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Alcohol Intake Increases High-grade Prostate Cancer Risk Among Men Taking Dutasteride in the REDUCE Trial

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Abstract

Background—Although most studies found no association between alcohol intake and prostate cancer (PCa) risk, an analysis of the Prostate Cancer Prevention Trial found that high alcohol intake significantly increased PCa risk among men randomized to the 5 α -reductase inhibitor (5-ARI) finasteride.

Objective—Determine whether alcohol affects PCa risk among men taking the 5-ARI dutasteride.

Design, settings, and participants—Reduction by Dutasteride of Prostate Cancer Events was a 4-yr, multicenter, randomized, double-blind, placebo-controlled trial to compare PCa after dutasteride administration (0.5 mg/d) with placebo. Participants had a baseline prostate-specific

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antigen between 2.5 and 10.0 ng/ml and a recent negative prostate biopsy. Alcohol intake was determined by baseline questionnaire, and participants underwent a prostate biopsy to determine PCa status at 2 yr and 4 yr of follow-up.

Outcome measurements and statistical analysis—Multivariable logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between alcohol intake and low-grade (Gleason <7) and high-grade (Gleason >7) PCa.

Results and limitations—Of 6374 participants in our analysis, approximately 25% reported no alcohol consumption, 49% were moderate drinkers (one to seven drinks per week), and 26% were heavy drinkers (more than seven drinks per week). Alcohol intake was not associated with low- or high-grade PCa in the placebo arm and was not associated with low-grade PCa among men taking dutasteride. In contrast, men randomized to dutasteride and reporting more than seven drinks per week were 86% more likely to be diagnosed with high-grade PCa ($p=0.01$). Among alcohol abstainers, dutasteride was associated with significantly reduced risk of high-grade PCa (OR: 0.59; 95% CI, 0.38–0.90), but dutasteride was no longer associated with reduced high-grade PCa among men reporting high alcohol intake (OR: 0.99; 95% CI, 0.67–1.45).

Conclusions—Alcohol consumption negated a protective association between dutasteride and high-grade PCa.

Patient summary—We confirmed a prior study that alcohol affects PCa prevention in patients taking 5-ARIs. Patients taking 5-ARIs may wish to eliminate alcohol intake if they are concerned about PCa.

Keywords

Prostate cancer; Dutasteride; Alcohol trial

1. Introduction

Alcohol consumption may increase oxidative stress and alter steroid hormone metabolism [1], and increasing alcohol intake is associated with a modest increase in the risk of several cancers, including cancers of the oral cavity, esophagus, liver, female breast, and colon [2,3]. However, although prostate carcinogenesis also likely involves steroidal and inflammatory pathways, the relationship between alcohol intake and prostate cancer (PCa) risk remains unclear. Indeed, most cohort and case-control studies report no evidence of an association [4,5]. Other studies report an effect of alcohol specific to high-grade PCa [6], low-grade PCa [7], heavy alcohol consumers [8,9], increased frequency of alcohol intake [10], lifetime alcohol intake [11,12], or beer intake specifically [11]. Alcohol intake may change over time and with aging; vary with culture, region, and education [13]; and correlate with diet and other health behaviors [14]. As such, inconsistency in research results may be a function of the difficulty of measuring habitual and lifetime alcohol intake among older men across different populations while also controlling for differences in health behaviors or PCa screening or detection potentially correlated with alcohol use [6].

Although most studies report little to no association, it remains possible that the effects of alcohol intake on PCa risk may be restricted to a subset of men under metabolic or

physiologic distress who are thus more susceptible to the otherwise modest procarcinogenic effects of alcohol intake. Interestingly, a recent analysis of the Prostate Cancer Prevention Trial (PCPT) found that the highest category of alcohol intake was significantly associated with increased risk of both low-grade (Gleason <7) and high-grade (Gleason >7) PCa at follow-up biopsy but only among men taking finasteride [15,16]. Finasteride is a 5 α -reductase inhibitor (5-ARI) that blocks the conversion of testosterone to the more biologically active dihydrotestosterone (DHT), such that men taking finasteride have a reduced capacity to activate the androgen receptor. As such, an increase in total PCa associated with high alcohol intake only among men taking finasteride may suggest that any procarcinogenic effect of alcohol, presumably a marginal effect, requires decreased androgen receptor activity to be observed. In PCPT, the protective association between finasteride and low-grade PCa diagnosis was lost among heavy drinkers [15,16], suggesting that heavy drinking promotes PCa risk or negates a PCa risk reduction among finasteride users.

