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Alcohol consumption across the life course and mammographic density in premenopausal women

Ying Liu[1,2], **Rulla M. Tamimi**[3,4], **Graham A. Colditz**[1,2], and **Kimberly A. Bertrand**[5]

[1]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO

[2]Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, MO

[3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[5]Slone Epidemiology Center at Boston University, Boston, MA

Abstract

Purpose—Consumption of alcoholic beverages during adolescence and early adulthood has been consistently associated with higher breast cancer risk. The influence of alcohol consumption early in life on mammographic breast density, a marker of breast cancer risk, is inconclusive. This study examined associations of alcohol consumption across the life course with premenopausal mammographic density.

Methods—The study population included 1,211 premenopausal women in the Nurses' Health Study II without cancer, recalled their alcohol consumption at age 15 through enrollment in 1989 (baseline), and had mammograms available. Recent alcohol consumption was updated over follow-up. Percent and absolute measures of mammographic density were quantified on digitized film mammograms. Generalized linear regression was used to assess associations.

Corresponding Author: Kimberly Bertrand, Slone Epidemiology Center at Boston University, 72 East Concord Street, L-7, Boston, MA 02118, 617-206-6174, kab15@bu.edu.

COMPLIANCE WITH ETHICAL STANDARDS:

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All authors have no conflict of interest.

Ethical approval:
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:
Participants implied consent with the return of questionnaires. The study was approved by the Human Subjects Committees at the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

Author's contributions:
Study concept and design: Liu, Tamimi, and Bertrand Acquisition of data: Tamimi and Colditz
Analysis and interpretation of data: Liu, Tamimi, Colditz, and Bertrand
Drafting of the manuscript: Liu and Bertrand
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Results—There were no notable differences in any of three density measures for alcohol consumption at any age (15–17, 18–22, 23–30, and 31-mammogram). Neither alcohol consumption before first pregnancy nor after first pregnancy was significantly associated with any of three density measures.

Conclusions—Moderate alcohol consumption during different age intervals during adolescence and early adulthood was not associated with mammographic density in premenopausal women.

Keywords

Breast cancer; mammographic density; alcohol; adolescence

INTRODUCTION

Alcoholic beverages are Group 1 carcinogens according to the International Agency for Research on Cancer [1]; breast cancerrisk increases by 7%–10% per 10g (approximately 1 drink) alcohol consumed daily during adulthood [2–4]. Premenopausal and postmenopausal women have a comparable magnitude of association [2, 5].

Mammographic density (MD), measured as the relative amount of radiographically dense epithelial and stromal tissue in the breast, is an established, independent breast cancer risk factor. Women with high MD have 4–6 times higher risk compared to those with predominantly fatty breasts [6]. Some, but not all, studies report positive, though moderate, associations of alcohol consumption with MD (for review, see [7]). These studies have largely focused on current/recent alcohol consumption, and the majority were based on populations of predominantly postmenopausal women.

Early life exposures are recognized to be particularly relevant to lifetime risk of breast cancer. For example, women with earlier age at menarche and later age at first pregnancy have higher risk of breast cancer later in life. The risk of breast cancer accumulates during a woman's life, with adolescence and early adulthood (e.g., from menarche to first pregnancy) representing a particularly susceptible exposure window for rapid risk accumulation [8–10]. We have demonstrated that drinking alcohol this time period is associated with increased risks of invasive breast cancer [relative risk (RR) per 10 g/day of intake: 1.11; 95% CI: 1.00, 1.23] and proliferative benign breast disease, a well-established breast cancer risk marker (RR per 10 g/day of intake: 1.16; 95% CI: 1.02, 1.23) [11]. Therefore, we examined the associations of alcohol consumption during different life periods with MD among premenopausal women.

