Alcohol Consumption and Incidence of Benign Breast Disease[1]

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Abstract

We evaluated whether moderate alcohol consumption is associated with increased risk of developing benign breast disease (BBD), a potential "precursor" or marker for breast cancer development. This study evaluated associations between reported alcohol consumption and BBD diagnosis among 75,826 women in the Nurses' Health Study II. Between 1989 and 1997, 16,035 women reported a first diagnosis of BBD (317/10,000 person-years), of which 2,999 diagnoses were confirmed by tissue biopsy (59/10,000 person-years). Of the pathology specimens reviewed, 532 were nonproliferative benign breast conditions, and 932 were proliferative conditions. Person-time models provided estimates of the rate ratio (RR) and 95% confidence interval (CI). Reported recent adult consumption of alcohol was not associated with increased BBD incidence. Compared with women who did not drink alcohol, the age- and body mass index (BMI)-adjusted RRs for any reported BBD were 0.98 (95% CI, 0.95–1.02) for those who consumed <5 g/day, 0.93 (95% CI, 0.89–0.98) for those who consumed 5–14.9 g/day, and 0.90 (95% CI, 0.83–0.98) for those who consumed ≥15 g/day. The adjusted RRs for biopsy confirmed BBD and any proliferative benign condition were similiar. However, reported alcohol consumption of ≥15 g/day between ages 18 and 22 years was associated with higher rates of biopsy-confirmed BBD (age- and body mass index-adjusted RR = 1.14; 95% CI, 1.00–1.30), nonproliferative BBD (RR = 1.46; 95% CI, 1.09–1.96), and any proliferative BBD (RR = 1.33; 95% CI, 1.05–1.69), but not atypical hyperplasia. In this study, recent alcohol consumption was associated with slightly lower rates of reported BBD. However, greater alcohol consumption earlier in life (ages 18–22 years) was associated with higher proliferative BBD rates, suggesting that timing of exposure may be relevant to disease incidence.

Introduction

Moderate intake of alcohol is associated with an increased risk of breast cancer. A meta-analysis of both case-control (28 studies) and cohort (10 studies) data found that compared with nondrinkers, risk of breast cancer increased 24% (95% CI,[4] 1.15–1.34) with consumption of 2 drinks/day (1). Consistent with the meta-analysis report, a pooled analysis of six prospective studies reported a 9% (95% CI, 1.04–1.13) increase in breast cancer incidence with each 10 g of alcohol consumed per day (2). The majority of the data in these studies were from postmenopausal women. Although there was no significant difference in the effects of alcohol on breast cancer risk by menopause status in the meta-analysis, there was significant heterogeneity of effects across the studies among premenopausal women. An updated meta-analysis of 45 studies reported an overall monotonic but modest increase in the relative risk of breast cancer with increased alcohol consumption (3). The relative risks were slightly greater for cohort studies with shorter length of follow-up (<10 years).

Although it is difficult to separate the impact of early-age intake and recent intake, particularly among premenopausal women, for whom the early-age period may be fairly recent, several studies provide some data to address this issue. Among both premenopausal and postmenopausal women in a large multistate case-control study, recent alcohol consumption was associated with a 21% (95% CI, 1.09–1.34) increase in risk of breast cancer per 13 g/day intake, whereas the same level of alcohol consumption before age 30 years was not associated (RR = 0.95; 95% CI, 0.63–1.45) with increased risk. However, this lack of an overall association with early (before age 30 years) alcohol consumption appeared to be driven by effects among postmenopausal women because among the premenopausal women in this study, each 13 g/day alcohol consumption before age 30 years was associated with a 34% (95% CI, 1.02–1.75) increase in breast cancer risk, whereas more recent alcohol consumption had little effect (4). With 6 years of follow-up among the predominantly premenopausal women participating in the NHS II cohort, recent intake was associated with a 23% (95% CI, 0.68–2.21) increase in breast cancer risk (5). In evaluating intake at specific age intervals (18–22, 23–30, and 31–40 years) in the NHS II, only alcohol consumption between ages 23–30 years was significantly associated with increased breast cancer incidence (5).

