The Association of Alcohol Consumption with Coronary Heart Disease Mortality and Cancer Incidence Varies by Smoking History

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OBJECTIVE: To evaluate the effect of alcohol on coronary heart disease (CHD), cancer incidence, and cancer mortality by smoking history.

DESIGN/SETTING: A prospective, general community cohort was established with a baseline mailed questionnaire completed in 1986.

PARTICIPANTS: A population-based sample of 41,836 Iowa women aged 55–69 years.

MEASUREMENTS: Mortality (total, cancer, and CHD) and cancer incidence outcomes were collected through 1999. Relative hazard rates (HR) were calculated using Cox regression analyses.

MAIN RESULTS: Among never smokers, alcohol consumption ($\geq$ 14 g/day vs none) was inversely associated with age-adjusted CHD mortality (HR, 0.40; 95% confidence interval [CI], 0.19 to 0.84) and total mortality (HR, 0.71; 95% CI, 0.55 to 0.92). Among former smokers, alcohol consumption was also inversely associated with CHD mortality (HR, 0.45; 95% CI, 0.23 to 0.88) and total mortality (HR, 0.78; 95% CI, 0.62 to 0.97), but was positively associated with cancer incidence (HR, 1.25; 95% CI, 1.03 to 1.51). Among current smokers, alcohol consumption was not associated with CHD mortality (HR, 1.05; 95% CI, 0.73 to 1.50) or total mortality (HR, 1.07; 95% CI, 0.92 to 1.25), but was positively associated with cancer incidence (HR, 1.30; 95% CI, 1.10 to 1.54).

CONCLUSIONS: Health behavior counseling regarding alcohol consumption for cardioprotection should include a discussion of the lack of a decreased risk of CHD mortality for current smokers and the increased cancer risk among former and current smokers.

KEY WORDS: ethanol; coronary disease; neoplasms; smoking; mortality.
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Over the last 2 decades, at least 34 large prospective cohorts around the world have examined the association of alcohol consumption with coronary heart disease (CHD) incidence or mortality.[1–34] Moderate alcohol intake in the form of beer, wine, or spirits consistently appears to reduce the risk from CHD morbidity and mortality by 10%–70% in ecologic, case-control, and cohort studies.[35,36] While fewer studies have examined the association of alcohol consumption with CHD morbidity or mortality in women,[1,2,4,7,9,10,16,24,26,29,32,34,37,38] a majority of these have suggested an inverse association.[4,10,16,24,26,34,37,38] Few studies have evaluated the differing effect of alcohol consumption on CHD morbidity and mortality by smoking history (interaction) among males,[7,23,28,39] females,[7,10,24] or a combined group,[17,40] and no clear interactions have been reported.

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While evidence suggests alcohol consumption is associated with a decreased risk for CHD mortality in women, alcohol is associated with an increased risk for cancer.[9,41–48] The International Agency for Research on Cancer has labeled alcohol a Group 1 carcinogen, which indicates that there is sufficient evidence to suggest that exposure in humans is carcinogenic.[49] Consequently, consensus panels and organizations differ on their recommendations for alcohol consumption.[47,50] If cigarette smoking negates any beneficial effect of alcohol consumption on CHD mortality in women, then the increased risk of cancer may outweigh the benefits of alcohol consumption. Health behavior counseling including alcohol consumption for cardioprotection would, therefore, need to be based upon knowledge of patient smoking history.

In order to clarify the association between smoking history and alcohol consumption with the risk for CHD mortality, cancer mortality, and cancer incidence in women, we analyzed a population-based prospective cohort of older women.

