Alcohol Consumption, Finasteride, and Prostate Cancer Risk

Results From the Prostate Cancer Prevention Trial

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BACKGROUND: Current research is inconclusive regarding the relation between alcohol consumption and prostate cancer risk. In this study, the authors examined the associations of total alcohol, type of alcoholic beverage, and drinking pattern with the risk of total, low-grade, and high-grade prostate cancer. **METHODS:** Data for this study came from the 2129 participants in the Prostate Cancer Prevention Trial (PCPT) who had cancer detected during the 7-year trial and 8791 men who were determined by biopsy to be free of cancer at the trial end. Poisson regression was used to calculate relative risks (RRs) and 95% confidence intervals (95% CIs) for associations of alcohol intake with prostate cancer risk. **RESULTS:** Associations of drinking with high-grade disease did not differ by treatment arm. In combined arms, heavy alcohol consumption (≥50 g of alcohol daily) and regular heavy drinking (≥4 drinks daily on ≥5 days per week) were associated with increased risks of high-grade prostate cancer (RR, 2.01 [95% CI, 1.33-3.05] and 2.17 [95% CI, 1.42-3.30], respectively); less heavy drinking was not associated with risk. Associations of drinking with low-grade cancer differed by treatment arm. In the placebo arm, there was no association of drinking with risk of low-grade cancer. In the finasteride arm, drinking ≥50 g of alcohol daily was associated with an increased risk of low-grade disease (RR, 1.89; 95% CI, 1.39-2.56); this finding was because of a 43% reduction in the risk of low-grade cancer attributable to finasteride treatment in men who drank <50g of alcohol daily and the lack of an effect of finasteride in men who drank ≥50 g of alcohol daily ($P_{interaction}$ = .03). **CONCLUSIONS:** Heavy, daily drinking increased the risk of high-grade prostate cancer. Heavy drinking made finasteride ineffective for reducing prostate cancer risk. **Cancer 2009;115:3661–9. © 2009 American Cancer Society.**

KEY WORDS: alcohol consumption, finasteride, low-grade prostate cancer, high-grade prostate cancer.

Whether alcohol affects prostate cancer risk is uncertain. Most studies have reported no significant associations,[1-7] although 2 meta-analyses reported an approximate 20% increase in risk among heavy drinkers.[2,4] Among the studies that have reported significant associations, there is little consistency in the effect size or direction, pattern of dose-response, or associations specific to type of alcoholic beverage, clinical stage, or pathologic grade.[8-16] Studies that can clarify the association of alcohol consumption with

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prostate cancer risk are important, because, beyond obesity,[17] smoking,[18-21] and perhaps diet,[18,22,23] prostate cancer has no well established, modifiable risk factors.

In this article, we report results on the association of alcohol consumption and risk of prostate cancer from the Prostate Cancer Prevention Trial (PCPT). We examined the relations of total alcohol consumption, alcohol from different types of beverages, and usual drinking pattern with the risks of total, low-grade, and high-grade prostate cancer. We also examined whether the effects of finasteride (the PCPT study drug) were modified by alcohol consumption, because both affect the metabolism of testosterone.[24,25] Results of this study address whether alcohol consumption is associated with risks of biopsy-detected presence or absence of local stage prostate cancer and whether alcohol consumption should be considered when making clinical recommendations for the use of finasteride for prostate cancer prevention.

