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ARTICLE

Alcohol Intake Between Menarche and First Pregnancy: A Prospective Study of Breast Cancer Risk

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Background Adult alcohol consumption during the previous year is related to breast cancer risk. Breast tissue is particularly susceptible to carcinogens between menarche and first full-term pregnancy. No study has characterized the contribution of alcohol consumption during this interval to risks of proliferative benign breast disease (BBD) and breast cancer.

Methods We used data from 91 005 parous women in the Nurses' Health Study II who had no cancer history, completed questions on early alcohol consumption in 1989, and were followed through June 30, 2009, to analyze breast cancer risk. A subset of 60 093 women who had no history of BBD or cancer in 1991 and were followed through June 30, 2001, were included in the analysis of proliferative BBD. Relative risks (RRs) were estimated using Cox proportional hazard regression.

Results We identified 1609 breast cancer cases and 970 proliferative BBD cases confirmed by central histology review. Alcohol consumption between menarche and first pregnancy, adjusted for drinking after first pregnancy, was associated with risks of breast cancer (RR = 1.11 per 10 g/day intake; 95% confidence interval [CI] = 1.00 to 1.23) and proliferative BBD (RR = 1.16 per 10g/day intake; 95% CI = 1.02 to 1.32). Drinking after first pregnancy had a similar risk for breast cancer (RR = 1.09 per 10 g/day intake; 95% CI = 0.96 to 1.23) but not for BBD. The association between drinking before first pregnancy and breast neoplasia appeared to be stronger with longer menarche to first pregnancy intervals.

Conclusions Alcohol consumption before first pregnancy was consistently associated with increased risks of proliferative BBD and breast cancer.

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Alcohol is considered by the International Agency for Research on Cancer to be causally related to invasive breast cancer (hereafter called "breast cancer") (1), with a 7% to 10% increase in risk for each 10 g alcohol consumed daily by adult women (2–4). One mechanism may be alcohol-induced increases in circulating estrogens and subsequently epithelial cell proliferation (3). However, the risk attributable to alcohol intake during adolescence and early adulthood remains inconclusive (2,5–12).

Younger age at menarche and older age at first full-term pregnancy (hereafter called "pregnancy") are associated with increased risk for breast cancer (13–15). Breast tissue undergoes rapid cellular proliferation between these reproductive events, and risk accumulates most rapidly until the terminal differentiation that accompanies first pregnancy. First pregnancy has both a short-term adverse effect on risk and a long-term reduction in subsequent risk accumulation (16). The longer the interval between menarche and first pregnancy the greater is a woman's breast cancer risk (14,15,17). Therefore, menarche to first pregnancy represents a window of time when breast tissue is particularly vulnerable to carcinogenic stimuli (18). Alcohol consumption in late adolescence and early adulthood is associated with increased risk of proliferative benign breast disease (BBD), a known risk marker for breast cancer (19,20).

We therefore hypothesized that alcohol consumed before first pregnancy is associated with risks of both proliferative BBD and breast cancer, independent of drinking after first pregnancy. Such an association may be stronger when the menarche to first pregnancy interval is longer.

Methods

The Nurses' Health Study II (NHSII) was established in 1989 when 116 671 female registered nurses aged 25 to 44 years completed a mailed questionnaire about their medical history, reproductive history, and lifestyles. Follow-up questionnaires mailed biennially updated information on lifestyles, reproductive factors, and medical events. The overall response rate to each questionnaire through

2003 was 90% (20). NHSII participants provided implied consent with return of biennial questionnaires. This study was approved by the Human Subjects Committees at the Harvard School of Public Health and Brigham and Women's Hospital.

Alcohol Consumption

Participants were asked in 1989 about their alcohol consumption in four age periods (ages 15–17, 18–22, 23–30, and 31–40 years). Participants were asked about the total number of drinks of alcohol (including beer, wine, and liquor together) consumed at different ages, with nine response categories ranging from "none or <1/month" to "40+/week." One drink was defined as one bottle/can of beer, a 4-ounce glass of wine, or a shot of liquor. The estimated content of ethanol per alcoholic drink was 12.0 g (19).

Alcohol consumption over the previous year was asked separately for beer, for wine, and for liquor in the nine categories ranging from "none or <1/month" to "40+/week." Total amounts of alcohol consumed in the previous year were calculated based on the equivalents of 12.8 g for regular beer, 11.0 g for wine, and 14.0 g for liquor (19). Current drinking was updated in 1991, 1995, 1999, and 2003. During the follow-up, participants were asked about their alcohol consumption separately for regular and light beer, red and white wine, and liquor. The estimated ethanol content of a serving of light beer was 11.3 g (21).

