Alcohol consumption and breast cancer risk among postmenopausal women following the cessation of hormone therapy use: the California Teachers Study

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Abstract

Background—Alcohol consumption increases breast cancer risk, but its effect may be modified by hormone therapy (HT) use, such that exposure to both may be synergistic. Because many women stopped taking HT after mid-2002, it is important to quantify risks associated with alcohol consumption in the context of HT cessation, as these risks may be more relevant to cancer prevention efforts today.

Methods—Among 40,680 eligible postmenopausal California Teachers Study cohort participants, 660 were diagnosed with invasive breast cancer before 2010. Multivariate Cox proportional hazards regression models were used to estimate relative risks (RR) and 95% confidence intervals (CI).

Results—Increased breast cancer risk associated with alcohol consumption was observed among postmenopausal women who were current HT users (RR=1.60, 95% CI: 1.13–2.26 and RR=2.11, 95% CI: 1.41–3.15 for <20 and 20 g/d of alcohol), with risks being similar by HT preparation. Alcohol did not increase risk among women who had stopped using HT within 3 years or 3–4 years before completing the follow-up questionnaire or in the more distant past. Results were similar for ER+ and ER+PR+ tumors; while power was limited, no increase in risk was observed for ER- tumors.

Conclusions—Following the cessation of HT use, alcohol consumption is not significantly associated with breast cancer risk, although a non-significant increased risk was observed among women who never used HT.

Impact—Our findings confirm that concurrent exposure to HT and alcohol has a substantial adverse impact on breast cancer risk. However, after HT cessation, this risk is reduced.

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Keywords

breast cancer; alcohol; hormone therapy; cessation; epidemiology

INTRODUCTION

In a recent meta-analysis of the association between alcohol consumption and breast cancer risk, an international expert panel found convincing evidence that women who consume greater amounts of alcohol are at increased risk of breast cancer (1). However, substantial heterogeneity between studies was observed and the report did not specifically address the joint effects of alcohol and menopausal hormone therapy (HT) use. Results from the California Teachers Study (CTS) cohort (2) and some (3–7), but not all (8–10), previous studies have suggested that alcohol may increase breast cancer risk only among women who also used HT but not among those who did not. Only a few studies have distinguished never and former HT users when examining modification of the alcohol-breast cancer association. As with the effects of current HT use, results for former use are also mixed; some studies report a non-significant increase in risk of about 20%–30% (4, 8), while others have found no increase in risk (2, 7). On the other hand, a pooled analysis suggested a significant 9% increase in risk per 10g/d of alcohol, a result similar to that seen among never and current HT users (9). Understanding the joint association between alcohol consumption, HT use, and breast cancer risk has increasingly important implications in light of the substantial decline in HT use after mid-2002 when the findings from the Women's Health Initiative (WHI) reported adverse effects of some HT (11–13). In the CTS, the percent of postmenopausal women using HT has fallen from 60% at baseline, in 1995–1996, to 20% in our 10-year follow-up in 2005–2006 (14). Thus, we evaluate the timely question of whether and when the cessation of HT use among CTS participants affects the association between alcohol consumption and breast cancer risk.

MATERIALS AND METHODS

The CTS includes 133,479 women who were active or retired teachers or administrators participating in the California State Teachers Retirement System in 1995–96 when the cohort was established (15). In 2005–06, a 10-year follow-up (hereafter referred to simply as follow-up) questionnaire was mailed to cohort members; this was the fourth questionnaire completed by participants. Both the baseline and follow-up questionnaires covered a wide variety of issues related to breast cancer risk and women's health, including alcohol consumption and hormone therapy use.

The CTS study has been approved by the Institutional Review Boards of the Cancer Prevention Institute of California, the State of California, the University of California, Irvine, the University of Southern California, and the City of Hope.

