

BRIEF COMMUNICATION

Cancer of the Oral Cavity and Pharynx in Nonsmokers Who Drink Alcohol and in Nondrinkers Who Smoke Tobacco

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In developed countries, cancer of the oral cavity and pharynx is rare in individuals who do not smoke and do not drink alcohol. Few studies, however, have included large enough groups of case and control subjects to provide useful information on the effect of alcohol consumption in the absence of tobacco smoking and the effect of tobacco smoking in the absence of alcohol consumption (1).

A multicenter, population-based, case-control study (2) included 49 male and 53 female nonsmoking case subjects from the United States. In that study, males who were nonsmokers and heavy drinkers (≥ 30 drinks per week) had an odds ratio (OR) of 5.8 for cancer of the oral cavity and pharynx, but there was a weaker association for women because of their lower consumption of alcohol. A hospital-based U.S. study (3) of nonsmokers who had cancer of the oral cavity included 73 male and 100 female subjects. That study found that in nonsmoking men, there was a strong relationship between consumption of alcohol and cancer of the oral cavity and pharynx, with an OR of 4.4 for men who had seven drinks or more per day. In females, however, the pattern was inconsistent, but the OR was 2.6 for women who had seven drinks or more per day. In an Italian study (4) of cancer of the oral cavity and pharynx that included six male and 21 female nonsmoking case subjects, the OR was 2.2 for individuals who had 56 drinks or

more per week when compared with individuals who were nondrinkers or moderate drinkers. In another Italian study (5) that included 13 nonsmoking individuals who had oral cancer, no consistent risk trend was observed.

Information on cancer of the oral cavity and pharynx in lifelong nondrinkers is more scarce (6). An Italian case-control study (4) that included 14 male and five female case subjects who were nondrinkers found that nondrinkers who were heavy smokers of tobacco had a statistically significant OR of 12.9 for cancer of the oral cavity and pharynx. A large U.S. study (2) provided data on the risk of cancer of the oral cavity and pharynx in smokers of tobacco who were also nondrinkers or occasional drinkers (< 1 drink per week); the OR reached 7.4 in males who were heavy smokers, and the OR reached 2.2 in females who were heavy smokers.

In this brief communication, we report results of a large study of cancer of the oral cavity and pharynx that we conducted in Italy (province of Pordenone and Rome) and Switzerland (Vaud Canton) during the period from 1992 through 1997. Overall, this study included 754 case subjects with incident, histologically confirmed cancer of the oral cavity and pharynx and 1775 control subjects who were in the hospital for acute non-neoplastic conditions that were unrelated to alcohol consumption or tobacco use. Sixty case subjects and 692 control subjects were "never smokers," and 32 case subjects and 224 control subjects were "never drinkers" (Table 1). These groups were the subjects of the present communication. Control subjects belonged to the following diagnostic categories: traumas, mostly fractures and sprains (28%); other orthopedic disorders, such as low back pain and disc disorders (26%); acute surgical conditions (25%); eye diseases (14%); and other miscellaneous diseases, such as skin and dental conditions (8%). About 5% of case and control subjects approached during their hospital stay refused to be interviewed.

The questionnaire asked for information on the following topics: sociodemographic characteristics, physical activity, body size measurements at various ages, a problem-oriented personal medical history, and a family history of cancer.

A validated food-frequency questionnaire was also administered. In the main questionnaire, the section on smoking habit included questions on smoking status ("never smoker," "ex-smoker," or "current smoker"), number of cigarettes and/or cigars habitually smoked per day, grams of tobacco for pipe smoking, age at which the individual started smoking, duration of the habit, and years since stopping for "ex-smokers." "Ever smokers" were subjects who had smoked at least one cigarette per day for at least 1 year. For alcohol consumption, the weekly number of drinks of wine (125 mL), beer (330 mL), grappa (30 mL; a typical Italian liquor), amari (30 mL), digestives (30 mL), and spirits (30 mL) was obtained from the study subjects. "Never drinkers" were individuals who had abstained from drinking any alcoholic beverage throughout their life. "Ex-smokers" and "ex-drinkers" were individuals who had abstained from any type of smoking or drinking for at least 12 months at the time of cancer diagnosis or interview (for control subjects).

