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Moderate Alcohol Consumption During Adult Life, Drinking Patterns, and Breast Cancer Risk

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IN MANY STUDIES, HIGHER CONSUMPTION of alcohol has been associated with an increased risk of breast cancer.¹⁻³ However, the effect of low levels of drinking as is common in the United States has not been well quantified. A few studies showed increased risk,^{1,4} but in most, no significant association was observed.^{2,3,5-11} Many of these studies did not regularly update assessments of alcohol intake, which may change over a person's lifetime and obscure the ability to detect an effect. In addition, most lacked information on drinking patterns, such as regularity of drinking and heavy episodic ("binge") drinking. Because some breast cancer risk factors, such as first full-term pregnancy¹² and ionizing radiation,¹³ have different effects depending on age at exposure, it is important to evaluate the role of alcohol intake at different times in a woman's life.

METHODS

The Nurses' Health Study (NHS) cohort was established in 1976, when 121 700 female registered nurses aged 30 to 55 years completed a baseline questionnaire including items on risk factors for cancer and cardiovascular disease. Every 2 years, follow-up questionnaires have been

For editorial comment see p 1920.

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Context Multiple studies have linked alcohol consumption to breast cancer risk, but the risk of lower levels of consumption has not been well quantified. In addition, the role of drinking patterns (ie, frequency of drinking and "binge" drinking) and consumption at different times of adult life are not well understood.

Objective To evaluate the association of breast cancer with alcohol consumption during adult life, including quantity, frequency, and age at consumption.

Design, Setting, and Participants Prospective observational study of 105 986 women enrolled in the Nurses' Health Study followed up from 1980 until 2008 with an early adult alcohol assessment and 8 updated alcohol assessments.

Main Outcome Measures Relative risks of developing invasive breast cancer.

Results During 2.4 million person-years of follow-up, 7690 cases of invasive breast cancer were diagnosed. Increasing alcohol consumption was associated with increased breast cancer risk that was statistically significant at levels as low as 5.0 to 9.9 g per day, equivalent to 3 to 6 drinks per week (relative risk, 1.15; 95% CI, 1.06-1.24; 333 cases/100 000 person-years). Binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. Alcohol intake both earlier and later in adult life was independently associated with risk.

Conclusions Low levels of alcohol consumption were associated with a small increase in breast cancer risk, with the most consistent measure being cumulative alcohol intake throughout adult life. Alcohol intake both earlier and later in adult life was independently associated with risk.

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sent to update risk factor information and disease development. Based on self-report, the NHS population is predominantly white (93.7% white, 2% black, 0.7% Asian, and 3.6% other or unknown race/ethnicity), reflecting the demographics of registered nurses in the United States in 1976. Follow-up has been extremely high with 4.4% of person-time lost to follow-up. We routinely search the National Death Index every 2 years for nonresponders.¹⁴ In 1976, written informed consent was not required; instead, return of completed questionnaires was considered consent to enroll in the study. The institutional review board of the Brigham and Women's Hospital reviewed and approved the study protocol.

Population for Analysis

For the main analysis, the analytic period began in 1980 when alcohol intake was first assessed. From the initial cohort of 121 700 women enrolled in 1976, 105 986 women entered the analysis beginning in 1980, after we excluded women who died or developed

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cancer before 1980 ($n=5565$) and women who did not return any alcohol assessments ($n=10\,149$). Women who developed any type of cancer (except nonmelanoma skin cancer) were censored at the time of their diagnosis. For analyses of drinking patterns and drinking during early adult life, follow-up began with the 1988 questionnaire and included 74 854 participants who answered questions regarding their current and past drinking patterns.

Alcohol Consumption

Information on alcohol consumption was first collected in 1980 when participants completed a semiquantitative food frequency questionnaire and reported their average frequency of consumption of specific food and beverage items during the previous 12 months. Consumption of beer, wine, and liquor was ascertained as separate items.

