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

The association between early-life alcohol intake and high-grade prostate cancer in an equal access, racially diverse biopsy cohort

Jamie Michael[1], Lauren E. Howard[2], Sarah C. Markt[3], Amanda De Hoedt[1], Charlotte Bailey[1], Lorelei A. Mucci[3], Stephen J. Freedland[1,4], Emma H. Allott[3,5,6]

[1]Division of Urology, Veterans Affairs Medical Center, Durham, NC

[2]Duke Cancer Institute, Duke University School of Medicine, Durham, NC

[3]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA

[4]Cedars-Sinai Medical Center, Los Angeles, CA

[5]Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC

[6]Department of Histopathology and Morbid Anatomy, Trinity Translational Medicine Institute, Trinity College Dublin, Ireland

Running title (60 character limit): Early-life alcohol intake and prostate cancer risk

Keywords: African American, alcohol, prostate biopsy, early-life, lifetime, prostate cancer

Financial support: American Institute for Cancer Research (E.H. Allott), Irish Cancer Society John Fitzpatrick Fellowship (E.H. Allott), and NIH 1K24CA160653 (S.J. Freedland)

Corresponding author: Dr. Emma H. Allott, Department of Nutrition, CB 7461, University of North Carolina at Chapel Hill, 135 Dauer Drive, Chapel Hill, NC 27599, USA. Phone: +1 919-966-7230; Fax: +1 919-966-2089; E-mail: allott@email.unc.edu

Conflicts of interest: The authors have no conflicts of interest

Word count (text, excluding abstract and references): 2,331

Number of Tables: 4

Statement of translational relevance:

Epidemiologic evidence for an association between alcohol and prostate cancer is mixed. The prostate undergoes growth and maturation during puberty, and may be particularly susceptible to potentially carcinogenic exposures during this period. However, there is a lack of research investigating early-life alcohol intake as a risk factor for overall or high-grade prostate cancer. Using data from a Durham Veterans Affairs Medical Center biopsy cohort, we found that, relative to non-drinkers, men who consumed ≥7 drinks/week at ages 15-19 had increased odds of high-grade prostate cancer diagnosis, with similar findings for ages 20-29 and 30-39. Consistent with these results, higher cumulative lifetime intake was also associated with increased odds of high-grade prostate cancer diagnosis. In contrast, we found no significant association between any level of current alcohol use and overall or high-grade prostate cancer diagnosis. These data support exploring early-life alcohol intake as a potential risk factor for high-grade prostate cancer.

Abstract

Background: Epidemiologic evidence for an association between alcohol and prostate cancer (PC) is mixed. Moreover, there is a lack of research investigating early-life alcohol intake as a risk factor for either overall or high-grade PC. We examined lifetime alcohol intake in association with PC diagnosis in an equal-access, multiethnic prostate biopsy cohort.

Methods: Men undergoing prostate biopsy at the Durham Veterans Affairs Medical Center from 2007-2018 completed a survey indicating average number of alcoholic beverages consumed per week (categorized as none (ref), 1-6, and ≥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 PC (GG 3-5).

Results: Of 650 men who underwent biopsy, 325 were diagnosed with PC, 238 with low-grade and 88 with high-grade disease. Relative to non-drinkers, men who consumed ≥7 drinks/week at ages 15-19 had increased odds of high-grade PC diagnosis (OR 3.21, p-trend=0.020), with similar findings for ages 20-29 and 30-39. Consistent with these results, men in the upper tertile of cumulative lifetime intake had increased odds of high-grade PC diagnosis (OR 3.74, p-trend<0.001). In contrast, current alcohol intake was not associated with PC.

Conclusion: Among men undergoing prostate biopsy, heavier alcohol intake earlier in life and higher cumulative alcohol intake were positively associated with high-grade PC diagnosis, while current alcohol intake was unrelated to PC. Our findings suggest that early-life alcohol intake should be explored as a potential risk factor for high-grade PC.

Introduction

Prostate cancer is the most frequently diagnosed non-skin cancer in men in the United States (US), 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.

