

Short Communication

Alcohol Consumption and the Risk for Prostate Cancer in the European Prospective Investigation into Cancer and Nutrition

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Abstract

Alcohol is a risk factor for several types of cancer. However, the results for prostate cancer have been inconsistent, with most studies showing no association. Within the European Prospective Investigation into Cancer and Nutrition, detailed information were collected from 142,607 male participants on the intake of alcoholic beverages at recruitment (for 100% of the cohort) and over lifetime (for 76% of the cohort) between 1992 and 2000. During a median follow-up of 8.7 years, 2,655 prostate cancer cases were observed. Multivariate Cox proportional hazard models were used to examine the association of alcohol consump-

tion at recruitment and average lifetime alcohol consumption with prostate cancer adjusted for age, center, smoking, height, weight, physical activity, and nonalcohol energy intake. Overall, neither alcohol consumption at baseline nor average lifetime alcohol consumption was associated with the risk for prostate cancer in this cohort of men. Men who consumed ≥ 60 g alcohol per day had a relative risk of 0.88 [95% confidence interval (95% CI) 0.72-1.08] compared with men with an intake of 0.1-4.9 g/d; the respective relative risk for average lifetime intake was 1.09 (95% CI, 0.86-1.39). For advanced prostate cancer ($n = 537$), the relative risks

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for ≥ 60 and 0.1-4.9 g alcohol per day at baseline were 0.98 (95% CI, 0.66-1.44) and 1.28 (95% CI, 0.79-2.07), respectively, for average lifetime intake. No statistically significant association was observed for alcohol intake

from specific alcoholic beverages. Our results indicate no association between the consumption of alcohol and prostate cancer in this cohort of European men. (Cancer Epidemiol Biomarkers Prev 2008;17(5):1282-7)

Introduction

Prostate cancer is the most common incident cancer and the third most common cause of cancer death in men in more developed countries (1). The only well-recognized risk factors are age, African heritage, and family history of prostate cancer (2). However, dietary factors may also contribute to prostate cancer risk. Alcohol consumption is of interest because it is a risk factor for some other cancer sites (3) and might affect prostate cancer risk by altering circulating sex steroid hormone concentrations (4, 5). In addition, although moderate alcohol consumption has been associated with decreased inflammation and oxidative stress (6, 7), higher alcohol consumption might lead to higher free radical generation (8). However, to date, the results of studies considering associations between alcohol consumption and prostate cancer risk have been inconsistent.

Within the European Prospective Investigation into Cancer and Nutrition (EPIC), we examined whether baseline or average lifetime alcohol consumption was associated with the subsequent risk for prostate cancer.

Materials and Methods

Population. EPIC is a large prospective cohort study conducted in 23 centers in 10 European countries [Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Great Britain (Cambridge, Oxford), Greece, Italy (Florence, Naples, Ragusa, Turin, Varese), The Netherlands (Bilthoven, Utrecht), Norway, Spain (Asturias, Granada, Murcia, Navarre, San Sebastian), and Sweden (Malmö, Umeå)], including more than 500,000 participants. At baseline, men were between 40 and 65 years old. Participants were recruited between 1992 and 2000, usually from the general population. Spanish and Italian participants were recruited among blood donors, members of several health insurance programs, employees of several enterprises, civil servants, and also the general population. In Oxford, half of the cohort consisted of "health conscious" subjects from England, Wales, Scotland, and Northern Ireland. The cohorts of France, Naples, Norway, and Utrecht included women only (9).

The cohort included 148,372 men without prevalent cancers other than nonmelanoma skin cancer. Of these, we excluded men with missing information on dietary ($n = 2,177$) or nondietary data ($n = 712$), or if they were in the top or bottom 1% of the distribution of the ratio of reported energy intake to energy requirement ($n = 2,876$), thus leaving 142,607 men for analysis.

