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Original Contribution

Alcoholic Beverages and Prostate Cancer in a Prospective US Cohort Study

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Despite numerous investigations, the correlation between alcohol consumption and prostate cancer risk remains uncertain. This report investigated the association between alcohol use and prostate cancer risk in a prospective cohort study of 294,707 US men aged 50–71 years in 1995–1996. Cox proportional hazards regression models with hazard ratios and 95% confidence intervals were adjusted for characteristics including age, race, body mass index, physical activity, and family history of prostate cancer, as well as testing for prostate-specific antigen and a digital rectal examination. There were 15,327 nonadvanced and 1,900 advanced prostate cancers identified through 2003 and 514 fatal cases through 2005. Risk of nonadvanced prostate cancer was 25% higher for men consuming $\geq$6 drinks daily (hazard ratio = 1.25, 95% confidence interval: 1.13, 1.37), 19% higher for men consuming 3–<6 drinks daily, and 6% higher for men consuming up to 3 drinks daily, compared with nondrinkers. The association between alcohol consumption and nonadvanced prostate cancer risk did not differ appreciably by age, family history of prostate cancer, smoking status, body mass index, or self-reported prostate-specific antigen testing and digital rectal examination (the latter available for >60% of respondents). The authors observed no association between alcohol intake and advanced prostate cancer and an inverse association with fatal prostate cancer among heavy drinkers. These findings suggest that higher alcohol consumption modestly increases nonadvanced prostate cancer risk.

alcoholic beverages; prostatic neoplasms

Abbreviations: BMI, body mass index; CI, confidence interval; DRE, digital rectal examination; HR, hazard ratio; NIH, National Institutes of Health; PSA, prostate-specific antigen; RR, relative risk.

Alcohol is an established risk factor for many cancers, including those of the esophagus, liver, colon, rectum, and breast (1), yet the definitive correlation between alcohol and prostate cancer risk remains to be established. The report by the World Cancer Research Fund (2) on nutrition, physical activity, and cancer concluded that the data were too limited to determine an association between alcohol and prostate cancer. Although there have been more than 60 studies of this association, the results are inconsistent, and several critical gaps remain to be addressed using prospective data with sample sizes sufficient to detect small to modest associations, including whether the effect of alcohol differs by prostate cancer stage, how patterns of alcohol consumption influence risk, and alcohol's role in fatal prostate cancers. Most epidemiologic studies have reported no association between alcohol consumption and prostate cancer risk, yet many others have reported modest increases in prostate cancer risk with higher intake (3–7). Strong associations between alcohol and prostate cancer are seen in smaller studies of alcoholics and heavy drinkers (8, 9).

Generally, associations did not differ according to the type of alcohol consumed (i.e., beer, liquor, or wine) (10, 11). One case-control study reported a protective association between prostate cancer incidence and red wine (12), but a subsequent cohort investigation found no such association (10). In 2 other cohort studies, white wine (13) and liquor (14) were associated with an increased prostate cancer risk, but there was no association with any of the other forms of alcohol.

In this study, we prospectively examined whether alcohol consumption affected prostate cancer risk for 294,707 men

enrolled in the Diet and Health Study cosponsored by the National Institutes of Health (NIH) and AARP (formerly, the American Association of Retired Persons). To our knowledge, this is the largest study to date of alcohol and prostate cancer, providing substantial power to investigate this hypothesis, along with issues examined in smaller studies (e.g., of heavy drinkers and fatal cancers).

MATERIALS AND METHODS

Study population

We used data from the NIH–AARP Diet and Health Study, a large prospective cohort study of dietary and environmental risk factors and cancer (15). Questionnaires were mailed to AARP members who were aged 50–71 years in 1995–1996 and residing in one of 8 US states (California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina, and Pennsylvania). The NIH–AARP Diet and Health Study was reviewed and approved by the Special Studies Institutional Review Board of the National Cancer Institute. We excluded those members whose questionnaires were completed by proxies for the intended respondent ($n = 15{,}760$). Of the 325,174 men who returned questionnaires with satisfactory, complete data, we excluded those with histories of cancer (except nonmelanoma skin cancer) diagnosed before baseline ($n = 27{,}240$) and those who reported end-stage renal disease at baseline ($n = 626$). In addition, we excluded men who reported extreme intakes (beyond 2 times the interquartile ranges of Box–Cox log-transformed intake) of total energy ($n = 2{,}601$). After exclusions, the analytical cohort consisted of 294,707 men.

