Research Article

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Alcohol Use and Breast Cancer Survival among Participants in the Women's Health Initiative

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Abstract

Background: Alcohol increases the risk of breast cancer even at moderate levels of intake. However, the relationship between alcohol consumption and mortality among breast cancer patients is less clear.

Methods: This study included women from the Women's Health Initiative observational study and randomized trial diagnosed with breast cancer ($n = 7,835$). Cox proportional hazards regression was used to estimate adjusted HRs and 95% confidence intervals (CI) for overall and breast cancer–specific (BCS) mortality associated with drinking alcohol before or after a breast cancer diagnosis. We also assessed whether changes in drinking habits after diagnosis are related to mortality.

Results: Women who were consuming alcohol prior to their breast cancer diagnosis had a nonstatistically significant 24% (95% CI, 0.56–1.04) reduced risk of BCS mortality and a 26% (95% CI, 0.61–0.89) reduced risk of all-cause mortality. Some variation was observed by estrogen receptor (ER) status as alcohol consumption was associated with a 49% (95% CI, 0.31–0.83) reduced risk of BCS mortality among ER^- patients with no change in risk observed among ER^+ patients (HR = 0.97; 95% CI, 0.31–1.54), though the difference between these risks was not statistically significant (P for interaction = 0.39). Postdiagnosis alcohol consumption, and change in consumption patterns after diagnosis, did not appear to be associated with all-cause or BCS mortality.

Conclusion: In this large study, consumption of alcohol before or after breast cancer diagnosis did not increase risks of overall or cause-specific mortality.

Impact: Coupled with existing evidence, alcohol consumption is unlikely to have a substantial impact on mortality among breast cancer patients. *Cancer Epidemiol Biomarkers Prev; 25(8); 1268–73. ©2016 AACR.*

Introduction

Alcohol intake, even at low levels, is an established risk factor for breast cancer (1, 2), possibly due to its effects on pathways related to estrogen metabolism and/or DNA damage and repair (3–6). It is not clear, however, whether alcohol intake influences breast cancer mortality, and results from prior studies are mixed. Existing data have been summarized in a recent report that included both a meta-analysis and three pooled analyses (7). The meta-analysis of 11 published studies ($n = 29,239$ cases) reported 20% better overall survival associated with prediagnosis alcohol consumption [95% confidence interval (CI), 0.73–0.88] and no association with postdiagnosis alcohol intake (HR, 0.95; 95% CI, 0.85–1.05); however, it did not examine breast cancer–specific mortality or if risk varied according to estrogen receptor (ER) status. The pooled analyses ($n =$ between 8,000 and 11,000 cases each) were stratified by ER status, and among women with ER^+ disease, alcohol intake (before or after diagnosis) was not associated with breast cancer–specific survival, but there was some evidence for an association between prediagnosis intake and improved overall survival. For ER^- disease, there was no association with prediagnosis intake, but some evidence of improved survival (overall and breast cancer–specific) associated with postdiagnosis intake (7). However, several potential limitations related to variations in the compositions of the study populations included, and in some cases the length of follow-up, may have influenced these findings (see Discussion section). Only one prior study investigated the possible relationship between a change in alcohol consumption before and after breast cancer diagnosis, and observed that an increase of one or more drinks per week was associated with a 24% lower risk of death due to any cause (95% CI, 0.60–0.97) compared with women who never drank; decreasing alcohol consumption did not affect risk (8).

Given that alcohol consumption is a common exposure and that the population of breast cancer survivors continues to grow as survival rates have continued to improve, further characterization of alcohol's potential associations with breast cancer mortality is needed. Understanding this relationship may have implications for improving survival in women diagnosed with breast cancer, as alcohol intake is a potentially modifiable factor. In this study, we investigated whether various aspects of alcohol consumption are associated with mortality (overall and breast cancer–specific) in a prospective cohort of breast cancer patients who participated in the Women's Health Initiative (WHI).