Finasteride and other 5-ARIs are widely administered to treat benign prostatic hyperplasia (BPH), and PCPT data suggest that BPH patients taking a 5-ARI who also consume alcohol may be at greater risk for PCa. The goal of this analysis was to confirm an association between alcohol intake and PCa found in PCPT using data from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, a 4-yr randomized, double-blind trial investigating the 5-ARI dutasteride and PCa detection among men with a prostate-specific antigen (PSA) level between 2.5 and 10.0 ng/ml and a recent negative prostate biopsy [17]. Dutasteride inhibits both 5 α -reductase type 1 and type 2, and dutasteride administration in REDUCE was significantly associated with a lower PCa detection rate at follow-up. If we find that high alcohol intake increases PCa detection among men on dutasteride coupled with the prior PCPT study, our data would suggest that men on 5-ARIs should be counseled about the risks of alcohol consumption.

2. Methods

2.1. Study population

Details of the REDUCE trial have been published [17]. The 4-yr trial included 8231 men randomized to dutasteride (0.5 mg/d; n = 4105) or placebo (n = 4126). Eligibility criteria included men with a baseline PSA of 2.5–10 ng/ml or 3.0–10 ng/ml for men 50–59 yr of age or 60–75 yr of age, respectively. Participants must also have had a prior single prostate biopsy within the 6 mo prior to enrollment without evidence of PCa, high-grade prostatic intraepithelial neoplasia, atypia, or a prostate volume 80 ml measured by transrectal ultrasound (TRUS). Men who had severe lower urinary tract symptoms (LUTS) were also excluded. After randomization, 109 participants were determined to be ineligible for the study, leaving 8122 men in the trial.

2.2. Prostate cancer diagnosis

Subjects received PSA tests every 6 mo, and a 10-core TRUS-guided prostate biopsy was performed at years 2 and 4, regardless of PSA level. Unscheduled biopsies were also performed if clinically indicated, and results would replace protocol-dependent biopsies if

performed during study months 19–24 or 43–49. From the initial cohort, 6729 (82.8%) had at least one prostate biopsy during the 48-mo study period. The characteristics of those undergoing at least one on-study biopsy have been published previously [18]. Prostate biopsy specimens were categorized as negative, low-grade (Gleason <7) PCa, and high-grade (Gleason 7) PCa.

2.3. Data collection

Digital rectal exam (DRE) findings and TRUS prostate volume were reported from the prestudy biopsy. PSA, height, and weight were measured during the baseline physical exam. All REDUCE participants in this analysis completed a medical history questionnaire prior to randomization, including age, race, smoking, medication use, and alcohol use. Intake of beer, wine, and liquor was converted to standard units of alcoholic drinks per week (1 U equals half pint of beer, one glass of wine, or one measure of liquor). Alcohol intake was analyzed as a continuous variable (units per week) and also categorized to represent nondrinkers (0 U/wk), moderate drinkers (<7 U/wk) and heavy drinkers (>7 U/wk). Men who reported alcohol intake >84 U/wk (n = 17) were excluded from all analyses.

