Research Article

Cancer Prevention Research

Early-Life Alcohol Intake and High-Grade Prostate Cancer: Results from an Equal-Access, Racially Diverse Biopsy Cohort

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Abstract

Epidemiologic evidence for an association between alcohol and prostate cancer is mixed. Moreover, there is a lack of research investigating early-life alcohol intake as a risk factor for either overall or high-grade prostate cancer. We examined lifetime alcohol intake in association with prostate cancer diagnosis in an equal-access, racially diverse prostate biopsy cohort. Men undergoing prostate biopsy at the Durham Veterans Affairs Medical Center from 2007 to 2018 completed a survey indicating average number of alcoholic beverages consumed per week [categorized as none (ref), 1–6, ≥7] during each decade of life. Multivariable logistic regression was used to test the association between alcohol intake across decades and diagnosis of overall, low-grade [grade group (GG) 1–2] and high-grade prostate cancer (GG 3–5). Of 650 men ages 49–89 who underwent biopsy, 325 were diagnosed with prostate cancer, 238 with low-grade and 88 with high-grade disease. Relative to nondrinkers, men who consumed ≥7 drinks/week at ages 15 to 19 had increased odds of high-grade prostate cancer diagnosis (OR = 3.21, P_{trend} = 0.020), with similar findings for ages 20 to 29, 30 to 39, and 40 to 49. Consistent with these results, men in the upper tertile of cumulative lifetime intake had increased odds of high-grade prostate cancer diagnosis (OR = 3.20, P_{trend} = 0.003). In contrast, current alcohol intake was not associated with prostate cancer. In conclusion, among men undergoing prostate biopsy, heavier alcohol intake earlier in life and higher cumulative lifetime intake were positively associated with high-grade prostate cancer diagnosis, while current intake was unrelated to prostate cancer. Our findings suggest that earlier-life alcohol intake should be explored as a potential risk factor for high-grade prostate cancer. *Cancer Prev Res; 11(10); 621–8. ©2018 AACR.*

Introduction

Prostate cancer is the most frequently diagnosed non-skin cancer in men in the United States and the second leading cause of male cancer deaths (1). In addition, alcohol consumption accounts for a substantial amount of deaths worldwide, with cancer contributing to this burden. Mounting evidence supports alcohol as a risk factor for female breast, colorectal, oral cavity, pharynx, larynx, esophagus, and liver cancers (2), but there is little agreement concerning its effect on prostate cancer risk.

An early meta-analysis examining the relationship between alcohol and prostate cancer risk reported no association (3). However, subsequent meta-analyses reported a modest increase in prostate cancer risk with higher levels of alcohol consumption (4–6). A meta-analysis published in 2015 concluded that there is accumulating evidence that alcohol drinking is associated with prostate cancer (7). Moreover, results of a recent meta-analysis found a statistically significant dose–response relationship between the quantity of alcohol consumption and overall prostate cancer risk or mortality (8). Although meta-analyses to date have focused on risk of overall prostate cancer, one study found that heavier drinking was associated with increased risk of high-grade disease, but had no association with low-grade prostate cancer risk (9). Finally, one case–control study found that current alcohol intake was not associated with prostate cancer risk but that cumulative lifetime intake increased significantly the risk of both aggressive and non-aggressive prostate cancer (10), suggesting that alcohol exposure earlier in life may be important.

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Using data from a prostate biopsy cohort at the Durham Veteran Affairs Medical Center, our objective was to test the association between early-life alcohol consumption and prostate cancer diagnosis. In addition, we aimed to determine if early-life alcohol consumption was associated with tumor aggressiveness at diagnosis. Given that carcinogenic exposures during prostate development might affect prostate cancer risk later in life (11), we hypothesized that heavier alcohol intake earlier in life would be associated with increased odds of prostate cancer diagnosis at biopsy, particularly high-grade disease.

Materials and Methods

Study design

Men undergoing prostate biopsy for an elevated PSA and/or abnormal digital rectal examination (DRE) at the Durham Veterans Affairs Medical Center between January 2007 and January 2018 were recruited to participate in an ongoing biopsy cohort study. Methods for the identification and accrual of participants have been described previously (12). Men were between the ages of 49 and 89, were able to provide informed consent, had a PSA test within 12 months prior to enrollment, and had no history of prostate cancer. Of the 1,595 eligible men who underwent biopsy, 1,221 (77%) consented to participate. Of these, we excluded 12 patients missing biopsy results, 528 patients who did not complete or partially completed the study questionnaire, and 31 missing key covariates, resulting in a study cohort of 650 patients. Men missing study questionnaires were slightly younger, less likely to be white, had higher PSA at biopsy, and were more likely to be diagnosed with overall prostate cancer but, among those diagnosed with prostate cancer, equally likely to be diagnosed with high-grade prostate cancer. The study was approved by the Institutional Review Board at Durham Veterans Affairs Medical Center and all patients provided written consent.