METHODS

Study population

The Nurses' Health Study II (NHSII) began in 1989 and included 116,671 female registered nurses ages 25 to 44 years. Participants responded to a baseline mailed questionnaire about their health status, weight, reproductive history, medication use, and lifestyle habits, including alcohol use. Biennial questionnaires are administered through the mail and online to update information and to identify incident cancer and other diagnoses. Through 2009,

follow-up has been higher than 90% of the total potential person-years [12]. The return of questionnaires implied consent of participants. The Human Subjects Committees at the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital approved this study.

A nested case-control study was established within the NHSII to conduct biomarker-based studies of breast cancer. Controls were matched to incident breast cancer cases (2:1) by age, race/ethnicity, menopausal status, and factors related to blood draw [13]. As part of this nested case-control study, we collected mammograms conducted near blood draw years (1996–1999) from approximately 80% of participants [14]. In a separate collection effort, we also retrieved mammograms performed close to 1997 from women with and without breast cancer in the NHSII who were not part of the case-control study. There were no differences in family history of breast cancer, parity, or body mass index (BMI) between women with available mammograms and women for whom we were unable to obtain mammograms [15].

Alcohol consumption

Information onalcohol consumption was queried on the 1989 baseline questionnaire for four ages: ages 15–17, 18–22, 23–30, and 31–40 years. Usual number of alcoholic drinks (sum of bottles/cans of beer, 4-ounce glasses of wine, and shots of liquor) consumed during these age intervals was also reported; women responded by selected one of nine consumption categories from "none or <1/month" to "40+/week." To estimate total grams of alcohol/day, we assumed that each alcoholic drink contained 12.0 g of alcohol [16].

Current (i.e., over the past year) consumption of alcohol, including beer, wine, and liquor separately, was also asked in 1989 . We summed reports of beer, wine and liquor consumption to estimate total alcohol consumption assuming 12.8 g of ethanol in a bottle/can of regular beer, 11.0 g in a 4-oz glass of wine, and 14.0 g in a shot of liquor [16]. Alcohol drinking was updated in 1991, 1995 and subsequently every four years, and further separated regular vs. light beer and red vs. white wine. A bottle/can of light beer was assumed to contain 11.3 g of ethanol [17].

We considered cumulative average consumption of alcohol from the time of menarche to first pregnancy as a proxy for intensity of drinking during this interval [11]. Briefly, alcohol intake (g/day) in each age interval prior to first pregnancy was weighted by number of years of the interval, and the sum of contributions of each age interval was divided by the interval length in years. For women who reported menarche occurring before age 15, cumulative average alcohol consumption was calculated beginning at age 15 because information on alcohol intake before age 15 was not avaialble. Cumulative average alcohol consumption after first pregnancy through the time of mammogram was calculated in a similar manner.

Mammographic density assessment

Percent and absolute MD was assessed quantitatively using Cumulus, a computer-assisted thresholding software program (University of Toronto, Toronto, Canada), from digitized film mammograms (cranio-caudal view) [15]. The three density measures were then calculated, including absolute dense area (in cm^2), absolute non-dense area (in cm^2) (total breast area

minus dense area), and percent MD (dense area divided by the total breast area). All images were assessed by a single reader (within-person intra-class correlation coefficient >0.90) [14, 19] in three batches. Observed inter-batch variability in MD measures was adjusted for as described elsewhere [15]. Due to a strong correlation between MD in the right and left breasts (r=0.92–0.96) [20], we considered average measures from both breasts in this analysis.

Covariates

Potential covariates, including age at menarche and BMI at age 18, were collected in 1989. Time-varying covariates were obtained from the last questionnaire before mammogram, including parity, age at first pregnancy, breast cancer in first-degree relatives, benign breast disease, use of oral contraceptives, duration of breastfeeding, and current BMI.

