Research Article

Cancer Epidemiology, Biomarkers & Prevention

Alcohol Intake and Breast Cancer Risk in African American Women from the AMBER Consortium

Lindsay A. Williams[1], Andrew F. Olshan[1], Chi-Chen Hong[2], Elisa V. Bandera[3], Lynn Rosenberg[4], Ting-Yuan David Cheng[2], Kathryn L. Lunetta[5], Susan E. McCann[2], Charles Poole[1], Laurence N. Kolonel[6], Julie R. Palmer[4], Christine B. Ambrosone[2], and Melissa A. Troester[1]

Abstract

Background: Alcohol is a recognized risk factor for invasive breast cancer, but few studies involve African American women.

Methods: The current analysis included 22,338 women (5,108 cases of invasive breast cancer) from the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium. The association between number of alcoholic drinks per week (dpw) and breast cancer was estimated using logistic regression, adjusting for potential confounders, and stratifying by breast cancer subtype.

Results: Approximately 35% of controls were current drinkers at interview. Women who reported current drinking of ≥14 dpw had an elevated risk of breast cancer compared with light drinkers (>0–<4 dpw) [adjusted OR (OR_{adj}), 1.33; 95% confidence interval (CI), 1.07–1.64]. We observed elevated risk among women drinking ≥7 dpw for ER^- [OR_{adj}, 1.31; 95% CI, 1.00–1.72], PR^- [OR_{adj}, 1.28; 95% CI, 1.00–1.63], $HER2^-$ [OR_{adj}, 1.36; 95% CI, 1.09–1.70], and triple-negative [OR_{adj}, 1.39; 95% CI, 0.98–2.00] molecular subtype. Among receptor-positive cases, ORs remained elevated but attenuated relative to receptor-negative cases. Sensitivity analysis of age-defined windows of exposure (<30 years, 30–49, 50+ years of age) did not reveal variation in patterns of association. Risk associated with alcohol intake did not vary significantly by oral contraceptive use, smoking status, or menopausal status.

Conclusions: Among African American women, similar to women of European descent, drinking ≥7 alcoholic dpw was associated with an increased risk of breast cancer regardless of subtype.

Impact: Alcohol intake is a modifiable risk factor for breast cancer, and reduced intake among African American women should be encouraged. *Cancer Epidemiol Biomarkers Prev; 26(5); 787–94.* ©2017 AACR.

Introduction

Although alcohol is an established risk factor for breast cancer, most studies have been conducted in predominantly white populations (1–9). African Americans report less alcohol intake than whites for a variety of reasons including religious beliefs and prevalence of comorbid conditions, such as type 2 diabetes or hypertension (10–18). Furthermore, African American women have different patterns of exposure to other breast cancer risk factors, including parity, oral contraceptive use, age at menarche, breastfeeding, and age at first birth (11, 13, 19–21). Many risk factors, including alcohol exposure, contribute to breast cancer development by altering duration of exposure or activity of hormones (22, 23). Thus, it is important to understand the relationship between alcohol and breast cancer risk in context of other exposures.

Many breast cancer risk factors have distinct effects on risk of ER-positive versus ER-negative breast cancers (21, 24, 25), and several studies have shown distinct risk factor profiles for triple-negative breast cancers (26–31). Despite suggestions that alcohol exposure may modulate estrogen metabolism pathways (32), there has been limited evidence that alcohol exposure produces distinct effects on risk of ER-positive versus ER-negative breast cancer. Moreover, very few studies have evaluated alcohol-associated risk of triple-negative breast cancers (1, 14). Alcohol is hypothesized to be a "complete carcinogen" acting as both an initiator and promoter of the disease through inhibition of DNA synthesis and repair (33–36). The current study used data from the African American Breast Cancer Epidemiology and Risk (AMBER) consortium to examine alcohol drinking among African American women as a risk factor for invasive breast cancer overall, by hormone receptor status, and triple-negative subtype. Both recent and age-defined periods of alcohol exposure were evaluated in association with risk.

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. [2]Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York. [3]Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, Rutgers, The State University of New Jersey, New Brunswick, New Jersey. [4]Slone Epidemiology Center, Boston University, Boston, Massachusetts. [5]Department of Biostatistics, Boston University School of Public Health, Crosstown Center, Boston, Massachusetts. [6]Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii.

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Corresponding Author: Melissa A. Troester, University of North Carolina at Chapel Hill, Department of Epidemiology, 135 Dauer Drive, Chapel Hill, NC 27599. Phone: 919-966-7408; Fax: 919-966-2089; E-mail: troester@email.unc.edu