Data collection

Patients completed a questionnaire, including demographic, medical, and lifestyle characteristics. Alcohol intake was assessed by a question that asked "At each age, what is the average number of drinks that you consume(d) weekly?" (Supplementary Entry 3). In response to this question, men indicated the average number of alcoholic beverages consumed per week (0, <1, 1, 2–3, 4–6, 7–10, 11–15, 16–20, >20) during each decade of their life (ages 15–19, 20–29, 30–39, etc.). Type of beverage and serving size was not indicated. Cumulative lifetime alcohol consumption (i.e., the total number of drinks consumed over the lifetime prior to biopsy) was calculated by summing the number of drinks/week over each decade of life, which was categorized into tertiles (10). For example, for a 55-year-old man, cumulative lifetime alcohol consumption was calculated by summing drinks/week over the age intervals: before 15, 15 to 19, 20 to 29, 30 to 39, 40 to 49, and the first 5 years of the 50 to 59 interval. Similarly, patients were asked to indicate number of cigarettes/day (0, 1–4, 5–14, 15–24, 25–34, 35–44, 45+) during each decade of their life. Pack years was calculated by summing the number of cigarettes/day over each decade of life and dividing by 20 (cigarettes per pack; ref. 13). All questionnaires were self-administered and median (IQR) time between biopsy and questionnaire completion was 3 days (0, 17). Given this timeframe, although the date on which men were informed of their biopsy results was not recorded, it is likely that only a subset of men knew their cancer status before completing the questionnaire. Anthropometric measurements [measured weight and height, used to calculate body mass index (BMI)], DRE findings, prostate volume, and PSA level were abstracted from urology clinic notes from either the visit at which biopsy was performed or the most recent visit prior to biopsy.

Outcome ascertainment

Biopsy tissue was assessed by a pathologist per standard of care, and prostate cancer grade was abstracted from the resulting pathology report. Grade was assigned using the Epstein 5-grade group system where low-grade disease was defined as grade group (GG) 1 to 2 (Gleason score $\leq 3+4$) and high-grade prostate cancer as GG 3 to 5 (Gleason score $\geq 4+3$; ref. 14).

Statistical methods

Patient characteristics were summarized by alcohol consumption at age 15 to 19 and differences were tested using Kruskal–Wallis tests for continuous variables and χ^2 test for categorical variables.

Logistic regression was used to test the association between alcohol consumption and overall prostate cancer diagnosis at biopsy. Multinomial logistic regression was used to test the association between alcohol consumption, low-grade, and high-grade prostate cancer diagnosis. The primary exposure was early-life alcohol consumption, measured by the average number of alcoholic drinks consumed per week at age 15 to 19. We also examined alcohol intake at ages 20 to 29, 30 to 39, and 40 to 49. In addition, we tested current alcohol consumption at the time of biopsy. For these exposures, the number of drinks per week was categorized as 0, 1 to 6, and ≥ 7, in line with previous studies (15, 16). Finally, we examined tertiles of cumulative lifetime alcohol consumption.

We fit age-adjusted models and multivariable models adjusted for age, race, DRE (suspicious vs. normal), prostate volume (log-transformed), PSA at biopsy (log-transformed), year of biopsy, smoking pack years (log-transformed), previous prostate biopsy (yes vs. no), and BMI (log-transformed). For analyses of alcohol intake across different decades, models examining past alcohol consumption were additionally adjusted for current alcohol consumption (0, 1–7, ≥ 7 drinks per week), and

models examining current alcohol consumption were adjusted for past alcohol consumption (yes vs. no). We also repeated our analysis of the association between early-life alcohol intake and prostate cancer without adjusting for current alcohol intake, and vice versa. *P* values for trend were calculated by assigning the median number of alcoholic drinks among patients in each category to that category and treating it as a continuous variable. For example, for analyses of alcohol intake across different decades, median drinks per week in the ≥7 drinks per week category were 7 to 10 for ages 15 to 19, so all patients were assigned a value of 8.5 (median value of 7 to 10 category) for the trend analysis.

We examined whether associations between alcohol consumption and overall prostate cancer differed by race (white vs. non-white) by including a cross product term in the multivariable model and testing its significance using a Wald test. Low numbers of men prevented race-stratified analysis of the association between alcohol intake and high-grade prostate cancer.

All statistical tests were two sided, and *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SAS v9.4 (SAS Institute, Inc.).

Results

Patient characteristics

Age range at biopsy in our cohort was 49 to 89, and 47% of patients were white (Table 1). Median (IQR) PSA was 5.7 ng/mL (4.5–7.9 ng/mL). During ages 15 to 19, there were 317 (49%) men who reported not drinking, 279 (43%) men who reported drinking 1 to 6 drinks per week, and 54 (8%) who reported drinking ≥7 drinks per week. Men who reported ≥7 drinks per week at ages 15 to 19 had higher smoking pack years ($P < 0.001$), but otherwise characteristics were balanced among groups.