Cohort follow-up and identification of cancer cases

We identified the first primary incident cases of prostate cancer (*International Classification of Diseases for Oncology*, Third Edition, code C619) that occurred during follow-up through December 31, 2003. Only first incident cases were included because alcohol consumption patterns are likely to change after a cancer diagnosis. Cases were identified through probabilistic linkage with the 11 state cancer registry databases (the 8 states used at baseline plus Arizona, Nevada, and Texas) serving our study (16). These registries are certified by the North American Association of Central Cancer Registries as being 90% complete within 2 years of cancer occurrence. Information on prostate cancer stage and histologic grade was also obtained from cancer registry databases. Vital status was ascertained through annual linkage of the cohort to the Social Security Administration Death Master File in the United States, follow-up searches of the National Death Index Plus for participants matched to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings.

During follow-up, we identified 17,227 incident prostate cancer cases and further classified cases as nonadvanced ($n = 15{,}327$), advanced ($n = 1{,}900$), and fatal ($n = 514$). Advanced prostate cancer cases were defined as those with clinical stages T3–T4, N1–3, or M1 according to the American Joint Committee on Cancer's 1997 Tumor-Node-Metastasis classification system, as well as men who died of prostate cancer during follow-up through 2003. The remaining cases were considered nonadvanced. Fatal cases were those who died of prostate cancer through December 31, 2005.

Data collection

The baseline questionnaire contained items about demographics, medical history, smoking, race, education, and physical activity, as well as a food frequency questionnaire of 124 items. The food frequency questionnaire queried for consumption of beer during the summer, beer during the rest of the year, liquor or mixed drinks, and wine or wine coolers during the entire year, with 10 categories of frequency ranging from "never" to "six or more times per day" and 3 portion sizes (<1, 1–2, >2 drinks). Portion sizes and nutrients were determined using databases from the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intakes by Individuals (7). One drink was defined as one 12-fluid-ounce beer, one 5-ounce glass of wine, or one 1.5-ounce shot of liquor, all equaling approximately 13 g of alcohol. Consumption was further categorized as none, up to 1 drink per day, 1–3, >3–<6, and >6 drinks per day. No information was available on past alcohol consumption or whether the participant engaged in binge drinking patterns.

Other categorical variables based on the baseline questionnaire data included smoking status (current, former, never), self-reported health status (excellent, very good, good, fair, poor), and body mass index (BMI) in kg/m^2 (<20.0, 20–22.4, 22.5–24.9, 25–27.4, 27.5–29.9, 30–31.9, 32–33.9, ≥ 34). In a subsequently mailed questionnaire in 1996–1997 (69% response rate), we requested information on prostate cancer screening by the use of a prostate-specific antigen (PSA) test and/or digital rectal examination (DRE) during the past 3 years.

Statistical methods

We used Cox proportional hazards models (17) with person-years as the underlying metric to estimate hazard ratios and 95% confidence intervals of prostate cancer. Person-years of follow-up were calculated from the date of study entry until the date of cancer diagnosis (all cancer sites, not prostate specific), death, moving out of the study area, or the end of follow-up, whichever occurred first. The proportional hazards assumption was evaluated by modeling an interaction term of time and alcohol and was upheld in all analyses. Risk was calculated for all cases combined and separately for advanced, nonadvanced, and fatal cancers.

All multivariate models adjusted for hypothesized a priori risk factors related to both alcohol and prostate cancer, including baseline age, race, education, marital status, height, BMI, physical activity, family history of prostate cancer, diabetes, self-reported health status, smoking status, PSA test and DRE, energy intake (excluding energy from alcohol), and intake of α-tocopherol, calcium, red meat, fish, tomatoes, α-linolenic acid, and selenium. All dietary exposures were analyzed as quintiles of intake, except for continuous total energy. Additional covariates considered but

not included were intakes of fruit and vegetables; BMI at age 18 years; multivitamin use; supplemental use of vitamin E, calcium, and selenium; leisure-time physical activity; and workplace physical activity. Indicator variables were used for missing responses. Effect modification was evaluated in stratified multivariate analyses and was also tested by adding product interaction terms and comparing *P* values for the likelihood ratio tests (<0.05) for the models with and without interaction terms for alcohol and BMI, smoking, race, family history of prostate cancer, PSA test, and DRE. We also examined whether the association of prostate cancer risk with alcohol consumption differed by type of alcohol consumed. Age-adjusted incidence rates were calculated according to Breslow and Day's (18) method with 5-year age categories and age- and gender-specific rates standardized to the entire NIH–AARP Diet and Health Study population.

