

## Alcohol and Prostate Cancer

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### INTRODUCTION

Alcohol use, and particularly heavy use, causes cancers of the oral cavity, pharynx, larynx, esophagus, and liver (1), with risks for the aero-digestive cancers rising to about two- to fourfold among heavy drinkers. Alcohol consumption may also cause cancer at other sites; however, the evidence is less certain. Moderate use among women has been related to increases in breast cancer, with summary analyses showing about a 10 percent increase in incidence of this disease with each alcoholic drink consumed daily (2, 3). Increased risks for pancreatic cancer (4) and colon tumors (5) have also been related to alcohol use in some studies. In this presentation, the epidemiologic evidence that alcohol consumption is related to risk for prostate cancer is reviewed.

### ALCOHOLIC BEVERAGES

Alcohol consumption is generally measured in drinks per day, with a "typical" drink of alcohol containing about 15 g of ethanol irrespective of the type of beverage consumed (wine, beer, and liquor, straight or mixed). Alcohol consumption in relation to prostate cancer has been reported quantitatively, by drinks per day, qualitatively, by heavy or excess drinking, and by the diagnostic category of alcoholism. Here we consider alcohol consumption of less than three drinks per day as moderate and consumption of seven or more drinks per day as abusive.

### EPIDEMIOLOGIC STUDIES OF ALCOHOL USE AND PROSTATE CANCER

#### Alcohol abusers and prostate cancer

Significantly increased risks of prostate cancer have been seen in a large cohort of alcohol abusers from Denmark (6) and among alcoholics from Sweden (7) who were less than 65 years of age, but not among those 65 years or older (table

1). The pooled standardized incidence ratio for alcohol abusers was 1.22 (95 percent confidence interval (CI): 1.04, 1.42) for these two studies (8). A mortality study among DuPont employees found three alcoholic men that died of prostate cancer compared with no deaths among controls after following 899 alcoholics and 921 controls for 5 years (9). A study based on vital statistics in Japan reported a 2.5-fold increase in prostate cancer deaths among daily drinkers of strong liquor (10). None of these studies provided quantitative information about the amount of alcohol use.

Two small autopsy studies reported in the 1960s (11, 12) found a lower prevalence of prostate cancer in cirrhotics than in controls, suggesting that physiologic changes associated with cirrhosis may reduce prostate cancer risk. Small latent cancers, which are over-represented in autopsy series, were not distinguished from more aggressive tumors in these studies.

#### Heavy alcohol consumption and prostate cancer

Few studies have examined a quantitative relation between heavy alcohol use and prostate cancer. In a US population-based case-control study (13), consumers of eight or more drinks per day had a significantly increased risk of this disease (relative risk = 1.9; 95 percent CI: 1.3, 2.7). Risks were similarly elevated among blacks and whites and among recent and former drinkers, and similar risks were seen for beer and liquor independently, but not seen for wine (table 2). A US cohort study of participants in a prepaid health plan (14) showed no excesses after an average follow-up of 4.6 years; however, only five cases of prostate cancer occurred in the high-consumption group (table 2). A nonsignificant excess risk was noted among heavy drinkers in one hospital-based case-control study (15), but no excess was seen in three other hospital-based studies (16-18) (table 3).

#### Moderate alcohol consumption and prostate cancer

Most of the quantitative studies on alcohol use and prostate cancer have considered risks only up to levels of consumption of about three drinks or more per day. Increased prostate cancer risk was found in an Iowa cohort at less than one drink per day (19), and a nonsignificant increase in risk was found in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study cohort I at more than three drinks per day (20). Other cohort studies showed no association in the range of alcohol use up to about three drinks per day (14, 20-22). No prostate

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Abbreviation: CI, confidence interval.

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TABLE 1. Studies of prostate cancer among alcoholics or alcohol abusers

Study (reference no.) and year	Study population/location	Population characteristics	Measure of alcohol	Excess risk reported		
				No. of cases	Standardized incidence ratio	95% confidence interval
Tonnesen et al. (6), 1994	Denmark	Alcohol abusers	15,241 alcohol abusers compared with Denmark population		1.4	1.2, 1.8
Adami et al. (7), 1992	Sweden	Alcoholics	Alcoholics		1.0	0.8, 1.3
Pell and D'Alonzo (9), 1973	DuPont employees	Mortality (over 5 years) Matched controls	899 alcoholics 921 non-alcoholics	3 0		

cancer excesses were noted at moderate levels of alcohol use in population-based case-control studies that reported detailed information on alcohol consumption (13, 23-25), except for a modest nonsignificant excess noted in a Swedish study (26) at one or more drinks per day (table 2).

