Cancer Causes and Control, 3, 419 - 425

Alcoholism and cancer risk: a population-based cohort study

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(Received 23 March 1992; accepted in revised form 16 June 1992)

The incidence of cancer was studied in a population-based cohort of 9,353 individuals (8,340 men and 1,013 women) with a discharge diagnosis of alcoholism in 1965-83, followed up for 19 years (mean 7.7). After exclusion of cancers in the first year of follow-up, 491 cancers were observed *cf* 343.2 expected through 1984 (standardized incidence ratio [SIR] = 1.4, 95 percent confidence interval [CI] = 1.3-1.6). A similar excess risk of cancer was seen among men (SIR = 1.4, CI = 1.3-1.6) and among women (SIR = 1.5, CI = 1.1-2.0). We observed the established associations with cancers of the oral cavity and pharynx (SIR = 4.1, CI = 2.9-5.7), esophagus (SIR = 6.8, CI = 4.5-9.9), larynx (SIR = 3.3, CI = 1.7-6.0), and lung (SIR = 2.1, CI = 1.7-2.6), although confounding by smoking likely increased these risk estimates. While there was evidence of increased risk for pancreatic cancer (SIR = 1.5, CI = 0.9-2.3), alcoholism did not elevate the incidence of cancer of the stomach (SIR = 0.9, CI = 6-1.4), large bowel (SIR = 1.1, CI = 0.8-1.5), prostate (SIR = 1.0, CI = 0.8-1.3), urinary bladder (SIR = 1.0, CI = 0.6-1.5), or of malignant melanoma (SIR = 0.9, CI = 0.3-1.9). Among women, the number of breast cancers observed was close to expected (SIR = 1.2, CI = 0.6-2.2), although a significant excess number of cervical cancers occurred (SIR = 4.2, CI = 1.5-9.1). The results of this study, one of the first to evaluate the incidence of cancer in a population-based cohort of alcoholics of both sexes, are consistent with smaller previous studies, which were usually limited to cancer mortality and of short follow-up.

Key words: Alcoholism, cancer risk, cohort study, Sweden.

Introduction

According to the International Agency for Research on Cancer, alcohol is related causally to malignant tumors of the oral cavity, pharynx, larynx, esophagus, and liver.[1] It is still debated whether alcohol is related etiologically to cancer of the large bowel (mainly rectum)[1] and of the breast (notably at premenopausal ages).[1-5] Overall, available data do not support a causal role of alcohol in the development of stomach, pancreas, and lung cancer, nor has any association been found with cancer of the urinary organs, prostate, or ovary. For a number of sites—*e.g.*, skin, uterus, testis, brain, and thyroid—available data have been too limited to allow any conclusion.[1]

Follow-up studies of cancer among alcoholics[6-12] have had significant limitations such as small study size and short or incomplete follow-up.[7,8-11] In addition, all studies except one[7] reported on cancer mortality rather than incidence, and most of them were confined to men.[6,7,11,12]

Our study, based on almost 500 incident cancers in a

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population-based cohort of patients diagnosed with alcoholism, has two purposes: first, to provide quantitative estimates of the risk of cancers known to be associated etiologically with alcohol intake; second, to study the occurrence of cancers for which alcohol has been reported to increase risk, but is not considered yet a cause (such as breast, colon, rectum, and pancreas), and to report other cancer sites for which epidemiologic data are sparse or largely lacking, *e.g.*, malignant melanoma, uterus, prostate, and brain.

Patients and methods

Study population

The methods used in this study have been described in detail elsewhere.[13,14] Briefly, a population-based study was carried out in the Uppsala Health Care Region in central Sweden with a total population of 1.2-1.3 million people. From 1965 through 1983, the Swedish National Board of Health and Welfare received annual reports from all inpatient medical institutions in Sweden on Uppsala-area residents with hospital admissions and discharges. Besides a unique national registration number assigned to every Swedish citizen, each inpatient record contains data on place of residence, and discharge diagnoses coded according to the seventh revision of the International Classification of Diseases (ICD-7)[15] through 1968 and according to the eighth revision (ICD-8)[16] thereafter. A recent publication estimated that under-reporting to the Uppsala Inpatient Register was less than two percent.[13]

The cohort

All records in the Inpatient Register containing a diagnostic code for alcoholism (ICD-7 codes 307, 322; ICD-8 codes 291, 303) were considered for inclusion in the study. The national registration number allowed us to select the first recorded discharge with this diagnosis for each individual.