All statistical tests were 2-sided, and $P \leq 0.05$ was considered statistically significant. *P* values for trend tests were calculated using ordinal variables representing the categories of alcohol consumption. Data analyses were conducted using Stata software (version SE 9; STATACorp, College Station, Texas).

RESULTS

Comparisons of baseline characteristics are presented by category of alcohol consumption (i.e., nondrinkers, <1 drink/day, 1–3 drinks/day, and >3 drinks/day) in Table 1. Nondrinkers were less likely to be non-Hispanic whites and more likely to have diabetes than men who consumed alcohol. There was little difference across categories of alcohol intake by age, BMI, family history of prostate cancer, physical activity, screening (both PSA test and DRE), self-reported health status, and multivitamin use. Both nondrinkers and men who had <1 drink per day were less likely to be former or current smokers than those who reported >3 drinks per day. There was no difference in energy intake between the highest and lowest categories of alcohol consumption when energy from alcohol was excluded. Because alcoholic beverages are energy dense, total energy was approximately 30% higher for men consuming >3 drinks daily compared with nondrinkers. Compared with nondrinkers, men who had >3 drinks per day also had higher intakes of red meat and selenium and lower consumption of fruits.

Of the 17,227 men diagnosed with prostate cancer, 1,818 died from causes other than prostate cancer, most often other cancers or cardiovascular disease (~40% for each). The average follow-up time was 7.0 years for men not diagnosed with prostate cancer, 3.9 years for men diagnosed with prostate cancer, and 3.3 years for men who died from prostate cancer. The mean time from diagnosis to death for men with fatal prostate cancer was 2.3 years, and the median was 2.8 years. Approximately 1% of the men diagnosed with prostate cancer had distant metastases at diagnosis ($n = 220$), and, of those, 129 died from prostate cancer.

Higher alcohol consumption was associated with increased incidence of nonadvanced prostate cancer, but not advanced cancer (Table 2). There was a 25% increase in risk of nonadvanced incident prostate cancer associated with ≥6 drinks per day (95% confidence interval (CI): 1.13, 1.37), a 19% increase with 3–6 drinks daily, and a 6% increase for both <1 and 1–3 drinks per day compared with nondrinkers. When alcohol was examined as a continuous variable, the hazard ratios associated with each additional drink were 1.05 (95% CI: 1.03, 1.07), 1.02 (95% CI: 0.96, 1.08), and 0.95 (95% CI: 0.85, 1.05) for nonadvanced, advanced, and fatal prostate cancers, respectively. The overall age-adjusted prostate cancer incidence rates were 793, 867, 883, 942, and 938 per 100,000 person-years for nondrinkers and for men consuming <1 drink per day, 1–3 drinks per day, <3–<6 drinks per day, and ≥6 drinks per day, respectively. There was an inverse association between alcohol and fatal prostate cancer, with a hazard ratio of 0.45 (95% CI: 0.25, 0.81) for heavy drinkers (≥6 drinks/day). The alcohol–prostate cancer association did not differ by cancer grade or stage at diagnosis, and the proportion of nonadvanced, advanced, and fatal prostate cancers did not differ by alcohol intake (data not shown).

The positive association between alcohol consumption and nonadvanced prostate cancer risk did not differ appreciably by age, family history of prostate cancer, smoking status, BMI, or PSA test and DRE. For example, hazard ratios for men consuming ≥3 drinks daily compared with nondrinkers were similar for those who reported having received a PSA test (hazard ratio (HR) = 1.15, 95% CI: 1.04, 1.27), those not tested (HR = 1.19, 95% CI: 0.97, 1.47), and those whose PSA status was unknown (HR = 1.22, 95% CI: 1.11, 1.33). There were, however, interactions for fatal prostate cancer between alcohol and BMI ($P < 0.001$) and smoking ($P = 0.02$), with a linear inverse trend for overweight men and nonsmokers, but not for other men. Among men with diabetes, the hazard ratios were similar to those in the overall analysis: 1.01 for <1 drink/day, 1.26 for 1–3 drinks/day, 1.27 for >3–<6 drinks/day, and 1.17 for ≥6 drinks/day (*P* trend = 0.02) compared with nondrinkers. There was no difference by diabetes status for fatal or advanced cancers.