Statistical analysis

This analysis included premenopausal controls for whom both alcohol consumption during early age periods and mammographic density were available (n=1,259). We excluded women who had no information about BMI at time of mammogram (n=48). Alcohol consumption during different life periods was categorized as 0, <5 g/day, 5–<10 g/day, and ≥10 g/day. Three categories of alcohol consumption between ages 15–17 were used because few women reported drinking more than 5g/day during this age interval. Generalized linear regression models were used to assess the association between alcohol consumption and the three MD phenotypes. The correlation between matched controls was accounted for by generalized estimating equations. The models were adjusted for age (continuous), parity, breast cancer family history (yes or no), benign breast disease (yes or no), use of oral contraceptives (never or ever use), and BMI (continuous), all at or close to mammography, as well as age at menarche (< 12 or ≥12) and age at first pregnancy. Parity and age at first pregnancy were combined as follows: nulliparous; 1–2 kids, age<25 years; 1–2 kids, age 25–29 years; 1–2 kids, age≥30 years; ≥3 kids, age<25 years; ≥3 kids, age 25–29 years; ≥3 kids, age≥30 years. Least square means of percent MD, absolute dense breast area, and and absolute non-dense breast area were estimated for each category of alcohol consumption. Trend across exposure categories was tested using Wald statistic by including the medians of alcohol consumption categories as continuous variables in multivariable models. Square-root transformation of dense and nondense breast area were performed to approximate the normal distribution. Based on a prior report of potential effect modification of the alcohol-MD association by BMI [21, 22], we stratified analyses by BMI at mammogram . We tested for statistical interaction by modeling the cross-product term. Analyses were performed using SAS version 9.3 for UNIX (SAS Institute, Cary, NC). All statistical tests were two-sided using a significance level of P <0.05.

RESULTS

Among 1,211 premenopausal controls, 133 (11.0%) never drank alcohol from age 15 through time of mammogram. Among 1,078 ever alcohol drinkers, 269 (25.0%) drank alcohol at the ages of 15–17, 904 (83.9%) at the ages of 18–22, 931 (86.4%) at the age of 23–30, and 950 (88.2%) after age 30 through time of mammogram. The median amount of

alcohol consumed among drinkers was 1.7 g/day at the ages of 15–17, 5.2 g/day at the ages of 18–22, 1.7 g/day at the ages of 23–30, and 2.3 g/day after age 30 through the time of mammogram. The correlation between alcohol consumption during different age periods ranged from 0.17 to 0.66.

Table 1 shows age-standardized characteristics of the study population by categories of alcohol drinking between ages 18 and 22 years. Women with higher alcohol intake at the ages of 18–22 years were younger at mammogram, had higher BMI both at mammogram and at age 18, were more likely to be nulliparous or (among parous) older at the time of first birth, were more likely to report use of oral contraceptives, and were less likely to have a mother or sister diagnosed with breast cancer or a history of benign breast disease themselves.

Table 2 and Supplementary Table 1 show the adjusted means of three MD measures by categories of alcohol consumption during different age intervals among premenopausal women. There was no association between drinking alcoholic beverages during any of the four age intervals evaluated and any of three MD measures. When stratifying by BMI at mammogram, results were similarly null in each of the two BMI strata (data not shown).

We further examined the associations of cumulative average alcohol intake before and after first pregnancy with MD measures among 986 parous women (Table 3 and Supplementary Table 2). Neither alcohol consumption prior to first pregnancy nor after first pregnancy was significantly associated with any of the three MD measures. However, there was statistically significant interaction of drinking before first pregnancy and BMI at mammogram for absolute dense breast area ($P_{interaction}$=0.04; Supplementary Table 3). Among overweight or obese women at mammogram, drinking alcohol prior to first pregnancy was marginally associated with a higher absolute dense area (P_{trend}=0.05). This was not apparent for women with BMI at mammogram of <25 kg/m^2 (P_{trend}=0.80). There was no significant trend by BMI at mammogram for associations of alcohol consumption before first pregnancy with percent MD or absolute non-dense breast area. Further, there was no effect modification by BMI for any of the density measures (Supplementary Table 3).