METHODS

Study Cohort

The Iowa Women's Health Study (IWHS) is a prospective cohort study of risk factors for cancer and chronic diseases in women initially aged 55–69 years.[51,52] In January 1986, a questionnaire was mailed to 99,826 women randomly selected from a list of women with a valid Iowa driver's license in 1985. The 41,836 respondents (42.7% response rate) form the cohort under observation. The cohort was 98% white and 65% lived in towns of less than 10,000 inhabitants. Compared to nonrespondents, respondents were on average 3 months younger and more likely to live in rural areas. The nonrespondents have been demonstrated to have a slightly higher mortality rate from smoking-related diseases than the respondents.[53]

The baseline survey ascertained demographics, educational history, weight history, smoking history, hormone replacement status, reproductive history, and physical activity. Usual diet in the year prior to the survey was assessed using a semiquantitative food frequency questionnaire.[54] Nutrient intakes were then estimated using a semiquantitative food frequency questionnaire program and nutrient database developed for the Nurses' Health Study.[55] Assessment of usual alcohol consumption included dose-frequency and type. Categories of intake ranged from "never or less than once per month" to "6 or more times per day." Participants reported how often over the last year they had consumed each of the following: beer (1 glass, bottle, or can), red wine (4 oz glass), white wine (4 oz glass), and liquor (1 drink or shot). Grams per day of alcohol were calculated by multiplying the frequency that each beverage was consumed by the ethanol content in grams (g): 13.5 g/drink for beer, 11 g/drink for red and white

Table 1. Baseline Characteristics of Cohort Stratified by Smoking and Alcohol Use, Iowa Women's Health Study, 1986

Risk factors	Never Smokers		
	None $n=12,289$	<14 g/day $n=6,906$	≥ 14 g/day $n=771$
	Mean ± SD		
Age, y	61.9 ± 4.2	61.3 ± 4.1	61.2 ± 4.1
Waist-to-hip ratio	0.84 ± 0.08	0.82 ± 0.08	0.83 ± 0.08
BMI (kg/m^2)	27.7 ± 5.2	26.5 ± 4.4	25.9 ± 4.2
Total calories (kcal/day)	1,786 ± 595	1,857 ± 603	1,959 ± 608
Alcohol (g/day)			
Mean	0	3.4 ± 3.2	26.4 ± 15.0
Median	0	2.0	19.0
Fruit/veg (g/day)	557.3 ± 299.2	577.1 ± 293.1	545.5 ± 276.0
Red meat (g/day)	91.8 ± 63.6	92.1 ± 62.8	94.3 ± 57.1
Whole grains (servings/wk)	11.7 ± 9.0	11.8 ± 8.6	10.3 ± 8.1
Cholesterol (mg/day)	273.6 ± 133.7	282.1 ± 128.0	288.7 ± 145.4
Vitamin E (mg/day)	66.8 ± 149.3	68.3 ± 148.9	57.7 ± 139.5
	Percent Distribution		
Married	78	81	84
>High school Education	37	43	45
Pack-years			
1–19	—	—	—
20–39	—	—	—
40+	—	—	—
Low physical activity	47	40	41
History of hypertension	37	32	34
History of diabetes	7	2	3
Hormone replacement therapy			
Current	10	13	13
Former	25	25	27
Never	65	62	60
Vitamin supplement Use	62	66	65

BMI, body mass index; SD, standard deviation.

wine, and 16 g/drink for liquor. This methodology has been shown to be reproducible in a smaller subset of this cohort (Pearson correlations >0.98 across 3 repeat food frequency questionnaires).[56]

Cohort Follow-up

We have followed this cohort for cancer incidence by annual computer linkage of participant identifiers to the Iowa Health Registry, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[57] Information on the vital status of the cohort was collected by several methods. Date and cause of death were determined by annual computer linkage of participant identifiers to a database of Iowa death certificates at the Iowa Health Registry. Decedents outside of Iowa (along with date and cause of death) were identified through mailed follow-up surveys in 1987, 1989, 1992, and 1997, and for survey nonrespondents, through linkage to the National Death Index. Underlying causes of deaths were coded according to the International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10.[58] We estimate that 99% of deaths in the cohort have been identified.

Population for Analysis

We excluded women at baseline who reported a history of cancer or prior cancer chemotherapy ($n=3,881$); women who left 30 or more items blank on the dietary questionnaire or had implausibly high or low total energy intake (less than 600 or more than 5,000 kcal/day; $n=3,096$); women who were not postmenopausal ($n=569$); and women who self-reported a history of heart disease or heart attack ($n=5,116$). After the above exclusions (not mutually exclusive), a total of 30,518 women remained for analysis.