Cumulative average alcohol intake, a measure of intensity of drinking, between menarche and first pregnancy (of ≥6 months gestation) was calculated by multiplying drinking (grams per day) in each individual age period before first pregnancy by the length of the corresponding period, summing the contributions from each age period, and dividing by the interval length (years). For example, for a woman who had menarche at age 15 years and first pregnancy at age 25 years, cumulative drinking was obtained by summing alcohol consumed at three different ages (ages 15–17 years, 18–22 years, and 23–30 years) that were separately adjusted for the proportions of the corresponding individual age periods in her total menarche to first pregnancy duration of 10 years. Because alcohol consumption before age 15 years was not collected, cumulative drinking from age 15 onward was calculated if menarche occurred before age 15 years.

We also calculated cumulative average alcohol consumption between first pregnancy and menopause (or current age for premenopausal women) in a similar manner to examine whether the association with alcohol consumption before first pregnancy is independent of drinking after first pregnancy. Similarly, estimates of cumulative average drinking after first pregnancy were updated during the follow-up until menopause.

Study Sample for Analysis

Among 116 671 participants in the original cohort, 3929 were excluded because of lack of data on age at menarche, parity, age at first pregnancy, or alcohol consumption at baseline and during four age periods—the variables that were used to estimate cumulative drinking between menarche and first pregnancy. We also excluded women who developed cancer before 1989 (n = 1004) and women who had never carried a pregnancy achieving at least 6 months of gestation at baseline and during the follow-up (n = 20 733), leaving 91 005 participants included in the analysis of breast cancer risk.

Because biopsy specimens were reviewed for women who reported a first diagnosis of biopsy-confirmed BBD during the previous 2 years on the 1993 to 2001 questionnaires, the analytic period for proliferative BBD was from 1991 to 2001. Among the 91 005 participants eligible for the analysis of breast cancer risk, 30 912 were excluded from the analysis of proliferative BBD because they reported a prior history of BBD (n = 29 496) on the 1989 or 1991 questionnaires, died or developed cancer before 1991 (n = 261), their biopsy date was before the return date of the 1991 questionnaire (n = 40), or their parity was missing in 1991 (n = 1115). Therefore, 60 093 women were included in the analysis of proliferative BBD.

Breast Cancer Cases

Incident breast cancer cases were ascertained on biennial follow-up questionnaires or by a search of the National Death Index. For self-reported breast cancer cases, permission to review medical records was requested. A review of pathology reports, which were obtained for 92% of the self-reported diagnoses, confirmed 99% of self-reported breast cancers (21). Carcinoma in situ was excluded from the analysis. Estrogen receptor (ER) and progesterone receptor (PR) status were abstracted from pathology reports.

Biopsy-Confirmed Proliferative BBD

Slides from benign breast biopsies were reviewed by one of three pathologists (L. C. Collins, S. J. Schnitt, J. L. Connolly) who were blinded to participants' exposures. BBD was classified according to the criteria of Dupont and Page (22) into one of three categories: nonproliferative, proliferative without atypia, and atypical hyperplasia. Among 3273 participants reporting a first diagnosis of biopsy-confirmed BBD on the 1993 to 2001 questionnaires, breast biopsy specimens were reviewed for 2120 women, and 2056 BBD cases were confirmed (20). Given that proliferative BBD is an established predictor of breast cancer, the analysis of BBD risk was restricted to 1348 proliferative BBD cases with or without atypia (20).

Statistical Analyses

For the analysis of breast cancer risk, participants contributed person-time from the return date of the 1989 questionnaire until the date of diagnosis, date of death, date of drop-out, date of self-reported cancer other than nonmelanoma skin cancer, or June 2009, whichever came first. Women who developed any type of cancer (except nonmelanoma skin cancer) were censored at the time of their diagnosis. We used Cox proportional hazards models to compute relative risks (RRs) and 95% confidence intervals (CIs). Assumptions of proportionality for Cox models were confirmed based on scaled Schoenfeld residuals. The models were controlled for established risk factors of breast cancer, including age (continuous), questionnaire year (continuous), current body mass index (quintiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or unknown), average body size between ages 5 and 10 years (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, ≥5, or unknown), family history of breast cancer in mother or sister(s) (yes or no), postmenopausal hormone use (never use, ever use, or unknown), total duration of breastfeeding (0, 0.1–11 months, ≥12 months, or unknown), and parity and age at first pregnancy (nulliparous; 1–2 pregnancies, age at first pregnancy <25 years; 1–2 pregnancies, age at first

pregnancy 25–29 years; 1–2 pregnancies, age at first pregnancy ≥30 years; ≥3 pregnancies, age at first pregnancy <25 years; ≥3 pregnancies, age at first pregnancy 25–29 years; ≥3 pregnancies, age at first pregnancy ≥30 years, or unknown). Age, body mass index, menopausal status, postmenopausal hormone use, total duration of breastfeeding, parity, and age at first pregnancy were updated in each questionnaire cycle. Family history of breast cancer was initially asked on the 1989 questionnaire and was updated in 1997. We also stratified the analysis of cumulative drinking before first pregnancy by the median menarche to first pregnancy interval.