Exposure Assessment. Diet over the previous 12 months was assessed using dietary assessment instruments that were specifically developed for each participating country (9). Baseline ethanol intake was calculated from the dietary instruments applied in each center (9). Participants reported on how many standard glasses (the standard size depends on center and beverage type)

of beer and/or cider, wine, sweet liquor, distilled spirits, or fortified wines they consumed per day or week during the 12 months before recruitment (baseline consumption). Alcohol intake was calculated by multiplying the mean glass volume with the ethanol content for each type of alcoholic beverage (10). Ethanol intake calculated from the dietary assessment instruments was highly correlated with the intake assessed by means of 12 times-repeated, 24-hour dietary recalls ($r = 0.76-0.90$, depending on country) and between 2 dietary questionnaires conducted 12 months apart in EPIC validation studies ($r = 0.87-0.94$; ref. 11). Information on past alcohol consumption was assessed as glass(es) of beverage consumed per week at 20, 30, 40, and 50 years of age. This information was not collected in Bilthoven, Naples, and Sweden, and was available for 109,275 participants. Average lifetime ethanol intake was calculated as a weighted mean of the intake at different ages and at baseline, with weights equal to the total subject specific time under investigation. Energy intake was estimated from the dietary assessment instruments. Detailed information was also assessed on lifetime smoking history; leisure-time, occupational, and household physical activity; education; and marital status. A set of core questions that were similar in all participating centers allowed for comparability of non-dietary questions and questions on past alcohol consumption (9). Height and weight were measured in all EPIC centers except in Oxford, where self-reported height and weight were assessed via questionnaire (9).

Outcome Assessment. Mortality data were obtained from either cancer or mortality registries at the regional or national level. Cancer diagnoses were based on population registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom; participants were censored between December 2002 and December 2005, depending on the study center. An active follow-up through study subjects and next-of-kin information, the use of health insurance records, and cancer and pathology registries were used in Germany and Greece; in these countries, the end of the follow-up was the last known contact, date of diagnosis, or date of death, whichever came first. Currently, vital status is known for 98.4% of all EPIC subjects.

The definition of prostate cancer cases was based on the second revision of the International Classification of Diseases for Oncology and included all invasive malignant neoplasms that were coded as C61. Information on tumor-node-metastasis stage and tumor grade were collected from each center, where possible. Of 2,655 incident prostate cancer cases, information on stage and grade were available for 1,646 (62%) and 1,587 (60%) men, respectively. Tumors were classified as localized (T_0 , T_1 , or T_2 ; N_0 or N_x ; and M_0 ; or stage-coded in the recruitment center as localized; $n = 1,109$) or advanced (T_3 or T_4 , N_{1+} , and/or M_1 , or stage-coded in the recruitment center as metastatic; $n = 537$). In addition, tumors were divided into low grade (Gleason score, 2-6

Table 1. Case distribution and alcohol consumption in male EPIC participants by country

	Non-consumers at baseline (%)	Ethanol intake at baseline [g/d; median (IQR)]*	Average lifetime ethanol intake [g/d; median (IQR)]* [†]	Cases	Cases (subgroup) [‡]	Advanced cases	High-grade cases	Person-years
Denmark	1.8	22.0 (12.1-44.9)	18.1 (10.4-30.1)	368	368	104	112	198,667
Italy	4.0	23.2 (6.4-36.6)	20.5 (8.2-34.7)*	141	140 [†]	30	30	120,440
Germany	4.1	19.6 (8.6-36.6)	19.8 (10.6-34.3)	406	406	92	99	177,079
Greece	10.1	11.2 (4.2-24.6)	18.1 (7.3-39.4)	40	40 [†]	9	8	73,990
The Netherlands	9.0	13.5 (5.1-27.2)	—*	58	— [†]	29	14	81,984
Spain	14.4	30.5 (12.6-54.0)	40.6 (19.3-70.4)	204	201 [†]	23	46	156,086
Sweden	7.8	6.9 (3.1-14.3)	—*	971	— [†]	153	170	233,510
United Kingdom	6.4	8.6 (2.6-17.1)	10.1 (4.7-19.6)	467	453	98	165	193,608
All	6.5	14.5 (5.6-32.1)	18.4 (8.6-34.4)	2,655	1,608	537	644	1,235,364

Abbreviation: IQR, interquartile range.

*In consumers.

[†]Information on life-long alcohol consumption was not available for Naples, Bilthoven, and Sweden.[‡]Cases with information on past alcohol consumption.

or equivalent; cases coded as well or moderately differentiated; $n = 943$) or high grade (Gleason score, ≥ 7 or equivalent; cases coded as poorly differentiated or undifferentiated; $n = 644$).

