Effect of Prediagnostic Alcohol Consumption on Survival after Breast Cancer in Young Women

Kerryn W. Reding,[1,2] Janet R. Daling,[1] David R. Doody,[1] Cecilia A. O'Brien,[1] Peggy L. Porter,[1] and Kathleen E. Malone[1,2]

[1]Fred Hutchinson Cancer Research Center and [2]University of Washington, Seattle, Washington

Abstract

Background: **Alcohol consumption has been comprehensively investigated as an etiologic risk factor for breast cancer but has received little attention in terms of its effect on prognosis after breast cancer, particularly for young women.**

Methods: **1,286 women diagnosed with invasive breast cancer at age ≤45 years from two population-based case-control studies in the Seattle-Puget Sound region were followed from their diagnosis of breast cancer (between January 1983 and December 1992) for survival through June 2002, during which time 364 women had died. Cox proportional hazards modeling was used to assess the effect of prediagnostic alcohol consumption on the risk of dying.**

Results: **After adjusting for age and diagnosis year, compared with nondrinkers, women who consumed alcohol in the 5 years before diagnosis had a decreased risk of death [>0 to <3 drinks per week: hazard ratio, 0.7; 95% confidence interval (95% CI), 0.6-0.95; 3 to <7 drinks per week: risk ratio, 0.6; 95% CI, 0.4-0.8;7 drinks per week: risk ratio, 0.7; 95% CI, 0.5-0.9]. This association was unchanged on additional adjustment for potential confounders including most notably treatment, stage at diagnosis, and mammogram history.**

Conclusion: **These results suggest that women who consume alcohol before a diagnosis of breast cancer have improved survival, which does not appear to be attributable to differences in stage, screening, or treatment.** (Cancer Epidemiol Biomarkers Prev 2008;17(8):1988–96)

Introduction

Although alcohol consumption has been identified as one of the few, known modifiable risk factors for breast cancer (1-5), its possible role in breast cancer recurrence and mortality has received little research attention, particularly in younger women. Light to moderate amounts of alcohol consumption have been associated with lower overall and coronary heart disease–associated mortality among women (6, 7). However, evidence has been sparse and inconsistent for the effect of alcohol consumption on breast cancer mortality in young women (8-10).

There is an indication that the effects of alcohol may take place during late breast carcinogenesis due to the association between alcohol consumption and late-stage breast cancer and lack of association between alcohol and benign proliferative epithelial disorders of the breast (11, 12). Prior etiologic studies have shown that the most relevant timing of exposure for certain exogenous risk factors for breast cancer, including alcohol, may be the years immediately preceding diagnosis (13-15). Furthermore, in a meta-analysis of 38 studies investigating alcohol consumption and breast cancer risk, Longnecker describes the finding that cohort studies with longer follow-up time showed weaker effects of alcohol use on breast cancer incidence, indicating that the salient period for alcohol use was recent use (3).

Given the consistent nature of the association of alcohol and breast cancer risk as well as the common nature of alcohol consumption, we evaluated the effect of prediagnostic alcohol consumption on the risk of death (overall and breast cancer mortality) in a population-based cohort study of breast cancer patients diagnosed at age <45 years, focusing primarily on recent use of alcohol.

Materials and Methods

Study Population. The 1,286 women with invasive breast cancer in the current study were drawn from two previously completed population-based case-control studies of breast carcinoma conducted at the Fred Hutchinson Cancer Research Center. The methods for both studies were essentially the same and have been described previously (16, 17). The cases were identified from the Cancer Surveillance System (CSS), which is part of the Surveillance, Epidemiology, and End Results (SEER) Program, with eligibility criteria for the first study including first primary breast carcinoma diagnosis between January 1983 and April 30, 1990; diagnosed at age <45 years; women born after 1944; and women of Caucasian race. Interviews were completed on 845 women (83.3% of eligible cases). In the second study, cases were also identified through CSS with eligibility criteria including first primary breast carcinoma identified from May 1, 1990 to December 31, 1992;

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Requests for reprints: Kathleen E. Malone, Fred Hutchinson Cancer Research Center, M4-C308, Box 19024, Seattle, WA 98109-1024. Phone: 206-667-4630; Fax: 206-667-5948. E-mail: kmalone@fhcrc.org

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diagnosed at age <45 years; and women of any race; 643 women (83.9% of eligible cases) were interviewed as part of this study.

In-person interviews conducted through these previous studies included questions ascertaining lifetime history of a variety of known and suspected breast cancer risk factors including prediagnostic history of alcohol consumption and smoking, body size history, and reproductive risk factors. With regard to alcohol use, participants were asked about their volume (number of drinks), frequency (times per day/week/month), and type (beer/wine/liquor) of alcohol use from the time alcohol use began until their diagnosis of breast cancer. Participants self-defined the relevant time spans for the various patterns of consumption of each type of beverage throughout their lives. The protocol of this study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Follow-up. The methods used to follow up the breast carcinoma cases have been reported previously and are summarized only briefly here (18). Active (hospital and physician annual follow-up) and passive (National Death Index) surveillance of vital status of study participants was done by CSS. For women whose cause of death was unavailable through the CSS, death certificates were obtained and causes of death were classified as breast cancer related or not using the CSS protocol. Participants underwent follow-up until the earliest of the date of death, the date last known to be alive, or the end date of our follow-up period (June 2002). Among those not reported to be dead, 93.1% had been contacted within 12 months of the end of the follow-up period.