Alcohol consumption and overall prostate cancer

There were 325 of 650 men diagnosed with prostate cancer, 238 with grade group 1 to 2 and 88 with grade group 3 to 5. There was no association between alcohol intake at ages 15 to 19 and odds of overall prostate cancer diagnosis, on either age-adjusted or multivariable analysis ($P_{trend} = 0.57$ and $P_{trend} = 0.76$, respectively; Table 2). On age-adjusted analysis, both 1 to 6 drinks per week at ages 20 to 29 and 1 to 6 and ≥7 drinks per week at ages 30 to 39 and 40 to 49 were associated with increased odds of prostate cancer diagnosis (Table 2). This association held

Table 1. Baseline characteristics overall and stratified by weekly alcohol consumption at ages 15 to 19

		Average alcohol consumption at age 15–19			
	Overall (*N* = 650)	**0 drinks/week (*N* = 317)**	**1–6 drinks/week (*N* = 279)**	**≥7 drinks/week (*N* = 54)**	***P***
Age at biopsy, median (IQR)	64 (60, 68)	64 (61, 68)	64 (59, 68)	63 (61, 67)	0.109[a]
Race					0.332[b]
Non-white	346 (53%)	175 (55%)	147 (53%)	24 (44%)	
White	304 (47%)	142 (45%)	132 (47%)	30 (56%)	
Year of consent, median (IQR)	2011 (08, 15)	2011 (09, 15)	2011 (08, 15)	2011 (08, 15)	0.925[a]
Digital rectal exam					0.290[b]
Not suspicious for cancer	491 (76%)	248 (78%)	203 (73%)	40 (74%)	
Suspicious for cancer	159 (24%)	69 (22%)	76 (27%)	14 (26%)	
TRUS prostate volume (cc) Median (IQR)	42.0 (30.0, 58.2)	44.0 (31.0, 61.2)	40.0 (28.0, 58.1)	40.0 (28.7, 52.0)	0.182[a]
PSA at biopsy (ng/mL), median (IQR)	5.7 (4.5, 7.9)	5.9 (4.6, 7.8)	5.5 (4.4, 8.1)	5.8 (4.6, 8.0)	0.573[a]
BMI (kg/m^2), median (IQR)	29.2 (26.5, 32.7)	29.4 (26.5, 32.8)	28.8 (26.3, 32.4)	30.2 (27.3, 34.6)	0.267[a]
Previous prostate biopsy	102 (16%)	58 (18%)	36 (13%)	8 (15%)	0.192[b]
Smoking pack years, median (IQR)	16.1 (0.9, 37.1)	5.5 (0, 30.4)	21.0 (6.6, 41.6)	34.5 (14.4, 59.9)	<0.001[a]
Alcohol consumption, age 20–29					<0.001[b]
0 drinks/week	120 (18%)	112 (35%)	7 (3%)	1 (2%)	
1–6 drinks/week	365 (56%)	167 (53%)	194 (70%)	4 (7%)	
≥7 drinks/week	165 (25%)	38 (12%)	78 (28%)	49 (91%)	
Alcohol consumption, age 30–39					<0.001[b]
0 drinks/week	146 (22%)	114 (36%)	27 (10%)	5 (9%)	
1–6 drinks/week	336 (52%)	161 (51%)	164 (59%)	11 (20%)	
≥7 drinks/week	168 (26%)	42 (13%)	88 (32%)	38 (70%)	
Alcohol consumption, age 40–49					<0.001[b]
0 drinks/week	200 (31%)	135 (43%)	54 (19%)	11 (21%)	
1–6 drinks/week	302 (47%)	139 (44%)	150 (54%)	13 (25%)	
≥7 drinks/week	144 (22%)	41 (13%)	74 (27%)	29 (55%)	
Current alcohol consumption					<0.001[b]
0 drinks/week	322 (50%)	191 (60%)	106 (38%)	25 (46%)	
1–6 drinks/week	260 (40%)	100 (32%)	141 (51%)	19 (35%)	
≥7 drinks/week	68 (10%)	26 (8%)	32 (11%)	10 (19%)	
Cumulative lifetime alcohol consumption					<0.001[b]
Tertile 1 (<3,094 drinks)	226 (35%)	164 (52%)	58 (21%)	4 (7%)	
Tertile 2 (3,094–10,659 drinks)	209 (32%)	97 (31%)	109 (39%)	3 (6%)	
Tertile 3 (≥10,660 drinks)	215 (33%)	56 (18%)	112 (40%)	47 (87%)	

[a]Kruskal–Wallis.
[b]The χ^2 test.