Alcohol may affect breast cancer risk by increasing circulating levels of endogenous estrogens (6). In a controlled dietary study of premenopausal women, 30 g/day of ethanol increased blood levels of total and bioavailable estrogen (7). In

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[4] The abbreviations used are: CI, confidence interval; BBD, benign breast disease; RR, rate ratio; BMI, body mass index; NHS, Nurse's Health Study.

contrast, in a cross-sectional analysis of 107 premenopausal women, alcohol intake assessed at different times in the menstrual cycle by questionnaire was not associated with plasma estrogens but was associated with plasma androstenedione (8).

Numerous studies found an increased risk of developing breast cancer among women with benign epithelial proliferation, particularly atypical hyperplasia (9–13). Because endogenous hormonal levels are associated with epithelial proliferation (14), alcohol consumption may promote epithelial proliferation. A few studies evaluated the association between alcohol consumption and the presence of proliferative epithelial conditions. In a case-control study of predominantly (~80%) premenopausal women, no association was noted between alcohol consumption and benign proliferative disease ($n = 383$) compared with either unbiopsied community controls ($n = 383$) or women with biopsy-confirmed nonproliferative benign breast conditions ($n = 192$; Ref. 15). A higher percentage of women (48.7%) with fibrocystic BBD who had been diagnosed as part of a screening program reported consuming alcohol than women attending the breast screening program who had no breast condition diagnosed (41.4%; Ref. 16). In another case-control study among predominantly postmenopausal women, drinking alcohol was associated with a 15% increased risk of having benign proliferative breast disease compared with nondrinkers (17).

Thus, results have been inconsistent regarding whether early-life or recent consumption of alcohol is related to premenopausal breast cancer. Clarification of the relation between alcohol consumption and proliferative benign breast conditions may provide further understanding regarding the effects of alcohol consumption on breast cancer incidence. To address these issues, we evaluated the association between alcohol consumption and diagnosis of benign breast conditions in a prospective study of young women.

Materials and Methods

The NHS II is a prospective cohort study established in 1989 when 116,671 female registered nurses who were aged 25–44 years responded to a baseline questionnaire about their medical history and lifestyle. Additional questionnaires, mailed biennially, request updated information on risk factors and medical events. Follow-up of this cohort in each 2-year interval is >90%. On every questionnaire, participants are asked to report if they have had a physician's diagnosis of fibrocystic or other BBD and if the diagnosis was confirmed by a breast biopsy and/or aspiration.

This paper reports results from two slightly different follow-up periods based on the end point of interest. We had information regarding self-report of BBD from 1989 to 1997 and information from histological reviews of BBD with biopsy from 1991 to 1997. For the analyses of self-reported BBD from 1989 to 1997, the study population excluded all women who had reported on the baseline questionnaire in 1989 a prior physician diagnosis of fibrocystic or other BBD ($n = 33,375$) or a prior cancer diagnosis ($n = 691$) or who did not respond to the baseline questions on alcohol intake, reported being pregnant, or were missing information on BMI ($n = 5,281$). Follow-up ended at the date a woman returned her last questionnaire up until the 1997 questionnaire. Of the remaining 77,323 women with information to study the association between current alcohol intake and subsequent report of benign breast conditions, 1,497 contributed no follow-up. On the 1989 baseline questionnaire, participants were asked the total number of drinks of alcohol (none or <1/month, 1–3/month, 1/week, 2–4/week, 5–6/week, 7–13/week, 14–24/week, 25–39/week, and 40+/week) consumed at different ages (ages 15–17 or 18–22 years). One drink was considered equal to one bottle/can of beer, a 4-ounce glass of wine, or a shot of liquor. Usual consumption during the past year was asked separately for beer, wine, or liquor in the same categories as for the age-specific questions. In both 1991 and 1995, as part of a food frequency questionnaire, participants were asked to report their average use during the past year of regular beer, light beer, red wine, white wine, and liquor in the nine frequency categories. Total alcohol (g ethanol/day) consumption was calculated based on the equivalents of 12.8 g for regular beer, 11.3 g for light beer, 11.0 g for wine, and 14.0 g for liquor. Of the eligible participants who answered the baseline alcohol consumption questions, 14.5% did not respond to the 1991 questions on alcohol consumption, and 22.2% did not respond to the 1995 questions. Similar questions on alcohol intake have been shown to be highly reproducible in repeated assessments during the early 1980s in a cohort of slightly older nurses (18).