Assessment of Alcohol Consumption

On the follow-up questionnaire women were asked how often they drank beer, white wine or champagne, red wine, and cocktails or liquor. Response categories ranged from never to 5 or more servings per day. They were also asked how much they consumed in each serving based on photos of different size glasses ranging in volume from 5 to 16 ounces for wine and cocktails and from 8 to 48 ounces for beer. For beer, portion size could also be reported as the number of cans per serving, ranging from ½ to 4. Grams of alcohol per fluid ounce of beverage were assigned as 1.1 for beer, 3.17 for wine, and 10.0 for liquor. When calculating alcohol intake from liquor and cocktails, we assigned each drink 1 shot of alcohol (1.5 ounces) regardless of the portion size reported assuming that a larger portion size indicated

more non-alcoholic components. Daily intake of grams of alcohol was calculated for each woman. In analyses we used the following categories of exposure based on our previous findings for the association between alcohol and breast cancer risk (2): non-drinkers (during the past year), drinkers consuming <20 grams of total alcohol per day, and drinkers consuming   20 g/d; the latter category being equivalent to approximately two or more drinks per day.

Assessment of Hormone Therapy Use

On the follow-up questionnaire women were asked whether they had used HT (any type) in the last five years and if so, the total months of HT use during that time period (with response categories: 1–6, 7–12, 13–24, 25–36, 37–48, or 49–60 months). They were also asked if they had used HT in the past month. HT use was also assessed on the 5-year follow-up questionnaire and the baseline questionnaire. HT use at these three time points was used to define five subgroups of women with different HT use patterns defined in relation to status at the time the 10-year follow-up questionnaire was completed: currently using HT at follow-up, stopped HT use in the past three years, stopped HT use 3–4 years ago, stopped HT use more than 5 years ago, or never used HT.

Follow-up for Events

The CTS cohort is followed for cancer diagnoses, death, and changes of address. Annual linkage between the California Cancer Registry (CCR) and the cohort membership is used to identify incident cancer cases. The CCR is a population-based cancer registry that is anchored in legislation that mandates reporting. It covers the entire state of California, has interstate agreements with 13 other states for case-sharing purposes, is estimated to be over 99% complete (16), and is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Thus, follow-up for cancer outcomes is virtually complete as long as the cohort members reside in California. ER and PR results were obtained from the CCR; a previous expert review, conducted for breast cancers diagnosed as part of the SEER programs in Los Angeles and Detroit, found high concordance with hormone receptor classification from registry data, which is obtained from the individual hospital pathologists (17).

California and national mortality files are used to ascertain date and cause of death. Changes of address are obtained by annual mailings, responses from participants, and routine record linkages with multiple sources, including the US Postal Service National Change of Address database.

Study population

For purposes of the present analyses, we excluded women who at baseline: were not residing in California (n=8,867), had never had menstrual periods (n=62), or had a prior (n=6,215) or an unknown (n=135) history of breast cancer; and who prior to the 10-year follow-up questionnaire being mailed (for non-responders) or completed (for responders): had died (n=8,644), refused further participation in the CTS (n=924), permanently (for more than 4 months) moved out of California (n=8,362), were age 85 years or older (n=5,131), or had developed breast cancer (n=3,941). Among the remaining 91,198 cohort participants, 61,537 (67%) completed the follow-up questionnaire. From these women, we further excluded those who returned the questionnaire in 2008 (n=16), who did not complete or incorrectly completed the alcohol section of the follow-up questionnaire (n=2,100), or who completed the short-form which did not include questions on alcohol consumption (n=6,617), or who were not postmenopausal at the time of completing the follow-up questionnaire (n=12,124). Among the 40,680 women eligible for this analysis, 660 were diagnosed with invasive breast cancer after completing the follow-up questionnaire and before January 1, 2010. Of

these 660 women, 530 (80%) had estrogen receptor positive (ER+) tumors, 94 (14%) had ER negative (ER-) tumors, and 36 (5%) were missing information on ER status. Progesterone receptor (PR) data were available for 92% of these 660 women.

Data Analysis

Follow-up time was calculated as the number of days from the date the follow-up questionnaire was completed until the first of the following possible outcomes: date of invasive breast cancer diagnosis, date of *in-situ* breast cancer diagnosis, date of death, date the woman moved out of California (for at least four months), or December 31, 2009. Women diagnosed with *in-situ* breast cancer (n=198) contributed person-days to the analysis only up to the date of diagnosis, at which time they were censored from the analysis. For analyses by tumor subtype, women whose ER status was unknown were excluded from the analyses.

