

Alcohol and Cancers of the Upper Aerodigestive Tract in Men and Women¹

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Abstract

In order to explore the potential differences in the effect of alcohol in men and women we took advantage of a case-control study of upper aerodigestive tract tumors conducted between 1986 and 1991 in Northern Italy. Five hundred forty-six incident cases of cancer of the oral cavity and pharynx (of whom 81 were women), 410 of cancer of the esophagus (of whom 67 were women), and 388 with cancer of the larynx, (of whom 19 were women) were interviewed. The control group included 2263 inpatients (of whom 557 were women) with acute conditions unrelated to alcohol and tobacco consumption. Among alcohol drinkers, similar odds ratios were detected in men and women. In the highest, well comparable intake category (*i.e.*, ≥ 42 drinks/week in women and 42-55 drinks/week in men), odds ratios were 4.5 and 3.8 for cancer of the oral cavity and pharynx, 3.0 and 4.7 for cancer of the esophagus, and 2.6 and 2.0 for cancer of the larynx in women and men, respectively, as compared to light drinkers. However, for all cancer sites a reduced risk was found among abstaining women but not in abstaining men, when compared with light-to-moderate drinkers. The present study, therefore, does not support the hypothesis that women may be substantially more vulnerable than men to alcohol carcinogenesis, at least at the level of the upper aerodigestive tract. It highlights, however, the importance of the choice of the reference category (*i.e.*, abstainers versus the combination of abstainers and light drinkers) in the comparison of risk estimates across population groups who greatly differ with respect to drinking patterns and other correlates of alcohol consumption.

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Introduction

There is a vast amount of evidence that consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx, esophagus, and larynx (1). The risks are principally due to the content of ethanol (1, 2) and increase with the amount consumed. A weakness of studies on this subject is, however, the relative lack of data on women, on account of the rarity of upper aerodigestive tract malignancies in the female sex. Although women drink less than men, concern has been raised that women may be especially vulnerable to some of the effects of alcohol (3). Women's tolerance to alcohol is lower than men's because they are smaller and because they have a high ratio of fat to water in their bodies (so the alcohol becomes more concentrated) (4). The bioavailability of ethanol may also be greater in women than in men because women have less gastric first-pass metabolism of ethanol (5). Indeed, a few studies (3, 6, 7) show that women incur liver damage and cirrhosis with shorter drinking history and at lower levels of alcohol intake (even accounting for differences in body weight) compared with men. Finally, women may be especially prone to some nutritional deficiencies which are frequent correlates of high ethanol intake and which may also enhance the local adverse effect of alcohol on the mucosa of the upper aerodigestive tract (3, 8).

This article describes the relationship between intake of alcoholic beverages and risk of cancers of the oral cavity, pharynx, esophagus, and larynx. The ascertainment of a substantial number of female cancer cases from an ongoing case-control study in Northern Italy enabled, for the first time, a meaningful comparison of such relationships in men and women.

Materials and Methods

A hospital-based case-control study on tumors of the upper aerodigestive tract has been conducted since 1986. Trained interviewers identified and questioned patients admitted to the hospitals of the area under surveillance (*i.e.*, Pordenone province and the Greater Milan area, Northern Italy) for cancers of the upper aerodigestive tract and for a wide spectrum of other conditions. The general design of the investigation has already been described (9, 10). Cases and controls were not individually matched, but an attempt was made to balance them by sex and age in broad strata. All the interviews were conducted in hospital and approximately 2% of cases and 3% of control subjects refused to be interviewed. This article deals with data collected up to September 1990 in Pordenone and to December 1991 in Milan.

Five hundred forty-six cases with histologically confirmed cancer of the oral cavity and pharynx (of whom 81 were women), 410 cases with cancer of the esophagus (of whom 67 were women), and 388 with cancer of the larynx

Table 1 Distribution of 1344 cases of cancer of the upper aerodigestive tract and 2263 controls by age, smoking habit, alcohol intake, and gender, Italy, 1984–1991