Table 2. Odds ratios for the association between alcohol consumption across different ages and overall prostate cancer

		Age-adjusted		Multivariable[a]	
	N	OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
Alcohol consumption, age 15–19			0.57		0.76
0 drinks/week	159/317	Ref.		Ref.	
1–6 drinks/week	137/279	0.98 (0.71–1.36)		0.91 (0.62–1.35)	
≥7 drinks/week	29/54	1.19 (0.67–2.14)		1.13 (0.56–2.26)	
Alcohol consumption, age 20–29			0.63		0.28
0 drinks/week	52/120	Ref.		Ref.	
1–6 drinks/week	196/365	1.57 (1.03–2.38)		1.35 (0.82–2.24)	
≥7 drinks/week	77/165	1.19 (0.74–1.92)		0.95 (0.52–1.76)	
Alcohol consumption, age 30–39			0.35		0.91
0 drinks/week	57/146	Ref.		Ref.	
1–6 drinks/week	182/336	1.88 (1.26–2.80)		1.64 (1.02–2.63)	
≥7 drinks/week	86/168	1.65 (1.05–2.59)		1.39 (0.77–2.51)	
Alcohol consumption, age 40–49			0.047		0.28
0 drinks/week	83/200	Ref.		Ref.	
1–6 drinks/week	160/302	1.61 (1.12–2.32)		1.63 (1.04–2.56)	
≥7 drinks/week	80/144	1.76 (1.14–2.72)		1.71 (0.93–3.13)	
Alcohol consumption, current			0.11		0.39
0 drinks/week	150/322	Ref.		Ref.	
1–6 drinks/week	136/260	1.35 (0.97–1.89)		1.12 (0.75–1.69)	
≥7 drinks/week	39/68	1.61 (0.95–2.75)		1.34 (0.71–2.53)	

[a]Adjusted for age, race, DRE, prostate volume, PSA, year of consent, smoking, BMI, previous biopsy, and current alcohol consumption (model for current alcohol consumption is adjusted for past alcohol consumption).

N represents the number of men diagnosed with prostate cancer over the total number of men undergoing prostate biopsy.

for 1 to 6 drinks per week at ages 30 to 39 (OR, 1.64; 95% CI, 1.02–2.63) and 40–49 (OR, 1.63; 95% CI, 1.04–2.56), but was attenuated and no longer significant for ≥7 drinks per week after adjusting for demographic and prostate characteristics in multivariable analysis.

Alcohol consumption, low-grade, and high-grade prostate cancer

Like our analysis of overall prostate cancer, we found no association between alcohol intake at ages 15 to 19 and odds of low-grade prostate cancer (Table 3). Neither did we find any consistent associations between alcohol intake during other decades and low-grade prostate cancer diagnosis. In contrast, on both age-adjusted and multivariable analyses, consumption of ≥7 drinks per week at ages 15 to 19 was significantly associated with an increased odds of high-grade prostate cancer diagnosis (multivariable OR, 3.21; 95% CI, 1.22–8.41), with a significant trend across categories of increasing alcohol intake ($P_{trend} = 0.020$). We observed similar estimates for alcohol intake at ages 20 to 29 (multivariable OR, 3.14; 95% CI, 1.14–8.65, $P_{trend} = 0.034$), ages 30 to 39 (multivariable OR, 3.09; 95% CI, 1.20–8.00, $P_{trend} = 0.019$), and ages 40 to 49 (multivariable OR, 3.64, 95% CI, 1.45–9.15, $P_{trend} = 0.007$). In contrast, current alcohol consumption was not significantly associated with high-grade prostate cancer diagnosis (Table 3), with similarly null findings when models were not adjusted for past alcohol consumption.

There were no differences in associations between alcohol consumption and overall prostate cancer diagnosis between white and non-white men (Supplementary Table S1). Our findings were similar when models for earlier-life alcohol intake were not adjusted for current alcohol consumption (Supplementary Table S2).

Cumulative lifetime alcohol consumption and prostate cancer

On age-adjusted analysis, the middle tertile of cumulative lifetime alcohol intake was associated with moderately increased odds of overall and low-grade prostate cancer diagnosis, though trends across increasing tertiles were not statistically significant (Table 4). Consistent with our findings for earlier-life alcohol intake, we found that men in the upper tertile of cumulative lifetime alcohol intake had significantly increased odds of high-grade prostate cancer diagnosis, relative to those in the lowest tertile (multivariable OR 3.20; 95% CI, 1.47–6.98; Table 4). There was a significant trend across increasing tertiles of cumulative lifetime alcohol intake in association with high-grade prostate cancer diagnosis ($P_{trend} = 0.003$).