Relative risks (RR; hazard rate ratios) and 95% confidence intervals (CI) were estimated using Cox regression models with age (in days) used as the time-scale and stratification by age (in years) at follow-up. Relative risks were adjusted for the following potential confounders: age at first full-term pregnancy (nulliparous, age <25 years, age 25 years, missing), a family history of breast cancer in a first degree relative (yes, no, missing/ adopted), body mass index (kg/m^2; <25, 25–29.9, 30, missing), and average long-term (from high school through age 54 years) physical inactivity (hours per week of moderate activity; <1 (inactive), 1, missing). All covariates were assessed at baseline except body mass index, which, along with updated alcohol consumption and HT use, were assessed at follow-up. Effect modification under a multiplicative model was formally assessed by computing likelihood ratio tests based on cross-product terms in the Cox regression models.

RESULTS

Table 1 presents the characteristics of the women included in the current analysis. In addition, to assess how representative these women were of the cohort, we compared these women to those meeting similar eligibility criteria but who not included in the current analysis, i.e., postmenopausal women completing the short-version of the follow-up questionnaire and women who did not respond to the follow-up questionnaire but were age 50 years or older at the time it was mailed (as a proxy indicator of postmenopausal status). Both groups of women were similar on the factors included in this analysis as well as alcohol consumption at baseline.

The impact of HT use on breast cancer risk in this sub-cohort was similar to that observed in the total cohort (18): compared to never HT users, past users were not at increased risk (RR=1.06, 95% CI: 0.85–1.33), while current users were (RR=1.63, 95% CI: 1.29–2.06). Among past users, risk did not vary substantially by time since last use (defined as <3, 3–4, or 5 years). Among current users, risk associated with ET use (RR=1.43, 95% CI: 1.09–1.88) was statistically significant but lower than that associated with EPT use (RR=2.11, 95% CI: 1.53–2.91).

Alcohol consumption of <20 g/d at follow-up was not associated with breast cancer risk overall or when stratified by time since HT cessation; with the exception of an increase in risk among current HT users (RR=1.60, 95% CI: 1.13–2.26). While alcohol consumption of 20 g/d was associated with an overall increased risk of breast cancer (RR=1.26, 95% CI: 1.02–1.56; Table 2), this risk was limited to women who were current HT users (RR=2.11, 95% CI: 1.41–315 compared to non-drinkers who never used HT) with a statistically non-significant elevation observed among women who never used HT (RR=1.52, 95% CI: 0.94–2.47). Women who had stopped using HT before follow-up were not at increased risk even

when consuming 20 g/d of alcohol, regardless of whether they had stopped taking HT recently (within three and 3–4 years prior to follow-up) or in the more distant past. The interaction between alcohol consumption and HT use, however, was not statistically significant ($p_{interaction}$=0.38). When splitting women who were non-drinkers at follow-up into never drinkers and former drinkers, the results were very similar (data not shown).

Since some previous studies have shown that the effects of alcohol are stronger for ER+ and ER+PR+ breast tumors (6, 7), we examined the joint effects of alcohol and HT use and cessation for specific hormone receptor subtypes. Table 3 presents the results for ER+ tumors and divides current HT users into those who used estrogen-only (ET) in the previous five years and those who used combination estrogen-progesterone (EPT); women reporting current HT use but with missing data on HT type (2%), who used progestin-only (<1%), or who indicated using both ET and EPT during the previous five years (18%) were excluded from this analysis. Compared to women who never used HT and did not consume alcohol, those who consumed 20 or more g/d of alcohol and were current HT users were at significantly increased risk of ER+ breast cancer (RR=2.03, 95% CI: 1.16–3.55 and RR=4.09, 95% CI: 2.29–7.30 for ET and EPT users, respectively); however, no increase in risk was observed for alcohol consumption of 20 g/d among those who had ceased using HT (RR=1.20, 95% CI: 0.78–1.84; $p_{interaction}$=0.40). Given the breast cancer risk associated with HT use alone (RR=1.05, 95% CI: 0.61–1.79 and RR=1.91, 95% CI: 1.01–3.59 for ET and EPT use, respectively, among non-drinkers), the effects associated with the addition of 20 g/d of alcohol are similar, and approximately two-fold in magnitude, for ET and EPT users. Alcohol consumption of 20 g/d among never HT users was slightly lower (RR=1.61, 95% CI: 0.93–2.77). Results were similar for ER+PR+ breast cancer (n=421; data not shown). Statistical power was limited for examining risk for ER- breast cancer; however, no increase in risk was observed (RR=0.65, 95% CI: 0.17–2.45 for alcohol of 20 g/d among current HT users compared to non-drinkers who never used HT).