Participants contributed person-time to the analysis of BBD from the return date of the 1991 questionnaire until the date of diagnosis, date of death, date of drop-out, date of self-reported cancer other than nonmelanoma skin cancer, or June 2001, whichever came first. The multivariable analyses were adjusted for the covariables as described above.

Tests for trend were performed by using alcohol consumption as a continuous variable in the multivariable model. Interactions were assessed by entering cross-product terms in multivariable-adjusted models. The statistical significance of an interaction term was evaluated by using the likelihood ratio test. Because two alcohol consumption variables were assessed in the same cohort of women, we computed Wald statistics to compare cumulative drinking before first pregnancy with after first pregnancy regarding their relative risks of breast cancer and proliferative BBD. To determine whether alcohol intake before first pregnancy is differentially associated with hormone receptor–defined tumor subtypes, the Cox proportional hazards model was used with different subtypes treated as competing risks (23). Specifically, we estimated the relative risks of tumor subtypes using the approach described by Lunn and McNeil (24) and computed the Wald statistic to test for heterogeneity. We did not stratify all analyses by race/ethnicity because 96% of the participants were white. All statistical analyses were performed by SAS (version 9.1; SAS Institute, Cary, NC). *P* values less than or equal to .05 were considered statistically significant, and all statistical tests were two-sided.

Results

Among 91 005 women eligible for the analysis of breast cancer risk, 20.4% did not drink alcohol between menarche and first pregnancy, and 3.8% reported moderate to high alcohol consumption (≥15 g/day). Compared with nondrinkers, women who drank alcohol between menarche and first pregnancy were younger (Table 1). After adjustment for age, drinkers reported an older age at first pregnancy and were more likely to have a first-degree family history of breast cancer. Cumulative average alcohol consumption between menarche and first pregnancy was moderately correlated with both current drinking at baseline (Pearson correlation coefficient $r = 0.32$; $P < .001$) and cumulative average drinking since first pregnancy ($r = 0.59$; $P < .001$).

Breast Cancer

We identified 1609 breast cancer cases between 1989 and 2009. Cumulative average alcohol consumption between menarche and first pregnancy was associated with increased risk for breast cancer (RR = 1.13 per 10 g/day [approximately 6 drinks/week] intake; 95% CI = 1.03 to 1.24) as was alcohol intake after first pregnancy (RR = 1.11 per 10 g/day intake; 95% CI = 0.99 to 1.24) (Table 2). Age-adjusted incidence rates were 197 cases per 100 000 person-years among women who had at least 15 g/day alcohol intake before first pregnancy and 144 cases per 100 000 person-years among nondrinkers before first pregnancy. Age-adjusted

Table 1. Characteristics* of parous women (n = 91 005) aged 25 to 44 years in 1989, according to cumulative average alcohol consumption between menarche and first full-term pregnancy†, Nurses' Health Study II

Characteristic	Cumulative average alcohol intake, g/day			
	0	0.1–4.9	5.0–14.9	≥15.0
No. of participants	18 555	50 513	18 485	3452
Age at baseline, mean (SD), y	35.5 (4.6)	34.5 (4.7)	33.2 (4.5)	32.7 (4.5)
Age at menarche, mean (SD), y	12.3 (1.4)	12.4 (1.4)	12.5 (1.4)	12.5 (1.5)
Body mass index at baseline, mean (SD), kg/m^2	24.3 (5.1)	23.9 (4.7)	23.8 (4.6)	24.6 (5.3)
Average body size between ages 5 and 10 y‡, mean (SD)	2.5 (1.2)	2.6 (1.2)	2.6 (1.2)	2.7 (1.3)
Premenopausal at baseline, %	97	98	98	97
Family history of breast cancer in mother or sister(s) at baseline, %	5	6	6	7
Current alcohol intake at baseline, mean (SD), g/day	0.8 (3.4)	2.3 (4.4)	5.1 (6.9)	8.5 (13.7)
No. of full-term pregnancies, mean (SD)	2.4 (1.0)	2.3 (0.9)	2.2 (0.9)	2.2 (0.9)
Age at first full-term pregnancy, mean (SD), y	24.5 (4.6)	26.8 (4.5)	27.6 (4.8)	27.8 (5.0)
Interval between menarche and first full-term pregnancy, mean (SD), y	9.4 (4.6)	11.8 (4.5)	12.5 (4.8)	12.7 (5.0)
Total duration of breastfeeding, %				
None	22	24	25	27
0.1–11 months	36	35	33	31
≥12 months	25	27	29	29
Missing	17	14	13	14
Cumulative alcohol intake after first pregnancy at baseline, mean (SD), g/day	0.6 (2.3)	2.2 (3.1)	6.1 (5.7)	13.1 (11.7)

* All variables except for age are age-standardized. SD = standard deviation.