A total of 10,350 individuals (1,101 females and 9,249 males) were given a discharge diagnosis of alcoholism at least once during 1965-83 and thus were potentially eligible. We excluded 923 (nine percent) of these individuals because they had an incomplete or inconsistent national registration number and hence were not available for follow-up. Another 74 (one percent) patients were excluded due to invalid codings or record linkage. Thus, a total of 9,353 patients were entered into the study. The cohort is characterized further in Table 1. Among the patients, a total of 4,611 (49 percent) had alcoholism as their first (main) discharge diagnosis at entry (start of follow-up).

Record-linkage to the nationwide Registry of Causes of Death provided information on the date of death among those deceased through 1984. The National Swedish Cancer Registry was used to ascertain all incident cancers diagnosed in the cohort from start of follow-up through 1984.[15] Follow-up was calculated from the date of entry into the cohort (registration date of the first diagnosis of alcoholism) until the occurrence of a cancer diagnosis, death, or the end of the observation period (31 December 1984). The duration of follow-up varied with a mean value of 7.7 years and a maximum of 19 completed years (Table 1).

Statistical analysis

The expected number of cancers was calculated by multiplying the number of person-years for each gender by age-specific cancer-incidence rates for each five-year age-group and calendar year of observation. These expected rates were derived from the study population, *i.e.*, the Uppsala health care region,[17] and included the cases observed and the person-years accumulated in the cohort. We excluded cancers from the first year of follow-up in order to eliminate or reduce the possible impact of selection bias. Such bias occurs in patients whose first cancer symptoms, rather than alcoholism, gave rise to the hospitalization. The standardized incidence ratio (SIR) was defined as the ratio of observed numbers of cancers to those expected. The 95 percent confidence interval (CI) of the standardized incidence ratio then was calculated on the assumption that the observed number followed a Poisson distribution.[18] During the first year of follow-up, a total of 86 cancers were diagnosed among men (SIR = 2.5, CI = 2.0-3.1) and 17 among women (SIR = 3.9, CI = 2.3-6.3).

Results

Excluding first year after entry into the cohort, a total of 491 cancers occurred compared with 343.2 expected for an SIR of 1.4 (CI = 1.3-1.6). Approximately 94 percent of the cancers were confirmed microscopically. The excess risk was of similar magnitude among men and women (Table 2). SIRs for all major cancers are shown in Table 2. Separate risks were calculated for the subcohort of patients (4,611) with alcoholism as their first discharge diagnosis, and overall cancer SIRs of 1.4 (CI = 1.2-1.6) were seen among men, and of 1.5 (CI = 1.0-2.2) among women, virtually identical with those of the total cohort (Table 2). Likewise, the pattern by site and type of cancer in the subcohort was strikingly similar to that found in the entire cohort. Thus, all further analyses are based on the entire cohort.

Cancers of the oral cavity and pharynx are relatively

Table 1. Characteristics of patients assigned a hospital discharge diagnosis of alcoholism[a] in the Uppsala Health Care Region during 1965-83, by sex (patients with alcoholism as their first main discharge diagnosis are shown separately)

	Alcoholism		Alcoholism as 1st diagnosis	
	Men	Women	Men	Women
Number of patients	8,340	1,013	4,136	475
Total person-years	63,956	7,079	34,056	3,586
Years of follow-up, mean (range 0-19)	7.7	7.0	8.2	7.6
Age at entry, mean	49.8	49.4	48.3	47.4
Average age at cancer diagnosis	68.1	60.0	65.7	58.4

[a] ICD-7 = 307,322 or ICD-8 = 291,303.

Table 2. Standardized incidence ratio (SIR) with 95% confidence intervals (CI) of developing cancer among patients with alcoholism during 1-18 completed years of follow-up, by sex