All women first reporting a diagnosis of BBD from 1989 through 1997, whether or not it was confirmed by breast biopsy, were considered to have self-reported a physician's diagnosis of BBD. Fifty-one women who reported BBD and breast cancer on the same questionnaire were excluded from all of the BBD case groups because it was not possible to accurately determine the relative timing of the two diagnoses. Exact date of diagnosis of BBD was not asked on the questionnaire and was estimated by the midpoint between the date of return of the questionnaire reporting incident BBD and the immediately prior questionnaire with no report of BBD.

Women who reported on the 1993, 1995, or 1997 questionnaires that they had a physician's diagnosis of with BBD from 1991 through 1997 that was confirmed by biopsy were asked to confirm the BBD diagnosis and to grant permission to review their pathology specimens. Of these 2198 women from whom permission was sought, 1761 (80%) confirmed the diagnosis and granted permission for review of the pathology slides and records from the biopsy. The main reasons for nonresponse were that the woman could not be contacted (6%), did not confirm the biopsy (6%), or did not give permission for her slides to be reviewed (7%). Pathology material was obtained and reviewed for 1577 women (92% of those who had given permission/72% of those sought). Of these for whom pathology material was reviewed for this study, 1465 (93% of those with pathology/67% of those sought) were confirmed as eligible cases, and a valid diagnosis was obtained. The main reasons for exclusion were that the pathology specimen did not contain breast tissue ($n = 41$) or that the biopsy date was before June 1991 ($n = 38$). In addition women were excluded if their biopsy date was after the date they reported BBD ($n = 16$), if they had a prior cancer ($n = 9$), a diagnosis of breast cancer within 1 year of diagnosis of BBD ($n = 3$), or a diagnosis of carcinoma *in situ* ($n = 5$). Alcohol intake did not differ between those for whom pathology material was obtained and those for whom no pathology was obtained ($P = 0.86$).

All biopsy materials were reviewed without knowledge of the exposure histories. The slides from the breast biopsy were classified by one of four pathologists (S. J. S., J. L. C., T. W. J., or G. P.) as normal or nonproliferative, proliferative without atypia, or atypical hyperplasia according to the criteria of Dupont and Page (9). Any biopsies that showed atypia or questionable atypia were jointly reviewed by two pathologists (S. J. S. and J. L. C.) with one of the other pathologists (T. W. J. or G. P.), and a consensus diagnosis was reached. Biopsy tissue with intraductal papilloma, radial scar, sclerosing

Table 1 Baseline cohort distribution by reported alcohol consumption (1989) among 77,323 women 25–45 years of age

	Alcohol intake			
	None	<5 g/day	5–14.9 g/day	≥15 g/day
Total *n* =	29,310	32,458	12,174	3,381
Mean alcohol intake	0	1.75 g/day	8.27 g/day	24.88 g/day
Baseline covariates				
Age (mean yrs)	34.3	33.9	33.7	34.7
BMI (mean kg/m^2)	25	24.1	23.1	23.4
Age at menarche (mean yrs)	12.4	12.4	12.5	12.5
Parity (mean)	1.7	1.4	1.2	1.1
Age at first birth (mean years for parous only)	25.4	25.5	25.6	25.5
Past OC[a] use (%)[b]	67.9	67.9	67.6	70.8
Current OC use (%)[b]	10.8	16.2	19.9	18.4
Family history of breast cancer (%)[b]	4.8	5.2	5.5	5.4
Screening mammogram in last 2 years (%)[b]	18.8	19.5	19.1	23.3
Past smokers (%)[b]	15.2	20.9	28.4	30.8
Current smokers (%)[b]	9.9	12.8	19.3	31.1

[a] OC, oral contraceptives.
[b] Percentage of column total.

adenosis, fibroadenoma, fibroadenomatous change, or moderate to florid ductal hyperplasia in the absence of atypical hyperplasia was classified as proliferative without atypia.