Alcohol consumption in grams per day was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage (12.8 g of alcohol per 12-oz serving of beer, 11.0 g per 4-oz serving of wine, and 14.0 g per standard serving of liquor).¹⁵ Alcohol intake measured by the food frequency questionnaire was highly correlated with intake calculated from detailed food diaries completed by a sample of study participants (Spearman rank-correlation coefficient=0.90) and with high-density lipoprotein levels ($r=0.40$).¹⁶

Data on current alcohol consumption were updated in 1984, 1986, 1990, 1994, 1998, 2002, and 2006. Cumulative average alcohol intake was calculated by averaging alcohol use over time beginning in 1980. For example, cumulative average alcohol use in 1986 was obtained by averaging the daily consumption reported in 1980, 1984, and 1986. If a participant was missing alcohol consumption for a certain year, the measurements from the available years were averaged. For analyses of current alcohol use, alcohol intake was updated at each alcohol questionnaire

without accounting for prior use. For current alcohol analyses, person-time for people missing alcohol consumption during a specific questionnaire cycle was excluded, but they could re-enter the analysis when alcohol intake data became available.

To maintain the prospective nature of the study, analyses on drinking patterns began with the 1988 questionnaire when participants were first asked the usual number of days alcohol was consumed in a typical week and largest number of alcoholic drinks consumed in 1 day in a typical month (none, 1-2, 3-5, 6-9, 10-14, or 15+ drinks). These questions were updated in 1996, 2000, and 2004. For alcohol consumption at different times of life, analyses also began in 1988 when participants were asked about the usual number of alcoholic drinks per week at 3 different age periods (ages 18-22 years, 25-30 years, and 35-40 years). This information was not updated.

Breast Cancer Cases

The primary end point was the diagnosis of invasive breast cancer. On each questionnaire, we asked whether breast cancer had been diagnosed and, if so, the date of diagnosis. We search the National Death Index routinely for deaths among women who did not respond to the questionnaires; the last search was conducted in December 2010. We asked all women who reported breast cancer (or next of kin for those who died) for permission to review the pertinent medical records for confirmation. Pathology reports, obtained in 96% of the cases, showed a 99.4% confirmation rate. Carcinomas in situ were excluded. Estrogen receptor and progesterone receptor (ER/PR) status were abstracted from pathology reports.

Statistical Analyses

For this analysis, follow-up time began in 1980 and terminated with the diagnosis of any type of cancer, death, or June 1, 2008, whichever came first. Cox proportional hazards models were used to compute hazard ratios as estimates

for age-adjusted and multivariate-adjusted relative risks (RRs) and 95% confidence intervals. The underlying time variables for the Cox model are questionnaire year and age. Additional covariates in the model were chosen to represent possible confounders and commonly accepted breast cancer risk factors and included menopausal status, age at menarche, parity, age at first birth, body mass index, family history of breast cancer in a first-degree relative, breastfeeding, cigarette smoking, and self-report of benign breast disease. All variables except age at menarche and breastfeeding were updated from follow-up questionnaires. For postmenopausal women, terms were also included for age at menopause, type of menopause, and duration and type of hormone therapy use.

We included dummy variables for missing covariate data, which comprised less than 5% of total person-time (except for missing breastfeeding, which was 9.5%). Tests for trend were calculated using alcohol consumption as a continuous variable. Tests for interaction were performed using the Wald test for the cross-product interaction term. The proportional hazards assumption was not violated. All analyses were performed using SAS version 9.1 with a 2-sided significance P value of $<.05$.

RESULTS

From 1980 until June 2008, 7690 cases of invasive breast cancer were diagnosed among 2.4 million years of person-time. TABLE 1 illustrates the characteristics of the study population according to cumulative average alcohol intake in 1994, the midpoint of the follow-up period. Breast cancer risk factors were distributed fairly evenly across the groups except that higher alcohol consumers were more likely to have had natural menopause, have a lower body mass index, and be current smokers. Although tumor characteristics, current use of hormone therapy, and adherence with mammography and clinical breast examinations did vary slightly across groups, none of these variables

nor any other of the standard breast cancer risk factors displayed a consistent linear trend across categories of increasing alcohol use.

For the primary analyses, RRs were calculated using average cumulative alcohol consumption since baseline (1980). Initially, analyses were also performed using baseline intake and simple current updating of alcohol use (ie, consumption was updated with the return of each questionnaire, and therefore past use would not be carried forward). Although the relationship with baseline and current alcohol use

closely approximated that of cumulative average intake (TABLE 2), cumulative average use provided the most linear and consistent associations, suggesting that this represents the most accurate measure over time, and also provided more statistical power by using assessments throughout all follow-up periods. Our assessment of cumulative average alcohol intake reflects predominantly alcohol intake in mid to later adult life, because we first began assessing alcohol use in 1980 when the participants were aged 34 to 59 years.