MATERIALS AND METHODS

Study Design and Study Population

All data for this study were collected as part of the PCPT, a randomized, placebo-controlled trial testing whether finasteride, a 5α-reductase inhibitor, could reduce the 7-year period prevalence of prostate cancer. Informed consent was obtained from each participant before the study. Details of the study design and participant characteristics have been described previously.[26] Briefly, in total, 18,880 men aged ≥55 years with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level ≤3.0 ng/mL were randomized to receive either finasteride (5 mg daily) or placebo. During the PCPT, men underwent DRE and PSA determinations annually, and a prostate biopsy was recommended for participants who had an abnormal DRE or a PSA ≥4.0 ng/mL. At the final study visit in Year 7, all men who had not previously been diagnosed with prostate cancer were offered an end-of-study biopsy. All biopsies were collected under transrectal ultrasonographic guidance and involved a minimum of 6 specimens (cores). All biopsies were reviewed to confirm the diagnosis of adenocarcinoma both by the pathologist at the local study site and by a central pathology laboratory. Tumors were graded centrally and were categorized as low-grade (Gleason sum, 2-6) or high-grade (Gleason sum, 7-10) prostate cancer.

Of 18,880 participants, we excluded 7539 men (39.9%) who did not have an end-of-study biopsy, which included 1393 men who died, 6141 men who were medically unable or refused, and 5 men who underwent prostatectomy for reasons other than cancer, leaving 2400 cases and 8941 noncases. Next, we excluded 173 men who were diagnosed after the trial end date (June 23, 2003), 90 men who were diagnosed ≥180 days after their planned end-of-study visit, and 99 men (noncases) whose end-of-study biopsy was completed ≥180 days before their end-of-study visit. From the 10,979 men remaining for study, we also excluded 59 men who had incomplete or missing questionnaire data on any of the following factors: alcohol consumption (n = 4), current smoking status (n = 5), physical activity (n = 48), education (n = 1), and both education and physical activity (n = 1), which left 10,920 men for the current analyses.

Data Collection

Details regarding age, race, education, diabetes status, family history of prostate cancer in first-degree relatives, physical activity, history of smoking, and usual alcohol consumption were collected at baseline using self-administered questionnaires. Participants reported the frequency of consuming each type of beverage (beer, wine, and liquor) over the past year in 7 categories (never, 1 day per month, 2-3 days per month, 1-2 days per week, 3-4 days per week, 5-6 days per week, or every day). They reported the usual number of drinks on each drinking day and the usual size of each drink (small, medium, or large, treated as 0.5, 1.0, and 1.5, respectively, in our analyses). We calculated the number of standard servings per week for each type of alcoholic beverage by multiplying the days of drinking per week by number of drinks per drinking day and serving size. Standard servings were converted into grams of ethanol (beer, 12.96 g; wine, 12.35 g; and liquor, 13.93 g), and these were summed to obtain total alcohol intake in grams per week. Daily average grams of alcohol were categorized as 0 g, 0.1 g to <3 g, 3 g to <15 g, 15 g to <30 g, 30 g to <50 g, and ≥50 g. Informed consent was obtained from all participants.

Statistical Analysis

Multivariate models were used to estimate associations of alcohol intake with the risks of total, low-grade, and high-

grade prostate cancer while controlling for covariates. We used Poisson regression with a robust error variance, a modified Poisson regression approach proposed by Zou,[27] to calculate relative risks (RRs) and 95% confidence intervals (95% CIs). Regressions were completed using the SAS GENMOD procedure with the Log-link function, and the robust error variances were estimated by using a repeated statement and the subject identifier as the class variable.[27] Results are given adjusted for age (ages <60 years, 60-69 years, and ≥70 years), race (white, African American, and other) and body mass index (BMI) (<25 kg/m^2, 25-29.9 kg/m^2, and ≥30 kg/m^2). Further control for education, diabetes, smoking, family history of prostate cancer, physical activity, and baseline PSA level (<1 ng/mL, 1-1.9 ng/mL, and ≥2 ng/mL) did not affect the results. In the analyses of a specific type of alcoholic beverage, other types of alcoholic beverages were included as covariates. Tests for linear trend across categories were based on an ordinal variable corresponding to rank from lowest to highest category, as described by Breslow and Day.[28]

Drinking pattern was defined as the number of days per week on which men drank alcoholic beverages (<1 day, 1-4 days, and ≥5 days) stratified by the number of drinks per drinking day (1-3 drinks or ≥4 drinks). This distinguished men who drank heavily on a few days from those who drank modestly on many days.

