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Association between lifetime alcohol consumption and prostate cancer risk: A case-control study in Montreal, Canada

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ABSTRACT

Background: Alcohol intake may increase the risk of prostate cancer (PCa). Many previous studies harbored important methodological limitations.
Methods: We conducted a population-based case-control study of PCa comprising 1933 cases and 1994 controls in Montreal, Canada. Lifetime alcohol consumption was elicited, by type of beverage, during in-person interviews. Odds ratios (OR) and 95% confidence intervals (CI) assessed the association between alcohol intake and PCa risk, adjusting for potential confounders and considering the subjects' PCa screening history.
Results: We observed a weak, non-significant positive association between high consumption of total alcohol over the lifetime and risk of high-grade PCa (OR = 1.18, 95% CI 0.81–1.73). Risk estimates were more pronounced among current drinkers (OR = 1.40, 95%CI 1.00–1.97), particularly after adjusting for the timing of last PCa screening (OR = 1.52, 95%CI 1.07–2.16). These associations were largely driven by beer consumption. The OR for high-grade PCa associated with high beer intake was 1.37 (95%CI 1.00–1.89); it was 1.49 (95%CI 0.99–2.23) among current drinkers and 1.68 (95% CI 1.10–2.57) after adjusting for screening recency. High cumulative consumption of spirits was associated with a lower risk of low-grade PCa (OR = 0.75, 95%CI 0.60–0.94) but the risk estimate no longer achieved statistical significance when restricting to current users. No association was found for wine consumption.
Conclusion: Findings add to the accumulating evidence that high alcohol consumption increases the risk of high-grade PCa. This association largely reflected beer intake in our population, and was strengthened when taking into account PCa screening history.

1. Introduction

High alcohol intake is a risk factor for many cancers, including those of the oral cavity, pharynx, larynx, esophagus, colorectum, liver and female breast [1]. In 2012, the International Agency for Research on Cancer concluded that there was little evidence in support of an association between consumption of alcoholic beverages and risk of prostate cancer (PCa) [1]. However, subsequent studies have suggested that alcohol intake might in fact increase risks for this cancer [2–8]. In a meta-analysis conducted recently, there was indication of a positive association between alcohol consumption and risk of overall PCa [9].

Earlier studies may have been more likely to harbor methodological limitations, resulting in a shift in findings over time. These include insufficient statistical power, crude alcohol exposure metrics, timing of assessment, non-differentiation of types of beverages, low exposure levels in some study populations, use of various disease endpoints, lack of consideration of cancer aggressiveness, confounding or biases [1,10]. Recent reports also stress the importance of considering PCa screening when studying associations with alcohol use [11–13]. Moreover, previous

Abbreviations: PCa, prostate cancer; PSA, prostate screening antigen; DRE, digital rectal exam; OR, odds ratio; CI, confidence interval.

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evidence rests largely on studies overlooking the issue of latent (undiagnosed) cancers in non-cases.

The objective of the present study was to provide additional evidence on the alcohol intake – PCa relationship while minimizing previous methodological issues.

2. Materials and methods

2.1. Study population

We used data from the Prostate Cancer & Environment Study (PROtEuS) [14], a large population-based case-control study in Montreal assessing the role of potential risk factors in PCa development.

Eligible subjects were men, younger than 76 years at diagnosis or selection, residents of Greater Montreal, registered on Quebec's permanent electoral list (continually updated) and Canadian citizen. Cases were all patients newly diagnosed with primary PCa, actively ascertained through pathology departments across the main French hospitals (7 out of 9 hospitals) in the Montreal area between 2005 and 2009. Based on registry information, this covered at least 80% of all PCa cases diagnosed in the area during the study period. Control subjects were selected concurrently from the population-based provincial electoral list of French-speaking men, and frequency-matched to cases by 5-year age groups.

The participation rate among eligible subjects was 79% for cases and 56% for controls. The study was approved by the Ethics Committees of all participating institutions. All participants provided written informed consent.

2.2. Data collection

Eligible subjects were sent an introductory package and were reached by telephone by interviewers to set up an appointment. In-person interviews collected socio-demographic and lifestyle characteristics, family history of cancer, medical and PCa screening histories, and self-reported weight and height. Subjects reported their overall physical activity level at work (Very/Moderately/Not very active), at home (Very/Moderately/Not very active) and their engagement in any leisure physical activity during adulthood [15], along with their frequency of use of 44 fruit and vegetables.