Analytic Methods. For cohort analyses of self-reported BBD, each participant contributed person-time of follow-up from the time she returned the baseline questionnaire in 1989 until the end of follow-up defined by the first of the return date of the 1997 questionnaire, death from any cause, report of BBD or cancer other than non-melanoma skin cancer, or loss to follow-up. Analyses of histologically reviewed BBD counted person-time from the return of the 1991 questionnaire until the end of follow-up (as defined above). Alcohol intake for women who were pregnant at the time of the questionnaire was not considered to necessarily represent typical adult intake, and therefore these women did not contribute person-time during the interval that a pregnancy was reported. For time-varying covariates, such as age, cases and person-time were reassigned every 2 years. Alcohol intake was analyzed using the baseline 1989 exposure and updating the 1989 exposure with reports in 1991 and 1995. In updated analyses, the person-time and events of women missing the 1991 or 1995 data were not counted in the related intervals. Additional analyses evaluated the 1989 report alone and the report of consumption at ages 15–17 years and ages 18–22 years. Age- and BMI-standardized rates of BBD were calculated from the person-time distribution (19). Pooled logistic regression for grouped failure times was used to estimate RRs and 95% CIs controlling simultaneously for other covariates (20).

Results

In the 505,666 person-years of follow-up contributed by the 75,826 women in this study, 41.0% of the person-years were from women who did not drink beer, wine, or liquor, 39.8% of the person-years were from women with intake of <5 g/day or on average ≤1 drink/week, 15.2% of the person-years were from women with consumption of 5–14.9 g/day, and only 4.0% of the person-years were from women with consumption of ≥15 g/day. Table 1 presents the distribution of other covariates by alcohol intake in the study cohort. Among women who reported drinking alcohol, those consuming ≥15 g/day were slightly older than women reporting lower intake. Women who reported that they did not consume alcohol had the highest mean BMI at baseline (BMI = 25.0). Those with higher levels of reported alcohol intake had a lower mean number of children. The percentage of current users of oral contraceptives was higher among women who reported ≥5 g/day alcohol intake. Women consuming ≥5 g/day alcohol were also more likely to be past or current smokers.

During the 8 years from 1989 to 1997, 16,035 women reported a diagnosis of fibrocystic disease or other BBD for the first time. At the start of each follow-up cycle, alcohol intake was updated based on the most recent questionnaire response (1989, 1991, and 1995). Overall, women reported a diagnosis of BBD at a rate of 317/10,000 person-years. Higher levels of alcohol consumption were not associated with an increased rate of reported BBD but instead were associated with decreased rates of any reported BBD (P for trend = 0.001). The age- and BMI-adjusted incidence rate per 10,000 person-years between 1989 and 1997 for self-reported BBD declined slightly across increasing intake categories of alcohol. Of women reporting a first diagnosis of BBD, 18.7% reported that the diagnosis was confirmed by biopsy; the overall rate was 59/10,000 person-years for biopsy-confirmed BBD. The rate of biopsy-confirmed BBD in the cohort did not increase with increased levels of alcohol consumption (Table 2). In analyses restricted to women who reported having had a mammogram and/or physician breast exam in the 2-year interval before the first report of BBD (385,342 person-years; 76.2% of total person-time), greater alcohol intake was associated with decreased self-reported BBD ($P < 0.001$) and decreased biopsy-confirmed BBD ($P = 0.04$, not shown in Table 2).