Primary analyses were completed in each treatment arm separately. When there were no differences between arms, post hoc analyses are given for both study arms combined. We also examined whether the effect of finasteride was modified by level of alcohol consumption. All statistical tests were 2-sided and were considered statistically significant when $P < .05$. Statistical analyses were conducted using SAS software (version 9.1; SAS Institute, Inc., Cary, NC).

RESULTS

Among the total 10,920 men in this analysis, 2129 men (19.5%) were diagnosed with prostate cancer, including 1425 men (66.9%) with Gleason scores from 2 to 6, 564 men (26.5%) with Gleason scores ≥7, and 140 men (6.5%) with unknown Gleason scores. With regard to tumor classification (T), of 2129 cases, 1515 (71.2%) were stage T1, 505 (23.7%) were stage T2, 37 (1.7%) were stage T3, and 72 (3.4%) were of unknown stage. Younger age, white race, advanced education, no diabetes, a BMI <30 kg/m^2, smoking, and physical inactivity all were associated with higher alcohol consumption (Table 1). Other strong predictors of prostate cancer risk in this cohort, including PSA at baseline, finasteride treatment, and family history of prostate cancer, were not associated with alcohol consumption.

Only heavy drinking (≥50 g of alcohol per day) was associated with cancer risk, and there was no dose-response at lower levels of alcohol intake (Table 2). In the placebo arm, heavy alcohol intake was not associated with risk of total or low-grade cancer but was associated with a nonsignificant 67% increase in the risk of high-grade cancer. In the finasteride arm, heavy drinking was associated with a 89% increased risk of total cancer, a 101% increased risk for low-grade cancer, and a 115% increased risk of high-grade cancer (all $P < .01$). In a post hoc analysis, the RR for high-grade cancer associated with heavy drinking in the combined study arms was 2.01 (95% CI, 1.33-3.05; $P = .009$).

Table 3 shows associations of specific types of alcoholic beverages with prostate cancer risk. Heavy beer consumption was associated with a significant and large increased risk of high-grade cancer in both study arms; the RR for high-grade cancer contrasting no intake to heavy beer intake in the combined arms was 2.89 (95% CI, 1.76-4.76; $P < .0001$). In the placebo arm, heavy wine consumption was associated with a 79% increased risk of low-grade cancer ($P = .03$); whereas, in the finasteride arm, heavy beer drinking was associated with a 103% increased risk of low-grade cancer ($P < .0001$). There were no significant associations of liquor with cancer risk.

Occasional heavy drinking (≥4 drinks per day on <5 days per week) was not associated with cancer risk (data not shown). Heavy drinking on ≥5 days per week, compared with not drinking, was associated with a significantly increased risk of high-grade cancer in both the placebo arm (RR, 2.05; 95% CI, 1.04-4.04 [$P = .04$]) and the finasteride arm (RR, 2.25; 95% CI, 1.31-3.86 [$P = .003$]). In the combined arms, the RR was 2.17 (95% CI, 1.42-3.30; $P = .0003$).

Table 4 presents the effects of finasteride treatment in the risk of prostate cancer by levels of alcohol consumption. We dichotomized alcohol intake into <50 g daily versus ≥50 g daily based on results in Table 2 and noted that the effects of finasteride were similar across all levels

Table 1. Associations of Demographic, Health, and Lifestyle Characteristics With Alcohol Consumption: The Prostate Cancer Prevention Trial

