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Alcohol Consumption and Bladder Cancer Risk: Results from the Netherlands Cohort Study

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Although several epidemiologic studies have been conducted on alcohol consumption and bladder cancer risk, the risk according to quantity and type of alcohol consumed is not clear. The authors investigated these associations in a large prospective cohort study on diet and cancer among 120,852 subjects in the Netherlands aged 55–69 years at baseline (1986). Subjects completed a questionnaire on risk factors for cancer, including alcohol consumption. Follow-up for incident cancer was established by record linkage to cancer registries. The case-cohort analysis was restricted to a follow-up period of 6.3 years and was based on 594 cases with bladder cancer and 3,170 subcohort members. The authors corrected for age and smoking in multivariable analyses. The incidence rate ratios for men who consumed <5, 5–<15, 15–<30, and ≥30 grams of alcohol per day were 1.49, 1.52, 1.16, and 1.63 compared with nondrinkers, respectively (p for trend = 0.13). Alcohol consumed from beer, wine, and liquor was associated with moderately elevated risks, although most were not statistically significant. The incidence rate ratios for women varied around unity. The results of this study do not suggest an important association between alcohol consumption and bladder cancer risk. *Am J Epidemiol* 2001;153:38–41.

alcohol drinking; alcoholic beverages; bladder neoplasms; urologic neoplasms

Although several epidemiologic studies have been conducted to investigate the association between alcohol consumption and bladder cancer risk, the risk according to quantity and type of alcohol consumed is still not clear. In a recent meta-analysis of these studies, a slightly elevated risk of bladder cancer was demonstrated for men currently drinking alcohol compared with abstainers (1). In this meta-analysis, however, no data were available to explore the influence of quantity and types of alcoholic beverages consumed. These results prompted us to investigate these associations in more detail in the ongoing Netherlands Cohort Study.

MATERIALS AND METHODS

Cohort

The study design has been described in detail previously (2). The study population originated from 204 municipal population registries throughout the Netherlands, and the cohort includes 58,279 men and 62,573 women who were aged 55–69 years at baseline (1986). We used the case-cohort approach for data processing and analysis (3). A subcohort of 3,500 subjects was randomly sampled from the cohort after baseline exposure measurement and was followed up to obtain vital status information. No subcohort members were lost to follow-up during the follow-up period.

Follow-up

Follow-up for incident cancer was established by record linkage to cancer registries and the Dutch database of pathology reports (4), and follow-up was more than 95 percent complete (5). The present analysis was restricted to 6.3 years of follow-up. After we excluded prevalent cases, 3,346 subcohort members and 619 incident cases with microscopically confirmed carcinomas of the bladder, ureters, renal pelvis, or urethra were identified. Because the overwhelming majority of tumors occurred in the bladder, and because the renal pelvis and ureter are covered by the same urothelium, the term bladder cancer was used as a synonym for these neoplasms.

Questionnaire

All subjects completed a self-administered questionnaire on risk factors for cancer. The food-frequency section concentrated on habitual consumption during the year before the study began. Consumption of alcoholic beverages was addressed by questions on beer, red wine, white wine, sherry, other fortified wines, liqueur, and liquor. The questionnaire data were keyed twice and were processed in a standardized manner blinded with respect to case-subcohort

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Abbreviation: CI, confidence interval.

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status. The questionnaire has been proven to be valid and reproducible (6, 7).

Data analysis

People who drank alcoholic beverages less than once a month were considered nondrinkers. Four items from the questionnaire (i.e., red wine, white wine, sherry, and liqueur) were combined into a wine variable, since these items were substantially correlated and separate treatment would have resulted in a sparsity of data. Mean daily alcohol consumption was calculated by using the computerized Dutch food composition table (8). On the basis of pilot study data, standard glass sizes were defined as 200 ml for beer, 105 ml for wine, 80 ml for sherry, and 45 ml for both liqueur and liquor, corresponding to 8, 10, 11, 7, and 13 grams of alcohol, respectively.

The following variables were considered as potential confounders: age (years); consumption of coffee (ml/day), water (ml/day), vegetables (g/day), and fruit (g/day); cigarette smoking status (never/former/current), amount (cigarettes/day), and duration (years of cigarette smoking); occupational exposure to dye, rubber, leather, or vehicle fumes (ever/never); and first-degree family history of bladder cancer (yes/no). Incidence rate ratios and corresponding 95 percent confidence intervals for bladder cancer were estimated by using exponentially distributed failure time regression models (9).