Individual studies have found mixed results regarding the effect of alcohol consumption and overall prostate cancer risk; including null(3-6), inverse(7, 8) and positive associations(9, 10). Results of a recent meta-analysis found a statistically significant dose-response relationship between the quantity

of alcohol consumption and overall prostate cancer risk(11). Another study found that heavier drinking was associated with increased risk of high-grade disease, but had no association with low-grade prostate cancer risk(12). 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 nonaggressive prostate cancer (13), suggesting that alcohol exposure earlier in life may be important.

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(14), 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 identification and accrual of participants have been described previously(15). Men were at least 18 years of age, had a PSA test within 12 months prior to enrollment, and had no history of prostate cancer. Of the 1595 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 equally likely to be diagnosed with

high-grade prostate cancer (data not shown). 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?” 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 (age 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 prostate cancer diagnosis), was calculated by summing the number of drinks/week over each decade of life, which was categorized into tertiles (13). 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)(16). All questionnaires were self-administered and typically filled out shortly after the biopsy and returned by mail. 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 Epstein’s five grade group system where low-grade disease was defined as grade group (GG) 1-2 (Gleason score ≤3+4) and high-grade prostate cancer as GG 3-5 (Gleason score ≥4+3)(17).

Statistical Methods

Patient characteristics were summarized by alcohol consumption at age 15-19 and differences were tested using Kruskal-Wallis tests for continuous variables and chi-squared 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 15-19. We also examined alcohol intake at age 20-29, and age 30-39. 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, 1-6, and ≥7, in line with previous studies(18, 19). 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 was 7-10 for ages 15-19, so all patients were assigned a value of 8.5 (median value of 7-10 category) for the trend analysis.

We examined whether associations between alcohol consumption and 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.

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.; Cary, NC).

Results

Patient characteristics

Median (IQR) age at biopsy in our cohort was 64 (60-68) and 47% of patients were white (Table 1). Median (IQR) PSA was 5.7 ng/ml (4.5-7.9 ng/ml). During ages 15-19, there were 317 (49%) men who reported not drinking, 279 (43%) men who reported drinking 1-6 drinks per week, and 54 (8%) who reported drinking ≥7 drinks per week. Men who reported ≥7 drinks per week at ages 15-19 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 1-2 and 88 with grade group 3-5. There was no association between alcohol intake at ages 15-19 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 1-6 drinks per week at ages 20-29 and 1-6 and ≥7 drinks per week at ages 30-39 were associated with increased odds of prostate cancer diagnosis, although the trends across increasing categories of alcohol intake were not statistically significant (Table 2). This association held for 1-6 drinks per week at ages 30-39 (OR 1.64, 95% CI 1.02-2.63), 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 15-19 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 analysis, consumption of ≥7 drinks per week at ages 15-19 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 20-29 (multivariable OR 3.14, 95%CI 1.14-8.65, p-trend=0.034), and ages 30-39 (multivariable OR 3.09, 95%CI 1.20-8.00, p-trend=0.019). 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 (data not shown).

There were no differences in associations between alcohol consumption and prostate cancer diagnosis between white and non-white men (data not shown). Our findings were similar when models for earlier-life alcohol intake were not adjusted for current alcohol consumption (Supplementary Table 1).

Cumulative lifetime alcohol consumption and prostate cancer

On age-adjusted and multivariable 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 3.74; 95% CI 1.70-8.25; Table 4). There was a significant trend across increasing tertiles of cumulative lifetime alcohol intake in association with high-grade prostate cancer diagnosis ($p<0.001$).

Discussion

Both clinical and epidemiological evidence suggests that prostate carcinogenesis may span decades(20). 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(14). 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 be diagnosed with high-grade prostate cancer at biopsy, compared to men with no early-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.

