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# Prospective Study of Adolescent Alcohol Consumption and Risk of Benign Breast Disease in Young Women

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## Abstract

**OBJECTIVE—**To investigate prospectively, using alcoholic beverage consumption data collected in real time, the association between adolescent drinking and risk of biopsy-confirmed benign breast disease (BBD) in young women.

**PARTICIPANTS AND METHODS—**The Growing Up Today Study (GUTS) is a prospective cohort study of U.S. females, aged 9 to 15 years at baseline, with annual questionnaires from 1996 through 2001, followed by questionnaires in 2003, 2005 and 2007. On the 2003 survey, the participants (then aged 16 to 23 years) provided information about their past-year alcoholic beverage consumption. On the 2005 and 2007 surveys, a total of 6899 females (aged 18 to 27 years) reported whether a health care provider had ever diagnosed them with BBD (n=147 cases) and whether it was confirmed by biopsy (n=67 cases); 6752 females reported never being diagnosed with BBD.

**RESULTS—**Adjusted for age and BMI, quantity of alcohol consumed was associated with increased risk of biopsy-confirmed BBD (OR=1.50 per drink/day, 95%CI: 1.19, 1.90). Females who typically drank six or seven days a week were at higher risk (OR=5.50, 95%CI: 1.23, 24.53) compared to those who never drank or who drank less than once per week.

**CONCLUSION—**Higher amounts consumed, and more frequent consumption, of alcoholic beverages in adolescence may increase the occurrence of BBD in young women. Advising teens to avoid alcoholic beverages, along with smoking and sun exposure, may reduce cancer incidence in adulthood.

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**Author Contributions**

All authors contributed to the collection of data from the GUTS cohort over the years. Drs. Berkey, Colditz and Willett conceived the hypotheses investigated in this manuscript. All authors participated in the design of this particular study; Dr. Berkey performed the analyses and drafted the manuscript. Funding was obtained by Dr. Colditz. All authors assisted in the interpretation of the data and writing/revision of the manuscript. Dr. Berkey had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

### Keywords

teens; BBD; alcohol; drinking; BMI; breast cancer; beer; wine; liquor; longitudinal

A critical period for certain exposures related to risk of breast cancer occurs between menarche and first pregnancy, when mammary gland cells are undergoing rapid proliferation and may be more vulnerable to malignant transformation.[1] A massive body of evidence indicates that adult alcohol intake increases risk of breast cancer,[2–7] but alcoholic beverage consumption often begins between menarche and first pregnancy. Benign breast disease (BBD), particularly certain histologic subtypes, predicts increased risk for breast cancer.[1,8–9] Thus, the relationship between adolescent alcohol consumption and BBD has implications for breast cancer. A retrospective study, in which adult women recalled (decades later) their adolescent diets, implicated alcoholic beverage consumption at ages 18–22yr as a risk factor for biopsy-confirmed BBD.[10]

Using data from a prospective cohort of children initiated when they were 9–15 years old, we investigated whether drinking during adolescence is associated with BBD in young women.

## METHODS

### Subjects

Established in 1996, the Growing Up Today Study (GUTS) includes 9037 girls from 50 states who are daughters of Nurses' Health Study II (NHSII) participants.[11] The study, approved by Human Subjects Committees at Harvard School of Public Health and Brigham and Women's Hospital, is described elsewhere.[12] Mothers provided informed consent, and their daughters assented by completing baseline questionnaires. The cohort returned follow-up questionnaires annually through 2001, followed by surveys in 2003, 2005 and 2007. The girls' response rate to one or more follow-ups after baseline was 97%. A total of 73% (n=6576) returned the 2003 survey, containing a series of alcohol consumption questions, and 77% (n=6927) returned either the 2005 or 2007 (through December 2008) surveys enquiring about BBD. A total of 6899 females provided information on BBD; excluded were 8 girls whose mothers reported their daughters had been diagnosed with childhood cancer. The number of girls in each analysis will be determined by the number providing alcohol information on the particular survey being analyzed (2000, 2001 or 2003) as well as BBD information.

