The Effect of Pre-Diagnostic 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, Seattle, WA; 2. University of Washington, Seattle, WA

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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 impact on prognosis after breast cancer, particularly for young women.

Methods: 1286 women diagnosed with invasive breast cancer at or before 45 years of age 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 pre-diagnostic alcohol consumption on the risk of dying.

Results: After adjusting for age and diagnosis year, compared to non-drinkers, women who consumed alcohol in the 5 years prior to diagnosis had a decreased risk of death [>0

to <3 drinks per week: HR(hazard ratio) = 0.7 (95% CI: 0.6-0.95); 3 to <7 drinks per week: RR = 0.6 (95% CI: 0.4-0.8); ≥ 7 drinks per week: RR = 0.7 (95% CI: 0.5-0.9)]. This association was unchanged upon additional adjustment for potential confounders including most notably treatment, stage at diagnosis, and mammogram history. Conclusion: These results suggest that women who consume alcohol prior to a diagnosis of breast cancer have improved survival which does not appear to be attributable to differences in stage, screening or treatment.

INTRODUCTION

While alcohol consumption has been identified as one of the few, known modifiable risk factors for breast cancer,[2;17;22;34;42] 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.[11;36] However, evidence has been sparse and inconsistent for the effect of alcohol consumption on breast cancer mortality in young women.[14;24;29]

There is an indication that alcohol's effects 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.[33;38] 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.[21;30;35] 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 time period for alcohol use was recent use.[22]

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 pre-diagnostic alcohol consumption on the risk of death (overall and breast cancer mortality) in a population-based cohort study of breast cancer patients diagnosed before 45 years of age, 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.[1;6] 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 before age 45; women born after 1944; 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 through December 31, 1992; diagnosed before age 45; women of any race were included. 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 pre-diagnostic 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. This study's protocol 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.[5] Active (i.e. hospital and physician annual follow-up) and passive (i.e. National Death Index) surveillance of vital status of study participants was performed 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 end point 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 end point and censoring women with other causes of death at the time of their death and results were unchanged (see Results section).

Pathology review, testing of tumor samples for prognostic markers, and collection of treatment information

Tumor specimens were available for a centralized pathology review on 1019 (79.2%) of the 1286 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-*erb* B-2 oncogene protein, apoptosis regulatory protein bcl-2, cyclin E protein, s-phase fraction, and p27 protein, as previously described.[4;12] 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 vs. high; for bcl-2, negative and low-intensity stains were categorized as low, while 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 35 years and older) 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 years to 2 years prior to diagnosis. To compute the weekly average number of drinks consumed over this time 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 or more drinks per week; from this point forward, we refer to these categories as non-drinkers, light, moderate, and heavy drinkers,

respectively. A woman who had consumed less than 12 alcoholic beverages in her lifetime or less than one drink per month for 6 months or more was considered a never drinker. Alcohol consumption during the two year period immediately preceding diagnosis was omitted from computations in order to exclude any disease-related changes in alcohol consumption.[35] For the sake of brevity, we will henceforth refer to the 7 to 2 years before diagnosis as the 5 years prior to diagnosis.

The lifetime average weekly intake of alcohol was determined by calculating the average amount of alcohol consumed per week from age 15 until diagnosis. We also investigated alcohol exposure by beverage type: wine, liquor, and beer. One drink was defined as 12 oz of beer, 1.5 oz liquor, and 4 oz 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 prior to this. Interaction terms were investigated using the likelihood ratio test (LRT).

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 (<high school, high school/some college, graduated college), income (<$15,000/year, $15,000 to $50,000/year, >$50,000/year), race (Caucasian, African American, Asian, and other) and OC use (never use, < 10 years of OC use, 10 or more years of use).

The Mantel-Haenszel Chi-Square test was used for all bivariate anlayses. 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 which altered the estimate in the multivariate model by 10% or more 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 (ORs) and 95% CIs. 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 previously shown in this dataset, the highest quartile of BMI ($\geq$25.8 kg/m^2) was associated with an increased risk of mortality compared to the first quartile ($\leq$20.6 kg/m^2); the recency of pregnancy increased the risk of mortality compared to nulliparous women; women with a first or second degree

relative with breast cancer were at a lower risk of mortality compared to women with no family history.[4;5;23] Higher income (≥ $50,000/year) was associated with reduced mortality compared to income of less than $15,000/year. However, education was not associated with mortality. Compared to White women, Black women were found to be at increased risk of mortality while Asian women were not.

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

Compared to women who reported no alcohol consumption in the five 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 on the basis of the average number of drinks consumed [compared to non-drinkers, the risk of death for light drinkers was 0.7 (95% CI, 0.6-0.95); for moderate drinkers was 0.6 (95% CI, 0.4-0.8); for heavy drinkers was 0.7 (95% CI, 0.5-0.9)]. We found similar patterns of risk in relation to average lifetime alcohol consumption.

