. This finding could be expected for several reasons. First, biologically, the estrogen receptor, by binding directly to DNA, can influence the expression of the progesterone receptor gene (15). Second, as a result of this biological correlation, most ER+ tumors are also PR+ and most ER- tumors are also PR- and ER/PR discordance is a reflection of estrogen receptor malfunction (16). Thus, while PR status relative to ER status has been shown to be an important prognostic indicator, it may not be as important in etiologic studies (17). In our present study we will focus on estrogen receptor status.

We hypothesize that reproductive factors may explain racial variation in ER+ breast cancer. We used data from the Black Women's Health Study and the Nurses' Health Study II, to

examine whether differences in reproductive factors explain the higher incidence of ER+ breast cancer among Whites relative to Blacks.

Methods

Study population and data collection

Nurses' Health Study II (NHS II)—An ongoing prospective study of 116,608 female registered nurses (96% of whom were white), the NHS II began in 1989 when participants were ages of 25 to 42 (18). Nurses complete mailed self-administered questionnaires on medical history and lifestyle and health-related behaviors every two years. Follow-up has been approximately 90% complete for each subsequent follow-up cycle.

Black Women's Health Study (BWHS)—The Black Women's Health Study is an ongoing prospective cohort study of African-American women from all regions of the United States (19). In 1995, approximately 59,000 women aged 21-69 enrolled by responding to health questionnaires mailed to Essence magazine subscribers, members of several black professional organizations, and friends or relatives of early responders. Every two years participants complete questionnaires obtaining information on medical status and behavioral, dietary, and anthropomorphic risk factors. Follow-up has been at least 80% complete for each questionnaire cycle.

Study Population—To synchronize the calendar period under study in both cohorts, follow-up in NHS II was started in 1995, the baseline for BWHS. Women were excluded if at baseline they had a previous cancer diagnosis (BWHS n=1,475; NHS II n=2,719), or died prior to 1995 (NHSII n=234) (figure 1). In NHS II, women were also excluded if they did not identify as White/Caucasian or Black/African-American (n=8,030). Due to differing age distributions between the cohorts, women in BWHS were excluded if at baseline they were under age 30 (n=12,759) or age 50 or older (n=9,455). Women age 50 or older in 1995 were also excluded from NHS II (n=49). After exclusions there were 37,406 black women (35,338 from BWHS and 2,068 from NHSII) contributing 399,192 person-years of follow-up, and 103,508 white women contributing 1,182,891 person-years of follow-up from NHS II through 2007.

Case Identification—In both cohorts, the women were asked whether breast cancer had been diagnosed and to report the date of diagnosis. Pathology data, obtained from hospital (NHS, BWHS) or cancer registry records (BWHS) for women reporting a breast cancer diagnosis, were reviewed by study staff, blinded to reported exposure information, to confirm the diagnosis. Deaths are reported through family members or identified through review of the National Death Index.

ER status was determined by review of pathology data from medical records (BWHS and NHSII) or from state cancer registries (BWHS only). Receptor status was determined by biochemical or immunohistochemical assay (10, 20). Cases of invasive breast cancer classified as ER+ by these assays were included in the analyses. In total, 1,506 incident invasive cases of ER+ breast cancers were identified among women in the two cohorts.

Exposure Assessment—All exposures are self-reported on biennial questionnaires in both cohorts. For time-varying covariates, person-time is reassigned using updated information every two years. At baseline, women in both cohorts were asked whether they were currently pregnant and to report their pregnancy history by each year of age. Subsequent questionnaires queried whether the respondent was currently pregnant or had been pregnant and/or given birth since the prior questionnaire. Data on parity and age at

each birth were carried forward if there was missing information in a given questionnaire cycle.

Women were classified as premenopausal, postmenopausal or unknown menopausal status. Women were considered postmenopausal if they reported no menstrual periods within the previous 12 months with natural menopause or bilateral oophorectomy. Women with hysterectomies with one or more ovaries retained were considered premenopausal if younger than age 43 and postmenopausal if they were 56 years or older and their age at menopause was considered unknown, otherwise their menopausal status was unknown. In both cohorts, premenopausal status was carried back and postmenopausal status was carried forward in the case of missing data. If data remained missing after these procedures, a category for missing or unknown data was created and missing indicators were used in the analysis.