Even a low level of alcohol consumption was modestly but significantly associated with breast cancer risk (for 5-9.9 g per day [equivalent to 3-6 glasses of wine per week] multivariate RR, 1.15; 95% CI, 1.06-1.24; 333 cases/100 000 person-years). In addition, women who consumed at least 30 g of alcohol daily on average (at least 2 drinks per day) had a greater risk of breast cancer (RR, 1.51; 95% CI, 1.35-1.70; 413 cases/100 000 person-years) compared with women who never consumed alcohol. The percent attributable risk (PAR) for each alcohol category in the study population was still low (1%-3%) given the low prevalence of higher levels of alcohol consumption, but the PAR for alcohol overall was 10%.

When stratified by menopausal status, the association with alcohol appeared stronger among postmenopausal women, but the interaction was not significant ($P = .74$) (eTable 1, available at <http://www.jama.com>). We also evaluated whether the associations varied by type of alcohol and found little difference (RR per 10 g per day for wine, 1.12; 95% CI, 1.07-1.18; beer RR, 1.09; 95% CI, 1.03-1.15; and liquor RR, 1.09; 95% CI, 1.05-1.13).

Because one potential mechanism for alcohol's effect on breast cancer risk involves hormonal effects,¹⁷ we examined the association by ER/PR status of the tumor (TABLE 3). For this analysis, we excluded 1620 cases with unknown ER status, PR status, or both. Alcohol consumption seemed to be more strongly associated with risk of ER-positive status, PR-positive status, or both, but the P value for interaction was not significant. Results were similar for ductal and lobular histology (eTable 2).

In 1988, we first asked about drinking patterns, including frequency of drinking and quantity of drinking. Heavy episodic or binge drinking is not consistently defined across studies, but one commonly used definition in the United States is 4 or more drinks at one time for a woman. When cumulative alcohol use was not included in the model, both regularity of drinking and binge drinking were strongly associ-

Table 1. Demographic Characteristics

	Cumulative Average Daily Alcohol Consumption, g/d ^a				
	0	0.1-4.9	5-9.9	10-19.9	≥20
All women, No.	18 967	37 700	11 559	10 212	6 192
Age, mean (SD), y	61.2 (7.2)	60.0 (7.2)	60.2 (7.1)	60.8 (6.9)	61.5 (6.8)
Age at menarche, mean (SD), y	12.4 (1.8)	12.4 (1.8)	12.5 (1.8)	12.5 (1.7)	12.5 (1.8)
Body mass index, mean (SD) ^b	27.6 (5.8)	27.0 (5.3)	25.7 (4.5)	25.1 (4.2)	25.1 (4.3)
Premenopausal, %	10.4	10.5	10.8	10.6	9.3
Nulliparous, %	5.2	4.8	5.8	6.3	7.7
Benign breast disease, %	18.9	19.0	18.7	17.8	17.2
Family history, %	9.2	10.0	10.2	10.5	10.3
Tobacco use, %					
Never	62.2	45.7	35.0	27.5	20.4
Past	27.8	41.4	51.0	54.3	53.0
Current	9.8	12.7	13.8	18.1	26.5
Parous women only, No.	17 614	35 267	10 699	9 412	5 623
Total duration breastfeeding, mo, % ^c					
None	32.2	34.4	33.0	31.7	32.1
0.1-11	38.9	42.1	42.4	44.4	45.0
≥12	19.2	17.2	18.0	16.8	16.2
Postmenopausal women only, No.	17 183	32 032	9 931	9 125	5 805
Current hormone therapy use, %	35.7	40.3	43.5	44.3	40.5
Natural menopause, %	56.8	60.1	62.4	62.0	63.7
Age at menopause, mean (SD), y	49.5 (6.5)	49.4 (5.8)	49.5 (5.8)	49.7 (5.9)	49.6 (6.0)
Women ≥50 y old, No.	18 182	35 831	11 078	10 019	6 195
Mammogram or clinical breast examination in past 2 y, %	71.6	79.8	81.2	79.3	76.6
Mammogram and clinical breast examination in past 2 y, %	61.1	69.8	72.3	70.0	67.5
Tumor characteristics, No. (%) ^d	1 669	3 143	1 063	1 091	724
Stage I	707 (42.4)	1 399 (44.5)	521 (49.0)	527 (48.3)	334 (46.1)
Stage II	413 (24.8)	806 (25.6)	243 (22.9)	262 (24.0)	184 (25.4)
Stage III	174 (10.4)	341 (10.9)	100 (9.4)	107 (9.8)	79 (10.9)
Stage IV	36 (2.2)	58 (1.9)	13 (1.2)	17 (1.6)	16 (2.2)
Missing stage information	339 (20.3)	539 (17.2)	186 (17.5)	178 (16.3)	111 (15.3)