2.4. Statistical analysis

Kruskal-Wallis and χ^2 tests were used for univariable comparisons of study characteristics among levels of alcohol consumption. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between alcohol intake and PCa risk detected during the study were estimated using logistic regression. Similarly, multinomial logistic regression was used to estimate the association between alcohol intake and risk of low-grade (vs no PCa) and high-grade PCa (vs no PCa). All models were adjusted for age (continuous), race, body mass index (BMI; log-transformed), family history of PCa, diabetes, smoking status, geographic region, PSA, prostate volume, and REDUCE study treatment arm. We also controlled for age as a categorized variable (see Table 1 categories) to evaluate any nonlinear relationship between age and alcohol consumption but found no difference in results. Similarly, we repeated all analyses without controlling for PSA and prostate volume and found nearly identical results. Analysis of influential observations found that no observation strongly affected model coefficients. Interaction between alcohol (none, moderate, heavy) and study arm was tested by including the cross-product with the main effects in the multinomial logistic regression model. All statistical analyses were performed using Stata 11.2 software (StataCorp, College Station, TX, USA). Statistical significance was defined as $p < 0.05$.

3. Results

Analysis included 6374 REDUCE participants, including 998 and 435 men diagnosed with low-grade or high-grade PCa, respectively. Median age at baseline was 63 yr of age.

Approximately 25% of participants reported no alcohol consumption, while 49% and 26% were categorized as moderate or heavy drinkers, respectively (Table 1). Greater alcohol intake was significantly associated with white race, lower BMI, European region, and smoking, while diabetics were more likely to be abstainers. PSA levels, DRE result, and prostate volume were not significantly associated with alcohol intake overall or in the

dutasteride study arm. Nondrinkers were marginally more prevalent in the dutasteride study arm (48% vs 52%; $p = 0.055$).

Table 2 summarizes the association between alcohol and PCa by study treatment arm while controlling for factors related to alcohol intake. Among men in the dutasteride intervention, an increasing number of alcoholic drinks was significantly associated with a study diagnosis of high-grade PCa (OR: 1.02; 95% CI, 1.00–1.03; $p = 0.04$). Similarly, moderate and heavy alcohol consumption were significantly associated with increased risk of a high-grade PCa diagnosis by 57% and 86% ($p < 0.02$), respectively, compared with nondrinkers. Similar results were found when categorizing moderate alcohol intake at 14 drinks per week (OR: 1.67; 95% CI, 1.15–2.45; $p < 0.01$) and heavy intake as >14 drinks per week (OR: 1.60; 95% CI, 0.98–2.51; $p = 0.06$), although the number in the heavy drinker group was reduced substantially. In contrast, heavy alcohol consumption was not associated with high-grade PCa diagnosis among men in the placebo study arm.

We next investigated the effect of dutasteride on PCa across categories of alcohol intake (Table 3). Among all men, dutasteride administration was associated with a significant reduction in total PCa (OR: 0.73; 95% CI, 0.64–0.82; $p < 0.001$) and low-grade PCa (OR: 0.67; 95% CI, 0.58–0.77; $p < 0.001$) and remained consistently associated with lower risks across all alcohol exposure groups. In contrast, dutasteride was significantly associated with a lower risk of high-grade PCa only among alcohol abstainers (OR: 0.59; 95% CI, 0.38–0.90; $p = 0.015$). Dutasteride was no longer significantly associated with a lower risk of high-grade PCa with moderate (OR: 0.99; 95% CI, 0.74–1.31) or heavy alcohol (OR: 0.99; 95% CI, 0.67–1.45) intakes.

4. Discussion

Chronic alcohol consumption is a risk factor for several cancers, but the impact on PCa risk has been unclear. In REDUCE, we found that alcohol intake was not associated with low-grade or high-grade PCa for men in the placebo study arm, suggesting that in general and within the amounts consumed within REDUCE, alcohol intake is unrelated to PCa risk. In contrast, the associations between alcohol intake and PCa risk for men on dutasteride were more complex. Although alcohol intake was not associated with low-grade PCa for men assigned to dutasteride, increasing alcohol intake combined with dutasteride administration increased the risk of high-grade PCa. Men randomized to dutasteride and reporting more than seven alcoholic drinks per week were 86% more likely to be diagnosed with high-grade PCa during follow-up prostate biopsy compared with alcohol abstainers on dutasteride. Viewed alternatively, dutasteride actually reduced PCa risk for alcohol abstainers, an effect that was lost in alcohol consumers. As such, consuming alcohol appears to negate the potential benefits of dutasteride for high-grade PCa.