Characteristic ^a	Cancer site						Controls	
	Oral cavity and pharynx		Esophagus		Larynx		Females No. (%)	Males No. (%)
	Females No. (%)	Males No. (%)	Females No. (%)	Males No. (%)	Females No. (%)	Males No. (%)		
Age (yrs)								
≤49	15 (18.5)	107 (23.0)	11 (16.4)	44 (12.8)	4 (21.1)	35 (9.5)	145 (26.0)	528 (31.0)
50–59	32 (39.5)	159 (34.2)	12 (17.9)	121 (35.3)	5 (26.3)	120 (32.5)	152 (27.3)	578 (33.9)
60–69	28 (34.6)	160 (34.4)	27 (40.3)	136 (39.7)	8 (42.1)	184 (49.9)	165 (29.6)	446 (26.1)
≥70	6 (7.4)	39 (8.4)	17 (25.4)	42 (12.2)	2 (10.5)	30 (8.1)	95 (17.1)	154 (9.0)
Smoking habit								
Never smoker	33 (40.7)	12 (2.6)	35 (52.2)	20 (5.8)	2 (10.5)	19 (5.2)	399 (71.6)	404 (23.7)
Ex-smoker	7 (8.6)	105 (22.6)	5 (7.5)	90 (26.2)	2 (10.5)	108 (29.3)	52 (9.3)	527 (30.9)
Cigar or pipe smoker only	0 (0.0)	9 (1.9)	0 (0.0)	16 (4.7)	0 (0.0)	1 (0.3)	0 (0.0)	22 (1.3)
Cigarette smoker								
≤14 cigarettes/day	21 (25.9)	73 (15.7)	9 (13.4)	51 (14.9)	2 (10.5)	40 (10.8)	61 (11.0)	253 (14.8)
≥15 cigarettes/day	20 (24.7)	266 (57.2)	18 (26.9)	166 (48.4)	13 (68.4)	201 (54.5)	45 (8.1)	500 (29.3)
Alcohol intake (drinks/week) ^b								
0	12 (14.8)	25 (5.5)	18 (26.9)	23 (6.8)	1 (5.3)	48 (13.2)	197 (35.4)	145 (8.5)
1–13	15 (18.5)	6 (1.3)	14 (20.9)	11 (3.3)	3 (15.8)	18 (4.9)	136 (24.4)	135 (7.9)
14–27	29 (35.8)	23 (5.0)	25 (37.3)	31 (9.2)	9 (47.4)	50 (13.7)	187 (33.6)	403 (23.7)
28–41	13 (16.1)	53 (11.6)	7 (10.5)	61 (18.1)	3 (15.8)	54 (14.8)	28 (5.0)	412 (24.2)
42–55	4 (4.9)	57 (12.4)	2 (3.0)	59 (17.5)	1 (5.3)	51 (14.0)	6 (1.1)	202 (11.9)
≥56	8 (9.9)	295 (64.3)	1 (1.5)	152 (45.1)	2 (10.5)	144 (39.5)	3 (0.5)	406 (23.8)

^a Total sample size varies with the number of cases and controls with incomplete information.

^b One drink corresponds to 150 cc of wine, 330 cc of beer and 30 cc of spirits (*i.e.*, approximately 12 g of ethanol).

(of whom 19 were women) were interviewed. All cancer cases had their diagnoses within 6 months before the date of interview and most (90%) within 2 months, thus minimizing losses caused by patient death and disability. Median age was 60 years in both men and women (Table 1).

The control group included 2263 subjects, of whom 557 were women. None of these patients had been admitted to hospital for malignant tumors, diabetes, digestive or respiratory tract diseases, or any condition causally related to alcohol or tobacco consumption or which might have resulted in long-term modification of diet. The main diagnostic categories were: traumas (32%); nontraumatic orthopedic disorders (19%); acute surgical conditions, including plastic surgery (27%); eye disorders (11%); and other illnesses such as diseases of the ear, nose, skin, or teeth (11%). Median age (years) was 55 in men and 59 in women (Table 1).

A structured questionnaire was used to obtain information on sociodemographic factors, life-style habits including smoking, coffee drinking, and frequency of intake of 40 indicator foods. The part of the questionnaire relating to alcohol habits included the number of days per week that most common alcohol-containing beverages (wine, beer, and hard liquors) were consumed, the average lifelong number of drinks per day before the onset of the symptoms or signs of the disease which led to the current hospital admission, and the duration of the habit in years. Abstainers were defined as subjects who had never drunk alcohol regularly (*i.e.*, <1 drink/week lifelong). Taking into account the different alcohol concentration, one drink corresponded to approximately 150 cc of wine, 330 cc of beer, and 30 cc of hard liquors (*i.e.*, about 12 g of ethanol). Total intake per week is presented, but the number of drinks can be easily

translated into daily consumption since 97% of men and 94% of women (abstainers excluded) drank on a daily basis.