Characteristic	Total Cohort: No. (%), n=10,920	Total Alcohol Intake, %*				P†
		0 g/d, n=8655	0.1-14.9 g/d, n=1357	15-49.9 g/d, n=648	≥50 g/d, n=260	
Age, y						
<60	3528 (32.3)	21.8	57.5	18	2.7	.007
60-69	5993 (54.9)	24.3	54.6	18.7	2.4	
≥70	1399 (12.8)	25.3	55.3	17.9	1.5	
Race						.02
White	10,167 (93.1)	23.6	55.4	18.6	2.4	
African American	370 (3.4)	26.2	59.2	14.1	0.5	
Other	383 (3.5)	23.8	58.7	15.1	2.4	
Education level						
High school	2445 (22.4)	31.7	51.7	13.9	2.7	<.0001
College degree	4434 (40.6)	22.2	55.8	19.7	2.3	
Advanced degree	4041 (37)	20.4	57.7	19.6	2.3	
Family history of prostate cancer						
No	9080 (83.2)	23.8	55.5	18.3	2.4	.84
Yes	1840 (16.8)	23	56.2	18.6	2.2	
Diabetes						
No	10204 (93.4)	23.2	55.8	18.6	2.4	.0001
Yes	716 (6.6)	30.3	52.7	14.8	2.2	
Treatment						
Placebo	5587 (51.2)	23.4	55.8	18.6	2.2	.37
Finasteride	5333 (48.8)	23.9	55.4	18.1	2.6	
BMI, kg/m^2						
<25	2768 (25.4)	24.1	55.4	18.2	2.3	.01
25-29	5546 (50.8)	22.5	55.7	19.4	2.4	
≥30	2506 (22.9)	25.6	55.7	16.1	2.6	
Missing data	100 (0.9)	27	52	21	0	
Current smoking						
No	10,184 (93.3)	23.8	56	18	2.2	<.0001
Yes	736 (6.7)	21.5	50.5	23.5	4.5	
PSA, ng/mL						
<1	4541 (41.6)	24.2	55.4	18	2.4	.87
1-1.9	4239 (38.8)	23.1	55.7	18.9	2.3	
≥2.0	2140 (19.6)	23.6	55.9	18.1	2.4	
Physical activity						
Sedentary	1897 (17.4)	26.5	54.7	16.3	2.5	.01
Light	4526 (41.5)	22.2	56.8	18.6	2.4	
Moderate	3411 (31.2)	23.4	55	19.3	2.3	
Very active	1086 (9.9)	25.4	53.9	18.4	2.3	

BMI indicates body mass index; PSA, prostate-specific antigen.
* Row percentage.
† *P* values were determined by using the chi-square test.

of alcohol intake <50 g daily (data not shown). For total cancer, finasteride lowered risk by 29% among men who drank <50 g of alcohol per day but increased risk by 17% among heavy alcohol drinkers ($P_{interaction} = .03$). For low-grade cancer, finasteride decreased the risk by 43% among men who drank <50 g of alcohol per day and increased the risk by 12% among heavy drinkers ($P_{interaction} = .03$). For high-grade cancer, finasteride increased the risk by 19% among men who drank <50 g of alcohol per day and by 78% among heavy drinkers ($P_{interaction} = .36$).

Table 2. Associations of Alcohol Consumption With Risks of Total, Low-Grade, and High-Grade Prostate Cancer Stratified by Study Arm: The Prostate Cancer Prevention Trial

