

BLADDER CANCER AND ALCOHOLIC BEVERAGE CONSUMPTION

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A population-based case-control study of bladder cancer was conducted in 10 geographic areas in the United States. Risk of bladder cancer was not related to overall alcohol intake, nor to amounts of wine, beer, or spirits consumed. Alcohol also did not interact with known or suspected bladder carcinogens to increase risk, and no evidence was found that indirect mechanisms associated with alcohol ingestion increase the risk of bladder cancer.

alcohol, ethyl; bladder neoplasms

In humans, alcohol appears to exert a carcinogenic effect primarily on those tissues which come in direct contact with undigested imbibed ethanol. Thus, alcohol consumption is a well documented risk factor for squamous cell carcinomas

of the mouth (1-7) and esophagus (1-4, 8-13). It probably also contributes to the development of laryngeal carcinomas (3, 11, 14-21), especially those arising in the supraglottic portion of the larynx (15), which is the portion exposed to ingested materials. Studies of gastric cancer and alcohol consumption have yielded inconsistent results, but most do not show alcohol to increase risk (22).

Hepatocellular carcinomas develop with unusually high frequency in alcoholics with cirrhosis (23). With this exception, observed associations between neoplasms at sites where there is little or no direct impingement of alcohol on tissue are few and inconsistent among investigations. However, one or more studies have shown an association between alcohol in one form or another and cancers of the breast (19, 24), colon (25, 26), rectum (25, 26), and pancreas (27, 28), which suggests that alcohol may influence risk of neoplasms by means other than those involving direct contact of ethanol with the tissues.

Most studies have not shown an association between bladder cancer and alcohol consumption (5, 8, 29-32). In one study, however, an increased risk associated with alcohol use was found in

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smokers but not in nonsmokers (14), suggesting a synergistic effect similar to that observed by some investigators for cancers of the mouth (7), larynx (16, 33), and esophagus (2).

Ethanol has not been found to be carcinogenic in animals, and probably is not a human carcinogen per se. Mechanisms by which alcohol consumption could nonetheless enhance the risk of cancer include

1. Irritation of the mucosa on direct contact, which somehow enhances the susceptibility of the tissues to carcinogenic agents. This is suggested by reports of esophageal cancer being more strongly related to consumption of distilled beverages than to wine or beer (5, 12, 31, 34, 35) as well as by the anatomic location of the above-mentioned sites of alcohol-associated neoplasms.

2. Contamination of alcoholic beverages with carcinogenic impurities. Evidence of this includes observed associations between esophageal cancer and home-brewed beverages (36-38).

3. Nutritional deficiencies associated with heavy alcohol use. Deficiencies of vitamin A have been related to cancers of the mouth (39, 40), larynx (21), esophagus (41), and bladder (42); deficiencies of vitamin C and riboflavin have been associated with esophageal (41, 43) and laryngeal cancers (21); these and other nutrient deficiencies have been documented in abusers of alcohol.

4. Serving as a solvent for carcinogens (such as those in tobacco smoke), thereby enhancing their absorption.

Only about 2 per cent of a moderate oral dose of ethanol is excreted in the urine (44, 45). An association between alcohol consumption and bladder cancer would thus probably indicate that alcohol can enhance risk of neoplasms by mechanisms other than direct action on mucosal surfaces.

This report is based on analyses of data from a sufficiently large population-based

case-control study of bladder cancer to detect with high probability even a small alteration in risk associated with alcohol consumption.

METHODS

Personal interviews were conducted in 1978-1979 with 2982 cases and 5782 controls as part of a collaborative population-based case-control study in 10 geographic areas of the United States (46). The case group consisted of all individuals in the 10 study areas with newly diagnosed and histologically confirmed bladder cancer in a one-year period (beginning in late 1977 or early 1978). Cases were identified from cancer registries, nine of which were part of the National Cancer Institute's Surveillance, Epidemiology and End Results Program. The control group consisted of a random sample of the population of the study areas stratified according to the age, sex, and geographic distribution of the cases. Controls aged 21-64 years were selected through random-digit telephone dialing. Controls aged 65-84 years were selected at random from the census files of the Health Care Financing Administration.

Eligible cases totaled 4086, of whom 2982 (73 per cent) were interviewed. The remaining 1104 cases were not interviewed because of death (25 per cent), illness (26 per cent), refusal to be interviewed (23 per cent), physician refusal (12 per cent), identification after the study period (6 per cent), not being found (7 per cent), and other reasons (1 per cent). Among the 4057 eligible controls aged 65-84 years, 3313 (82 per cent) were interviewed. The remaining 744 were not interviewed because of death (13 per cent), illness (23 per cent), refusal (47 per cent), not being found (14 per cent), and other reasons (3 per cent). Selection of controls aged 21-64 years began with 25,826 randomly dialed telephone numbers of which 88 per cent yielded household censuses. Among the 2928 ap-

proached for an interview, 2469 (84 per cent) provided one. The remaining 459 were not interviewed because of death (1.5 per cent), illness (5 per cent), refusal (73 per cent), not being found (19 per cent), and other reasons (1.5 per cent).