For subjects who reported ever consuming alcohol once a month for one year or more, lifetime alcohol consumption was recorded for beer, wine and spirits. Drinks were reported in commonly used servings, i.e., 375 ml for beer, 125 ml for wine and 45 ml for spirits. For each beverage type, each time the pattern of intake changed, participants were asked to report their drinking habits, including the time period (age started and age ended) and the frequency of drinking (number of drinks per month, week or day). This allowed taking into account changes in intake levels over the lifespan.

The degree of aggressiveness of PCa, defined by the Gleason score, was extracted from prostate biopsy pathology reports.

2.3. Exposure variables

Lifetime cumulative exposure variables were created for each type of beverages. These were defined as the product of the average number of drinks consumed per day and the duration of drinking in years for beer, wine, and spirits, and expressed as drink-years.

A composite exposure variable was also constructed to express the cumulative exposure to total alcohol by taking into account the ethanol content by volume of each type of beverages. Using the quantities of 14.8 g of ethanol per drink of beer, 11.8 g per drink of wine, and 14.2 g per drink of spirits [1,16], we calculated the cumulative intake in total grams of ethanol. The latter was divided by 14, which corresponds to the average amount of ethanol per drink weighted by the proportion of each type of drink in our study population, to estimate the total amount of alcohol used, in drink-years, standardized for ethanol content.

2.4. Statistical analyses

Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the association between alcohol consumption and PCa risk. Risks of low-grade and high-grade (Gleason scores >7 or [4+3]) PCa were estimated using unconditional polytomous logistic regression. Two models were developed. Model 1 was adjusted for the age at diagnosis or interview (continuous), ancestry (Black/Asian/European/Other), first-degree family history of PCa (Yes/No), education (Elementary/High School/College/University), smoking (cigarette pack-years, continuous), overall physical activity (Very/Moderately/Not very active), maximum body mass index (BMI, continuous), frequency of use of fruit and vegetables (categorical), and self-reported history of diabetes (Yes/No). Analyses focusing on specific beverages were adjusted for other types of beverages. Model 2 included all variables in Model 1 as well as the timing of the last PCa screening by prostatic specific antigen (PSA) and/or digital rectal exam (DRE) (Within the last 2 years, 2–5 years earlier, More than 5 years earlier, Never screened, Don't know).

Alcohol exposure was analyzed using quartiles of total alcohol, beer and wine drink-years, and tertiles of spirit drink-years (because of fewer drinkers) based on the distribution among controls. Non-drinkers (subjects who reported having consumed alcohol less than once a month over a year, or less) or non-drinkers of the specific beverage under study constituted the reference category in analyses for total alcohol and for specific beverages, respectively.

Since men who stopped drinking or never drinkers may differ in some qualitative way from current alcohol consumers, analyses were also conducted among current drinkers, defined as subjects reporting drinking in the two years before diagnosis or interview. In this analysis, subjects in the lowest quartile/tertile category were considered as the reference.

Sensitivity analyses were also performed excluding proxy respondents (<4% of subjects), restricting the sample to subjects of European ancestry (86% of subjects), and restricting controls to men who had been screened (PSA and/or DRE) in the 2 years preceding the interview to reduce the likelihood of undiagnosed PCa among controls.

3. Results

3.1. Study population

The characteristics of study participants are presented in Table 1. Average age was about 64 years. The case series included a greater proportion of subjects of African ancestry but a lower proportion of Asian subjects than controls. Cases reported more often a first-degree family history of PCa than controls. A lower proportion of cases than controls had been diagnosed with diabetes. Cases had a slightly lower maximum BMI. About 99% of cases and 76% of controls had been exposed to PCa early detection efforts in the form of PSA and/or DRE testing within the 2 years preceding the interview. There were little differences in terms of education, smoking history, physical activity, and frequency of use of fruit and vegetables according to case/control status.

3.2. Alcohol consumption patterns

Cases and controls presented similar percentages of never, current and former users of total alcohol (Table 1). They also

Table 1
Characteristics of the study population, PROtEuS, Montreal, Canada.

