VOLUME 28 · NUMBER 29 · OCTOBER 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Alcohol Consumption and Breast Cancer Recurrence and Survival Among Women With Early-Stage Breast Cancer: The Life After Cancer Epidemiology Study

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Submitted March 11, 2010; accepted June 9, 2010; published online ahead of print at www.jco.org on August 30, 2010.

Supported by Grant No. R01 CA129059 from the National Cancer Institute.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2829-4410/$20.00

DOI: 10.1200/JCO.2010.29.2730

ABSTRACT

Purpose
To examine the association of alcohol consumption after breast cancer diagnosis with recurrence and mortality among early-stage breast cancer survivors.

Patients and Methods
Patients included 1,897 LACE study participants diagnosed with early-stage breast cancer between 1997 and 2000 and recruited on average 2 years postdiagnosis, primarily from the Kaiser Permanente Northern California Cancer Registry. Alcohol consumption (ie, wine, beer, and liquor) was assessed at cohort entry using a food frequency questionnaire. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CI with adjustment for known prognostic factors.

Results
Two hundred ninety-three breast cancer recurrences and 273 overall deaths were ascertained after an average follow-up of 7.4 years. Nine hundred fifty-eight women (51%) were considered drinkers (> 0.5 g/d of alcohol), and the majority drank wine (89%). Drinking ≥ 6 g/d of alcohol compared with no drinking was associated with an increased risk of breast cancer recurrence (HR, 1.35; 95% CI, 1.00 to 1.83) and death due to breast cancer (HR, 1.51; 95% CI, 1.00 to 2.29). The increased risk of recurrence appeared to be greater among postmenopausal (HR, 1.51; 95% CI, 1.05 to 2.19) and overweight and obese women (HR, 1.60; 95% CI, 1.08 to 2.38). Alcohol intake was not associated with all-cause death and possibly associated with decreased risk of non–breast cancer death.

Conclusion
Consuming three to four alcoholic drinks or more per week after a breast cancer diagnosis may increase risk of breast cancer recurrence, particularly among postmenopausal and overweight/obese women, yet the cardioprotective effects of alcohol on non–breast cancer death were suggested.

J Clin Oncol 28:4410-4416. © 2010 by American Society of Clinical Oncology

INTRODUCTION

In the United States, breast cancer survival rates have been increasing steadily due to better detection methods and more effective adjuvant therapies.[1,2] Thus, research on the role of modifiable lifestyle factors that might impact breast cancer prognosis is growing. One factor is alcohol consumption, which is generally recognized to increase the risk of breast cancer.[3-5] However, mixed results have emerged from the few studies that have examined alcohol intake and breast cancer prognosis.

Studies to date have reported increased[6-8] and decreased risks of death[9-11] with alcohol consumption, as well as no association.[12-18] Only three studies have examined the influence of alcohol on risk of breast cancer recurrence. One found that daily beer consumption was associated with an increased risk of breast cancer recurrence,[6] while the other two reported no association between alcohol and recurrence.[19,20] Overall, studies conducted thus far have suffered from methodologic limitations such as small number of events, restricted exposure (drinking) range, and failure to adjust for important prognostic factors.[21]

We investigated the effects of alcohol on breast cancer prognosis and survival in the Life After Cancer Epidemiology (LACE) study, a prospective cohort study of 1,897 early-stage breast cancer survivors. Specifically, we examined the associations

by overall alcohol consumption and by type of alcoholic beverage consumed, and determined if variations in risk were present by menopausal status, body mass index (BMI), and estrogen receptor (ER) status.

PATIENTS AND METHODS

Study Population

The LACE Study cohort consisted of 2,269 women diagnosed with invasive breast cancer between 1997 and 2000 and recruited primarily from the Kaiser Permanente Northern California (KPNC) Cancer Registry (83%) and the Utah Cancer Registry (12%) from 2000 to 2002. Further details are provided elsewhere.[22]

In brief, eligibility criteria included age between 18 and 70 years at enrollment; diagnosis of early-stage primary breast cancer (stage I $\geq$ 1 cm, II, or IIIA); enrollment between 11 and 39 months postdiagnosis; completion of breast cancer treatment (except for adjuvant hormone therapy); free of recurrence; and no history of other cancers within 5 years before enrollment.

