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Alcohol and Breast Cancer: A Cohort Study[1]

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The relation between alcohol consumption and several causes of death, including breast cancer, was examined in a population of 581, 321 women enrolled in a prospective study in 1959 and followed for 12 years. Women who drank occasionally had about the same breast cancer mortality rate as nondrinkers; those who drank one to four drinks per day had SMRs 7–26% higher; five drinks per day, 1.89; and six or more drinks per day, 1.65. The two highest-consumption groups' risks were significantly higher than those of nondrinkers after multivariate adjustment for several breast cancer risk factors. Distinctive dose–response relationships were observed for two known alcohol-related conditions: cirrhosis of the liver and cancer of the aero-digestive tract, suggesting that results for other causes are not seriously biased by misclassification of drinking habits. Death rates from all causes combined were elevated for drinkers of three or more drinks per day. Whether or not the association of elevated breast cancer death rates ultimately turns out to be causal, there is ample reason to continue to warn the public against excessive drinking.

INTRODUCTION

Consumption of moderate quantities of alcohol has been found to be associated with an increased risk of breast cancer in a large number of studies (7–10, 12, 14, 16, 19), but not in others (1–3, 6, 13, 18). Data from most of the published case–control and cohort studies on alcohol and breast cancer are presented in this article, as well as data from some studies which have not been previously published (3, 6). The major interest focuses on the risk of "moderate" drinking, defined in some studies as 3–9 g of ethanol per week, or up to one drink of beer, wine, or whiskey per week.

We present here data on alcohol consumption in relation to breast cancer mortality rates from a large prospective study of more than one million men and women enrolled in the American Cancer Society's study 1959–1972.

It is important not only to know whether findings of an increased risk of breast cancer in moderate drinkers are confirmed, but also to assess whether moderate drinking increases (or decreases) the risk for other major causes of death and for total deaths. Consequently, one goal of our analysis is to examine the effect of moderate alcohol consumption on total death rates.

METHODS

From October 1959 through February 1960 more than one million men and women in 25 states were enrolled in a prospective epidemiological study of cancer

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mortality (4). Efforts were made to include all segments of the population except migrant workers and others who could not readily be traced. All subjects were required to be over 30 years of age, but generally were over 45 years old. Enrollment was by family group, with at least one member of the family age 45 years or over. Each subject was asked to complete a detailed, confidential questionnaire containing questions about family history, individual medical history, present physical complaints, occupation, and many personal habits including tobacco use and alcohol consumption.

Some 68,000 American Cancer Society volunteers collected the questionnaires and then reported periodically whether each enrolled person was alive or dead. If an enrollee was reported to have died, a death certificate was requested from the appropriate state health department. Underlying and contributing causes of death were coded according to the rules of the 7th Revision of the International Classification of Diseases. Tracing of subjects was completed annually for 6 years, and resumed in the 12th and 13th years, at which time 92.2% of the original cohort was completely accounted for. Additional details of the study procedures have been published previously (4, 5).

Subjects were asked how many cups, glasses, or drinks of various liquids (milk, coffee, tea, soft drinks) they consumed per day. They were also asked how many drinks of beer, wine, or whiskey they consumed per day. In this report alcohol consumption is reported in terms of whiskey equivalents (WE). One glass of beer is taken to be equivalent to one glass of wine and to one shot of whiskey. A "regular drinker" was defined as anyone who reported consuming at least one drink of alcohol per day in any form on the initial questionnaire; women who checked "occasional" for any of the three types of beverages, and who did not otherwise indicate regular alcohol consumption, were classified as "occasional drinkers"; women reporting no alcohol use were classified as "nondrinkers."

The standardized mortality ratio (SMR) is the statistical procedure used to compare death rates in various strata. Person-years of exposure (PYE) to risk of death from each cause of interest are calculated for each individual, beginning July 1, 1960, until date of death, withdrawal alive on June 30, 1972, or loss to follow-up. A cohort age analysis is used. In this type of analysis, PYE are stratified into 13 5-year age groups (which are equivalent to 5-year birth cohorts, since all subjects were enrolled at about the same time). Age-specific death rates among nondrinkers, the reference population, are multiplied by PYE in the alcohol consumption strata of interest to obtain expected numbers of deaths in those strata. The SMR is the ratio of the sum of observed deaths divided by the sum of expected deaths, with each figure summed over the 13 age strata. Confidence intervals are calculated using an approximation to the Poisson distribution (15).