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Materials and Methods

Details of the design and execution of the WHI have been described previously (9–11). Briefly, 161,808 postmenopausal women ages 50 to 79 years were enrolled from 40 clinical centers around the United States, including 93,676 women in the observational study (OS) and 68,132 women in the clinical trial (CT). CT enrollees were included in one, two, or all three of the following randomized trials: hormone therapy, dietary modification, or supplementation with both calcium and vitamin D. Women were recruited by a population-based mail campaign plus media awareness programs. They were eligible if, at baseline screening, they were between the ages of 50 and 79 years, postmenopausal, and likely to remain in the same geographic region for at least 3 years. They were excluded for conditions likely to present challenges in terms of study retention, adherence, or survival (for example, cancer, alcoholism, dementia, or transportation challenges).

The WHI collected data on a range of exposures, including alcohol use and other dietary factors, hormone therapy and other medications, supplement use, and other demographic and reproductive factors. Data used in this study were collected similarly for OS and CT participants. At an initial clinic visit, all participants completed a self-administered questionnaire, including questions on alcohol use, and underwent a physical exam. During follow-up, participants completed health questionnaires every 6 months and also attended annual clinic visits, which included standardized interviews to capture data on health conditions and symptoms, annual mammograms, and clinical breast exams. Follow-up also included self-reported alcohol use at years 1, 3, 6, and 9 for CT participants, and year 3 for OS participants. Prediagnosis alcohol intake was defined based on self-report of the number of servings of alcohol consumed per week using the closest available data prior to diagnosis, and was available for all women in these analyses. To define postdiagnosis alcohol intake, the closest data available following diagnosis were used (such data were available for a subset of the sample). Change in alcohol intake was calculated based on pre- and postdiagnosis intake, and was defined as no change (same number of drinks before and after diagnosis), increase (higher alcohol intake after diagnosis, by at least 1 drink/week), or decrease (lower intake after diagnosis, by at least 1 drink/week). The average time elapsed between assessment of pre- and postdiagnosis intake was 1,270 days (SD, 528 days; range, 365–3,287 days).

The average follow-up time of study participants was 7.9 years. Women were censored at their date of last follow-up. The present analyses ($n = 7,835$) include all subjects who were diagnosed with breast cancer after enrollment (and after randomization, for CT subjects; $n = 8,819$), except that women with incomplete alcohol and/or covariate data were excluded ($n = 1,034$).

Cox proportional hazards regression was used to estimate HR and 95% CIs for mortality (all-cause and breast cancer–specific) associated with alcohol intake, among women diagnosed with breast cancer. Analyses were adjusted for confounders which were selected *a priori*, including age, income, CT enrollment, family history of breast cancer, smoking status, menopausal hormone therapy at baseline, and body mass index (BMI). Analyses were conducted for prediagnosis intake, postdiagnosis intake, and changes in intake after diagnosis. We explored whether associations differed by ER status (positive or negative) of the disease at diagnosis.

We assessed (and ruled out) potential effect modification by CT/OS membership (P for interaction >0.05, data not shown). We also conducted a sensitivity analysis where models were refit with BMI as a time-varying confounder, in consideration of estrogen-related mechanisms between alcohol and obesity. However, results did not change appreciably and so the time-varying version of this variable was not included in the final model. We conducted secondary analyses limited to just those women for whom data on all 3 exposures of interest (before diagnosis, after diagnosis, and change in alcohol consumption) were available ($n = 20,633$ person-years, 352 deaths). The results, including strength and direction of associations, were all similar, though were no longer statistically significant for the association between prediagnosis alcohol intake and all-cause mortality (likely due to the smaller sample size; not shown). We also conducted analyses using an alternate cutoff of $\geq$9 drinks/week, instead of $\geq$7, for the highest level of alcohol intake, in order to more directly compare our results with those reported in with the meta-analysis by Ali and colleagues (7); results and conclusions were the same for all comparisons regardless of cutoff level (data not shown). We additionally conducted an analysis excluding women with stage IV cancers ($n = 81$, or 1% of study population); results were essentially identical and did not affect our conclusions (data not shown). The statistical programs SAS 9.3 and R 3.0.1 were used for all analyses.