Finally, we examined changes in usual alcohol consumption from before first pregnancy to after on MD measures (Supplementary Table 4). Women who had moderate to high alcohol consumption both before (≥5 g/day) and after (≥10 g/day) first pregnancy had similar percent MD, absolute dense breast area, and non-dense breast area as women who never drank alcohol. Similarly, there were no notable trends for women who either increased or decreased their alcohol consumption after pregnancy.

DISCUSSION

In this analysis of alcohol consumption during different age intervals and MD among premenopausal women, there was no evidence of an association between moderate alcohol consumption and MD. For parous women, neither drinking prior to or after first pregnancy was significantly associated with MD measures.

Evidence for an alcohol-MD association is inconclusive. Few studies have evaluated this association in premenopausal women [23–30]. A significant increase in percent MD and/or absolute dense breast area has been observed for recent and lifetime alcohol consumption in premenopausal women in four studies [23, 24, 29, 30]. In two of these four studies, alcohol consumption was evaluated qualitatively (yes or no alcohol intake) and the usual quantity of alcoholic drinks was not reported [24, 29]. Within the Minnesota Breast Cancer Family Cohort Study, 22% consumed ≥10 g/day and had higher percent MD compared with abstainers [30]. Among premenopausal women in the Norwegian Energy Balance and Breast Cancer Aspects Study, women who reported weekly alcohol consumption of at least 7 drinks (20%) had higher percent density and absolute dense area than women who consumed <1 drink/week [23]. In contrast, drinking was significantly inversely associated with MD in two US birth cohorts [28]. In that study, 12.8% of women reported weekly consumption of >7 alcoholic drinks during the past year. Our result is consistent with several studies that reported weak or no associations between alcohol and MD in premenopausal women [25–27]. In general, null findings were reported in study populations with low alcohol consumption as demonstrated by 6%–16% of participants with daily alcohol consumption of at least 1 drink. In the NHS II cohort, participants more likely reported the highest average alcohol intake during ages 18 to 22 years and intake was lower during their 20s and 30s. In our analysis, less than 10% of premenopausal women reported alcohol consumption of ≥10 g/day during different age intervals before mammogram.

Both epidemiological studies and animal models have demonstrated that the interval between menarche and first birth is an important window of susceptibility when undifferentiated breast tissue is particularly vulnerable to carcinogenesis (for review, see [7]). We previously demonstrated among the NHS II participants that higher consumption of alcohol during this period was associated with greater risks of both invasive breast cancer and proliferative benign breast disease, which was independent of alcohol consumption after first birth [11]. This current analysis of premenopausal NHS II participants showed similarities in percent MD, absolute dense breast area, and non-dense breast area between women with alcohol consumption of ≥10 g/day prior to first pregnancy and non-drinkers before first pregnancy. Five studies have evaluated alcohol drinking during early life and MD [23, 25, 27, 28, 31], with the majority reporting no association after adjustment for established breast cancer risk factors. The Energy Balance and Breast Cancer Aspects Study assessed alcohol consumption among 202 premenopausal women from age 15 through the time of interview when the average age was 30 years [23]. Women who reported a high level of alcohol consumption over the past year (≥7 drinks/week) had 48% higher absolute dense breast area and 27% increased percent MD compared to drinkers who consumed <1 drink/week (both $P_{trend}<0.01$). Absolute dense area was significantly increased by 15% and percent MD was marginally increased by 5% in women with lifetime alcohol consumption greater than 1 drink per week compared with nondrinkers. However, a higher MD was observed for current alcohol consumption, but not lifetime consumption, in other studies [25, 31]. Therefore, MD may not be involved in the pathway between alcohol exposure in early adulthood and breast cancer development later in life.