### Alcoholic Beverages

Alcohol intake was assessed two years prior to the initial inquiry about BBD. The 2003 survey, administered when participants were aged 16–23yr, asked about alcohol consumption through four questions. Participants were first asked "Have you ever tried drinking alcohol (beer, wine, or liquor), even a few sips?" to which 86% said yes. Those who had tried alcohol were asked three further questions. A drinking frequency question "On average, in the past year, how often did you drink beer, wine, or liquor?" had 7 response options ranging from "Don't drink" to "daily". A drinking quantity question "When you drink alcohol, how much do you usually drink at one time?" had 8 response categories ranging from "Don't drink" to "6 or more glasses/cans/drinks". The survey specified that 1 drink was equivalent to 1 can/bottle of beer, 1 glass of wine, 1 shot of liquor, or 1 mixed drink. The final question regarded binge drinking "During the past year, how many times did you drink 4 or more alcohol drinks over a few hours?" with 7 response categories ranging from "none" to "12 or more times". The derivation of typical past-year

alcoholic beverage consumption (drinks/day) utilized responses from frequency and quantity questions (after each converted to a continuous variable), but did not use the binge-drinking variable.

Separate analyses used data from two earlier GUTS surveys, each with a different alcohol question format. The 2000 survey asked directly about quantity consumed of "Beer, wine, liquor (1 glass, can, drink)" combined, with 8 options from "Never" to "More than 3 per day". The 2001 survey had a separate question for each beverage: "Beer (1 glass, bottle or can)", "wine or wine coolers (1 glass)" and "Liquor, like vodka or rum (1 drink or shot)", and each beverage had 8 response options from "Never" to "More than 3 per day". After converting beer, wine and liquor intakes to continuous variables, total 2001 alcohol intake was computed by adding the three together.

A review article on the validity of adolescent self-reports of risky behaviors concluded that the privacy of self-administered questionnaires produces higher, supposedly more valid, reported rates of alcohol use.[13] Test-retest reliability levels were generally high for alcohol, but it is difficult to do validation studies of long-term moderate alcohol use due to lack of biochemical measures.[13]

## Benign Breast Disease

The 2005 and 2007 surveys asked "Has a health care provider ever diagnosed you as having Benign Breast Disease?" and whether it had been "Confirmed by breast biopsy". A total of 6752 females who reported they had never been diagnosed with BBD provide the non-cases for analyses. Another 147 females reported that they had been given a diagnosis of BBD, though not all were confirmed by biopsy. BBD cases are those 67 girls whose diagnoses were confirmed by biopsy; these include 27 with biopsy-confirmed BBD reported in both 2005 and 2007, another 29 with confirmed BBD only in 2007 (some returned no 2005 survey), and 11 with confirmed BBD reported in 2005 (but no 2007 survey). These 67 cases and 6752 non-cases provide the data for the primary analyses of biopsy-confirmed BBD. We also perform sensitivity analyses utilizing alternative case definitions; a weaker case definition uses all 147 girls who ever reported BBD (confirmed or not), and a stronger case definition uses only those 27 girls who reported biopsy-confirmed BBD in both 2005 and 2007.

Questionnaires did not ask for dates of diagnosis. Most of these BBD cases were likely diagnosed because participants (or their physicians) found a clinically palpable mass, since they were too young to undergo routine screening mammography.

A validation study was performed on 729 young women (NHSII) who reported a first diagnosis of biopsy-confirmed BBD on their 1993, 1995, or 1997 questionnaires. Of these, 91% granted permission for review of biopsy records and pathology specimens. Adequate pathology material was obtained from hospitals and reviewed for 93% of these, of whom 95% were confirmed by detailed histologic review to be valid BBD cases.[14] This supports the ability of young women who are nurses, and hopefully our participants who are daughters of nurses, to provide valid self-reports of biopsy-confirmed BBD.