Trained interviewers administered a standardized questionnaire to all subjects in their homes. This included questions on the use of artificial sweeteners, coffee and other drinks, tobacco products, and an occupational history and residential history. Three questions about consumption of alcoholic beverages came near the middle of the questionnaire immediately after questions about a variety of nonalcoholic beverages. The subject was asked to estimate separately, the number of servings of beer, wine, and spirits consumed in a typical week in the winter one year previously. A serving was defined for the subject as a can, bottle, or draught of beer, a 4-ounce (118.3 ml) glass of wine, and a 1.5-ounce (44.4 ml) jigger of spirits.

The association between alcohol consumption and bladder cancer was assessed by the maximum likelihood esti-

mate of the relative risk, adjusted for potentially confounding variables by stratification into multiple contingency tables (47). Dose-related trends in relative risk were assessed by the Mantel extension of the Mantel-Haenszel test (48).

RESULTS

Risk of bladder cancer was independent of amount of alcohol consumed. The unadjusted relative risks suggested a weak association of bladder cancer with larger amounts of imbibed alcohol, but this was due largely to the confounding effect of cigarette smoking. It can be seen in table 1 that adjusted relative risks for those who consume various amounts of alcohol compared with nondrinkers range from 0.66–1.13 and there is no consistent relationship to amount of alcohol consumed. The 95 per cent confidence limits for the relative risks include 1.0. The relative risks in table 1 were adjusted by stratification for race (white vs. nonwhite), age (<65 vs. ≥65 years), cigarette smoking status (smoker vs. nonsmoker), and hazardous occupational exposure (ever vs.

TABLE 1
Relative risks of bladder cancer according to number of alcoholic drink servings per week by sex

Servings/week	Cases		Controls		Relative risk*
	No.	%	No.	%	
<i>Males</i>					
None	835	37.5	1604	37.7	1.00
<3	216	9.7	442	10.4	0.94
4-6	228	10.2	489	11.5	0.86
7-13	335	15.0	623	14.6	0.98
14-27	359	16.1	696	16.4	0.88
28-41	139	6.2	210	4.9	1.13
≥42	114	5.1	189	4.4	0.99
<i>Females</i>					
None	426	58.8	888	59.7	1.00
<3	92	12.7	211	14.2	0.80
4-6	75	10.3	148	10.0	0.93
7-13	62	8.6	132	8.9	0.77
14-27	59	8.1	90	6.1	0.97
28-41	9	1.2	14	0.9	0.87
≥42	2	0.3	4	0.3	0.66

* Adjusted by stratification for age, race, cigarette smoking status, and hazardous occupational exposure.

TABLE 2
 Relative risks of bladder cancer according to number of alcoholic drink servings
 per week by type of beverage

Servings/week	Cases		Controls		Relative risk*
	No.	%	No.	%	
			<i>Spirits</i>		
None	1261	52.8	2492	53.5	1.00
<3	294	12.3	694	14.9	0.78
4-6	259	10.8	494	10.6	0.91
7-13	255	10.7	456	9.8	0.95
14-27	235	9.8	391	8.4	0.99
28-41	53	2.2	89	1.9	1.04
≥42	31	1.3	44	0.9	1.14
			<i>Beer</i>		
None	1261	58.3	2492	59.7	1.00
<3	275	12.7	567	13.6	0.89
4-6	223	10.3	415	9.9	0.98
7-13	154	7.1	300	7.2	0.92
14-27	161	7.4	263	6.3	1.01
28-41	43	2.0	60	1.4	1.16
≥42	46	2.1	80	1.9	0.93
			<i>Wine</i>		
None	1261	61.9	2492	60.6	1.00
<3	370	18.2	753	18.3	0.94
4-6	175	8.6	386	9.4	0.86
7-13	128	6.3	284	6.9	0.81
14-27	89	4.4	155	3.8	1.00
≥28	15	0.7	44	1.1	0.60

* Adjusted by stratification for sex, age, race, cigarette smoking status, and hazardous occupational exposure.

never handled dye, rubber, leather, ink, or paint on any job). Relative risk estimates were unaffected by adjustment for measures of coffee consumption (<14, 14-27, and ≥28 cups per week), geographic area, or artificial sweetener use (<240 vs. ≥240 mg per week) when considered alone or in combination with sex, race, age, and smoking status.

Risks relative to nondrinkers were estimated separately for individuals reporting consumption of spirits, beer, and wine. Individuals who never drank the specific type of beverage in question, but who drank either of the other two types, were excluded from these analyses. As shown in table 2, risk of bladder cancer was independent of amount of consumption of any of these types of alcoholic beverages. The range of relative risks is from 0.60-1.16. The 95 per cent confidence limits include 1.0. These risk estimates were adjusted by stratification for sex,

race, age, hazardous occupational exposure, and cigarette smoking status.