We observed a suggestive trend of higher absolute dense area with greater alcohol consumption before first pregnancy among premenopausal women with BMI at

mammogram of at least 25 kg/m^2. This is opposite to a small multiethnic study (n=189) in which a stronger positive association for recent alcohol intake and MD was observed for leaner women compared to heavier women [21]. However, the modifying effect of BMI on the alcohol-breast cancer cancer association might be different for premenopausal vs. postmenopausal women [22]. Among premenopausal women, the positive association of lifetime drinking with breast cancer risk was stronger in heavier women than in leaner women. In contrast, among postmenopausal women, the association was stronger for leaner vs. heavier women. As a small number of women had alcohol consumption at least 10 g/day, the stratified analysis by BMI was adjusted for age and BMI at mammogram only in the current analysis. Hence, the observed interaction between alcohol consumption prior to first pregnancy and BMI for absolute dense area might be due to chance. Alternatively, this result could reflectresidual confounding resulting from unadjusted and/or unmeasured factors.

The major limitation of this study is that drinking habits in late adolescence and early adulthood was recalled by women when they were between ages 24 and 44 (average age, 35), and was likely reported with some error. Any measurement error would be expected to underestimate the association of adolescent alcohol consumption with MD. However, alcohol consumption during adolescence is recalled with acceptable reproducibility (intra-class correlation =0.50) in this population and and is independent of current reported intake (intra-class correlation =0.14) [32]. Prospective data collection avoided differential recall bias. The collection of screening mammograms was conducted 7–10 years after questionnaires were completed asking about early-life alcohol consumption. Importantly, while a positive association between moderate consumption of alcohol and risk of breast cancer in this cohort (n=1609 cases) [11], alcohol consumption is low in general among NHSII participants, which could have made it difficult to observe weak or moderate associations with mammographic density in the smaller sample size included in the current analyses. In fact, in a recent report that included only premenopausal women with mammograms from both the NHS and NHSII (n=559 breast cancer cases), there was no apparent association of alcohol consumption with risk [33]. There is also possible measurement error in our mammographic density assessment. However, digitized mammograms were reviewed by a single reader with a high reproducibility [14, 19]. While the use of continuous measurements of mammographic density improved the statistical power of this study, small subgroups of participants limited our confidence in point estimates for the stratified analysis and the analysis of alcohol consumption patterns.

In summary, this study did not provide evidence for an association of moderate alcohol consumption in early life with premenopausal MD. It suggests that the demonstrated association between consumption of alcohol early in life and risk of invasive breast cancer is not likely mediated through mammographic density.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age-adjusted characteristics of premenopausal women (n=1,211) in the Nurses' Health Study II at the time of mammogram by alcohol consumption from ages 18 to 22

	Alcohol consumption from ages to18–22, g/day			
	0	**>0–4.9**	**5.0–14.9**	**≥15**
No. of participants	307	385	394	125
Age at mammography, y	45.0 (3.9)	44.8 (3.8)	44.1 (4.1)	42.7 (4.2)
Body mass index at mammography, kg/m^2	26.0 (6.3)	25.5 (5.3)	25.7 (5.2)	27.5 (7.1)
Body mass index at age 18, kg/m^2	21.1 (3.2)	21.0 (2.7)	21.2 (2.9)	22.1 (3.2)
Age at menarche, y	12.4 (1.3)	12.2 (1.5)	12.6 (1.5)	12.5 (1.4)
Parity				
Nulliparous	19.4	16.8	16.5	21.9
1–2 pregnancies	49.2	52.2	53.1	56.1
≥3 pregnancies	31.3	31.1	30.4	22.1
Age at first pregnancy[†], y	25.6 (4.4)	26.2 (4.3)	27.3 (4.7)	27.9 (4.2)
Interval between menarche and first pregnancy[†], y	13.1 (4.5)	13.9 (4.4)	14.7 (4.9)	15.4 (4.4)
Total duration of breastfeeding[†]				
None	19.8	15.4	16.4	16.6
1–11 months	22.5	28.2	31.3	35.2
≥12 months	57.7	56.4	52.2	48.2
Breast cancer in first-degree relative(s)	9.3	9.3	7.6	8.0
Benign breast disease	19.6	20.2	12.9	10.6
Oral contraceptive use				
Never	93.6	95.6	92.4	89.1
Ever	6.4	4.4	7.6	10.9

[†]Variables were analyzed in 986 eligible women who had at least one full-term pregnancy by the time of mammogram.