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Materials and Methods

Study population

This analysis included 22,338 African American women from the AMBER consortium of four large epidemiologic studies of breast cancer. The parent studies include the Carolina Breast Cancer Study (CBCS; ref. 37), the Black Women's Health Study (BWHS; ref. 38), the Multiethnic Cohort Study (MEC; ref. 39) and the Women's Circle of Health Study (WCHS; ref. 40). The study details for the AMBER consortium have been previously described (41). Briefly, CBCS Phases I and II is a population-based case–control study conducted in North Carolina from 1993 to 2001. Breast cancer cases were identified through rapid case ascertainment in cooperation with the NC Central Cancer Registry. Controls were selected from North Carolina Department of Motor Vehicles (women ages 20 to 64) and Health Care Administration Financing lists (women ages 65 to 74). BWHS is a prospective cohort study of 59,000 African American women from around the United States enrolled by mailed questionnaire starting in 1995 with follow-up questionnaires administered every other year. Cases were identified by self-report and confirmed by medical record review or linkage with state cancer registries. MEC is a prospective cohort study based in Hawaii and Los Angeles, California, consisting of women from five different racial-ethnic groups with over 16,000 African American women enrolled from 1993 to 1996. Cases were identified via linkage to the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the Hawaii State Cancer Registry. WCHS is a case–control study started in 2002 in New York City hospitals and expanded into 10 counties in New Jersey, with cases identified by rapid case ascertainment by the New Jersey State Cancer Registry. Controls were identified by Random Digit Dialing in both sites, complemented in NJ with community-based recruitment (42). MEC and BWHS are prospective cohort studies sampled as nested case–control studies with cases and controls frequency matched by 5-year age categories, geographic location, and most recent questionnaire completed (43). Research protocols for each study were approved by the Institutional Review Board at the respective institutions. All subjects provided informed consent for study enrollment.

Eligible cases were women with a first diagnosis of invasive breast cancer ($N = 5{,}108$). Tumor subtype for estrogen receptor (ER), progesterone receptor (PR), and HER2 classification was based on pathology data from hospital records or cancer registry records. Cases were classified as ER^+ or PR^+ if marker expression was recorded as positive or borderline in the clinical record. ER and PR status was missing for approximately 25% of cases in the AMBER consortium (24). HER2 negative status was defined as immunohistochemistry (IHC) reported as 0 or 1+ staining intensity or a combination of negative by *fluorescence in situ hybridization* and 2+ by IHC. HER2 testing was not routine until the mid-2000's and is missing for approximately 50% of AMBER cases (24). Triple-negative cases were classified as negative for ER, PR, and HER2.

Exposure assessment

Each study ascertained alcohol intake via study questionnaire. For CBCS, type of alcohol (beer, wine, and liquor) and amount (drinks per day, week, month) was queried for the following age ranges for each participant: <25, 25 to 49, and ≥50. WCHS collected alcoholic drinks/day for each decade of life. For BWHS, type of alcohol (beer, wine, and liquor) and amount (drinks per day, week, month) was asked at baseline and amount was reported on the follow-up survey administered every other year. For MEC, alcohol intake data was gathered at baseline in 1993, and on the follow-up questionnaire in 2003. Participants reported the number of days per week they drank alcohol and how many glasses/cans/bottles/drinks of beer/wine/liquor they consumed. Level of recent alcohol intake was determined by the self-reported drinking in the age category that included diagnosis age (for cases) or enrollment age (for non-cases) for all studies. Forty-four cases (0.8%) and 256 controls (1.5%) were excluded from all analyses due to missing information on alcohol drinking.

Statistical analyses

Participants were coded as never, past, or current drinkers based on recent use. To be classified as a never drinker, participants had to report being a never drinker for each of the surveys preceding their index date. To be a past drinker, participants had to report drinking during a time period before the period most proximal to the index date and report no alcohol intake in the period most proximal to diagnosis. Exposure categories (drinks/week) for analyses stratified by subtype and modifiers were: never drinkers, past drinkers, >0 to <4 (referent), ≥4 to <7, and ≥7. The highest exposure category for stratified analyses was chosen because seven or more drinks exceeds the Dietary Guidelines for Americans as determined by Health and Human Services recommending no more than 1 drink a day for women. Further, a relatively small number of women in the study exceeded 7 drinks/week, so stratified analyses resulted in too few women in the highest category to produce reliable estimates. For the main analysis (overall invasive breast cancer risk), the highest category was divided into two: ≥7 to <14 and ≥14 drinks/week. The referent category, light drinking (>0 to <4 drinks/week), was selected using flexible modeling techniques with drinks/week modeled as a squared-term and graphed against the log odds of breast cancer with the corresponding 95% confidence intervals (95% CI) (Supplementary Fig. S1).

To examine critical exposure windows for alcohol intake, we created 3 age categories to describe intake during the following time periods: young adult (age <25 for CBCS, <30 for WCHS), middle adult (age 25–49 for CBCS, and 30–49 WCHS), and older adult (age 50 and older). Because WCHS asked about intake for each decade, the number of drinks/week for <20 and 20–29 was averaged to obtain the number of drinks/week for <30 years of age. This same rule was applied for 30–49 years of age (averaging the thirties and forties), and 50 years of age or greater (averaging the fifties and subsequent decades before diagnosis). The following alcohol intake categories (drinks/week) were used: 0, >0 to <4 (referent), ≥4 to <7, and ≥7.