We also calculated prostate cancer risk by type of alcoholic beverage consumed (Table 3). There were statistically significant, positive linear risk trends between nonadvanced prostate cancer and beer and liquor in models mutually adjusted for the other types of alcohol consumed. All alcoholic beverages impacted risk similarly, with risks ranging from 9% to 15% for those drinking more than 3 servings of beer, wine, or liquor per day, although the risk estimates for wine were not statistically significant. There was no association by type of alcohol with fatal disease.

DISCUSSION

In this large prospective study, we found that alcohol consumption increased the risk of nonadvanced prostate cancer, with approximately a 20% higher risk for men drinking ≥3 drinks daily. Similar associations were observed regardless of type of alcoholic beverage consumed. Our results suggest that alcohol does not increase the risk of more clinically relevant advanced prostate cancer and that heavier drinking may protect against fatal cancers. Although the vast majority of nonadvanced cancers are not life-threatening, many are treated and some progress to more serious disease. Observing an

Table 1. Selected Characteristics According to Alcohol Consumption Among Men in the NIH–AARP Diet and Health Study, 1995–2003 ($n = 294,707$)

Characteristic	Alcohol (Drinks/Day)			
	0 ($n = 61,431$)	<1 ($n = 146,027$)	1–3 ($n = 55,438$)	>3 ($n = 31,811$)
Median age, years	63.0	62.5	63.1	62.8
Race, %				
White, non-Hispanic	89.9	92.3	94.6	94.8
Black, non-Hispanic	4.1	2.6	1.8	2.2
Other/unknown	6.0	5.1	3.6	3.0
College graduate, %	34.9	45.5	52.6	44.4
Married, %	84.0	86.2	85.2	81.0
Height, m	1.78	1.78	1.78	1.78
Body mass index, kg/m^2	26.8	26.7	26.3	26.6
Family history of prostate cancer, %	8.3	8.3	8.4	8.2
History of diabetes, %	17.2	9.8	5.4	6.1
Never smoker, %	33.8	32.0	24.2	15.4
Former smoker, %	52.1	55.1	62.2	61.7
Current smoker, %	9.6	9.2	9.8	18.9
Vigorous physical activity (% at least 1 time/week)	66.9	71.5	76.2	68.6
Self-reported health status (% very good)	30.2	36.3	39.2	36.3
DRE in the past 3 years, %[a]	81.4	84.2	85.3	80.7
Screening for elevated PSA in the past 3 years, %[a]	68.5	72.6	73.5	67.8
Multivitamin use, %	60.3	64.1	65.9	62.3
Daily dietary intake				
Energy, excluding alcohol, kcal/day	1,918	1,755	1,748	2,019
Alpha-linolenic acid, g	1.2	1.2	1.3	1.4
Alpha-tocopherol, mg	7.0	6.8	7.2	7.2
Calcium, mg	724	696	698	716
Vitamin D, μg	4.1	4.1	4.2	4.1
Fish, ounces[b]	0.4	0.5	0.6	0.6
Red meat, ounces	1.9	1.9	2.1	2.5
Selenium, μg	92.1	93.4	98.9	111.0
Tomatoes, cup[c] equivalents	0.3	0.3	0.3	0.4
Fruits, cup equivalents	1.8	1.7	1.7	1.3
Vegetables, cup equivalents	1.7	1.7	1.8	1.8

Abbreviations: DRE, digital rectal examination; NIH, National Institutes of Health; PSA, prostate-specific antigen.

[a] Information on DRE and PSA testing comes from subsequently mailed questionnaire in 1996–1997 (available for approximately 60% of total sample); percentages in Table 1 compare only those who returned questionnaires.

[b] One ounce = 28.3 g.

[c] One cup = 237 ml.

alcohol association for only nonadvanced cases could signal detection bias if alcoholic beverage consumers had increased prostate screening or access to medical services. This was not likely the case, however, because the alcohol association was similar for men reporting PSA testing or DRE and those reporting no such testing, and a variable for PSA testing and DRE was included in all multivariate models.