Covariates

Covariates were selected based on having an established or suspected causal association with incidence of ER+ breast cancer. The variables included in multivariate adjusted models are family history of breast cancer in a first degree relative (yes/no), history of biopsy confirmed benign breast disease (yes/no), alcohol consumption (<1 drink/wk, 1-6 drinks/wk, 7-13 drinks/wk and 14drinks/wk), and oral contraceptive use (never, < 5 years, 5 years), BMI at age 18 (kg/m²), postmenopausal hormone use (never, current, past), weight change since age 18 (lost > 2 kg, stable, gained 2-9 kg, gained 10-19 kg, gained 20 kg).

Statistical Analysis—Women contributed person-time until the date they became a breast cancer case, were diagnosed with any other cancer (excluding non-melanoma skin cancer), the date of death, or June 2007, whichever occurred first. Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals for ER+ breast cancer associated with race and each reproductive risk factor for all women and for premenopausal women. We present models for black and white women separately and pooled estimates with both races. All p-values are two-sided and an alpha level of 0.05 was used to determine statistical significance. All analyses were performed using SAS version 9.1.3 in UNIX.

Results

Black women were younger on average (mean age 39.0 years) than were white women in (mean age 40.2 years) (table 1). A higher proportion of black women were nulliparous (27.0%) than were white women (21.0%). The prevalence of first births at young ages was higher among black women: one-third of parous black women (33.0%) reported a first birth before age 20 compared with only 6.0% of parous white women. Black women were heavier on average, with 32.0% obese in 1995, compared to 19.0% of white women. White women were more likely to have lost more than 2kg since age 18 (7% vs. 4%) and were significantly less likely to have gained 20 or more kilograms (22% vs. 42%) and were more likely to be current users of postmenopausal hormones (82% vs. 67%). Parous white women were less likely to have never breastfeed than parous black women (19% vs. 56%). Distributions of age at menarche, biopsy confirmed benign breast disease, oral contraceptive use and family history of breast cancer were similar across groups.

The mean age at diagnosis was 48.3 years among black women and 48.6 years among white women, with 6.7% of black women and 4.1% of white women diagnosed before age 40 (table 2). In both groups most cases were premenopausal at diagnosis. With respect to progesterone receptor status, 20.7% were PR– among Blacks compared to 14.5% PR– among Whites.

In pooled analyses, black women were at a significantly reduced risk of ER+ breast cancer as compared to white women (table 3). In the age-adjusted model, black women had a 33% lower incidence (HR: 0.67, 95% CI: 0.53, 0.84) (model 1). Parous women had a lower risk of ER+ breast cancer than nulliparous women among both white women (HR: 0.55, 95% CI: 0.40, 0.76) and black women (HR: 0.54, 95% CI: 0.18, 1.58). Each additional year of age at first birth was associated with a 4% increased risk of ER+ breast cancer in both racial groups. Lactation was associated with a reduced risk in white but not black women. After we accounted for differences in age at first birth, parity, lactation, and other reproductive factors, incidence among black women remained lower (HR: 0.77, 95% CI: 0.61, 0.99), but the difference was attenuated, going from 33% to 23% (model 2). In model 3, with adjustment for other potential confounders, such as alcohol intake and weight change since age 18, the estimate for race was further attenuated, with black women having 17% lower incidence of ER+ tumors as compared with white women (HR: 0.83, 95% CI: 0.70, 0.98). Because the distribution of PR status differed by race, we further examined associations between race and incidence of ER+/PR+ tumors and found similar results: black women had a 35% lower incidence than Whites in an age-adjusted model and a 25% lower incidence in the fully adjusted model (data not shown).

Among premenopausal women, in the age-adjusted model black women had 41% lower incidence of ER+ breast cancer than white women (HR: 0.59, 95% CI: 0.44, 0.80) (model 1, table 4). The HR was 0.63 (95% CI: 0.46, 0.85) in a model that controlled for reproductive factors. After adjustment for other potential confounders, the estimate for race was attenuated, with black women having 21% lower incidence of ER+ tumors as compared with white women (HR: 0.78, 95% CI: 0.65, 0.93).