The primary mortality endpoint used was all-cause mortality. In this age group, deaths from other causes are fairly minimal and the vast majority of deaths were related to breast cancer. Of 364 deaths, 335 (92.0%) were known to be due to breast carcinoma, 22 (6.0%) were due to other causes, and 7 (1.9%) were unknown as to the cause of death. Analyses were repeated using breast cancer death as the mortality endpoint and censoring women with other causes of death at the time of their death and results were unchanged (see Results).

Pathology Review, Testing of Tumor Samples for Prognostic Markers, and Collection of Treatment Information. Tumor specimens were available for a centralized pathology review on 1,019 (79.2%) of the 1,286 breast cancer cases. For the remaining samples, either permission was not given to access the tumor tissues or tumor blocks were not available or had been discarded by the laboratories; 907 (70.5%) cases had adequate tissue samples available for immunoperoxidase assays. Tumors were evaluated for expression of estrogen receptor (ER), progesterone receptor (PR), p53 tumor suppression gene protein, Ki-67 proliferation-related antigen, c-erbB-2 oncogene protein, apoptosis regulatory protein bcl-2, cyclin E protein, S-phase fraction, and p27 protein as described previously (19, 20). Tumors were classified as positive/high staining or negative/low staining based on the percentage of tumor cells staining positive and/or the pathologist's interpretation of staining intensity. For ER, PR, and p53, any nuclear staining was considered positive; the percentage of Ki-67 was averaged over four high-power fields with ≥25% considered high proliferation; for tumor necrosis factor, categories of none and intermediate were combined versus high; for bcl-2, negative and low-intensity stains were categorized as low, whereas intermediate and high-intensity stains were categorized as high.

Women whose tumors were available for analysis were on the whole similar to the women without tumor data available, with the exception that women with available tumor samples were older at diagnosis (80.1% were ages ≥35 years) than the women without tumor samples (72.3%; $P = 0.006$). There were no apparent differences in alcohol consumption or mortality between women whose tumor samples were and were not available for analyses ($P = 0.20$ and 0.32, respectively).

Medical records were abstracted to identify courses of treatment including surgery, radiation therapy, chemotherapy, and/or hormonal therapy; 1,113 cases (86.5%) included in this analysis had their medical record reviewed by trained medical record abstractors. For those participants who refused medical record review, whose records were destroyed, or who had incomplete information with respect to treatment, treatment information was obtained from the follow-up study questionnaires and the CSS.

Statistical Analysis. For the primary analysis focused on recent alcohol consumption, the average weekly alcohol consumption was computed for the period spanning 7 to 2 years before diagnosis. To compute the weekly average number of drinks consumed over this period, we calculated the total number of drinks consumed during the period (summing over all applicable episodes reported) and divided by 260, the total number of weeks in the 5-year period.

Average weekly alcohol consumption was categorized as never or none during this period, >0 to <3, 3 to <7, and ≥7 drinks per week; from this point forward, we refer to these categories as nondrinkers, light, moderate, and heavy drinkers, respectively. A woman who had consumed <12 alcoholic beverages in her lifetime or <1 drink per month for ≥6 months was considered a never drinker. Alcohol consumption during the 2-year period immediately preceding diagnosis was omitted from computations to exclude any disease-related changes in alcohol consumption (15). For the sake of brevity, we will henceforth refer to the 7 to 2 years before diagnosis as the 5 years before diagnosis.

The lifetime average weekly intake of alcohol was determined by calculating the average amount of alcohol consumed per week from age 15 years until diagnosis. We also investigated alcohol exposure by beverage type: wine, liquor, and beer. One drink was defined as 12 ounce beer, 1.5 ounce liquor, and 4 ounce wine.

Estimates of the relative risk of dying were calculated using Cox proportional hazards models. The hazard ratios (HR) were left-truncated to account for the time lag between diagnosis and interview. Censoring occurred at either the date of last known follow-up or the end date of follow-up (June 2002) if death had not occurred before this. Interaction terms were investigated using the likelihood ratio test.

Table 1. Relationship of demographic and tumor characteristics to the risk of dying among women diagnosed with breast cancer at age <45 y from 1983 to 1992