† Full-term pregnancy was defined as a pregnancy achieving at least 6 months of gestation.

‡ Childhood body size was estimated by averaging each participant's somatograms (1–9 scale) at ages 5 and 10 (25).

Table 2. Timing of alcohol consumption and risks of breast cancer and proliferative benign breast disease (BBD) among parous women*, Nurses' Health Study II

	Breast cancer			Proliferative BBD†		
Intake category	**Cases/ person-years**	**RR (95% CI)‡**	**RR (95% CI)§**	**Cases/ person-years**	**RR (95% CI)‡**	**RR (95% CI)§**
Cumulative average alcohol intake between menarche and first full-term pregnancy, g/day						
0	323/343 304	1.00 (referent)	1.00 (referent)	179/112 441	1.00 (referent)	1.00 (referent)
0.1–4.9	914/914 820	1.08 (0.94 to 1.23)	1.05 (0.90 to 1.22)	549/297 669	1.22 (1.02 to 1.46)	1.15 (0.94 to 1.41)
5.0–14.9	307/326 953	1.11 (0.94 to 1.32)	1.07 (0.89 to 1.29)	204/110 663	1.31 (1.06 to 1.62)	1.26 (0.99 to 1.62)
≥15.0	65/60 582	1.41 (1.07 to 1.86)	1.34 (1.00 to 1.80)	38/20 671	1.40 (0.97 to 2.01)	1.39 (0.94 to 2.05)
Per 10-unit increase	1609/1 645 659	1.13 (1.03 to 1.24)	1.11 (1.00 to 1.23)	970/541 444	1.15 (1.02 to 1.29)	1.16 (1.02 to 1.32)
P_{trend}		.01	.051		.02	.03
Cumulative average alcohol intake after first full-term pregnancy‖, g/day						
0	199/230 616	1.00 (referent)	1.00 (referent)	149/87 347	1.00 (referent)	1.00 (referent)
0.1–4.9	693/673 045	1.09 (0.93 to 1.28)	1.04 (0.86 to 1.26)	527/233 318	1.26 (1.04 to 1.51)	1.16 (0.93 to 1.44)
5.0–14.9	197/174 677	1.17 (0.95 to 1.43)	1.10 (0.87 to 1.40)	122/57 845	1.19 (0.93 to 1.52)	1.06 (0.80 to 1.41)
≥15.0	46/31 942	1.30 (0.93 to 1.83)	1.21 (0.84 to 1.76)	22/10 494	1.07 (0.67 to 1.72)	0.93 (0.56 to 1.54)
Per 10-unit increase	1135/1 110 281	1.11 (0.99 to 1.24)	1.09 (0.96 to 1.23)	820/389 003	1.01 (0.87 to 1.17)	0.94 (0.79 to 1.11)
P_{trend}		.06	.20		.93	.45
P for difference between two RRs¶		—	.89		—	.08

* The analyses of breast cancer and proliferative BBD included 91 005 participants and 60 093 participants, respectively. CI = confidence interval; RR = relative risk.

† The follow-up period for the analysis was from 1991 to 2001 because biopsy specimens were collected and reviewed for women who reported a first diagnosis of biopsy-confirmed BBD during the previous 2 years on the 1993–2001 questionnaires.

‡ Relative risks were adjusted for age (continuous), questionnaire year (continuous), current body mass index (quintiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or unknown), average body size between ages 5 and 10 years (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, ≥5, or unknown), family history of breast cancer in mother or sister(s) (yes or no), postmenopausal hormone use (never use, ever use, or unknown), total duration of breastfeeding (0, 0.1–11 months, ≥12 months, or unknown), and parity and age at first pregnancy (nulliparous; 1–2 pregnancies, age at first pregnancy <25 years; 1–2 pregnancies, age at first pregnancy 25–29 years; 1–2 pregnancies, age at first pregnancy ≥30 years; ≥3 pregnancies, age at first pregnancy <25 years; ≥3 pregnancies, age at first pregnancy 25–29 years; ≥3 pregnancies, age at first pregnancy ≥30 years, or unknown).

§ The relative risks for two cumulative average alcohol consumption variables were mutually controlled for each other in addition to the covariables listed in the above footnote.