Characteristics	Cases (n = 1933)	Controls (n = 1994)	p-value[a]
Age, mean ± SD	64 ± 7	65 ± 7	<0.0001
Ancestry, n (%)			<0.0001
Black	129 (7)	90 (5)	
Asian	24 (1)	72 (4)	
European	1693 (88)	1686 (85)	
Other	75 (4)	132 (7)	
Don't know	12 (1)	14 (1)	
First-degree family history of prostate cancer, n (%)			<0.0001
No	1417 (73)	1738 (87)	
Yes	450 (23)	199 (10)	
Don't know	66 (3)	57 (3)	
Education, n (%)			0.15
Elementary	449 (23)	429 (22)	
High School	576 (30)	578 (29)	
College	313 (16)	375 (19)	
University	590 (31)	610 (31)	
Other	5 (0)	2 (0)	
Smoking (pack-years), mean ± SD	23 ± 28	24 ± 28	0.13
Physical activity, n (%)			0.09
Not very active	475 (25)	547 (27)	
Moderately active	472 (24)	491 (25)	
Very active	980 (51)	953 (48)	
Don't know	6 (0)	3 (0)	
Maximum BMI[b], mean ± SD	28 ± 4	29 ± 5	<0.01
Daily frequency of use of fruit and vegetables, n (%)			0.22
≤6	476 (25)	498 (25)	
[6–9]	506 (26)	497 (25)	
[9–12]	430 (22)	497 (25)	
>12	510 (26)	498 (25)	
Don't know	11 (1)	4 (0)	
History of diabetes, n (%)			<0.001
No	1640 (85)	1596 (80)	
Yes	290 (15)	395 (20)	
Don't know	3 (0)	3 (0)	
Timing of the last prostate cancer screening by PSA or DRE[c]			<0.0001
Within last 2 years	1913 (99)	1511 (76)	
2–5 years earlier	1 (0)	154 (8)	
More than 5 years earlier	0 (0)	81 (4)	
Never screened	3 (0)	191 (10)	
Don't know	16 (1)	57 (3)	
Alcohol users, n (%)			0.11
Never	215 (11)	231 (12)	
Former	200 (10)	247 (12)	
Current	1511 (78)	1513 (76)	
Don't know	7 (1)	3 (0)	
Alcohol consumption in drink-years, mean ± SD (% of ever users)			
Beer	59 ± 104 (74)	56 ± 102 (74)	0.49
Wine	29 ± 46 (72)	29 ± 46 (72)	0.71
Spirits	27 ± 70 (42)	30 ± 98 (47)	0.36
Total alcohol[d]	85 ± 130 (88)	85 ± 148 (88)	0.94

[a] p-values for Chi-Square test for differences of proportions or T-test for differences of means.
[b] BMI: body mass index.
[c] PSA: prostate specific antigen; DRE: digital rectal exam.
[d] Based on 14 g of ethanol per drink.

showed the same percentages of ever users of beer or wine, but a slightly lower proportion of cases than controls reported having drunk spirits. Beer was the most frequently consumed beverage in this study population, with an overall cumulative frequency of use about twice of that of wine or spirits. Among drinkers, mean total alcohol consumption was the same between cases and controls. Cases declared, on average, slightly higher beer consumption levels than controls, and lower spirits consumption levels, but differences were not statistically significant.

3.3. Association between alcohol intake and PCa risk

Table 2 presents results for the association between lifetime consumption of total alcohol, beer, wine and spirits, and the risk of

Table 2
Odds ratio (OR) and 95% confidence interval (CI) for the association between lifetime alcohol consumption and prostate cancer risk, by disease aggressiveness, PROtEuS, Montreal, Canada.

