Published OnlineFirst February 16, 2010; DOI: 10.1158/1055-9965.EPI-09-0927

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Low to Moderate Alcohol Intake Is Not Associated with Increased Mortality after Breast Cancer

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Abstract

Background: Both alcohol consumption and obesity have been linked with breast cancer morbidity and mortality. An inverse association between alcohol intake and obesity suggests possible confounding between these variables (and perhaps other factors) with breast cancer outcomes.

Methods: Alcohol intake (beer, wine, spirits, and total) was examined in 3,088 women previously diagnosed and treated for breast cancer within an intervention trial that targeted vegetables, fiber, and fat but not alcohol or weight loss. Factors associated with baseline alcohol intake were included in Cox proportional hazards models for recurrence and mortality.

Results: Alcohol intake was significantly associated with higher education and physical activity levels. Neither light alcohol intake nor obesity was significantly associated with breast cancer recurrence, but moderate alcohol intake >300 g/mo was protective against all-cause mortality (hazard ratio, 0.69; 95% confidence intervals, 0.49-0.97) in a proportional hazards model adjusted for obesity. Obese women were 61% more likely to be nondrinkers than drinkers, and 76% more likely to be light drinkers than moderate/heavy drinkers. In nonobese women, alcohol intake >10 g/mo was associated with lower risk of all-cause mortality (hazard ratio, 0.68; 95% confidence intervals, 0.51-0.91).

Conclusion: Light alcohol intake, regardless of body weight, did not increase the risk of breast cancer recurrence or all-cause mortality in this cohort of middle-aged women previously diagnosed with breast cancer. Alcohol intake was associated with other favorable prognostic indicators, which may explain its apparent protective effect in nonobese women. *Cancer Epidemiol Biomarkers Prev; 19(3); 681–8. ©2010 AACR.*

Introduction

Alcohol consumption has been consistently associated with higher risk of incident breast cancer (1-4). However, the link between alcohol intake and all-cause mortality following the diagnosis of invasive breast cancer is less clear, with early studies finding no association (5-8), but two recent studies reported an inverse association with mortality (9, 10). Journal correspondence noted the lack of any protective association of alcohol in an analysis of Italian breast cancer survivors (11, 12), a null finding consistent with other studies cited in a review article (13). Franceschi et al. (12) suggested that the findings from the United States might be confounded given the high prevalence of minimal drinking in the sample. These conflicting reports suggest a need to investigate the influence of alcohol intake on prognosis in a large cohort of breast cancer survivors and to address the issue of confounding.

Body weight is a prominent potential confounder for studies evaluating associations between alcohol intake and breast cancer outcomes. Obesity at diagnosis has been consistently associated with increased mortality risk (14-17). Consistent evidence also suggests that a woman's weight may be related to her level of alcohol consumption. Obesity is associated with the lower likelihood of initiating alcohol use (18) and with lower odds of both any current drinking (18-20) and current heavy episodic drinking (20, 21). Thus, studies examining the effect of alcohol on health outcomes (including disease-free survival or overall survival) following breast cancer should control for body weight.

In this analysis, we investigate the roles of alcohol intake and obesity as predictors of additional breast cancer events and all-cause mortality in a cohort of 3,088 breast cancer survivors who participated in the Women's Healthy Eating and Living (WHEL) Study. This study was a randomized trial of a dietary intervention that

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Note: Supplementary data for this article are available at Cancer Epidemiology Biomarkers and Prevention Online (http://cebp.aacrjournals.org/).

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doi: 10.1158/1055-9965.EPI-09-0927

Published OnlineFirst February 16, 2010; DOI: 10.1158/1055-9965.EPI-09-0927

was not associated with breast cancer outcomes or overall mortality (22). The study verified both initial diagnoses and outcomes and had 96% follow-up through a median of 7.3 years. The WHEL Study did not include alcohol intake as a target behavior, and consumption did not change meaningfully in either study arm during the trial.