In analyses based on the 1989 reported alcohol intake alone (not updated with subsequent reports), compared with women who did not drink alcohol, the age- and BMI-adjusted RRs for any reported BBD were 0.99 (95% CI, 0.95–1.02) for those who consumed <5 g/day, 0.91 (95% CI, 0.87–0.96) for those who consumed 5–14.9 g/day, and 0.93 (95% CI, 0.86–1.01) for those who consumed ≥15 g/day. Likewise, the age- and BMI-adjusted RRs for biopsy-confirmed BBD were 1.02 (95% CI, 0.94–1.11) for those who consumed <5 g/day, 0.99 (95% CI, 0.89–1.11) for those who consumed 5–14.9 g/day, and 0.99 (95% CI, 0.82–1.18) for those who consumed ≥15 g/day.

Table 3 presents the RRs for nonproliferative BBD and proliferative BBD among the 388,250 person-years accumu-

Table 2 RRs and 95% CIs for the association between incidence of self-reported BBD and alcohol consumption (follow-up from 1989–1997)

Alcohol consumption (g/day)	Person-years[a]	Any BBD				BBD confirmed by biopsy			
		Cases	Rate/10,000 py[b]	RR[c]	95% CI	Cases	Rate/10,000 py[b]	RR[c]	95% CI
None	207,080	6,664	322	1.0	Reference	1,260	61	1.0	Reference
<5	201,155	6,378	317	0.98	0.95–1.02	1,173	58	0.99	0.92–1.08
5–14.9	77,076	2,377	308	0.93	0.89–0.98	450	58	0.98	0.88–1.10
≥15	20,355	616	303	0.90	0.83–0.98	116	57	0.92	0.76–1.12
			$P = 0.001$[d]				$P = 0.52$[d]		

[a] Person-years are the same for all case types in the table.
[b] Rate/10,000 py is the crude rate.
[c] RR adjusted for age and BMI (additional adjustment for age at menarche, smoking status, use or oral contraceptives, parity, age at first birth, and family history of breast cancer in logistic regression models did not alter the associations presented here).
[d] Test for linear trend across groups of alcohol intake.

Table 3 RRs and 95% CIs for the association between incidence of biopsy-confirmed proliferative and nonproliferative BBD and updated alcohol consumption (follow-up from 1991–1997)

Alcohol consumption (g/day)	Person-years[a]	Nonproliferative BBD				Proliferative BBD			
		Cases	Rate/10,000 py[b]	RR[c]	95% CI	Cases	Rate/10,000 py[b]	RR[c]	95% CI
None	163,156	202	12	1.0	Reference	404	25	1.0	Reference
<5	151,566	202	13	1.08	0.89–1.32	354	23	0.97	0.84–1.11
5–14.9	58,370	94	16	1.33	1.04–1.71	120	21	0.81	0.66–0.99
≥15	15,158	18	12	0.96	0.59–1.56	37	24	0.96	0.69–1.33
			$P = 0.16$[d]				$P = 0.21$[d]		

[a] Person-years are the same for all case types in the table.
[b] Rate/10,000 py is the crude rate.
[c] RR adjusted for age and BMI (additional adjustment for age at menarche, smoking status, use of oral contraceptives, parity, age at first birth, and family history of breast cancer in logistic regression models did not alter the associations presented here).
[d] Test for linear trend across groups of alcohol intake.