Between January 2000 and April 2002, 5,656 women who initially met the LACE eligibility criteria were sent a recruitment package. Of these, 2,614 (46%) agreed to participate and completed the questionnaires. Subsequent medical record review to confirm eligibility identified 345 exclusions. The remaining 2,269 women constituted the LACE cohort. Differences between KPNC participants and nonparticipants have been compared,[22] and found similar by cancer severity and treatment. The only significant differences were that women approached within 15 months of diagnosis were more likely to enroll than those approached later, and women younger than age 50 years were less likely to enroll than older women. This analysis was restricted to 1,897 women (84%) who completed a dietary questionnaire at baseline. The study was approved by the institutional review boards of KPNC and the University of Utah.

Data Collection

Alcohol intake was assessed at cohort entry (on average 2 years after diagnosis) using the Fred Hutchinson Cancer Research Center Food Questionnaire (FHCRC-FQ), a self-administered, semi-quantitative food frequency questionnaire (FFQ) with 122 food and beverage items.[23] For wine, beer, and liquor, participants marked frequency of consumption over the past 12 months and indicated the associated serving size as small, medium, or large. A medium serving size was defined as 1 medium glass (6 oz), 12 oz can or bottle, and 1 shot (1.5 oz), respectively.

Servings per week of wine, beer, and liquor were calculated by multiplying portion size by frequency of consumption and standardized to weekly consumption. For all alcohol, servings per day in oz was converted to grams (g) per day of alcohol (one standard drink in the United States = 13.7 g [0.6 oz] of pure ethanol[24]) and categorized as none ($\leq$ 0.5 g/d, the lowest category of intake, nondrinkers), 0.6 to 5.0 g/d (occasional drinkers), and $\geq$ 6 g/d (regular drinkers). Wine consumption was categorized as none, $\leq$ 1 serving, or $\geq$ 2 servings per week. For beer and liquor, the data could only be examined as none versus any consumption due to low intake in the cohort.

Information on clinical factors was obtained through electronic data sources available from KPNC or from medical chart review for the non-KPNC participants. Data included tumor size, number of positive lymph nodes, hormone receptor status, and treatment (ie, surgery, chemotherapy, radiation therapy, and hormone therapy). Tumor stage was calculated according to criteria of the American Joint Committee on Cancer (third edition). Data on race, education, smoking, menopausal status, and BMI were obtained from the mailed baseline questionnaire.

Four outcomes were considered: new breast cancer event (hereafter referred to as recurrence), overall death, death from breast cancer, and death from causes other than breast cancer. Recurrence includes a locoregional cancer recurrence, distant recurrence/metastasis, and development of a contralateral breast primary. Overall death includes death from any cause including breast cancer; death from breast cancer includes death attributable to breast cancer as a primary or underlying cause on the death certificate; and death from causes other than breast cancer includes all other deaths. A physician reviewer was consulted in the event a cause of death was unclear. Recurrences were ascertained by a mailed semi-annual or annual (after April 2005) health status update questionnaire asking participants to report any events occurring in the preceding 6 or 12 months, respectively. Nonrespondents were called to complete the questionnaire by telephone. Medical records were reviewed to verify reported outcomes. Participant deaths were determined through KPNC electronic data sources, a family member responding to a mailed questionnaire, or a phone call. Copies of death certificates were obtained to verify primary and underlying causes of death (International Classification of Diseases, 9th revision).

Statistical Analysis

Comparisons of baseline cohort characteristics by drinker and nondrinker status were conducted using Pearson χ^2 and Kruskal-Wallis tests.

Follow-up began at date of study entry and ended at date of first confirmed cancer recurrence or death, depending on the analysis. Individuals who did not have an event were censored at date of last contact. Hazard ratios (HRs) and 95% CIs representing the association between a defined event and alcohol intake were computed adjusting for covariates using the delayed-entry Cox proportional hazards model based on time since cohort enrollment until event or censoring.[25,26] Linear tests for trend were estimated by modeling the median value of each category on an ordinal scale.

Covariates considered were: age at diagnosis, race, BMI at 1 year prediagnosis, menopausal status, smoking status, total folate intake, stage of disease, hormone receptor status, definitive surgery, tamoxifen use, adjuvant treatment, and positive lymph nodes (specified in Table 1).