Table 2

Percent mammographic density (least square means and 95% confidence intervals) by alcohol consumption during different age intervals among premenopausal women.

Alcohol intake	No. of women	Model 1†	Model 2‡
Ages 15–17, g/day			
0	942	40.9 (39.9, 41.9)	41.6 (39.1, 44.1)
>0 – <5	159	37.7 (35.5, 40.0)	38.4 (35.4, 41.4)
≥5	110	39.9 (37.1, 42.6)	40.7 (37.1, 44.4)
		P_{trend} =0.43	P_{trend} =0.50
Ages 18–22, g/day			
0	307	41.4 (39.7, 43.2)	41.8 (38.8, 44.7)
>0 – <5	385	40.4 (38.8, 42.0)	41.1 (38.3, 43.8)
≥5 – <10	394	39.5 (38.1, 40.9)	40.1 (37.4, 42.7)
≥10	125	40.6 (38.0, 43.3)	41.0 (37.6, 44.4)
		P_{trend} =0.61	P_{trend} =0.59
Ages 23–30, g/day			
0	280	39.9 (38.0, 41.7)	40.4 (37.4, 43.5)
>0 – <5	475	41.2 (39.9, 42.5)	41.9 (39.3, 44.5)
≥5 – <10	387	39.6 (38.1, 41.1)	40.0 (37.4, 42.6)
≥10	69	41.6 (37.9, 45.3)	41.6 (37.1, 46.0)
		P_{trend} =0.94	P_{trend} =0.75
Ages 31 – at mammogram, g/day			
0	260	39.6 (37.7, 41.4)	40.0 (37.0, 43.0)
>0 – <5	660	40.7 (39.6, 41.9)	41.1 (38.5, 43.6)
≥5 – <10	166	40.1 (37.7, 42.5)	40.3 (37.2, 43.5)
≥10	124	40.5 (37.9, 43.1)	40.6 (37.1, 44.1)
		P_{trend} =0.90	P_{trend} =0.92

† adjusted for age (continuous) and BMI (continuous) at mammogram

‡ further adjusted for parity, breast cancer in first-degree relative(s), benign breast disease, and use of oral contraceptives, all at or close to mammogram, as well as age at menarche, age at first pregnancy, and BMI at age 18

Table 3

Percent mammographic density (least square means and 95% confidence intervals) by cumulative average consumption of alcohol prior to and after first full-term pregnancy[†] among premenopausal women.

Alcohol intake	No. of women	Model 1[‡]	Model 2[§]
Prior to first pregnancy, g/day			
0	187	41.6 (39.3, 44.0)	41.5 (37.7, 45.2)
>0 – <5	566	39.2 (37.9, 40.4)	39.0 (36.0, 41.9)
≥5 – <10	153	39.1 (36.7, 41.4)	38.6 (35.2, 41.9)
≥10	80	42.9 (39.5, 46.2)	42.4 (38.2, 46.6)
		P_{trend} =0.40	P_{trend} =0.50
After first pregnancy, g/day			
0	218	40.3 (38.2, 42.4)	39.4 (35.8, 43.0)
>0 – <5	548	39.3 (38.1, 40.5)	38.9 (35.9, 41.8)
≥5 – <10	142	41.5 (39.0, 44.1)	40.9 (37.3, 44.6)
≥10	65	40.6 (36.9, 44.3)	39.4 (35.0, 43.8)
		P_{trend} =0.36	P_{trend} =0.49

[†] Full-term pregnancy was defined as a pregnancy lasting at least six months.

[‡] adjusted for age (continuous) and BMI (continuous) at mammogram

[§] further adjusted for breast cancer in first-degree relative(s), benign breast disease, and use of oral contraceptives, all at or close to mammogram, as well as age at menarche, age at first pregnancy, and BMI at age 18