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WHAT'S KNOWN ON THIS SUBJECT: Alcohol consumption during adolescence and early adulthood has been associated with an increased risk of biopsy-confirmed benign breast disease (BBD), an established risk factor of breast cancer.

WHAT THIS STUDY ADDS: This is the first study to analyze the association between adolescent alcohol consumption and risk of biopsy-confirmed proliferative BBD by adolescent folate intake. The result provides no evidence for protective effects of adolescent folate intake on risk of alcohol-associated BBD.

abstract

OBJECTIVES: To examine the combined effect of alcohol and folate intake during adolescence on the risk of proliferative benign breast disease (BBD).

METHODS: We used data from 29 117 women in the Nurses' Health Study II who completed both adolescent alcohol consumption questions in 1989 and an adolescent diet questionnaire in 1998. A total of 659 women with proliferative BBD diagnosed between 1991 and 2001 were confirmed by central pathology review. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals (CIs), adjusted for established risk factors of breast cancer.

RESULTS: Adolescent alcohol consumption was dose-dependently associated with an increased risk of proliferative BBD (hazard ratio = 1.15 per 10 g/day consumption; 95% CI, 1.03–1.28). There was no significant association between adolescent folate intake and the risk of proliferative BBD. Stratified analyses showed that each 10-g/day alcohol intake during adolescence was associated with a 21% (95% CI, 1.01–1.45) increase in the risk of proliferative BBD among women with low folate intake during adolescence, which was not significantly different from the alcohol-associated risk among women with moderate and high folate intake during adolescence (*P* for interaction = 0.18).

CONCLUSIONS: Adolescent alcohol consumption is associated with increased risk of proliferative BBD, which may not be reduced by increased folate intake during adolescence. *Pediatrics* 2012;129: e1192–e1198

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KEY WORDS

alcohol, folate, adolescence, benign breast disease, premalignant breast lesions

ABBREVIATIONS

BBD—benign breast disease
CI—confidence interval
HR—hazard ratio
HS-FFQ—High School Food-Frequency Questionnaire
NHSII—Nurses' Health Study II

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Alcohol is an established risk factor for breast cancer; a 10-g/day increment in consumption by adult women is associated with a 7% to 10% increase in breast cancer risk.[1–3] However, the mechanism(s) underlying this association remains unclear. One potential mechanism relates to the impact of alcohol on folate metabolism; alcohol may hinder the bioavailability of dietary folate,[4] particularly in heavy drinkers.[5] Folate deficiency leads to aberrations in synthesis, repair, and methylation patterns of DNA.[6] Although a meta-analysis did not support the protective effect of folate intake on breast cancer risk,[7] a significant interaction between alcohol and folate intake has been reported for breast cancer.[8–13]

Given that proliferative benign breast disease (BBD) is associated with risk of subsequent invasive breast cancer,[14,15] the associations between intakes of alcohol and folate and the risk of proliferative BBD could have implications for the prevention of breast cancer. The results of epidemiologic studies of alcohol consumption and proliferative BBD have been inconsistent or even conflicting.[16–20] In a cohort of postmenopausal women, folate intake was not associated with the risk of proliferative BBD.[17] One possible explanation for the null findings is that these studies did not focus on an etiologically relevant exposure period.[21] The mammary glands may be most vulnerable to carcinogenic influences during the time between menarche and first childbirth because breast tissue undergoes rapid cellular proliferation during adolescence and terminal differentiation occurs during first pregnancy.[22] In support of this hypothesis, the Nurses' Health Study II (NHSII) found that the risk of proliferative BBD was similar in women with recent (adult) intake of 15+ g/day of alcohol and in nondrinkers but was positively associated with alcohol consumption at ages of 18 to 22 years.[16]

Using data from the NHSII, we updated and expanded on these findings by testing the hypotheses that adequate folate intake during adolescence would reduce the risk of proliferative BBD associated with alcohol consumption between ages 18 and 22 years, and that a protective effect of adolescent folate intake on risk of proliferative BBD would be limited to women with higher alcohol consumption between ages 18 and 22 years.

METHODS

Study Population

The NHSII was established in 1989 when 116 671 female registered nurses aged 25 to 44 years completed a mailed questionnaire about their medical history and lifestyle. Follow-ups were conducted biennially via mailed questionnaire to update information on lifestyle factors and medical events. The overall response rate to each questionnaire through 2001 was 90%. In 1998, a semiquantitative high school food-frequency questionnaire (HS-FFQ) was mailed to the participants who had previously indicated their willingness to participate in assessing their adolescent diet.