Statistical Methods

In the cancer incidence analysis, age time scales were constructed for age at baseline and age at cancer diagnosis, death, or relocation outside of Iowa. If none of these events occurred, the woman was assumed to be alive, cancer free, and living in Iowa through December 31, 1999. In the mortality analysis, age time scales were constructed for age at baseline and age at death; for women who did not die, follow-up was through December 31, 1999.

Each individual was classified according to her smoking history: current (smoked at least 100 cigarettes in her lifetime and currently smoking), former (smoked at least 100 cigarettes in lifetime and currently not smoking), and never (smoked fewer than 100 cigarettes in lifetime and currently not smoking). Pack-years of smoking (pack-years=total years of smoking multiplied by cigarette packs smoked per day) were also calculated for the former and current smokers.

We grouped alcohol consumption as follows: 0 g/day (abstainers), <14 g/day (approximately less than 1 drink

Table Continued

Former Smokers			Current Smokers		
None *n*=2,233	<14 g/day *n*=2,619	≥14 g/day *n*=771	None *n*=1,761	<14 g/day *n*=1,845	≥14 g/day *n*=915
Mean ± SD					
61.5 ± 4.1	61.0 ± 4.1	61.1 ± 4.0	60.9 ± 4.1	60.7 ± 4.0	60.5 ± 4.1
0.85 ± 0.09	0.83 ± 0.08	0.82 ± 0.08	0.85 ± 0.09	0.83 ± 0.09	0.84 ± 0.10
28.3 ± 6.0	26.5 ± 4.6	25.4 ± 4.3	25.9 ± 5.1	24.9 ± 4.3	24.3 ± 3.8
1,719 ± 616	1,745 ± 561	1,891 ± 602	1,720 ± 646	1,759 ± 618	1,902 ± 610
0	4.5 ± 3.9	29.1 ± 16.2	0	5.0 ± 4.1	35.0 ± 18.7
0	2.9	22.6	0	3.4	33.6
545.2 ± 307.7	550.1 ± 288.6	526.9 ± 291.0	460.1 ± 301.7	470.8 ± 265.6	438.7 ± 245.7
84.6 ± 66.3	81.2 ± 56.4	84.2 ± 53.3	90.9 ± 65.4	88.9 ± 56.2	93.4 ± 66.1
11.7 ± 9.6	11.9 ± 9.0	11.1 ± 9.3	9.1 ± 8.0	9.6 ± 8.4	8.2 ± 7.7
261.5 ± 140.4	261.7 ± 115.0	263.8 ± 108.6	271.7 ± 139.5	279.7 ± 141.3	277.8 ± 133.1
66.0 ± 149.4	69.7 ± 151.0	64.0 ± 142.3	56.3 ± 138.8	63.0 ± 147.1	61.3 ± 147.4
Percent Distribution					
74	77	82	68	70	72
36	50	57	30	39	47
54	61	51	19	22	16
27	27	26	42	43	38
16	11	22	37	34	44
51	39	37	63	56	59
38	32	30	30	27	31
9	3	2	7	2	3
11	15	13	10	11	12
31	29	32	30	29	28
59	56	56	60	60	59
62	68	69	54	62	60

daily), and ≥14 g/day (at least 1 drink daily). This cut point was chosen to correspond to approximately 1 drink per day, the lower end of the American Heart Association's definition of "moderate alcohol consumption."[50] Using splines, we analyzed the shape of the continuous alcohol variable and did not observe a "J-shaped" curve. The shape of the curve supported the selection of our cut points for alcohol.

For the primary analyses, we examined cancer incidence, total mortality, mortality (underlying cause) due to CHD, and cancer. Although self-reports of myocardial infarction were collected, we chose to present CHD mortality due to completeness of this end point in the IWHS cohort.