Covariates were retained in the final multivariable model if they substantially changed the effect estimate of alcohol consumption when added individually to the Cox model[27] or were considered a priori adjustment factors based on review of the literature. Standard step-wise forward selection was also performed to confirm the resultant factors in the model and produced similar study results as reported below. Two sensitivity analyses were conducted: (1) excluding 44 women who recurred or died within the first year of entering the cohort to address the possibility that women with underlying cancer recurrence and limited survival may have altered their alcohol intake and (2) excluding 219 women enrolled from the Utah Cancer Registry to address possible regional differences in alcohol consumption. Interactions by menopausal status (pre *v* post), prediagnosis BMI (normal weight *v* overweight/obese), and ER status (positive *v* negative) were examined by first generating stratum-specific estimates and then including interaction terms in the models to test for statistical significance.

RESULTS

Table 1 shows the characteristics of drinkers compared with nondrinkers. Drinkers (51%) tended to be slightly younger, predominantly white, more educated, former or current smokers, and enrolled from KPNC, and they had higher consumption of folate (ie, diet and supplements) and were of normal weight. The majority of drinkers were diagnosed with early-stage disease (stage I), and had breast-conserving surgery and adjuvant treatment. There were no significant differences between drinkers and nondrinkers by menopausal status, positive lymph nodes, and tamoxifen use.

Among the drinkers, most women drank wine (88.5%), followed by liquor (42.1%) and beer (35.7%), and the median amount of alcohol consumed was 5.96 g/d (standard deviation, 17.13; Table 2). Based on median levels, postmenopausal, normal weight, and ER-positive women drank more alcohol compared with premenopausal, overweight/obese, and ER-negative women, respectively.

Table 1. Baseline Characteristics of the LACE Study (n = 1,897), by Alcohol Consumption Status

Characteristic	Drinkers (> 0.5 g/d) No.	%	Nondrinkers (≤ 0.5 g/d) No.	%	P*
No.	958		939		
Mean age at diagnosis, years†	58.0		59.1		.03
SD	10.7		10.9		
Mean BMI 1 year prediagnosis, kg/m^2†	25.7		28.0		< .001
SD	5.0		6.2		
Median total folate intake, μg/d†	327.4		317.9		.02
Range	85.9-1,006.9		77.0-841.0		
Recruitment source					< .001
Kaiser Permanente Northern California Cancer Registry	849	94.7	712	80.5	
Utah Cancer Registry	47	5.3	172	19.5	
Race					< .001
White	841	87.9	715	76.2	
Black	22	2.3	54	5.8	
Hispanic	41	4.3	59	6.3	
Asian/Pacific Islander	26	2.7	79	8.4	
Other	27	2.8	31	3.3	
Menopausal status at diagnosis					.233
Post	611	63.8	619	66.0	
Pre	219	22.9	185	19.7	
Unknown	127	13.3	134	14.3	
Smoking status					< .001
Never	420	43.9	585	62.4	
Former	458	47.8	294	31.4	
Current	79	8.3	58	6.2	
Education					< .001
Less than high school	29	3.0	59	6.3	
High school/some college	517	54.1	596	63.5	
College graduate	409	42.8	283	30.2	
Stage					.003
I	496	51.8	407	43.5	
IIA	285	29.8	333	35.6	
IIB	146	15.3	168	17.9	
IIIA	30	3.1	28	3.0	
Hormone receptor status					.938
ER−/PR−	144	15.2	150	16.1	
ER−/PR+	17	1.8	18	1.9	
ER+/PR−	141	14.8	136	14.6	
ER+/PR+	647	68.2	625	67.3	
Surgery type					.0003
Conserving	520	54.3	432	46.0	
Mastectomy	438	45.7	507	54.0	
Treatment					.006
None	147	15.3	184	19.6	
Chemotherapy only	180	18.8	190	20.3	
Radiation only	277	28.9	214	22.8	
Both	354	36.9	350	37.3	
Tamoxifen use (yes)	739	77.2	737	78.6	.452
Positive lymph nodes (yes)	306	34.1	333	37.7	.118

Abbreviations: LACE, Life After Cancer Epidemiology; SD, standard deviation; BMI, body mass index; ER, estrogen receptor; PR, progesterone.
*Pearson χ^2 test, unless otherwise specified.
†Kruskal-Wallis test.