	Total Cancers		Low-Grade Cancers*		High-Grade Cancers	
Total Alcohol Consumption, g/d	Cases/ Cohort	RR† (95% CI)	Cases/ Cohort	RR† (95% CI)	Cases/ Cohort	RR† (95% CI)
Placebo arm‡						
No alcohol consumption	296/1306	1.00	217/1227	1.00	57/1284	1.00
>0 to <3	327/1488	0.97 (0.85-1.11)	245/1406	0.99 (0.84-1.16)	67/1473	1.03 (0.73-1.45)
3 to <15	359/1631	0.98 (0.85-1.12)	252/1524	0.94 (0.79-1.10)	81/1605	1.17 (0.84-1.62)
15 to <30	168/708	1.05 (0.89-1.23)	126/666	1.06 (0.87-1.30)	29/695	0.96 (0.62-1.48)
30 to <50	82/333	1.09 (0.88-1.35)	59/310	1.08 (0.83-1.40)	17/327	1.20 (0.71-2.04)
≥50	28/121	1.05 (0.75-1.46)	17/110	0.88 (0.56-1.38)	8/118	1.67 (0.81-3.41)
P_{trend}		.39		.82		.31
Finasteride arm‡						
No alcohol consumption	192/1277	1.00	106/1191	1.00	73/1264	1.00
>0 to <3	229/1444	1.08 (0.91-1.29)	136/1351	1.15 (0.90-1.46)	77/1428	0.97 (0.71-1.32)
3 to <15	260/1509	1.17 (0.98-1.38)	151/1400	1.23 (0.97-1.55)	93/1493	1.10 (0.82-1.49)
15 to <30	105/649	1.10 (0.88-1.36)	67/611	1.24 (0.93-1.66)	30/641	0.84 (0.56-1.28)
30 to <50	46/315	1.00 (0.74-1.35)	28/297	1.08 (0.72-1.60)	16/313	0.93 (0.55-1.60)
≥50	37/139	1.89 (1.39-2.56)	21/123	2.01 (1.30-3.09)	16/139	2.15 (1.33-3.71)
P_{trend}		.02		.02		.26
$P_{interaction}$ for alcohol intake as a 6-level ordinal variable		.22		.09		.93

RR indicates relative risk; 95% CI, 95% confidence interval.
* Men who were diagnosed with high-grade cancer were excluded from the cohort in the low-grade cancer analyses.
† The RR was adjusted for age, race, and body mass index.
‡ Eighty-five cases in the placebo arm and 55 cases in the finasteride arm with missing Gleason scores were not included in the analyses by grade.

DISCUSSION

In this large cohort of men with biopsy-determined presence or absence of prostate cancer, heavy alcohol consumption (≥50 g per day) was associated with a 101% increased risk of high-grade prostate cancer. Heavy beer drinking was associated independently with a 189% increased risk of high-grade cancer; because of lower consumption, the independent associations with heavy wine and liquor consumption could not be evaluated rigorously. The pattern of occasional heavy drinking (≥4 drinks per day on <5 days per week) was not associated with the risk of cancer, but heavy drinking on ≥5 days per week was associated with a 117% increased risk of high-grade cancer. Finally, there was a significant interaction between heavy alcohol consumption and finasteride treatment for low-grade cancer. Finasteride reduced the risk of low-grade cancer by 43% in men who drank <50 g of alcohol per day, but finasteride had no effect in heavy drinkers.

Overall, our results are consistent with findings from 2 meta-analyses and 1 review concluding that light-to-moderate alcohol consumption is not associated with the risk of prostate cancer.[1,2,4] Our findings on heavy drinking and, in particular, its association with the risk only for high-grade cancer are not consistent with relevant published studies. For comparison, we examined the 6 studies with alcohol intake categories that were at least as high as our heavy drinking category (≥4 drinks per day)[3,5,29-32] plus an additional 4 studies in which the highest alcohol intake category was at least as high as ≥2 drinks per day.[8,14,16,33] Of those 10 studies, 2 reported an RR <0.80,[5,8] and 1 reported an RR >1.20[31] associated with heavy drinking; statistically significant RRs were limited to 0.23 (95% CI, 0.06-0.95) associated with ≥22 drinks per week (based on 2 cases)[8] and 1.4 (95%CI, 1.0-1.8) and 1.9 (95% CI, 1.3-2.7) associated with 22 to 56 drinks per week and ≥57 drinks per week (based on 211 cases and 96 cases),[31] respectively. Furthermore, there were no differences in findings by measures of tumor aggressiveness in studies that conducted stratified analyses.[3,14,16,31,32] Several of those studies were small, used case-control designs, or did not comprehensively assess