In addition, relative risks for breast cancer in relation to alcohol consumption were computed via logistic regression in order to control for a variety of known and suspected risk factors for breast cancer, such as age of first pregnancy, age at menopause, and food consumption patterns.

RESULTS

The data in this report are based on the cohort's experience during the period,

July 1, 1960 to June 30, 1972. Women who gave a history of breast cancer at the time of enrollment were excluded from this study in order to reduce possible bias from inclusion of prevalent cases of breast cancer. Over the indicated 12-year period, 581,321 women contributed 6,139,265 person-years, and 73,387 deaths were reported. Within this population, 80.4% of the women were classified as nondrinkers, 5.7% as occasional drinkers, and 13.9% as regular drinkers.

Table 1 shows the standardized mortality ratios for four selected causes, as well as for total deaths, by drinking habit. Nondrinkers are the reference group, with an SMR of 1.00 by definition. The first two causes of death presented in Table 1 show the SMRs for cirrhosis of the liver and for "aerodigestive" cancers, that is, cancers of the mouth, pharynx, larynx, and esophagus combined. This group of cancers and cirrhosis of the liver are all well-established as alcohol-related, and one way of validating the use of the alcohol questions would be to confirm these previously known relationships in this cohort.

As can be seen in Table 1, the SMRs for death from cirrhosis of the liver and for aerodigestive cancers increased with the number of drinks per day, rising to 22.87 for cirrhosis death and 18.91 for cancer death in women who drank six or more WE/day. These distinctive dose–response relationships serve as ample validation of the alcohol questions specifically, and also justify the more general use of this cohort to study the relationship between alcohol consumption and cancer risk.

Women who drank at most one drink per day had a lower mortality rate for all-causes combined than nondrinkers (0.89 for occasional and 0.95 for one drink per day). The mortality ratios increased from 1.15 for two per day drinkers to about 1.5 for those who drank four or more drinks per day. The mortality ratios for coronary heart disease showed no relation to drinking except for a peculiar increase to 1.40 for those who drank four drinks per day. Other than this group all drinking categories had SMRs ranging from 0.85 to 1.01.

The final entry in Table 1 shows the SMRs for breast cancer by drinking habit; the data are illustrated in Fig. 1 as well. Occasional drinkers had about the same death rate as nondrinkers. Women who drank one to four drinks per day had

TABLE 1
STANDARDIZED MORTALITY RATIOS BY ALCOHOL CONSUMPTION FOR SELECTED CAUSES OF DEATHS: CANCER PREVENTION STUDY I 1960–1972

Cause of death		Alcohol consumption[a]							
		None	Occasional	1	2	3	4	5	6+
Cirrhosis of liver	SMR	1.00	1.05	1.99	5.98	11.49	12.21	17.33	22.87
	Deaths	320	21	50	75	50	26	13	34
Cancer of buccal cavity, larynx and esophagus	SMR	1.00	1.09	1.86	4.85	6.01	6.28	9.78	18.91
	Deaths	197	12	26	33	14	7	4	16
Total deaths	SMR	1.00	0.89	0.95	1.15	1.34	1.55	1.47	1.56
	Deaths	57,323	2,504	3,552	1,995	750	409	146	344
Coronary heart disease	SMR	1.00	0.87	0.85	1.01	0.89	1.40	0.90	1.00
	Deaths	17,349	677	876	457	129	90	23	60
Breast cancer	SMR	1.00	0.97	1.18	1.07	1.23	1.26	1.89	1.65
	Deaths	2,334	153	236	110	45	23	12	20

[a] Whiskey equivalents per day: 1 glass beer = 1 glass wine = 1 shot whiskey.