These and all other hazard ratios 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, namely stage, histologic grade, and treatment factors, did not change results (compared to non-drinkers,

HR = 0.7 [95% CI, 0.5-0.9] for light drinkers; 0.5 [95% CI, 0.3-0.7] for moderate drinkers; and 0.6 [95% CI, 0.4-0.8] for heavy drinkers). Also, there was no evidence of significant effect modification by BMI, 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 (RR= 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 a reduced odds of having a tumor with high tumor necrosis levels (OR =0.6 [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 (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 (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 to non-drinkers, HR = 0.7 [95% CI, 0.6-0.96] for light drinkers; 0.5 [95% CI, 0.4-0.8] for moderate drinkers; and 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; HR = 0.7 [95% CI, 0.5-0.9] for heavy drinkers). Additionally, because this study retrospectively ascertained breast cancer cases in 1983 – 1985, we repeated analyses excluding cases diagnosed before 1986 and again found our results were unchanged (HR = 0.7 [95% CI, 0.6-0.96] for light drinkers; 0.6 [95% CI, 0.4-0.8] for moderate drinkers; and 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; 0.6 [95% CI, 0.4-0.96] for moderate drinkers; and 0.8 [95% CI, 0.5-1.1] for heavy drinkers; in the study conducted with women diagnosed from 1990-1992, HR = 0.7 [95% CI, 0.5-1.0] for light drinkers; 0.5 [95% CI, 0.3-0.95] for moderate drinkers; and 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; 0.5 [95% CI, 0.3-0.7] for moderate drinkers; and 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 five

years, 43.5% of the non-interviewed cases and 14.5% of the interviewed cases were deceased. To the extent that non-interviewed cases differ from interviewed cases on the basis of 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 impact 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 examine whether dietary factors may modify the effect of alcohol consumption on risk of death. Also, since this study was performed 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.[7] 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, and thus misclassification within different categories of use would have minimal impact on the interpretation of our results. Because any misclassification resulting from this is likely to be non-differential, 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 pathological review and lab analyses performed on tissue samples.

Our results indicate that young women who consumed alcohol prior to a diagnosis of breast carcinoma were at a decreased risk of mortality compared to 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. A number of 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 Saxe, et al, while the risk of death among premenopausal breast cancer cases associated with alcohol consumption did not reach statistical significance (HR = 0.41 [0.01-16.35] per 2 drinks/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 (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=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 to the first quartile of alcohol consumption).[15] While 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). Lastly, Zhang, et al, observed a non-statistically significant reduction in risk of death for women consuming 4 grams or more of alcohol per day (risk of death 0.7 [0.3-1.5]) in a dataset of 698 breast cancer patients aged 55-69 years at baseline.[40]

Some studies with results which conflict with ours include 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 pre-menopausal women.[14] McDonald, et al, in a hospital-based cohort of 125 post-menopausal African American breast cancer cases, found pre-diagnostic consumption of at least one 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 pre-menopausal and post-menopausal breast cancer development differs,[27] and thus potentially alcohol's impact on tumorigenesis

differs among pre- and post-menopausal women which would create inconsistencies across studies with different age ranges.

Previous studies have not investigated the role of pre-diagnostic alcohol use on tumor characteristics in young women. Our data indicate that alcohol's role 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 P450 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. [8;37;41]

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.[31;41] The role of folate in breast cancer development is complex with indications that folate has a dual nature in tumorigenesis involving mechanisms that are anti- and pro- carcinogenic depending on the timing and dose of folate.[18-20] In breast cancer development, a hypothesis involving folate and alcohol could include folate's anti-carcinogenic (e.g. DNA repair capabilities) properties 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.[31] 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, and thus the pro-carcinogenic 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 alcohol's effects 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 alcohol's role in breast cancer etiology include the effect of alcohol on circulating hormone levels.[33] Recent findings from the Epic Cohort showed that levels of dehydroepiandrosterone (DHEAS), free testosterone, and estrone increase as alcohol consumption increases in pre- and post-menopausal women. However no statistically significant increase was observed for estradiol, free estradiol, or sex hormone binding globulin (SHBG) in response to increasing alcohol consumption in premenopausal women.[28] Additionally, alcohol has been shown to increase proliferation

in ER+, but not ER-, breast cancer cell lines.[32] 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 (IGF) has been developed to explain the increased risk of breast cancer associated with alcohol consumption.[9] In response to the observation that breast cancer risk did not increase further within the highest level of alcohol consumption,[34;41] Hu hypothesized that IGF levels decrease as a result of impaired liver function due to high consumption of alcohol.[39;41] With the observation that breast cancer risk was associated with high serum levels of IGF in pre-menopausal women,[13] Jones and Clemmons put forth a mechanism for IGF's role in carcinogenesis involving IGF's mitogenic effects and suppression of apoptosis, which counteracts the role of wildtype p53 protein.[16] It is possible that plasma IGF levels, as mediated by alcohol, are reduced and thus, the role of the wildtype p53 protein is more pronounced in tumorigenesis among women who consume alcohol; therefore, (and as our data suggests) variant p53 would play a greater role proportionately in the tumors of alcohol drinkers.