^aAll variables except for age and tumor characteristics are age-standardized. Demographic characteristics for study population based on alcohol consumption in 1994.

^bCalculated as weight in kilograms divided by height in meters squared.

^cNumbers do not sum to 100% because breastfeeding duration was missing for 9.5% of total person-time (ranging from 7% to 10% within each alcohol category).

^dAlcohol categories for tumor characteristics based on consumption immediately prior to breast cancer diagnosis. Most women missing stage information were confirmed via either cancer registry or death certificate data, which provide confirmation of invasive cancer but do not provide sufficient information to assign a TNM stage, or were diagnosed in the early 1980s when only limited data were available on pathology reports.

ated with breast cancer risk (TABLE 4). However, once cumulative alcohol consumption was added to the model, there was a weak association with binge drinking as evaluated by the trend test, but not with frequency of drinking.

We also examined associations with alcohol consumption at different periods of life. For this analysis, follow-up also began with the 1988 questionnaire cycle when questions were asked about alcohol consumption at ages 18

to 22 years, 25 to 30 years, and 35 to 40 years. Based on these answers, we calculated the cumulative average intake between the ages of 18 and 40 years as a representation of drinking during early adult life and cumulative intake

Table 2. Alcohol Consumption and Risk of Invasive Breast Cancer by Alcohol Intake

Alcohol Intake, g/d ^a	Baseline Intake, 1980			Current Updated Intake ^b			Cumulative Intake ^c			
	Cases, No.	Incidence Rate ^d	RR (95% CI) ^e	Cases, No.	Incidence Rate ^d	RR (95% CI) ^e	Cases, No.	Incidence Rate ^d	RR (95% CI) ^e	PAR
0	1776	312	1 [Reference]	2475	323	1 [Reference]	1669	281	1 [Reference]	
0.1-4.9	2016	331	1.07 (1.00-1.14)	1930	314	1.04 (0.98-1.11)	3143	309	1.06 (0.99-1.12)	2
5-9.9	723	363	1.15 (1.06-1.26)	692	334	1.11 (1.01-1.20)	1063	333	1.15 (1.06-1.24)	2
10-19.9	1020	370	1.15 (1.06-1.24)	863	340	1.11 (1.03-1.21)	1091	351	1.22 (1.13-1.32)	3
20-29.9	246	412	1.28 (1.12-1.47)	208	370	1.21 (1.05-1.40)	362	356	1.20 (1.07-1.35)	1
≥30	413	476	1.50 (1.34-1.67)	350	403	1.34 (1.19-1.50)	362	413	1.51 (1.35-1.70)	2
RR per 10-g increase			1.09 (1.07-1.11)			1.07 (1.05-1.10)			1.10 (1.07-1.12)	
P for trend	6194	344	<.001	6518	328	<.001	7690	316	<.001	10

Abbreviations: PAR, percent attributable risk; RR, relative risk.

^aFor example, a 4-ounce glass of wine contains 11 g of alcohol. The number of glasses of wine per week corresponding to the alcohol categories are 1-3 glasses/wk for 0.1-4.9 g/d, 3-6 glasses/wk for 5-9.9 g/d, 6-13 glasses/wk for 10-19.9 g/d, 13-19 glasses/wk for 20-29.9 g/d, and ≥19 glasses/wk for ≥30 g/d.

^bFor current intake, person-time for women missing alcohol intake during a specific questionnaire cycle was excluded, resulting in fewer cases for the analysis of current intake compared with that for cumulative use.