To ensure that the results were not influenced by changes in exposure for subjects with preclinical disease, we conducted analyses with and without cases diagnosed in the first 1 or 2 years of follow-up. The results from these analyses were similar; therefore, this paper presents results from the analyses in which all cases were included. This study was based on 594 cases (517 men and 77 women) and 3,170 subcohort members (1,591 men and 1,579 women) for whom data on alcohol consumption were complete.

RESULTS

Fifteen percent of the men and almost one third of the women were nondrinkers. Most men consumed all types of alcoholic beverages, whereas almost 50 percent of the women drank wine exclusively.

Of the potential risk factors, sex modified the association between alcohol consumption and bladder cancer incidence. Therefore, the analyses were stratified on sex. The age-adjusted risk for men was higher for alcohol drinkers than for nondrinkers (incidence rate ratio = 1.43, 95 percent confidence interval (CI): 1.06, 1.95).

As shown in table 1, this risk increased according to the quantity of alcohol consumed (p for trend < 0.01). After additional adjustment for cigarette smoking status, amount, and duration, the risk estimates remained practically stable for alcohol drinkers compared with nondrinkers (incidence rate ratio = 1.43, 95 percent CI: 1.02, 1.99), although the dose-response relation was found to be lower and not statistically significant (p for trend = 0.13). The association between alcohol consumption and bladder cancer risk did not differ within strata of smoking status, amount, or duration (data not shown). There was no indication of an association between alcohol consumption and risk of bladder cancer for women (table 1). Additional correction for other potential confounders did not change the risk estimates substantially.

Further analyses for specific alcoholic beverages were restricted to men only (table 2). When nondrinkers were used as the reference, the age- and smoking-adjusted incidence rate ratio for beer drinkers consuming 15–<30 g/day of alcohol increased slightly, to 1.70 (95 percent CI: 0.90, 3.23), with the quantity of alcohol consumed. Higher intakes from beer were not related to an increased risk. Consumption of wine was not related to an increased risk for men consuming <30 g/day, but men who drank ≥30 g/day of alcohol from

TABLE 1. Age- and smoking-adjusted incidence rate ratios (categorical and continuous analyses) for bladder cancer in men and women, according to total alcohol consumption from alcoholic beverages, Netherlands Cohort Study, 1986–1992

Alcohol consumption	No. of cases in cohort	No. of person-years in subcohort	Adjusted for age		Adjusted for age and smoking*	
			RR†	95% CI†	RR	95% CI
Men						
No alcohol intake	62	1,446	1.00	Reference	1.00	Reference
<5 g/day	108	1,947	1.43	1.00, 2.05	1.49	1.00, 2.21
5–<15 g/day	136	2,646	1.33	0.94, 1.88	1.52	1.04, 2.21
15–<30 g/day	109	2,192	1.24	0.86, 1.77	1.16	0.78, 1.71
≥30 g/day	102	1,324	1.98	1.37, 2.88	1.63	1.08, 2.47
p value for linear trend			<0.01		0.13	
Alcohol increment 10 g/day			1.09	1.03, 1.15	1.04	0.98, 1.10
Women						
No alcohol intake	25	3,147	1.00	Reference	1.00	Reference
<5 g/day	29	3,622	1.01	0.59, 1.76	0.97	0.56, 1.69
≥5 g/day	33	2,979	0.95	0.55, 1.76	0.75	0.41, 1.37
Alcohol increment 10 g/day			0.97	0.72, 1.32	0.85	0.60, 1.20

* Smoking status, amount, and duration.
† RR, incidence rate ratio; CI, confidence interval.

TABLE 2. Adjusted incidence rate ratios (categorical and continuous analyses) for bladder cancer in men, according to alcohol consumption from specific beverages, Netherlands Cohort Study, 1986–1992