#### Meta-analysis of alcohol and prostate cancer

A meta-analysis of epidemiologic studies published from 1976 to 1997 (8), including six cohort and 27 case-control studies, found an overall relative risk estimate of 1.05 (95 percent CI: 0.98, 1.11) for prostate cancer among men who reported any alcohol consumption. However, categorizing individuals as never or ever consuming alcohol was done in different time frames with varying definitions. This may lump light drinkers and former drinkers with nondrinkers for some study definitions. To avoid such misclassification, levels of consumption were pooled. Based on a linear dose-response model, a pooled analysis showed an odds ratio of 1.21 (95 percent CI: 1.05, 1.39) for prostate cancer among men who drank four drinks per day (8), suggesting that daily consumption of four alcoholic drinks per day is associated with about a 21 percent increased risk for prostate cancer among heavy drinkers, or that 17.4 percent of prostate cancer among men who drink heavily is attributable to alcohol. However, the linear estimate included data from studies without alcohol consumption levels as high as four drinks per day which required linear extrapolation (8).

#### MECHANISTIC CONSIDERATIONS

Both acute and chronic alcohol consumption tend to result in greater serum estrogen and lower androgen levels in both men and women (27). Breast cancer in women is widely considered to be a disease of estrogen excess (28), consistent with excesses of this disease found in women who consume alcohol. As prostate cancer appears to be more closely linked to androgen excess (28), alcohol-related prostate carcinogenesis could operate through other pathways.

Alcohol may improve the permeability of cell membranes to carcinogens, alter carcinogen metabolizing enzyme activity, and inhibit DNA repair (29). Alcohol can also alter first-pass metabolism in the liver of carcinogens, such as the nitrosamines, and may impact on DNA methylation affect-

ing gene regulation (30). Additionally, alcohol consumption impacts energy balance and body mass, factors that could be of importance for diseases such as breast and prostate cancer (31, 32).

#### METHODOLOGICAL ISSUES

If alcohol causes prostate cancer, this may occur only at high levels of exposure. Of the few analytical studies with quantitative estimates of alcohol intake, effects of high levels of consumption were considered in only one cohort study; however, this investigation was limited for assessment of high-exposure risks, reporting on only five cases in the high-exposure group.

One population-based and four hospital-based case-control studies reported on heavy alcohol use and prostate cancer. Alcohol consumption in cases compared with hospital controls may not give valid comparisons, as alcohol use among hospital controls may differ from that of the general population. Heavy alcohol use is associated with a number of diseases and conditions requiring hospitalization, while moderate alcohol consumption may actually reduce the likelihood of hospitalization because this level of consumption may lead to reduced risks of various diseases, including heart disease.

Heavy alcohol users may tend to be under-represented among study participants, and participants may tend to under-report alcohol use. If this occurred differentially for cases and controls, substantial bias could result.

The variation in reported risk of prostate cancer and alcohol consumption between studies may also be due to the varying methods of reporting alcohol consumption. In the various studies of prostate cancer, for example, measures of the timing of alcohol use included current use, more than six times per year, 24-hour recall, regular use for more than 6 months, use in the past year, use in the past 3 years, use in the 10 years prior to the reference date, and use during the "current" time when questionnaire data were being collected. Three studies reported on the number of occasions when alcohol was consumed (33-35). Two other studies (36, 37) did not clearly identify whether they were reporting volume of ethanol or volume of alcoholic beverages. A sixth study reported on men who never used alcohol, reformed drinkers, and those who consumed more than

**TABLE 2. Cohort and population-based case-control studies reporting quantitative levels of alcohol consumption of at least one drink per day in association with prostate cancer risk**