Table 2. Characteristics of Alcohol Consumption in the LACE Study

Characteristic	Total Alcohol Consumption (g/d) No.	%	Mean	SD	Median	Range
Total	1,897	100	5.86	13.47	0.50	0-149.32
Non-drinkers (≤ 0.5 g/d)	939	49.5	—	—	—	—
Drinkers (> 0.5 g/d)	958	50.5	11.58	17.13	5.96	0.50-149.32
Wine*	848	88.5	11.92	17.14	6.49	0.50-149.32
Beer*	342	35.7	15.08	21.85	7.81	0.77-149.32
Liquor*	403	42.1	15.81	20.26	8.49	0.52-149.32
Menopausal status†	830	100	—	—	—	—
Premenopausal	219	26.4	9.74	15.08	4.05	0.50-108.58
Postmenopausal	611	73.6	11.55	16.11	6.42	0.50-132.25
BMI 1 year prediagnosis†	949	100	—	—	—	—
Normal	516	54.4	11.40	15.92	6.50	0.50-138.40
Overweight/obese	433	45.6	11.83	18.62	4.03	0.50-149.32
ER status†	949	100	—	—	—	—
Positive	788	83.0	12.07	17.25	6.49	0.50-138.39
Negative	161	17.0	9.40	16.69	3.25	0.50-149.32

Abbreviations: LACE, Life After Cancer Epidemiology; SD, standard deviation; BMI, body mass index; ER, estrogen receptor.
*The totals are not mutually exclusive of other types of alcohol.
†Among drinkers.

A total of 293 breast cancer recurrences (of which 71.9% were distant metastases) and 273 deaths were ascertained through September 8, 2009. Among the 273 deaths, 154 (56.4%) were attributable to breast cancer, 24 (8.8%) to other cancers, 32 (11.7%) to cardiovascular causes, and 63 (23.1%) to other causes. Mean follow-up times from cohort entry until recurrence or death were 3.59 years (range, 0.27 to 9.11 years) and 4.83 years (range, 0.34 to 9.35 years), respectively. Overall, cohort members were followed 7.42 years (range, 0.11 to 9.62 years).

Drinking 6 or more grams of alcohol per day compared with no drinking was possibly associated with an increased risk of breast cancer recurrence (HR, 1.35; 95% CI, 1.00 to 1.83) and death from breast cancer (HR, 1.51; 95% CI, 1.00 to 2.29), adjusting for age at diagnosis, prediagnosis BMI, total folate intake, stage of disease, hormone receptor status, tamoxifen use, treatment, and positive lymph nodes (Table 3). A significant dose-response for greater alcohol intake and increasing risk of recurrence was also observed (P for trend = .04).

Similar to overall alcohol intake, drinking at least two servings per week of wine compared with none was also associated with an increased risk of recurrence (HR, 1.33; 95% CI, 0.97 to 1.81) and breast cancer death (HR, 1.37; 95% CI, 0.88 to 2.14; Table 3). No clear associations were observed for consumption of beer or liquor (not shown). There was a suggestion that consuming alcohol was associated with a decreased risk of death from non–breast cancer causes (HR, 0.73; 95% CI, 0.45 to 1.20 for consumption < 6 g/d; and HR, 0.77; 95% CI, 0.47 to 1.27 for consumption ≥ 6 g/d). No associations were observed for overall death and drinking 6 or more grams of alcohol per day. After excluding the 44 women who recurred or died within 1 year of study enrollment, the above results for drinking 6 or more grams of alcohol per day did not change and in fact became stronger for recurrence (HR, 1.44; 95% CI, 1.05 to 1.98; P for trend = .03) and breast cancer death (HR, 1.69; 95% CI, 1.08 to 2.64; P for trend = .03). Similarly, even with a smaller patient count after excluding 219 women who were enrolled from Utah, there was a modest increase in significance for recurrence (HR, 1.45; 95% CI, 1.05 to 2.00; P for trend = 02) and breast cancer death (HR, 1.59; 95% CI, 1.03 to 2.44; P for trend = .04).