^cCumulative intake calculated from baseline (1980) forward.

^dPer 100 000 person-years.

^eControlled for age, questionnaire year, ages at menarche and menopause, family history of breast cancer in first-degree relative, benign breast disease, body mass index, parity and age at first full-term birth, hormone therapy use, total duration of breastfeeding (months), and cigarette smoking.

Table 3. Alcohol and Breast Cancer Risk by Estrogen Receptor and Progesterone Receptor Status

Alcohol Intake, g/d	ER+/PR+		ER-/PR-		ER+/PR-		ER-/PR+	
	Cases, No.	Multivariate RR (95% CI) ^a	Cases, No.	Multivariate RR (95% CI) ^a	Cases, No.	Multivariate RR (95% CI) ^a	Cases, No.	Multivariate RR (95% CI) ^a
0	806	1 [Reference]	222	1 [Reference]	209	1 [Reference]	33	1 [Reference]
0.1-4.9	1569	1.03 (0.94-1.12)	447	1.14 (0.97-1.34)	435	1.15 (0.97-1.36)	74	1.29 (0.85-1.96)
5-9.9	542	1.14 (1.02-1.28)	151	1.25 (1.01-1.54)	129	1.07 (0.85-1.34)	27	1.47 (0.87-2.47)
10-19.9	564	1.27 (1.14-1.42)	135	1.17 (0.94-1.46)	140	1.19 (0.95-1.48)	23	1.26 (0.73-2.19)
20-29.9	185	1.20 (1.02-1.47)	40	1.05 (0.75-1.49)	57	1.39 (1.03-1.88)	8	1.40 (0.64-3.07)
≥30	181	1.58 (1.34-1.86)	38	1.24 (0.87-1.76)	43	1.35 (0.96-1.89)	12	2.45 (1.24-4.86)
P for trend	3847	<.001	1033	.23	1013	.04	177	.02

Abbreviations: ER+, estrogen receptor positive; ER-, estrogen receptor negative; PR+, progesterone receptor positive; PR-, progesterone receptor negative; RR, relative risk.

^aCovariates listed in footnote to Table 2. Cases were excluded if ER status, PR status, or both were unknown (n=1620).

Table 4. Drinking Patterns and Breast Cancer Risk

Days, No.	Days Alcohol Consumed in Typical Week				Largest No. of Alcoholic Drinks Consumed in 1 Day in Typical Month				
	Cases/Person-Years, No.	Incidence Rate ^a	Multivariate RR (95% CI) ^b		Drinks, No.	Cases/Person-Years, No.	Incidence Rate ^a	Multivariate RR (95% CI) ^b	
			Model 1	Model 2				Model 1	Model 2
0	2382/654 064	364	1 [Reference]	1 [Reference]	0	1736/476 522	364	1 [Reference]	1 [Reference]
1-2	1441/385 233	373	1.05 (0.99-1.13)	1.03 (0.95-1.11)	1-2	2559/653 056	392	1.08 (1.02-1.16)	1.07 (0.99-1.15)
3-4	500/132 420	378	1.05 (0.95-1.16)	0.97 (0.86-1.09)	3-5	905/233 786	387	1.16 (1.07-1.27)	1.08 (0.97-1.20)
5-7	961/217 546	442	1.20 (1.11-1.30)	1.05 (0.93-1.18)	≥6	131/31 614	414	1.33 (1.11-1.59)	1.21 (0.99-1.47)
P for trend	5284/1 390 704	380	<.001	.29		5331/1 394 978	382	<.001	.04

Abbreviation: RR, relative risk.

^aPer 100 000 person-years.

^bCovariates listed in footnote to Table 2. Analyses begin in 1988 when drinking patterns were first assessed. Model 1 does not control for cumulative alcohol intake. Model 2 does control for cumulative alcohol intake.