Logistic regression was used to calculate the odds ratio (OR) and 95% CI for alcohol drinking and breast cancer risk. Two-sided P values and a significance level of 0.05 were used for all tests of statistical significance. To evaluate modification by study, duration of oral contraceptive use, smoking status, and menopausal status, likelihood ratio tests were conducted comparing the model with the interaction term to a reduced model. Covariates selected as confounders in the multivariable (MV) logistic regression models were selected on the basis of subject matter knowledge and were used in the construction of a directed acyclic graph (44). Covariates were coded as follows: study time period (1993–1998, 1999–2005, 2006–2013),

United States geographic location of the participant (Northeast, South, Midwest, and West), parent study, age at diagnosis for cases or age at index date for controls (less than 40, 40–49, 50–59, 60–69, 70 or older), level of education (<12 years, 12 years, 13–15 years, 16 years, >16 years), age at menarche (<11 years, 11–12, 13–14, 15–16, 17 or older), parity (nulliparous, 1, 2, 3, or 4 or more live births), postmenopausal hormone therapy (HT) use defined as duration of combined estrogen and progesterone use (never used, ever used), recent body mass index (BMI). Smoking status (never, former, current smoker), duration of oral contraceptive use (never, 1–9 years, 10 or more years) and menopausal status (pre-, post-) were considered as possible effect modifiers, but ultimately added as adjustment variables in unstratified MV models. A complete case analysis was used for the basic and MV logistic models (resulting in exclusion of approximately 15% percent of cases and controls in the MV model, largely due to missing menopausal status). Analyses among excluded participants produced similar estimates to those from MV models presented. Tests for trend for drinks/week were conducted using >0 to <4 (referent), ≥4 to <7, ≥7–<14 and ≥14 where noted, and excluded never/past drinkers. Alcohol categories were treated as an ordinal variable with the beta coefficient p-value serving as the measure of significance for the test of linear trend. All analyses were done in SAS version 9.3 (SAS Institute).

Results

The current analysis includes 5,108 cases of invasive breast cancer and 17, 230 controls. Forty-five percent of participants were never drinkers and 20.8% were past drinkers. Recent drinking patterns differed by study (Table 1). Approximately 11% of cases and controls reported drinking ≥4 drinks/week. CBCS, BWHS and MEC had higher proportions of current drinkers (CBCS: 40.6% of cases, 42.1% of controls; BWHS: 35.4% of cases, 37.8% of controls; MEC: 35.1% of cases, 34.5% of controls) than WCHS (16.9% of cases, 17.5% of controls). Additional participant characteristics overall and by study can be found in Supplementary Table S1.

Case–control ORs and 95% CI for the overall association between alcohol intake and breast cancer are presented in Table 2. ORs for a minimally adjusted basic model and a multivariable (MV) model (adjusted ORs) are reported in the tables. We observed a J-shaped curve between recent alcohol intake categories (excluding past drinking) and risk of invasive breast cancer. Compared to light drinkers, overall, never drinking was associated with elevated risk of breast cancer [adjusted OR, 1.12; 95% CI, 1.02–1.24; Table 2]. Drinking ≥14 drinks/week was associated with significantly increased risk of invasive breast cancer [adjusted OR, 1.33; 95% CI, 1.07–1.64; Table 2]. When analyses were stratified by hormone receptor (HR) status, elevated risk was observed in the highest intake category for all subtypes. Table 2 shows slightly stronger risk associated with ≥7 drinks/week among ER-negative [adjusted OR, 1.31; 95% CI, 1.00–1.72], PR-negative [adjusted OR, 1.28; 95% CI, 1.00–1.63], HER2-negative [adjusted OR, 1.36; 95% CI,1.09–1.70], and triple-negative cases [adjusted OR, 1.39; 95% CI, 0.98–2.00]. Associations were in the same direction for ER^+, PR^+, and $HER2^+$ breast cancers, but were slightly attenuated and non-significant.

Among the four studies, CBCS had the strongest J-shaped pattern of risk: compared to drinking >0–<4 drinks/week, the adjusted ORs were [1.23; 95% CI; 0.92–1.65; 1.50; 95% CI, 1.11–2.03; and 2.03; 95% CI, 1.29–3.18], respectively, for never drinking, past drinking, and drinking ≥7 drinks/week (Table 3). There were no associations between risk of breast cancer and any alcohol intake in WCHS. In BWHS and MEC, associations between alcohol intake and risk were similar in direction to those in CBCS, but lower in magnitude (Table 3). BWHS never drinkers had a significantly elevated risk of breast cancer [adjusted OR, 1.17; 95% CI, 1.02–1.34]. The multivariable *P* value for heterogeneity was 0.10.