Prior observational studies of alcohol and prostate cancer have been inconsistent. Our results support findings from 4 cohort studies (4, 9, 13, 14) and 2 case-control studies (5, 19)

Table 2. Relative Risk of Prostate Cancer in Relation to Daily Alcohol Consumption Among Men in the NIH–AARP Diet and Health Study, 1995–2003

Alcohol (Drinks/Day)	No. of Cases	Age-adjusted Rate/10,000	Age-adjusted HR	95% CI	Multivariate HR[a]	95% CI
All cases[b]						
0	3,288	792.5	1.		1.	
<1	8,545	867.0	1.09	1.05, 1.14	1.06	1.01, 1.10
1–3	3,384	882.5	1.11	1.06, 1.17	1.07	1.01, 1.12
>3–<6	1,170	942.4	1.19	1.11, 1.27	1.18	1.10, 1.26
≥6	840	937.8	1.19	1.10, 1.28	1.21	1.11, 1.33
P for trend			<0.001		<0.001	
Nonadvanced cases						
0	2,921	706.0	1.		1.	
<1	7,614	775.5	1.10	1.05, 1.14	1.06	1.01, 1.11
1–3	2,981	779.4	1.10	1.05, 1.16	1.06	1.00, 1.12
>3–<6	1,048	847.9	1.19	1.13, 1.26	1.19	1.11, 1.29
≥6	763	854.8	1.21	1.14, 1.28	1.25	1.13, 1.37
P for trend			<0.001		<0.001	
Advanced cases						
0	367	91.2	1.		1.	
<1	931	97.1	1.06	0.94, 1.20	1.02	0.90, 1.16
1–3	403	109.5	1.20	1.04, 1.38	1.13	0.97, 1.31
>3–<6	122	100.7	1.11	0.90, 1.36	1.07	0.86, 1.33
≥6	77	89.1	0.98	0.77, 1.25	0.97	0.73, 1.29
P for trend			0.21		0.38	
Fatal cases						
0	125	41.5	1.		1.	
<1	237	32.1	0.81	0.65, 1.01	0.86	0.69, 1.08
1–3	102	37.2	0.88	0.68, 1.15	0.95	0.72, 1.26
>3–<6	33	37.3	0.90	0.61, 1.32	0.81	0.53, 1.21
≥6	17	34.6	0.63	0.38, 1.05	0.45	0.25, 0.81
P for trend			0.18		0.05	

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for age, race, education, marital status, height, body mass index, physical activity, family history of prostate cancer, diabetes, self-reported health status, cigarette smoking, prostate-specific antigen screening and digital rectal examination, total energy excluding alcohol, α-tocopherol, calcium, red meat, fish, tomato, α-linolenic acid, and selenium.

[b] Includes nonadvanced and advanced (which also includes fatal) cases.

that found a positive alcohol–prostate cancer association. The magnitudes of association reported here are similar to those in a population-based case-control study comparing men consuming 22–56 drinks per week and nondrinkers (relative risk (RR) = 1.4, 95% CI: 1.0, 1.8) (5), a cohort of Harvard University alumni where a relative risk of 1.33 was associated with >3 drinks per day (14), and findings from the Health Professionals Follow-up Study (HR = 1.05, 95% CI: 0.94, 1.18 for 5.0–14.9 g ethanol per day, and HR = 1.13, 95% CI: 0.96, 1.33, for 30.0–49.9 g ethanol per day, compared with nondrinkers (9); RR = 1.14, 95% CI: 0.99, 1.31 for ≥16.5 g ethanol per day (10)).

Three other large cohort studies found no association of alcohol with prostate cancer risk for European men consuming ≥60 g alcohol per day (RR = 0.88, 95% CI: 0.72, 1.08) (3), American men consuming up to 15–21 drinks per day (RR = 0.85, 95% CI: 0.41, 1.75) (20), and men in California reporting ≥3 drinks daily (HR = 1.03, 95% CI: 0.79, 1.35) (21). Three recent meta-analyses have found modest risk increases associated with alcohol use (6, 8, 22). Middleton Fillmore et al. (6) reported increased prostate cancer risk with alcohol consumption based on a meta-analysis of 21 case-control studies and 14 cohort studies (odds ratio = 1.16, 95% CI: 1.06, 1.26). Likewise, Dennis (23) reported a nonsignificant overall pooled estimate (RR = 1.05), while the meta-analysis performed by Bagnardi et al. (22) showed a relative risk of 1.19 (95% CI: 1.03, 1.37) comparing 100 g alcohol per day versus nondrinkers.