	Alive	Dead	HR* (95% CI)
Age at diagnosis (y)			
<35	179 (65.1)	96 (34.9)	1.0
≥35	743 (73.5)	268 (26.5)	0.9 (0.7-1.1)
Diagnosis year			
Before 1989	358 (65.3)	190 (34.7)	1.0 (Reference)
On or after 1989	564 (76.4)	174 (23.6)	0.8† (0.6-1.0‡)
Ever use of mammogram§			
No	506 (67.1)	248 (32.9)	1.0 (Reference)
Yes	416 (78.2)	116 (21.8)	0.7* (0.6-0.9)
Chemotherapy‖			
No	299 (75.3)	98 (24.7)	1.0 (Reference)
Yes	617 (70.0)	264 (30.0)	0.9 (0.7-1.1)
Radiotherapy‖			
No	414 (70.2)	176 (29.8)	1.0 (Reference)
Yes	502 (73.0)	186 (27.0)	0.9 (0.7-1.1)
Hormone therapy			
No	551 (71.0)	225 (29.0)	1.0 (Reference)
Yes	300 (70.9)	123 (29.1)	1.0 (0.9-1.0)
Stage			
Local	608 (82.5)	129 (17.5)	1.0 (Reference)
Regional	304 (59.6)	206 (40.4)	2.6* (2.1-3.2)
Distant	1 (4.0)	24 (96.0)	22.0* (14.0-34.4)
Tumor size (cm)			
≤2	527 (80.6)	127 (19.4)	1.0 (Reference)
>2-5	326 (65.3)	173 (34.7)	1.9* (1.5-2.4)
>5	51 (50.0)	51 (50.0)	3.0* (2.2-4.2)
Nodal status			
Negative	615 (82.3)	132 (17.7)	1.0 (Reference)
Positive	302 (56.0)	219 (42.0)	1.5* (1.4-1.6)
Body mass index			
Q1	241 (75.6)	78 (24.4)	1.0 (Reference)
Q2	230 (72.8)	86 (27.2)	1.1 (0.8-1.6)
Q3	238 (74.3)	82 (25.6)	1.2 (0.9-1.6)
Q4	205 (63.9)	116 (36.1)	1.9* (1.4-2.5)
Recency of pregnancy (y)			
Nulliparous	251 (74.9)	84 (25.1)	1.0 (Reference)
≥5	529 (74.0)	186 (26.0)	1.1 (0.8-1.4)
2 to <5	97 (67.8)	46 (32.2)	1.3 (0.9-1.9)
<2	45 (48.9)	47 (51.1)	2.2* (1.5-3.0)
First- or second-degree relative with breast cancer			
No	359 (69.2)	160 (30.8)	1.0 (Reference)
Yes	401 (75.8)	128 (24.2)	0.8* (0.6-1.0‡)
Smoking			
Never	464 (71.1)	189 (28.9)	1.0 (Reference)
Former	205 (73.5)	74 (26.5)	0.9 (0.7-1.2)
Current	253 (71.5)	101 (28.5)	1.0 (0.8-1.2)
Race			
White	874 (71.8)	344 (28.2)	1.0 (Reference)
Black	12 (54.6)	10 (45.4)	2.4* (1.2-4.5)
Asian/Pacific Islander	31 (77.5)	9 (22.5)	1.0 (0.5-2.0)
Income ($)			
<15,000	85 (65.9)	44 (34.1)	1.0 (Reference)
15,000-50,000	483 (69.1)	216 (30.9)	0.9 (0.7-1.3)
≥50,000	349 (77.7)	100 (22.3)	0.7* (0.5-1.0‡)
Education			
Less than high school	30 (71.4)	12 (28.6)	1.0 (Reference)
High school/some college	560 (71.0)	229 (29.0)	1.2 (0.7-2.2)
College graduate	332 (73.0)	123 (27.0)	1.2 (0.6-2.1)

*Adjusted for age, mammogram, and diagnosis year, except as noted.
†Statistically significant HR.
‡1.0 due to rounding; 95% CI excludes 1.0.
§Adjusted for age and diagnosis year.
‖Adjusted for age, diagnosis year, nodal status, stage, and tumor size.

Age and reference year were accounted for in all analyses. We assessed the following factors for their potential confounding or modifying effects: mammogram history (defined as ever having a mammogram), smoking history (never, former, current), body mass index (quartiles), education (less than high school, high school/some college, graduated college), income (<$15,000/yr, $15,000-50,000/yr, >$50,000/yr), race (Caucasian, African American, Asian, other), and oral contraceptive use (never, <10 years, ≥10 years).

The Mantel-Haenszel χ^2 test was used for all bivariate analyses. To be included as a potential confounder in the multivariate analysis, we required that a variable be associated with both alcohol consumption and the outcome. Variables that altered the estimate in the multivariate model by ≥10% were retained in the final model. The variables meeting these criteria within the Cox proportional hazards model were age and year of diagnosis and mammogram history.

We examined the association between alcohol consumption and tumor characteristics using logistic regression to assess the odds of breast cancer with specific tumor characteristics and reported odds ratios (OR) and 95% confidence interval (95% CI). An investigation into the potential confounding factors involved in this analysis indicated that age at diagnosis, diagnosis year, and smoking history all met the criteria, as set forth above, for confounding and thus were included in the logistic regression model.

Results

The association between mortality and demographic features and tumor characteristics is shown in Table 1. Women diagnosed before 1989 had a greater risk of dying; women reporting a history of a prior screening mammogram had a reduced risk of dying. As would be expected, tumor characteristics known to be unfavorable, including larger tumor size, later stage at diagnosis, and positive nodal status, were all associated with an increased risk of mortality in this cohort. As shown previously in this data set, the highest quartile of body mass index (≥25.8 kg/m^2) was associated with an increased risk of mortality compared with the first quartile (≤20.6 kg/m^2); the recency of pregnancy increased the risk of mortality compared with nulliparous women; women with a first- or second-degree relative with breast cancer were at a lower risk of mortality compared with women with no family history

Table 2. Relationship between alcohol consumption and factors observed to influence the risk of dying among women diagnosed with breast cancer at age <45 y from 1983 to 1992

	Alcohol consumption status in the 5 years before diagnosis		
	Nondrinkers*	Drinkers	*P*
Age at diagnosis (y)			
<35	50 (18.2)	224 (81.8)	0.002
≥35	274 (27.1)	736 (72.9)	
Ever had a mammogram			
No	175 (23.2)	579 (76.8)	0.046
Yes	149 (28.1)	381 (71.9)	
Oral contraceptive use (y)			
Never	99 (34.1)	191 (65.9)	<0.0001
<10	199 (24.3)	621 (75.7)	
≥10	26 (14.9)	148 (85.1)	
Diagnosis year			
Before 1989	93 (17.0)	454 (83.0)	<0.0001
On or after 1989	231 (31.3)	506 (68.7)	
Race			
White	287 (23.6)	929 (76.4)	<0.0001
Black	12 (54.6)	10 (45.4)	
Asian/Pacific Islander	23 (57.5)	17 (42.5)	
Education			
Less than high school	12 (28.6)	30 (71.4)	0.29
High school/some college	205 (26.0)	583 (74.0)	
College graduate	107 (23.6)	347 (76.4)	
Income ($)			
<15,000	31 (24.0)	98 (76.0)	0.17
15,000-50,000	191 (27.4)	506 (72.6)	
≥50,000	98 (21.8)	351 (78.2)	
Recency of pregnancy (y)			
Nulliparous	65 (19.4)	270 (80.6)	0.84
≥5	209 (29.3)	505 (70.7)	
2 to <5	33 (23.1)	110 (76.9)	
<2	16 (17.6)	75 (82.4)	
Smoking			
Never	212 (32.6)	439 (67.4)	<0.0001
Former	52 (18.6)	227 (81.4)	
Current	60 (16.9)	294 (83.1)	
Body mass index			
Q1	70 (22.0)	248 (78.0)	0.0002
Q2	59 (18.7)	256 (81.3)	
Q3	83 (25.9)	237 (74.1)	
Q4	106 (33.0)	215 (67.0)	