Table 3. Associations of Specific Types of Alcohol Consumption With Risks of Total, Low-Grade, and High-Grade Prostate Cancer, Stratified by Study Arm: the Prostate Cancer Prevention Trial

	Total Cancers		Low-Grade Cancers*		High-Grade Cancers	
Alcohol Consumption, g/d	Cases/ Cohort	RR† (95% CI)	Cases/ Cohort	RR† (95% CI)	Cases/ Cohort	RR† (95% CI)
Placebo arm‡						
Alcohol from beer						
No beer consumption	454/2044	1.00	325/1915	1.00	96/2011	1.00
>0 to <15	722/3165	1.02 (0.89-1.16)	532/2975	1.08 (0.92-1.26)	142/3117	0.83 (0.61-1.14)
15 to <50	64/286	1.02 (0.80-1.29)	48/270	1.08 (0.82-1.44)	13/283	0.87 (0.48-1.58)
≥50	12/55	1.10 (0.67-1.82)	5/48	0.72 (0.30-1.60)	6/54	2.65 (1.19-5.92)
P_{trend}		.99		.94		.85
Alcohol from wine						
No wine consumption	452/2067	1.00	328/1943	1.00	91/2034	1.00
>0 to <15	742/3271	1.03 (0.91-1.17)	543/3072	1.04 (0.90-1.21)	151/3223	1.04 (0.76-1.43)
15 to <30	44/172	1.16 (0.88-1.53)	30/158	1.12 (0.79-1.59)	10/168	1.34 (0.70-2.56)
≥30§	12/35	1.58 (1.00-2.51)	10/33	1.79 (1.06-3.02)	2/35	1.36 (0.35-5.34)
P_{trend}		.23		.20		.66
Alcohol from liquor						
No liquor consumption	548/2467	1.00	412/2331	1.00	102/2433	1.00
>0 to <15	624/2766	0.98 (0.86-1.10)	443/2585	0.91 (0.78-1.05)	138/2723	1.24 (0.91-1.69)
15 to <50	76/305	1.05 (0.85-1.31)	53/282	0.97 (0.74-1.27)	16/298	1.32 (0.77-2.29)
≥50	7/20	1.60 (0.89-2.87)	5/18	1.59 (0.75-3.34)	1/19	1.39 (0.20-9.62)
P_{trend}		.76		.66		.38
Finasteride arm‡						
Alcohol from beer						
No beer consumption	306/1949	1.00	176/1819	1.00	114/1933	1.00
>0 to <15	500/3018	1.04 (0.88-1.22)	299/2817	1.00 (0.80-1.25)	164/2981	0.94 (0.70-1.27)
15 to <50	42/287	0.92 (0.67-1.26)	23/268	0.83 (0.54-1.28)	17/285	1.00 (0.58-1.70)
≥50	18/55	2.20 (1.49-3.26)	9/46	2.03 (1.11-3.71)	9/55	3.04 (1.61-5.76)
P_{trend}		.18		.71		.24
Alcohol from wine						
No wine consumption	317/2001	1.00	171/1855	1.00	123/1978	1.00
>0 to <15	509/3087	1.04 (0.89-1.23)	312/2890	1.19 (0.95-1.49)	167/3057	0.88 (0.66-1.18)
15 to <30	30/157	1.26 (0.88-1.79)	18/145	1.39 (0.86-2.25)	11/156	1.24 (0.66-2.33)
≥30§	7/43	1.03 (0.51-2.08)	5/41	1.29 (0.54-3.03)	2/43	0.79 (0.20-3.19)
P_{trend}		.54		.13		.46
Alcohol from liquor						
No liquor consumption	395/2455	1.00	226/2286	1.00	138/2424	1.00
>0 to <15	416/2528	0.99 (0.85-1.15)	245/2357	0.97 (0.79-1.20)	149/2506	1.14 (0.87-1.51)
15 to <50	50/296	1.00 (0.76-1.34)	34/280	1.14 (0.79-1.64)	14/294	0.91 (0.52-1.60)
≥50	4/20	1.18 (0.50-2.81)	2/18	1.08 (0.30-3.84)	2/20	1.72 (0.44-6.76)
P_{trend}		.77		.86		.96

RR indicates relative risk; 95% CI, 95% confidence interval.