## Other Variables

At baseline, children reported their race/ethnic group by marking all (of six) options that applied. We computed ages from dates of questionnaire return and birth. On each survey, girls reported whether menstrual periods had yet begun; nearly all (99.9%) were post-menarche by 2003. Participants reported their heights and weights on every survey. We assessed relative weight status by computing body mass index (BMI= weight/height$^2$, (kg/m$^2$)). An analysis of NHANES III adolescents supported high validity for self-reported

height and weight.[15] The validity of self-reported BMI was demonstrated by National Longitudinal Study of Adolescent Health analyses that found high correlation between BMI computed from measured values and from self-reports by youth in grades 7–12.[16] Our participants' mothers reported their own diagnoses of biopsy-confirmed BBD and breast cancer.[11]

### Statistical Analyses

Primary analyses included females responding to surveys in 2003 enquiring about alcohol consumption and later surveys in 2005 or 2007 enquiring about BBD. Because we had no information on when cases were diagnosed, the outcome for analyses was prevalent BBD. Logistic regression models, estimated using SAS,[17] provided odds ratios (OR) and 95% confidence intervals (CI) for BBD risk associated with alcohol consumption reported in earlier years. Because age was related to how much alcohol a girl consumed, along with her chance of being diagnosed with BBD within the following few years, we adjusted all models for exact age (to the month) when alcohol data were provided. Due to concerns that overweight and obesity may reduce the likelihood of a BBD diagnosis, we adjusted all models for BMI at time of disease reporting (mean of 2005 and 2007 BMI's). Models tested hypotheses that typical alcohol consumption, frequency of drinking, amount consumed at each drinking occasion, and frequency of binge drinking, are associated with BBD.

Analyses of typical alcohol consumption reported earlier in years 2000 and 2001 were performed separately, since each collected alcoholic beverage data differently. Though three dissimilar formats, we further estimated cumulative average intakes, from 2000 through 2003, and performed analyses on them as well. Sensitivity analyses utilized the two alternative "BBD case" definitions described earlier.

## RESULTS

BBD information was obtained from 6899 females, who provided 67 biopsy-confirmed BBD cases and 6752 non-cases for analyses. Most GUTS females are white/non-Hispanic (95%), as are most of these BBD cases. One case reported "other" race, one case reported being both white and American Indian or Alaskan native, and one did not complete the race question.

Baseline (1996) data of females who returned the 2005 and/or 2007 survey(s) (77% of the original cohort) are compared with those who returned neither survey and thus had no BBD information to contribute to these analyses. At baseline, the included girls tended to be slightly younger (by 0.108 yr, $p<.01$) than those not included here; otherwise, they were similar at baseline, in body weight (age-adjusted baseline BMI difference of 0.08 $kg/m^2$, $p=.32$) and total calories (19 kcal/day difference, $p=.24$). Thus, we may be missing some older participants who were diagnosed with BBD during follow-up.

BBD cases and non-cases had similar mean age at menarche (12.8yr vs 12.6yr). Cases and non-cases became regular drinkers (drank at least monthly) at similar ages (both means 19.0yr) though more non-cases never became regular drinkers (20% vs 12%) through year 2008. More cases had mothers with a history of breast cancer (6% vs 3.2%) or BBD (26.9% vs 18.5%) than non-cases. Cases tended to be thinner at time of disease reporting (mean BMI= 22.9 $kg/m^2$ for cases compared to 23.7 for non-cases).

Table 1 shows means and percents, by BBD case status, of alcohol factors from the 2003 survey. Females were aged 16 through 23 years when they provided these alcohol data; the BBD cases were about 8 months older in 2003, drank alcohol more frequently, consumed

more at each drinking occasion, and average daily consumption was more than twice as high. Cases also reported more episodes of binge drinking.