‖ Women who did not complete the questions on their alcohol consumption over the previous year or during the age periods after first full-term pregnancy were excluded, resulting in fewer cases for the analysis of cumulative alcohol consumption since first full-term pregnancy compared with that for cumulative intake before first full-term pregnancy. Cumulative average alcohol consumption since first full-term pregnancy was updated in 1991, 1995, 1999, and 2003.

¶ *P* values from the comparisons of cumulative average alcohol consumption before first full-term pregnancy and cumulative average alcohol consumption after first full-term pregnancy with regard to their relative risk estimates. The comparison was made when two alcohol variables were included in the same model.

incidence rates were 195 cases per 100 000 person-years for at least 15-g/day alcohol intake after first pregnancy and 138 cases per 100 000 person-years for non drinking after first pregnancy. The relative risk for cumulative drinking between menarche and first pregnancy remained statistically significant after additional adjustment for drinking after first pregnancy (RR = 1.11 per 10g/day intake; 95% CI = 1.00 to 1.23; P_{trend} = .051); the relative risk was 1.34 (95% CI = 1.00 to 1.80; P = .051) for those with alcohol intake of at least 15 grams per day (approximately 1.3 drinks/day) compared with nondrinkers. Additional adjustment for cumulative drinking before first pregnancy slightly attenuated the RR for alcohol intake after first pregnancy to 1.09 (95% CI = 0.96 to 1.23) per 10 g/day drinking; the RR was 1.21 (95% CI = 0.84 to 1.76) for daily alcohol intake of at least 15 grams after first pregnancy as compared with nondrinkers. The results remained unchanged when the analysis was further adjusted for oral contraceptive use or limited to premenopausal women.

We further analyzed the association between cumulative average alcohol consumption before first pregnancy and breast cancer risk according to the length of the menarche to first pregnancy interval (Table 3; Figure 1). The risk estimates for alcohol intake before first pregnancy were stronger among women with 10 years or more between these two reproductive events as compared with women with a duration of less than 10 years ($P_{interaction}$ = .01). A 10-g increase in cumulative daily alcohol consumption before first pregnancy was associated with a relative risk of 1.21 (95% CI = 1.08 to 1.36) among women with a duration of 10 years or more. We further subdivided this group and observed that the relative risk per 10 g/day drinking was 1.14 (95% CI = 0.97 to 1.34) among women with a duration between 10 and 14 years and 1.25 (95% CI = 1.06 to 1.48) among women with a duration of 15 years or more.

To explore if BBD is in the causal pathway between drinking before first pregnancy and breast cancer, we adjusted the multivariable model for self-reported BBD, and the relative risk for drinking before first pregnancy was attenuated to 1.07 (95% CI = 0.96 to 1.20) per 10 g/day intake. Among BBD cases (n = 18 473), per 10 g/day drinking before first pregnancy was associated with a 13% (RR = 1.13; 95% CI = 0.94 to 1.37) increase in risk.

We also analyzed the risks associated with cumulative drinking between menarche and first pregnancy by ER/PR status (Table 4). Cumulative drinking before first pregnancy tended to be more strongly related to risks of ER^{+}/PR^{+} tumors (RR = 1.18 per 10 g/day intake; 95% CI = 1.03 to 1.34) compared with the risks for ER^{+}/PR^{-} tumors (RR = 0.86; 95% CI = 0.60 to 1.22) and ER^{-}/PR^{-} tumors (RR = 0.84; 95% CI = 0.60 to 1.16; $P_{heterogeneity}$ = .06).

Proliferative BBD

A total of 970 proliferative BBD cases were diagnosed between 1991 and 2001 and confirmed by central histology review. An increasing trend in the risk of proliferative BBD was observed with a 10-g increase in cumulative alcohol consumed between menarche and first pregnancy after adjustment for cumulative drinking after first pregnancy (RR = 1.16; 95% CI = 1.02 to 1.32; 298 cases per 100 000 person-years for at least 15 g/day intake and 271 cases per 100 000 person-years for nondrinkers), which appeared to be stronger than the risk for cumulative drinking after first pregnancy ($P_{heterogeneity}$ = 0.08) (Table 2). The association between alcohol consumption before first pregnancy and proliferative BBD appeared to be restricted to women with longer durations between menarche and first pregnancy. Among women with less than 10 years between menarche and first pregnancy, the relative risk per 10 g/day drinking was 1.06 (95% CI = 0.85 to 1.31); among women with duration of 10 or more years the relative risk was 1.20 (95% CI = 1.03 to 1.40) (Table 3; Figure 1). This pattern is similar to what was observed with breast cancer, although the difference by duration between menarche and first pregnancy was not statistically significant for proliferative BBD.