OR,³ together with their 95% approximate CI, according to weekly total alcohol consumption were computed by means of unconditional multiple logistic regression equations with maximum likelihood fitting (11, 12). At variance with men, few women reported 42 drinks or more per week (Table 1). Also the median intake in the group of subjects who reported ≥42 drinks per week differed markedly (49 drinks in women and 56 in men). Thus, highest open-ended categories were defined differently in women (≥42) and men (≥56). Allowance was made for age, study center, and smoking habit, on three levels: (a) lifetime nonsmokers; (b) ex-smokers and smokers of fewer than 15 cigarettes per day; (c) smoker of 15 or more cigarettes per day, pipe or cigar. Ex-smokers were defined as those who had stopped smoking at least 1 year before diagnosis. Men were, on the average, taller than women (median height 170, and 160 cm, respectively) and heavier (72 and 62 kg, respectively) but equally educated (median age of schooling, 5 years in both sexes). Terms for these variables, body mass index (weight, kg/height/m²) and average weekly intake of fresh fruit and vegetables and two micronutrients (*i.e.*, β-carotene and ascorbic acid) were also included into the regression model.

Finally, in order to account for the low number of abstainers in the present series, and the lack of substantial risk elevation up to at least 27 drinks per week, the comparison of OR in men and women was replicated with two

³ The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 OR and 95% CI^a of cancer of the upper aerodigestive tract by level of total alcohol intake and gender, Italy, 1984–1991

Total alcohol intake (drinks/week) ^b	Cancer site ^b					
	Oral cavity and pharynx		Esophagus		Larynx	
	Females	Males	Females	Males	Females	Males
0 ^c	1	1	1	1	1	1
1–13	1.76 (0.78–4.00)	0.28 (0.11–0.71)	1.28 (0.60–2.72)	0.60 (0.27–1.29)	8.02 (0.73–88.22)	0.51 (0.27–0.96)
14–27	2.08 (1.01–4.30)	0.31 (0.17–0.58)	1.60 (0.82–3.11)	0.45 (0.25–0.81)	11.51 (1.33–99.66)	0.35 (0.22–0.56)
28–41	3.94 (1.51–10.22)	0.60 (0.35–1.04)	3.45 (1.23–9.67)	1.03 (0.60–1.76)	11.33 (0.98–130.23)	0.38 (0.24–0.61)
42–55 ^d	8.82 (2.70–28.82)	1.17 (0.68–2.04)	4.38 (0.98–19.45)	2.25 (1.29–3.93)	26.54 (1.86–378.92)	0.76 (0.47–1.25)
≥56		2.39 (1.45–3.93)		3.69 (2.19–6.22)		1.06 (0.68–1.65)

^a From multiple logistic regression including terms for age, study center and smoking habit. Numbers in parentheses, confidence intervals.

^b One drink corresponds to 150 cc of wine, 330 cc of beer, and 30 cc of spirits (*i.e.*, approximately 12 g of ethanol).

^c Reference category.

^d ≥42, in women.

Table 3 OR and 95% CI^a of cancer of the upper aerodigestive tract by level of alcohol intake and gender, Italy, 1984–1991

Alcohol intake (drinks/week) ^b	Cancer site					
	Oral cavity and pharynx		Esophagus		Larynx	
	Females	Males	Females	Males	Females	Males
0	0.51 (0.26–1.01)	3.27 (1.82–5.86)	0.68 (0.37–1.25)	2.07 (1.19–3.62)	0.10 (0.01–0.80)	2.60 (1.67–4.05)
1–27 ^c	1	1	1	1	1	1
28–41	2.00 (0.89–4.52)	1.97 (1.21–3.20)	2.34 (0.89–6.15)	2.13 (1.39–3.25)	1.08 (0.22–5.20)	0.98 (0.66–1.46)
42–55 ^d	4.48 (1.53–13.13)	3.83 (2.34–6.29)	2.98 (0.70–12.66)	4.66 (2.97–7.33)	2.56 (0.37–17.66)	1.98 (1.30–3.03)
≥56		7.79 (5.06–12.01)		7.65 (5.10–11.47)		2.76 (1.93–3.95)

^a From multiple logistic regression including terms for age, study center, and smoking habit. Numbers in parentheses, confidence intervals.

^b One drink corresponds to 150 cc of wine, 330 cc of beer, and 30 cc of spirits (*i.e.*, approximately 12 g of ethanol).

^c Reference category.

^d ≥42, in women.

different reference categories (abstainers and moderate drinkers). All analyses were repeated also for individuals below age 60 and above and for intake of wine only, by far the most popular alcoholic beverage in the study areas. Sixty-six % of women and 90% of men reported to drink wine, while 64 and 75%, respectively, reported drinking only wine.