lated between 1991 and 1997 in the cohort. Due to the small number of cases ($n = 69$) with atypical hyperplasia (1.8/10,000 person-years), all cases of proliferative disease (with or without atypia) are presented together. Whereas women consuming 5–14.9 g/day of alcohol had a 33% increased rate of nonproliferative BBD compared with nondrinkers, the rate was not increased with higher alcohol intake level (RR = 0.96; 95% CI, 0.59–1.56). There was no indication of an increased rate of proliferative BBD with ≥15 g/day of alcohol. There was no indication of an increase in proliferative BBD incidence with greater alcohol consumption levels. There was a slight suggestion of increased incidence of nonproliferative BBD with greater alcohol consumption up to 5–14.9 g/day (0.5–1 drink/day), but the rate then fell slightly in women consuming ≥15 g/day. The rates of biopsy-confirmed BBD, where pathology was not obtained for review, were between those of nonproliferative and proliferative BBD, declining slightly with greater alcohol intake. The age- and BMI-adjusted RRs for those whose pathology was not reviewed were 0.98 (95% CI, 0.83–1.16) for those who consumed <5 g/day, 0.94 (95% CI, 0.75–1/17) for those who consumed 5–14.9 g/day, and 0.80 (95% CI, 0.53–1.21) for those who consumed ≥15 g/day of alcohol (P for trend = 0.36). In analyses of current alcohol intake restricted to the women who reported having had a mammogram and/or a physician breast exam in the 2-year interval before reporting BBD confirmed by biopsy, compared with those with no alcohol intake, alcohol intake of 5–14.9 g/day was associated with higher rates of nonproliferative BBD. However, among these women increased alcohol intake was associated with lower rates of proliferative BBD ($P = 0.02$).

The cohort was predominantly premenopausal (96.6% person-years). In analyses restricted to premenopausal women, the associations with alcohol intake were not different than in the whole cohort for those reporting any BBD, those reporting BBD confirmed by biopsy, or by histological subtype. Previous studies have suggested that the effect of alcohol on breast cancer risk is greater among women with low dietary folate intake. There was no evidence of an association between alcohol intake and either self-reported BBD or histologically confirmed BBD among women with lower dietary folate intake in this cohort (lowest tertile of consumption). In analyses among drinkers, by source of alcohol, neither beer, wine, nor liquor was associated with increased rates of any BBD or biopsy-confirmed BBD. From pooled logistic regression analyses adjusting for other alcohol intake, age, BMI, oral contraceptive use, family history of breast cancer, age at menarche, parity, and smoking history, the RR for any BBD was 0.93 (95% CI, 0.88–0.99) for each gram of beer intake, 0.95 (95% CI, 0.87–1.04) for liquor, and 0.99 (95% CI, 0.93–1.05) for wine. At baseline, only 19.3% of the cohort reported having had mammographic screening in the previous 2 years. The percentage of women reporting previous screening increased during the follow-up period. In analyses restricted to women who had previous screening, the rates of any BBD (350/10,000 person-years) and BBD confirmed by biopsy (67/10,000 person-years) were slightly greater, but the associations with alcohol intake did not differ for any BBD or any BBD confirmed by biopsy.

Alcohol consumption at younger ages (ages 15–17 years and 18–22 years) was also evaluated in relation to the rate of BBD diagnosis. Higher alcohol intake at ages 15–17 years was not associated with higher rates of reporting any BBD or biopsy-confirmed BBD. Reported alcohol intake at ages 18–22 years was also not associated with the rate of any BBD, but greater intake (≥15 g/day) at between ages 18 and 22 years was associated with a modest increase in the rate of biopsy-confirmed BBD (RR = 1.14; 95% CI, 1.00–1.30; see Table 4).

Table 4 RRs and 95% CIs for incidence of self-reported BBD and alcohol consumption at ages 15–17 years and 18–22 years assessed in 1989 (follow-up from 1989–1997)

	Person-years[a]	Any BBD				BBD confirmed by biopsy			
		Cases	Rate/10,000 py[b]	RR[c]	95% CI	Cases	Rate/10,000 py[b]	RR[c]	95% CI
Alcohol consumption at ages 15–17 yrs (g/day)									
None	380,946	12,450	327	1.0	Reference	2,348	62	1.0	Reference
<5	67,364	1,980	294	0.94	0.90–0.99	378	56	1.03	0.93–1.15
5–14.9	44,129	1,219	276	0.91	0.85–0.96	195	44	0.84	0.73–0.98
≥15	8,532	244	286	0.97	0.86–1.11	44	52	1.04	0.77–1.41
			$P = 0.001$[d]				$P = 0.25$[d]		
Alcohol consumption at ages 18–22 yrs (g/day)									
None	131,567	4,220	321	1.0	Reference	771	59	1.0	Reference
<5	152,278	4,968	326	1.02	0.98–1.07	952	63	1.09	0.99–1.20
5–14.9	160,657	5,020	313	1.00	0.96–1.04	920	57	1.07	0.97–1.18
≥15	58,119	1,742	300	0.99	0.94–1.05	338	58	1.14	1.00–1.30
			$P = 0.66$[d]				$P = 0.10$[d]		