Materials and Methods

Participants and Covariates

Women whose first invasive breast cancer was diagnosed between 1991 and 2000 were enrolled in the WHEL Study at seven sites in the western United States between 1995 and 2000. Eligible participants had stage I (≥1 cm), II, or IIIA breast carcinoma within the past 4 y; were aged 18 to 70 y at diagnosis, had no evidence of recurrent disease or new cancer, and were able to communicate by telephone. Women who were pregnant, had cirrhosis, were scheduled for additional chemotherapy, or were currently taking estrogen replacement therapy were excluded. Further details of eligibility criteria, data collection, and assessment of cancer outcomes have been published elsewhere (23). Briefly, cancer characteristics were obtained by medical record review and confirmed by an oncologist. Weight and height were measured at a clinic visit at study entry, an average of 2 y, and a maximum of 4 y, after diagnosis. Body mass index (BMI) was calculated (kg/m^2) and participants were classified as normal, overweight, or obese using standard definitions (24). Prior to this baseline visit and at four time points in the study, participants completed a questionnaire (that was developed for the Women's Health Initiative) on their personal habits (smoking, weight history, alcohol history, and current physical activity; ref. 25). The nine-item measure of physical activity was validated for the WHEL Study (26), and responses were converted to metabolic equivalent tasks (min/wk; ref. 27).

Assessment of Alcohol Intake

We assessed alcohol intake using two independent measures: the Arizona Food Frequency questionnaire and a set of four 24-h recalls. The Arizona Food Frequency questionnaire estimated the usual quantity and frequency of beer, wine, spirits, and total alcohol consumed over the previous 3 mo. The dietary recalls were conducted by telephone shortly before the clinic visit on random days over a 3-wk period, stratified for weekends versus weekdays. Concerns with the validity of estimates of consumption from each of these measures have led to recommendations to use multiple measures (28). To be conservative, we used the higher of the two estimates (Arizona Food Frequency questionnaire or set of 24-h recalls), and converted reported alcohol consumption to grams with 10 g of alcohol equivalent to 10 oz of beer, 3.5 oz of wine, or a 1-oz shot of 80-proof alcohol in a mixed drink (29). Thus, a woman consuming >300 g/mo would have reported an intake, on average, of one alcoholic beverage daily and would be categorized as a moderate/heavy drinker in our analysis. Seven categories of alcohol consumption were used to evaluate trends for mortality and death, but for the remainder of the bivariate and multivariate analyses, we collapsed seven categories into three categories. We classified women who consumed no alcohol or <10 g per month as "nondrinkers" or "minimal drinkers."

Assessment of Study Outcomes

Primary study outcomes were invasive breast cancer recurrence or new primary breast cancer and death due to any cause. Throughout the study, participants were contacted every 6 mo to obtain information on any hospitalizations or new breast cancer events. Medical records and death certificates were collected for each potential study outcome and these were centrally adjudicated by the study medical director. At the close of the study in June 2006, vital status was known for 96% of participants [see consort diagram in Pierce (22)]. During follow-up (median 7.3 y), 518 breast cancer events (69% of which were distal recurrences) and 315 deaths were confirmed, 83% of which were breast cancer–related, and only 8% of which were not from any cancer (22).

Statistical Analysis

Although the WHEL Study intervention did not attempt to modify alcohol intake, we developed mixed models to explore whether alcohol consumption differed between the intervention and comparison groups, by time period (over 6 y of dietary data collection), or whether a group by time interaction occurred in alcohol consumption. Because no such associations were found, we present baseline alcohol intake in multivariate models, but report on 1-y data among the results.

Alcohol intake was analyzed categorically (with χ^2 tests against categorical covariates and t tests against continuous covariates) for bivariate associations with cancer characteristics, demographic and personal characteristics, and physical activity. Because of the highly skewed-to-zero distribution of alcohol intake, median and interquartile ranges for alcohol intake are reported for each category of covariate. Median changes in alcohol intake from baseline to 1 y were tested with a Wilcoxon signed rank test.

We modeled factors related to alcohol intake using binary logistic regression. The first model compared non/minimal alcohol intake (<10 g/mo) to the two other intake categories; the second model compared light alcohol intake (10-299 g/mo) to moderate/heavy intake (>300 g/mo). Any covariate associated with alcohol intake at a significance level of $P < 0.05$ in the logistic regression models was included in each of two delayed entry multivariate Cox proportional hazards models evaluating the joint association of alcohol and other covariates with all-cause mortality or additional breast cancer events. A delayed entry Cox model (30) was used because this

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approach accounts for varying times from diagnosis to study entry. Schoenfeld residuals were plotted to validate conformity with the proportional hazards assumption of the Cox models. Each model included an interaction term for obesity and alcohol intake, which was investigated using the likelihood ratio test. Finally, we computed hazard ratios (HR) and 95% confidence intervals (CI) for mortality by categories of BMI and alcohol consumption, controlled for tumor characteristics. All analyses were conducted in SAS version 9.2.