Study (reference no.) and year	Study population/location	Diseased/reference	Alcohol measures reported	Equivalent alcohol in drinks/day	Relative risk	95% confidence interval
<i>Cohort studies</i>						
Schuurman et al. (21), 1999	The Netherlands	109/1,428	Nondrinker		Ref*	
		143/1,931	0-14 g/day		1.1	0.8, 1.5
		161/2,624	5-14 g/day	<1 drink/day	0.9	0.7, 1.3
		161/2,162	15-29 g/day	1-2 drinks/day	1.1	0.8, 1.4
		101/1,324	≥30 g/day	≥2 drinks/day	1.1	0.8, 1.6
Breslow et al. (20), 1999	NHANES I†, cohort I	96/22,580‡	Nondrinker		Ref*	
		41/11,183‡	<1 drink/week		0.97	0.67, 1.41
		65/26,972‡	2-7 drinks/week	≤1 drink/day	0.88	0.64, 1.21
		25/9,872‡	8-14 drinks/week	>1-2 drinks/day	0.96	0.61, 1.50
		8/4,365‡	15-21 drinks/week	>2-3 drinks/day	0.85	0.41, 1.75
Breslow et al. (20), 1999	NHANES I, cohort II	17/5,192‡	≥22 drinks/week	>3 drinks/day	1.42	0.84, 2.40
		59/8,453‡	Nondrinker		Ref*	
		19/5,247‡	<1 drink/week		0.74	0.44, 1.25
		29/6,928‡	2-7 drinks/week	≤1 drink/day	1.13	0.70, 1.80
		16/3,519‡	8-14 drinks/week	>1-2 drinks/day	1.05	0.60, 1.86
Parker et al. (19), 1999	Iowa	9/1,834‡	15-21 drinks/week	>2-3 drinks/day	1.12	0.55, 2.30
		2/2,707‡	≥22 drinks/week	>3 drinks/day	0.23	0.06, 0.95
		26/2,934‡	No adult use		Ref*	
		14/1,462‡	<22 g/week		1.3	0.7, 2.5
		25/1,522‡	23-92 g/week	<1 drink/day	2.4	1.3, 4.2
Hiatt et al. (20), 1994	Kaiser Permanente, Northern California	16/1,430‡	≥92 g/week	≥1 drink/day	1.6	0.9, 3.1
		25/§	Never drinker		Ref*	
		17/§	Past drinker		1.4	0.7, 2.7
		37/§	Occasional drinker		1.4	0.8, 2.3
		73/§	<1 drink/day	<1 drink/day	1.3	0.8, 2.2
		59/§	1-2 drinks/day	1-2 drinks/day	1.2	0.7, 2.1
		22/§	3-5 drinks/day	3-5 drinks/day	1.1	0.6, 2.0
5/§	≥6 drinks/day	≥6 drinks/day	1.0	0.4, 2.8		
Le Marchand et al. (22), 1994	Hawaii	238/93,432	Total subjects			
		198/20,316	0 g/week		Ref*	
		Reported tertiles	<156 g/week	≤1 drink/day	1.0	0.7, 1.6
		≥156 g/week	>1 drink/day	1.1	0.7, 1.6	
<i>Population-based case-control studies</i>						
Villeneuve et al. (23), 1999	Canada	403/474			Ref*	
		666/637	≤1 drink/day	≤1 drink/day	1.1	0.9, 1.3
		217/379	1-4 drinks/day	1-4 drinks/day	1.1	0.9, 1.4
		198/95	>4 drinks/day	>4 drinks/day	1.1	0.9, 1.6
Jain et al. (24), 1998	Ontario, Quebec, British Columbia, Canada	175/160	Nondrinker		Ref*	
		168/189	0-10 g/day	<1 drink/day	0.80	0.59, 1.08
		82/93	10-20 g/day	~1 drink/day	0.80	0.55, 1.15
		57/68	20-30 g/day	~2 drinks/day	0.75	0.50, 1.14
		135/126	>30 g/day	>2 drinks/day	0.89	0.64, 1.25
Key et al. (25), 1997	Oxfordshire, West Berkshire, Leeds, England	105/109	<3.6 g/day		Ref*	
		118/110	3.6-16.5 g/day	~1 drink/day	1.13	0.77, 1.66
		105/109	≥16.6 g/day	>1 drink/day	1.04	0.71, 1.54
Andersson et al. (26), 1996	Sweden	106/121	Nondrinker		Ref*	
		18/24	≤24.4 g/week		0.9	0.4, 1.7
		23/23	24.4-48.5 g/week		1.1	0.6, 2.1
		29/23	48.6-96 g/week	<1 drink/day	1.4	0.8, 2.6
		31/23	>96 g/week	≥1 drink/day	1.5	0.4, 2.8
Hayes et al. (13), 1996	Georgia, Michigan, New Jersey	184/283	Never used		Ref*	
		232/339	≤7 drinks/week	≤1 drink/day	1.1	0.9, 1.4
		253/365	8-21 drinks/week	1-3 drinks/day	1.1	0.9, 1.4
		211/242	22-56 drinks/week	3-8 drinks/day	1.4	1.0, 1.8
		96/85	≥57 drinks/week	>8 drinks/day	1.9	1.3, 2.7

\* Ref = reference category.

† NHANES I, First National Health and Nutrition Examination Survey.