Discussion

In this prospective analysis, we observed that alcohol intake before first pregnancy was consistently associated with increased risks of proliferative BBD and breast cancer, independent of drinking after first pregnancy. Such associations tended to be stronger among women with 10 or more years between menarche and first pregnancy. These findings add support to the importance of exposure between menarche and first pregnancy in breast cancer development (18).

Given the susceptibility of the undifferentiated nulliparous breast tissue to carcinogenic insults, alcohol consumed between menarche and first pregnancy may have a greater adverse effect. A small number of epidemiological studies have addressed the timing of alcohol consumption in relation to breast cancer risk, with the majority reporting no association with drinking in early life (5–7,9,11). However, the timing of alcohol consumption was evaluated only in terms of chronological age in these studies, mixing exposure before and after first pregnancy. In a prospective analysis of the NHS data, Chen et al. (2) used chronological age cutoffs and compared cumulative drinking between ages 18 and 40 years and after age 40 years with breast cancer risk, observing statistically significant associations of similar magnitude (RR = 1.07–1.08 per 10 g/day consumption) for drinking in early and late life. In that analysis, drinking before first pregnancy was not explicitly addressed. Using the NHSII data, we refined the approach to specifically address how alcohol intake before first pregnancy affects risks of proliferative BBD and breast cancer.

We observed that cumulative alcohol consumption before, rather than after, first pregnancy was associated with elevated incidence of proliferative BBD. This finding is consistent with previous analyses in this cohort that drinking between ages 18 and 22 years is associated with increased risk of proliferative BBD (19,20). Among their daughters, drinking between ages 16 and 22 years was associated with increased risk of biopsy-confirmed BBD (odds ratio = 1.50 per drink per day; 95% CI = 1.19 to 1.90) (27). However, drinking in the past year was not related to risk of proliferative BBD in two case–control studies (28,29) and a prospective study among postmenopausal women (30). These results suggest that drinking early in life may have a greater adverse effect on risk of proliferative BBD compared with drinking later in life. Given that proliferative BBD is a well-confirmed risk marker for breast cancer, the association observed between drinking early in life and breast cancer may be, in part, mediated through proliferative BBD. In our study, additional adjustment for BBD reduced the relative risk of breast cancer for drinking before first pregnancy; drinking before first pregnancy was

Table 3. Cumulative average alcohol consumption between menarche and first full-term pregnancy: risks of breast cancer and proliferative benign breast disease (BBD) among parous women* by duration between these two reproductive events

		Breast cancer			Proliferative BBD		
Menarche to first birth duration	**Alcohol intake, g/day**	**Cases/ person-years**	**Joint-classified RR (95% CI)†**	**Stratified RR (95% CI)†**	**Cases/ person-years**	**Joint-classified RR (95% CI)†**	**Stratified RR (95% CI)†**
<10 years	0	190/200 357	1.00 (referent)	1.00 (referent)	106/63 597	1.00 (referent)	1.00 (referent)
	0.1–4.9	290/310 301	1.04 (0.86 to 1.27)	1.11 (0.90 to 1.37)	216/97 294	1.31 (1.03 to 1.67)	1.21 (0.94 to 1.57)
	5–14.9	63/94 166	0.88 (0.65 to 1.19)	0.94 (0.68 to 1.29)	67/31 163	1.44 (1.05 to 1.99)	1.29 (0.92 to 1.81)
	≥15	7/17,490	0.63 (0.29 to 1.34)	0.64 (0.30 to 1.39)	10/6088	1.22 (0.63 to 2.36)	1.12 (0.57 to 2.19)
	Per 10-unit increase‡	550/622 314	—	0.87 (0.69 to 1.10)	399/198 142	—	1.06 (0.85 to 1.31)
	P_{trend}‡		—	.25		—	.61
≥10 years	0	133/142 947	1.26 (0.66 to 2.41)	1.00 (referent)	73/48 844	1.81 (0.86 to 3.82)	1.00 (referent)
	0.1–4.9	624/604 519	1.39 (0.74 to 2.62)	1.06 (0.84 to 1.32)	333/200 374	1.88 (0.92 to 3.86)	1.10 (0.81 to 1.48)
	5–14.9	244/232 788	1.52 (0.80 to 2.88)	1.16 (0.90 to 1.50)	137/79 500	2.10 (1.01 to 4.38)	1.24 (0.88 to 1.75)
	≥15	58/43 091	2.10 (1.06 to 4.15)	1.66 (1.17 to 2.36)	28/14 584	2.45 (1.09 to 5.49)	1.46 (0.90 to 2.38)
	Per 10-unit increase‡	1059/1 023 345	—	1.21 (1.08 to 1.36)	571/343 302	—	1.20 (1.03 to 1.40)
	P_{trend}‡		—	<.01		—	.02
$P_{interaction}$			—	.01		—	.69

* The analyses of breast cancer and proliferative BBD included 91 005 participants and 60 093 participants, respectively. CI = confidence interval; RR = relative risk.