Also, 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 demonstrated 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.[26] Research investigating the protective effects of wine has mostly centered around mechanisms involved in cardiovascular disease, including the antioxidant effects of polyphenols.[3;10] In cancer it is possible that the antioxidant properties of wine's components 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 polyphenol's antioxidant effects.

While alcohol may increase the risk of developing breast cancer in young women, [2;17;22;42] 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 prior to a diagnosis of breast cancer have improved survival compared to non-drinkers 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, we discussed above. The findings presented here need to be replicated in similar study populations with an emphasis on elucidating mechanisms.

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TABLES

Table 1. Relationship of Demographic and Tumor Characteristics to the Risk of Dying among Women Diagnosed with Breast Cancer under 45 Years of Age from 1983 to 1992

		Alive	Dead	HR[1]	95% CI	
Age at diagnosis	< 35	179 (65.1)	96 (34.9)	1.0		
	≥ 35	743 (73.5)	268 (26.5)	0.9	0.7	1.1
Diagnosis Year	< 1989	358 (65.3)	190 (34.7)	1.0 (ref)		
	≥ 1989	564 (76.4)	174 (23.6)	0.8*	0.6	1.0**
Ever use of Mammogram[2]	No	506 (67.1)	248 (32.9)	1.0 (ref)		
	Yes	416 (78.2)	116 (21.8)	0.7*	0.6	0.9
Chemotherapy[3]	No	299 (75.3)	98 (24.7)	1.0 (ref)		
	Yes	617 (70.0)	264 (30.0)	0.9	0.7	1.1
Radiotherapy[3]	No	414 (70.2)	176 (29.8)	1.0 (ref)		
	Yes	502 (73.0)	186 (27.0)	0.9	0.7	1.1
Hormone Therapy	No	551 (71.0)	225 (29.0)	1.0 (ref)		
	Yes	300 (70.9)	123 (29.1)	1.0	0.9	1.0
Stage	Local	608 (82.5)	129 (17.5)	1.0 (ref)		
	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	≤ 2 cm	527 (80.6)	127 (19.4)	1.0(ref)		
	>2 – 5 cm	326 (65.3)	173 (34.7)	1.9*	1.5	2.4
	> 5 cm	51 (50.0)	51 (50.0)	3.0*	2.2	4.2
Nodal Status	Negative	615 (82.3)	132 (17.7)	1.0 (ref)		
	Positive	302 (56.0)	219 (42.0)	1.5*	1.4	1.6
BMI	1st quartile	241 (75.6)	78 (24.4)	1.0 (ref)		
	2nd	230 (72.8)	86 (27.2)	1.1	0.8	1.6
	3rd	238 (74.3)	82 (25.6)	1.2	0.9	1.6
	4th	205 (63.9)	116 (36.1)	1.9*	1.4	2.5
Recency of Pregnancy	Nulliparous	251 (74.9)	84 (25.1	1.0 (ref)		
	5+ yrs	529 (74.0)	186 (26.0)	1.1	0.8	1.4
	2 - < 5 yrs	97 (67.8)	46 (32.2)	1.3	0.9	1.9
	< 2 yrs	45 (48.9)	47 (51.1)	2.2*	1.5	3.0

1st or 2nd degree relative with breast cancer	No	359 (69.2)	160 (30.8)	1.0 (ref)		
	Yes	401 (75.8)	128 (24.2)	0.8*	0.6	1.0**
Smoking	Never	464 (71.1)	189 (28.9)	1.0 (ref)		
	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 (ref)		
	Black	12 (54.6)	10 (45.4)	2.4*	1.2	4.5
	Asian/Pac Isl.	31 (77.5)	9 (22.5)	1.0	0.5	2.0
Income	<15,000	85 (65.9)	44 (34.1)	1.0 (ref)		
	15000-50000	483 (69.1)	216 (30.9)	0.9	0.7	1.3
	≥ 50000	349 (77.7)	100 (22.3)	0.7*	0.5	1.0**
Education	< High School	30 (71.4)	12 (28.6)	1.0 (ref)		
	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