While 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. Two meta-analyses found no association between alcohol consumption and risk of prostate cancer(3, 4), while the most recent meta-analysis reported a modest yet significant dose-response relationship between increasing alcohol intake and overall prostate cancer risk(11). Moreover, a secondary analysis of the ProtecT trial by Zuccolo et al., showed higher risk of high-grade disease for heavy drinkers, and no association of alcohol with low-grade disease(12). 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-ARIs)(18, 21). 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 association between high alcohol intake over the lifetime and prostate cancer risk(22). In another Canadian population-based case-control study, McGregor et al., 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(13). Breslow et al. reported a significant inverse association between heavy drinking at ages 25, 35 and 45 and prostate cancer risk(8), 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. While 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(23, 24), suggesting that early-life exposures may be important to consider in prostate carcinogenesis. While 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 fifteen known and suspected human carcinogens, including acetaldehyde, ethanol, and formaldehyde, occurring in alcoholic beverages(25). Chronic alcohol consumption might increase cancer risk by enhancing activation of these carcinogens via an ethanol-inducible cytochrome P450 enzyme(26). A study in rats showed that prostate cytosolic xanthine oxidase can bioactivate ethanol to acetaldehyde and free radicals(27). It has been shown in cell culture that acetaldehyde induces point mutations, sister chromatid exchanges and gross chromosomal aberrations(28-30). Finally, alcohol can act as an

endocrine disruptor by altering circulating levels of sex hormone-binding globulin thereby affecting total and free testosterone concentrations(31, 32). How this may affect prostate cancer risk is unclear, given mixed evidence for a role of circulating sex hormone levels in prostate cancer(33-35).

Our study has some limitations. First, our study may be subject to recall bias as alcohol intake was based on questionnaires completed after biopsy. 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 non-differential with regard to prostate cancer diagnosis, likely bringing associations towards the null. 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. 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(36) and therefore this is unlikely to substantially change our results. Fourth, our reference group of non-drinkers in later decades contained past drinkers, though this would likely bias our estimates towards 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 15-19 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. 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 – 39 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 early-life alcohol exposure and cumulative lifetime intake may be important variables to consider when analyzing prostate cancer risk. Further studies should explore early-life exposure to alcohol to validate these results.

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians. 2018;68:7-30.
2. Roswall N, Weiderpass E. Alcohol as a risk factor for cancer: existing evidence in a global perspective. Journal of preventive medicine and public health = Yebang Uihakhoe chi. 2015;48:1-9.
3. Dennis LK. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. The Prostate. 2000;42:56-66.
4. 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. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2012;21:350-9.
5. Chao C, Haque R, Van Den Eeden SK, Caan BJ, Poon KY, Quinn VP. Red wine consumption and risk of prostate cancer: the California men's health study. International journal of cancer. 2010;126:171-9.
6. Rohrmann S, Linseisen J, Key TJ, Jensen MK, Overvad K, Johnsen NF, et al. Alcohol consumption and the risk for prostate cancer in the European Prospective Investigation into Cancer and Nutrition. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008;17:1282-7.
7. Barba M, McCann SE, Schunemann HJ, Stranges S, Fuhrman B, De Placido S, et al. Lifetime total and beverage specific--alcohol intake and prostate cancer risk: a case-control study. Nutrition journal. 2004;3:23.
8. 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. Annals of epidemiology. 1999;9:254-61.
9. Putnam SD, Cerhan JR, Parker AS, Bianchi GD, Wallace RB, Cantor KP, et al. Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. Annals of epidemiology. 2000;10:361-9.
10. Platz EA, Leitzmann MF, Rimm EB, Willett WC, Giovannucci E. Alcohol intake, drinking patterns, and risk of prostate cancer in a large prospective cohort study. Am J Epidemiol. 2004;159:444-53.
11. 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.
12. 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. International journal of cancer. 2013;132:2176-85.