Cancer site/type	Men				Women			
	Obs	Exp	SIR	CI	Obs	Exp	SIR	CI
Buccal cavity[a]	33	8.4	3.9	2.7-5.5	3	0.4	7.0	1.4-20.3
Esophagus	26	3.8	6.9	4.5-10.0	1	0.2	5.9	0.1-32.6
Stomach	23	25.1	0.9	0.6-1.4	1	1.4	0.7	0.0-4.0
Colon	26	21.4	1.2	0.8-1.8	4	2.3	1.7	0.5-4.4
Rectum	12	15.1	0.8	0.4-1.4	1	1.2	0.8	0.0-4.6
Primary liver	23	4.2	5.4	3.4-8.1	4	0.2	12.5	3.4-32.0
Biliary tract	2	3.6	0.6	0.1-2.0	0	0.9	0.0	0.0-4.2
Pancreas	19	13.5	1.4	0.9-2.2	3	1.2	2.6	0.5-7.6
Larynx	10	3.3	3.1	1.5-5.7	1	0.04	23.2	0.3-129.1
Lung[b]	76	36.2	2.1	1.7-2.6	3	1.1	2.7	0.6-8.0
Breast	1	0.5	2.2	0.0-12.0	10	8.6	1.2	0.6-2.2
Cervix uteri	—	—	—	—	6	1.4	4.2	1.5-9.1
Corpus uteri	—	—	—	—	3	2.1	1.4	0.3-4.2
Ovary	—	—	—	—	4	2.1	1.9	0.5-4.9
Prostate	68	65.6	1.0	0.8-1.3	—	—	—	—
Testis	4	3.2	1.3	0.3-3.2	—	—	—	—
Melanoma	5	6.4	0.8	0.3-1.8	1	0.7	1.5	0.0-8.2
Bladder	20	20.2	1.0	0.6-1.5	1	0.6	1.6	0.0-8.7
Kidney	20	15.1	1.3	0.8-2.1	2	1.0	2.0	0.2-7.1
Brain	15	9.8	1.5	0.9-2.5	0	1.1	0.0	0.0-3.5
Thyroid	3	1.8	1.7	0.3-4.9	0	0.5	0.0	0.0-8.0
Lymphatic and hematopoietic[c]	19	25.2	0.8	0.5-1.2	0	1.9	0.0	0.0-1.9
All	441	310.5	1.4	1.3-1.6	50	32.7	1.5	1.1-2.0

[a] ICD-7 codes 140-148.
[b] ICD-7 codes 162-163.
[c] ICD-7 codes 200-209.

rare and sometimes difficult to classify accurately with respect to site of origin. They were merged therefore into one broad category (ICD-7 codes 140-148) designated 'buccal' cancer. A highly significant excess of buccal cancers was found overall (SIR = 4.1, CI = 2.9-5.6), and among both sexes (Table 2). Likewise, the risk of developing esophageal cancer was increased markedly and significantly when both sexes were combined (SIR = 6.8, CI = 4.5-9.9), although there was only one case among women. In contrast, there was no significant association between alcoholism and other gastrointestinal cancers: stomach (SIR = 0.9, CI = 0.6-1.4); colon (SIR = 1.3, CI = 0.9-1.8); or rectum (SIR = 0.8, CI = 0.4-1.4). When all cancers of the large bowel were analyzed together, 43 cases occurred *cf* 40.0 expected (SIR = 1.1, CI = 0.8-1.4).

The risk of developing primary liver cancer (ICD-7 code 155.0) was significantly and markedly increased in both sexes. In contrast, there was no association between alcoholism and biliary tract cancer (Table 2); nor was there any increased risk of liver cancer classified as a secondary cancer (ICD-7 code 156), since two cases

Table 3. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) of developing selected cancers among patients with alcoholism, by duration of follow-up

Cancer site	Years of follow-up					
	1-4		5-9		10-19	
	SIR	CI	SIR	CI	SIR	CI
Buccal[a]	3.6	1.9-6.2	3.7	1.8-6.6	5.4	2.8-9.4
Esophagus	11.7	6.9-18.4	3.7	1.2-8.7	4.6	1.5-10.7
Lung[b]	2.2	1.5-3.1	1.8	1.1-2.7	2.4	1.6-3.6
Stomach	1.3	0.7-2.2	0.7	0.3-1.5	0.6	0.2-1.6
Large bowel[c]	0.9	0.5-1.5	1.5	1.0-2.4	0.7	0.3-1.5
Primary liver	4.3	1.7-8.9	8.4	4.5-14.3	5.1	2.0-10.5
Pancreas	1.9	1.0-3.4	0.6	0.1-1.8	2.0	0.9-4.0
Prostate	1.0	0.6-1.5	1.1	0.7-1.6	1.1	0.7-1.6

[a] ICD-7 codes 140-148.
[b] ICD-7 codes 162-163.
[c] ICD-7 codes 153-154.