DISCUSSION

We found that alcohol consumption significantly increased the risk of breast cancer among women who were concurrently using HT. Regardless of the type of HT used, HT plus alcohol consumption of 20 g/d was associated with an approximately 2-fold increase in risk over HT use alone. Former HT users, including women who stopped taking HT less than three years before the follow-up questionnaire, who consumed 20 g/d of alcohol were not at increased risk for breast cancer. However, a non-significant increase in risk with this level of alcohol consumption was observed among never HT users. While statistical power to detect differences by tumor type was limited, the effects for ER+ and ER+PR+ tumors were similar to those observed overall and no indication of increased risk for ER- tumors was seen.

Though not all studies (including two large pooling projects) have observed different effects of alcohol on breast cancer risk according to HT use (9, 10, 19), a number of studies, including more recently published results, have found some indication that differences may exist (2, 4, 5, 7, 8, 20). Only a few studies have examined the effects of alcohol among past HT users (2, 4, 7, 8). In our previous analysis of the CTS cohort, we observed no increased risk associated with alcohol use among former users of estrogen-only therapy (ET) but observed a significant increased risk among current ET users (2). Similar null associations among former HT (type not specified) users were observed in the National Institutes of Health-American Association for Retired Persons (NIH-AARP) Study, the Nurses' Health Study, and the Women's Health Study cohorts (4, 7, 8). However, we believe that this is the first study to examine the effects of alcohol intake by specific gradients of time since HT cessation rather than combining all "former" users into a single group. The mass cessation of

HT use following the publication of the WHI findings in mid-2002 provided a natural experiment upon which ongoing cohort studies could capitalize. In the CTS, approximately 60% of postmenopausal participants were HT users at baseline but about two-thirds of these women had stopped taking HT by the time of the 2005–2006 follow-up questionnaire. Our findings suggest that the increased risk associated with the consumption of 20 g/d of alcohol diminishes within the first three years following HT cessation. Unfortunately, the small number of cases diagnosed within the first three years following HT cessation does not allow us to determine more precisely how quickly the risk associated with alcohol consumption disappears.

Unlike the results of the WHI randomized trial (21), ET is associated with increased breast cancer risk in the CTS (18), as well as several other studies (22–24), albeit to a lesser extent than EPT use. Reasons for this difference may be related to population differences in prior hysterectomy (i.e., the WHI prescribed ET only to women with a hysterectomy while, in the CTS about 20% of ET users had not had a hysterectomy (18)) or prior patterns of HT use (25). Further, in the CTS, risks associated with both ET use and alcohol consumption are greater among women with lower body mass index (BMI) (2, 18) and, the effects of ET use on breast cancer risk increased with duration of use (18). On average, the CTS participants have lower overall BMI and longer duration of ET use than other populations (15, 18). Thus, the distribution of these lifestyle factors may contribute to the overall association we observed between alcohol consumption, ET use, and breast cancer risk. Previous studies addressing the alcohol-breast cancer relationship have not examined effects specific to HT preparation (4, 7, 8).

Alcohol likely affects breast cancer risk, at least in part, through its influence on steroid hormones. Consistent with our findings, a number of studies, including two meta-analyses, have shown that alcohol increases the risk of ER+ and ER+PR+, but not ER- or triple negative, breast cancers (6, 7, 26, 27). Alcohol has been shown to increase ER expression and ER-α activity *in vitro* (28). It has also been associated with increased production and reduced metabolism and clearance of estradiol and other steroid hormones, and with the stimulation of P450-mediated conversion of pro-carcinogens and the inhibition of phase II detoxification of carcinogens and DNA repair (28–31). In the absence of HT, alcohol may result in a modest increase in serum estrogens or androgens (28). However, Ginsburg et al. (30) found that estradiol levels among HT users who drank alcohol were three times higher than those who did not drink alcohol, suggesting that the modest impact of alcohol on estradiol levels may have a greater impact when combined with HT due to other metabolic alterations (28). Consistent with this latter supposition, our findings suggest a minimal impact of alcohol in the absence of concurrent HT use but a substantial alteration in risk when alcohol and HT are combined. However, the statistically non-significant, elevation in risk associated with alcohol consumption of 20 g/d among women who never used HT suggests that this may be a heterogeneous group which includes women who are particularly susceptible to the adverse effects of alcohol. Further mechanistic research, evaluation of gene-alcohol interactions and breast cancer risk among women who have not used HT, and additional investigation of the temporal impact of mass HT cessation in other cohorts or pooled cohort data, particularly for finer subdivisions of the period within five years of cessation, will help elucidate these relationships.