Results

Similarities in distributions of age, first-degree family history of breast cancer, and parity were observed across prediagnosis alcohol use categories (Table 1). Women who were alcohol consumers before diagnosis had somewhat higher household incomes and were somewhat more likely to be past or current smokers, current users of estrogen+progestin menopausal hormones, non-Hispanic whites, and college graduates compared with never and past alcohol consumers (Table 1). Women from the OS study were overall similar to those in the CT study (not shown). OS participants were somewhat more likely to be $\geq$60 years old (70% vs. 66%), to be white (89% vs. 86%), to have an income $\geq$\$75,000 (22% vs. 18%), to have ever smoked (52% vs. 50%), to have a lower BMI (median 26 vs. 28 kg/m^2) to be nulliparous (15% vs. 12%), and to have ever used estrogen only (36% vs. 33%) or estrogen+progestin (36% vs. 29%) compared with CT participants. OS participants were also more likely to have data on postdiagnosis alcohol intake (26% vs. 22%), and they had slightly shorter average times to diagnosis (5.4 vs. 5.9 years), times between prediagnosis alcohol assessment and diagnosis (3.4 vs. 4.3 years), and times between diagnosis and postdiagnosis alcohol assessment (1.4 vs. 2.0 years). Among cases who died, OS participants had a slightly longer time from postdiagnosis alcohol assessment to death (average 9.4 vs. 8.5 years). Stage at diagnosis and disease histology were very similar for OS and CT participants (not shown).

Adjusting for age, income, study (CT vs. OS), family history of breast cancer, smoking history, BMI, and history of menopausal hormone therapy, there were similar 24% (95% CI, 0.56–1.04) and 26% (95% CI, 0.61–0.89) reduced risks of breast cancer–specific and all-cause mortality, respectively, among women who consumed alcohol prior to diagnosis, though the former risk estimate was within the limits of chance (Table 2). However, neither alcohol consumption after diagnosis nor changes in

Table 1. Selected characteristics according to categories of prediagnosis alcohol intake