Table 4. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) for selected cancers during 1-19 completed years of follow-up of patients with alcoholism, by age at follow-up

Cancer site[a]	Age (years)					
	<50		50-64		65+	
	SIR	CI	SIR	CI	SIR	CI
Buccal	9.4	1.9-27.3	10.1	6.6-14.7	1.0	0.4-2.2
Esophagus	43.1	4.8-155.7	11.7	5.9-21.0	4.7	2.6-7.9
Stomach	4.4	0.5-15.9	1.0	0.3-2.3	0.8	0.5-1.3
Large bowel	2.1	0.3-7.7	1.8	1.0-2.9	0.8	0.5-1.2
Primary liver	0	0.0-28.4	4.9	2.1-9.6	2.9	1.8-4.4
Pancreas	0	0.0-16.5	3.3	1.6-5.8	1.0	0.5-1.8
Lung	6.7	2.2-15.7	3.5	2.4-4.9	1.5	1.0-2.0
Prostate	10.5	0.1-58.7	2.5	1.5-4.1	0.9	0.6-1.1

[a] Defined as in Table 3.

were observed *cf* 1.6 expected. Twenty-two pancreatic cancers occurred *cf* 14.7 expected for an SIR of 1.5 (CI = 0.9-2.3) (Table 2). The risk of larynx cancer was increased significantly among patients with alcoholism (SIR = 3.3, CI = 1.7-6.0) as was the risk of lung cancer (SIR = 2.1, CI = 1.7-2.6).

For cancers of the female and male reproductive organs, this study had limited power to detect associations (Table 2). Among women, 10 breast cancers occurred and SIRs were similar for those below age 50 at entry into the cohort (SIR = 1.2, CI = 0.3-3.1) and for those 50 years or older (SIR = 1.1, CI = 0.4-2.5). The risk of cervical cancer was increased significantly (Table 2), and the excess was confined mainly to women less than 50 years of age at start of follow-up (SIR = 6.5, CI = 2.1-15.2). There was no excess risk of prostate cancer among the alcoholics.

No association was observed between alcoholism and malignant melanoma (SIR = 0.9, CI = 0.3-1.9), or cancer of the bladder (SIR = 1.0, CI = 0.6-1.5),whereas relatively small nonsignificant excesses of kidney (SIR = 1.4, CI = 0.9-2.1) and brain cancers (SIR = 1.4, CI = 0.8-2.3) were observed.

When all malignant diseases of the lymphatic and hematopoietic system (ICD-7 codes 200-209) were merged together, there was no evidence of excess risk; the small number of observed cases precluded meaningful analyses of specific types.

Tumor sites with a reasonable number of observed cases were analyzed further to reveal whether possible alcohol-related cancers were distributed unevenly over time since first hospital admission (Table 3). There was no clear evidence of increasing or decreasing risk over time for any of the cancers.

The risk of developing a number of major cancers was analyzed by age at follow-up (Table 4). For buccal cancer, the increased risk seemingly was confined to subjects below 65 years of age. The risk of developing

esophageal cancer decreased markedly with increasing age at follow-up. A similar pattern was seen for lung cancer and (with lower statistical power) for prostate cancer. No trend with age was evident for the other cancer sites.

The number of hospital admissions with alcoholism as a discharge diagnosis might reflect, at least crudely, the severity and/or duration of abuse. Hence, the risk of developing all cancer types shown in Table 2 was analyzed separately in those with one, two, and three or more diagnoses of alcoholism. These categories comprised 57 percent, 18 percent, and 25 percent, respectively, of all cohort members. With increasing number of admissions, the relative risk increased for cancer of the buccal cavity (from 2.6 to 5.4), esophagus (from 5.2 to 9.9), and liver (from 3.2 to 8.1). No consistent trend was seen for any of the other sites or types of cancer including larynx and lung.

Discussion

Due to its undesirable connotations, the diagnosis of alcoholism generally is used with some reluctance in Sweden,[19] as elsewhere.[20] Therefore, the specificity of the discharge diagnosis is likely to be high and the risk estimates probably pertain to severe abusers. Most alcoholics in Sweden start their abuse early in life,[19] whereas the mean age at entry in this study was close to 50 years (Table 1), suggesting that several decades of high consumption often preceded the first registered hospital admission for alcoholism. The annual mean *per capita* intake among adults in Sweden varied between 6.0 and 7.7 l of pure alcohol during 1965-84.[21] A smaller proportion of the adult population who are alcoholics or high consumers accounts for a substantial proportion of the total. The contrast in exposure between the cohort and the background population—although impossible to quantify—therefore should be considerable.