In BMI- and age-adjusted analyses, typical alcohol intake (OR=1.50 per drink/day, 95%CI: 1.19, 1.90) from the 2003 survey was associated with higher BBD risk (Table 2). Stratifying by BMI quartiles showed the risk persisted within BMI subgroups (OR=1.61 per drink/day for the most lean, and OR=1.51 for the heaviest women; not shown). BMI- and age-adjusted analyses of drinking frequency also found an association (OR=5.50 for those drinking 6 or 7 days/week relative to those drinking less than once per week; 95%CI: 1.23, 24.53) (Table 2). The two variables "drinking frequency" and "drinks per occasion" are highly correlated; when included together in a model, frequency of drinking was more important (Table 2, bottom).

To show that these findings were not confounded by a series of other factors, we re-fit the "drinks per day" model adjusting for them individually. Including age at menarche (not itself significant) in the model did not modify the estimate of risk for alcohol, nor did adjusting for maternal breast cancer and maternal biopsy-confirmed BBD, neither of which were significant. Adjusting for age at onset of regular drinking (among those who became regular drinkers; also not significant) similarly did not substantially affect the estimated risk per drink/day in 2003.

Mean alcohol intakes generally doubled from one year of age to the next until age 18yr, and therefore intakes at ages younger than 18 may not correspond to the exposure levels relevant to BBD risk (particularly for girls who did not drink at all before college). Analyses stratified by age (Table 3) found elevated BBD risk with higher alcohol consumption at ages 19 (OR=1.76 per drink/day, 95%CI: 1.19–2.60) and 21+ (OR=1.51 per drink/day; 95%CI 1.02–2.26). Intakes at other ages suggested similarly elevated risks, though not statistically significant (Table 3). Pooling together females aged 18yr+ at time of 2003 alcohol report, the BBD risk was OR=1.51 per drink/day (95%CI: 1.19, 1.92).

To see if conclusions persisted, models were re-estimated using alcohol data obtained from earlier survey years, 2000 and 2001. Of the females who provided BBD information, 54 cases and 5623 non-cases returned surveys in year 2000, and 53 cases and 5542 non-cases in year 2001. From year 2000 alcohol intakes, the risk of BBD was OR=1.56 per drink/day (95%CI: 0.87, 2.77), and from year 2001 intakes OR=1.46 per drink/day (95%CI 0.96, 2.19). Restricting estimation of these models to females who were 18yr and older when reporting alcohol, the BBD risk was OR=2.24 (95%CI: 1.20, 4.18) per drink/day reported in 2000, and OR=1.51 per drink/day (95%CI: 0.99, 2.31) reported in 2001. The 18+ year-olds in year 2000 have more years of alcohol exposure before BBD reporting began in 2005, than the larger number of 18+ year-olds in 2003, which may explain their different estimates. The 2001 survey asks separately about beer, wine and liquor, and thus the 2001 summed intake may differ in accuracy from the other surveys. The dissimilarities among the alcoholic beverage question formats on the surveys (2000, 2001, 2003) hinder the analysis of cumulative mean exposures; however, we cautiously report that analyzing cumulative average consumption (2000 through 2003) also indicated increased risk (OR=1.64 per drink/day, 95%CI: 1.11, 2.42) for BBD.

Sensitivity analyses were conducted to see how results differed under alternative case definitions. Using a weaker definition, in which all reports of BBD (including those not confirmed by biopsy) are considered cases (n=147), the risk associated with 2003 alcohol was OR=1.26/drink per day (95%CI: 1.04, 1.53). A stronger case definition that required two reports of biopsy-confirmed BBD (in both 2005 and 2007; n=27 females) estimated the 2003 alcohol risk as OR=1.60 per drink/day (95%CI: 1.16, 2.19). Thus, 2003 alcohol

consumption was significantly associated with increased risk of BBD, no matter how we defined BBD cases.