	Prediagnosis alcohol intake				
Characteristic	**Never** ***n*** **(%)**	**Past** ***n*** **(%)**	**<1 drink/week** ***n*** **(%)**	**1–6/week** ***n*** **(%)**	**≥7/week** ***n*** **(%)**
Age (years)					
50 to 54	70 (10%)	131 (11%)	360 (13%)	235 (12%)	117 (11%)
55 to 59	137 (19%)	207 (17%)	587 (21%)	431 (21%)	193 (18%)
60 to 69	347 (48%)	595 (48%)	1,271 (46%)	954 (47%)	508 (48%)
70 to 79	174 (24%)	299 (24%)	570 (20%)	399 (20%)	250 (23%)
WHI study					
CT	330 (45%)	556 (45%)	1266 (45%)	820 (41%)	383 (36%)
OS	398 (55%)	676 (55%)	1,522 (55%)	1,199 (59%)	685 (64%)
Income					
<$20,000	147 (21%)	247 (21%)	335 (12%)	165 (8%)	63 (6%)
$20,000–$49,999	364 (51%)	593 (50%)	1,280 (47%)	814 (41%)	420 (40%)
$50,000–$99,999	174 (25%)	282 (24%)	852 (31%)	692 (35%)	381 (36%)
≥$100,000	24 (3%)	74 (6%)	257 (9%)	301 (15%)	180 (17%)
Race/ethnicity					
Non-Hispanic white	538 (75%)	1,008 (83%)	2,399 (87%)	1,887 (94%)	1,025 (96%)
Black	84 (12%)	151 (12%)	205 (7%)	77 (4%)	22 (2%)
Hispanic white	28 (4%)	30 (2%)	81 (3%)	30 (1%)	7 (1%)
Asian	67 (9%)	28 (2%)	71 (3%)	10 (0%)	8 (1%)
American Indian	4 (1%)	2 (0%)	10 (0%)	4 (0%)	1 (0%)
Missing	7	13	22	11	5
Education					
Less than high school	15 (2%)	11 (1%)	11 (0%)	8 (0%)	3 (0%)
High school graduate	191 (26%)	274 (22%)	485 (17%)	281 (14%)	126 (12%)
Some college	286 (40%)	517 (42%)	1,064 (38%)	657 (33%)	342 (32%)
College graduate	231 (32%)	426 (35%)	1,215 (44%)	1,059 (53%)	587 (55%)
Missing	5	4	13	14	10
First-degree family history of breast cancer					
Yes	187 (26%)	298 (24%)	681 (24%)	505 (25%)	259 (24%)
No	541 (74%)	934 (76%)	2,107 (76%)	1,514 (75%)	809 (76%)
Smoking history					
Never	630 (87%)	576 (47%)	1,463 (52%)	871 (43%)	301 (28%)
Former	82 (11%)	582 (47%)	1,148 (41%)	1,021 (51%)	667 (62%)
Current	16 (2%)	74 (6%)	177 (6%)	127 (6%)	100 (9%)
BMI (kg/m^2)					
<18.5	4 (1%)	7 (1%)	13 (0%)	12 (1%)	13 (1%)
18.5–24.9	211 (29%)	318 (26%)	770 (28%)	802 (40%)	504 (47%)
25.0–29.9	246 (34%)	383 (31%)	977 (35%)	739 (37%)	381 (36%)
≥30.0	267 (37%)	524 (43%)	1,028 (37%)	466 (23%)	170 (16%)
Menopausal hormone therapy, estrogen only					
Never used	456 (63%)	786 (64%)	1,870 (67%)	1,326 (66%)	695 (65%)
Past user	93 (13%)	163 (13%)	329 (12%)	246 (12%)	136 (13%)
Current user	179 (25%)	283 (23%)	589 (21%)	447 (22%)	237 (22%)
Menopausal hormone therapy, estrogen+progestin					
Never used	551 (76%)	918 (75%)	1,849 (66%)	1,236 (61%)	664 (62%)
Past user	59 (8%)	100 (8%)	229 (8%)	209 (10%)	110 (10%)
Current user	118 (16%)	214 (17%)	710 (25%)	574 (28%)	294 (28%)
Parity					
Nulliparous	86 (12%)	159 (13%)	356 (13%)	283 (14%)	182 (17%)
Parous	636 (88%)	1,068 (87%)	2,416 (87%)	1,724 (86%)	882 (83%)
Missing	6	5	16	12	4
Age at first birth among parous women (years)					
<20	108 (20%)	185 (19%)	286 (13%)	184 (11%)	76 (9%)
20–29	395 (76%)	676 (70%)	1,639 (75%)	1,235 (77%)	641 (78%)
≥30	46 (8%)	100 (10%)	261 (12%)	190 (12%)	109 (13%)
Missing	5	5	10	6	4
ER/PR status					
ER^+/PR^+	398 (67%)	661 (68%)	1,549 (71%)	1,092 (67%)	615 (72%)
ER^+/PR^-	99 (17%)	137 (14%)	274 (13%)	272 (17%)	125 (15%)
ER^-/PR^+	9 (2%)	17 (2%)	30 (1%)	21 (1%)	16 (2%)
ER^-/PR^-	85 (14%)	154 (16%)	335 (15%)	234 (14%)	104 (12%)
Missing	137	263	600	400	208

alcohol consumption before versus after diagnosis were related to either breast cancer–specific or all-cause mortality. In analyses stratified by breast cancer subtype, reduced risks of both breast cancer–specific and all-cause mortality were observed for ER^- (HR = 0.51; 95% CI, 0.31–0.83 and HR = 0.49; 95% CI, 0.34–0.72, respectively), but not for ER^+ disease (HR = 0.97; 95% CI,

Table 2. Alcohol consumption and risk of breast cancer–specific and overall mortality

Alcohol consumption	Person-years at risk	Breast cancer–specific mortality		Overall mortality	
		n	HR[a] (95% CI)	*n*	HR[a] (95% CI)
Prediagnosis					
Never	5,394	51	1.00 (ref.)	135	1.00 (ref.)
Past	9,251	97	1.01 (0.71–1.43)	255	0.96 (0.77–1.19)
Current drinkers[b]	47,388	329	0.76 (0.56–1.04)	883	0.74 (0.61–0.89)
<1 drink/week	21,905	166	0.80 (0.57–1.10)	404	0.72 (0.59–0.88)
1–6 drinks/week	16,766	111	0.74 (0.52–1.06)	300	0.74 (0.60–0.92)
≥7 drinks/week	8,716	52	0.67 (0.44–1.01)	179	0.80 (0.63–1.02)
Postdiagnosis					
Never	1,625	10	1.00 (ref.)	31	1.00 (ref.)
Past	2,864	22	1.19 (0.56–2.55)	67	1.04 (0.67–1.61)
Current drinkers[b]	16,144	119	1.21 (0.62–2.34)	254	0.76 (0.51–1.12)
<1 drink/week	8,323	76	1.42 (0.72–2.80)	141	0.81 (0.54–1.21)
1–6 drinks/week	5,274	28	0.88 (0.41–1.87)	82	0.77 (0.49–1.19)
≥7 drinks/week	2,547	15	0.93 (0.40–2.14)	31	0.54 (0.32–0.91)
Change in alcohol consumption					
No change	14,497	105	1.00 (ref.)	247	1.00 (ref.)
Decrease	3,909	34	1.20 (0.81–1.78)	76	1.14 (0.87–1.49)
Increase	2,227	12	0.78 (0.43–1.43)	29	0.76 (0.52–1.13)