We evaluated effect modification by smoking status, duration of oral contraceptive use, and menopausal status (Supplementary Tables S2–S4, respectively). We did not observe evidence for

Table 1. Exposure characteristics of cases and controls in the AMBER Consortium stratified by study: recent alcohol intake, smoking status, oral contraceptive use, and menopausal status

	CBCS *N* (%)		WCHS *N* (%)		MEC *N* (%)		BWHS *N* (%)		Total *N* (%)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Number of alcoholic drinks per week										
Never drinkers	293 (37.5)	309 (39.4)	798 (65.4)	791 (65.1)	629 (55.5)	2,360 (53.3)	797 (40.4)	4,063 (37.6)	2,517 (49.3)	7,523 (43.4)
>0–<4	193 (24.7)	232 (29.6)	113 (9.3)	111 (9.1)	226 (19.9)	906 (20.5)	492 (24.9)	2,868 (26.6)	1,024 (20.1)	4,117 (23.9)
≥4–<7	32 (4.1)	44 (5.6)	40 (3.3)	43 (3.5)	43 (3.8)	174 (3.9)	109 (5.5)	615 (5.7)	224 (4.4)	876 (5.1)
≥7–<14	46 (5.9)	24 (3.1)	30 (2.5)	38 (3.1)	46 (4.1)	192 (4.3)	68 (3.5)	351 (3.3)	190 (3.7)	605 (3.5)
≥14	42 (5.4)	30 (3.8)	23 (1.9)	22 (1.8)	83 (7.3)	259 (5.9)	30 (1.5)	135 (1.3)	178 (3.5)	446 (2.6)
Past drinkers	175 (22.4)	145 (18.5)	216 (17.7)	211 (17.4)	107 (9.4)	540 (12.2)	477 (24.2)	2,767 (25.6)	975 (19.1)	3,663 (21.3)
Smoking status										
Never smoker	435 (55.7)	467 (59.6)	745 (61.1)	702 (57.7)	508 (45.7)	2,050 (46.9)	1,168 (59.3)	6,288 (58.3)	2,856 (56.2)	9,507 (55.4)
Current smoker	134 (17.2)	150 (19.1)	199 (16.3)	244 (20.1)	216 (19.4)	807 (18.5)	343 (17.4)	1,978 (18.3)	892 (17.6)	3,179 (18.5)
Former smoker	212 (27.1)	167 (21.3)	276 (22.6)	270 (22.2)	388 (34.9)	1,515 (34.7)	460 (23.3)	2,525 (23.4)	1,336 (26.3)	4,477 (26.1)
Missing	0	0	0	0	22	59	2	8	24	67
Oral contraceptive use										
Never, <1 year	380 (48.7)	386 (49.4)	589 (48.6)	593 (49.1)	688 (63.1)	2,780 (66.1)	825 (41.8)	4,831 (44.7)	2,482 (49.1)	8,590 (55.6)
1–9 years	276 (35.3)	295 (37.8)	422 (34.8)	441 (36.5)	279 (25.6)	994 (23.7)	820 (41.6)	4,398 (40.7)	1,797 (35.5)	6,128 (36.1)
10+years	125 (16.0)	100 (12.8)	202 (16.7)	175 (14.5)	123 (11.3)	429 (10.2)	328 (16.6)	1,570 (14.5)	778 (15.4)	2,274 (13.4)
Missing	0	3	7	7	44	228	0	0	51	238
Menopausal status										
Pre-	286 (40.9)	298 (43.1)	574 (49.6)	565 (49.1)	140 (12.7)	388 (9.0)	717 (42.7)	4,179 (43.6)	1,717 (37.0)	5,430 (34.5)
Post-	413 (59.1)	393 (56.9)	583 (50.4)	587 (50.9)	964 (87.3)	3,905 (91.0)	964 (57.4)	5,412 (56.4)	2,924 (63.0)	10,297 (65.5)
Missing	82	93	63	64	30	138	292	1,208	467	1,503

Table 2. Recent alcohol intake in relation to Hormone Receptor status among invasive breast cancer cases in the AMBER consortium