Lifetime alcohol intake	Model 1[a]					Model 2[b]	
	controls	low-grade PCa		high-grade PCa		low-grade PCa	high-grade PCa
	n	n	OR (95%CI)	n	OR (95%CI)	OR (95%CI)	OR (95%CI)
Total alcohol							
Never drank alcohol	231	159	ref	56	ref	ref	ref
≤16 drink-years	438	321	0.89 (0.68;1.17)	106	0.96 (0.66;1.40)	0.85 (0.64;1.14)	0.94 (0.63;1.38)
]16–45] drink-years	439	331	0.89 (0.68;1.17)	118	1.06 (0.72;1.55)	0.78 (0.58;1.04)	0.93 (0.63;1.38)
]45–101] drink-years	437	296	0.82 (0.63;1.09)	108	0.95 (0.64;1.39)	0.72 (0.53;0.97)	0.84 (0.56;1.26)
>101 drink-years	439	274	0.80 (0.60;1.06)	140	1.18 (0.81;1.73)	0.80 (0.59;1.08)	1.21 (0.82;1.80)
p for trend[c]			p = 0.15		p = 0.20	p = 0.42	p = 0.08
Beer							
Never drank beer	522	376	ref	120	ref	ref	ref
≤6 drink-years	366	262	0.83 (0.66;1.04)	98	1.18 (0.86;1.62)	0.79 (0.62;1.00)	1.13 (0.82;1.58)
]6–23] drink-years	364	259	0.83 (0.66;1.05)	96	1.20 (0.87;1.66)	0.78 (0.61;0.99)	1.14 (0.82;1.59)
]23–63] drink-years	369	248	0.83 (0.66;1.05)	93	1.12 (0.81;1.56)	0.80 (0.63;1.02)	1.09 (0.78;1.53)
>63 drink-years	367	242	0.83 (0.65;1.05)	124	1.37 (1.00;1.89)	0.85 (0.66;1.10)	1.46 (1.04;2.03)
p for trend[c]			p = 0.39		p = 0.11	p = 0.80	p = 0.04
Wine							
Never drank wine	561	362	ref	167	ref	ref	ref
≤4 drink-years	361	269	1.12 (0.90;1.41)	93	0.88 (0.65;1.20)	1.03 (0.81;1.31)	0.79 (0.58;1.09)
]4–13] drink-years	343	258	1.07 (0.84;1.35)	91	0.92 (0.67;1.26)	0.93 (0.72;1.19)	0.79 (0.56;1.09)
]13–35] drink-years	369	247	0.97 (0.76;1.24)	86	0.82 (0.59;1.15)	0.86 (0.66;1.12)	0.72 (0.52;1.02)
>35 drink-years	356	252	1.12 (0.88;1.43)	95	0.99 (0.72;1.37)	0.98 (0.76;1.26)	0.87 (0.62;1.21)
p for trend[c]			p = 0.58		p = 0.73	p = 0.08	p = 0.94
Spirits							
Never drank spirits	1,047	797	ref	305	ref	ref	ref
≤3 drink-years	312	212	0.86 (0.70;1.07)	68	0.78 (0.57;1.05)	0.86 (0.69;1.08)	0.78 (0.57;1.06)
]3–15] drink-years	309	215	0.94 (0.76;1.17)	72	0.81 (0.60;1.10)	0.92 (0.74;1.15)	0.79 (0.58;1.08)
>15 drink-years	321	164	0.75 (0.60;0.94)	85	0.92 (0.69;1.23)	0.78 (0.61;0.99)	0.96 (0.71;1.30)
p for trend[c]			p = 0.02		p = 0.87	p = 0.07	p = 0.89

[a] Model 1 adjusted for age, ancestry, family history of prostate cancer, education, smoking, physical activity, body mass index, fruit and vegetables consumption, history of diabetes and other types of beverages.
[b] Model 2 adjusted for variables in Model 1 as well as for timing since last prostate cancer screening.
[c] p for trend using an ordinal variable corresponding to the median drink-years of the category.

PCa by disease aggressiveness. Results of analyses are shown before (Model 1) and after (Model 2) adjusting for the timing of last PCa screening. We observed a slight, non-significant increase in risk of high-grade PCa (OR = 1.18, 95% CI 0.81–1.73) among men in the highest cumulative intake category (over 101 drink-years) of total alcohol. However, men in the upper quartile of beer consumption (over 63 drink-years) had an increased risk of high-grade PCa (Model 1: OR = 1.37, 95% CI 1.00–1.89). This relationship was more pronounced (Model 2: OR = 1.46, 95% CI 1.04–2.03, p for trend = 0.04) when adjusting for the timing of last PCa screening. No association emerged for wine consumption. Contrastingly, men in the upper tertile of spirits consumption had a reduced risk of low-grade PCa risk; for those consuming more than 15 drink-years the OR was 0.75 (95% CI 0.60–0.94), based on Model 1. After adjusting for the timing of last PCa screening, this association was slightly weakened (Model 2: OR = 0.78, 95% CI 0.61–0.99).

Excluding former and never drinkers from the analyses had little influence on findings for low-grade PCa (Table 3). However, this resulted in greater risks of high-grade cancers, which was true for the highest levels of consumption for total alcohol, and for all three specific beverages. For instance, results from Model 2 show statistically significant increases in risk of high-grade PCa for high consumption levels of total alcohol (OR = 1.52, 95% CI 1.07–2.16) and beer (OR = 1.68, 95%CI 1.10–2.57). Both relationships exhibited statistically significant dose-response trends.