* Men who were diagnosed with high-grade cancer were excluded from the cohort in the low-grade cancer analyses.

† The RR was adjusted for age, race, body mass index, and other types of beverage intake for each specific type of alcohol intake.

‡ Eighty-five cases in the placebo arm and 55 cases in the finasteride arm with missing Gleason scores were not included in the analyses by grade.

§ This category was reduced to ≥30 g/d of alcohol because of the small numbers of heavy wine drinkers.

usual alcohol intake, but the inconsistency of the current study with results from other large and well conducted studies is difficult to explain. It is possible that other studies were affected by a PSA detection bias, which would mask an association if heavy drinkers were less likely to get PSA screening.[34] It is also possible that the characteristics of cancer cases in the PCPT, nearly all of which were screen-detected and local stage, could have affected our findings, for example, if heavy alcohol consumption reduced prostate size or modified the appearance of small, intermediate-grade cancers. The mean prostate volume was smaller in heavy drinkers compared with others (25.7 mL vs 28.0 mL; $P = .04$), but this magnitude of difference is not likely to affect disease detection substantially.

Table 4. Associations Between Finasteride Treatment and the Risk of Prostate Cancer Stratified by Alcohol Consumption: The Prostate Cancer Prevention Trial

	Total Cancers		Low-Grade Cancers*		High-Grade Cancers	
Alcohol Consumption	Cases/ Cohort	RR† (95% CI)	Cases/ Cohort	RR† (95% CI)	Cases/ Cohort	RR† (95% CI)
<50 g/d						
Placebo arm‡	1232/5466	1.00	899/5133	1.00	251/5384	1.00
Finasteride arm‡	832/5194	0.71 (0.66-0.77)	488/4850	0.57 (0.52-0.64)	289/5139	1.19 (1.01-1.41)
≥50 g/d						
Placebo arm	28/121	1.00	17/110	1.00	8/118	1.00
Finasteride arm	37/139	1.17 (0.77-1.79)	21/123	1.12 (0.62-2.00)	16/139	1.78 (0.79-4.01)
$P_{interaction}$		.03		.03		.36

RR indicates relative risk; 95% CI, 95% confidence interval.

* Men who were diagnosed with high-grade cancer were excluded from the cohort in the low-grade cancer analyses.

† The RR was adjusted for age, race, and body mass index.

‡ Eighty-five cases in the placebo arm and 55 cases in the finasteride arm with missing Gleason scores were not included in the analyses by grade.

Clearly, the replication of these findings and an investigation into potential biases affecting studies of alcohol and prostate cancer are needed.

Among the different types of alcoholic beverages, only heavy beer consumption was associated consistently with prostate cancer risk. Results of previous studies examining types of alcoholic beverages and prostate cancer risk have been inconsistent.[3,5-7,9-16,35-37] Most reported no differences in prostate cancer risk between different types of alcoholic beverages[3,5-7,11-13]; some studies reported higher risks associated with beer consumption,[9,36] and others reported higher risks associated with liquor consumption.[10,37] Whether beer is uniquely associated with the risk of prostate cancer is uncertain. Few studies, including ours, had enough heavy liquor or wine consumers to detect a unique effect, and it is possible that the unique effects of beer are attributable to its high consumption relative to other alcoholic beverages. The effects of wine also may be masked because of differences between red and white wines[3,12,35]; however, we lacked data to address this question.