13. McGregor SE, Courneya KS, Kopciuk KA, Tosevski C, Friedenreich CM. Case-control study of lifetime alcohol intake and prostate cancer risk. Cancer causes & control : CCC. 2013;24:451-61.
14. Sutcliffe S, Colditz GA. Prostate cancer: is it time to expand the research focus to early-life exposures? Nature reviews Cancer. 2013;13:208-518.
15. Vidal AC, Williams CD, Allott EH, Howard LE, Grant DJ, McPhail M, et al. Carbohydrate intake, glycemic index and prostate cancer risk. The Prostate. 2015;75:430-9.
16. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. Jama. 2011;305:2548-55.
17. Epstein JI. A new contemporary prostate cancer grading system. Annales de pathologie. 2015;35:474-6.
18. Fowke JH, Howard L, Andriole GL, Freedland SJ. Alcohol intake increases high-grade prostate cancer risk among men taking dutasteride in the REDUCE trial. European urology. 2014;66:1133-8.
19. 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 : CCC. 2014;25:1-10.
20. Isaacs JT. Role of androgens in prostatic cancer. Vitamins and hormones. 1994;49:433-502.
21. 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.
22. Demoury C, Karakiewicz P, Parent ME. Association between lifetime alcohol consumption and prostate cancer risk: A case-control study in Montreal, Canada. Cancer epidemiology. 2016;45:11-7.
23. Aarestrup J, Gamborg M, Cook MB, Baker JL. Childhood height increases the risk of prostate cancer mortality. European journal of cancer (Oxford, England : 1990). 2015;51:1340-5.
24. 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. Journal of the National Cancer Institute. 2017;109.
25. Alcohol consumption and ethyl carbamate. IARC monographs on the evaluation of carcinogenic risks to humans. 2010;96:3-1383.
26. Lieber CS. Herman Award Lecture, 1993: a personal perspective on alcohol, nutrition, and the liver. The American journal of clinical nutrition. 1993;58:430-42.
27. Castro GD, Delgado de Layno 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. Teratogenesis, carcinogenesis, and mutagenesis. 2001;21:109-19.
28. 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.
29. Ristow H, Seyfarth A, Lochmann ER. Chromosomal damages by ethanol and acetaldehyde in Saccharomyces cerevisiae as studied by pulsed field gel electrophoresis. Mutation research. 1995;326:165-70.
30. 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.
31. 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 : CCC. 2009;20:877-86.
32. Gordon GG, Altman K, Southren AL, Rubin E, Lieber CS. Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. The New England journal of medicine. 1976;295:793-7.
33. 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. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18:3648-57.
34. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. Journal of the National Cancer Institute. 2008;100:170-83.
35. Schatzl G, Madersbacher S, Thurridl T, Waldmuller J, Kramer G, Haitel A, et al. High-grade prostate cancer is associated with low serum testosterone levels. The Prostate. 2001;47:52-8.
36. 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.

Table 1: Baseline characteristics overall and stratified by weekly alcohol consumption at ages 15-19