Discussion

In this combined analysis of the Black Women's Health Study and Nurses' Health Study II, we set out to examine whether reproductive factors could explain the higher incidence of ER+ tumors among white women as compared to black women. In pooled models adjusted for reproductive factors, the incidence gap narrowed, but incidence of ER+ tumors remained 23% lower among black women as compared to Whites. Adjustment for additional breast cancer risk factors reduced the difference to 17%. Thus, the higher observed incidence of ER+ tumors among white women can largely, but not fully, be explained by reproductive factors or other breast cancer risk factors such as alcohol intake and use of postmenopausal hormones.

Researchers have suggested several reasons why white women have the highest incidence of breast cancer of any racial/ethnic group in the United States; possible reasons include differences in reproductive patterns (particularly age at first birth), use of hormone supplements, and utilization of mammography (21). We found that black women did have more favorable reproductive patterns with respect to risk of ER+ breast cancer, and that this explained some of the difference in incidence between the two groups. Postmenopausal hormone use was also considerably higher among Whites than Blacks and contributed to higher incidence among white women. Nevertheless, some of the racial variation remained unexplained. Similarly, the Women's Health Initiative showed that adjustment for the elements of the Gail model plus other known risk factors attenuated differences in total breast cancer incidence between black and white women, but did not fully account for variation (22). Differences in mammography, which tends to detect tumors that are small and slow-growing, are unlikely to explain our findings as utilization was high and was nearly identical across cohorts. For example, in the 2005 questionnaire cycle 91.3% of women aged 50-54 in NHSII reported having had a mammogram in the past two years

compared to 88.5% of women in BWHS. For younger women, age 45-49, 88.7% and 86.5% of NHSII and BWHS participants reported a mammogram in that two-year period.

It is of note that the gap in breast cancer incidence between white and black women has narrowed in recent years and while incidence of ER+ tumors is lower among black women relative to Whites, black women still have incidence rates that are higher than any non-White racial/ethnic group in the U.S. (23-25). There may be benefit to exploring the relationship between lifestyle and behavioral factors and incidence of ER+ tumors in other racial/ethnic groups such as Asian women who have lower incidence, but more similar reproductive patterns to Whites, or in Hispanic women who have a reproductive pattern similar to Blacks but have much lower incidence.

This analysis combined data from two separate cohorts, one largely comprised of white women and the other entirely black women. The nature of this comparison could lead to concerns about cross-cohort comparison validity due to measurement error and potential confounding. These concerns are mitigated by several factors. The two cohorts have very nearly identical data collection protocols and surveys, run on the same two-year data collection cycle and have similar procedures for case ascertainment and follow-up. Black women in NHS II were more similar to women in the BWHS than to white women in the NHSII. For example, while only 6% of white women in NHS II had a first birth before age 20, 33% of black women in BWHS and 22.1% of black women in NHS II did (data not shown). Both NHSII participants and BWHS participants have higher educational levels than the general population of U.S. women, with virtually all having some post-high school education and many having college degrees. Importantly, the distribution of ER status by race in our sample is consistent with nationally representative Surveillance, Epidemiology and End Results (SEER) data and other published reports (2, 3, 26, 27) and the age-adjusted incidence of ER+ tumors was 35% lower among black women as compared to white women. Chu and Anderson (2002) used SEER data to show that incidence of ER+ tumors was 36% lower among Blacks under age 50 and 41% lower among Blacks age 50-64 than Whites in those age groups. While absolute incidence rates of ER+ breast cancer in both cohorts are unknown, the comparison of incidence rate ratios before and after control of reproductive factors is valid. Thus, any change observed by accounting for reproductive factors and other breast cancer risk factors could not be attributed to this.

The present analysis has important strengths. With over 37,000 black women and 103,000 white women, it is one of the largest prospective analyses of breast cancer incidence by race and hormone receptor status. Both cohorts have strong and repeated measures of reproductive exposures and low levels of loss to follow-up. Ascertainment of ER status was good in both cohorts.

In summary, we found that reproductive factors attenuated differences in incidence of ER+ cancer between black and white women, but did not fully explain the variation.