‡ Reported person-years.

§ Control information not reported by level of alcohol consumed.

three drinks per day (38). Among the remaining studies with quantitative dose data, the average alcohol consumption rate per study ranged from 0.3 drinks per day to 5.3

drinks per day (8), suggesting a wide variation in consumption by heterogeneous populations or potential errors in reporting.

TABLE 3. Hospital-based studies of prostate cancer and heavy alcohol consumption consistent with alcohol abuse

Study (reference no.) and year	Study population/ location	Population characteristics	Alcohol measures reported	Equivalent alcohol in drinks/day	Excess risk reported	
					Relative risk	95% confidence interval
Lumey et al. (16), 1998	US hospitals	Hospital-based 699 cases, 2,041 controls	≤7 drinks/week	≤1 drink/day	1.2	0.9, 1.6
			8–21 drinks/week	>1–≤3 drinks/day	1.1	0.8, 1.5
			22–56 drinks/week	≤3–≤8 drinks/day	1.3	1.0, 1.8
			57 drinks/week	>8 drinks/day	1.1	0.7, 1.5
De Stefani et al. (15), 1995	Uruguay	Hospital-based 156 cases, 302 controls	1–45 ml/day	≥3 drink/day	1.4	0.8, 2.4
			46–120 ml/day	>3–≤8 drinks/day	0.9	0.5, 1.7
			≥121 ml/day	>8 drinks/day	1.8	0.9, 3.1
Tavani et al. (18), 1994	Italy	Hospital-based 281 cases, 599 controls	<3 drinks/day	<3 drinks/day	1.3	0.7, 2.4
			3–<5 drinks/day	3–<5 drinks/day	0.9	0.5, 1.6
			5–<8 drinks/day	5–<8 drinks/day	1.2	0.6, 2.3
			≥8 drinks/day	≥8 drinks/day	1.1	0.6, 2.1
Wynder et al. (17), 1971	New York	Hospital-based 217 cases, 200 controls	1–2 units/day	1–2 units/day	0.7	0.4, 1.3
			3–6 units/day	3–6 units/day	0.8	0.4, 1.6
			≥7 units/day	≥7 units/day	0.8	0.4, 1.6

## CONCLUSIONS

Moderate alcohol consumption up to about three drinks per day does not appear to influence prostate cancer risk; however, heavy consumption of about seven or more drinks per day may be associated with an excess risk for this disease, as indicated by some studies among alcoholics and other heavy users of alcohol. The level of risk at this level of exposure is modest, however, and could be due to confounding by other causal factors or due to biases inherent in observational studies.

As alcohol use patterns can vary with age, time-dependent evaluations of alcohol use and prostate cancer risk are needed. Cohort studies with quantitative assessment among heavy alcohol users are needed to address the limitations of retrospective studies. Also, the findings from early autopsy studies (11, 12) suggesting that liver cirrhosis is negatively associated with prostate cancer, need to be re-evaluated employing modern pathologic concepts to focus research on prostate tumors of potential clinical significance.