A joint association between alcohol intake and dutasteride with risk of high-grade PCa is consistent with data from PCPT. In PCPT, there was a significant increase in high-grade PCa diagnoses associated with alcohol intake ≥ 50 g/d among men randomized to finasteride. Also similar to the PCPT, we saw the effect of high alcohol intake on high-grade PCa appeared to be derived from counteracting an otherwise-protective effect of dutasteride on

high-grade PCa. Among men reporting as alcohol abstainers, dutasteride was significantly associated with a reduction in high-grade PCa, but as reported alcohol intake increased, the protective association between dutasteride and high-grade PCa was lost. Unlike PCPT, however, we did not see a significant effect of alcohol with low-grade PCa. This difference may be related to differences in dutasteride versus finasteride activities or the lower apparent alcohol intake levels or the shorter follow-up period in the REDUCE trial. It is also possible that differences in latent low-grade PCa prevalence or other participant characteristics between PCPT and REDUCE influenced the ability to identify an association between alcohol intake and low-grade PCa at follow-up, as the PCPT targeted men with a normal DRE and PSA levels <3.0 ng/ml [15], while REDUCE targeted men with PSA levels between 2.5 and 10 ml and a prior negative biopsy [17]. However, across both PCPT and REDUCE, alcohol intake was not significantly associated with PCa in the placebo study arm, consistent with the majority of studies reporting that alcohol intake alone is insufficient to induce or promote PCa among men without some form of metabolic stress (eg, 5-ARI use) [4,5]. These data suggest that alcohol consumption counteracts the benefits 5-ARIs to reduce PCa risk or that a low-androgen environment permits alcohol-related effects to advance high-grade PCa.

Increased oxidative stress with alcohol intake could play an import role in countering the relationship between 5-ARIs and PCa. After consumption, ethanol is absorbed predominately through the linings of the stomach, mouth, and esophagus, and then rapidly distributed throughout the body. The majority of metabolism occurs in the liver, as alcohol induces expression of alcohol dehydrogenase (ADH), which converts ethanol to acetaldehyde and is then converted to acetate and acetyl coenzyme A [19]. Acetaldehyde is a carcinogen that leads to the generation of reactive oxygen species (ROS) that promote lipid oxidation, DNA adducts, and DNA mutations [20]. ADH is also induced in the rat prostate in response to alcohol consumption [21], suggesting the possibility that alcohol may increase ROS directly in prostate tissue. DHT may also inhibit ADH [22] to slow alcohol metabolism and reduce ROS levels. In this situation, lower DHT levels associated with dutasteride use might lead to increased ADH activity and greater production of acetaldehyde and increased ROS levels, possibly explaining why alcohol is associated with PCa risk in men taking 5-ARIs. Alcohol intake may also increase estrogen levels [23] to potentially promote PCa [24–27]. These processes may be coupled with increased insulin levels [28–30] or folate depletion [31] to create a procarcinogenic effect with exposure to alcohol in a low-androgen environment.

An advantage of our analysis within REDUCE is that randomization provides confidence that men randomized to either the dutasteride and placebo study arm are similar with respect to alcohol intake levels and other factors potentially related to a PCa diagnosis. Alcohol intake has been associated with lower PSA levels [6], but we found no association between alcohol intake with PSA levels, DRE result, or prostate size. Our results were nearly identical regardless of whether we controlled for PSA and prostate size. A centralized pathology review protocol was used to standardize the criteria defining PCa at biopsy. Furthermore, the REDUCE study design minimizes potential bias derived from differential PCa screening, because all participants regardless of PSA level underwent prostate biopsy during the follow-up period.