[a]All HRs are adjusted for age, income, race, study (CT vs. OS), family history of breast cancer, smoking status, menopausal hormone therapy use, and BMI.
[b]Note that the two "Current drinkers" rows were estimated in a separate model from the three subgroups of <1, 1–6, and ≥7 drinks/week.

0.31–1.54 and HR = 0.81; 95% CI, 0.63–1.04, respectively; Table 3). However, neither of the interaction terms assessing heterogeneity by ER status were statistically significant ($P = 0.30$ and 0.09 for breast cancer–specific and all-cause mortality, respectively).

Discussion

We investigated three aspects of alcohol use (prediagnosis and postdiagnosis alcohol intake, and change in drinking habits after diagnosis) in relation to mortality after breast cancer diagnosis. Overall, there was some suggestion that women who were consuming alcohol prior to their breast cancer diagnosis had a reduced risk of mortality that appeared to be primarily limited to patients with ER^- disease. However, there were no associations between alcohol intake after diagnosis or changes in alcohol consumption patterns and mortality. These findings are relatively consistent with most previous studies, which have generally reported either null or slightly protective associations between alcohol intake and mortality among women with breast cancer. However, past studies have investigated varying aspects of alcohol intake (before vs. after diagnosis; categories of alcohol quantity consumed), on different outcomes (breast cancer–specific vs. overall), and in different populations (varying ages and levels of alcohol consumption), which complicates comparison of findings. A recent meta-analysis of 11 studies investigating only "moderate" intake (defined as ≥14 units, or approximately 9 drinks, per week) reported 20% better overall survival associated with prediagnosis intake (95% CI, 0.7–3–0.88; based on 6 studies), and no association with postdiagnosis intake (HR, 0.95; 95% CI, 0.85–1.05; based on 5 studies). These analyses were not stratified by ER status, and authors did not perform a meta-analysis for breast cancer–specific survival, citing heterogeneity across studies.

This publication also included pooled analyses from three separate cohorts, stratifying by ER status, and assessing both

Table 3. Prediagnosis alcohol consumption and risk of breast cancer–specific and overall mortality by breast cancer subtype

Prediagnosis Alcohol consumption	ER^+ breast cancer ($n = 5,222$)			ER^- breast cancer ($n = 1,005$)		
	n	Person-years at risk	HR[a] (95% CI)	*n*	Person-years at risk	HR[a] (95% CI)
Breast cancer–specific mortality						
Never	21	3,758	1.00 (ref.)	21	659	1.00 (ref.)
Past	49	5,991	1.36 (0.81–2.30)	31	1,290	0.69 (0.39–1.22)
Current drinkers[b]	210	31,626	0.97 (0.31–1.54)	38	6,080	0.51 (0.31–0.83)
<1 drink/week	79	14,702	0.97 (0.60–1.59)	52	2,746	0.56 (0.33–0.95)
1–6 drinks/week	62	11,072	1.00 (0.60–1.67)	31	2,183	0.44 (0.25–0.78)
≥7 drinks/week	28	5,853	0.86 (0.48–1.54)	15	1,152	0.49 (0.25–0.98)
P value for interaction by ER status: 0.30[c]						
All-cause mortality						
Never	77	3,758	1.00 (ref.)	37	659	1.00 (ref.)
Past	161	5,991	1.15 (0.88–1.53)	46	1,290	0.57 (0.36–0.89)
Current drinkers[b]	594	31,626	0.81 (0.63–1.04)	92	6,080	0.49 (0.34–0.72)
<1 drink/week	230	14,702	0.77 (0.59–1.00)	78	2,746	0.51 (0.34–0.76)
1–6 drinks/week	188	11,072	0.94 (0.63–1.11)	54	2,183	0.47 (0.31–0.74)
≥7 drinks/week	110	5,853	0.89 (0.65–1.22)	29	1,152	0.54 (0.32–0.89)
P value for interaction by ER status: 0.09[c]						