In our study, as in other studies of alcoholics[6-12] or heavy drinkers,[22,23] we had no information on individual consumption, nor on exposure to potential confounders, of which tobacco smoking is likely the most important. Smoking, etiologically related to many cancers,[24] is more common among alcoholics than the general population.[25] Socioeconomic status (SES) is also a potential confounder; however, in Sweden for most cancer sites there is little or no association between SES and cancer risk.[26] Because alcohol often accounts for a substantial proportion of their total caloric intake, alcohol abusers have a different dietary composition, and perhaps altered energy expenditure compared with nonalcoholics.[27] Although confounding by diet may differ among cancer sites, the most likely situation is one in which there is low intake of fruits, vegetables, fiber, and vitamins,[28] and likely malabsorption, which would increase rather than decrease cancer risk in most instances.[27,29] A positive association between alcohol intake and consumption of foods high in fat might also increase cancer risk among alcoholics.[27]

Our study confirmed results from most previous cohort[6,7,10-12] and case-control[1] studies by showing an approximate fourfold increased risk of developing cancer of the oral cavity and pharynx, and a sevenfold increase for esophageal cancer. Although these risk estimates are likely to be confounded by smoking, other studies of these cancers have reported a strong independent effect for alcohol.[30-33] By showing relative risks (RR) close to unity for cancer of the stomach and large bowel, this study supports the conclusion that alcohol has no causal role. The idea that alcohol is associated with rectal but not with colonic cancer[1] was not supported by our data. If anything, confounding by dietary habits (and, for large bowel cancer, conceivably a more sedentary life)[34] should have biased risk estimates upwards.[31]

The association between alcoholism and primary liver cancer has been studied in greater detail in a companion publication.[35] When all patients with liver cirrhosis as a discharge diagnosis were excluded from the cohort of alcoholics, about a threefold increased risk of primary liver cancer was observed. Without such restriction, the findings of the cohort are more comparable with other cohorts of alcoholics.[6-12] However, the overall RR of 6.0 for primary liver cancer in this study is substantially higher than the 50 percent excess found when a number of smaller studies were summarized.[1] The reason for this discrepancy is not known. The marked decrease in RR (from 6.0 to 3.1) when patients with liver cirrhosis were excluded suggests that cirrhosis might be an important, or perhaps necessary, intermediary step in a causal pathway from alcohol to liver cancer.[35]

The slight excess number of pancreatic cancers (greater among young patients) (Table 4) needs cautious interpretation in view of the possible confounding effect of smoking[31] and diet.[36] Although reviews of alcohol and pancreatic cancer, in general, have come to the conclusion that a causal association does not exist,[31,37] cohort studies of alcoholics so far have been based on few cases.[1] Larger studies with proper adjustment for confounders are therefore necessary to reveal or exclude a weak association.

The possible role of alcohol in breast cancer has attracted considerable interest recently.[15] We had about 75 percent power (assuming one-sided $\alpha = 0.05$)

to detect an RR of two or higher based on 8.6 expected cases.[38] The RR estimate of 1.2 with an upper CI of 2.2 in hospital-diagnosed alcoholics is not consistent with the finding of a 60-100 percent increased risk among women consuming moderate amounts of alcohol.[2,3] Nor do our results agree with a more than threefold increased risk reported among high consumers (six or more drinks per day) in another prospective study.[39] A recent combined analysis of six case-control studies suggested a threshold effect of alcohol on breast cancer risk; an excess RR of 1.7 was confined to an intake of 40 g alcohol or more per day.[40] Consumption among women diagnosed as alcoholics in Sweden is likely to be substantially higher.[19] The relatively small number of cases and the absence of information on confounders, however, limits interpretation of our finding.

The significantly increased risk of cervical cancer among female alcoholics was not unexpected. Confounding by smoking, sexual habits, dietary pattern, and, perhaps, a lower compliance with cytologic screening programs[31] (which have been highly effective in Sweden[41]) are likely explanations of this excess.

With regard to cancers of the prostate, testis, and bladder, this study provides reassuring evidence by showing risk estimates close to unity. Slightly elevated but nonsignificant SIRs for cancers of the kidney, brain, thyroid, and lymphatic and hematopoietic system were observed, but are unlikely to reflect any causal link.[1]

The decreasing RR with increasing age at follow-up for a number of cancer sites (Table 4) was unexpected. We do not known whether this finding was due to chance alone, to an additive rather than multiplicative effect of alcoholism, which entails decreasing RR as the baseline risk rises at higher ages, to a greater resistance among those who survive longer, or to any other mechanism.

In summary, our study has confirmed and quantified, in a population-based cohort of alcoholics, associations with upper aerodigestive and liver cancers. It also has presented fairly stable risk estimates that indicate no association between alcohol and cancers of the stomach, large bowel, and prostate. Larger studies, however, are necessary to confirm or exclude weak associations, *e.g.*, with cancer of the breast, pancreas, and brain.

Acknowledgement—The authors thank David Hacker and Eric Berger at Information Management Services, Silver Spring, MD, USA, for excellent programming support.

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