The major strengths of this analysis include the high reliability and validity of alcohol measurements within the cohort (32) and the ability of cohort studies to capture ongoing changes in population exposures while minimizing recall biases. Potential limitations include non-response to the 10-year follow-up questionnaire, exposure misclassification, limited statistical power for some analyses, and lack of generalizability to very high levels of alcohol consumption. While response to the detailed 10-year follow-up questionnaire was

only 67%, as seen in Table 1, the sub-cohort evaluated here was similar to the comparable sub-cohort who did not complete the full 10-year follow-up questionnaire, suggesting minimal bias from non-response. Misclassification of exposure is always of concern when assessing dietary factors using a food-frequency questionnaire (FFQ) approach. However, the reproducibility and validity of alcohol intake in our cohort is quite high: r=0.87 for reproducibility and r~0.75 for alcohol compared to 24-hour recalls for our baseline assessment (32). Stability of alcohol intake between our baseline and 10-year follow-up questionnaire was moderate [r=0.50 for absolute consumption (g/d), 69% absolute agreement for categories of intake (never, <20, and 20 g/d) with equal numbers of women reducing and increasing their intake, and kappa=0.47]. The follow-up questionnaire asked about the number of months that HT had been used in the last five years and provided response categories that included several years. We used the median number of years in each category to calculate when HT use ceased, thus, some misclassification of the time since cessation may have occurred. In addition, we had a limited number of breast cancer cases subsequently diagnosed among women who ceased using HT during the period <3 year before completing the follow-up questionnaire, thus, it was not possible to adequately evaluate risk for finer gradations of time since HT cessation. Thus, it remains unclear whether the greater risk of breast cancer associated with alcohol consumption of 20 g/d persists for some short time following HT cessation or diminishes very quickly. Therefore, in terms of public health recommendations, we would conservatively suggest that alcohol consumption remain limited to one drink per day for up to several years following HT cessation, until more data for this early period is obtained. The group of women who consumed 20 g/d of alcohol included primarily moderate drinkers, with only 5% of the cohort consuming the equivalent of four or more drinks per day. Thus, our conclusions should be interpreted in this context and not assumed to apply to greater amounts of alcohol consumption.

In summary, we observed that among current HT users, alcohol consumption substantially increased risk of ER+ tumors, the most common type of breast cancer. Among women who had ceased using HT, risk associated with two or more alcoholic drinks per day was not apparent; although a non-significant increased risk was observed among women who never used HT. Thus, our findings confirm that concurrent exposure to HT and alcohol has a substantial adverse impact on breast cancer risk. However, after HT cessation, the risk associated with moderate alcohol consumption is reduced.

Acknowledgments

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Table 1

Selected characteristics of the cohort included in the present analysis and women meeting similar eligibilty criteria but who did not complete the full 10-year follow-up questionnaire.

	Follow-up cohort		Non-participants	
	N	%	N	%
N	40,680	100%	25,165	100%
At baseline				
Age at first full-term pregnancy (yrs)				
<25 yrs	12,446	31%	7,311	29%
25–29	12,381	30%	7,453	30%
30	6,598	16%	4,377	17%
nulliparous	8,640	21%	5,544	22%
missing	615	2%	480	2%
Family history of breast cancer (1st degree relative)				
yes	5,203	13%	3,022	12%
no	34,372	84%	21,069	84%
missing/adopted	1,105	3%	1,074	4%
Average long-term physical activity (hrs/wk)				
<1 (inactive)	13,099	32%	8,755	35%
1	27,382	67%	16,208	64%
missing	199	1%	202	1%
Alcohol consumption (g/d)				
none	12,157	30%	7,980	32%
<20	23,685	58%	13,950	55%
20	3,457	9%	1,919	8%
missing	1,381	3%	1.316	5%
At 10-year follow-up				
Age (yrs)				
54	3,467	9%		
55–64	18,040	44%		
65–74	11,676	29%		
75–84	7,497	18%		
Body mass index (kg/m2)				
<25	20,379	50%		
25–29	12,369	30%		
30	7,516	18%		
missing	416	1%		
HT use				
current	9,249	23%		
stopped <5 yrs prior	10,112	25%		
stopped 5 yrs prior	10,788	27%		
never	9,342	23%		