## DISCUSSION

This is the first study of alcohol intake assessed during adolescence, rather than recalled many years later, and risk of BBD. These analyses provide evidence that regular drinking by adolescent females is associated with increased risk for biopsy-confirmed BBD; this conclusion persisted under alternative BBD case definitions. Our age- and BMI-adjusted estimates of risk persisted when we further adjusted for age at menarche, age when regular drinking began, and maternal history of BBD and breast cancer. The latter four adjustment factors were not themselves significantly associated with BBD risk, but the higher rates of maternal BBD and breast cancer among our BBD cases may suggest detection bias in those with a maternal history of disease. Because alcohol intakes increase dramatically when adolescents enter college, consumption at ages 18 and beyond probably better reflect the exposure levels that present risk for BBD; odds ratios estimated from females aged 18+yr provided stronger conclusions. But the consistency of our risk estimates across ages at exposure, and similarly across BMI subgroups, strengthens our findings.

Our results are consistent with a retrospective study in which adult recall of age 18–22yr alcohol consumption of ≥15g/day was associated with higher rates of biopsy-confirmed BBD (RR=1.14, 95%CI 1.00–1.30) and proliferative BBD (RR=1.33, 95%CI 1.05–1.69), though alcohol consumed at younger ages (15–17yr) was not.[10] That study also found alcohol intakes between 18–22yrs associated with increased risk of non-proliferative BBD (OR=1.46 for ≥15g/day compared to nondrinkers, 95%CI 1.09–1.96).[10] Interestingly, those women with recent (adult) consumption of 5–14.9 g/day had increased risk of non-proliferative BBD (RR=1.33 compared with nondrinkers, 95%CI: 1.04–1.71), but not of proliferative BBD.[10] A study by Tamimi et al.[9] linked recent adult alcohol consumption to increased breast cancer risk (OR=1.10 per daily 5 g, 95%CI: 0.95–1.27) among adult women with non-proliferative BBD, while there was no positive association among women with proliferative BBD. Though we do not yet have BBD histologic subtype data and have thus included both non-proliferative and proliferative cases in these analyses, there is likely heterogeneity in the alcohol effects that we were unable to assess here.

Retrospective studies have also suggested that adolescent intakes of vitamin E, fiber, and vegetable fat[19] and being heavier in childhood and adolescence[18] are protective against proliferative BBD. It will be interesting to see whether future studies suggest adolescent dietary correlates of BBD that are similar to those noted for breast cancer. Studies on whether early drinking has a role in breast cancer have provided inconsistent results, though all utilized alcohol data collected retrospectively, and most were case-control studies.[20–22] In the NHSI cohort, high adolescent alcohol intakes appeared to increase premenopausal breast cancer risk by nearly 50% and postmenopausal risk by nearly 70%, though these estimates were not statistically significant.[23] In the NHSII cohort, high alcohol intakes at ages 15–17 appeared to increase breast cancer risk by 71% (not significant) and high intakes at ages 23–30 were significantly associated (RR=1.72, 95%CI 1.01–2.91), but recalled intakes for ages 18–22 were not (RR=0.77, 95%CI 0.48–1.24).[24] These inconsistent findings emphasize the need for continued follow-up of the GUTS cohort to observe the development of breast cancer in young women.

Regarding possible mechanisms, a crossover trial demonstrated that alcohol consumption was responsible for increases in total estrogen levels and amount of bioavailable estrogens.[25] Other evidence that alcohol acts early in the carcinogenic process is provided by studies showing that recent alcohol consumption is positively associated with

mammographic density.[26–28] In another study, dietary intake of ethanol was marginally (p=.07) inversely associated with estrogen receptor alpha (ER-alpha) expression in normal mammary tissue that was obtained from women with breast cancer or BBD.[29]

Our finding that alcoholic beverages may increase BBD risk is somewhat curious, given that alcohol promotes adolescent weight gain.[30–31] Consistent with our BBD analyses, other cohorts found greater body weight associated with lower risk of BBD[18] and premenopausal breast cancer.[23,32]

## CONCLUSIONS

This study suggests that consumption of alcoholic beverages in adolescence increases the occurrence of BBD in young women. This finding raises concern because alcohol intakes by college students has increased greatly in recent years,[33] while drinking by adult women is one of few known dietary risk factors for breast cancer. If future work confirms our findings, then clinician efforts to delay the onset of alcohol consumption and to reduce amounts consumed may prevent some cases of BBD and breast cancer.