[a]Adjusted for age, income, race, study (CT vs. OS), family history of breast cancer, smoking status, menopausal hormone therapy use, and BMI.
[b]Note that the two "Current drinkers" rows were estimated in a separate model from the three subgroups of <1, 1–6, and ≥7 drinks/week.
[c]Evaluated via an interaction term between alcohol use and ER status.

overall and breast cancer–specific survival. Of the two analyses of prediagnosis alcohol intake, one found no association with either all-cause or breast cancer–specific survival, overall or when stratified by ER status, though the follow-up period was as brief as 2 years for some cases (7). In the other, prediagnosis intake was associated with 36% to 44% better overall survival, in women with ER^+ disease only (95% CIs all within 0.47–0.88; ref. 7), which differs from our findings. However, the original goal of this larger international pooled cohort was to investigate genetic causes of breast cancer, and several of its component studies enrolled only younger cases, making it less comparable with our study (overall average age, 54 years, vs. 63 years in our study). It also had higher proportions of ER^- cases (20% vs. 13%) and of non-drinkers (34% vs. 9%). There was also greater potential for uncontrolled confounding based on disproportionate representation of different countries in the referent (nondrinker) group compared with the exposure groups (e.g., 66% of study participants from Japan were non-drinkers, vs. <1% of those from Finland). This could lead to confounding by country-level differences (e.g., in breast cancer treatment and prognosis) and/or genetic differences (in disease subtype and course; in alcohol metabolism). Such differences could also potentially explain discrepancies in findings between our study and those analyses.

The third pooled analysis investigated postdiagnosis alcohol intake and observed 46% and 49% lower all-cause mortality in ER^- cases who consumed moderate (>7–≤14 units/week) and high levels of alcohol (>14 units/week) after diagnosis (95% CIs, 0.33–0.78 and 0.30–0.97, respectively), and 42% better breast cancer–specific survival in ER^- moderate drinkers (95% CI, 0.37–0.92) compared with nondrinkers (7). However, that cohort was also from a study designed to assess genetic risk factors for breast cancer, and the study population had a greater proportion of younger cases (45% were ≤50 years at diagnosis), as well as cases with longer survival (median follow-up time: 7 years; 5-year survival: 87%), limiting its comparability.

Another more recent study, not included in the meta-analysis, reported a 15% to 20% lower all-cause mortality associated with moderate prediagnosis intake (HR, 0.80; 95% CI, 0.74–0.86 for 3 to 6 drinks per week; HR, 0.85; 95% CI, 0.77–0.93 for 7 to 9 drinks per week), but no association with higher levels of intake (8). That study also reported 15% lower breast cancer–specific mortality in women who drank 3 to 6 drinks per week before diagnosis (95% CI, 0.75–0.95), and weaker, borderline associations at higher and lower levels of intake (i.e., only 5% to 10% better survival, with 95% CIs just barely including the null) compared with nondrinkers; ER^-status-specific estimates were not provided. That study also assessed postdiagnosis alcohol consumption, and unlike ours, observed 23% to 37% lower all-cause mortality for consumption of ≥3 drinks/week compared with nondrinkers (95% CIs all within 0.45–0.98), though study subjects had much longer survival time (postdiagnosis alcohol intake was assessed a median of 6 years after diagnosis, vs. an average of 1.7 years in our study; ref. 8). Perhaps any protective effect of moderate postdiagnosis alcohol on overall survival is limited to women with less advanced or less aggressive disease. Alcohol has been shown to have a protective effect on cardiovascular disease (CVD) mortality (12), but presumably this effect is not immediate. Thus, we might expect that an effect of postdiagnosis alcohol intake on all-cause mortality would only be apparent among women with longer survival.