BBD Cases

Slides from the breast biopsies were reviewed by 1 of 3 pathologists (L.C.C., S.J.S., J.L.C.) who were blinded to participants' exposure status. BBD was classified according to the criteria of Dupont and Page[23] into 1 of 3 categories: nonproliferative, proliferative without atypia, and atypical hyperplasia. Among 3273 participants reporting a first diagnosis of biopsy-confirmed BBD on the 1993–2001 questionnaires, breast biopsy specimens were reviewed for 2120 women, and 2056 BBD cases were confirmed. Given that proliferative BBD is a strong predictor of breast cancer, 1348 proliferative BBD cases with or without atypia confirmed by central pathology review was the outcome of interest in the analysis.

Alcohol Consumption

Because of the susceptibility of breast tissue to carcinogenic exposure during the time period between menarche and first childbirth,[21,22] alcohol consumption between ages 18 and 22 years was the exposure of primary interest in the analysis. A previous analysis in the NHSII cohort revealed an increased risk of proliferative BBD with high alcohol consumption at ages of 18 to 22 years, but this did not consider the influence of folate intake during adolescence on the association.[16]

On the 1989 baseline questionnaire, participants were asked the total number of drinks of alcohol (none or <1 per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 7–13 per week, 14–24 per week, 25–39 per week, and 40 + per week) consumed between ages 18 and 22 years. One drink was defined as 1 bottle or can of beer, a 4-ounce glass of wine, or a shot of liquor, with ethanol estimates of 12.8 g for regular beer, 11.3 g for light beer, 11.0 g for wine, and 14.0 g for liquor.[16] Total alcohol consumption was expressed in grams of ethanol per day. The report of adolescent alcohol consumption has been shown to be valid in the NHSII participants.[24]

HS-FFQ

The 131-item HS-FFQ that was derived from the validated FFQ on adult diets used in the NHS and NHSII cohorts was completed in 1998 by 45 948 NHSII participants.[25] Participants were asked how often, on average, they had consumed a specified quantity of 122 foods and beverages during high school, further defined as ages of 13 to 18 years. The daily nutrient intake from a given food was calculated by multiplying its portion size by the number of servings per day and its nutrient content. The daily nutrient intake for each participant was then estimated by summing across all food items. Because the composition of some foods had changed

over time, food composition data from the relevant time period (1960s and 1970s) were used, when available, to obtain the best approximation of intake during adolescence. Multivitamin use in high school was used to estimate supplemental folic acid intake at that time period. Total folate intake was estimated by summing folate consumed per day from food and supplemental sources.

Statistical Analysis

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, the follow-up period for this analysis was from 1991 to 2001. Participants (n = 45 716) were eligible for the current analysis if they provided their alcohol consumption between ages 18 and 22 years, returned the HS-FFQ in 1998, and had reasonable values for total energy intake (a range of 600–5000 kcal/day) in high school. Participants (n = 16 378) were excluded from the analysis if they reported a previous history of BBD (n = 15 990) or cancer other than nonmelanoma skin cancer (n = 370) on the 1989 and 1991 questionnaires or if their biopsy date was before the return date of the 1991 questionnaire (n = 18). Additionally, we excluded 221 women from the analysis because they were identified to have statistical outlier values on the high end of alcohol distribution using the generalized extreme studentized deviate many-outlier detection approach.[26] The results were similar when these 221 (0.7% of eligible women) were included in the analysis. Here we reported the analysis including 29 117 women.

Alcohol consumption between ages 18 and 22 years was categorized into 4 groups: no consumption (none), any consumption up to 5 g of ethanol/day (0.1–4.9 g/day), between 5 and 15 g/day (5.0–14.9 g/day), and 15+ g/day. Total and dietary folate intakes during adolescence were adjusted for energy intake using the residual method[27] and were then categorized into tertiles based on the distributions of intake among all eligible women.

Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs), which were used as estimates for relative risks (RRs) of proliferative BBD with adolescent intake of alcohol and folate because HRs and RRs approximate to each other when HRs for a rare disease are <2.0.[28] Participants contributed person-time to the study 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 the follow-up cut-off date (June 2001), whichever came first. In multivariate analyses, we controlled for established risk factors of breast cancer: age in months, total energy intake (quintiles), age at menarche ($<$12, 12, 13, or $\geq$14 years), menopausal status (premenopausal, postmenopausal, or uncertain), average body size between ages 5 and 10 years (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, or $\geq$5), family history of breast cancer in mother or sister(s) (yes versus no), recency and duration of oral contraceptive (OC) use (never, past $<$4 years, past $\geq$4 years, current $<$4 years, or current $\geq$4 years), current alcohol consumption (none, 0.1–4.9 g/day, 5.0–14.9 g/day, 15+ g/day, or missing), and parity and age at first birth (nulliparous; 1–2 pregnancies, age at first birth $<$25 years; 1–2 pregnancies, age at first birth 25–29 years; 1–2 pregnancies, age at first birth $\geq$30 years; $\geq$3 pregnancies, age at first birth $<$25 years; $\geq$3 pregnancies, age at first birth 25–29 years; or $\geq$3 pregnancies, age at first birth $\geq$30 years). Age, menopausal status, OC use, current alcohol consumption, and parity and age at first birth were updated in each questionnaire cycle. Family history of breast cancer was initially asked on the 1989 questionnaire and was updated in 1997. Tests for trend were performed by using the median value for each category of alcohol or folate intake as a continuous variable in the multivariate model.

The interaction between adolescent intake of alcohol and folate in the risk of proliferative BBD was assessed by entering a cross-product term of 4 categories of alcohol consumption and tertiles of folate intake in a multivariate-adjusted model. The statistical significance of the interaction term was evaluated by using the likelihood ratio test. All statistical analyses were performed by SAS (version 9.1; SAS Institute Inc, Cary, NC). P values $<$.05 were considered statistically significant, and all statistical tests were 2-sided.

RESULTS

Among 29 117 women free from BBD and cancer at baseline who responded to questions regarding adolescent intake of alcohol and folate, 7374 (25.3%) did not drink alcohol, 8907 (30.6%) had intake of 0.1 to 4.9 g/day alcohol, 9578 (32.9%) reported moderate alcohol consumption (5.0–14.9 g/day), and 3258 (11.2%) reported high alcohol consumption (15+ g/day) between ages 18 and 22 years. Median total folate intake in high school for the whole sample was 310 μg/day and median intakes in energy-adjusted tertiles ranged from 239 μg/day to 430 μg/day, which were primarily from food alone. Only 16% of women reported multivitamin use during high school. Table 1 summarizes the distribution of selected characteristics of women in the NHSII cohort by adolescent intake of alcohol and total folate. Compared with nondrinkers, women who reported alcohol consumption between ages 18 and 22 years had larger

TABLE 1 Age and Age-Standardized Characteristics of 29 117 Participants in the Nurses' Health Study II According to Alcohol Consumption Between Ages 18 and 22 y and Total Folate Intake During Adolescence

	Alcohol Consumption, g/day				Tertile of Total Folate Intake		
	None	0.1–4.9	5.0–14.9	15+	T1, <279 μg/day	T2, 279–343 μg/day	T3, ≥344 μg/day
No. of women	7374	8907	9578	3258	9700	9711	9706
Percentage, %							
Family history of breast cancer in mother or sister(s)	4.7	4.8	4.6	5.1	4.7	4.5	5.0
Age at menarche <12 y	25.1	24.8	22.9	23.1	23.8	23.4	25.3
Premenopausal	97.7	97.8	98.3	97.7	97.7	98.0	98.1
Average body size between ages 5 and 10 (somatotype pictogram) >3	26.1	27.4	26.7	32.7	27.5	27.0	27.6
Nulliparous	26.5	25.5	27.3	31.9	24.7	26.2	30.1
Age at first birth ≥30 y	14.0	17.1	21.1	21.8	15.7	18.6	20.2
Former oral contraceptive use	77.4	84.2	87.0	89.5	85.8	84.7	82.0
Multivitamin use in high school	15.0	16.3	15.9	15.1	7.6	12.5	25.0
Mean/median							
Age, y	35.7	35.7	35.6	35.5	35.8	35.7	35.6
Average body size between ages 5 and 10	2.6	2.6	2.6	2.8	2.6	2.6	2.7
Parity	2.2	2.1	2.1	2.1	2.2	2.2	2.1
Age at first birth, y	25.2	25.8	26.5	26.6	25.5	26.1	26.3
Alcohol consumption between ages 18 and 22, g/day	0	1.1	6.8	21.1	5.0	5.0	4.8
Adolescent total folate intake, μg/day, energy-adjusted	331	330	328	325	239	310	430
Adolescent dietary folate intake, μg/day, energy-adjusted	320	320	318	317	239	310	408