Only 2 studies have examined associations of patterns of heavy drinking with the risk of prostate cancer. One reported an increased risk (RR, 1.64; 95% CI, 1.13-2.38) among men who drank large amounts of alcohol (≥105 g per week) on 1 or 2 days per week but no risk when men drank a similar daily amount on average (≥50 g daily) every day of the week.[13] A second study reported a nonsignificant trend for increasing risk among men who drank ≥140 g per week when spread over a few days of the week (RR for 7 days, 4-6 days, and 1-3 days: 1.00, 1.20, and 1.56, respectively), but no increased risk was associated with drinking a similar daily amount on average (≥60 g daily) every day of the week.[3] We observed no evidence that drinking ≥4 drinks daily on <5 days per week was associated with cancer risk. It is difficult to hypothesize a mechanism whereby occasional drinking, but not regular heavy drinking, would increase cancer risk; and findings in previous studies, which were based on very small numbers, may have been because of chance. Indeed, binge drinking is rare in middle-aged and older men[38] and is rarer still in the men who participate in most research studies; much larger studies with detailed alcohol assessment will be needed to address this association in the future. On the basis of current evidence, there appears to be no association between occasional heavy drinking and the risk of prostate cancer.

There are several mechanisms whereby alcohol consumption may influence prostate carcinogenesis. Alcohol itself may be carcinogenic.[39] It affects the metabolism of carcinogens and suppresses DNA repair[40,41]; it may increase DNA damage because of oxidative stress[42,43]; and, at high levels, it impairs immune response and increases the risk of micronutrient deficiencies.[44] Unlike the digestive tract and liver, which have characteristics that make them uniquely susceptible to 1 or more of these effects of alcohol, we know of no such characteristics of the prostate. Planned future analyses of circulating steroid hormones, genetic characteristics, markers of oxidative stress, and prostate tissue pathology in the PCPT may

better elucidate the mechanisms underlying the effects of alcohol reported here.

The observation that finasteride did not reduce the risk of low-grade cancer among heavy drinkers is notable. In the sample of PCPT participants that we used in these analyses, finasteride treatment decreased the risk of total and low-grade prostate cancer by 28% (95% CI, 33%-22%) and 42% (95% CI, 47%-36%), respectively, and it increased the risk of high-grade cancer by 22% (95% CI, 4%-43%). Our results suggest that finasteride will not lower prostate cancer risk among men who are heavy drinkers. This finding is not because of poor adherence, because compliance based on pill counts was 66% in both heavy drinkers and nonheavy drinkers. Several mechanisms are plausible: Alcohol induces the expression of 5α-reductase (the action of finasteride is through competitive inhibition of 5α-reductase),[45] and it affects enzyme expression and oxidative stress in the liver (in which finasteride primarily is metabolized).[46] Future studies in the PCPT will examine whether heavy drinking affects finasteride metabolism or finasteride induces changes in steroid hormone metabolism.

Our study had several strengths. First, all men had biopsy-proven absence or presence of prostate cancer, and this minimized the potential misclassification bias. Second, alcohol intake was assessed using a detailed questionnaire and not with a food frequency questionnaire, allowing us to examine the effects of specific types of alcoholic beverages as well as heavy or binge drinking patterns. Third, all men were screened for prostate cancer by both PSA level and DRE during the study period, which eliminated any potential bias from PSA screening. This study also had several limitations. The number of men who were heavy drinkers was modest; and, when the results were stratified by study arm and cancer grade, the statistical power was limited. Data on alcohol consumption were available only for the year preceding study entry. Finally, because almost all cases of prostate cancer were screen detected, we could not examine associations with regional or distant stage disease.

In summary, we observed that heavy drinking was associated with an increased risk of high-grade, screen-detected prostate cancer. This finding is somewhat unique in the literature and requires replication; however, physicians may choose to consider this finding when counseling men on reducing their risk of prostate cancer. We also observed that heavy drinkers did not benefit from finasteride treatment. It would be prudent for physicians who are recommending finasteride for prostate cancer prevention to assess their patients' alcohol consumption and recommend drinking no more than 2 or 3 drinks per day.

Conflict of Interest Disclosures

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