			Basic model[a]			MV model[b]		Basic model[a]		MV model[b]
	Controls *N* (%)	Cases *N* (%)	OR (95% CI)	Controls *N* (%)	Cases *N* (%)	OR (95% CI)	Cases *N* (%)	OR (95% CI)	Cases *N* (%)	OR (95% CI)
Drinks per week	All invasive breast cancer									
Never drinkers	7,516 (43.7)	2,517 (49.3)	1.12 (1.03–1.22)	6,476 (43.4)	2,134 (49.1)	1.12 (1.02–1.24)				
>0–<4	4,114 (23.9)	1,023 (20.0)	Ref.	3,539 (23.7)	862 (19.8)	Ref.				
≥4–<7	876 (5.1)	223 (4.4)	0.99 (0.84–1.17)	750 (5.0)	192 (4.4)	1.04 (0.86–1.25)				
≥7–<14	605 (3.5)	190 (3.7)	1.13 (0.94–1.36)	534 (3.6)	159 (3.7)	1.07 (0.88–1.32)				
≥14	446 (2.6)	178 (3.5)	1.34 (1.10–1.63)	394 (2.6)	149 (3.4)	1.33 (1.07–1.64)				
Past drinkers	3,661 (21.3)	973 (19.1)	1.01 (0.91–1.12)	3,224 (21.6)	853 (19.6)	1.04 (0.93–1.17)				
P_{trend}[c]			0.01			0.09				
Drinks per week	ER^+						ER^-			
Never drinkers	7,516 (43.7)	1,259 (49.4)	1.10 (0.98–1.23)	6,476 (43.4)	1,072 (48.9)	1.13 (0.99–1.29)	638 (46.3)	1.12 (0.96–1.30)	536 (45.7)	1.07 (0.90–1.27)
>0–<4	4,114 (23.9)	508 (19.9)	Ref.	3,539 (23.7)	428 (19.5)	Ref.	297 (21.5)	Ref.	254 (21.7)	Ref.
≥4–<7	876 (5.1)	109 (4.3)	0.98 (0.78–1.23)	750 (5.0)	98 (4.5)	1.10 (0.86–1.40)	61 (4.4)	0.97 (0.72–1.31)	53 (4.5)	1.02 (0.74–1.41)
≥7	1,051 (6.1)	189 (7.4)	1.20 (1.00–1.45)	928 (6.2)	161 (7.3)	1.20 (0.97–1.47)	111 (8.1)	1.35 (1.06–1.72)	91 (7.8)	1.31 (1.00–1.72)
Past drinkers	3,661 (21.3)	484 (19.0)	0.99 (1.00–1.45)	3,224 (21.6)	434 (19.8)	1.07 (0.92–1.24)	272 (19.7)	1.11 (0.92–1.33)	238 (20.3)	1.11 (0.91–1.35)
P_{trend}[c]			0.12			0.18		0.03		0.08
Drinks per week	PR^+						PR^-			
Never drinkers	7,516 (43.7)	1,001 (49.5)	1.12 (0.99–1.28)	6,476 (43.4)	852 (48.8)	1.14 (0.98–1.32)	825 (47.0)	1.10 (0.96–1.26)	688 (46.6)	1.07 (0.92–1.25)
>0–<4	4,114 (23.9)	395 (19.5)	Ref.	3,539 (23.7)	336 (19.2)	Ref.	377 (21.5)	Ref.	318 (21.5)	Ref.
≥4–<7	876 (5.1)	77 (3.8)	0.87 (0.67–1.13)	750 (5.0)	72 (4.1)	1.02 (0.77–1.35)	82 (4.7)	1.04 (0.80–1.35)	70 (4.7)	1.08 (0.81–1.43)
≥7	1,051 (6.1)	142 (7.0)	1.18 (0.95–1.45)	928 (6.2)	121 (6.9)	1.19 (0.95–1.50)	138 (7.9)	1.32 (1.06–1.64)	112 (7.6)	1.28 (1.00–1.63)
Past drinkers	3,661 (21.3)	406 (20.1)	1.07 (0.95–1.46)	3,224 (21.6)	366 (21.0)	1.14 (0.97–1.35)	333 (19.0)	1.02 (0.87–1.20)	290 (19.6)	1.04 (0.88–1.25)
P_{trend}[c]			0.30			0.29		0.03		0.08
Drinks per week	$HER2^+$						$HER2^-$			
Never drinkers	7,516 (43.7)	254 (46.8)	1.01 (0.80–1.28)	6,476 (43.4)	212 (45.8)	0.93 (0.72–1.21)	1,007 (46.9)	1.01 (0.88–1.15)	857 (46.4)	1.04 (0.90–1.21)
>0–<4	4,114 (23.9)	115 (21.2)	Ref.	3,539 (23.7)	101 (21.8)	Ref.	436 (20.3)	Ref.	367 (19.9)	Ref.
≥4–<7	876 (5.1)	31 (5.7)	1.21 (0.80–1.83)	750 (5.0)	28 (6.0)	1.34 (0.87–2.09)	87 (4.1)	0.91 (0.70–1.18)	79 (4.3)	1.04 (0.79–1.37)
≥7	1,051 (6.1)	44 (8.1)	1.33 (0.93–1.92)	928 (6.2)	33 (7.1)	1.17 (0.77–1.77)	169 (7.9)	1.27 (1.03–1.56)	149 (8.0)	1.36 (1.09–1.70)
Past drinkers	3,661 (21.3)	99 (18.2)	0.94 (0.72–1.25)	3,224 (21.6)	89 (19.2)	0.99 (0.73–1.73)	450 (20.9)	1.08 (0.93–1.26)	398 (21.5)	1.15 (0.99–1.37)
P_{trend}[c]			0.06			0.38		0.05		0.01
Drinks per week	Non triple negative						Triple negative			
Never drinkers	7,516 (43.7)	2,195 (50.3)	1.14 (1.04–1.25)	6,476 (43.4)	1,867 (50.1)	1.14 (1.03–1.26)	322 (43.4)	0.97 (0.77–1.20)	267 (42.7)	0.96 (0.76–1.22)
>0–<4	4,114 (23.9)	859 (19.7)	Ref.	3,539 (23.7)	725 (19.5)	Ref.	164 (22.1)	Ref.	137 (21.9)	Ref.
≥4–<7	876 (5.1)	188 (4.3)	0.99 (0.82–1.18)	750 (5.0)	161 (4.3)	1.02 (0.84–1.24)	35 (4.7)	1.01 (0.68–1.51)	31 (5.0)	1.14 (0.74–1.74)
≥7	1,051 (6.1)	305 (7.0)	1.21 (1.04–1.40)	928 (6.2)	255 (6.9)	1.16 (0.98–1.37)	63 (8.5)	1.39 (1.01–1.92)	53 (8.5)	1.39 (0.98–2.00)
Past drinkers	3,661 (21.3)	815 (18.7)	0.99 (0.89–1.11)	3,224 (21.6)	716 (19.2)	1.02 (0.91–1.15)	158 (21.3)	1.19 (0.93–1.50)	137 (21.9)	1.21 (0.93–1.58)
P_{trend}[c]			0.04			0.18		0.06		0.06

Abbreviation: CI, confidence interval.