body size between ages 5 and 10 years, were older at first birth, were more likely to have ever used OC, and tended to report lower levels of total and dietary folate intake during adolescence. Compared with women who had the lowest tertile of total folate intake, women with higher levels of total folate intake during adolescence were less likely to have children and were more likely to have taken multivitamins. Alcohol consumption between ages 18 and 22 years was similar across 3 tertiles of total folate intake.

TABLE 2 HRs of Proliferative BBD by Alcohol Consumption Between Ages 18 and 22 y and Adolescent intake of Folate From All Sources Combined and From Food Only

	No. of Cases	Person-years	Age-adjusted HR, (95% CI)	Multivariate HR,[a] (95% CI)
Alcohol intake, g/day				
None	155	64 827	1.00	1.00
0.1–4.9	193	78 363	1.06 (0.85–1.31)	1.11 (0.89–1.38)
5.0–14.9	236	84 310	1.26 (1.02–1.54)	1.36 (1.09–1.69)
≥15	75	29 052	1.22 (0.92–1.62)	1.35 (1.01–1.81)
			P for trend = 0.10	*P* for trend = 0.03
Per 10 g/day increase			1.11 (1.00–1.24)	1.15 (1.03–1.28)
Tertile of total folate intake				
T1 (Lowest)	233	85 014	1.00	1.00
T2	227	85 183	0.99 (0.82–1.19)	1.00 (0.83–1.21)
T3 (Highest)	199	86 355	0.92 (0.76–1.12)	0.95 (0.78–1.15)
			P for trend = 0.39	*P* for trend = 0.58
Tertile of dietary folate intake				
T1 (Lowest)	234	85 138	1.00	1.00
T2	227	85 178	0.99 (0.82–1.19)	1.00 (0.83–1.20)
T3 (Highest)	198	86 235	0.89 (0.74–1.08)	0.92 (0.76–1.12)
			P for trend = 0.24	*P* for trend = 0.39

[a] The model adjusted for age in months, total energy intake (quintiles), age at menarche (<12, 12, 13, or ≥14 y), menopausal status (premenopausal, postmenopausal, or uncertain), average body size between ages 5 and 10 y (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, or ≥5), family history of breast cancer in mother or sister(s) (yes versus no), recency and duration of oral contraceptive (OC) use (never, past <4 y, past ≥4 y, current <4 y, or current ≥4 y), current alcohol consumption (none, 0.1–4.9 g/day, 5.0–14.9 g/day, 15+ g/day, or missing), and parity and age at first birth (nulliparous; 1–2 pregnancies, age at first birth <25 y; 1–2 pregnancies, age at first birth 25–29 y; 1–2 pregnancies, age at first birth ≥30 y; ≥3 pregnancies, age at first birth <25 y; ≥3 pregnancies, age at first birth 25–29 y; or ≥3 pregnancies, age at first birth ≥30 y).

Over an average of 10 years of follow-up, 659 incident cases of proliferative BBD were identified, including 59 with atypia and 600 without atypia. Table 2 shows the associations of proliferative BBD with alcohol consumption between ages 18 and 22 years and folate intake in high school. Alcohol consumption was significantly associated with an increased RR of proliferative BBD (multivariate-adjusted HR = 1.15 per 10 g/day [~1 drink per day], 95% CI, 1.03–1.28). Compared with nondrinkers, the multivariate-adjusted HRs were 1.11 (95% CI, 0.89–1.38) for those who consumed <5 g/day, 1.36 (95% CI, 1.09–1.69) for moderate alcohol consumers, and 1.35 (95% CI, 1.01–1.81) for high drinkers (*P* for trend = 0.03). We observed no significant associations of prolife rative BBD with adolescent folate intake, regardless of the source of folate.