Statistical Analysis. Cox proportional hazards regression was used to examine the association of alcohol intake with prostate cancer, modeling daily alcohol intake as categorical variables (0, 0.1-4.9, 5-14.9, 15-29.9, 30-59.9, and ≥ 60 g/d). The same categories were used for baseline and average lifetime intake. Participants with a low alcohol intake of 0.1-4.9 g/d were used as

the reference group for nonconsumers and consumers of 5 g/d or more. Age was the primary time variable in the Cox models. Time at entry was age at baseline, exit time was age when participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. The analyses were stratified by center and age at recruitment in 1-year categories. Multivariate models were adjusted for tobacco smoking (never smoker, former smoker, current smoker, and smoking status unknown), weight and height at recruitment (as continuous variables),

Table 2. Baseline characteristics of male EPIC participants by alcohol consumption

	Alcohol consumption (g/d)					
	0	0.1-4.9	5-14.9	15-29.9	30-59.9	≥ 60
N	9,242	30,629	37,227	29,507	25,379	10,619
Cases (n)	204	615	745	531	422	138
Age (y)*	54.4 (47.2-61.8)	51.2 (42.6-59.9)	52.28 (44.5-59.8)	53.08 (46.5-59.2)	53.1 (47.1-58.6)	53.5 (48.4-58.4)
Height (cm) *	172.0 (167.0-177.0)	175.0 (170.0-180.0)	175.5 (170.5-180.0)	175.0 (170.0-180.0)	174.8 (170.0-179.5)	174.0 (169.0-179.0)
Body mass index (kg/m ²)*	26.5 (24.2-29.1)	25.8 (23.6-28.3)	25.8 (23.7-28.2)	26.1 (24.1-28.4)	26.4 (24.3-28.8)	27.2 (24.9-29.7)
Red meat (g/d)*	46.6 (24.2-73.8)	37.5 (18.7-66.4)	47.0 (25.1-77.1)	57.3 (31.7-87.4)	63.9 (35.4-91.1)	75.1 (47.0-106.7)
Processed meat (g/d)*	28.1 (8.8-56.2)	28.2 (10.9-50.9)	32.0 (13.7-55.2)	35.7 (17.1-61.8)	37.9 (17.8-61.8)	41.2 (22.6-68.8)
Energy (kcal/d)*	2,222 (1,808-2,716)	2,168 (1,772-2,643)	2,261 (1,877-2,705)	2,382 (2,007-2,815)	2,506 (2,124-2,951)	2,840 (2,417-3,324)
Total physical activity (%) [†]						
Inactive	16.6	18.3	23.3	28.8	28.8	23.7
Moderately inactive	38.5	26.7	29.5	31.5	30.4	30.1
Moderately active	29.4	24.6	26.0	27.9	30.1	34.8
Active	6.9	6.8	7.2	7.8	8.7	10.5
Smoking status (%) [†]						
Never	33.9	42.3	37.4	29.5	23.7	16.7
Former	34.3	32.3	36.3	40.4	40.2	33.6
Current	30.2	23.4	24.7	29.2	35.2	49.4
Married/living together (%)	75.8	80.0	82.3	81.9	81.1	79.4
Education (%)						
Primary school completed	40.5	27.6	24.9	24.8	25.0	34.2
University degree	14.7	22.5	28.7	30.5	29.3	22.3

*Median (IQR).

[†]Does not add up to 100% because information on smoking status ($n = 1921$) and physical activity ($n = 15,085$) is missing.

nonethanol energy intake (continuous), and combined occupational and recreational physical activity (physically inactive, moderately inactive, moderately active, active, and unknown). In addition, adjusting for marital status, level of education, and intake of red meat, processed meat, tomato sauce, vitamin E, and calcium did not materially alter the results. Subanalyses were done by stage and grade of prostate cancer, by age at baseline (<60 and ≥60 years), and by body mass index (less than the median and more than or equal to the median). We tested for the interaction of age and body mass index with alcohol intake by modeling cross-product terms of dichotomized variables multiplied by the midpoint of the alcohol intake category to which the subject belonged, along with the main effect terms in the Cox regression model. The statistical significance of the cross-product term was evaluated with the likelihood ratio test. Heterogeneity between countries was assessed with likelihood χ^2 tests. SAS version 9.1 (SAS Institute) was used for all analyses.

Results

In the EPIC cohort 2,655 incident prostate cancer cases were identified in 1,235,364 person-years of follow-up. Median age at diagnosis was 66.4 years (interquartile range, 62.4-70.6). Median alcohol intake among men who consumed alcoholic beverages at baseline was 14.5 g/d (interquartile range, 5.6-32.1); the intake was lowest in Sweden and highest in Spain (Table 1). The variation in alcohol consumption within each country is indicated by the interquartile range (Table 1). Baseline characteristics by alcohol consumption at baseline are shown in Table 2.