*Nondrinkers include those who did not drink during the 5-y period as well as those who did not drink in their lifetime.

Table 3. Risk of dying after breast cancer in relation to level of alcohol consumption among women diagnosed with breast cancer at age <45 y from 1983 to 1992

Average weekly alcohol consumption as drinks per week	Alive	Dead	HR* (95% CI)
5 y before diagnosis			
Nondrinkers†	216 (67.1)	106 (32.7)	1.0 (Reference)
Drinkers	701 (73.4)	254 (26.6)	0.7‡ (0.5-0.9)
>0 to <3	370 (72.0)	144 (28.0)	0.7‡ (0.6-1.0)§
3 to <7	150 (78.1)	42 (21.9)	0.6‡ (0.4-0.8)
≥7	181 (72.7)	68 (27.3)	0.7‡ (0.5-0.9)
Wine drinkers			
Non-wine drinkers	307 (67.6)	147 (32.4)	1.0 (Reference)
Wine drinkers	615 (73.9)	217 (26.1)	0.7‡ (0.6-0.9)
>0 to <3	430 (72.9)	160 (27.1)	0.8 (0.6-1.1)
3 to <7	100 (75.8)	32 (24.2)	0.7 (0.5-1.1)
≥7	85 (77.3)	25 (22.7)	0.7 (0.5-1.1)
Beer drinkers			
Non-beer drinkers	503 (70.8)	207 (29.2)	1.0 (Reference)
Beer drinkers	412 (72.5)	156 (27.5)	0.9 (0.7-1.1)
>0 to <3	309 (72.7)	116 (27.3)	0.9 (0.7-1.1)
3 to <7	55 (75.3)	18 (24.7)	0.8 (0.5-1.2)
≥7	48 (68.8)	22 (31.4)	1.0 (0.6-1.5)
Liquor drinkers			
Non-liquor drinkers	353 (70.9)	145 (29.1)	1.0 (Reference)
Liquor drinkers	567 (72.1)	219 (27.9)	0.9 (0.7-1.1)
>0 to <3	460 (72.3)	176 (27.7)	0.9 (0.7-1.1)
3 to <7	53 (68.0)	25 (32.0)	1.1 (0.6-1.5)
≥7	54 (75.0)	18 (25.0)	0.8 (0.5-1.2)
Over the lifetime			
Never drinkers	160 (65.8)	83 (34.2)	1.0 (Reference)
Ever drinkers	756 (73.0)	280 (27.0)	0.7‡ (0.5-0.8)
>0 to <3	432 (74.0)	152 (26.0)	0.6‡ (0.5-0.8)
3 to <7	178 (70.6)	74 (29.4)	0.7‡ (0.5-1.0)§
≥7	146 (73.0)	54 (27.0)	0.6‡ (0.5-0.9)

*Adjusted for age, diagnosis year, and mammography.
†Nondrinkers include those who did not drink during the 5-y period as well as those who did not drink in their lifetime.
‡Statistically significant HR.
§Due to rounding, $P < 0.05$.

(18, 19, 21). Higher income (≥$50,000/yr) was associated with reduced mortality compared with income of <$15,000/yr. However, education was not associated with mortality. Compared with White women, Black women were found to be at increased risk of mortality, whereas Asian women were not.

Factors associated with mortality after breast cancer were examined for their relationship with alcohol consumption in the 5-year period before diagnosis (Table 2). Most of these factors varied significantly by alcohol consumption status, including age at diagnosis, mammogram history, history of oral contraceptive use, diagnosis year, race, smoking status, and quartile of body mass index.

Compared with women who reported no alcohol consumption in the 5-year period before diagnosis, women who consumed alcohol during the same interval had a 30% reduction in the risk of dying after breast cancer (0.7; 95% CI, 0.5-0.9; Table 3). This reduction in the risk of dying did not vary substantively based on the average number of drinks consumed [compared with nondrinkers, the risk of death was 0.7 (95% CI, 0.6-0.95) for light drinkers, 0.6 (95% CI, 0.4-0.8) for moderate drinkers, and 0.7 (95% CI, 0.5-0.9) for heavy drinkers]. We found similar patterns of risk in relation to average lifetime alcohol consumption.

These and all other HR reported henceforth were adjusted for age, diagnosis year, and mammography. The association between recent alcohol consumption and the risk of dying was not altered by adjustment for any additional potential confounders. Further, adjustment for factors related to mortality (stage, histologic grade, and treatment factors) did not change results [compared with nondrinkers: HR, 0.7 (95% CI, 0.5-0.9) for light drinkers; HR, 0.5 (95% CI, 0.3-0.7) for moderate drinkers; and HR, 0.6 (95% CI, 0.4-0.8) for heavy drinkers]. In addition, there was no evidence of significant effect modification by body mass index, smoking, or age.