Alcohol consumption	No of cases in cohort	No. of person-years in subcohort	Adjusted for age		Adjusted for age and smoking*	
			RR†	95% CI†	RR	95% CI
No alcohol intake	62	1,446	1.00	Reference	1.00	Reference
Alcohol from beer						
<5 g/day	174	3,383	1.32	0.95, 1.85	1.35	0.94, 1.95
5–<15 g/day	89	1,607	1.49	1.02, 2.18	1.44	0.95, 2.18
15–<30 g/day	22	331	1.94	1.07, 3.52	1.70	0.90, 3.23
≥30 g/day	10	170	1.45	0.66, 3.20	1.09	0.46, 2.57
p value for linear trend			<0.01		0.12	
Alcohol increment 10 g/day			1.07	0.96, 1.19	1.03	0.91, 1.16
Adjusted from wine‡						
<5 g/day	151	2,686	1.38	0.98, 1.94	1.54	1.06, 2.23
5–<15 g/day	67	1,417	1.19	0.80, 1.77	1.23	0.80, 1.90
15–<30 g/day	25	581	1.13	0.66, 1.93	1.14	0.65, 2.00
≥30 g/day	11	135	2.08	0.94, 4.61	1.73	0.74, 4.05
p value for linear trend			0.24		0.46	
Alcohol increment 10 g/day			1.00	0.88, 1.15	0.99	0.87, 1.13
Alcohol from liquor						
<5 g/day	114	2,207	1.30	0.91, 1.86	1.44	0.98, 2.11
5–<15 g/day	89	1,603	1.37	0.94, 2.00	1.38	0.92, 2.08
15–<30 g/day	70	1,155	1.41	0.95, 2.10	1.25	0.81, 1.91
≥30 g/day	50	512	2.48	1.57, 3.92	1.94	1.17, 3.22
p value for linear trend			<0.01		0.03	
Alcohol increment 10 g/day			1.14	1.05, 1.23	1.06	0.97, 1.16

* Smoking status, amount, and duration.
† RR, incidence rate ratio; CI, confidence interval.
‡ Among male wine drinkers in the subcohort, 63% drank red wine, 58% drank white wine, 48% drank sherry, and 16% drank liqueur.

wine had an increased incidence rate ratio of 1.73 (95 percent CI: 0.74, 4.05) compared with nondrinkers. The highest risk was found for men who drank ≥30 g/day from liquor compared with nondrinkers. The corresponding incidence rate ratio was 1.94 (95 percent CI: 1.17, 3.22). Lower intakes from liquor did not seem to be related to an elevated risk. Adjustment for age only or simultaneous inclusion of alcohol consumption from beer, wine, and liquor in one regression model did not change the results substantially. Although some point estimates suggested increased risks for alcohol consumers, practically none of the incidence rate ratios or dose-response trends was statistically significant (table 2).

DISCUSSION

The results of this prospective study do not suggest an important association between alcohol consumption and bladder cancer risk. If any, the association between alcohol consumption and male bladder cancer is probably small.

Some authors have suggested that residual confounding due to tobacco smoking could explain an increased risk as a result of alcohol drinking (10, 11). We attempted to model cigarette smoking habits such that they best explained bladder cancer by using smoking status, amount, and duration. However, correction for smoking did not change the incidence rate ratios substantially. Therefore, the association observed between alcohol consumption and bladder cancer risk did not seem to be entirely due to residual confounding by smoking, although some influence cannot be excluded.

A recent meta-analysis based on predominantly case-control studies concluded that alcohol consumption slightly increases male bladder cancer risk (summary odds ratio = 1.35, 95 percent CI: 0.91, 2.02), an estimate that might not be of practical importance (1). We repeated this meta-analysis to evaluate whether the summary odds ratio for male alcohol consumers compared with nondrinkers remained stable after the present study was included (1). We found that the new age- and smoking-adjusted summary odds ratio was 1.35 (95 percent CI: 0.96, 1.91). Associations between specific alcoholic beverages and bladder cancer risk were reported in nine studies without consistent results (12–20).

The literature to date does not support a causal role for alcohol consumption in bladder cancer etiology. Several mechanisms have been postulated to explain ethanol-related carcinogenesis. Ethanol slows down protein synthesis. One consequence is that cell repair mechanisms might be inhibited, which could lead to malignant changes (21, 22). Furthermore, ethanol might improve permeability of membranes to carcinogens and might enhance carcinogenic activity (22–24). Other explanations include the effect of ethanol on cell proliferation, possibly caused by acetaldehyde (22, 23, 25). Animal experiments have shown that nitrosamines

might be carcinogenic in the bladder (21, 26). However, the quantities of these carcinogens in alcohol are small (17), and certain nitrosamines, upon direct instillation into the bladder, do not cause bladder cancer (25). The urogenous-contact hypothesis associates development of bladder cancer with prolonged exposure to carcinogens in urine (27, 28). High consumption of fluids may reduce this exposure. One prospective study demonstrated this negative association (28), whereas other studies reported positive associations (13, 29–33) or no association (15, 34). Correction for total water intake did not change the results substantially.

In accordance with earlier studies, the results of this prospective study do not suggest an important increased risk of bladder cancer for male alcohol consumers. If any such association exists, it is probably small. In our study, we found that the risk of bladder cancer increased slightly according to the quantity of alcohol consumed, irrespective of the type of alcoholic beverage, although no statistically significant dose-response trends were identified. We found no association between alcohol consumption and bladder cancer risk for women.

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