Discussion

Both clinical and epidemiologic evidence suggests that prostate carcinogenesis may span decades (17). The prostate undergoes significant growth and maturation during puberty, so presumably, during this period it might be particularly susceptible to carcinogenic exposures. As such, consideration of early-life exposures may be important for understanding prostate cancer etiology (11). To address this, we analyzed the association between early-life alcohol exposure and high-grade prostate cancer diagnosis among men undergoing a prostate biopsy at the Durham Veterans Affairs Medical Center. We found that men with a history of heavier alcohol exposure earlier in life were more likely to

Table 3. Odds ratios for the association between alcohol consumption across different ages and low-grade and high-grade prostate cancer

		Age-adjusted		Multivariable[a]	
	N	**OR (95% CI)**	P_{trend}	**OR (95% CI)**	P_{trend}
Low-grade prostate cancer (GG 1–2)					
Alcohol consumption, age 15–19			0.73		0.81
0 drinks/week	77/235	Ref.		Ref.	
1–6 drinks/week	58/200	0.88 (0.62–1.25)		0.84 (0.57–1.26)	
≥7 drinks/week	11/36	0.92 (0.47–1.78)		0.94 (0.44–1.99)	
Alcohol consumption, age 20–29			0.10		0.051
0 drinks/week	26/94	Ref.		Ref.	
1–6 drinks/week	94/263	1.50 (0.96–2.35)		1.28 (0.77–2.14)	
≥7 drinks/week	26/114	0.89 (0.53–1.52)		0.72 (0.38–1.38)	
Alcohol consumption, age 30–39			0.88		0.56
0 drinks/week	28/117	Ref.		Ref.	
1–6 drinks/week	83/237	1.87 (1.22–2.86)		1.64 (1.00–2.68)	
≥7 drinks/week	35/117	1.33 (0.81–2.19)		1.17 (0.62–2.19)	
Alcohol consumption, age 40–49			0.42		0.86
0 drinks/week	41/158	Ref.		Ref.	
1–6 drinks/week	70/212	1.66 (1.12–2.45)		1.65 (1.03–2.62)	
≥7 drinks/week	35/99	1.42 (0.88–2.31)		1.37 (0.72–2.61)	
Alcohol consumption, current			0.26		0.51
0 drinks/week	68/240	Ref.		Ref.	
1–6 drinks/week	60/184	1.39 (0.97–1.99)		1.25 (0.82–1.92)	
≥7 drinks/week	18/47	1.46 (0.81–2.61)		1.33 (0.68–2.59)	
High-grade prostate cancer (GG 3–5)					
Alcohol consumption, age 15–19			0.011		0.020
0 drinks/week	82/240	Ref.		Ref.	
1–6 drinks/week	79/221	1.35 (0.81–2.26)		1.30 (0.70–2.42)	
≥7 drinks/week	18/43	2.76 (1.27–6.03)		3.21 (1.22–8.41)	
Alcohol consumption, age 20–29			0.025		0.034
0 drinks/week	26/94	Ref.		Ref.	
1–6 drinks/week	102/271	1.76 (0.85–3.63)		1.81 (0.75–4.42)	
≥7 drinks/week	51/139	2.57 (1.20–5.54)		3.14 (1.14–8.65)	
Alcohol consumption, age 30–39			0.004		0.019
0 drinks/week	29/118	Ref.		Ref.	
1–6 drinks/week	99/253	1.88 (0.95–3.72)		1.66 (0.73–3.78)	
≥7 drinks/week	51/133	2.98 (1.46–6.09)		3.09 (1.20–8.00)	
Alcohol consumption, age 40–49			0.001		0.007
0 drinks/week	42/159	Ref.		Ref.	
1–6 drinks/week	90/232	1.55 (0.84–2.83)		1.67 (0.79–3.53)	
≥7 drinks/week	45/109	2.90 (1.52–5.54)		3.64 (1.45–9.15)	
Alcohol consumption, current			0.062		0.41
0 drinks/week	82/254	Ref.		Ref.	
1–6 drinks/week	76/200	1.29 (0.76–2.18)		0.73 (0.37–1.40)	
≥7 drinks/week	21/50	2.07 (0.98–4.38)		1.27 (0.51–3.19)	

[a]Adjusted for age, race, DRE, prostate volume, PSA, year of consent, smoking, BMI, previous biopsy, and current alcohol consumption (model for current alcohol consumption is adjusted for past alcohol consumption).

N represents the number of men diagnosed with low-grade or high-grade prostate cancer, respectively, over the total number of men undergoing prostate biopsy.

be diagnosed with high-grade prostate cancer at biopsy, compared with men without earlier-life alcohol exposure. We also found that higher cumulative lifetime alcohol intake was associated with increased odds of high-grade disease. In contrast, we found no association between current drinking patterns and overall or high-grade prostate cancer diagnosis. Though additional studies are needed, these data suggest that heavier drinking patterns earlier in life may be associated with high-grade prostate cancer.