Further examination by beverage type revealed that this reduction in risk of dying associated with recent alcohol consumption was limited to wine consumption (risk ratio, 0.7; 95% CI, 0.6-0.9). These results were unchanged when adjusted for beer and liquor drinking. There was no association observed with beer or liquor consumption (Table 3).

To assess possible mechanisms underlying the association between alcohol and improved survival, we examined the relationship of recent alcohol consumption to selected tumor characteristics that are markers of adverse prognosis. Alcohol consumption was unrelated to ER or PR status, Bcl-2 expression, stage, or percentage of tumor cells in S phase (Table 4). Alcohol consumption was related to reduced odds of having a tumor with high tumor necrosis levels (OR, 0.6; 95% CI, 0.4-0.98) and marginally to p53-positive tumors (OR, 0.7; 95% CI, 0.5-1.0).

Including p53 and tumor necrosis in the Cox model for recent alcohol use did not affect the significance of the association for moderate drinkers (HR, 0.5; 95% CI,

0.3-0.8) or heavy drinkers (HR, 0.7; 95% CI, 0.5-0.98) but did affect the statistical significance for light drinkers (HR, 0.8; 95% CI, 0.6-1.1).

Finally, we examined our main results to assess variation according to several sources of effect modification or bias. Results were similar to those reported above when analyses were restricted to premenopausal women [compared with nondrinkers: HR, 0.7 (95% CI, 0.6-0.96) for light drinkers; HR, 0.5 (95% CI, 0.4-0.8) for moderate drinkers; and HR, 0.7 (95% CI, 0.5-0.95) for heavy drinkers]. Results were also unchanged when we restricted to deaths due to breast cancer [excluding the small number of non-breast cancer-related deaths; HR, 0.7 (95% CI, 0.6-0.97) for light drinkers; HR, 0.6 (95% CI, 0.4-0.9) for moderate drinkers; and HR, 0.7 (95% CI, 0.5-0.9) for heavy drinkers]. Additionally, because this study retrospectively ascertained breast cancer cases in 1983 to 1985, we repeated analyses excluding cases diagnosed before 1986 and again found that our results were unchanged [HR, 0.7 (95% CI, 0.6-0.96) for light drinkers; HR, 0.6 (95% CI, 0.4-0.8) for moderate drinkers; and HR, 0.6 (95% CI, 0.5-0.9) for heavy drinkers]. Also, as this analysis combined two study populations, we conducted the analysis separately within each study and found similar results in each study, although individually these results lack the same precision as found in the combined analysis due to the smaller sample sizes [in the study conducted with women diagnosed from 1983 to 1990: HR, 0.8 (95% CI, 0.6-1.1) for light drinkers; HR, 0.6 (95% CI, 0.4-0.96) for moderate drinkers; and HR, 0.8 (95% CI, 0.5-1.1) for heavy drinkers; in the study conducted with women diagnosed from 1990 to 1992: HR, 0.7 (95% CI, 0.5-1.0) for light drinkers; HR, 0.5 (95% CI, 0.3-0.95) for moderate drinkers; and HR, 0.6 (95% CI, 0.3-1.0) for heavy drinkers]. Lastly, in analyses restricted to women with available tumors, the results were unchanged [HR, 0.7 (95% CI, 0.6-0.97) for light drinkers; HR, 0.5 (95% CI, 0.3-0.7) for moderate drinkers; and HR, 0.6 (95% CI, 0.5-0.9) for heavy drinkers].

Discussion

In the interpretation of the above findings, we should consider the limitations of our study. First, we were unable to interview 15% of the women eligible for the original case-control studies on which this population-based cohort study was based. At 5 years, 43.5% of the noninterviewed cases and 14.5% of the interviewed cases were deceased. To the extent that noninterviewed cases differ from interviewed cases based on their alcohol consumption, our results may be biased. Because this differential was greatest for women in the earliest years of the cohort (due to a lag in interviewing), we assessed its potential effect through a subset analysis limited to women diagnosed after 1986. The absence of any change in results suggests that our results may be generalizable to the entire spectrum of breast cancer cases. A second potential limitation was the possibility of confounding. Despite the breadth of data available to us to assess potential confounding influences, including comprehensive treatment data and other lifestyle variables, we could not exclude the possibility of unmeasured or residual confounding that accounts for our findings.

Additionally, this study did not collect information on dietary factors, and as a result, we were unable to

Table 4. Relationship of average weekly alcohol consumption in 5 y before diagnosis to tumor characteristics

Alcohol consumption*	Tumor characteristic		OR (95% CI) †
ER	Positive	Negative	
Nondrinkers	148 (27.7)	92 (25.1)	1.0 (Reference)
Drinkers	386 (72.3)	274 (74.9)	1.1 (0.8-1.4)
PR	Positive	Negative	
Nondrinkers	150 (27.6)	89 (25.1)	1.0 (Reference)
Drinkers	394 (72.4)	266 (74.9)	1.0 (0.7-1.4)
Tumor necrosis factor	None-intermediate	High	
Nondrinkers	222 (25.5)	35 (33.3)	1.0 (Reference)
Drinkers	650 (74.5)	70 (66.7)	0.6 ‡ (0.4-1.0)§
Ki-67	Low	High	
Nondrinkers	140 (26.0)	98 (27.8)	1.0 (Reference)
Drinkers	399 (74.0)	255 (72.2)	0.9 (0.7-1.3)
Bcl-2	High	Low	
Nondrinkers	109 (28.9)	128 (24.8)	1.0 (Reference)
Drinkers	266 (70.9)	389 (75.2)	1.3 (0.9-1.7)
p53	Negative	Positive	
Nondrinkers	132 (24.6)	105 (29.3)	1.0 (Reference)
Drinkers	405 (75.4)	254 (70.8)	0.7 (0.5-1.0)
% S phase	Low	High	
Nondrinkers	80 (24.6)	92 (28.1)	1.0 (Reference)
Drinkers	245 (75.4)	235 (71.9)	0.8 (0.5-1.1)
Stage	Local	Regional/distant	
Nondrinkers	183 (24.9)	137 (25.7)	1.0 (Reference)
Drinkers	551 (75.1)	396 (74.3)	1.1 (0.8-1.4)
Grade	Low/intermediate	High	
Nondrinkers	137 (25.3)	116 (26.9)	1.0 (Reference)
Drinkers	405 (74.7)	315 (73.1)	1.2 (0.9-1.6)