† Relative risk estimates were controlled for cumulative average alcohol intake after first pregnancy and age (continuous), questionnaire year (continuous), current body mass index (quintiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or unknown), average body size between ages 5 and 10 years (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, ≥5, or unknown), family history of breast cancer in mother or sister(s) (yes or no), postmenopausal hormone use (never use, ever use, or unknown), total duration of breastfeeding (0, 0.1–11 months, ≥12 months, or unknown), and parity and age at first pregnancy (nulliparous; 1–2 pregnancies, age at first pregnancy <25 years; 1–2 pregnancies, age at first pregnancy 25–29 years; 1–2 pregnancies, age at first pregnancy ≥30 years; ≥3 pregnancies, age at first pregnancy <25 years; ≥3 pregnancies, age at first pregnancy 25–29 years; ≥3 pregnancies, age at first pregnancy ≥30 years, or unknown).

‡ Relative risks per 10 g/day intake and trend tests were performed in the stratified analysis.

Table 4. Cumulative average alcohol consumption between menarche and first full-term pregnancy and breast cancer risk among parous women (n = 91 005) by estrogen receptor (ER) and progesterone receptor (PR) status*

	ER^+/PR^+		ER^+/PR^-		ER^-/PR^-	
Alcohol intake, g/day	**Cases, No.**	**RR (95% CI)†**	**Cases, No.**	**RR (95% CI)†**	**Cases, No.**	**RR (95% CI)†**
0	190	1.00 (referent)	25	1.00 (referent)	60	1.00 (referent)
0.1–4.9	536	1.20 (0.97 to 1.49)	88	1.01 (0.58 to 1.76)	162	0.80 (0.54 to 1.17)
5–14.9	182	1.33 (1.02 to 1.74)	29	0.86 (0.42 to 1.74)	62	0.87 (0.54 to 1.39)
≥15	41	1.67 (1.11 to 2.51)	5	0.60 (0.17 to 2.07)	10	0.76 (0.33 to 1.71)
Per 10-unit increase	949	1.18 (1.03 to 1.34)	147	0.86 (0.60 to 1.22)	294	0.84 (0.60 to 1.16)
P_{trend}		.01		.39		.28
$P_{heterogeneity}$		.06				

* Cases were excluded if ER status, PR status, or both were missing (n = 169). Cases with ER-negative and PR-positive tumors (n = 50) were excluded because this subtype may largely be the result of technical artifacts in immunohistochemistry (26). CI = confidence interval; RR = relative risk.

† The relative risks were adjusted for current alcohol intake and age (continuous), questionnaire year (continuous), current body mass index (quintiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or unknown), average body size between ages 5 and 10 years (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, ≥5, or unknown), family history of breast cancer in mother or sister(s) (yes or no), postmenopausal hormone use (never use, ever use, or unknown), total duration of breastfeeding (0, 0.1–11 months, ≥12 months, or unknown), and parity and age at first pregnancy (nulliparous; 1–2 pregnancies, age at first pregnancy <25 years; 1–2 pregnancies, age at first pregnancy 25–29 years; 1–2 pregnancies, age at first pregnancy ≥30 years; ≥3 pregnancies, age at first pregnancy <25 years; ≥3 pregnancies, age at first pregnancy 25–29 years; ≥3 pregnancies, age at first pregnancy ≥30 years, or unknown).