Although few studies have focused on early-life alcohol consumption, multiple studies have examined the association between current alcohol consumption and prostate cancer risk, though findings are contradictory. A meta-analysis in 2000 found no association between alcohol consumption and risk of prostate cancer (3), while the most recent meta-analysis reported a modest yet significant dose–response relationship between increasing alcohol intake and overall prostate cancer risk (8). Moreover, a secondary analysis of the ProtecT trial by Zuccolo and colleagues, showed higher risk of high-grade disease for heavy drinkers, and no association of alcohol with low-grade disease (9). Similarly, secondary analyses of the Prostate Cancer Prevention (PCPT) and REDUCE trials also showed positive associations between alcohol intake and risk of high-grade prostate cancer, though associations were significant only in men randomized to 5-alpha reductase inhibitors (5-ARI; refs. 15, 18). Together, these studies suggest that heavier alcohol intake may be more strongly related to high-grade than overall prostate cancer risk.

Several studies have investigated lifetime alcohol exposure and prostate cancer risk. A Canadian population-based case–control study showed a weak positive

Table 4. Odds ratios for the association between cumulative lifetime alcohol consumption and overall, low-grade and high-grade prostate cancer

		Age-adjusted		Multivariable[a]	
	N	**OR (95% CI)**	**P_{trend}**	**OR (95% CI)**	**P_{trend}**
Overall prostate cancer					
Cumulative lifetime alcohol consumption			0.095		0.32
Tertile 1 (<3,094 drinks)	97/226	Ref.		Ref.	
Tertile 2 (3,094–10,659 drinks)	115/209	1.72 (1.17–2.53)		1.51 (0.97–2.35)	
Tertile 3 (≥10,660 drinks)	113/215	1.50 (1.03–2.19)		1.36 (0.64–2.19)	
Low-grade prostate cancer					
Cumulative lifetime alcohol consumption			0.86		0.97
Tertile 1 (<3,094 drinks)	79/207	Ref.		Ref.	
Tertile 2 (3,094–10,659 drinks)	89/183	1.57 (1.05–2.36)		1.41 (0.90–2.22)	
Tertile 3 (≥10,660 drinks)	70/172	1.12 (0.74–1.70)		1.06 (0.64–1.74)	
High-grade prostate cancer					
Cumulative lifetime alcohol consumption			<0.001		0.003
Tertile 1 (<3,094 drinks)	19/147	Ref.		Ref.	
Tertile 2 (3,094–10,659 drinks)	26/120	2.11 (1.09–4.09)		1.81 (0.84–3.90)	
Tertile 3 (≥10,660 drinks)	43/145	3.07 (1.67–5.64)		3.20 (1.47–6.98)	

[a]Adjusted for age, race, DRE, prostate volume, PSA, year of consent, smoking, BMI, and previous prostate biopsy.
N represents the number of men diagnosed with overall, low-grade or high-grade prostate cancer, respectively, over the total number of men undergoing prostate biopsy.

association between high alcohol intake over the lifetime and prostate cancer risk (19). In another Canadian population-based case–control study, McGregor and colleagues showed that current alcohol intake was not associated with prostate cancer risk but that lifetime intake was associated with significantly increased risk of both low-grade and high-grade prostate cancer (10). Breslow and colleagues reported a significant inverse association between heavy drinking at ages 25, 35, and 45 and prostate cancer risk (20), with the inverse direction of association potentially attributable to detection bias due to lower screening rates among heavy drinkers and/or competing causes of death in this group. Although relatively few studies have investigated early-life exposure to alcohol, childhood height and early-life BMI have both been associated with increased risk of fatal prostate cancer (21, 22), suggesting that early-life exposures may be important to consider in prostate carcinogenesis. Whether associations between early-life exposures and prostate cancer are due to specific windows of susceptibility, higher cumulative lifetime exposure, or changing patterns of behavior close to prostate cancer diagnosis, is unclear (5, 11). Although future studies are needed to better understand the relationship between lifetime alcohol intake and prostate cancer risk, our findings, combined with those from prior studies, suggest that considering earlier-life alcohol intake patterns may be important.

The mechanisms by which alcohol consumption contributes to cancer risk are complex and not fully understood. The International Agency for Research on Cancer reports 15 known and suspected human carcinogens, including acetaldehyde, ethanol, and formaldehyde, occurring in alcoholic beverages (23). Chronic alcohol consumption might increase cancer risk by enhancing activation of these carcinogens via an ethanol-inducible cytochrome P450 enzyme (24). A study in rats showed that prostate cytosolic xanthine oxidase can bioactivate ethanol to acetaldehyde and free radicals (25). It has been shown in cell culture that acetaldehyde induces point mutations, sister chromatid exchanges and gross chromosomal aberrations (26–28). Finally, alcohol can act as an endocrine disruptor by altering circulating levels of sex hormone-binding globulin, thereby affecting total and free testosterone concentrations (29, 30). How this may affect prostate cancer risk is unclear, given mixed evidence for a role of circulating sex hormone levels in prostate cancer (31–33), and very sparse data examining hormone exposure in early life (11, 34). Our findings, in addition to those from other groups (10), may support additional studies of early-life exposures in relation to prostate cancer risk.