*During the 5-y period before diagnosis, nondrinkers include those who did not drink during the 5-y period.
†Adjusted for age, diagnosis year, and smoking status.
‡Statistically significant OR.
§Due to rounding, $P < 0.05$.

examine whether dietary factors may modify the effect of alcohol consumption on risk of death. In addition, because this study was done in a sample of predominantly White women, reflecting to a great extent the underlying racial distribution of the Seattle-Puget Sound area, we cannot be sure these results are generalizable to non-White populations. Lastly, the ascertainment of alcohol exposure relied on self-reported drinking history. The interviewer-guided questionnaires were developed to chart the pattern of exposure beginning with the age at which alcohol consumption began and document the changes in this pattern over time. Overall, the quantity/frequency method for ascertaining alcohol exposure is a reliable approach to estimate alcohol use and the accompanying strategy of using a lifetime calendar with milestones noted further facilitated recall (22). In our analysis, we found an effect achieved by any intake of alcohol and the magnitude of this association did not vary further according to levels of alcohol consumption; thus, misclassification within different categories of use would have minimal effect on the interpretation of our results. Because any misclassification resulting from this is likely to be nondifferential, misclassification in this case would lead to an attenuation of the real effect of alcohol in our results.

The strengths of this study are also worth noting, including the population-based design, which heightens the generalizability of the results, the large sample size, particularly the large numbers of very young cases, and the centralized pathologic review and laboratory analyses done on tissue samples.

Our results indicate that young women who consumed alcohol before a diagnosis of breast carcinoma were at a decreased risk of mortality compared with women who consumed no alcohol. There was some suggestion that the decreased risk of death was limited to wine consumption. This reduction in risk of dying does not appear to be due to differences in mammography screening history, tumor characteristics, treatment, or other exposures.

Little research has been focused on the association between alcohol and risk of dying after a breast cancer diagnosis, particularly among young women. Several studies have found results broadly similar to ours in terms of the direction and magnitude of effects, although in general these studies represent an older demographic than ours. In the Saxe et al. study, although the risk of death among premenopausal breast cancer cases associated with alcohol consumption did not reach statistical significance (HR, 0.41; 95% CI, 0.01-16.35 per 2 drinks per day), the magnitude of the observed effect was consistent with our findings. Their sample of 149 breast cancer patients consisted of 51 (34.2%) premenopausal and 98 (65.8%) postmenopausal women with a median age of 57.8 years (in our study, 92.5% were premenopausal). Similarly, Holmes et al. observed a decreased risk of death among breast cancer cases in relation to prior alcohol consumption in the Nurses' Health Study. However, these results also failed to reach statistical significance [HR (95% CI), 0.79 (0.61-1.02), 0.86 (0.63-1.16), and 0.92 (0.66-1.27) for the second, third, and fourth quartiles, respectively, compared with the first quartile of alcohol consumption; ref. 23]. Although this study had a generous sample size of 1,982 women with invasive breast cancer, it reflected a wider age spectrum and older age group than ours, with a mean age of 54 years (versus our study's 37.7 years). Lastly, Zhang et al. observed a nonstatistically significant reduction in risk of death for women consuming $\geq$4 g/d alcohol (risk of death, 0.7; 95% CI, 0.3-1.5) in a data set of 698 breast cancer patients ages 55 to 69 years at baseline (24).

Some studies with results that conflict with ours include the study of Hebert et al., who observed in their hospital-based cohort of 546 early-stage breast cancer cases that beer (but not wine or liquor) consumption was related to an increased risk of breast cancer mortality among premenopausal women (8). McDonald et al., in a hospital-based cohort of 125 postmenopausal African American breast cancer cases found prediagnostic consumption of at least 1 drink per week was associated with a 2.7 times greater risk of all-cause mortality (25). The inconsistencies in these epidemiologic studies, as a whole, potentially reflect the heterogeneity of alcohol as an exposure and the relatively small samples of breast cancer patients that have been studied in many of these analyses. Additionally, there is reason to believe that premenopausal and postmenopausal breast cancer development differs (26); thus, potentially the effect of alcohol on tumorigenesis differs among premenopausal and postmenopausal women, which would create inconsistencies across studies with different age ranges.

Previous studies have not investigated the role of prediagnostic alcohol use on tumor characteristics in young women. Our data indicate that the role of alcohol in decreasing the risk of death among breast cancer death may be through its effect on reducing the risk of p53-positive tumors and tumors with high necrosis levels, both of which are associated with decreased survival. However, adjusting for these factors did not fully explain the association of alcohol with improved mortality, particularly in moderate and heavy drinkers.