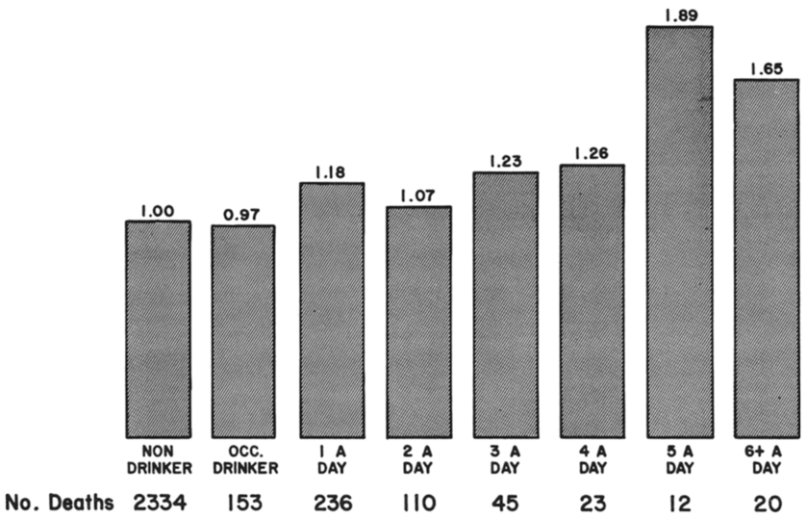

FIG. 1. Mortality ratios by drinking habits: Breast cancer.

somewhat elevated SMRs, in the range 7–26% higher. Those who drank five drinks per day had an SMR of 1.89; six or more per day, 1.65.

These initial observations, especially with regard to the higher breast cancer risks among those who drank at least 5 WE per day, indicated that a more elaborate analysis should be done, one which took into account known risk factors for breast cancer as possible confounders. Table 2 shows the relationship of drinking

TABLE 2
PERCENTAGE OF REGULAR DRINKERS ACCORDING TO BREAST CANCER RISK FACTORS AND OTHER VARIABLES

	% Drinkers		% Drinkers
Education		Eat meat	
Not a high school graduate	9.5	<2–4 times per week	9.6
H.S. graduate	14.4	2–4 times per week	9.7
College	17.8	5–7 times per week	14.8
Breast cancer in mother or sister		Consume fruits and fruit juice	
		<3 times per week	14.4
Yes	16.3	3–6 times per week	12.0
No	13.7	7 times per week	14.6
Age at first pregnancy		Residence	
<20 years	9.4	Metropolitan area	17.8
20–24 years	13.1	Nonmetropolitan area	7.7
25–29 years	15.7	Smoking habit	
30+ years	15.1	Never smoked regularly	7.3
Never pregnant	15.3	Current or exsmoker of cigarettes	26.9
Previous breast operation			
Yes	16.0		
No	13.8		

to a number of risk factors for breast cancer, as well as educational level, place of residence, and smoking habit. Drinking was highest among college-educated women, and those with a history of a previous breast operation. It was also high among women who ate meat five or more times per week, those who lived in metropolitan areas, and particularly high among smokers. Drinking was lowest among women whose first pregnancy was prior to age 20.

Table 3 shows the relative risks (RR) for breast cancer in relation to daily alcohol consumption, as determined via a logistic regression analysis in which many of the possible confounding factors identified in the preceding table were controlled for: age, education, age at first pregnancy, family history of breast cancer, meat consumption, and cigarette smoking. The initial SMRs, controlled for age only, are also shown, along with 95% confidence intervals for both the SMRs and RRs. Controlling for five additional variables besides age produced little meaningful change in the SMRs, except that the RR among women who drank five drinks per day increased to 2.10 and become statistically significant. Otherwise the standardized mortality ratios are virtually identical to the adjusted RRs. The risks for one drink per day and for six or more per day were significant in both sets of analyses.

It is possible that some subjects who classified themselves as nondrinkers did so because they were ill when they entered the study. The logistic regression analysis was therefore repeated, but restricted to those who said they were not sick when they entered the study and had no history of heart disease, stroke, or cancer. The RRs in this analysis were very close to those of the original logistic regression displayed in Table 3.

It has been suggested in at least one study that the greatest relationship between alcohol and breast cancer is in lean women (16). In a previous analysis within this cohort we found that women 20% or more underweight had a mortality ratio for breast cancer of 0.82 compared with women of average weight (11). Table 4 shows

TABLE 3
STANDARDIZED MORTALITY RATIOS FOR BREAST CANCER IN RELATION TO ALCOHOL CONSUMPTION

	Controlled for age only		Logistic regression[b]	
Alcohol consumption[a]	SMR	95% confidence interval	RR	95% confidence interval
None	1.00	—	1.00	—
Occasional	0.97	0.82–1.13	0.96	0.82–1.13
1 per day	1.18	1.04–1.34	1.18	1.03–1.36
2 per day	1.07	0.88–1.29	1.06	0.86–1.30
3 per day	1.23	0.90–1.65	1.28	0.95–1.74
4 per day	1.26	0.80–1.89	1.36	0.90–2.07
5 per day	1.89	0.98–3.31	2.10	1.18–3.72
6+ per day	1.65	1.01–2.55	1.60	1.00–2.56

[a] Whiskey equivalents per day: 1 glass beer = 1 glass wine = 1 shot whiskey.
[b] Controlled for age, education, age at first pregnancy, family history of breast cancer, meat consumption, and cigarette smoking.