Person-years are the same for all case types in the table.
[b] Rate /10,000 py is the crude rate.
[c] RR adjusted for age and BMI.
[d] Test for linear trend across groups of alcohol intake.

Table 5 RRs and 95% CIs for incidence of histologically confirmed BBD alcohol consumption at ages 15–17 years and 18–22 years assessed in 1989 (follow-up from 1991–1997)

	Person-years[a]	Nonproliferative BBD				Proliferative BBD			
		Cases	Rate/10,000 py[b]	RR[c]	95% CI	Cases	Rate/10,000 py[b]	RR[c]	95% CI
Alcohol consumption at ages 15–17 yrs (g/day)									
None	292,813	393	13	1.0	Reference	717	25	1.0	Reference
<5	51,584	71	14	1.05	0.82–1.35	113	22	1.00	0.81–1.22
5–14.9	33,577	35	10	0.80	0.57–1.13	68	20	0.94	0.73–1.22
≥15	6,510	16	25	1.89	1.18–3.03	7	11	0.54	0.27–1.08
			$P = 0.51$[d]				$P = 0.27$[d]		
Alcohol consumption at ages 18–22 yrs (g/day)									
None	10,128	121	12	1.0	Reference	211	21	1.0	Reference
<5	116,975	151	13	1.07	0.84–1.37	289	25	1.21	1.01–1.44
5–14.9	123,272	168	14	1.20	0.95–1.52	298	25	1.25	1.05–1.49
≥15	44,369	73	77	1.46	1.09–1.96	111	25	1.33	1.05–1.69
			$P = 0.02$[d]				$P = 0.007$[d]		

[a] Person-years are the same for all case types in the table.
[b] Rate /10,000 py is the crude rate.
[c] RR adjusted for age and BMI.
[d] Test for linear trend of rate ratios across alcohol intake groups.

Furthermore, compared with never-drinkers, greater alcohol consumption (≥15 g/day) between ages 18 and 22 years was associated with increased rates of nonproliferative BBD (RR = 1.46; 95% CI, 1.09–1.96; *P* for trend = 0.02) and any proliferative BBD (RR = 1.33; 95% CI, 1.05–1.69; *P* for trend = 0.007; Table 5) but not with atypical hyperplasia, (RR = 1.19; 95% CI, 0.50–2.82; *P* for trend = 0.44).

Discussion

This study found no evidence of increased rates of self-reported BBD, biopsy-confirmed BBD, or histological proliferative disease among women who reported recent consumption of ≥15 g/day of alcohol compared with those who consumed none. If anything, this study's findings suggest that the rates of self-reported BBD decreased slightly with higher levels of recent adult alcohol consumption. If BBD and particularly proliferative benign conditions are markers of future breast cancer risk or potential "precursors" of breast cancer, then the findings of this study suggest that recent alcohol intake does not increase breast cancer risk by increasing the risk of benign proliferative disease, and thus recent alcohol consumption may impact more on later stages of cancer development. These findings may be considered consistent with the findings of a large case-control study of women younger than 45 years in one way. Despite an overall finding that >14 drinks/week was associated with a 70% increased rate of breast cancer (95% CI, 1.2–2.5), the effect of recent alcohol use on breast cancer varied by disease stage. The RR decreased with decreasing severity of the lesion. Women with regional/distant disease had a RR of 2.4, those with local disease had a RR of 1.5, and those with *in situ* disease had a RR of 1.2 (21). If this decreased risk with decreased severity is accurate, one may not expect to see any increase in risk with BBD, although alcohol is still related to invasive breast cancer.