We estimated the relative hazard rates (HR) of total cancer incidence (excluding nonmelanoma skin cancer), cancer mortality (ICD-9 codes 140–239 and ICD-10 codes C, D), CHD mortality (ICD-9 codes 410–414, 429.2 and ICD-10 codes I20–I25, I5.16), and all-cause mortality for women using Cox proportional hazards regression models. Each woman's age was her own time scale for the baseline risk.[59] Separate analyses were performed for never, former, and current smokers. Initially, we examined whether the association of alcohol intake with cancer incidence, CHD mortality, cancer mortality, and total mortality was modified by smoking history. The referent group was alcohol abstainers (0 g/day), and the current and former smoking models were adjusted for pack-years of smoking. We then adjusted all of the incidence and mortality models for the following covariates generally considered to be important risk factors for cardiovascular and/or cancer outcomes and available in the IWHS: hypertension, diabetes, education, marital status, physical activity, body mass index (BMI), waist-to-hip ratio, hormone replacement therapy (never, former, current user), vitamin supplement use, fruit/vegetable consumption, red meat consumption, total caloric intake, whole-grain intake, cholesterol intake, and vitamin E intake. The proportional hazard assumptions underlying the models were examined. For the models in which there was strong evidence of nonproportionality, the age axis was partitioned and the proportional hazard assumption was found to be tenable over the shorter time interval.[60] Interactions were assessed on a multiplicative scale and statistical significance was tested with a Wald test with 4 degrees of freedom. All analyses were performed on S-Plus 6.1.2 (Insightful Corporation, Seattle, WA).

RESULTS

The results are based upon observations made through 14 years of follow-up, 370,149 person-years for cancer incidence and 404,377 person-years for mortality. There were 4,695 incident cancers (excluding nonmelanoma skin cancers) and 3,929 deaths: 757 from CHD (19.3% of all deaths) and 1,607 from cancer (41.0% of all deaths).

Former and current smokers reported higher average levels of alcohol intake than never smokers (Table 1). Among the never smokers, 4% consumed more than 14 g of alcohol daily, while 14% of the former smokers and 20% of the current smokers consumed more than 14 g of alcohol daily. Current smokers reported lower mean body mass indices and lower frequency of vegetable intake than former and never smokers. For all other variables, never, former, and current smokers

Table 2. Age- and Multivariate-adjusted Relative Hazard Rates for Coronary Heart Disease Mortality, Cancer Mortality, Total Mortality, and Cancer Incidence by Smoking History and Alcohol Use, Iowa Women's Health Study, 1986–1999

			Mortality					
			Coronary Heart Disease Mortality			Cancer Mortality		
Smoking History at Baseline	Alcohol Use	Person-years	Events	Age-adjusted HR (95% CI)*	Multivariate HR (95% CI)†	Events	Age-adjusted HR (95% CI)*	Multivariate HR (95% CI)†
Never smoker	0 g/day	163,971	303	1.00 (reference)	1.00 (reference)	554	1.00 (reference)	1.00 (reference)
	<14 g/day	93,156	95	0.59 (0.47 to 0.75)	0.77 (0.61 to 0.97)	276	0.92 (0.79 to 1.06)	0.96 (0.83 to 1.12)
	≥14 g/day	10,433	7	0.40 (0.19 to 0.84)	0.50 (0.24 to 1.07)	31	0.93 (0.64 to 1.33)	0.99 (0.69 to 1.43)
Former smokers	0 g/day	29,002	65	1.00 (reference)	1.00 (reference)	129	1.00 (reference)	1.00 (reference)
	<14 g/day	35,137	45	0.59 (0.40 to 0.86)	0.77 (0.52 to 1.14)	96	0.63 (0.48 to 0.82)	0.71 (0.54 to 0.93)
	≥14 g/day	10,204	10	0.45 (0.23 to 0.88)	0.69 (0.35 to 1.35)	55	1.24 (0.90 to 1.69)	1.35 (0.97 to 1.88)
Current smokers	0 g/day	22,012	89	1.00 (reference)	1.00 (reference)	183	1.00 (reference)	1.00 (reference)
	<14 g/day	23,634	83	0.88 (0.65 to 1.19)	1.05 (0.77 to 1.42)	159	0.82 (0.66 to 1.01)	0.87 (0.70 to 1.08)
	≥14 g/day	11,478	46	1.05 (0.73 to 1.50)	1.19 (0.82 to 1.72)	104	1.13 (0.89 to 1.44)	1.19 (0.93 to 1.52)
Interaction *P* value				.03	<.001		.05	.51