Results

Table 1 shows the distribution of cases of cancers of the upper aerodigestive tract and controls according to age, smoking habit, and total alcohol intake, separately in the two sexes. The proportion of subjects in each drinking category differed markedly by sex, with 1.6% of females controls but 35.7% of male controls reporting 42 or more alcoholic drinks per week (median weekly intake in control subjects: 7 drinks in women; 28 in men).

OR are presented in Tables 2 and 3. In Table 2, abstainers were the reference category and different risk patterns emerged in the two sexes. Whereas for all three cancer sites, risk in women raised steeply from the lowest levels of alcohol intake, in men no significantly elevated OR emerged up to ≥42 drinks/week, with respect to cancer of the esophagus (OR = 2.3; 95% CI: 1.3–3.9), and up to ≥56

with respect to cancer of the oral cavity and pharynx (OR = 2.4; 95% CI: 1.5–3.9) (Table 2). No elevation in the risk of laryngeal cancer could be detected in drinking men as compared to abstainers. As a consequence of this U-shaped curve in men, OR seemed severalfold more elevated in women for each level of alcohol intake. The most extreme sex-related difference was thus seen for cancer of the larynx (Table 2).

Since, however, the risk curves were, in both sexes, relatively flat in light-to-moderate drinkers, the comparison between sexes was replicated taking people who reported 1–27 drinks per week (*i.e.*, 24% of men and 55% of women) as the reference category (Table 3). Such a different approach substantially reduced the apparent sex-related difference in the effect of alcohol and suggested that, at least among drinking individuals, similar significant trends of increasing risk with increasing levels of alcohol consumption can be detected in men and women. In the highest, well comparable intake category (*i.e.*, ≥42 drinks/week in women and 42–55 drinks/week in men) OR were, for instance, 4.5 and 3.8 for cancer of the oral cavity and pharynx, 3.0 and 4.7 for cancer of the esophagus, and 2.6 and 2.0 for cancer of the larynx, in women and men, respectively (Table 3). Conversely, for all three cancer sites a

significant interaction between sex and cancer risk emerged among abstainers. Whereas abstaining women were at reduced, albeit nonsignificant, risk of cancers of the upper aerodigestive tract, the few abstaining men were at 2-to-3-fold significantly elevated risk as compared to drinkers of ≤ 27 drinks/week (Table 3).

Allowance for education and body mass index left alcohol-related OR unmodified. Adjustment for intake of fresh fruit and vegetables and two micronutrients (β -carotene and ascorbic acid), as indicators of a balanced diet, also did not produce changes in the association of alcohol and cancer risk and the comparison between the two sexes (data not shown). Only with respect to cancer of the esophagus, adjustment for intake of selected micronutrients somewhat altered OR in nondrinking women (from 0.7 to 1.1) and in women who reported 28–41 alcoholic drinks per week (from 2.3 to 1.3).

Analyses in Tables 2 and 3, when replicated in men and women younger and older than age 60, achieved very similar results in the two age groups. For cancer of the oral cavity and pharynx and esophagus (but not larynx) OR in abstainers, as compared to light-to-moderate drinkers, were somewhat higher in men younger than age 60 (3.7 for cancer of the oral cavity and pharynx, and 2.6 for cancer of the esophagus) than in men 60 years old or older (2.2 and 1.5, respectively) (data not shown). OR were also very similar when the comparison was restricted to major disease categories in the control group (*i.e.*, traumas, orthopaedic conditions, surgical conditions, and other).

Discussion

The present study provides evidence that, among individuals who drink alcoholic beverages, the association between total alcohol intake and risk of cancers of the upper aerodigestive tract is similar in men and women. However, abstaining women had a lower cancer risk, as compared to light-to-moderate drinkers, whereas abstaining men had an appreciably increased risk. The choice of the reference category is confirmed as a key issue in any risk-relationship analysis, but, especially, in the study of the effect of alcohol (1, 13).