Table 4 presents analyses of total alcohol consumption stratified by menopausal status, prediagnosis BMI, and ER status and risk of

Table 3. Alcohol Consumption and Breast Cancer Recurrence and Survival in the LACE Study

Parameter	No.	Recurrence of Breast Cancer			Overall Death			Death From Breast Cancer			Death From Other Causes		
		No. of Events	HR	95% CI	No. of Events	HR	95% CI	No. of Events	HR	95% CI	No. of Events	HR	95% CI
Age adjusted models*													
Total alcohol, grams/d													
None	939	137	Reference	—	141	Reference	—	73	Reference	—	68	Reference	—
< 6.0	480	78	1.09	0.83 to 1.45	64	0.95	0.70 to 1.27	39	1.07	0.72 to 1.58	25	0.81	0.51 to 1.28
≥ 6.0	478	78	1.11	0.84 to 1.47	68	0.98	0.74 to 1.31	42	1.13	0.78 to 1.66	26	0.84	0.54 to 1.33
P for trend			.53			.97			.54			.56	
Wine, servings/week													
None	1,030	156	Reference	—	154	Reference	—	82	Reference	—	72	Reference	—
≤ 1	473	72	0.98	0.74 to 1.30	66	0.97	0.72 to 1.29	39	1.05	0.71 to 1.53	27	0.89	0.57 to 1.39
≥ 2	390	64	1.06	0.80 to 1.43	51	0.91	0.66 to 1.25	32	1.02	0.68 to 1.54	19	0.82	0.49 to 1.36
P for trend			.64			.59			.95			.48	
Fully adjusted models†													
Total alcohol, grams/d													
None	939	126	Reference	—	135	Reference	—	69	Reference	—	66	Reference	—
< 6.0	480	68	1.05	0.78 to 1.42	58	0.96	0.70 to 1.32	36	1.13	0.74 to 1.70	22	0.73	0.45 to 1.20
≥ 6.0	478	74	1.35	1.00 to 1.83	64	1.19	0.87 to 1.62	39	1.51	1.00 to 2.29	25	0.77	0.47 to 1.27
P for trend			.04			.23			.05			.44	
Wine, servings/week													
None	1,030	142	Reference	—	148	Reference	—	78	Reference	—	70	Reference	—
≤ 1	473	64	1.01	0.75 to 1.36	59	1.00	0.73 to 1.36	35	1.12	0.75 to 1.68	24	0.79	0.49 to 1.28
≥ 2	390	61	1.33	0.97 to 1.81	48	1.08	0.77 to 1.52	30	1.37	0.88 to 2.14	18	0.73	0.42 to 1.27
P for trend			.06			.64			.18			.34	

Abbreviations: LACE, Life After Cancer Epidemiology; SD, standard deviation; BMI, body mass index.
*Adjusted for age at diagnosis only.
†All models adjusted for age at diagnosis, prediagnosis BMI, total folate intake, stage of disease, hormone receptor status, tamoxifen use, treatment, and positive lymph nodes, as designated in Table 1. Models considering death from other causes also adjusted for smoking status.

recurrence and breast cancer death. Among postmenopausal women, consuming 6 or more grams of alcohol per day was associated with an increased risk of recurrence (HR, 1.51; 95% CI, 1.05 to 2.19) and breast cancer death (HR, 1.72; 95% CI, 1.05 to 2.81) with a positive dose-response of greater alcohol intake and increasing risk (*P* for trend = .03 and .04, respectively). For premenopausal women, no associations were apparent. Similarly, among overweight and obese women, consuming 6 or more grams of alcohol per day was associated with an increased risk of recurrence (HR, 1.60; 95% CI, 1.08 to 2.38) and an elevated, yet nonsignificant, risk of breast cancer death (HR, 1.61; 95% CI, 0.94 to 2.76) with a positive dose-response (*P* for trend = .03 and .09, respectively). For normal weight women, no associations were found. Finally, while the number of women with ER-negative tumors was small, no difference in risk of recurrence and breast cancer death by ER status was observed for alcohol intake.