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## Abbreviations

| | |
|---|---|
| **BBD** | benign breast disease |
| **GUTS** | Growing Up Today Study |
| **BMI** | body mass index |

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## TABLE 1

Alcoholic beverage factors, reported in 2003, by benign breast disease (BBD) case status, reported from 2005 through 2008[a]

| | No BBD | BBD Case (Biopsy confirmed) |
|---|---|---|
| Total N= | 6752 | 67 |
| Age (yr) at alcohol report in 2003 | 19.3 | 20.0 |
| Ever try alcohol (% yes) | 86.0 | 90.2 |
| Drinking Frequency (%) | | |
| Don't Drink | 26.7 | 25.5 |
| Less than once a month | 28.2 | 13.7 |
| Less than once a week | 21.0 | 15.7 |
| 1–2 days per week | 18.7 | 27.5 |
| 3–5 days pr week | 4.8 | 13.7 |
| Almost everyday | 0.6 | 3.9 |
| Daily | 0.1 | 0.0 |
| Drinks consumed each occasion | 2.4 | 2.8 |
| Drinks/day (derived) | 0.37 | 0.82 |
| Any binge drinking past year (%) | 66.3 | 65.4 |
| Binge 12+ times past year (%) | 20.9 | 42.3 |
| Past year # occasions binge drink | 4.70 | 6.40 |

[a]Means and percents for alcohol data were derived from 2003 survey.

## TABLE 2

Alcoholic beverage variables (2003) and risk of benign breast disease (diagnoses reported from 2005 through 2008)[a]

| | OR | (95%CI) |
|---|---|---|
| Drinking Frequency | | |
| Never to less than weekly | 1.00 | (referent) |
| 1–2 days per week | 1.57 | (0.80–3.09) |
| 3–5 days per week | 3.01 | (1.27–7.14) |
| 6–7 days per week | 5.50 | (1.23–24.53) |
| Drinks per Occasion | 1.06 | (0.92,1.21) |
| Drinks/day | 1.50 | (1.19,1.90) |
| Past-yr Binge Drinking: Continuous, Per Binge | 1.04 | (0.99,1.10) |
| Past-yr Binge Drinking: 12 or More Binges vs None | 1.50 | (0.78, 2.86) |
| Drinking Frequency and Drinks per Occasion in model together: | | |
| Drinking Frequency | | |
| Never to less than weekly | 1.00 | (referent) |
| 1–2 days per week | 1.72 | (0.80–3.71) |
| 3–5 days per week | 3.34 | (1.28–8.74) |
| 6–7 days per week | 5.94 | (1.29–27.44) |
| Drinks Per Occasion | 0.96 | (0.81,1.13) |

[a] Adjusted for age (when 2003 survey returned, to the month) and BMI (when BBD disease data provided). N=57 cases and 5839 non-cases provided 2003 survey data for these analyses.

**TABLE 3**

Adolescent alcohol intake and risk of benign breast disease in young women, by age when alcohol intake was reported[a]

| Age group in 2003 | 16–17 | 18 | 19 | 20 | 21+ |
|---|---|---|---|---|---|
| N= | 1513 | 1131 | 1098 | 1018 | 1136 |
| BBD cases N= | 8 | 6 | 13 | 9 | 21 |
| Mean daily alcohol | 0.115 | 0.310 | 0.503 | 0.516 | 0.590 |
| OR (95%CI) | 1.52 (0.51,4.53) | 1.45 (0.59,3.52) | 1.76 (1.19,2.60) | 1.10 (0.53,2.30) | 1.51 (1.02,2.26) |

[a]Adjusted for BMI at time of BBD disease reporting. N=57 cases provided 2003 survey data for these analyses.

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