Results

Details regarding the WHEL Study sample have been published (22, 23). In this sample of 3,088 women previously diagnosed and treated for breast cancer, the mean (SD) baseline age was 52(9) years, BMI was 27.3 (6.1) kg/m^2; 54% were college graduates, and 85% were non-Hispanic white.

Characteristics of Alcohol Consumption

Energy intake from alcohol ranged from 0% to 34% of total energy intake, with the median 0.1% of energy intake and the mean 2.0% of energy intake. Beer consumption accounted for 23% of alcohol intake reported, and wine and spirits comprised 47% and 30%, respectively. Among the small group (8%) of women who reported drinking >600 g/mo of alcohol, 46% of intake was consumed as spirits and 31% as wine. Non-Hispanic whites constituted 97% of these heavier drinkers. Overall, ~37% of women were minimal drinkers (<10 g/mo), 43% were light drinkers and 20% were moderate/heavy drinkers (>300 g/mo).

Women with better prognosis [lower cancer stage and grade, estrogen receptor positive (ER+) tumors, no chemotherapy] had higher median alcohol intakes (Table 1). Compared with non-Hispanic white women in multivariate regression models, African American and Asian women were more than twice as likely to be non/minimal drinkers and, less likely to be moderate/heavy drinkers. Obese women were more likely to be non/minimal drinkers than light or moderate drinkers (odds ratio, 1.61; 95% CI, 1.35-1.93) and to be light compared with moderate/heavy drinkers (odds ratio, 1.76; 95% CI, 1.35-2.29). Women who were better educated, physically active, or nulliparous were 22% to 33% less likely to be non/minimal drinkers. Women who had ever smoked were half as likely to be nondrinkers and twice as likely to be moderate/heavy versus light drinkers.

Alcohol intake at either baseline or at 1-year of follow-up was not related to intervention group assignment. Median alcohol consumption decreased in both groups over 1 year, by 0.9 g/mo ($P < 0.05$) on the combined measure (Arizona Food Frequency questionnaire and recalls), with median decrease even less on each individual instrument.

Association with Study Outcomes

In bivariate analyses, higher alcohol intake was significantly associated with lower all-cause mortality ($P = 0.02$), but not with additional breast cancer events, using seven categories of alcohol consumption (Fig. 1). Within the simplified three consumption categories, the 634 women in the highest consumption category (>300 g/mo) had a mortality rate of 8.2% compared with 9.4% for those with light alcohol intake (10-299 g/mo) and 12.3% for those with minimal alcohol intake ($P = 0.03$). Non/minimal drinkers were also more likely to have an additional breast cancer event than those reporting light or moderate alcohol consumption (18.8% versus 15.7%; $P = 0.03$). The type of alcoholic beverage consumed was not related to mortality, but among all drinkers, the unadjusted risk for additional breast cancer events was lower in those who reported drinking spirits (12.8%) compared with those who primarily drank wine (16.3%) or beer (19.5%; $P = 0.02$).

In the multivariate analysis, controlling for stage, grade, time from diagnosis to study entry, ethnicity, education, physical activity, parity, BMI, and smoking status, (but not including ER status, chemotherapy, or tamoxifen use because they did not meet the inclusion criteria), higher alcohol intake was not associated with risk for either additional breast cancer events (Table 2) or additional distal breast cancer events (data not shown). However, compared with non/minimal drinkers, moderate/heavy drinkers had a decreased risk for all-cause mortality (HR, 0.69; 95% CI, 0.49-0.97) and for breast cancer mortality (HR, 0.70; 95% CI, 0.48-1.02). Women who had ever smoked were at increased risk for all-cause mortality (HR, 1.32; 95% CI, 1.04-1.66) but not for additional breast cancer events. College-educated women had 19% lower probability of an additional breast cancer event and 26% lower risk for death from any cause. In this analysis, obesity was not associated with additional breast cancer events but was marginally associated with all-cause mortality (HR, 1.28; 95% CI, 0.97-1.70; $P = 0.09$). The interaction term between obesity and alcohol consumption in the model for mortality suggested a weak effect ($P = 0.11$) in the likelihood ratio test.

We provide as Supplementary Table S1 the HRs for light and moderate alcohol intake compared with minimal intake, repeating our preferred multimode approach per Table 2, and also showing analyses using alcohol intake from Food Frequency questionnaires only or from 24-hour recalls only. In all models, light or moderate alcohol intake did not increase risk for recurrence or death.