Analyses restricted to former drinkers (who quit drinking more than 2 years before the index date) showed lower risks for the upper category of total alcohol consumption for high-grade PCa (OR = 0.75, 95%CI 0.34–1.63) but numbers were small (247 controls, 128 low-grade and 72 high-grade PCa).

Exclusion of proxy respondents did not alter findings, nor did the restriction to European subjects, or to controls recently screened (data not shown).

We compared PSA levels at diagnosis among cases across quartiles of total alcohol intake. There was no evidence of an association between alcohol intake levels and PSA levels, either among low- or high-grade cases (data not shown).

4. Discussion

We observed an increased risk of high-grade PCa among current alcohol users, largely driven by beer drinking. The lower numbers of wine and spirits users might explain the lack of clear associations for these beverages. Although trend analyses suggested some dose-response relationships, significant associations emerged only for upper intake categories, raising the possibility of a threshold effect. Under a hypothetical scenario, assuming that men having consumed over 101 drink-years over their lifetime had started drinking at age 20, this would translate into >2 drinks/day for a 65 year old man, or >3 drinks/day for a 50 year old man. These are above levels currently considered not to be harmful to general

Table 3
Odds ratio (OR) and 95% confidence interval (CI) for the association between lifetime alcohol consumption among current drinkers and prostate cancer risk, by disease aggressiveness, PROtEuS, Montreal, Canada.

Lifetime alcohol intake	Model 1[a]					Model 2[b]	
	controls	low-grade PCa		high-grade PCa		low-grade PCa	high-grade PCa
	n	n	OR (95%CI)	n	OR (95%CI)	OR (95%CI)	OR (95%CI)
Total alcohol							
≤16 drink-years	365	287	ref	87	ref	ref	ref
]16–45] drink-years	396	306	0.97 (0.77;1.21)	103	1.09 (0.79;1.51)	0.90 (0.71;1.14)	1.00 (0.71;1.39)
]45–101] drink-years	404	272	0.88 (0.70;1.11)	92	0.94 (0.67;1.31)	0.81 (0.64;1.04)	0.87 (0.62;1.24)
>101 drink-years	343	229	0.89 (0.69;1.14)	119	1.40 (1.00;1.97)	0.97 (0.74;1.27)	1.52 (1.07;2.16)
p for trend[c]			p = 0.34		p = 0.04	p = 0.97	p = 0.01
Beer							
≤6 drink-years	268	199	ref	64	ref	ref	ref
]6–23] drink-years	277	201	1.04 (0.79;1.37)	72	1.11 (0.75;1.64)	1.02 (0.76;1.36)	1.08 (0.72;1.61)
]23–63] drink-years	282	208	1.13 (0.86;1.49)	66	1.00 (0.67;1.49)	1.15 (0.86;1.54)	1.01 (0.67;1.53)
>63 drink-years	234	176	1.11 (0.82;1.51)	94	1.49 (0.99;2.23)	1.25 (0.90;1.74)	1.68 (1.10;2.57)
p for trend[c]			p = 0.55		p = 0.04	p = 0.15	p = 0.01
Wine							
≤4 drink-years	318	242	ref	81	ref	ref	ref
]4–13] drink-years	314	241	0.94 (0.73;1.21)	81	1.01 (0.71;1.44)	0.89 (0.69;1.16)	0.96 (0.67;1.39)
]13–35] drink-years	340	237	0.88 (0.68;1.13)	80	0.95 (0.66;1.36)	0.85 (0.65;1.11)	0.93 (0.64;1.34)
>35 drink-years	316	224	0.96 (0.75;1.25)	86	1.17 (0.82;1.67)	0.92 (0.71;1.21)	1.14 (0.79;1.64)
p for trend[c]			p = 0.96		p = 0.32	p = 0.71	p = 0.07
Spirits							
≤3 drink-years	208	146	ref	37	ref	ref	ref
]3–15] drink-years	207	127	0.96 (0.69;1.33)	36	0.92 (0.55;1.55)	0.96 (0.68;1.36)	0.92 (0.54;1.57)
>15 drink-years	181	87	0.86 (0.59;1.23)	43	1.40 (0.84;2.36)	0.92 (0.63;1.36)	1.49 (0.87;2.54)
p for trend[c]			p = 0.41		p = 0.11	p = 0.85	p = 0.34

[a] Model 1 adjusted for age, ancestry, family history of prostate cancer, education, smoking, physical activity, body mass index, fruit and vegetables consumption, history of diabetes and other types of beverages.
[b] Model 2 adjusted for variables in Model 1 as well as for timing since last prostate cancer screening.
[c] p for trend using an ordinal variable corresponding to the median drink-years of the category.

health (15 drinks/week) for men in Canada [16], yet they were not uncommon in our study population (22% of controls).