However, in this study, a higher level of reported alcohol consumption at ages 18–22 years was significantly associated with increased rates of biopsy-confirmed BBD, nonproliferative BBD, and any proliferative BBD. More women reported alcohol intake and higher levels of alcohol intake between ages 18 and 22 years than at any other time. Thus, these findings may reflect either a sufficient exposure level to detect an effect, an exposure at the appropriate "susceptible" time period (when most participants

were nulliparous), or an exposure that allowed for a sufficiently long induction period, or higher reported alcohol at ages 18–22 years may have been more associated with the probability of having a biopsy rather than developing BBD. The observation that alcohol consumption between ages 18–22 years was related to increased biopsy-confirmed BBD, nonproliferative BBD, and any proliferative BBD supports the theory that the time period of alcohol consumption may have a different impact on premenopausal *versus* postmenopausal disease. In other studies, alcohol consumption at an earlier age was related to premenopausal breast cancer risk (4, 5), but not postmenopausal risk (4). For premenopausal women, alcohol consumption before first birth may impact subsequent disease processes due to the timing of the exposure, whereas in postmenopausal women, in whom levels of circulating hormones are naturally lower, it may be the influence of alcohol on hormone levels that has a greater impact on disease risk.

Another possible explanation of these patterns of associations may be the changing habits of alcohol consumption in United States women. In the NHS II cohort, the highest average intake of alcohol was reported for ages 18–22 years. Reported consumption then decreased for women during their late 20s and 30s. Whereas alcohol intake over a woman's life is highly correlated, there were very different consumption patterns at different ages. Current alcohol intake in this cohort is generally quite low, with mean alcohol intake (3 g/day) of approximately 2 drinks/week in the cohort, and $<5\%$ of the cohort reported consumption of ≥ 15 g/day. Therefore, there may be an association between higher levels of alcohol intake and BBD, but these intake levels were only reached during ages 18–22 years in this cohort.

By having information on multiple categories of BBD (any reported diagnosis, diagnosis with biopsy, and histologically confirmed) and screening practices, this study was able to consider some of the potential sources of bias that exist in many studies of BBD. Because most BBD is undiagnosed, and factors related to a woman receiving a "diagnosis" without a biopsy or a recommendation for a biopsy may be associated with her subsequent disease risk, knowledge of level of BBD is important. In this study, women who reported higher alcohol consumption were less likely to have a physician's diagnosis of BBD, but having a biopsy-confirmed BBD was not related to alcohol consumption. Initially, this difference in association, if not causal, would support the idea that women who consume higher levels of alcohol may not receive as much breast screening. However, in the analyses restricted to women who had a mammogram and/or physician's breast exam in the 2-year interval before first BBD diagnosis, greater alcohol intake was associated with reduced rates of any reported BBD, biopsy-confirmed BBD, and proliferative BBD, suggesting that these findings are not an artifact of who was screened. Past studies have compared women with a biopsy to community controls, assuming no BBD if no biopsy, and have not been able to consider the factors related to getting the diagnosis without biopsy (15). These issues of selection, detection, and potential surveillance bias are essential to understanding the disease process (22). Although we had information of the histological subtypes of BBD, due to the small number of women with atypical hyperplasia, these data were not as informative as anticipated. We found that increased alcohol intake at ages 18–22 years was associated with increased rates of proliferative BBD. However, the RR for atypical hyperplasia among women consuming ≥ 15 g/day of alcohol was not significant (RR = 1.19; 95% CI, 0.50–2.82).

In summary, reported higher current alcohol intake was possibly associated with a decreased rate of having a diagnosis of BBD in this cohort, but greater alcohol intake at ages 18–22 years was possibly related to increased rates of BBD. These findings suggest that alcohol intake at an early age may affect premenopausal breast cancer rates by increasing rates of proliferative BBD, but recent adult consumption is not related to the development of proliferative BBD.

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