[a]Basic model adjusted for age, study, time period, and geographic region.

[b]Multivariable model adjusted for age, study, time period, geographic region, education, age at menarche, BMI, menopausal status (pre-/post-), HT use (ever/never), parity, smoking status, and duration of oral contraceptive use.

[c]P_{trend} excludes never and past drinkers.

Table 3. Recent alcohol intake and invasive breast cancer by study from the AMBER consortium

	Controls *N* (%)	Cases *N* (%)	Basic model[a] OR (95% CI)	Controls *N* (%)	Cases *N* (%)	MV model[b] OR (95% CI)
			CBCS			
Number of alcoholic drinks per week						
Never drinkers	309 (39.4)	293 (37.5)	1.16 (0.90–1.50)	258 (39.0)	253 (37.5)	1.23 (0.92–1.65)
>0–<4	232 (29.6)	193 (24.7)	Ref.	199 (30.0)	166 (24.6)	Ref.
≥4–<7	44 (5.6)	32 (4.1)	0.88 (0.53–1.43)	36 (5.4)	28 (4.2)	0.95 (0.55–1.64)
≥7	54 (6.9)	88 (11.3)	2.02 (1.37–2.99)	46 (6.9)	72 (10.7)	2.03 (1.29–3.18)
Past drinkers	145 (18.5)	75 (22.4)	1.50 (1.11–2.03)	123 (18.6)	155 (23.0)	1.53 (1.09–2.14)
P_{trend}[c]			<0.01			0.01
			WCHS			
Number of alcoholic drinks per week						
Never drinkers	791 (65.1)	798 (65.4)	0.96 (0.72–1.27)	742 (66.0)	727 (65.1)	0.89 (0.66–1.21)
>0–<4	111 (9.1)	113 (9.3)	Ref.	101 (8.9)	104 (9.3)	Ref.
≥4–<7	43 (3.5)	40 (3.3)	0.91 (0.55–1.51)	37 (3.3)	38 (3.4)	1.01 (0.59–1.73)
≥7	60 (4.9)	53 (4.3)	0.84 (0.53–1.32)	57 (5.1)	50 (4.5)	0.81 (0.51–1.31)
Past drinkers	211 (17.4)	216 (17.7)	0.96 (0.70–1.34)	187 (16.6)	198 (17.7)	0.98 (0.69–1.39)
P_{trend}[c]			0.42			0.40
			MEC			
Number of alcoholic drinks per week						
Never drinkers	2,360 (53.3)	629 (55.5)	1.07 (0.90–1.27)	1,908 (51.4)	478 (53.0)	1.10 (0.91–1.34)
>0–<4	906 (20.5)	226 (19.9)	Ref.	759 (20.5)	183 (20.3)	Ref.
≥4–<7	174 (3.9)	43 (3.8)	0.99 (0.69–1.43)	150 (4.0)	32 (3.6)	0.92 (0.60–1.39)
≥7	451 (10.2)	129 (11.4)	1.15 (0.90–1.47)	411 (11.8)	108 (12.0)	1.06 (0.81–1.40)
Past drinkers	540 (12.2)	107 (9.4)	0.79 (0.62–1.03)	481 (13.0)	101 (11.2)	0.87 (0.66–1.14)
P_{trend}[c]			0.29			0.63
			BWHS			
Number of alcoholic drinks per week						
Never drinkers	4,056 (37.6)	797 (40.5)	1.15 (1.02–1.30)	3,568 (37.9)	676 (40.8)	1.17 (1.02–1.34)
>0–<4	2,865 (26.6)	491 (24.9)	Ref.	2,480 (26.3)	409 (24.7)	Ref.
≥4–<7	615 (5.7)	108 (5.5)	1.02 (0.82–1.28)	527 (5.6)	94 (5.7)	1.08 (0.85–1.38)
≥7	486 (4.5)	98 (5.0)	1.17 (0.92–1.49)	414 (4.4)	78 (4.7)	1.13 (0.87–1.48)
Past drinkers	2,765 (25.6)	475 (24.1)	0.99 (0.87–1.14)	2,433 (25.8)	399 (24.1)	1.02 (0.88–1.19)
P_{trend}[c]			0.23			0.38

Abbreviation: CI, confidence interval.

[a]Basic model adjusted for age, study, time period, and geographic region.

[b]Multivariable model adjusted for age, study, time period, geographic region, education, age at menarche, BMI, menopausal status (pre-/post-), HT use (ever/never), parity, smoking status, and duration of oral contraceptive use.