Assessing alcohol use at study enrollment could lead to misclassification (as nondrinkers) of former drinkers who

Table 3. Relative Risk of Prostate Cancer in Relation to Type of Alcoholic Beverage Consumed by Men in the NIH–AARP Diet and Health Study, 1995–2003

Alcohol (Drinks/Day)	No. of Cases	Age-adjusted HR	95% CI	Multivariate HR[a]	95% CI	Multivariate HR[b]	95% CI
Nonadvanced Prostate Cancer							
Wine							
0	5,581	1.		1.		1.	
<1	8,485	1.11	1.07, 1.15	1.05	1.01, 1.09	1.02	0.97, 1.06
1–3	1,197	1.14	1.08, 1.22	1.07	1.01, 1.15	1.04	0.97, 1.11
>3	64	1.25	0.97, 1.59	1.17	0.91, 1.50	1.14	0.89, 1.47
P for trend		<0.001		0.003		0.22	
Beer							
0	4,759	1.		1.		1.	
<1	8,998	1.11	1.07, 1.15	1.08	1.04, 1.12	1.05	1.00, 1.09
1–3	938	1.05	0.98, 1.13	1.05	0.98, 1.13	1.02	0.95, 1.10
>3	632	1.10	1.02, 1.20	1.11	1.01, 1.21	1.09	1.00, 1.20
P for trend		<0.001		0.001		0.06	
Liquor							
0	6,211	1.		1.		1.	
<1	6, 959	1.09	1.06, 1.13	1.05	1.02, 1.09	1.02	0.98, 1.07
1–3	1,327	1.16	1.10, 1.23	1.12	1.06, 1.20	1.09	1.03, 1.17
>3	830	1.19	1.11, 1.28	1.17	1.08, 1.27	1.15	1.06, 1.24
P for trend		<0.001		<0.001		<0.001	
Fatal Prostate Cancer							
Wine							
0	230	1.		1.		1.	
<1	256	0.82	0.69, 0.98	0.92	0.76, 1.11	0.99	0.79, 1.23
1–3	28	0.65	0.44, 0.97	0.83	0.55, 1.26	0.90	0.58, 1.37
>3	0						
P for trend		0.003		0.18		0.49	
Beer							
0	197	1.		1.		1.	
<1	267	0.80	0.67, 0.97	0.85	0.70, 1.03	0.87	0.69, 1.10
1–3	29	0.82	0.55, 1.21	0.78	0.52, 1.18	0.80	0.52, 1.22
>3	21	0.93	0.59, 1.45	0.78	0.48, 1.27	0.80	0.49, 1.31
P for trend		0.13		0.09		0.18	
Liquor							
0	238	1.		1.		1.	
<1	202	0.84	0.70, 1.01	0.87	0.71, 1.06	0.94	0.74, 1.18
1–3	55	1.22	0.91, 1.64	1.20	0.88, 1.64	1.31	0.93, 1.83
>3	19	0.69	0.43, 1.10	0.67	0.41, 1.08	0.73	0.45, 1.19
P for trend		0.38		0.35		0.85	

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] Adjusted for age at study entry, race, education, marital status, height, body mass index, vigorous physical activity, family history of prostate cancer, personal history of diabetes, self-reported health status, cigarette smoking, prostate-specific antigen screening and digital rectal examination, total energy excluding energy from alcohol, and quintiles of intake of α-tocopherol, calcium, red meat, fish, tomato, α-linolenic acid, and selenium.

[b] Adjusted for all covariates and the other types of alcohol (i.e., wine, beer, and liquor) consumed.

recently stopped drinking. Two cohort investigations assessed alcohol consumption at varying points over a lifetime and found that associations did not change whether using alcohol consumption at baseline or average lifetime intake (3, 13). By contrast, 2 other studies reported an inverse association with prostate cancer and past alcohol consumption but no

association with current consumption (20, 24). If there were considerable misclassification in the nondrinker category with sicker men who had stopped drinking at baseline but had high prior alcohol consumption, then the association with alcohol would be attenuated, and, with extreme misclassification, alcohol could appear protective for prostate cancer. Since our results suggest a linear trend for risk of nonadvanced prostate cancer, our results are less likely to be the result of misclassification bias. Furthermore, assessing alcohol intake through a self-administered questionnaire has been shown to provide a valid estimate in prospective studies (25).

Alcoholic beverages have been identified as known human carcinogens, with several biologically plausible mechanisms that may influence prostate cancer (5, 8, 9). Acetaldehyde, the major metabolite of alcohol, may be a direct carcinogen capable of forming DNA adducts (1). Men consuming at least one drink daily had lower levels of sex hormone-binding globulin, which has been inversely associated with prostate cancer risk (27, 28), than nondrinking men (26). We cannot explain the suggested protective effect of heavy drinking in fatal cancers, although alcohol, especially high exposures, has been shown to alter hormonal profiles through diminishing testicular function (29) and lowering circulating testosterone (30). However, a recent analysis of 18 pooled prospective studies did not find an association between either testosterone or estradiol and prostate cancer risk (27), and there was no improvement in prostate cancer survival among men consuming at least 50 g of alcohol per day (HR = 1.35, 95% CI: 0.83, 1.21) or men reporting drinking daily (HR = 0.76, 95% CI: 0.51, 1.14) in a similar cohort study of health professionals (9).