	Follow-up cohort		Non-participants	
	N	**%**	**N**	**%**
missing	1,189	3%		
Alcohol consumption (g/d)				
none	14,894	37%		
<20	18,896	46%		
20	6,890	17%		

Table 2

Alcohol consumption at follow-up and breast cancer risk overall and by HT use in the CTS cohort.

Alcohol (g/d)	Person-years	Cases	RR[a]	95% CI	RR[b]	95% CI
All women						
non-drinker	56,085	233	1.0		1.0[c]	
<20	71,632	293	1.01	0.85–1.20	1.01	0.85–1.20
20	26,144	134	1.24	1.00–1.53	1.26	1.02–1.56
Never used HT						
non-drinker	14,267	50	1.0		1.0	
<20	15,858	40	0.77	0.50–1.16	0.78	0.51–1.18
20	5,160	25	1.47	0.91–2.38	1.52	0.94–2.47
Past HT use						
non-drinker	28,379	117	1.02	0.73–1.42	1.05	0.75–1.47
<20	36,889	145	0.98	0.71–1.36	1.03	0.74–1.43
20	13,826	58	1.04	0.71–1.52	1.10	0.75–1.62
Stopped HT 5 yrs[d]						
non-drinker	15,748	65	0.99	0.68–1.44	1.02	0.70–1.48
<20	17,859	82	1.11	0.78–1.59	1.16	0.81–1.66
20	6,814	30	1.05	0.66–1.66	1.11	0.70–1.76
Stopped HT 3–4 yrs[d]						
non-drinker	6,888	31	1.15	0.73–1.81	1.20	0.76–1.89
<20	10,843	36	0.87	0.57–1.34	0.91	0.59–1.40
20	4,007	15	0.97	0.54–1.74	1.04	0.58–1.86
Stopped HT <3 yrs[d]						
non-drinker	5,186	17	0.82	0.47–1.43	0.84	0.49–1.47
<20	7,435	26	0.87	0.54–1.41	0.93	0.57–1.49
20	2,748	11	1.00	0.52–1.92	1.06	0.55–2.04
Current HT use						
non-drinker	11,588	58	1.28	0.87–1.88	1.34	0.91–1.97
<20	17,031	98	1.50	1.06–2.12	1.60	1.13–2.26
20	6,486	50	1.96	1.32–2.91	2.11	1.41–3.15

[a] Age was the time-scale and analyses were stratified by age at follow-up.

[b] Adjusted for age at first full-term pregnancy/nulliparity, family history of breast cancer in a first degree relative, body mass index, and long-term physical inactivity; age was the time-scale and analyses were stratified by age at follow-up.

[c] Additionally adjusted for HT use.

[d] Time period is relative to completion of the 10-year follow-up questionnaire.

Table 3

Alcohol consumption at follow-up and risk of ER+ breast cancer risk by HT use and type in the CTS cohort.

				HT use										
	Never			Past			Current ET			Current EPT		
Alcohol (g/d)	Cases	RR[a]	95% CI	Cases	RR[a]	95% CI	Cases	RR[a]	95% CI	Cases	RR[a]	95% CI
non-drinker	39	1.0		91	1.05	0.72–1.54	21	1.05	0.61–1.79	13	1.91	1.01–3.59
<20	35	0.89	0.56–1.40	112	1.04	0.71–1.51	41	1.51	0.97–2.37	20	2.00	1.16–3.45
20	20	1.61	0.93–2.77	48	1.20	0.78–1.84	19	2.03	1.16–3.55	17	4.09	2.29–7.30

[a] Adjusted for age at first full-term pregnancy/nulliparity, family history of breast cancer in a first degree relative, body mass index, and long-term physical inactivity; age was the time-scale and analyses were stratified by age at follow-up.