**Age-adjusted models are adjusted for age.*
†Multivariate models are additionally adjusted for hypertension, diabetes, education, marital status, physical activity, BMI, waist-to-hip ratio, hormone replacement therapy, vitamin supplement use, fruit/vegetable consumption, red meat consumption, total caloric intake, whole-grain intake, cholesterol intake, vitamin E intake, and pack-years.
‡Alcohol's association with cancer incidence was found to be nonproportional in the age-adjusted models only. Among moderate drinkers (< 14 g/day), risk plateaued until age 75, then increased. Among heavy drinkers (≥ 14 g/day), risk declined until age 67 and then plateaued.
HR, hazard rate; CI, confidence interval; BMI, body mass index.

were similar with respect to established risk factors for the outcomes of interest.

The age- and multivariate-adjusted relative HRs for cancer incidence and CHD, cancer, and total mortality with daily alcohol consumption within each level of smoking are presented in Table 2. In the age-adjusted models for never smokers who consumed ≥14 g/day of alcohol versus none, there were statistically significant inverse associations of alcohol consumption with CHD (HR, 0.40; 95% CI, 0.19 to 0.84) and total mortality (HR, 0.71; 95% CI, 0.55 to 0.92), while there were weak, nonsignificant inverse associations with cancer mortality (HR, 0.93; 0.64 to 1.33) and cancer incidence (HR, 0.98; 95% CI, 0.80 to 1.20). Among former smokers consuming ≥14 g/day of alcohol versus none, there were statistically significant inverse associations of alcohol consumption with CHD (HR, 0.45; 95% CI, 0.23 to 0.88) and total mortality (HR, 0.78; 95% CI, 0.62 to 0.97), a J-shaped association with cancer mortality, and a positive association with cancer incidence (HR, 1.25; 95% CI, 1.03 to 1.51). Among current smokers consuming ≥14 g/day of alcohol versus none, there was no clear association of alcohol consumption with CHD, cancer, or total mortality, and there was a statistically significant positive association with cancer incidence (HR, 1.30; 95% CI, 1.10 to 1.54). A formal test for interaction between smoking history and alcohol consumption was statistically significant for CHD mortality (P=.03) and total mortality (P<.001), and was suggestive for cancer mortality (P=.05) and cancer incidence (P=.08). Multivariate adjustment generally paralleled age-adjusted estimates (Table 2). We repeated the primary analysis using drinks per day versus grams per day of alcohol, and the findings were unchanged.

In secondary analyses, we analyzed the age- and pack-year-adjusted mortality risk by type of alcohol (red wine, white wine, beer, and liquor). Subjects were included in an alcohol category if they reported consuming any amount and the reference group was always nonusers of any alcohol. Although based upon small numbers, we observed no striking difference in pattern by type of alcohol consumed, and the overall results are consistent with the results for all alcohol in Table 2 (data not shown). Excluding heavier drinkers (≥40 g/day) in all groups, the point estimates in Table 2 did not change but the confidence intervals widened for cancer incidence among former smokers (HR, 1.37; 95% CI, 1.10 to 1.69) and current smokers (HR, 1.23; 95% CI, 1.01 to 1.49) consuming ≥14 g/day.

DISCUSSION

In this prospective cohort of postmenopausal women, alcohol consumption among never smokers was inversely associated with CHD mortality. Among former smokers, alcohol consumption was inversely associated with CHD mortality but consuming at least 1 drink daily was positively associated with cancer incidence. Among current smokers, alcohol consumption was not associated with CHD mortality but was positively associated with cancer incidence among those consuming at least 1 drink daily. The differing associations of alcohol with CHD mortality by smoking history were statistically significant, and approached significance for cancer mortality and cancer incidence. Our finding of an inverse association of moderate alcohol consumption with CHD mortality among never and former smokers is consistent in direction[61,62] and magnitude with previously published reports (HR, 0.5).[63] Our findings contribute to the literature by simultaneously evaluating an interaction of alcohol consumption and cigarette smoking on CHD mortality and cancer incidence and mortality.