DISCUSSION

In this prospective cohort study of early-stage breast cancer survivors, we found that regular drinking equivalent to three to four standard drinks or more per week was associated with a 1.3-fold and 1.5-fold increased risk of breast cancer recurrence and breast cancer death, respectively. Furthermore, the associations appeared stronger among postmenopausal women and overweight/obese women separately, suggesting that the effects of alcohol might be specific to certain subgroups of women previously diagnosed with breast cancer. Alcohol intake was associated with a possible decreased risk of death from non–breast cancer causes, consistent with literature on alcohol's likely protective effects on cardiovascular-related outcomes.[28,29] Overall, no association was observed with all-cause death.

The current research on alcohol's impact on breast cancer recurrence is sparse. One small prospective study of 149 breast cancer patients followed for at least 5 years found no association between alcohol intake (two drinks/wk) and risk of recurrence.[19] In another prospective study of 472 women diagnosed with early-stage breast cancer and followed for 8 to 10 years, daily consumption of beer was associated with a 1.4-fold increased risk of recurrence and a 1.6-fold increased risk of breast cancer death.[6] The increased risk was stronger among premenopausal women (1.7-fold), in contrast to our finding of an elevated risk among postmenopausal women. Previous large cohort studies on risk of primary breast cancer have also reported an increased risk among postmenopausal women.[30,31] Most recently, in a cohort of 3,088 early-stage breast cancer survivors followed for median 7.3 years, neither light (< 1 drink/d) nor moderate (≥ 1 drink/d or more) alcohol intake was associated with recurrence, yet moderate intake was protective against overall mortality, particularly among nonobese women.[20] Interestingly, while the outcome of interest was not recurrence, in a nested case-control study, consuming at least seven alcoholic beverages per week was associated with an increased risk of second contralateral breast cancer.[32] In our study, when we excluded the small number (n = 32; 10.9%) of contralateral breast cancers in the recurrence category, the results did not change substantially.

Table 4. Alcohol Consumption and Risk of Breast Cancer Recurrence and Death by Selected Factors in the LACE Study

Parameter	No.	No. of Events	Total Alcohol Consumption: None HR	None 95% CI	< 6.0 g/d HR	< 6.0 g/d 95% CI	≥ 6.0 g/d HR	≥ 6.0 g/d 95% CI	*P*: For Trend	*P*: For Interaction
Recurrence of breast cancer										
Menopausal status*										
Premenopausal	404	51	Reference		1.01	0.52 to 1.96	1.25	0.61 to 2.54	.52	.67
Postmenopausal	1,230	175	Reference		1.12	0.76 to 1.64	1.51	1.05 to 2.19	.03	
BMI 1-year prediagnosis†										
Normal	864	110	Reference		0.81	0.50 to 1.31	1.09	0.70 to 1.68	.47	.29
Overweight/obese	1,012	158	Reference		1.27	0.87 to 1.87	1.60	1.08 to 2.38	.03	
ER status‡										
Positive	1,549	216	Reference		1.00	0.71 to 1.40	1.23	0.89 to 1.72	.19	.48
Negative	329	52	Reference		1.29	0.66 to 2.54	2.00	0.96 to 4.14	.07	
Death from breast cancer										
Menopausal status*										
Premenopausal	404	22	Reference		1.27	0.47 to 3.38	0.77	0.20 to 2.90	.61	.26
Postmenopausal	1,230	101	Reference		1.25	0.76 to 2.07	1.72	1.05 to 2.81	.04	
BMI 1-year prediagnosis†										
Normal	864	56	Reference		0.99	0.51 to 1.93	1.21	0.65 to 2.25	.50	.77
Overweight/obese	1,012	88	Reference		1.21	0.71 to 2.04	1.61	0.94 to 2.76	.09	
ER status‡										
Positive	1,549	116	Reference		1.04	0.65 to 1.68	1.48	0.94 to 2.32	.08	.82
Negative	329	28	Reference		1.38	0.57 to 3.33	1.62	0.57 to 4.58	.43	

Abbreviations: LACE, Life After Cancer Epidemiology; SD, standard deviation; BMI, body mass index; ER, estrogen receptor.

*Adjusted for age at diagnosis, prediagnosis BMI, total folate intake, stage of disease, hormone receptor status, tamoxifen use, treatment, and positive lymph nodes, as designated in Table 1.