Unadjusted mortality rates were 11.7% of nonobese nondrinkers, 7.9% of nonobese drinkers, 13.3% of obese nondrinkers, and 12.9% of obese drinkers. We present the HRs for all-cause mortality for combinations of binary variables for obesity (obese versus nonobese) and alcohol consumption (minimal drinker versus other), adjusted for cancer stage and grade (Fig. 2). Alcohol intake did not significantly alter mortality risk in obese women, but was associated with a 32% lower probability of

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Table 1. Alcohol intake at baseline by cancer/demographic characteristics and lifestyle variables in a cohort of breast cancer survivors from the United States followed for a median of 7.3 y (*N* = 3,088)

		Median (quartiles) intake g/mo	% Minimal (<10 g/mo)	% Light (10-299 g/mo)	% Moderate/heavy (>300 g/mo)	*P**
	N		1,079	1,375	634	
Stage						0.003
I	1,190	50 (3-276)	30.5	46.1	23.5	
II	1,407	24 (3-202)	38.0	44.0	18.1	
III	491	33 (3-237)	37.1	42.4	20.6	
Grade						
Unspecified	256	48 (3-336)	33.2	40.6	26.2	0.01
1	484	52 (3-284)	30.4	46.3	23.4	
2	1,239	33 (3-246)	34.8	44.2	21.1	
3	1,109	27 (3-184)	37.5	45.1	20.0	
Diagnosis to randomization						0.10
<2 y	1,698	31 (3-222)	36.6	43.7	19.7	
2-4 y	1,390	45 (3-249)	33.0	45.5	21.5	
ER status						0.02
Negative	756	25 (3-177)	38.0	44.8	17.2	
Positive	2,286	39 (3-249)	34.1	44.3	21.7	
BMI (kg/m^2)						<0.0001
Low (<18.5)	31	3 (0-87)	54.8	38.7	6.5	
Normal (18.5-24.99)	1,299	67 (3-295)	29.0	46.2	24.7	
Overweight (25-29.99)	955	39 (3-246)	34.2	44.0	21.8	
Obese (30+)	803	15 (1-117)	44.6	42.6	12.8	
Physical activity						<0.0001
<540 MET min/wk	1,380	22 (3-174)	32.6	45.0	22.4	
≥540 MET min/wk	1,605	63 (3-282)	29.3	47.3	23.4	
Race/ethnicity						<0.0001
White	2,634	49 (3-258)	32.6	45.0	22.4	
African American	118	3 (0-31)	56.8	34.8	8.5	
Hispanic	165	15 (1-96)	44.9	41.8	13.3	
Asian/Pacific Islander	119	6 (3-17)	43.7	52.9	3.4	
Mixed/other	52	8 (0-159)	51.9	32.7	15.4	
Education						<0.001
Not college graduate	1,414	23 (3-195)	39.5	41.8	18.7	
College graduate	1,674	51 (3-264)	31.1	46.8	22.1	
Parity						0.0001
Nulliparous	683	67 (3-330)	28.6	43.9	27.5	
Parous, first birth < age 35	2,246	31 (3-207)	36.8	44.8	18.4	
Parous, first birth ≥ age 35	136	32 (3-264)	34.6	42.7	22.8	
Smoking status						<0.0001
Current	138	76 (3-342)	34.8	37.0	28.3	
Former	1,276	82 (3-333)	29.4	44.2	27.4	
Never	1,643	17 (3-165)	39.9	45.5	14.6	

NOTE: Alcohol intake of 10 g is equivalent to 10 oz of beer, 3.5 oz of wine, or a 1-oz shot of 80-proof alcohol.
Abbreviation: MET, metabolic equivalent tasks.
**P* for trend in ordinal variables, or *P* from χ^2 for categorical variables.

mortality in nonobese women (HR, 0.68; 95% CI, 0.51-0.91). In this nonobese group, African American and Asian American women were three times more likely to report non/minimal alcohol intake compared with other drinking categories (Table 3). Nonobese women who were current or former smokers, physically active, or college educated were 48%, 21%, or 33% less likely, respectively, to be in the non/minimal drinking category.