Among the limitations of this study, alcohol assessment included only a single patient response to the usual number of drinks per day at study baseline. We could not differentiate former drinkers from those who had never been drinkers, and to the extent that past alcohol consumption increases PCa risk, our results could be biased to the null in either study arm. Similarly, we did not have data on duration of alcohol consumption prior to baseline, binge drinking, the types of alcohol consumed, or changes in intake from baseline to follow-up. Data regarding compliance with dutasteride or placebo administration were not available to us, although reductions in low-grade PCa were similar in drinkers and nondrinkers, providing evidence that reduced compliance with dutasteride among alcohol drinkers cannot explain our results. Baseline inclusion criteria for REDUCE targeted men with a recent negative biopsy, such that our observed null association between alcohol intake and PCa in the placebo arm may not generalize whether alcohol intake led to earlier PCa and thus exclusion from the REDUCE study. Chance is an alternative explanation, but our results are confirmatory for prior analyses from the PCPT [16].

5. Conclusions

Increasing alcohol intake reduced the protective association between dutasteride and high-grade PCa. Dutasteride was significantly associated with reduced risk of high-grade PCa among abstainers, but dutasteride was unrelated to high-grade disease in men with high alcohol intake. Both finasteride and dutasteride, although not approved for PCa prevention, are widely used for the treatment of LUTS related to prostate enlargement and BPH. As such, our results, combined with data from the PCPT, would suggest that physicians advise their patients on 5-ARIs to eliminate alcohol intake if there is also interest in reducing the risk of high-grade PCa.

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Table 1

Baseline demographic and clinical characteristics for patients by alcohol consumption category

	Alcohol intake			p value
	None	Moderate	Heavy	
Patients, no. (%)	1608 (25)	3136 (49)	1630 (26)	–
Drinks per week, median (Q1–Q3)	0 (0–0)	3 (1–5)	14 (10–20)	–
Age, no. (%)				
49–54	144 (9)	286 (9)	149 (9)	0.013
55–59	367 (23)	727 (23)	386 (24)	
60–64	431 (27)	823 (26)	458 (28)	
65–69	395 (24)	834 (27)	446 (27)	
70–77	271 (17)	466 (15)	191 (12)	
Median (Q1–Q3)	63 (58–68)	63 (58–67)	63 (58–67)	
Race, no. (%)				
White	1380 (86)	2901 (92)	1572 (96)	<0.001
Black	55 (3)	55 (2)	7 (1)	
Other	173 (11)	180 (6)	51 (3)	
BMI, no. (%)				
Normal weight (<25 kg/m ²)	452 (28)	856 (27)	419 (26)	0.017
Overweight (25.0–29.9 kg/m ²)	793 (49)	1667 (53)	892 (55)	
Obese (≥ 30 kg/m ²)	363 (23)	613 (20)	319 (19)	
Geographic region, no. (%)				
Europe	725 (45)	1925 (61)	1056 (65)	<0.001
Canada, United States, and Puerto Rico	514 (32)	771 (25)	253 (15)	
Other	369 (23)	440 (14)	321 (20)	
PSA, no. (%)				
0–3.9 ng/ml	287 (18)	517 (16)	269 (16)	0.271
4–5.9 ng/ml	605 (38)	1,213 (39)	584 (36)	
6–7.9 ng/ml	444 (28)	887 (28)	469 (29)	
8 ng/ml	272 (17)	519 (17)	308 (19)	
TRUS prostate volume, ml				
Median (Q1–Q3)	43.9 (33.7–57.4)	43.4 (32.8–56.2)	43.2 (33.0–56.0)	0.173
Abnormal DRE, no. (%)	65 (4)	128 (4)	46 (3)	0.073
Family history of PCa, no. (%)	201 (13)	403 (13)	230 (14)	0.343
Diabetes, no. (%)	129 (8)	163 (5)	80 (5)	<0.001
Hypercholesterolemia, no. (%)	225 (14)	397 (13)	221 (14)	0.394
Hypertension, no. (%)	412 (26)	760 (24)	403 (25)	0.577
Smoker, no. (%)				
No	840 (52)	1503 (48)	575 (35)	<0.001
Yes	211 (13)	399 (13)	309 (19)	
Former	557 (35)	1234 (39)	746 (46)	
No. of packs per year of smoking				