Overall, neither alcohol consumption at baseline nor average lifetime alcohol consumption was associated with the risk for prostate cancer in this cohort of men (Table 3). These results were not materially altered when excluding the first 2 years of follow-up ($n = 275$ cases) from the analysis [baseline alcohol consumption: relative risk, 0.86; 95% confidence interval (95% CI), 0.70-1.07; average lifetime intake: relative risk, 1.01; 95% CI,

Table 3. Association of alcohol consumption at baseline and average lifetime alcohol consumption with prostate cancer

Intake (g/d)	Alcohol consumption at baseline			Average lifetime alcohol consumption		
	Cases (<i>n</i>)	Relative risk*	Relative risk [†] (95% CI) [†]	Cases (<i>n</i>)	Relative risk*	Relative risk [†] (95% CI) [†]
All cases						
0	204	0.95	0.95 (0.81-1.12)	20	0.82	0.82 (0.51-1.29)
0.1-4.9	615	1.00	1.00	260	1.00	1.00
5-14.9	745	1.00	0.99 (0.89-1.11)	482	1.02	1.03 (0.88-1.21)
15-29.9	531	0.96	0.95 (0.84-1.08)	421	1.05	1.08 (0.91-1.27)
30-59.9	422	1.02	1.03 (0.90-1.18)	283	0.98	1.02 (0.85-1.23)
≥60	138	0.86	0.88 (0.72-1.08)	142	1.03	1.09 (0.86-1.39)
Prostate cancer stage (localized cases) [‡]						
0	77	0.87	0.87 (0.67-1.13)	10	0.92	0.91 (0.46-1.70)
0.1-4.9	254	1.00	1.00	93	1.00	1.00
5-14.9	296	0.98	0.97 (0.86-1.16)	235	1.15	1.16 (0.91-1.48)
15-29.9	227	0.99	0.98 (0.81-1.19)	215	1.22	1.24 (0.96-1.61)
30-59.9	190	1.01	1.02 (0.83-1.25)	132	0.97	1.01 (0.76-1.35)
≥60	65	0.73	0.76 (0.57-1.02)	85	1.04	1.11 (0.79-1.57)
Prostate cancer stage (advanced cases)						
0	33	0.74	0.74 (0.50-1.10)	4	0.80	0.81 (0.29-2.25)
0.1-4.9	136	1.00	1.00	65	1.00	1.00
5-14.9	161	0.97	0.97 (0.77-1.23)	110	0.91	0.90 (0.65-1.25)
15-29.9	93	0.73	0.73 (0.55-0.97)	76	0.73	0.72 (0.50-1.03)
30-59.9	76	0.77	0.77 (0.57-1.05)	66	0.98	0.96 (0.65-1.40)
≥60	38	0.99	0.98 (0.66-1.44)	33	1.34	1.28 (0.79-2.07)
Prostate cancer grade (low-grade cases) [§]						
0	93	0.99	0.99 (0.76-1.29)	77	1.18	1.16 (0.59-2.25)
0.1-4.9	342	1.00	1.00	243	1.00	1.00
5-14.9	379	0.95	0.95 (0.79-1.14)	263	0.98	1.01 (0.77-1.33)
15-29.9	254	0.79	0.79 (0.64-0.98)	167	1.04	1.11 (0.84-1.47)
30-59.9	213	0.87	0.91 (0.73-1.13)	149	0.81	0.89 (0.65-1.22)
≥60	67	0.60	0.65 (0.46-0.91)	44	0.97	1.13 (0.78-1.62)
Prostate cancer grade (high-grade cases)						
0	44	0.90	0.91 (0.64-1.28)	4	0.56	0.56 (0.20-1.53)
0.1-4.9	154	1.00	1.00	89	1.00	1.00
5-14.9	175	0.97	0.97 (0.78-1.22)	132	0.84	0.84 (0.63-1.11)
15-29.9	120	0.95	0.95 (0.73-1.23)	104	0.83	0.83 (0.61-1.13)
30-59.9	105	1.07	1.07 (0.82-1.40)	83	1.02	1.03 (0.74-1.44)
≥60	46	1.18	1.17 (0.81-1.67)	43	1.23	1.22 (0.79-1.89)

*Stratified by age (1-year categories) and study center.

[†]Stratified by age (1-year categories) and study center; adjusted for weight (continuous), height (continuous), total physical activity (5 categories), smoking status (4 categories), and energy intake without energy from alcohol (continuous).