TABLE 4
RELATIVE RISKS (RR) FOR BREAST CANCER BY ALCOHOL CONSUMPTION AND RELATIVE WEIGHT[a,b]

	Relative weight					
	<90		90–119		120+	
Alcohol consumption[c]	R.R.	95% confidence interval	R.R.	95% confidence interval	R.R.	95% confidence interval
None	1.00 (339)	—	1.00 (1,163)	—	1.00 (191)	—
Occasional	0.99 (38)	(0.71–1.39)	0.95 (102)	(0.86–1.29)	1.01 (10)	(0.52–1.88)
1	1.01 (49)	(0.73–1.36)	1.18 (125)	(0.98–1.42)	1.26 (9)	(0.65–2.47)
2	1.01 (27)	(0.69–1.50)	0.99 (54)	(0.75–1.80)	1.44 (5)	(0.59–3.52)
3+	1.50 (27)	(1.01–2.23)	1.36 (53)	(1.22–1.80)	1.31 (4)	(0.48–03.53)

Note. No. deaths shown in parentheses.

[a] Restricted to women who were not sick at time of enrollment and who did not give a history of heart disease, cancer, or stroke.

[b] Controlled via logistic regression for age, age at first pregnancy, family history of cancer, and education.

[c] Whiskey equivalents per day: 1 glass beer = 1 glass wine = 1 shot whiskey.

the results of an analysis in which women in different relative weight categories are considered separately. Relative weight in this study is recorded weight divided by the average weight for all study subjects of the same height, age (5 years), and sex, times 100. Relative weight is divided into three groups: <90, 90–119, and 120 lbs or greater. The analysis is restricted to those who said they were not sick on enrollment and did not have a history of heart disease, stroke, or cancer. These conditions would affect the recorded weight on enrollment. There is not much difference in RRs among occasional drinkers in the average- and below-average-weight groups. As can be seen from Table 4, there were too few observations among overweight women (relative weight 120 lbs or more) to permit meaningful statistical evaluation.

DISCUSSION

These data are consistent with those of a number of previous reports that showed higher breast cancer risk among women who drank alcohol regularly. In this study, the increased risk was observed mainly in women who drank at least five WE per day, and was little affected by other risk factors for breast cancer. This dosage is, however, considerably higher than the three to nine drinks per week reported by Willett *et al.* (19) to lead to an RR of 1.3.

The "nondrinkers" category presumably included some exdrinkers and some who drank only rarely or occasionally. However, drinking habits are rather stable during adult life, and an analysis of current and past drinking habit of a sample of

women enrolled in 1982 in the new American Cancer Society prospective study (17) showed that only 5.7% of them would be misclassified if only the current habit were analyzed.

Demonstration of increased risk is a necessary factor in establishing a causal relationship, but it is not a sufficient one, especially when the association involved is a "weak" one in epidemiological terms. It is also important to consider whether the population itself is an appropriate one for this type of study, and to examine the validity of the alcohol consumption data within that population. The demonstration of dose–response relationships for "traditionally" alcohol-related causes of death (cirrhosis of the liver and aerodigestive cancers) is a strong argument for assuming validity of the self-reported alcohol consumption levels in this study group. However, the actual proportion of regular drinkers among these women was quite small (13.9%). Furthermore, even though the overall analysis was based upon 12 years of follow-up, drinking status was classified according to the 1959 baseline questionnaire, and changes in habit over the following decade were not taken into account.

Despite the concordance of this study with many others, we believe considerably more investigation needs to be done before a causal relationship can be considered demonstrated. Other authors have expressed similar reservations (7–9). Nevertheless, in view of the potential public health importance which a causal relationship would imply, further studies need to be undertaken. We are currently conducting a 6-year follow-up study of 1.2 million men and women which was begun in 1982 (17), and will report on any alcohol–breast cancer relationship in due course. Even if the excess breast cancer risk were eventually shown to be smaller than has been observed, or even to be an artifact, the very real increase in risk of death in regular drinkers from all causes combined would serve to underscore the importance of the long-standing recommendation by the American Cancer Society and other organizations in favor of moderating alcohol consumption.

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