To assess the potential role of alcohol as a cocarcinogen, possible interactions of alcohol with cigarette smoking, hazardous occupational exposure, coffee consumption, and artificial sweetener use were examined. Each cofactor-specific estimation of relative risk in alcohol users was adjusted by stratification for race, age, geographic area, and cigarette smoking status (except for the smoking-specific estimates themselves). Among the cofactor- and sex-specific relative risks, where the number of cases and controls combined was at least 50, the risk estimates ranged from 0.56-1.40, and the 95 per cent confidence limits included 1.0. There was no indication of any trend toward increasing risks associated with higher levels of alcohol consumption with increasing amounts of smoking (0, <20, 20-39, ≥40 cigarettes per day), in-

creasing amounts of coffee consumption (<14, 14–27, \geq 28 cups per week), hazardous occupational exposure, or increasing amounts of artificial sweeteners (<240 vs. \geq 240 mg per week).

DISCUSSION

In an era in which the public sometimes perceives epidemiologic inquiries to be "alarmist," there is some reassurance in the present findings which attest to an absence of any increased risk of bladder cancer attributable to alcohol consumption. It is always wise to remember that the null hypothesis cannot be proven, but the present data provide a basis for more than the usual confidence that bladder cancer and alcohol consumption are independent. The sample of cases and controls was large enough to detect an association with a power of 0.80 or greater for any of the presently analyzed levels of drinking among men if the true relative risk was approximately 1.45 or greater (at a 0.05 significance level). There were other research design and statistical strengths in the present data favoring the detection of an association between alcohol and bladder cancer if one exists. This study was a population-based case-control study in which the cases constituted a reasonably high proportion of all incident cases in 10 geographic regions, and the controls constituted a probability sample of the populations from which the cases came. Selection bias is, therefore, unlikely to have been a problem. There was a sufficient range of alcohol consumption reported, and a large enough number of male heavy drinkers (i.e., 42+ drinks per week) to identify risk if risk only accrues to those whose drinking is at the high end of the population distribution. Similarly, the range of alcohol consumption reported permitted a statistically powerful test of any possible dose-response relationship, and none was found.

If alcohol itself is not a bladder carcinogen, it still could be a cocarcinogen in interaction with some other risk factor (49–52). Cigarette smoking is known to be a risk factor for bladder cancer (19, 53–58), and there is evidence of a synergistic interaction between alcohol and cigarette smoking in cancers of the upper respiratory tract (2, 7, 14–16, 33, 50, 59, 60). However, we were unable to find any evidence of an interaction between alcohol and cigarette smoking. Occupational exposures to chemicals involved in the manufacture or application of dye, rubber, leather, ink, or paint are other known risk factors for bladder cancer (55, 58); we were also unable to find evidence of an interaction between alcohol and such exposures. Finally, our examination of alcohol in interaction with coffee consumption and with the use of artificial sweeteners, two suspected human bladder carcinogens (58, 61), failed to produce any evidence of alcohol cocarcinogenesis.

There are limitations to the present findings. The interviewers asked about amount drunk during a typical week in the previous winter. Results could be different if information on lifetime consumption were obtained. The interview questions did not ask about patterns of drinking over time (e.g., binge drinking), which might be associated with different bladder cancer experience. Respondents were also not asked about the brands and sources of their alcoholic beverages (e.g., a particular type of home brew) which might contain carcinogenic nonalcohol components. There may also be undetermined exposures with which alcohol could interact as a cocarcinogen. However, because there was no overall increase in risk due to alcohol, if alcohol escaped our detection as a risk factor for bladder cancer for one or more of these reasons, it is unlikely that more than a minute fraction of bladder cancers could be attributed to such exposures.

There are reasons to be moderately confident about the accuracy of the limited data on alcohol consumption in this study. The age- and sex-adjusted percentage of abstainers in our sample was similar to that found in the 1979 United States National Survey on drinking (62) (43.1 and 39.8 per cent, respectively). Heavy drinking, defined as 14 or more drinks per week, was more prevalent in our sample than in the 1979 United States survey (15.5 and 8.0 per cent, respectively), suggesting that the common problem of underreporting of alcohol consumption (62) was not more severe with the method used in this study. The three interview questions about alcohol consumption were embedded in the middle of the interview in the context of questions about drinking beverages of all kinds, and the thrust of the interview was toward matters pertaining to artificial sweetener use, occupation, and tobacco use, rather than alcohol consumption; this may have helped to minimize the problem of underreporting of alcohol consumption. Nevertheless, some underreporting probably occurred. There is evidence that there is less drinking among older groups (62). Since the present sample was predominantly elderly, former drinkers might have responded as if they were abstainers or light drinkers. To the extent this happened, it would have biased the results toward the null findings.

Only about 2 per cent of the alcohol ingested by humans is excreted in the urine (44, 45), making the bladder a site relatively unexposed to ethanol. Therefore, if an association between bladder cancer and alcohol consumption had been observed, this would have suggested that one or more indirect mechanisms might have been involved. Thus, our negative results provide no evidence that indirect mechanisms such as nutritional deficiencies associated with alcoholism or ingestion of true carcinogens in conjunction

with the imbibing of alcohol increase the risk of bladder cancer. No potentiation of the effects of known bladder carcinogens by alcohol was observed. This suggests that alcohol does not enhance risk by acting as a solvent for such substances.

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