We next examined the combined effect of alcohol and folate intake during adolescence on the RR of proliferative BBD (Table 3). Among women with low total folate intake, moderate alcohol consumption was related to a 67% increased risk (95% CI, 1.17–2.39) and high alcohol consumption was related to

a 57% increased risk (95% CI, 0.97–2.56). There was no evidence that increased folate intake significantly reduced the excess risk of proliferative BBD associated with higher alcohol consumption; a 10-g increase in daily alcohol consumption was associated with a 21% increased risk (95% CI, 1.01–1.45) among women with low total folate intake, a 15% increased risk (95% CI, 0.95–1.38) among women with moderate total folate intake, and a 13% increased risk (95% CI, 0.92–1.40) among women with high total folate intake. The interaction between alcohol and total folate intake was not statistically significant ($P = .18$). There was no interaction between alcohol and dietary folate intake in proliferative BBD (data not shown).

DISCUSSION

This analysis revealed that the risk of proliferative BBD increased by 15% for each 10 g of alcohol consumed per day at the ages of 18–22 years and did not differ significantly across tertiles of total folate intake in high school.

To date, 6 epidemiologic studies have examined alcohol consumption as a risk factor for proliferative BBD, with inconsistent results.[16–20,29] Neither recent nor lifetime alcohol consumption was associated with the risk of proliferative BBD in 2 case-control studies[18,19] and a cohort study of postmenopausal women.[17] During the 6-year follow-up, the NHSII participants with recent (adult) intake of 15+ g/day of alcohol had similar risk of biopsy-confirmed proliferative BBD as nondrinkers; however, the risk was positively associated with alcohol consumed between ages 18 and 22 years.[16] A prospective assessment of alcohol consumption in daughters of NHSII participants also showed that alcohol consumption between ages 16 and 22 years was associated with a 50% (odds ratio, 1.50 per drink per day; 95% CI, 1.19–1.90) increased risk of overall BBD (including both proliferative and nonproliferative BBD [not confirmed by central pathology review]).[29] Taken together, these findings suggest that alcohol consumption during adolescence and early adulthood may have more impact on the early stages of breast tumor progression than consumption of alcohol later in life.

We further analyzed the combined effect of alcohol consumption at the ages of 18–22 years and folate intake in high school on proliferative BBD. To the best of our knowledge, this is the first study to examine the modifying effect of adolescent folate intake on the association between alcohol consumption during adolescence and early adulthood and proliferative BBD. Our study did not support the hypothesized interaction between adolescent alcohol and folate intake in proliferative BBD; although among women with low folate intake, risk of proliferative BBD increased with higher alcohol consumption, increased folate intake did not significantly reduce the risk associated with high alcohol consumption. The null finding was consistent with the Women's Health Initiative randomized clinical trials that provided no evidence for the interaction between recent (adult) alcohol and

TABLE 3 HRs and Their 95% CIs for Combined Intakes of Alcohol and Folate During Adolescence and Risk of Proliferative BBD

Tertile of Total Folate Intake	Alcohol Consumption, g/d	No. of Cases	Person-years	Jointly classified[a]		Stratified[a]	
				HR	95% CI	HR	95% CI
T1 (Lowest)	None	50	23 063	Reference		Reference	
	0.1–4.9	71	25 808	1.33	0.92–1.91	1.33	0.91–1.93
	5.0–14.9	86	26 869	1.67	1.17–2.39	1.74	1.20–2.53
	15+	26	9275	1.57	0.97–2.56	1.64	0.98–2.73
						P for trend = 0.07	
	Per 10 g/day increase					1.21	1.01–1.45
T2	None	59	20 844	1.33	0.91–1.94	Reference	
	0.1–4.9	57	26 012	1.11	0.75–1.63	0.83	0.57–1.21
	5.0–14.9	84	28 685	1.59	1.11–2.28	1.17	0.81–1.68
	15+	27	9642	1.61	0.99–2.61	1.17	0.71–1.91
						P for trend = 0.21	
	Per 10 g/day increase					1.15	0.95–1.38
T3 (Highest)	None	46	20 921	1.10	0.74–1.65	Reference	
	0.1–4.9	65	26 543	1.35	0.92–1.96	1.24	0.83–1.84
	5.0–14.9	66	28 756	1.36	0.93–2.00	1.20	0.80–1.81
	15+	22	10 135	1.42	0.84–2.38	1.38	0.79–2.41
						P for trend = 0.41	
	Per 10 g/day increase					1.13	0.92–1.40

P for interaction = .18.