[c]P_{trend} excludes never and past drinkers.

statistical interaction between alcohol intake and smoking status in the multivariable model (MV $P = 0.58$, Supplementary Table S2). Risk was elevated in the highest alcohol intake category across all strata of smoking status. Similarly, we did not observe evidence of statistical interaction for alcohol intake and duration of oral contraceptive use (MV $P = 0.17$, Supplementary Table S3) or menopausal status (MV $P = 0.38$, Supplementary Table S4).

We evaluated drinking during specific age-defined periods. Associations between recent drinking and risk were attenuated when alcohol drinking was assessed by age-at-exposure, but only two of the four AMBER studies (CBCS and WCHS) had data available for drinking at different time periods so sample size is limited. ORs for early, middle, and later life were close to the null and did not show the dose–response trend observed for recent drinking (Table 4).

Discussion

In this study among African American women in the AMBER consortium, we found evidence of a J-shaped curve for alcohol drinking and invasive breast cancer risk. Women who reported drinking 14 or more drinks/week as compared to those drinking >0–<4 drinks/week experienced the highest risk of invasive breast cancer. Never drinkers also experienced a significantly elevated risk of breast cancer. The J-shaped curve was not substantially altered when stratifying by hormone receptor status or triple negative subtype. In subtype-stratified analyses, alcohol intake of 7 or more drinks/week was associated with increased risk of breast cancer across all subtypes studied. There was no evidence for statistical interaction by smoking, oral contraceptive use, or menopausal status. Interestingly, past drinkers were most often found to have a lower risk of breast cancer than women reporting recent use, suggesting that decreasing alcohol consumption may reduce risk. We conclude that alcohol is a risk factor for invasive breast cancer among African American women, as has been consistently shown among studies primarily involving white women.

Previous studies of alcohol and cancer have found J-shaped curves similar to those observed in this study (6, 45), but few breast cancer studies have assessed or reported this dose-response pattern (3–8, 11, 46–48). We hypothesize that J-shaped curve morphology may be attributable in part to women with unmeasured comorbidities that preclude alcohol drinking, yet contribute to increased risk of breast cancer among never drinkers, such as type 2 diabetes (6, 49). A behavioral study found that as self-reported health status moves from poor to excellent among African American women, there is a 10% increase in the odds of alcohol drinking (16). In our study, women who were never drinkers were more frequently of obese BMI, had lower education (with the exception of BWHS), and were more likely report never

Table 4. Sensitivity analysis to examine alcohol intake (drinks per week) among ever drinkers during different age periods before diagnosis in relation to invasive breast cancer for CBCS and WCHS

	Controls *N* (%)	Cases *N* (%)	Basic model[a] OR (95% CI)	Controls *N* (%)	Cases *N* (%)	MV model[b] OR (95% CI)
			Young age drinks per week (<30 years old)[c]			
Number of alcoholic drinks per week						
0	1,287 (64.3)	1,295 (64.7)	1.05 (0.90–1.23)	1,156 (64.7)	1,159 (64.6)	1.04 (0.88–1.23)
>0–<4	463 (23.1)	439 (21.9)	Ref.	410 (22.9)	396 (22.1)	Ref.
≥4–<7	95 (4.8)	96 (4.8)	1.06 (0.78–1.45)	82 (4.6)	88 (4.9)	1.09 (0.78–1.52)
≥7	157 (7.8)	173 (8.6)	1.16 (0.90–1.49)	139 (7.8)	150 (8.4)	1.07 (0.81–1.41)
P_{trend}			0.25			0.64
			Middle age drinks per week (30–<50 years old)[d]			
Number of alcoholic drinks per week						
0	1,265 (63.3)	1,227 (62.1)	1.01 (0.86–1.19)	1,140 (64.4)	1,102 (62.4)	0.97 (0.81–1.16)
>0–<4	442 (22.3)	420 (21.3)	Ref.	383 (21.6)	369 (20.9)	Ref.
≥4–<7	109 (5.5)	132 (6.7)	1.26 (0.95–1.68)	92 (5.2)	124 (7.0)	1.38 (1.01–1.88)
≥7	176 (8.9)	197 (10.0)	1.17 (0.92–1.49)	155 (8.7)	171 (9.7)	1.14 (0.87–1.49)
P_{trend}			0.12			0.25
			Older age drinks per week (50+ years old)			
Number of alcoholic drinks per week						
0	879 (78.8)	906 (80.3)	1.04 (0.81–1.34)	770 (78.7)	786 (79.9)	1.00 (0.75–1.32)
>0–<4	145 (13.0)	141 (12.5)	Ref.	132 (13.4)	125 (12.6)	Ref.
≥4–<7	45 (4.0)	30 (2.7)	0.70 (0.41–1.17)	36 (3.7)	27 (2.7)	0.76 (0.43–1.34)
≥7	46 (4.1)	51 (4.5)	1.08 (0.68–1.72)	42 (4.3)	47 (4.7)	1.07 (0.65–1.76)
P_{trend}			0.98			0.94
			Restricted to women 50+ with data for all age periods			
Number of alcoholic drinks per week						
0	875 (78.9)	893 (80.2)	1.25 (0.92–1.69)	767 (78.7)	774 (79.6)	1.22 (0.87–1.71)
>0–<4	145 (13.1)	140 (12.6)	Ref.	132 (13.5)	124 (12.8)	Ref.
≥4–<7	44 (4.0)	30 (2.7)	0.63 (0.36–1.11)	35 (3.6)	27 (2.8)	0.68 (0.37–1.26)
≥7	45 (4.1)	51 (4.6)	1.14 (0.68–1.89)	41 (4.2)	47 (4.8)	1.14 (0.66–1.97)
P_{trend}			0.69			0.65

Abbreviation: CI, confidence interval.