†Adjusted for age at diagnosis, total folate intake, stage of disease, hormone receptor status, tamoxifen use, treatment, and positive lymph nodes, as designated in Table 1.

‡Adjusted for age at diagnosis, pre-diagnosis BMI, total folate intake, stage of disease, tamoxifen use, treatment, and positive lymph nodes, as designated in Table 1.

Our results point to a potential positive association between alcohol intake and risk of recurrence and breast cancer death, which appeared to be limited to overweight and obese, but not normal weight, women. Consistent with previous literature,[33-36] overweight and obese women in our cohort were less likely to consume alcohol (4.03 median g/d) compared with normal weight women (6.50 g/d), yet alcohol was still associated with a detrimental effect among heavier women. In a prior analysis, we found that higher BMI before diagnosis was associated with a borderline increased risk of recurrence,[37] and in our analyses, we adjusted for possible confounding by prediagnosis BMI.

Our observation of no relation of alcohol consumption with overall mortality among breast cancer survivors is consistent with several past studies. In the Nurses' Health Study (NHS), postdiagnosis moderate alcohol intake was not associated with overall mortality among 1,982 women diagnosed with invasive breast cancer and observed for 13.1 years.[16] In a smaller prospective cohort study of 1,453 patients with breast cancer observed for 12.6 years in Italy, no association was observed between overall alcohol drinking[12] and wine drinking[14] within 1 year after diagnosis and risk of overall death and breast cancer death. Participants in this Italian study reported drinking more alcohol (≥ 7 drinks/wk) compared with United States study populations.[11,14]

Alcohol can possibly influence the risk of primary breast cancer by increasing estrogen metabolism and endogenous estrogen levels in pre- and postmenopausal women.[38-41] In addition to the effects of alcohol, obesity can elevate circulating sex hormones[42,43] and insulin levels,[44] thereby promoting estrogen production and breast cell proliferation,[45,46] particularly among postmenopausal women.[47] The combination of these mechanisms could perhaps explain why we observed an increased risk of recurrence among postmenopausal women, as well as those who were overweight and obese. Furthermore, one could speculate that use of antiestrogen therapy, such as aromatase inhibitors, could possibly counteract the effects of alcohol on the endogenous estrogen supply. In other studies, alcohol was found to increase the expression and proliferation of ERs in cultured human breast cancer cells,[41,48] and thus could possibly be associated with the development of positive, but not negative, ER breast cancer cells.[49,50] When we conducted a stratified analysis by ER status, there was no difference in risk between ER subgroups, although we were constrained by limited numbers in the ER- subgroup.

The LACE study is one of the larger prospective studies of breast cancer survivors to examine the role of alcohol intake on risk of breast cancer outcomes. Our analyses relied on self-report of alcohol use from the Fred Hutchinson Cancer Research Center Food Questionnaire, which has been validated in the Women's Health Initiative Study.[51,52] The levels of postdiagnosis alcohol use in our cohort were comparable to those in other US study populations[8,16] yet lower than levels in Italian[12,14] and British[9] study populations, thus limiting our power to examine the impact of higher frequency of intake (eg, > 1 drink/d[24]) on prognosis. Although misclassification of cause of

death from death certificates can be an issue in studies of cause-specific mortality, our distribution of deaths is consistent with other large studies like the NHS.[16,53] As the LACE cohort consists of early-stage breast cancer survivors who were enrolled on average 2 years after diagnosis, we acknowledge the inability to examine associations with recurrence and death that occurred in the immediate survivorship period (within 2 years). In addition, our results are only generalizable to women diagnosed with early-stage breast cancer who have survived on average 2 years.

In summary, we observed that regular drinking of at least three to four alcoholic drinks per week was associated with an increased risk of recurrence and death due to breast cancer among women previously diagnosed with early-stage breast cancer, independent of prognostic factors, and that the increased risk appeared to be confined to postmenopausal women and overweight/obese women. Furthermore, any alcohol consumption was associated with a possible reduction in non–breast cancer mortality due to the probable cardioprotective effects of alcohol. Our findings are consistent with alcohol's role in increasing risk of primary breast cancer, yet considering the few studies to date that have addressed alcohol and its influence on breast cancer prognosis, our results warrant confirmation in other large, prospective studies of breast cancer survivors with long-term follow-up.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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