Published OnlineFirst February 16, 2010; DOI: 10.1158/1055-9965.EPI-09-0927

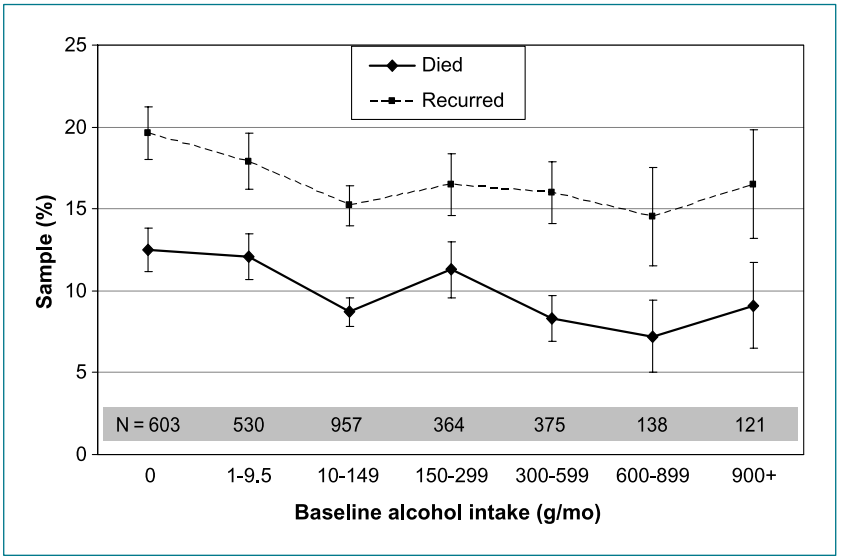

Figure 1. Unadjusted mortality/additional breast cancer events by baseline alcohol intake in a cohort of breast cancer survivors from the United States. Points, mean; bars, SEM.

Discussion

In this large cohort of breast cancer survivors, moderate alcohol intake compared with non/minimal drinking was associated with reduced all-cause mortality. However, alcohol consumption among WHEL Study breast cancer survivors was low, with only 21% consuming >300 g/mo (about one alcoholic drink a day). This level is comparable to that reported for other samples from the United States (2, 9) and less than half that reported in the Italian sample (11, 12). Some of this difference may be associated with the more heterogeneous population in the United States which has significant numbers of African Americans and Asian Americans. Both of these racial/ethnic groups have traditionally reported lower levels of alcohol consumption (31, 32) than non-Hispanic white women. Another reason for the difference could be that the WHEL sample represents women with more serious breast disease (83% of deaths were from breast cancer) and that oncologists from the United States may be more assertive in recommending reduced alcohol intake for these patients. Previously, we have noted that 41% of the WHEL sample reported reducing their alcohol consumption following breast cancer diagnosis (33). One year alcohol intake, which changed little after baseline in the WHEL Study, suggests that these postdiagnosis

Table 2. Multivariate models for additional breast cancer events and mortality

Variable	*N* in category	Additional breast cancer events			Mortality		
		N events	HR	95% CI	*N* events	HR	95% CI
Minimal alcohol intake (<10 g/mo)	1,133	213	1.00		139	1.00	
Light alcohol intake (10-290 g/mo)	1,321	205	0.89	(0.73-1.08)	124	0.81	(0.63-1.04)
Moderate/heavy alcohol intake (>300 g/mo)	634	100	0.91	(0.71-1.18)	52	0.69	(0.49-0.97)
Never smoker	1,643	273	1.00		150	1.00	
Ever smoker	1,414	237	1.01	(0.84-1.21)	159	1.32	(1.04-1.66)
Not college graduate	1,414	260	1.00		171	1.00	
College graduate	1,674	258	0.81	(0.67-0.97)	144	0.74	(0.58-0.94)
Parous	2,382	386	1.00		233	1.00	
Nulliparous	683	127	1.26	(1.02-1.55)	79	1.37	(1.05-1.79)
Normal weight	1,299	212	1.00		113	1.00	
Overweight	955	148	0.91	(0.74-1.13)	92	0.98	(0.74-1.30)
Obese	803	151	1.10	(0.88-1.38)	105	1.28	(0.97-1.70)

NOTE: Models are controlled for cancer stage, grade, years between diagnosis and study entry, physical activity, and ethnicity in addition to all variables listed in the body of the table.