A potential mechanism involving alcohol consumption in breast cancer survival includes the role of genes involved in metabolism of drugs and other toxins, such as the cytochrome *P*450 and glutathione *S*-transferase enzymes. Some of the women who chose not to drink may have a deficiency in their metabolism of alcohol causing their bodies to react unfavorably to the ingestion of alcohol; this same subset of women could also experience poor metabolism of chemotherapeutic agents based on poor drug metabolism, resulting in higher toxicity to typical doses. This mechanism would require the genes involved in alcohol metabolism to be the same genes involved in chemotherapy metabolism. Some support for the hypothesis that chemotherapy and alcohol metabolism operate in a shared pathway is the observation that alcohol and certain chemotherapeutic agents, including methotrexate and 5-fluorouracil, are involved in the folate pathway (27-29).

Interestingly, several studies have shown an interaction between folate and alcohol in breast cancer, indicating that the effect of alcohol on breast cancer incidence may be reduced by dietary folate (29, 30). The role of folate in breast cancer development is complex with indications that folate has a dual nature in tumorigenesis involving mechanisms that are anticarcinogenic and procarcinogenic depending on the timing and dose of folate (31-33). In breast cancer development, a hypothesis involving folate and alcohol could include the anticarcinogenic (e.g., DNA repair capabilities)

properties of folate being diminished by alcohol consumption, which is compatible with the increased breast cancer risk associated with low folate levels occurring only among regular alcohol drinkers (30). However, with regard to survival from breast cancer, it is less clear how folate and alcohol would interact. Perhaps, alcohol diminishes the amount of folate available; thus, the procarcinogenic properties (e.g., increased proliferation) of folate that are proposed to occur later in tumor development are diminished, which is consistent with the timing of the effects of alcohol as suggested to occur later in tumorigenesis. This would be compatible with the finding in our data that alcohol consumption did not lead to tumors with high proliferation as indicated by the Ki-67 index; however, we were unable to directly test a mechanism involving folate because our study did not collect information on dietary factors.

Current hypotheses regarding the role of alcohol in breast cancer etiology include the effect of alcohol on circulating hormone levels (11). Recent findings from the European Prospective Investigation into Cancer and Nutrition cohort showed that levels of dehydroepiandrosterone, free testosterone, and estrone increase as alcohol consumption increases in premenopausal and postmenopausal women. However, no statistically significant increase was observed for estradiol, free estradiol, or sex hormone binding globulin in response to increasing alcohol consumption in premenopausal women (34). Additionally, alcohol has been shown to increase proliferation in ER-positive, but not ER-negative, breast cancer cell lines (35). Our data did not provide support for the role of alcohol in breast cancer survival to involve hormones in that there were no clear associations with hormone-related tumor markers. This would make sense if alcohol acts later in tumorigenesis when some of the tumor features, such as ER/PR status, have already been established.

Additionally, a hypothesis involving insulin-like growth factor has been developed to explain the increased risk of breast cancer associated with alcohol consumption (36). In response to the observation that breast cancer risk did not increase further within the highest level of alcohol consumption (4, 29), Hu hypothesized that insulin-like growth factor levels decrease as a result of impaired liver function due to high consumption of alcohol (29, 37). With the observation that breast cancer risk was associated with high serum levels of insulin-like growth factor in premenopausal women (38), Jones and Clemmons put forth a mechanism for the role of insulin-like growth factor in carcinogenesis involving the mitogenic effects of insulin-like growth factor and suppression of apoptosis, which counteracts the role of wild-type p53 protein (39). It is possible that plasma insulin-like growth factor levels, as mediated by alcohol, are reduced; thus, the role of the wild-type p53 protein is more pronounced in tumorigenesis among women who consume alcohol; therefore (and as our data suggest), variant p53 would play a greater role proportionately in the tumors of alcohol drinkers.

In addition, with the suggestion in our results that wine, but not beer or liquor, may reduce the risk of death among breast cancer patients, we speculate that components of wine such as polyphenols (e.g., reservatrol and cinnamic acid) could be contributory factors. Several long-term epidemiologic cohort studies have shown that wine is associated with a decreased overall mortality and that the effect is not as strong or not observed at all in drinkers of beer or liquor (40). Research investigating the protective effects of wine has mostly centered around mechanisms involved in cardiovascular disease, including the antioxidant effects of polyphenols (41, 42). In cancer, it is possible that the antioxidant properties of the components of wine have a role in decreasing the process of tumorigenesis, although their role in survival would be less clear. Perhaps in breast cancer, the pathway leading to p53-negative tumors and low necrosis levels in tumors are mediated by the antioxidant effects of polyphenol.

Although alcohol may increase the risk of developing breast cancer in young women (1-3, 5), an age group where tumors tend to be aggressive and mortality is high, it does not appear to have an adverse effect on progression. The results from this study suggest that women who consume alcohol before a diagnosis of breast cancer have improved survival compared with nondrinkers, which does not appear to be attributable to differences in stage, screening, treatment, or other confounders. Our results do not exclude the possibility that abstainers are at an increased risk of death due to the potential clustering of confounders for which we were unable to adjust, and may be separate from the biologic pathways, such as inability to metabolize alcohol adequately, as we discussed above. The findings presented here need to be replicated in similar study populations with an emphasis on elucidating mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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References

1. Collaborative Group on Hormonal Factors in Breast Cancer Alcohol, Tobacco and Breast Cancer. Collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234–45.
2. Key J, Hodgson S, Omar RZ, et al. Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. Cancer Causes Control 2006;17:759–70.
3. Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. Cancer Causes Control 1994;5:73–82.
4. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998; 279:535–40.
5. Zhang SM, Lee IM, Manson JE, Cook NR, Willett WC, Buring JE. Alcohol consumption and breast cancer risk in the Women's Health Study. Am J Epidemiol 2007;165:667–76.
6. Fuchs CS, Stampfer MJ, Colditz GA, et al. Alcohol consumption and mortality among women. N Engl J Med 1995;332:1245–50.
7. Thun MJ, Peto R, Lopez AD, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997;337:1705–14.