Table 5. Alcohol Consumption in Earlier and Later Adult Life and Breast Cancer Risk

Cumulative Alcohol Intake, g/d	All Invasive Breast Cancers							
	Ages 18-40 y				Age >40 y			
	Cases/ Person-Years, No.	Incidence Rate ^a	RR (95%CI)		Cases/ Person-Years, No.	Incidence Rate ^a	RR (95%CI)	
			Model 1 ^b	Model 2 ^c			Model 1 ^b	Model 2 ^c
0	816/235 246	347	1 [Reference]	1 [Reference]	976/283 346	344	1 [Reference]	1 [Reference]
0.1-4.9	3028/828 044	366	1.06 (0.97-1.14)	1.02 (0.93-1.12)	2162/606 120	357	1.03 (0.95-1.11)	1.02 (0.93-1.10)
5-9.9	748/189 544	395	1.13 (1.02-1.26)	1.05 (0.93-1.18)	704/185 852	379	1.09 (0.99-1.20)	1.07 (0.96-1.19)
10-19.9	322/74 250	434	1.25 (1.09-1.43)	1.15 (0.99-1.33)	690/162 162	426	1.20 (1.09-1.33)	1.17 (1.04-1.31)
≥20	42/91 28	429	1.33 (0.97-1.82)	1.21 (0.88-1.67)	424/98 732	429	1.23 (1.09-1.39)	1.18 (1.03-1.34)
RR per 10-g increase			1.16 (1.08-1.25)	1.08 (1.00-1.18)			1.08 (1.05-1.12)	1.07 (1.03-1.10)
P for trend	4956/1 336 212	371	<.001	.05	4956/1 336 212	371	<.001	<.001

Abbreviation: RR, relative risk.

^aPer 100 000 person-years.^bModel 1 analyses begin with 1988 follow-up period when drinking in earlier adult life was first assessed. For cumulative alcohol intake after age 40 years, cumulative intake was calculated from baseline (1980) going forward for nurses 40 years or older at baseline and from the time the nurse turned 40 years old for those younger than 40 years at baseline. All relative risks were controlled for same variables as listed in footnote to Table 2.^cModel 2 is the same as model 1, but both alcohol intake at ages 18-40 years and cumulative alcohol intake are included in the same model.

after age 40 years as representing intake later in life. When examined separately, alcohol consumption levels at ages 18 to 40 years and after age 40 years were both strongly associated with breast cancer risk (TABLE 5). The association with drinking in early adult life still persisted even after controlling for alcohol intake after age 40 years.

COMMENT

In this large prospective cohort study, we observed an association between even low levels of alcohol consumption and breast cancer risk. The most relevant measure was cumulative average alcohol consumption over long periods of time, and both drinking earlier and later in adult life were independently associated with breast cancer risk. We also saw a modest association with binge drinking but not frequency of drinking.

Prior studies have consistently demonstrated a linear dose-response relation between alcohol consumption and breast cancer risk, with an increased risk mainly observed among women who consumed the equivalent of at least 1 alcoholic beverage daily, but power was limited at the lower levels of alcohol consumption to determine whether there was a lower threshold.^{2,3,5-11} Our data demonstrated that even consumption of alcohol as low as 5 to 9.9 g per day (3-6 glasses of wine per week) may

be associated with a modest increase in risk. We observed a 10% increase in risk with each 10 g per day of alcohol intake, which is somewhat stronger than the risk reported in a previous large meta-analysis that used a single measure of alcohol intake at baseline (RR for each 10 g per day, 1.07).¹ Consistent with other studies, we did not find any difference by type of alcoholic beverage (ie, beer, wine, or liquor).^{2,3,18,19}

Although the exact mechanism for the association between alcohol consumption and breast cancer is not known, one probable explanation would involve alcohol's effects on circulating estrogen levels. Most other large studies have shown a stronger association with ER-positive breast cancers.^{8,9,20-24} In short-term feeding studies, moderate levels of alcohol consumption increased circulating sex hormone levels in both premenopausal and postmenopausal women.^{25,26} Cross-sectional studies also support a positive association between alcohol consumption and plasma sex hormone levels.^{27,28} Alcohol may increase sex hormone levels in several ways: increased aromatase activity,²⁹ decreased hepatic catabolism of androgens,³⁰ or effects on adrenal steroid production.²⁶ In vitro studies have demonstrated that alcohol can increase the transcriptional activity of ER- α ³¹ (which may influence breast tissue's sensitivity to es-

trogens) and preferentially enhance proliferation and ER- α content in ER-positive cell lines.³²