Similar results, albeit infrequently discussed, emerged rather consistently from several case-control investigations on alcohol and cancers of the upper aerodigestive tract. Out of 19 case-control investigations concerning cancer of the oral cavity and pharynx (9, 14–31), 6 showed a U-shaped curve, with OR below 1 in light drinkers as compared to abstainers (9, 17, 20, 23, 28, 32), chiefly in males. The same was often observed for cancer of the larynx, with OR below 1 in some categories of light drinkers in 8 (9, 20–22, 25, 33–35) of 16 investigations (9, 15, 20–22, 25, 33–42), and for cancer of the esophagus, with OR below 1 in 8 (9, 17, 20, 43–47) of 12 case-control studies (17, 20, 43–45, 48–54). Lower cancer risk in moderate drinkers were seen also in some investigations where light drinkers were combined to abstainers in the reference category (9, 32). It is plausible that some U-shaped curves for alcohol intake were concealed, in a few studies, by broad reference category [for instance, <4 drinks/day in Brugère *et al.* (22)].

Interestingly, such U-shaped risk pattern seems more frequent in studies from Latin countries, where wine is the most popular alcoholic beverage and daily consumption of alcohol at meals is very common. In the study by Blot *et al.* (29) lowered OR were detected only for wine in moderate

consumers (<30 drinks/week, after allowance for other alcoholic beverages) of both sexes.

Whereas the subdivision of alcohol consumption in too many categories may lead to undesirable erratic behavior of the risk estimates (11), it seems that reduced risks in light-to-moderate drinkers are a relatively systematic phenomenon, at least in case-control investigations. Bias and confounding may play some role. In fact, in case-control studies, selective misclassification as lifelong abstainers of a few diseased individuals who had stopped drinking cannot be totally excluded. Prospective studies, which may be less subject to these problems, are not very helpful since they either deal with cohorts of alcoholics or included too few events to study the dose-response curve of alcoholic intake in detail (1). For oral cancer, but not for esophageal cancer, Boffetta and Garfinkel (55) found OR below 1 (0.7) in men who drank up to 1 drink per day. In another prospective study, Kato *et al.* (56) showed a U-shaped effect of the intake of beer, but not total alcohol, on the risk of cancer of the oral cavity, pharynx, esophagus, and larynx combined.

More general differences between abstainers and drinkers are also conceivable, but extremely difficult to control in the analyses. Some studies have shown a higher risk of certain diseases in abstainers compared with moderate drinkers (57–59) and, in the present study population, heavy alcohol consumption was associated with a diet poorer in several aspects, including lower consumption of fresh fruit and vegetables and higher intake of fat (60). With respect to the possibility of dietary habits exerting a confounding or modifying effect on the association between alcohol and risk of upper aerodigestive tract cancer (or on the comparison between the two sexes) we were able to allow for average weekly intake of fresh fruit and vegetables and β -carotene and ascorbic acid. This had, however, a negligible influence on the present results.

Some limitations of the present study must also be borne in mind in the interpretation of its findings. The choice of hospital controls, for instance, may have resulted in selection bias. However, great attention was paid to obtain cases and controls from the same catchment areas and to ensure that no inconsistencies in the results existed in either sex across the major diagnostic categories of controls, and, particularly, between trauma patients and the other control subjects. The replication of the findings between the two study areas (one of which is a large town, the other is partly rural), in addition to the very high participation rate, gives further credibility to the findings. It is known that alcohol intake is reported with reasonable accuracy, at least among nonalcoholics (61, 62), and is socially accepted in Italy, even for women. Some concern can remain about potential differences in the reliability of self-reports of alcohol consumption in men and women. A selective underreport in women would have led, if anything, to an overestimation of OR in them and, therefore, an artifactual difference in the effect of alcohol in the two sexes. Finally, the very broad confidence intervals of OR in women, particularly with respect to cancer of the larynx, are difficult to avoid, on account of the rarity of tumors of the upper aerodigestive tract in the female sex.

In conclusion, the findings of the present study cast serious doubts on the hypothesis that women may be substantially more vulnerable than men to alcohol carcinogenesis, at least at the level of the upper aerodigestive tract where the main effect of alcohol is probably a local one. Similar relative risk estimates in the two sexes actually

correspond to a greater absolute increase in risk due to alcohol in men than in women, since the absolute underlying risk is higher in the male sex.

The present data help, moreover, to elucidate further an important problem in the study of alcohol-related health effects: the choice of the reference category. Among drinkers risk increases are consistently seen for increasing levels of alcohol intake in both sexes. Abstainers, however, besides being often too few, are not necessarily the lowest-risk category, at least in retrospective studies. This may particularly apply to men in countries where substantial chronic intakes of alcoholic beverages (mainly wine) are the norm. Therefore, the use of abstainers or of a combination of abstainers and light drinkers as the reference category can produce different results and hamper the comparability of risk estimates across population groups who greatly vary with respect to drinking patterns and other correlates of alcohol consumption.

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