[‡]Tumors were classified as localized (T₀, T₁, or T₂; N₀ or N₁; and M₀); or stage-coded in the recruitment center as localized) or advanced (T₃ or T₄, N₁₊, and/or M₁, or stage-coded in the recruitment center as metastatic).

[§]Tumors were divided into low grade (Gleason score, 2-6 or equivalent; cases coded as well or moderately differentiated) or high grade (Gleason score, ≥7 or equivalent; cases coded as poorly differentiated or undifferentiated).

0.78-1.30 for ≥ 60 versus 0.1-4.9 g/d] or when excluding stage T_{1a} cases ($n = 49$), which might have been detected by chance (baseline alcohol consumption: relative risk, 0.88; 95% CI, 0.72-1.08; average lifetime intake: relative risk, 1.07; 95% CI, 0.84-1.36 for ≥ 60 versus 0.1-4.9 g/d). For each additional 10 g of alcohol intake per day at baseline, we observed a relative risk of 1.00 (95% CI, 0.98-1.02) and a relative risk of 1.01 (95% CI, 0.99-1.03) for lifetime intake. Furthermore, there was no statistically significant heterogeneity by country for alcohol consumption at baseline ($P = 0.27$) or for average lifetime alcohol intake ($P = 0.88$). In addition, the associations between baseline or average lifetime alcohol consumption and prostate cancer risk were not modified by age at baseline (p-interaction, 0.34 and 0.82, respectively) or body mass index (p-interaction, 0.92 and 0.87, respectively). Former drinkers did not have a significantly higher risk for prostate cancer than never drinkers (relative risk, 1.22; 95% CI, 0.75-1.99). Consumption of wine, beer, or spirits was not significantly associated with the risk for prostate cancer in this cohort of men, even after mutually adjusting for different types of alcoholic beverages (data not shown).

No consistent association of baseline or average lifetime alcohol consumption with prostate cancer was observed when we stratified by stage or grade of disease (Table 3).

Discussion

In this large prospective European cohort study, we did not observe an association between alcohol consumption and prostate cancer risk. In addition, we did not see consistent associations with prostate cancer by stage or grade.

Most epidemiologic studies did not report an association between alcohol consumption and the risk for prostate cancer, although an increased risk for high alcohol consumption cannot be ruled out. Based on a meta-analysis that included 15 studies in which alcohol consumption was assessed quantitatively, no increased prostate cancer risk was associated with one additional drink per day (relative risk, 1.05; 95% CI, 0.91-1.20), but a higher risk was observed for four additional drinks per day (relative risk, 1.21; 95% CI, 1.05-1.39; ref. 12). Recent epidemiologic studies similarly reported either no (13-17) or a slightly to moderately increased risk for prostate cancer (18-21) among men with a high consumption of alcoholic beverages. Only few studies examined the association of lifetime alcohol consumption and the risk for prostate cancer. In this cohort of European men, no association of average lifetime alcohol consumption with prostate cancer was observed. This is in line with results from the Vitamins and Lifestyle cohort, where men with a lifetime intake of ≥ 2 drinks per day had a relative risk of 1.02 (95% CI, 0.64-1.64) compared with men who drank no alcohol or < 1 drink per month (21). Similarly, no association was observed in two U.S. case-control studies (22, 23).

We found no indication for a stronger association between alcohol consumption and advanced or high-grade prostate cancer than with total prostate cancer risk, which is in agreement with previous studies (16, 20). In addition, we did not detect any differences in the

association with prostate cancer for the specific beverage types; results of previous epidemiologic studies were inconsistent (13, 20, 23-25).

Because EPIC is a prospective study, recall bias of alcohol consumption can be ruled out with respect to disease status. We cannot rule out that some subjects misreported their alcohol consumption, especially those with a high intake, despite high validity and reliability of the dietary assessment instruments. If high consumers were falsely categorized as moderate consumers, this could lead to an underestimation of the risk of high consumers. Further limitations of this study were the lack of information on prostate-specific antigen testing and incomplete information on alcohol consumption in the past, as well as incomplete information on tumor stage and grade. In addition, because of the lack of information on consumption pattern, we were not able to investigate whether binge drinking increases relative risk for prostate cancer, as was seen among the participants of the Health Professionals Follow-up Study (20).

We conclude from our results that the use of alcohol has little or no association with the risk for prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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