[a] The model adjusted for age in months, total energy intake (quintiles), age at menarche (<12, 12, 13, or ≥14 y), menopausal status (premenopausal, postmenopausal, or uncertain), average body size between ages 5 and 10 y (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, or ≥5), family history of breast cancer in mother or sister(s) (yes versus no), recency and duration of oral contraceptive (OC) use (never, past <4 y, past ≥4 y, current <4 y, or current ≥4 y), current alcohol consumption (none, 0.1–4.9 g/day, 5.0–14.9 g/day, 15+ g/day, or missing), and parity and age at first birth (nulliparous; 1–2 pregnancies, age at first birth <25 y; 1–2 pregnancies, age at first birth 25–29 y; 1–2 pregnancies, age at first birth ≥30 y; ≥3 pregnancies, age at first birth <25 y; ≥3 pregnancies, age at first birth 25–29 y; or ≥3 pregnancies, age at first birth ≥30 y.

folate intake in the risk of proliferative BBD.[17] In addition, 3 cohort studies reported that the risk of invasive breast cancer associated with recent alcohol consumption did not significantly vary with recent folate intake,[30–32] although 8 cohort studies showed stronger positive associations between recent alcohol consumption and the risk of invasive breast cancer in women who had low folate intake or circulating folate concentrations versus women with high folate intake or circulating folate concentrations.[8–13,33]

Despite the critical role of folate in gene expression and DNA repair, the reported relationship between folate intake or circulating folate levels and breast cancer risk has been inconsistent.[7] Our study provides no evidence for a protective effect of folate intake during adolescence on risk of proliferative BBD. Among adult women with recent alcohol consumption 15+ g/day, consumption of $\geq$600 μg of total folate per day was associated with a 44% (RR = 0.56, 95% CI, 0.41–0.79) decreased risk of invasive breast cancer in comparison with consumption of 150–299 μg of total folate/day.[13] Therefore, our null finding could be due to the average level of total folate intake (median = 310 μg/day) in our sample that was too low to detect a significantly inverse association with risk of proliferative BBD.

The primary limitation of this study concerns the reliability of recalled alcohol and folate intake during adolescence. In the NHSII participants, recall of adolescent diet occurred an average of 25 years later. However, the HS-FFQ has been demonstrated in the NHSII participants to have moderate 4-year reproducibility (folate intraclass correlation coefficient = 0.72) and to be independent of adult diet.[24] Furthermore, the HS-FFQ was compared with 24-hour recalls in NHSII offspring; the FFQ collected when the participants were in high school showed moderate correlations.[34] Therefore, the HS-FFQ provides a reasonable record of adolescent diet. In addition, the moderately high correlation between folate intake from the first HS-FFQ and from the second HS-FFQ (4 years later) suggested that use of folate intake collected 9 years after collection of adolescent alcohol intake should have little impact on the current analysis. Further, differential recall bias should be minimal because women with proliferative BBD in our study had no previous cancer diagnosis, although some reported their folate intake in high school after being diagnosed with BBD. The current analysis focused on alcohol consumption at ages 18 to 22 years, which is later than folate intake in high school. In our sample, folate intake is unlikely to have changed substantially between adolescence and early adulthood because folate fortification in the United States was not introduced until 1998.[35,36] However, we cannot evaluate how much individuals modified their own diets after high school; folate intake during the same time period as alcohol consumption may be more relevant, and our use of high school folate intake may underestimate this association.

Proliferative BBD is histologically divided into 2 groups based on the presence of atypia. Atypical hyperplasia confers higher risk of subsequent breast cancer than hyperplasia without atypia.[14,15,37,38] Due to the very small number of cases with atypia in the current analysis, we were unable to address whether alcohol consumption during adolescence is differentially associated with proliferative BBD with and without atypia.

CONCLUSIONS

This study suggests a dose-dependent increase in risk of proliferative BBD with alcohol consumption during adolescence and early adulthood, which may not be reduced through increased folate intake. This result, if confirmed in studies performed in other populations, indicates that increased folate intake during adolescence may not effectively prevent alcohol-associated breast cancer. Since alcohol use is common in adolescent girls and young women,[39,40] reducing alcohol consumption during adolescence and early adulthood is currently the only dietary strategy that may reduce risk of proliferative BBD.

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