4.1. Former evidence

In a recent meta-analysis [9], relative risks of overall PCa were 1.04 (95% CI 1.01–1.08), 1.06 (95% CI 1.01–1.11) and 1.09 (95% CI 0.98–1.21) for light, moderate and heavy alcohol drinkers, respectively. Pooled relative risks were similar for case-control and cohort studies, but more pronounced in North American populations, especially among heavy drinkers. Analyses were not performed according to cancer aggressiveness. Subsequently, a large cohort study in the United-States found a non-significant increased risk of overall PCa with lifelong intake in average drinks per day [17]. In the Asian Cohort Consortium, no association was found with PCa mortality [11]. However, Murphy et al. [13] highlighted that the most consistent relationships between alcohol consumption and PCa were found at consumption levels higher than those observed in the Asian Consortium, which is the case for our study population. In a nested case-control study conducted in the United Kingdom, a small increase in risk of high-grade and a decreased risk of low-grade PCa was reported for higher levels of usual weekly intake in the previous year [8]. In a prospective study, Sawada et al. observed a dose-dependent association between the frequency of use of alcohol at baseline and advanced PCa in Japanese men [6]. In a Brazilian case-control study [4], higher current alcohol consumption levels increased the risk of developing overall PCa. In a case-control study from Alberta, Canada, McGregor et al. found that lifetime alcohol consumption increased risk for both non-aggressive and aggressive cancers, but only beer intake achieved statistical significance [3]. In this latter study, stages T1 were excluded and cases were classified as non-aggressive if they were stage II and Gleason score <8 whereas in our study, 75% of low-grade PCa had T1 clinical stage. Differences in aggressiveness definitions in the two Canadian studies may possibly explain the different findings for less aggressive cancers.

4.2. Methodological considerations

4.2.1. Alcohol exposure assessment

Alcohol consumption was self-reported, necessarily entailing some measurement error. If misclassification was non-differential, this attenuated true associations. Recall bias, whereas cases could over-report their alcohol consumption, is a potential problem in case-control studies. However, several observations suggest that this is probably not the main underlying explanation to our findings. First, cases and controls declared the same average cumulative intake of total alcohol over their lifetime. Second, under an over-reporting scenario by cases, one would have expected that higher risks would have emerged for all beverage types, which is not what we observed. Third, positive associations, especially for beer, were observed for high-grade but not for low-grade PCa. It is unclear why cases in the former group would have tended to over-report their intake levels to a greater extent than those in the latter. In a previous validation study, recall bias was found to have only minor effects on reported intake of alcohol [18]. In addition, there is no widespread public knowledge that alcohol intake increases the risk of PCa, which could have led to over-reports by cases, or biased interviewers who could not be blinded to the disease status of participants. Similar pooled estimates from cohort and case-control studies further argue against recall bias issues [9].

Our assessment covered exposure over the lifetime, considering beverage sizes, intensity, frequency and duration of use. It

accounted for changes in intake patterns over time with consumption periods specific to each respondent. Many previous studies did not collect information on types of beverages and modelled grams of ethanol in average consumption patterns at a given point in time, rather than over the lifetime. We used an exposure metric that captures both the intensity and duration of alcohol consumption. Such an approach is frequently used for other lifestyle exposures in epidemiologic investigations, such as cigarette smoking [19]. Cumulative exposure over the lifetime may be a better predictor of disease than assessment at one time point, especially if intake patterns changed over time. Moreover, our variable representing total alcohol considered the ethanol content of the different types of beverages, which is relevant when a drink is the unit of measurement.

Like most others, our study did not collect information on binge drinking. Due to its often episodic nature, binge drinking is particularly difficult to assess with validity [20].

4.2.2. Selection bias

Selection bias based on alcohol use is unlikely to have occurred, other perhaps than for individuals with very severe consumption issues. We assessed the possibility of selection bias in the study based on factors that could be related to alcohol use. A comparison of non-respondents to respondents in terms of several census-based socio-economic variables (education, income, unemployment, % of recent immigrants) revealed minimal differences, suggesting that selection bias in the study is not of concern. Moreover, there was no mention to potential participants that the study assessed alcohol intake patterns, which could also have led to differential selection based on alcohol use.