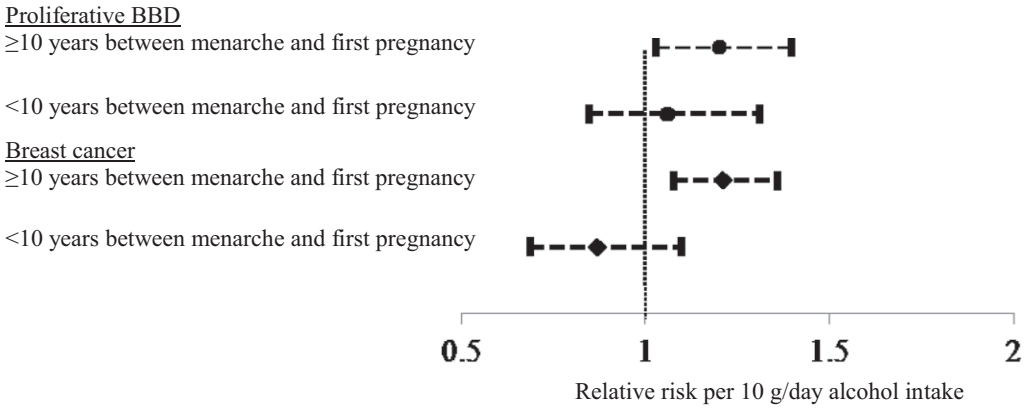

Figure 1. Relative risks (RRs) of breast cancer (**solid diamonds**) and proliferative benign breast disease (**solid circles**) per 10 g/day alcohol consumption between menarche and first pregnancy, according to the length of duration between these events, among parous women participating in the Nurses' Health Study II. The releative risks were adjusted for cumulative alcohol consumption after first pregnancy and other breast cancer risk factors including age (continuous), questionnaire year (continuous), current body mass index (quintiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or unknown), average body size between ages 5 and 10 years (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, ≥5, or unknown), family history of breast cancer in mother or sister(s) (yes or no), postmenopausal hormone use (never use, ever use, or unknown), total duration of breastfeeding (0, 0.1–11 months, ≥12 months, or unknown), and parity and age at first pregnancy (nulliparous; 1–2 pregnancies, age at first pregnancy <25 years; 1–2 pregnancies, age at first pregnancy 25–29 years; 1–2 pregnancies, age at first pregnancy ≥30 years; ≥3 pregnancies, age at first pregnancy <25 years; ≥3 pregnancies, age at first pregnancy 25–29 years; ≥3 pregnancies, age at first pregnancy ≥30 years, or unknown).

related to a non-statistically significant increase in risk among BBD cases. This indicates that BBD may be a pathway linking drinking in early life and breast cancer but not the only route.

The longer the duration of menarche to first pregnancy, the higher is a woman's risk of breast cancer (14,15,17). Compared with nondrinkers with a shorter duration, nondrinkers with duration of 10 or more years between menarche and first pregnancy had 26% and 81% increased risk of breast cancer and proliferative BBD in our analysis, respectively. Pregnancy induces decreases in the number of hormone-sensitive luminal cells and downregulation of the Wnt signaling pathway in basal stem/progenitor cells, making breast tissue less susceptible to carcinogens (31). Additionally, first pregnancy induces long-term hormonal changes, including reduced prolactin and estrogen and increased sex hormone–binding globulin, which may provide further protection against breast cancer (32,33). Importantly, we observed that alcohol drinking between menarche and first pregnancy conferred excess risk of breast cancer and of proliferative BBD among women who had first pregnancy 10 or more years after menarche.

The primary limitation of this analysis is the reliability of recalled drinking in the specific age periods. However, recalled drinking during adolescence is moderately reproducible (intraclass correlation coefficient = 0.50) and is largely independent of current (adult) alcohol intake (intraclass correlation coefficient = 0.14) in the NHSII participants (34). The prospective data collection and evaluation of incident disease avoids differential recall bias. Proliferative BBD is histologically divided into two groups, with atypia conferring higher risk of subsequent breast cancer than hyperplasia without atypia (35–38). However, the small number of cases with atypia limited our ability to examine this subgroup.

Population attributable risk estimates (39) showed that 4% of breast cancer cases and 11% of proliferative BBD cases were attributable to drinking before first pregnancy. It is estimated that 232 340 breast cancer cases will be diagnosed in 2013 (40). Thus, approximately 11 617 breast cancer cases would not occur if the persons at risk did not drink alcohol before their first pregnancy.

In conclusion, this prospective study provides evidence that alcohol consumption before first pregnancy was dose-dependently associated with increased risk of both proliferative BBD and breast cancer, independent of drinking after first pregnancy. This increase in risk tended to be more pronounced among women with a longer time interval between menarche and first pregnancy compared with women with a shorter interval, consistent with breast cancer risk models (13–15). The general consistency in the patterns of association between alcohol and risk of proliferative BBD and of breast cancer lends support to the hypothesis that alcohol intake, particularly before first pregnancy when breast tissue is likely at its most vulnerable stage, may play an important role in the etiology of breast cancer. Reducing alcohol consumption during this period may be an effective prevention strategy for breast cancer.

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Notes

YL had full access to all of the deidentified data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YL, GAC, and WCW were responsible for study concept and design. WCW and GAC were responsible for acquisition of data. YL, GAC, BR, CSB, LCC, SJS, JLC, WYC, WCW, and RMT were responsible for analysis and interpretation of data. YL and GAC were responsible for drafting of the manuscript. YL, GAC, BR, LCC, SJS, JLC, WYC, WCW and RMT were responsible for critical revision of the manuscript for important intellectual content. YL, GAC, BR, and RMT were responsible for statistical analysis. WCW and GAC obtained funding.

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