	Overall	Average alcohol consumption at age 15-19			
		0 drinks/wk	1-6 drinks/wk	≥7 drinks/wk	
	(N=650)	(N=317)	(N=279)	(N=54)	p value
Age at biopsy					0.109[1]
Median	64	64	64	63	
Q1, Q3	60, 68	61, 68	59, 68	61, 67	
Race					0.332[2]
Non-white	346 (53%)	175 (55%)	147 (53%)	24 (44%)	
White	304 (47%)	142 (45%)	132 (47%)	30 (56%)	
Year of consent					0.925[1]
Median	2011	2011	2011	2011	
Q1, Q3	2008, 2015	2009, 2015	2008, 2015	2008, 2015	
Digital rectal exam					0.290[2]
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)					0.182[1]
Median	42.0	44.0	40.0	40.0	
Q1, Q3	30.0, 58.2	31.0, 61.2	28.0, 58.1	28.7, 52.0	
PSA at biopsy (ng/mL)					0.573[1]
Median	5.7	5.9	5.5	5.8	
Q1, Q3	4.5, 7.9	4.6, 7.8	4.4, 8.1	4.6, 8.0	
BMI (kg/m^2)					0.267[1]
Median	29.2	29.4	28.8	30.2	
Q1, Q3	26.5, 32.7	26.5, 32.8	26.3, 32.4	27.3, 34.6	
Previous prostate biopsy	102 (16%)	58 (18%)	36 (13%)	8 (15%)	0.192[2]
Smoking pack years					<0.001[1]
Median	15.4	5.6	20.1	31.8	
Q1, Q3	0.6, 35.5	0.0, 29.0	5.9, 39.9	14.3, 57.6	
Alcohol consumption, age 20-29					<0.001[2]
0 drinks/wk	120 (18%)	112 (35%)	7 (3%)	1 (2%)	
1-6 drinks/wk	365 (56%)	167 (53%)	194 (70%)	4 (7%)	
≥7 drinks/wk	165 (25%)	38 (12%)	78 (28%)	49 (91%)	
Alcohol consumption, age 30-39					<0.001[2]
0 drinks/wk	146 (22%)	114 (36%)	27 (10%)	5 (9%)	
1-6 drinks/wk	336 (52%)	161 (51%)	164 (59%)	11 (20%)	
≥7 drinks/wk	168 (26%)	42 (13%)	88 (32%)	38 (70%)	
Current alcohol consumption					<0.001[2]
0 drinks/wk	322 (50%)	191 (60%)	106 (38%)	25 (46%)	
1-6 drinks/wk	260 (40%)	100 (32%)	141 (51%)	19 (35%)	
≥7 drinks/wk	68 (10%)	26 (8%)	32 (11%)	10 (19%)	
Cumulative lifetime alcohol consumption (number of drinks)					<0.001[2]
Tertile 1 (<2860 drinks)	220 (34%)	164 (52%)	52 (19%)	4 (7%)	
Tertile 2 (2860-9879 drinks)	215 (33%)	97 (31%)	116 (42%)	2 (4%)	
Tertile 3 (≥9880 drinks)	215 (33%)	56 (18%)	111 (40%)	48 (89%)	

[1]Kruskal Wallis [2]Chi-Square

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

		Age-adjusted			Multivariable*		
	N	**OR**	**95% CI**	**p-trend**	**OR**	**95% CI**	**p-trend**
Alcohol consumption, age 15-19				0.57			0.76
0 drinks/wk	159/317	Ref.			Ref.		
1-6 drinks/wk	137/279	0.98	0.71-1.36		0.91	0.62-1.35	
≥7 drinks/wk	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/wk	52/120	Ref.			Ref.		
1-6 drinks/wk	196/365	1.57	1.03-2.38		1.35	0.82-2.24	
≥7 drinks/wk	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/wk	57/146	Ref.			Ref.		
1-6 drinks/wk	182/336	1.88	1.26-2.80		1.64	1.02-2.63	
≥7 drinks/wk	86/168	1.65	1.05-2.59		1.39	0.77-2.51	
Alcohol consumption, current				0.11			0.39
0 drinks/wk	150/322	Ref.			Ref.		
1-6 drinks/wk	136/260	1.35	0.97-1.89		1.12	0.75-1.69	
≥7 drinks/wk	39/68	1.61	0.95-2.75		1.34	0.71-2.53	

* 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

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

		Age-adjusted			Multivariable		
	N	**OR**	**95% CI**	**p-trend**	**OR**	**95% CI**	**p-trend**
Low grade PC (GG 1-2)							
Alcohol consumption, age 15-19				0.73			0.81
0 drinks/wk	77/235	Ref.			Ref.		
1-6 drinks/wk	58/200	0.88	0.62-1.25		0.84	0.57-1.26	
≥7 drinks/wk	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/wk	26/94	Ref.			Ref.		
1-6 drinks/wk	94/263	1.50	0.96-2.35		1.28	0.77-2.14	
≥7 drinks/wk	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/wk	28/117	Ref.			Ref.		
1-6 drinks/wk	83/237	1.87	1.22-2.86		1.64	1.00-2.68	
≥7 drinks/wk	35/117	1.33	0.81-2.19		1.17	0.62-2.19	
Alcohol consumption, current				0.26			0.51
0 drinks/wk	68/240	Ref.			Ref.		
1-6 drinks/wk	60/184	1.39	0.97-1.99		1.25	0.82-1.92	
≥7 drinks/wk	18/47	1.46	0.81-2.61		1.33	0.68-2.59	
High Grade PC (GG 3-5)							
Alcohol consumption, age 15-19				0.011			0.020
0 drinks/wk	82/240	Ref.			Ref.		
1-6 drinks/wk	79/221	1.35	0.81-2.26		1.30	0.70-2.42	
≥7 drinks/wk	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/wk	26/94	Ref.			Ref.		