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Figure 1.
Flow diagram of baseline study participant exclusions by cohort

Table I

Age-standardized baseline characteristics by cohort in the Nurses' Health Study II and Black Women's Health Study, 1995

Characteristic	Black women N=37,406	White women N=103,508
Mean age (SD)	39.0 (5.5)	40.2 (4.7)
Parity, %		
Nulliparous	27	21
1	25	16
2	28	38
3	20	25
Age at first birth ^I , %		
<20	33	6
20-24	33	30
25-29	22	43
30-34	9	17
35	3	4
Lactation ^I , %		
Never	56	19
< 6 months	23	16
6 months	20	65
Premenopausal, %	91	93
Age at menarche, %		
<12	28	24
12	28	30
13	24	27
14	19	18
Current body mass index, %		
<20	4	10
20-22.5	13	25
22.5-24	19	22
25-29	32	24
30	32	19
Weight change since age 18, %		
Lost > 2 kg	4	7
Stable ($\pm$ 2kg)	2	10
Gained 2-9 kg	20	34
Gained 10-19 kg	32	27
Gained 20kg	42	22
Alcohol consumption, %		

Characteristic	Black women N=37,406	White women N=103,508
<1 drink per week	73	56
1-6 drinks per week	20	35
7 drinks per week	6	9
Biopsy confirmed benign breast disease, %	11	13
OC use, %		
Never	19	15
< 5 years	18	20
5 years	64	65
Family history of breast cancer, %	7	6
Postmenopausal hormone use², %		
Never	27	9
Current	67	82
Past	7	9

Values are means(SD) or percentages and are standardized to the age distribution of the total study population

¹ Among parous women

² Among postmenopausal women. *Percentages of non-missing data;

Table 2

Characteristics of women diagnosed with estrogen receptor positive breast cancer in the Nurses' Health Study II and Black Women's Health Study

Characteristic	Black women Cases N=327 (%)	White women Cases N=1,179 (%)
Menopausal status		
Premenopausal	194 (71.3)	779 (72.3)
Postmenopausal	78 (28.7)	284 (26.7)
Mean age at diagnosis (SD)	48.3 (5.9)	48.6 (4.9)
Age at diagnosis (years)		
<40	22 (6.7)	48 (4.1)
40-44	71 (21.7)	227 (19.3)
45-49	97 (29.7)	418 (35.5)
50-54	88 (26.9)	370 (31.4)
55-60	49 (15.0)	116 (9.8)
Progesterone receptor status		
PR+	256 (79.3)	1008 (85.5)
PR-	67 (20.7)	171 (14.5)

*Numbers may not add to total due to missing data.

Table 3

Race and Risk of ER+ Breast Cancer among Women in the Black Women's Health Study and Nurses' Health Study II, 1995-2007

Characteristic	Races Combined N=1,506			Black N=327			White N=1,179		
	PT*	Cases	HR 95% CI	PT	Cases	HR 95% CI	PT	Cases	HR 95% CI
Model 1^a									
Race									
White	1,182,891	1,179	1.00						
Black	399,192	327	0.67 (0.53, 0.84)						
Model 2^b									
Race									
White	1,182,891	1,179	1.00						
Black	399,192	327	0.77 (0.61, 0.99)						
Parity									
Nulliparous	313,495	328	1.00	101,562	84	1.00	211,933	244	1.00
Parous	1,211,972	1,150	0.54 (0.40, 0.73)	294,698	241	0.54 (0.18, 1.58)	917,274	909	0.55 (0.40, 0.76)
Multiparity**									
Age at first birth (cont)	1,211,972	1,150	0.98 (0.92, 1.05)	294,698	241	0.95 (0.83, 1.09)	917,274	909	0.99 (0.92, 1.07)
Lactation*									
Never	313,264	300	1.00	157,771	116	1.00	155,493	184	1.00
<6 months	190,312	167	0.92 (0.76, 1.12)	67,751	66	1.34 (0.98, 1.83)	122,561	101	0.75 (0.59, 0.96)
6 months	607,711	623	1.02 (0.88, 1.20)	61,901	55	1.29 (0.91, 1.83)	545,810	568	0.92 (0.77, 1.10)
Model 3^c									
Race									
White	1,182,891	1,179	1.00						
Black	399,192	327	0.83 (0.70, 0.98)						
Parity									
Nulliparous	313,495	328	1.00	101,562	84	1.00	211,933	244	1.00
Parous	1,211,972	1,150	0.61 (0.45, 0.82)	44,506	32	0.59 (0.20, 1.77)	917,274	909	0.63 (0.45, 0.87)