To our knowledge, only one other study has reported on the association with a change in drinking habits after diagnosis: A 24% lower overall survival was observed in women who reported drinking ≥1 additional drink per week after diagnosis than before diagnosis (95% CI, 0.60–0.97), compared with women who never drank. This is somewhat similar in magnitude to our observation of a 38% lower mortality, though our finding was not statistically significant (95% CI, 0.33–1.16; ref. 8). No association was reported for a decrease in alcohol, or for *any* change in alcohol and breast cancer–specific mortality. It is unclear why an increase in drinking might be associated with longer survival, though moderate intake has a protective effect on CVD mortality (12, 13), and the same study noted that an increase, but not a decrease, in alcohol intake was associated with a lower risk of CVD mortality, compared with never-drinkers (8). Alternatively, there could be confounding by disease severity and/or overall health and well-being.

It is also not clear how alcohol might influence mortality, among women diagnosed with ER^- but not ER^+ breast cancer. The protective effect of alcohol on CVD mortality would predict better survival among ER^+ and ER^- cases alike. However, among women diagnosed with ER^+ disease, the adverse effects of alcohol on estrogen levels (and thus, perhaps, on disease progression and recurrence) may offset this benefit. Alcohol is thought to act on estrogen pathways, increasing serum levels of estrogen, disrupting estrogen metabolism (4), and enhancing expression of ERs in breast cells (14). These factors could conceivably affect breast-cancer progression and/or recurrence of ER^+, but not ER^-, disease.

This study has several strengths. The WHI study sample is a broad population from 40 clinics across the United States, making it more generalizable than many previous studies of this question. This study is one of only two which were able to measure alcohol intake both before and after diagnosis in same population, allowing for assessment of the potential association of a change in drinking habits and breast cancer survival. Other strengths include prospective study design, use of incident cases, postdiagnosis follow-up, and high levels of retention. Highly detailed data were available on alcohol use, allowing for categorization by level of intake, and data on prediagnosis alcohol use were collected before diagnosis, unlike many studies, leading to greater accuracy. We were able to consider time-varying variables in our analyses due to the availability of repeated follow-up measures in BMI.

A key limitation of this study is that data on postdiagnosis alcohol use were only available for 25% of the population. However, given the size of the study, these analyses still included 1,928 women. This subset is less likely to include women with the shortest survival; a mean time of 1.7 years elapsed between breast cancer diagnosis and postdiagnosis alcohol ascertainment, and so our findings on postdiagnosis alcohol consumption may be less generalizable to women with particularly advanced or aggressive disease. However, as noted, this was much more inclusive than some other recent studies, and a study which addressed this question by excluding early events in some analyses (deaths within 2 years of diagnosis) observed no difference in results (15). The potential for confounding by unmeasured factors is another concern; for example, overall fitness could influence both pre- and postdiagnosis alcohol intake, as well as survival, but no fitness data were available. Disease severity could also influence both postdiagnosis alcohol intake and survival. Treatment could

affect alcohol consumption, and the association of alcohol with survival could be dependent on its timing in relation to treatment.

Our findings, together with those of earlier studies, suggest that alcohol intake among women diagnosed with breast cancer has little to no impact on either breast cancer–specific or all-cause mortality. From a public health perspective, the evidence does not suggest that modification of alcohol intake after a breast cancer diagnosis is warranted, nor does it warrant concerns about prediagnosis intake in relation to breast cancer survival. If future studies provide stronger evidence for the observed suggestion of a small protective association of moderate alcohol intake with mortality in women with ER^- breast cancer, then future etiologic studies into the biologic role of alcohol on mortality, survival, recurrence, and disease progression could potentially shed more light on the reason for this. However, research into exposures other than alcohol that are hypothesized to affect breast cancer survival may be of greater relevance for understanding and ultimately improving breast cancer survival.

Disclosure of Potential Conflicts of Interest

R. Chlebowski has received honoraria from the speakers bureau of Pfizer and Novartis. He is also a consultant/advisory board member for Genentech, Genomic Health, Novartis, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Development of methodology: C.I. Li
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Chlebowski
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.J. Lowry, K. Kapphahn, R. Chlebowski, C.I. Li
Writing, review, and/or revision of the manuscript: S.J. Lowry, K. Kapphahn, R. Chlebowski, C.I. Li
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Kapphahn, C.I. Li
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