Our study has some limitations. First, our study may be subject to recall bias as alcohol intake was based on questionnaires completed after biopsy, in some cases after cancer status was known. However, given that alcohol is not an established risk factor for prostate cancer, any bias that occurred due to exposure misclassification would likely have been nondifferential with regard to prostate cancer diagnosis, bringing associations toward the null. Prospective cohorts, which avoid this potential source of bias by collecting exposure information prior to occurrence of the outcome of interest, are needed to validate our findings. Second, 39% of men participating in this cohort were excluded from the present analysis due to missing questionnaire data, creating a potential selection bias. The excluded men tended to be younger and African American, with higher PSA at biopsy and a higher likelihood of being diagnosed with prostate cancer overall, though they were equally likely to be diagnosed with high-grade disease, and were otherwise similar to men who completed study questionnaires. How this potential selection bias may have affected our results is unknown. In addition, all patients in our cohort had some indication for the biopsy (i.e., elevated PSA, abnormal DRE) possibly introducing additional selection bias. Although these indications for biopsy

were not related to early-life alcohol consumption, it is possible that our results cannot be generalized to the healthy population. Third, we ascertained prostate cancer status based on biopsy outcomes and it is well known that some men with a negative biopsy still harbor prostate cancer. However, other studies have shown that the rate of misclassification in men with repeat biopsy is low (35) and therefore this is unlikely to substantially change our results. Fourth, our reference group of nondrinkers in later decades contained past drinkers, though this would likely bias our estimates toward the null. Our analysis of cumulative lifetime intake includes alcohol intake across all decades of life and circumvents this limitation of studying specific decades of alcohol exposure. However, given that the vast majority of men reporting heavier alcohol intake at ages 15 to 19 were also in the upper tertile of cumulative lifetime alcohol intake, we were unable to definitively separate the potential effects of early-life exposure from cumulative lifetime exposure to alcohol in this study. Related, alcohol consumption was correlated across all earlier-life decades, which hampered the identification of the most relevant decade for alcohol exposure in relation to prostate cancer. In addition, due to wide categories of smoking data and the association with drinking at ages 15 to 19 years, there is possibility for residual confounding from smoking, and our study was too small to explore smoking as an effect modifier of associations between alcohol and prostate cancer. Finally, our study was limited because our participant population had relatively few heavy drinkers and we did not have access to information about binge drinking patterns or beverage-specific effects. In addition, our study population was comprised of veterans, who may have unique early drinking patterns that may not be generalizable to the general population. Despite these limitations, our study benefited from alcohol questionnaires that spanned all decades of life, enabling testing of potential windows of susceptibility to alcohol exposure in the context of equal access to care. Finally, our study population was strong in diversity as 54% of participants were non-white.

In the present analysis among veterans undergoing prostate biopsy, we found a significant positive association between heavier alcohol exposure between the ages of 15 and 49 and diagnosis of high-grade prostate cancer at time of biopsy, while current alcohol intake was unrelated to prostate cancer diagnosis. We also found a positive association between higher cumulative lifetime alcohol intake and high-grade prostate cancer diagnosis. These results suggest that earlier-life alcohol exposure and cumulative lifetime intake may be important variables to consider when analyzing prostate cancer risk. These data give insight into prostate cancer risk factors in general and how earlier in life exposures may be important to consider when analyzing prostate cancer risk. Further studies should explore earlier-life exposure to alcohol to validate these results.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Michael, A. De Hoedt, S.J. Freedland
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Michael, L.E. Howard, L.A. Mucci, S.J. Freedland, E.H. Allott
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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
2. Roswall N, Weiderpass E. Alcohol as a risk factor for cancer: existing evidence in a global perspective. J Prev Med Public Health 2015;48:1–9.
3. Dennis LK. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. Prostate 2000;42:56–66.
4. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer 2001;85:1700–5.
5. Middleton Fillmore K, Chikritzhs T, Stockwell T, Bostrom A, Pascal R. Alcohol use and prostate cancer: a meta-analysis. Mol Nutr Food Res 2009;53:240–55.
6. Rota M, Scotti L, Turati F, Tramacere I, Islami F, Bellocco R, et al. Alcohol consumption and prostate cancer risk: a meta-analysis of the dose-risk relation. Eur J Cancer Prev 2012;21:350–9.
7. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015;112:580–93.