	Alcohol intake			<i>p</i> value
	None	Moderate	Heavy	
0	850 (55)	1509 (50)	577 (37)	<0.001
1–25	382 (25)	956 (32)	597 (38)	
26–990	325 (21)	555 (18)	403 (26)	
Treatment arm, no. (%)				
Placebo	779 (48)	1635 (52)	829 (51)	0.055
Dutasteride	829 (52)	1501 (48)	801 (49)	

BMI = body mass index; DRE = digital rectal examination; PCa = prostate cancer; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

Effect of alcohol intake on prostate cancer with randomization to the dutasteride or placebo study arm of the Reduction by Dutasteride of Prostate Cancer Events trial

Table 2

Study arm	Alcohol	All PCa				Low-grade PCa				High-grade PCa			
		Cases	OR [†]	95% CI	p	Cases	OR [†]	95% CI	p	Cases	OR [†]	95% CI	p
Placebo	None	183	1.0	Ref	–	126	1.0	Ref	–	57	1.0	Ref	–
	Moderate [*]	409	1.02	0.83–1.25	0.84	301	1.08	0.86–1.37	0.51	108	0.87	0.62–1.24	0.45
	Heavy ^{**}	222	1.10	0.87–1.40	0.41	161	1.15	0.88–1.50	0.32	61	1.01	0.67–1.50	0.98
Dutasteride	Drinks per week	814	1.01	1.00–1.02	0.20	588	1.01	1.00–1.02	0.26	226	1.01	0.99–1.02	0.40
	None	157	1.0	Ref	–	116	1.0	Ref	–	41	1.0	Ref	–
	Moderate [*]	286	1.04	0.83–1.30	0.74	179	0.87	0.67–1.12	0.29	107	1.57	1.07–2.32	0.02
	Heavy ^{**}	176	1.30	1.00–1.67	0.047	115	1.12	0.84–1.50	0.45	61	1.86	1.20–2.87	0.01
	Drinks per week	619	1.01	1.00–1.02	0.12	410	1.00	0.99–1.02	0.53	209	1.02	1.00–1.03	0.04

BMI = body mass index; CI = confidence interval; OR = odds ratio; PCa = prostate cancer; PSA = prostate-specific antigen; Ref = reference; TRUS = transrectal ultrasound.

^{*} Moderate: 1–6 drinks per week.

^{**} Heavy: 7 drinks per week.

[†] ORs are adjusted for age, race, BMI, geographic region, family history of PCa, diabetes, smoking status, PSA, TRUS prostate volume, and treatment arm.

Table 3

Effect of dutasteride on prostate cancer across categories of alcohol intake

Alcohol														
All subjects				None			Moderate			Heavy				
Cases	OR *	95% CI		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI		
Total PCa														
Placebo	814	1.0	Ref	183	1.0	Ref	409	1.0	Ref	222	1.0	Ref		
Dutasteride	619	0.73	0.64–0.82	157	0.73	0.57–0.93	286	0.69	0.58–0.82	176	0.78	0.62–0.98		
Low-grade PCa														
Placebo	588	1.0	Ref	126	1.0	Ref	301	1.0	Ref	161	1.0	Ref		
Dutasteride	410	0.67	0.58–0.77	116	0.79	0.60–1.05	179	0.60	0.48–0.73	115	0.71	0.54–0.92		
High-grade PCa														
Placebo	226	1.0	Ref	57	1.0	Ref	108	1.0	Ref	61	1.0	Ref		
Dutasteride	209	0.88	0.72–1.08	41	0.59	0.38–0.90	107	0.99	0.74–1.31	61	0.99	0.67–1.45		

BMI = body mass index; CI = confidence interval; OR = odds ratio; PCa = prostate cancer; PSA = prostate-specific antigen; Ref = reference; TRUS = transrectal ultrasound.

* ORs are adjusted for age, race, BMI, geographic region, family history of PCa, diabetes, smoking status, PSA, and TRUS prostate volume. The cross-product interaction between alcohol intake (none, moderate, heavy) and study arm was statistically significant for moderate drinking and high-grade PCa (*p*-interaction = 0.043). The cross-product interaction between alcohol intake and study arm for heavy drinking and high-grade PCa had *p* = 0.10.