To our knowledge, this is the first study to evaluate breast cancer risk in relation to both frequency of drinking and binge drinking. Two other prospective studies have evaluated regularity of drinking and did not find a difference between less and more frequent drinking, but they had fewer breast cancer cases and used less detailed measures.^{10,11} In terms of binge drinking, a prospective study showed a nonlinear association with the highest risk among women who consumed 4 to 5 drinks per weekday or 16 to 21 drinks per weekend and lower risks for women who drank more, but they had few cases in the highest categories and contrary to most studies, nondrinkers had an increased risk of breast cancer.³³ A case-control study found a non-statistically significant increased risk associated with binge drinking limited to high alcohol consumers.³⁴ After controlling for cumulative average intake, we observed a modest association with binge drinking but not frequency of drinking. However, there may still be some residual confounding with the higher cumulative alcohol intake among binge drinkers.

Several other studies have evaluated drinking at different time periods in adult life, and most did not identify

an association with alcohol consumption in early adult life.^{3,5,11,21,35-37} A meta-analysis found that studies with shorter duration of follow-up reported higher RRs than studies with longer follow-up, suggesting that recent, rather than early, alcohol intake is more strongly associated with breast cancer risk.³⁸ Alternatively, for studies that do not obtain updated assessments through a person's lifetime, there may be increasing misclassification of alcohol consumption as dietary patterns change with age. Our study had greater statistical power than previous studies to evaluate the effect of drinking in early adult life. We found an association of similar magnitude for early and late life, even when mutually adjusted. Our study underscores the importance of considering the totality of a woman's exposure to alcohol over her lifetime as the best measure, rather than exposure during one specific time period. This type of temporal relationship for alcohol intake over longer periods parallels those of hormonal influences and breast cancer risk in which the broadest consideration of hormonal influences over a lifetime most accurately reflects risk.³⁹

The strengths of this study include the large number of cases, length of follow-up, and detailed prospective and updated assessments of alcohol consumption across different age periods affording the most comprehensive evaluation of the effect of alcohol consumption throughout a woman's life. Limitations include that this was an observational study, so alcohol use was not randomly assigned to women. However, it is unlikely that such a long-term randomized trial will ever be performed. We relied on self-reported alcohol use, but this has previously been shown to be highly reproducible within our cohort and strongly correlated with levels of high-density lipoprotein cholesterol.¹⁶ We have also previously demonstrated that measurement error does not strongly affect our estimates of the alcohol association.⁴⁰ Compared with some studies done in Europe, we do not have as many women with higher levels of alcohol consumption. However,

the distribution of alcohol intake in the NHS is fairly similar to that of US women.⁴¹

Our study population was predominantly white, but the limited available data suggest that the association between alcohol use and breast cancer does not differ by ethnicity.⁴² The referent group was women who completely abstained from alcohol. Although this may represent a unique group, there was a linear association with increasing alcohol consumption rather than an immediate jump from the referent group. In addition, PARs can provide a sense of the potential public health effect of alcohol, but they are dependent on the distribution of alcohol consumption in the population and also assume causality. Assuming a similar consumption of alcohol in the total US population of women with an estimated 172 000 new cases of invasive breast cancer in the United States, a PAR of 10% would translate to 17 200 cases prevented.⁴³

In summary, our study provides a comprehensive assessment of the relationship between alcohol intake and breast cancer risk in terms of timing, frequency, quantity, and types of alcohol in a large prospective cohort with detailed information on breast cancer risk factors. We did find an increased risk at low levels of use, but the risk was quite small. We found independent associations with drinking in early and later adult life with the strongest associations seen with cumulative drinking assessed over multiple decades. Our results highlight the importance of considering lifetime exposure when evaluating the effect of alcohol, and probably other dietary factors, on the carcinogenesis process. However, an individual will need to weigh the modest risks of light to moderate alcohol use on breast cancer development against the beneficial effects on cardiovascular disease⁴⁴ to make the best personal choice regarding alcohol consumption.

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Study concept and design: Chen, Colditz, Willett.

Acquisition of data: Willett.

Analysis and interpretation of data: Chen, Rosner, Hankinson, Colditz, Willett.

Drafting of the manuscript: Chen.

Critical revision of the manuscript for important intellectual content: Chen, Rosner, Hankinson, Colditz, Willett.

Statistical analysis: Chen, Rosner, Colditz, Willett.

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