8. Hebert JR, Hurley TG, Ma Y. The effect of dietary exposures on recurrence and mortality in early stage breast cancer. Breast Cancer Res Treat 1998;51:17–28.
9. McCullough ML, Feigelson HS, Diver WR, Patel AV, Thun MJ, Calle EE. Risk factors for fatal breast cancer in African-American women and White women in a large US prospective cohort. Am J Epidemiol 2005;162:734–42.
10. Saxe GA, Rock CL, Wicha MS, Schottenfeld D. Diet and risk for breast cancer recurrence and survival. Breast Cancer Res Treat 1999; 53:241–53.
11. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. JAMA 2001;286:2143–51.
12. Vaeth PA, Satariano WA. Alcohol consumption and breast cancer stage at diagnosis. Alcohol Clin Exp Res 1998;22:928–34.
13. Li CI, Malone KE, Daling JR. The relationship between various measures of cigarette smoking and risk of breast cancer among older women 65-79 years of age (United States). Cancer Causes Control 2005;16:975–85.
14. Schlesselman JJ. Net effect of oral contraceptive use on the risk of cancer in women in the United States. Obstet Gynecol 1995;85: 793–801.
15. Swanson CA, Coates RJ, Malone KE, et al. Alcohol consumption and breast cancer risk among women under age 45 years. Epidemiology 1997;8:231–7.
16. Brinton LA, Daling JR, Liff JM, et al. Oral contraceptives and breast cancer risk among younger women. J Natl Cancer Inst 1995;87: 827–35.
17. Daling JR, Malone KE, Voigt LF, White E, Weiss NS. Risk of breast cancer among young women: relationship to induced abortion. J Natl Cancer Inst 1994;86:1584–92.
18. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001; 92:720–9.
19. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL. The relation of reproductive factors to mortality from breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11:235–41.
20. Glogovac JK, Porter PL, Banker DE, Rabinovitch PS. Cytokeratin labeling of breast cancer cells extracted from paraffin-embedded tissue for bivariate flow cytometric analysis. Cytometry 1996;24: 260–7.
21. Malone KE, Daling JR, Doody D, O'Brien C, Ostrander EA, Porter P. Family history of breast cancer and BRCA1/BRCA2 in relation to tumor characteristics and mortality in a population-based study of young women with invasive breast cancer. New developments in the epidemiology of cancer prognosis: traditional and molecular predictors of treatment response and survival; 2006 Jan 12.
22. Del Boca FK, Darkes J. The validity of self-reports of alcohol consumption: state of the science and challenges for research. Addiction 2003;98 Suppl 2:1–12.
23. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. Cancer 1999;86:826–35.
24. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. Cancer 1995;76: 275–83.
25. McDonald PA, Williams R, Dawkins F, Adams-Campbell LL. Breast cancer survival in African American women: is alcohol consumption a prognostic indicator? Cancer Causes Control 2002;13:543–9.
26. Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 1993;15:17–35.
27. Dumitrescu RG, Shields PG. The etiology of alcohol-induced breast cancer. Alcohol 2005;35:213–25.
28. Ulrich R, Friend SH. Toxicogenomics and drug discovery: will new technologies help us produce better drugs? Nat Rev Drug Discov 2002;1:84–8.
29. Zhang S, Hunter DJ, Hankinson SE, et al. A prospective study of folate intake and the risk of breast cancer. JAMA 1999;281: 1632–7.
30. Sellers TA, Kushi LH, Cerhan JR, et al. Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. Epidemiology 2001;12:420–8.
31. Kim YI. Will mandatory folic acid fortification prevent or promote cancer? Am J Clin Nutr 2004;80:1123–8.
32. Kotsopoulos J, Medline A, Renlund R, et al. Effects of dietary folate on the development and progression of mammary tumors in rats. Carcinogenesis 2005;26:1603–12.
33. Lewis SJ, Harbord RM, Harris R, Smith GD. Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. J Natl Cancer Inst 2006;98:1607–22.
34. Rinaldi S, Peeters PH, Bezemer ID, et al. Relationship of alcohol intake and sex steroid concentrations in blood in pre- and postmenopausal women: the European Prospective Investigation into Cancer and Nutrition. Cancer Causes Control 2006;17:1033–43.
35. Singletary KW, Frey RS, Yan W. Effect of ethanol on proliferation and estrogen receptor-alpha expression in human breast cancer cells. Cancer Lett 2001;165:131–7.
36. Feigelson HS. Breast cancer: epidemiology and molecular endocrinology. In: Henderson BE, Ponder B, Ross RK, editors. Hormones, genes, and cancer. New York: Oxford University Press; 2003. p. 120–38.
37. Yu H, Berkel J. Do insulin-like growth factors mediate the effect of alcohol on breast cancer risk? Med Hypotheses 1999;52:491–6.
38. Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998;351:1393–6.
39. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. Endocr Rev 1995;16:3–34.
40. Opie LH, Lecour S. The red wine hypothesis: from concepts to protective signalling molecules. Eur Heart J 2007;28:1683–93.
41. Croft KD. The chemistry and biological effects of flavonoids and phenolic acids. Ann N Y Acad Sci 1998;854:435–42.
42. Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. Lancet 1993;341:454–7.