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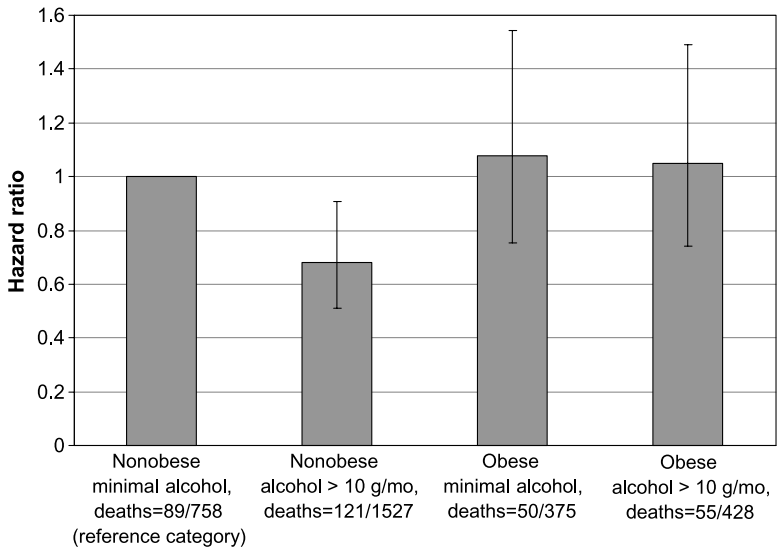

Figure 2. HRs, event counts, and 95% CIs for mortality by obesity and alcohol intake categories in a cohort of breast cancer survivors from the United States. Columns compare risk for all-cause mortality by obesity and alcohol intake. The reference category is minimal alcohol intake (<10 g/mo) and nonobese women. Models are adjusted for cancer stage and grade.

decreases in alcohol intake were maintained after study enrollment.

Our finding that light to moderate alcohol intake did not increase mortality after breast cancer was in line with that reported in two recent studies in breast cancer patients (9, 10), as well as a study in the general population (32). The protective HR in the WHEL Study for daily drinkers was comparable to that reported in the United Kingdom study (10). However, our data did not show a protective association between alcohol consumption and cancer recurrence. Of note, 92% of the WHEL population consumed fewer than two small drinks daily, and most "moderate drinkers" seemed to drink approximately one drink per day. Alcohol intake in a primarily white, educated population of breast cancer survivors who elected to participate in a dietary intervention trial may be associated with other healthy behaviors, as contrasted with alcohol intake in studies focusing on primary prevention, in which alcohol intake may be associated with less desirable health behaviors.

Table 3. Binary logistic regression model for minimal alcohol intake (<10 g/mo) in nonobese WHEL women (*N* = 2,285)

Predictor	Minimal alcohol (<10 g/mo) vs. light, moderate/heavy
	Odds (95% CI)
Node positive cancer	1.19 (0.99-1.43)
Time from diagnosis <2 y	1.26 (1.04-1.52)
Ethnicity	
African American	3.10 (1.78-5.37)
Asian	3.01 (1.89-4.78)
Hispanic	1.26 (0.83-1.91)
College graduate	0.67 (0.56-0.82)
Physical activity >540 METs/wk	0.79 (0.65-0.96)
Nulliparity	0.78 (0.62-0.97)
Ever smoker	0.52 (0.43-0.63)

NOTE: Model shows odds of consuming <10 g alcohol/mo, and are controlled for tumor estrogen receptor status and cancer grade. Reference category for ethnicity is non-Hispanic white.
Abbreviation: MET, metabolic equivalent tasks.

One of the mechanisms by which alcohol intake may influence risk for primary breast cancer is via effects on estrogen metabolism (34, 35). Alcohol intake has been observed to be directly associated with circulating sex hormones in several studies (36, 37). However, the hormonal milieu is considerably altered following the diagnosis and treatment of breast cancer, and the majority of women are treated with chemotherapy and/or antiestrogenic agents which further modify reproductive hormonal status. Li et al. showed a positive association between retrospectively self-reported alcohol consumption and second primary contralateral breast cancer (2), results which are difficult to compare given differences in sample characteristics including tumor ER status, frequency of chemotherapy use, different rates of new primaries, and greater frequency of metastatic disease in WHEL.

Bioactive constituents in beer and wine, such as flavonoids and polyphenols, have been hypothesized to reduce mortality risk after cancer (38). This effect was not observed in the WHEL sample, in which higher consumption of spirits was predictive of lower mortality. Indeed, the effect observed in this study may not be related to alcohol consumption per se but rather to correlates of alcohol intake. Further examination showed that

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the lower risk of death among alcohol consumers was confined to women who were not obese at enrollment in the study. In this subsample of the WHEL population, women with higher education and physical activity levels were more likely to be in the upper two categories of alcohol consumption. Both socioeconomic status/education (32) and physical activity (39, 40) have been associated with improved survival. Additionally, African American women, who have higher mortality following breast cancer diagnosis (41), were three times more likely to be non/minimal drinkers and this association could also partially explain the observed effect.