## REFERENCES

- Jensen OM, Paine SL, McMicheal AJ, et al. Alcohol. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. 2nd ed. New York, NY: Oxford University Press, 1996:290–318.
- Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes Control* 1994;5:73–82.
- Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998;279:535–40.
- Anderson KE, Potter JD, Mack TM. Pancreatic cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. 2nd ed. New York, NY: Oxford University Press, 1996:725–71.
- Schottenfeld D, Winawer SJ. Cancers of the large intestine. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. 2nd ed. New York, NY: Oxford University Press, 1996:813–40.
- Tonnesen H, Moller H, Andersen JR, et al. Cancer morbidity in alcohol abusers. *Br J Cancer* 1994;69:327–32.
- Adami HO, McLaughlin JK, Hsing AW, et al. Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control* 1992;3:419–25.
- Dennis LK. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. *Prostate* 2000;42:56–66.
- Pell S, D'Alonzo CA. A five-year mortality study of alcoholics. *J Occup Med* 1973;15:120–5.
- Hirayama T. Life-style and cancer: from epidemiologic evidence to public behavior change to mortality reduction of target cancers. *J Natl Cancer Inst Monogr* 1992;12:65–74.
- Glantz GM. Cirrhosis and carcinoma of the prostate. *J Urol* 1964;91:291–3.
- Robson MC. Cirrhosis and prostatic neoplasms. *Geriatrics* 1966;21:150–4.
- Hayes RB, Brown LM, Schoenberg JB, et al. Alcohol use and prostate cancer risk in US blacks and whites. *Am J Epidemiol* 1996;143:692–7.
- Hiatt RA, Armstrong MA, Klatsky AL, et al. Alcohol consumption, smoking, and other risk factors and prostate cancer in a large health plan cohort in California (United States). *Cancer Causes Control* 1994;5:66–72.
- De Stefani E, Fierro L, Barrios E, et al. Tobacco, alcohol, diet and risk of prostate cancer. *Tumori* 1995;81:315–20.
- Lumey LH, Pittman B, Wynder EL. Alcohol use and prostate cancer in US whites: no association in a confirmatory study. *Prostate* 1998;36:250–5.
- Wynder EL, Mabuchi K, Whitmore WF. Epidemiology of cancer of the prostate. *Cancer* 1971;28:344–60.
- Tavani A, Negri E, Franceschi S, et al. Alcohol consumption and risk of prostate cancer. *Nutr Cancer* 1994;21:24–31.
- Parker AS, Cerhan JR, Putnam SD, et al. A cohort study of farming and risk of prostate cancer in Iowa. *Epidemiology* 1999;10:452–5.
- Breslow RA, Wideroff L, Graubard BI, et al. Alcohol and prostate cancer in the NHANES I Epidemiologic Follow-up Study: First National Health and Nutrition Examination Survey of the United States. *Ann Epidemiol* 1999;9:254–61.
- Schuurman AG, Goldbohm RA, van den Brandt PA. A prospective cohort study on consumption of alcoholic beverages in relation to prostate cancer incidence (The Netherlands). *Cancer Causes Control* 1999;10:597–605.
- Le Marchand L, Kolonel LN, Wilkens LR, et al. Animal fat consumption and prostate cancer: a prospective study in Hawaii. *Epidemiology* 1994;5:276–82.
- Villeneuve PJ, Johnson KC, Kreiger N, et al. Risk factors for

- prostate cancer: results from the Canadian National Enhanced Cancer Surveillance System. The Canadian Cancer Registries Epidemiology Research Group. *Cancer Causes Control* 1999;10:355-67.
24. Jain MG, Hislop GT, Howe GR, et al. Alcohol and other beverage use and prostate cancer risk among Canadian men. *Int J Cancer* 1998;78:707-11.
  25. Key TJA, Silcocks PB, Davey GK, et al. A case-control study of diet and prostate cancer. *Br J Cancer* 1997;76:678-87.
  26. Andersson SO, Baron J, Bergström R, et al. Lifestyle factors and prostate cancer risk: a case-control study in Sweden. *Cancer Epidemiol* 1996;5:509-13.
  27. Alcohol drinking. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 44. Lyon, France: International Agency for Research on Cancer, 1988.
  28. Henderson BE, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis* 2000;21:427-33.
  29. Garro AJ, Lieber CS. Alcohol and cancer. *Annu Rev Pharmacol Toxicol* 1990;30:219-49.
  30. Kyrtpoulos SA, Anderson LM, Chhabra SK, et al. DNA adducts and the mechanism of carcinogenesis and cytotoxicity of methylating agents of environmental and clinical significance. *Cancer Detect Prev* 1997;21:391-405.
  31. Meister KA, Whelan EM, Kava R. The health effects of moderate alcohol intake in humans: an epidemiologic review. *Crit Rev Clin Lab Sci* 2000;37:261-96.
  32. Lieber CS. Metabolic consequences of ethanol. *Endocrinologist* 1994;4:127-39.
  33. Lund Nilssen TI, Johnsen R, Vatten LJ. Socio-economic and lifestyle factors associated with the risk of prostate cancer. *Br J Cancer* 2000;82:1358-63.
  34. Walker AR, Walker BJ, Tsotetsi NG, et al. Case-control study of prostate cancer in black patients in Soweto, South Africa. *Br J Cancer* 1992;65:438-41.
  35. Grönberg H, Damber L, Damber JE. Total food consumption and body mass index in relation to prostate cancer risk: a case-control study in Sweden with prospectively collected exposure data. *J Urol* 1996;155:969-74.
  36. Fincham SM, Hill GB, Hanson J, et al. Epidemiology of prostate cancer: a case-control study. *Prostate* 1990;17:189-206.
  37. Stemmerman GN, Nomura AM, Chyou PH, et al. Prospective study of alcohol intake and large bowel cancer. *Dig Dis Sci* 1990;35:1414-20.
  38. Baker LH, Mebust WK, Chin TD, et al. The relationship of herpesvirus to carcinoma of the prostate. *J Urol* 1981;125:370-4.