4.2.3. Current drinkers

In our analyses focusing on current drinkers, the associations for high-grade PCa were positive in the upper intake category for total alcohol as well as for all individual beverages, although statistical significance was reached for total alcohol and beer only. One can speculate that high levels of alcohol close to diagnosis might have a promoting effect with respect to high-grade cancer. Alternatively, it may be that former drinkers had specific characteristics that are related to both alcohol use and PCa risk.

4.2.4. Prostate cancer screening

It is now well recognized that lack of proper consideration of screening practices in Europe and North America may have seriously hampered the progress in the identification of risk factors for PCa in those populations [12,21]. The current study was conducted in the Province of Quebec, where health care is free and universal. Although PCa screening is not practiced or recommended there, at the time subjects were ascertained the practice of PSA measurement (which became available in the early 1990s), DRE or both was relatively frequent, often incorporated as part of yearly routine exams. Unlike most previous studies, we collected a detailed screening history, enabling us to assess potential influence of screening on the associations studied.

Substantial alcohol drinking may relate to lifestyle and health-related behaviors, including screening, and thus act as a confounder of alcohol-PCa associations. Taking into account screening practices had an appreciable influence on relationships, strengthening the positive association for total alcohol and beer consumption, whereas it drew the negative association for spirits consumption towards the null.

In cohort and case-control studies, the true PCa status of men being followed-up or of controls is typically unknown, potentially compromising the ability to observe associations. Our access to PCa screening information allowed us to conduct a sub-analysis excluding controls not screened within the previous two years (24% of controls) and thus more likely to have latent, undiagnosed PCa. This had a marginal influence on our findings, probably because of the generally high screening rates in our population at the time of study.

Theoretically, heavy beer drinkers could have been more likely to get screened for PCa if experiencing health-related symptoms. However, there was no evidence of this in our study as the percentages of subjects screened within the previous two years were similar across alcohol intake categories.

4.2.5. Confounding

Our models were adjusted for a wide range of socio-demographic and lifestyle characteristics, and the high beer intake—high-grade PCa association persisted. Nevertheless, residual confounding or confounding by an unmeasured factor, perhaps one specifically related to beer drinking, remains a possibility.

4.3. Mechanisms

The postulated biological underlying mechanisms between alcohol intake and cancer are numerous, but not fully understood, particularly with respect to PCa. Acetaldehyde, the first metabolite of ethanol, is a carcinogen that can promote cancer development through several mechanisms, including interference with DNA replication, induction of DNA damage, and formation of DNA adducts. Some of these mechanisms involve polymorphisms in genes that encode the alcohol dehydrogenase and aldehyde dehydrogenase enzymes for the metabolism of ethanol and acetaldehyde affecting the ethanol/acetaldehyde oxidising capacity [22], reactive oxygen species generated predominantly by cytochrome P450 2E1 (CYP2E1), particularly after chronic heavy alcohol consumption and leading to oxidative stress [1,22,23]. Studies of genetic variants using Mendelian randomization [24] may thus help towards a better understanding of the alcohol-PCa association. Other hypotheses concern folate deficiency due to ethanol associated with high alcoholic beverage consumption [25,26] or immunosuppression that may facilitate tumor spread [27]. If alcohol plays a role in PCa development, it could also be by shifting the balance between androgens and estrogens. Alcohol may alter hormonal profiles through diminishing testicular function and lowering circulating testosterone [25]. These potential mechanisms would apply regardless of the type of beverages consumed. Positive associations were largely attributable to beer intake in our study, as observed previously [3,28]. To our knowledge, no mechanism has been proposed to date to explain a specific role of beer intake in PCa.

5. Conclusions

Results from this study provide evidence that high alcohol consumption levels over the lifetime increase the risk of high-grade PCa. This relationship was largely driven by beer consumption and was stronger among current alcohol users. No increase in risk was observed for low grade PCa. Our findings also point out to the importance of considering PCa screening practices, which have been largely ignored in the past, when studying this association.

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Conflicts of interest

None.

Authorship contribution

1) substantial contributions to conception and design, acquisition of data:
Marie-Elise Parent
or analysis and interpretation of data:
Claire Demoury, Marie-Elise Parent
2) drafting the article:
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