The association of alcohol consumption with decreased all-cause mortality may be attributed to other potential confounders. In the WHEL Study, women with more serious disease (node positive, higher grade, ER– tumors, or a history of chemotherapy) were more likely to be minimal drinkers. Furthermore, women who were more highly educated (and presumably had higher socioeconomic status) were less likely to be minimal drinkers. The association between socioeconomic status and improved health outcomes has been well established (32, 42).

A number of strengths as well as limitations of this analysis should be considered. Many of the measures in the WHEL Study were validated, although alcohol consumption was self-reported. The alcohol data in this study were collected shortly after the publication of observational studies which suggested that alcohol increased breast cancer risk. Thus, social desirability may have led some participants to underreport their alcohol intake. However, the strengths of our study include our use of two separate instruments to measure alcohol intake and our application of a conservative algorithm for assigning participants to a category of consumption. Furthermore, the WHEL Study assessed alcohol intake five times over the duration of the study and intake showed considerable stability in measurement (data not shown). A major strength in the WHEL Study is the oncologist verification of initial diagnosis and reported outcomes. Nevertheless, the WHEL Study results cannot be generalized to all breast cancer survivors. The WHEL population was comprised of women who elected to participate in a dietary intervention trial, excluded breast cancer survivors with low level disease (e.g., <1 cm tumors or carcinoma *in situ*), and was limited to early stage disease (through stage IIIA using the American Joint Committee on Cancer classification IV edition). Furthermore, the WHEL Study allowed enrollment up to 4 years postdiagnosis and therefore may underrepresent women diagnosed with ER– tumors (43).

In summary, light alcohol consumption reported by breast cancer survivors in the United States was not associated with adverse outcomes (either additional breast cancer events or death). A moderate level of alcohol consumption, approximately one alcoholic drink per day, was associated with reduced all-cause mortality in the study, particularly among women who were not obese. However, this study cannot rule out that women at lower risk for death were more likely to be moderate drinkers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

WHEL Study Coordinating Center: University of California, San Diego, Cancer Prevention and Control Program, Moores UCSD Cancer Center, San Diego, CA (John P. Pierce, PhD; Susan Faerber, BA; Barbara A. Parker, MD; Loki Natarajan, PhD, Cheryl L. Rock, PhD; Vicky A. Newman, MS; Shirley W. Flatt, MS; Sheila Kealey, MPH; Ruth Patterson, PhD, Linda Wasserman, MD; Wayne A. Bardwell, PhD; Lisa Madlensky, PhD; Wael Al-Delaimy MD).

WHEL Study Clinical Sites: Center for Health Research-Portland, Portland, OR (Njeri Karanja, PhD; Mark U. Rarick, MD); Kaiser Permanente Northern California, Oakland, CA (Bette J. Caan, PhD; Lou Fehrenbacher, MD); Stanford Prevention Research Center, Stanford University, CA (Marcia L. Stefanick, PhD; Robert Carlson, MD); University of Arizona, Tucson & Phoenix, AZ (Cynthia Thomson, PhD; James Warneke, MD); University of California, Davis, Davis, CA (Ellen B. Gold, PhD; Sidney Scudder, MD); University of California, San Diego, Moores UCSD Cancer Center, San Diego, CA (Kathryn A. Hollenbach, PhD; Vicky Jones, MD); and University of Texas M.D. Anderson Cancer Center, Houston, TX (Lovell A. Jones, PhD; Richard Hajek, PhD; Richard Theriault, DO).

Grant Support

The WHEL Study was initiated with the support of the Walton Family Foundation and continued with funding from National Cancer Institute grant CA 69375. Some of the data were collected from General Clinical Research Centers, NIH grants M01-RR00070, M01-RR00079, and M01-RR00827.

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Received 09/09/2009; revised 12/15/2009; accepted 12/16/2009; published OnlineFirst 02/16/2010.

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Published OnlineFirst February 16, 2010; DOI: 10.1158/1055-9965.EPI-09-0927

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Cancer Epidemiol Biomarkers Prev 2010;19:681-688. Published OnlineFirst February 16, 2010.