1-6 drinks/wk	102/271	1.76	0.85-3.63		1.81	0.75-4.42	
≥7 drinks/wk	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/wk	29/118	Ref.			Ref.		
1-6 drinks/wk	99/253	1.88	0.95-3.72		1.66	0.73-3.78	
≥7 drinks/wk	51/133	2.98	1.46-6.09		3.09	1.20-8.00	
Alcohol consumption, current				0.062			0.41
0 drinks/wk	82/254	Ref.			Ref.		
1-6 drinks/wk	76/200	1.29	0.76-2.18		0.73	0.37-1.40	
≥7 drinks/wk	21/50	2.07	0.98-4.38		1.27	0.51-3.19	

* 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

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

		Age-adjusted			**Multivariable***		
Outcome	**N**	**OR**	**95% CI**	**p-trend**	**OR**	**95% CI**	**p-trend**
Overall PC				0.22			0.57
Tertile 1	95/220	Ref.			Ref.		
Tertile 2	120/215	1.75	1.19-2.57		1.67	1.07-2.59	
Tertile 3	110/215	1.40	0.96-2.04		1.26	0.78-2.04	
Low-grade PC				0.57			0.48
Tertile 1	78/202	Ref.			Ref.		
Tertile 2	96/191	1.65	1.10-2.47		1.56	1.00-2.44	
Tertile 3	64/169	0.98	0.64-1.49		0.91	0.55-1.52	
High-grade PC				<0.001			<0.001
Tertile 1	18/142	Ref.			Ref.		
Tertile 2	24/119	1.94	0.99-3.82		1.93	0.88-4.24	
Tertile 3	46/151	3.22	1.75-5.95		3.74	1.70-8.25	

* Adjusted for age, race, DRE, prostate volume, PSA, year of consent, smoking, BMI, and previous prostate biopsy

Supplementary Table 1: Odds ratios for the association between alcohol consumption across different ages and low-grade and high-grade prostate cancer, without adjusting models for current alcohol consumption

		Multivariable		
	N	**OR**	**95% CI**	**p-trend**
Low grade PC (GG 1-2)				
Alcohol consumption, age 15-19				0.89
0 drinks/wk	77/235	Ref.		
1-6 drinks/wk	58/200	0.87	0.59-1.30	
≥7 drinks/wk	11/36	0.97	0.46-2.07	
Alcohol consumption, age 20-29				0.086
0 drinks/wk	26/94	Ref.		
1-6 drinks/wk	94/263	1.39	0.84-2.29	
≥7 drinks/wk	26/114	0.80	0.43-1.51	
Alcohol consumption, age 30-39				0.83
0 drinks/wk	28/117	Ref.		
1-6 drinks/wk	83/237	1.74	1.09-2.80	
≥7 drinks/wk	35/117	1.29	0.71-2.33	
High Grade PC (GG 3-5)				
Alcohol consumption, age 15-19				0.020
0 drinks/wk	82/240	Ref.		
1-6 drinks/wk	79/221	1.31	0.71-2.44	
≥7 drinks/wk	18/43	3.21	1.22-8.42	
Alcohol consumption, age 20-29				0.033
0 drinks/wk	26/94	Ref.		
1-6 drinks/wk	102/271	1.78	0.74-4.26	
≥7 drinks/wk	51/139	3.05	1.14-8.18	
Alcohol consumption, age 30-39				0.020
0 drinks/wk	29/118	Ref.		
1-6 drinks/wk	99/253	1.59	0.71-3.52	
≥7 drinks/wk	51/133	2.85	1.16-7.01	

* 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 low-grade or high-grade prostate cancer, respectively, over the total number of men undergoing prostate biopsy