* statistically significant HR

** 1.0 due to rounding, CI excludes 1.0

1 adjusted for age, mammogram, and diagnosis year, except as noted

2 adjusted for age and diagnosis year

3 adjusted for age, diagnosis year, nodal status, stage, and tumor size

Table 2. Relationship between Alcohol Consumption and Factors Observed to Influence the Risk of Dying among Women Diagnosed with Breast Cancer under 45 Years of Age from 1983 to 1992

		Alcohol consumption status in the 5 years prior to diagnosis		
		Non-Drinker[1]	**Drinker**	**p-value**
Age at diagnosis	< 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)	
OC use	Never	99 (34.1)	191 (65.9)	<0.0001
	< 10 yrs	199 (24.3)	621 (75.7)	
	≥10 yrs	26 (14.9)	148 (85.1)	
Diagnosis Year	< 1989	93 (17.0)	454 (83.0)	<0.0001
	≥ 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/Pac Islander	23 (57.5)	17 (42.5)	
Education	< 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
	15000-50000	191 (27.4)	506 (72.6)	
	≥ 50000	98 (21.8)	351 (78.2)	
Recency of Pregnancy	Nulliparous	65 (19.4)	270 (80.6)	0.84
	5+ yrs	209 (29.3)	505 (70.7)	
	2 - < 5 yrs	33 (23.1)	110 (76.9)	
	< 2 yrs	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)	
BMI quartile	1st	70 (22.0)	248 (78.0)	0.0002
	2nd	59 (18.7)	256 (81.3)	
	3rd	83 (25.9)	237 (74.1)	
	4th	106 (33.0)	215 (67.0)	

1. Non-drinkers includes those who did not drink during the 5 year 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 under 45 Years of Age from 1983 to 1992

Average Weekly Alcohol Consumption as drinks per week	Alive	Dead	HR[1]	95% CI	
5 Years Prior to Diagnosis					
Non-drinkers[2]	216 (67.1)	106 (32.7)	1.0 (ref)		
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 (ref)		
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 (ref)		
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 drinker					
Non-liquor drinkers	353 (70.9)	145 (29.1)	1.0 (ref)		
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 (ref)		
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

* statistically significant HR

** due to rounding, p-value < 0.05

[1] adjusted for age, diagnosis year, mammography

[2] Non-drinkers include those who did not drink during the 5 year period, as well as those who did not drink in their lifetime

Table 4. Relationship of Average Weekly Alcohol Consumption in 5 Years Prior to Diagnosis to Tumor Characteristics

Alcohol Consumption[1]	**Tumor Characteristic**		**OR (95% CI)**[2]
	ER		
	Positive	Negative	OR
Non-drinkers	148 (27.7)	92 (25.1)	1.0 (ref)
Drinkers	386 (72.3)	274 (74.9)	1.1 (0.8-1.4)
	PR		
	Positive	Negative	
Non-drinkers	150 (27.6)	89 (25.1)	1.0 (ref)
Drinkers	394 (72.4)	266 (74.9)	1.0 (0.7-1.4)
	Tumor Necrosis		
	None-Intermediate	High	
Non-drinkers	222 (25.5)	35 (33.3)	1.0 (ref)
Drinkers	650 (74.5)	70 (66.7)	0.6* (0.4-1.0**)
	Ki-67		
	Low	High	
Non-drinkers	140 (26.0)	98 (27.8)	1.0 (ref)
Drinkers	399 (74.0)	255 (72.2)	0.9 (0.7-1.3)
	BCL-2		
	High	Low	
Non-drinkers	109 (28.9)	128 (24.8)	1.0 (ref)
Drinkers	266 (70.9)	389 (75.2)	1.3 (0.9-1.7)
	P53		
	Negative	Positive	
Non-drinkers	132 (24.6)	105 (29.3)	1.0 (ref)
Drinkers	405 (75.4)	254 (70.8)	0.7 (0.5-1.0)
	% S phase		
	Low	High	
Non-drinkers	80 (24.6)	92 (28.1)	1.0 (ref)
Drinkers	245 (75.4)	235 (71.9)	0.8 (0.5-1.1)
	Stage		
	Local	Regional/Distant	
Non-drinkers	183 (24.9)	137 (25.7)	1.0 (ref)
Drinkers	551 (75.1)	396 (74.3)	1.1 (0.8-1.4)
	Grade		
	Low/Intermediate	High	
Non-drinkers	137 (25.3)	116 (26.9)	1.0 (ref)
Drinkers	405 (74.7)	315 (73.1)	1.2 (0.9-1.6)

* statistically significant OR
** due to rounding, p-value < 0.05
[1] during the 5 year period prior to diagnosis; non-drinkers include those who did not drink during the 5 year period
[2] adjusted for age, diagnosis year, smoking status