Numerous reports from cohort studies on the association of alcohol consumption with CHD morbidity and mortality have been published and adjustment for smoking history has generally not affected this association.[35] However, relatively few studies have formally evaluated whether this association varies by smoking history (interaction). We identified 9 cohort analyses that explicitly evaluated and reported on whether there was an interaction among males,[7,23,28,39] females,[7,10,24] and a combined group[17,40] (gender-specific re-

Table
Continued

Mortality						
Total Mortality			Cancer Incidence			
Events	Age-adjusted HR (95% CI)*	Multivariate HR (95% CI)†	Person-years	Events	Age-adjusted HR (95% CI)*	Multivariate HR (95% CI)†
1417	1.00 (reference)	1.00 (reference)	151,643	1,789	1.00 (reference)	1.00 (reference)
591	0.79 (0.71 to 0.86)	0.88 (0.80 to 0.97)	85,647	923	1.01 (0.93 to 1.09)‡	0.97 (0.89 to 1.05)
59	0.71 (0.55 to 0.92)	0.76 (0.58 to 0.99)	9,420	98	0.98 (0.80 to 1.20)‡	0.95 (0.77 to 1.17)
380	1.00 (reference)	1.00 (reference)	26,453	359	1.00 (reference)	1.00 (reference)
244	0.55 (0.47 to 0.64)	0.64 (0.55 to 0.76)	31,484	390	0.93 (0.81 to 1.08)	1.00 (0.86 to 1.15)
101	0.78 (0.62 to 0.97)	0.94 (0.75 to 1.17)	8,885	150	1.25 (1.03 to 1.51)	1.38 (1.13 to 1.68)
452	1.00 (reference)	1.00 (reference)	20,156	351	1.00 (reference)	1.00 (reference)
380	0.79 (0.69 to 0.91)	0.89 (0.77 to 1.02)	21,387	356	0.97 (0.84 to 1.12)	0.99 (0.85 to 1.15)
240	1.07 (0.92 to 1.25)	1.14 (0.97 to 1.34)	10,147	222	1.30 (1.10 to 1.54)	1.33 (1.12 to 1.58)
	<.001	<.001			.08	.15

sults not reported). Among males, all 4 analyses found no evidence for an interaction. However, in 2 of these studies[28,39] alcohol was not inversely associated with CHD overall. In Suhonen et al.,[28] both smokers and nonsmokers who consumed alcohol had a higher relative risk of age-adjusted CHD death compared to nonsmoking abstainers. In Kivela et al.,[39] no statistically significant relationship existed between low and moderate or heavy alcohol consumption and the odds of CHD death among smokers and nonsmokers after adjustment relative to abstainers, although higher levels of alcohol consumption were observed to have a modest inverse relationship among nonsmokers and a modest direct relationship among smokers for the odds of CHD death. Among combined cohorts who did not provide gender-specific results, a possible interaction was suggested in two independent cohorts of subjects undergoing health examinations at Kaiser (1964–1968, 1978–1985).[17,40] In Klatsky et al.,[17] the reduced risk of CHD mortality for consumers of 1–2 drinks/day compared to lifelong abstainers was greatest among ex-smokers (HR, 0.5; $P<.001$) and nonsignificant for never smokers (HR, 1.0) and current smokers (HR, 0.6; P=NS). These results are similar to our findings in former smokers but contrast with our finding of a significant inverse association between alcohol consumption and CHD mortality in never smokers. Finally, among females, all 3 analyses found an overall inverse association of alcohol with CHD, but no evidence for an interaction. However, 2 of these studies were likely underpowered to evaluate the interaction (approximately 200 events each).[7,24] The third study was a follow-up of the National Health and Nutrition Examination Survey I (NHANES I) cohort[10] in which the inverse association was seen in both nonsmokers and smokers, but it was not clear which group included former smokers.