8. Zhao J, Stockwell T, Roemer A, Chikritzhs T. Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer 2016;16:845.
9. Zuccolo L, Lewis SJ, Donovan JL, Hamdy FC, Neal DE, Smith GD. Alcohol consumption and PSA-detected prostate cancer risk–a case-control nested in the ProtecT study. Int J Cancer 2013; 132:2176–85.
10. McGregor SE, Courneya KS, Kopciuk KA, Tosevski C, Friedenreich CM. Case-control study of lifetime alcohol intake and prostate cancer risk. Cancer Causes Control 2013;24:451–61.
11. Sutcliffe S, Colditz GA. Prostate cancer: is it time to expand the research focus to early-life exposures? Nat Rev Cancer 2013; 13:208–518.
12. Vidal AC, Williams CD, Allott EH, Howard LE, Grant DJ, McPhail M, et al. Carbohydrate intake, glycemic index and prostate cancer risk. Prostate 2015;75:430–9.
13. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA 2011;305: 2548–55.
14. Epstein JI. A new contemporary prostate cancer grading system. Ann Pathol 2015;35:474–6.
15. Fowke JH, Howard L, Andriole GL, Freedland SJ. Alcohol intake increases high-grade prostate cancer risk among men taking dutasteride in the REDUCE trial. Eur Urol 2014;66:1133–8.
16. Kubo JT, Henderson MT, Desai M, Wactawski-Wende J, Stefanick ML, Tang JY. Alcohol consumption and risk of melanoma and non-melanoma skin cancer in the Women's Health Initiative. Cancer Causes Control 2014;25:1–10.
17. Isaacs JT. Role of androgens in prostatic cancer. Vitam Horm 1994;49:433–502.
18. Gong Z, Kristal AR, Schenk JM, Tangen CM, Goodman PJ, Thompson IM. Alcohol consumption, finasteride, and prostate cancer risk: results from the Prostate Cancer Prevention Trial. Cancer 2009;115:3661–9.
19. Demoury C, Karakiewicz P, Parent ME. Association between lifetime alcohol consumption and prostate cancer risk: a case-control study in Montreal, Canada. Cancer Epidemiol 2016; 45:11–7.
20. Breslow RA, Wideroff L, Graubard BI, Erwin D, Reichman ME, Ziegler RG, 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;9:254–61.
21. Aarestrup J, Gamborg M, Cook MB, Baker JL. Childhood height increases the risk of prostate cancer mortality. Eur J Cancer 2015;51:1340–5.
22. Kelly SP, Graubard BI, Andreotti G, Younes N, Cleary SD, Cook MB. Prediagnostic body mass index trajectories in relation to prostate cancer incidence and mortality in the PLCO cancer screening trial. J Natl Cancer Inst 2017;109.
23. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum 2010;96:3–1383.
24. Lieber CS. Herman Award Lecture, 1993: a personal perspective on alcohol, nutrition, and the liver. Am J Clin Nutr 1993;58: 430–42.
25. Castro GD, Delgado de Layño AM, Costantini MH, Castro JA. Rat ventral prostate xanthine oxidase bioactivation of ethanol to acetaldehyde and 1-hydroxyethyl free radicals: analysis of its potential role in heavy alcohol drinking tumor-promoting effects. Teratog Carcinog Mutagen 2001;21:109–19.
26. Fang JL, Vaca CE. Development of a 32P-postlabelling method for the analysis of adducts arising through the reaction of acetaldehyde with 2′-deoxyguanosine-3′-monophosphate and DNA. Carcinogenesis 1995;16:2177–85.
27. Ristow H, Seyfarth A, Lochmann ER. Chromosomal damages by ethanol and acetaldehyde in Saccharomyces cerevisiae as studied by pulsed field gel electrophoresis. Mutat Res 1995; 326:165–70.
28. Grafstrom RC, Dypbukt JM, Sundqvist K, Atzori L, Nielsen I, Curren RD, et al. Pathobiological effects of acetaldehyde in cultured human epithelial cells and fibroblasts. Carcinogenesis 1994;15:985–90.
29. Shiels MS, Rohrmann S, Menke A, Selvin E, Crespo CJ, Rifai N, et al. Association of cigarette smoking, alcohol consumption, and physical activity with sex steroid hormone levels in US men. Cancer Causes Control 2009;20:877–86.
30. Gordon GG, Altman K, Southren AL, Rubin E, Lieber CS. Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. N Engl J Med 1976;295: 793–7.
31. Salonia A, Abdollah F, Capitanio U, Suardi N, Briganti A, Gallina A, et al. Serum sex steroids depict a nonlinear u-shaped association with high-risk prostate cancer at radical prostatectomy. Clin Cancer Res 2012;18:3648–57.
32. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst 2008;100:170–83.
33. Schatzl G, Madersbacher S, Thurridl T, Waldmüller J, Kramer G, Haitel A, et al. High-grade prostate cancer is associated with low serum testosterone levels. Prostate 2001;47:52–8.
34. Tsai CJ, Cohn BA, Cirillo PM, Feldman D, Stanczyk FZ, Whittemore AS. Sex steroid hormones in young manhood and the risk of subsequent prostate cancer: a longitudinal study in African-Americans and Caucasians (United States). Cancer Causes Control 2006;17:1237–44.
35. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192–202.