Characteristic	Races Combined N=1,506			Black N=327			White N=1,179		
	PT*	Cases	HR 95% CI	PT	Cases	HR 95% CI	PT	Cases	HR 95% CI
Multiparity (cont) *	1,211,972	1,150	1.00 (0.93, 1.07)	52,539	54	0.96 (0.83, 1.10)	917,274	909	1.01 (0.93, 1.09)
Age at first birth (cont)	1,211,972	1,150	1.04 (1.03, 1.05)	137,776	88	1.04 (1.01, 1.06)	917,274	909	1.04 (1.03, 1.06)
Lactation *									
Never	313,264	300	1.00	157,771	116	1.00	155,493	184	1.00
<6 months	190,312	167	0.85 (0.70, 1.03)	67,751	66	1.31 (0.96, 1.80)	122,561	101	0.76 (0.60, 0.98)
6 months	607,711	623	0.95 (0.81, 1.10)	61,901	55	1.27 (0.90, 1.80)	545,810	568	0.90 (0.76, 1.07)

^aModel 1: adjusted for age and time

^bModel 2: adjusted for a and age at first birth, parity, lactation, age at menarche, menopausal status, age at menopause

^cModel 3: adjusted for b and first degree family history, BMI at age 18, weight change since age 18, history of benign breast disease, alcohol consumption, OC use, and postmenopausal hormone use.

* PT: person-time

** Effect of each additional pregnancy among parous women

Table 4

Race and Risk of ER+ Breast Cancer among Premenopausal Women in the Black Women's Health Study and Nurses' Health Study II, 1995-2007

Characteristic	Races Combined N=973	Cases	HR 95% CI	Black N=194	Cases	HR 95% CI	White N=779	Cases	HR 95% CI
Model 1^a									
Race									
White	793,096	779	1.00						
Black	270,144	194	0.59 (0.44, 0.80)						
Model 2^b									
Race									
White	793,096	779							
Black	270,144	194	0.63 (0.46, 0.85)						
Parity									
Nulliparous	214,572	201	1.00	74,227	48	1.00	140,345	153	1.00
Parous	828,465	753	0.64 (0.43, 0.94)	195,015	145	0.86 (0.20, 3.78)	633,449	608	0.58 (0.38, 0.87)
Multiparity (cont)*	828,465	753	0.96 (0.89, 1.05)	195,015	145	0.85 (0.70, 1.04)	633,449	608	0.99 (0.90, 1.09)
Age at first birth (cont)	828,465	753	1.04 (1.02, 1.06)	195,015	145	1.02 (0.99, 1.05)	633,449	608	1.04 (1.02, 1.06)
Lactation									
Never	191,601	173	1.00	96,994	67	1.00	94,607	106	1.00
<6 months	130,583	113	0.94 (0.74, 1.19)	47,823	44	1.35 (0.91, 2.00)	82,761	69	0.78 (0.58, 1.07)
6 months	450,104	433	0.97 (0.80, 1.18)	46,774	32	1.01 (0.64, 1.59)	403,330	401	0.92 (0.73, 1.14)
Model 3^c									
Race									
White	793,096	779	1.00						
Black	270,144	194	0.78 (0.65, 0.93)						
Parity									
Nulliparous	214,572	201	1.00	74,227	48	1.00	140,345	153	1.00
Parous	828,465	753	0.63 (0.42, 0.92)	195,015	145	0.78 (0.17, 3.53)	633,449	608	0.60 (0.39, 0.91)

	Races Combined N=973			Black N=194		White N=779		
Multiparity (cont) *	828,465	753	0.97 (0.89, 1.05)	195,015	145	633,449	608	1.00 (0.91, 1.10)
Age at first birth (cont)	828,465	753	1.04 (1.02, 1.05)	195,015	145	633,449	608	1.04 (1.02, 1.06)
Lactation *								
Never	191,601	173	1.00	96,994	67	94,607	106	1.00
<6 months	130,583	113	0.86 (0.67, 1.09)	47,823	44	82,761	69	0.79 (0.58, 1.07)
6 months	450,104	433	0.90 (0.74, 1.09)	46,774	32	403,330	401	0.89 (0.71, 1.11)

^aModel 1 :adjusted for age and time

^bModel 2:adjusted for a and age at first birth, parity, lactation, and age at menarche

^cModel 3: adjusted for b and first degree family history, BMI at age 18, weight change since age 18, history of benign breast disease, alcohol consumption, and OC use.

* PT: person-time

** Effect of each additional pregnancy among parous women