Alcohol appeared protective against fatal prostate cancer among overweight men (data not shown). It is possible that the estrogenic effect of alcohol combined with estrogen from adipose tissue decreased prostate cancer risk among overweight men, but it is more likely a result of chance, since a similar association was not noted in obese men. Smoking and energy intake (excluding calories from alcohol) confounded the association of alcohol and fatal prostate cancers here. Both smoking and high energy intake are demonstrated deleterious risk factors for fatal prostate cancers (31, 32).

All alcoholic beverage types contributed to increased risk. Beer and liquor were associated with modestly increased risk in a US population-based case-control study (5) and large cohort study (9). Most investigations have focused on wine rather than beer or liquor. Schoonen et al. (12) observed a 6% decrease in prostate cancer risk per glass of red wine in a large population-based case-control study among men 40–64 years of age (odds ratio = 0.45, 95% CI: 0.23, 0.85, comparing men who had 8 or more drinks per week with nondrinkers). A subsequent investigation in a cohort study with longer follow-up time and a more detailed assessment found no association with red wine but saw a positive linear trend for white wine and higher prostate cancer risk (RR = 1.43 comparing men who drank >1 glass/day with nondrinkers) (10). White wine was also associated with increased risk (HR = 1.27) in a large cohort study of men aged 50–76 years in Washington State; no association was seen for beer or liquor (13). We were unable to assess red and white wines separately because information on type of wine consumed was not collected.

A handful of studies suggest that men considered heavy alcohol consumers or alcohol abusers have higher prostate cancer incidence (5, 23). Men who reported 8 or more drinks per day in a US population-based case-control study were almost twice as likely to develop prostate cancer (RR = 1.9) (5). Two studies of alcoholics in Sweden and alcohol abusers in Denmark were pooled, with a standardized incidence ratio of 1.22 (95% CI: 1.04, 1.42) (23). There is also evidence, from a cohort of US health professionals (9), that men who drank large amounts of alcohol in a short time (i.e., binge drinkers) have a higher risk of prostate cancer (HR = 1.63). We did not have information on frequency of intake to examine binge drinking.

There are several notable strengths of our study. A large number of incident and fatal prostate cancer cases provided substantial power to detect modest potential associations that may have been obscured in smaller investigations. Furthermore, information about alcohol consumption was prospectively collected before cancer diagnosis, thus minimizing recall bias. We also acknowledge some limitations including the lack of information on lifetime drinking patterns, binge drinking, and type of wine consumed (red vs. white). Although all multivariate analyses included both PSA and DRE screening in response to a single question about testing in the past 3 years in a subset of participants (>60%) from a once-administered questionnaire, we must consider the possibility of confounding by screening. In addition, we did not have data about prostate cancer therapy, which could have affected our results for fatal prostate cancers if treatment is associated with alcohol consumption. Residual confounding by additional unmeasured or unexamined variables cannot be excluded; however, we controlled for numerous potential confounders, and none substantially affected our risk estimates.

In conclusion, we found higher alcohol consumption to be associated with increased nonadvanced prostate cancer risk. These findings from a large prospective cohort contribute evidence that moderate drinking may have a modest impact on early prostate cancers but is unlikely to affect advanced or fatal prostate cancers.

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REFERENCES

1. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol.* 2006;7(2):149–156.