Our observation that never smokers experience the greatest potential cardioprotection from alcohol may be related to the counteractive effects of alcohol and smoking on other risk factors for cardiovascular disease or events. Alcohol has been shown to raise high-density lipoprotein (HDL).[64] However, multivariate analyses of epidemiologic data suggest that HDL changes can explain only 50% of the inverse association, suggesting a role for other hematologic or vascular effects. In a meta-analysis of 42 experimental studies, alcohol was shown to be associated with significantly higher concentrations of not only HDL but also apolipoprotein A-1 and plasminogen as well as lower concentrations of fibrinogen.[65] Alcohol has also been suggested to be associated with increased fibrinolytic activity, decreased ADP-induced platelet aggregation,[35] and improved insulin sensitivity.[66] All of these effects could potentially decrease the risk for CHD events. However, these potentially cardioprotective effects may be negated by the adverse effects of smoking. Cigarette smoking has been associated with decreased concentrations of HDL[67] and increased concentrations of both triglycerides and low-density lipoprotein (LDL),[68] although more recent evidence suggests that the adverse effects of smoking operate independently of the lipid pathways.[26] Smoking has also been associated with biologic markers of endothelial dysfunction,[69] insulin resistance,[70] enhanced platelet aggregation,[71] and impaired fibrinolysis.[72] Smoking may also cause genomic destabilization, which may play an important role in the development of atherosclerosis.[73] Because we did not obtain biological samples in our population, we could not evaluate these potential pathways.

Based upon evidence from human studies, alcohol is classified as a Group 1 carcinogen by the International Agency for Research on Cancer.[49] Alcohol is considered to be causally associated with the development of cancer of the oral cavity, pharynx, larynx, esophagus, and liver, and data are suggestive for a positive association with rectal and breast cancer. No firm conclusions regarding alcohol's association with colon cancer have been made, and alcohol was considered unlikely for cancers of the lung, stomach, pancreatic cancer, urinary bladder, kidney, ovary, prostate, and lymphatic and hematopoietic systems. For all other sites, there were insufficient data regarding the role of alcohol. In our data, the differing effect of alcohol on cancer mortality varied by smoking history (test for interaction, P=.05). This is consistent with previously published reports in women.[40,74] We did not evaluate the association of alcohol with individual cancer sites, as this report was focused on cancer prevention more broadly defined. Furthermore, patients may be more concerned with preventing all types of cancer rather than site-specific cancers. Our results may inform general cancer risk reduction discussions that health professionals conduct with their patients.

This study has several strengths. First, this is a population-based study with 14 years of virtually complete follow-up for mortality. Second, we used a semiquantitative food frequency questionnaire for baseline data collection that has been shown

to be reproducible for alcohol consumption in this population.[56] Third, we excluded women with prior cardiovascular disease and cancer, decreasing the impact of including ex-drinkers with preexisting disease in the group of alcohol abstainers.[30] Fourth, cancer incidence data were collected through SEER, requiring both clinical and histologic verification of cancer diagnoses. Finally, we analyzed the association of alcohol across the major causes of morbidity and mortality, which gives a broad perspective on the global impact of alcohol in this population.

There are several potential limitations to this study. First of all, we are using CHD mortality data and not incidence. Therefore, we may be unable to estimate the association of alcohol with coronary artery disease overall. However, our results may represent a potentially less biased estimate, especially compared to self-reported cardiac events, because the sensitivity of self-report for myocardial infarction among older patients is problematic.[75] Another potential limitation relates to the fact that analyses were performed based upon alcohol consumption on the baseline questionnaire. This potentially results in misclassification of women whose alcohol pattern changed after completing the baseline survey. However, data from several U.S. prospective studies suggest that moderate drinkers and abstainers have more stable drinking patterns than heavy drinkers[76] and our population consisted of mostly light drinkers. Another limitation of this study relates to the external validity of our findings. Ninety-eight percent of the women in the cohort consumed ≤ 40 g/day of alcohol, or less than 3 drinks daily. This may not be representative of women from other geographic regions who may have a higher rate or intensity of use.[77] Further, we were unable to adequately assess the association of larger quantities of alcohol consumption (>3 drinks daily) on mortality and cancer incidence. Finally, while the inverse relationship between moderate alcohol consumption and CHD mortality has been demonstrated in multiple ethnic groups,[63] we only examined predominantly white, Midwestern women, so these results may not be generalizable to other ethnic populations.

At present, many health professionals do not discourage their patients from consuming alcohol and some health professionals may recommend it with appropriate screening and precautions.[78] If our observations are confirmed, our findings suggest that smoking history should be considered when clinicians engage patients in health behavior counseling relating to alcohol consumption and cardioprotection.

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