[a]Basic model adjusted for age, study, time period, and geographic region.

[b]Multivariable model adjusted for age, study, time period, geographic region, education, age at menarche, BMI, menopausal status (pre-/post-), HT use (ever/never), parity, smoking status, and duration of oral contraceptive use.

[c]<25 years old for CBCS.

[d]25–<50 years old for CBCS.

having a mammogram. Future studies that explicitly capture comorbidities and reasons for abstaining from alcohol would help to elucidate the reasons for our observed elevated risk in never drinkers.

Our findings of elevated risk among women drinking 14 or more drinks/week are consistent with two large meta-analyses and other epidemiologic studies conducted among primarily white women (3–8, 11, 46, 47). Our findings are also consistent with the literature showing an increased risk of both HR^+ and HR^- subtypes with increasing alcohol intake (3, 8, 47, 50–54). Considering other co-exposures, similar to our findings, smoking did not modify alcohol-associated risk in a meta-analysis of 53 epidemiologic studies and a separate pooled analysis where elevated risk was seen in the highest intake category of alcohol intake regardless of smoking status (5, 53). The patterns of risk for duration of oral contraceptive use mirrored those of our overall risk estimates, with a J-shaped curve and no evidence of statistical interaction, consistent with previous findings (2, 14).

The most important difference between our findings and previous literature was with regard to menopausal status and age-related patterns. We observed no differences in associations by menopausal status; previous studies among white women have suggested that postmenopausal women who consumed alcohol were at an elevated risk of breast cancer compared to premenopausal women (3, 8, 48, 51, 53). However, our menopause findings are echoed in our analysis of risk by age-period. Previous studies have suggested that drinking before 40 to 50 years of age has a greater impact on breast cancer risk relative to drinking at older ages (8, 51) These previous studies have been conducted predominantly in white women, and different patterns of co-exposures such as reproductive behavior may underlie inconsistencies.

Our study has some limitations. First, we did not have dietary intake or complete physical activity information for all the studies in the AMBER consortium and did not account for these covariates in our analyses. In addition, we did not have information on reasons for alcohol abstinence, which could shed light on the elevated risk observed among never drinkers in our study. Our pooled analysis approach may be affected by differences between studies. Differences in categorical data collection between studies prevented evaluation of intake as a continuous variable, by grams of alcohol or by alcohol type, but previous studies suggest that cancer risk is most strongly associated with the type of alcoholic beverage most frequently consumed in a population (3, 6). Furthermore, although we did not find statistical evidence of heterogeneity by study, we did observe some study-specific qualitative differences in the alcohol-risk association. Finally, case–control studies in the consortium may have been subject to recall bias, but work from the Nurses' Health Study did not find significant differences in recall of alcohol intake comparing pre- and post-diagnosis questionnaires among women with breast cancer (55).

To conclude, in a large consortium of African American women from around the United States, risk of breast cancer

was elevated among never drinkers as well as those who reported drinking 7 or more drinks/week, irrespective of HR status or triple-negative subtype. Our findings support alcohol as a risk factor for breast cancer in African American women, where risk associations have been less well-studied. Future work should seek to understand why African American women who abstain from alcohol have an increased risk of breast cancer. Finally, our results suggest that drinking cessation may be associated with a reduced risk of invasive breast cancer and may be a targetable public health intervention strategy among African American women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The results do not necessarily reflect the views of the NIH or the sponsors, who had no role in study design; data collection, analysis, or interpretation; or writing and submission of the article.

Authors' Contributions

Conception and design: L.A. Williams, A.F. Olshan, J.R. Palmer, C.B. Ambrosone, M.A. Troester

Development of methodology: L.A. Williams, M.A. Troester

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.F. Olshan, E.V. Bandera, L. Rosenberg, L.N. Kolonel, J.R. Palmer, C.B. Ambrosone

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.A. Williams, A.F. Olshan, E.V. Bandera, K.L. Lunetta, S.E. McCann, C. Poole, L.N. Kolonel, M.A. Troester

Writing, review, and/or revision of the manuscript: L.A. Williams, A.F. Olshan, C.-C. Hong, E.V. Bandera, L. Rosenberg, T.-Y. David Cheng, K.L. Lunetta, S.E. McCann, C. Poole, L.N. Kolonel, J.R. Palmer, C.B. Ambrosone, M.A. Troester

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.F. Olshan

Study supervision: A.F. Olshan, M.A. Troester

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