2. World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR). *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR; 2007.
3. Rohrmann S, Linseisen J, Key TJ, et al. Alcohol consumption and the risk for prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev.* 2008;17(5):1282–1287.
4. Putnam SD, Cerhan JR, Parker AS, et al. Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. *Ann Epidemiol.* 2000;10(6):361–369.
5. Hayes RB, Brown LM, Schoenberg JB, et al. Alcohol use and prostate cancer risk in US blacks and whites. *Am J Epidemiol.* 1996;143(7):692–697.
6. Middleton Fillmore K, Chikritzhs T, Stockwell T, et al. Alcohol use and prostate cancer: a meta-analysis. *Mol Nutr Food Res.* 2009;53(2):240–255.
7. Tippett KS, Cypel YS. *Design and Operation: The Continuing Survey of Food Intakes by Individuals and Diet and Health Knowledge Survey, 1994–96. Continuing Survey of Food Intakes by Individuals, Nationwide Food Surveys*. Washington, DC: Agricultural Research Service, US Department of Agriculture; 1997.
8. Dennis LK, Hayes RB. Alcohol and prostate cancer. *Epidemiol Rev.* 2001;23(1):110–114.
9. Platz EA, Leitzmann MF, Rimm EB, et al. Alcohol intake, drinking patterns, and risk of prostate cancer in a large prospective cohort study. *Am J Epidemiol.* 2004;159(5):444–453.
10. Sutcliffe S, Giovannucci E, Leitzmann MF, et al. A prospective cohort study of red wine consumption and risk of prostate cancer. *Int J Cancer.* 2007;120(7):1529–1535.
11. Baglietto L, Severi G, English DR, et al. Alcohol consumption and prostate cancer risk: results from the Melbourne Collaborative Cohort Study. *Int J Cancer.* 2006;119(6):1501–1504.
12. Schoonen WM, Salinas CA, Kiemeney LA, et al. Alcohol consumption and risk of prostate cancer in middle-aged men. *Int J Cancer.* 2005;113(1):133–140.
13. Velicer CM, Kristal A, White E. Alcohol use and the risk of prostate cancer: results from the VITAL Cohort Study. *Nutr Cancer.* 2006;56(1):50–56.
14. Sesso HD, Paffenbarger RS Jr, Lee IM. Alcohol consumption and risk of prostate cancer: the Harvard Alumni Health Study. *Int J Epidemiol.* 2001;30(4):749–755.
15. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health–American Association of Retired Persons Diet and Health Study. *Am J Epidemiol.* 2001;154(12):1119–1125.
16. Michaud D, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH–AARP Diet and Health Study. *J Registry Manage.* 2005;3270–3275.
17. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc Series B Stat Methodol.* 1972(34):187–220.
18. Breslow NE, Day NE. *Statistical Methods in Cancer Research*. Lyon, France: International Agency for Research on Cancer; 1987.
19. Sharpe CR, Siemiatycki J. Case-control study of alcohol consumption and prostate cancer risk in Montréal, Canada. *Cancer Causes Control*. 2001;12(7):589–598.
20. Breslow RA, Wideroff L, Graubard BI, et al. Alcohol and prostate cancer in the NHANES I epidemiologic follow-up study. First National Health and Nutrition Examination Survey of the United States. *Ann Epidemiol.* 1999;9(4):254–261.
21. Chao C, Haque R, Van Den Eeden SK, et al. Red wine consumption and risk of prostate cancer: the California Men's Health Study. *Int J Cancer.* 2010;126(1):171–179.
22. Bagnardi V, Blangiardo M, La Vecchia C, et al. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer.* 2001;85(11):1700–1705.
23. Dennis LK. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. *Prostate.* 2000;42(1):56–66.
24. Barba M, McCann SE, Schünemann HJ, et al. Lifetime total and beverage specific—alcohol intake and prostate cancer risk: a case-control study. *Nutr J.* 2004;3:23. (doi:10.1186/1475-2891-3-23).
25. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol.* 1991;133(8):810–817.
26. Shiels MS, Rohrmann S, Menke A, et al. Association of cigarette smoking, alcohol consumption, and physical activity with sex steroid hormone levels in US men. *Cancer Causes Control*. 2009;20(6):877–886.
27. Roddam AW, Allen NE, Appleby P. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. Endogenous Hormones and Prostate Cancer Collaborative Group. *J Natl Cancer Inst.* 2008;100(3):170–183.
28. Gann PH, Hennekens CH, Ma J, et al. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst.* 1996;88(16):1118–1126.
29. Gordon GG, Altman K, Southren AL, et al. Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. *N Engl J Med.* 1976;295(15):793–797.
30. Green GR. Mechanism of hypogonadism in cirrhotic males. *Gut.* 1977;18(10):843–853.
31. Platz EA, Leitzmann MF, Michaud DS, et al. Interrelation of energy intake, body size, and physical activity with prostate cancer in a large prospective cohort study. *Cancer Res.* 2003;63(23):8542–8548.
32. Watters JL, Park Y, Hollenbeck A, et al. Cigarette smoking and prostate cancer in a prospective US Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(9):2427–2435.