ORs and the corresponding 95% confidence intervals (CIs) were computed with the use of unconditional logistic regression analysis (7), including terms for study center, sex, age, and amount of education. All *P* values reported are two-sided.

For nonsmokers who drank alcohol, the OR was not increased by 35 drinks or fewer per week but rose to 5.0 for 35-55 drinks per week and 5.3 for 56 drinks or more per week (Table 2). The trend in risk was highly statistically significant. When drinkers who had 35 drinks or more per week were

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Table 1. Distribution of nonsmoking and nondrinking case subjects with cancer of the oral cavity and pharynx and nonsmoking and nondrinking control subjects by age, education, study center, and sex (1992–1997)

	No. of nonsmoking subjects				No. of nondrinking subjects			
	Male		Female		Male		Female	
	Case	Control	Case	Control	Case	Control	Case	Control
Age, y								
<50	6	102	8	85	—	28	6	58
50–59	5	121	12	104	3	23	7	40
60–69	6	96	13	128	5	16	6	36
≥70	3	27	7	29	2	12	3	11
Education, y								
<7	7	135	22	253	2	17	6	70
7–11	6	115	8	66	4	28	9	53
≥12	7	96	10	27	4	34	7	22
Study center								
Italy	14	259	35	324	7	46	13	122
Switzerland	6	87	5	22	3	33	9	23
Total	20	346	40	346	10	79	22	145

compared with nondrinkers, the OR seemed to be more elevated in women (OR = 14.4; 95% CI = 2.2–92.7) than in men (OR = 2.4; 95% CI = 0.5–12.1), but the risk estimates were not statistically heterogeneous (Wald $\chi_1^2 = 1.23$; $P = .27$).

For never drinkers who were current smokers of fewer than 25 cigarettes per day, the OR was 1.5; however, for never drinkers who were heavy smokers of tobacco, the OR rose to 7.2. When current smokers (any number of cigarettes) were compared with never smokers, the ORs were similar for men (OR = 1.2;

95% CI = 0.1–9.8) and women (OR = 1.9; 95% CI = 0.6–6.0).

This study thus confirms that there is a statistically significant risk of cancer of the oral cavity and pharynx associated with heavy alcohol intake in never smokers and associated with heavy tobacco smoking in never drinkers. Tobacco smoke contains a number of carcinogenic substances and comes in direct contact with the oral and pharyngeal mucosa (8). Consequently, the increased risk of cancer of the oral cavity and pharynx associated with tobacco use in never drinkers is not surprising.

The association with alcohol intake in never smokers is more difficult to interpret, because ethanol per se is not a proven carcinogen in animal experiments (1). For nonsmokers, there is a positive association with alcohol use; however, this does not imply per se that alcohol is a complete carcinogen. The oral cavity and pharynx, in fact, are exposed to other carcinogens, including those of dietary (9) or viral (10) origin, and alcohol may enhance the adverse effect of other carcinogenic agents in nonsmokers. As suggested before (11,12), women may be more vulnerable than men to alcohol-induced carcinogenesis.

Table 2. Odds ratio (OR) of cancer of the oral cavity and pharynx and 95% confidence interval (CI) for alcohol-drinking nonsmokers and tobacco-smoking nondrinkers (1992–1997)

	No. of subjects		OR*	95% CI
	Case	Control		
Alcohol consumption				
Never drinkers	16	139	1†	
Current drinkers				
<21 drinks/wk	23	334	0.8	(0.4–1.6)
21–34 drinks/wk	4	112	0.8	(0.2–2.7)
35–55 drinks/wk	7	47	5.0	(1.5–16.1)
≥56 drinks/wk	3	18	5.3	(1.1–24.8)
χ_1^2 trend			6.2; $P = .01$	
Ex-drinkers	7	42	2.0	(0.7–5.4)
Smoking status‡				
Never smokers	16	139	1†	
Current smokers‡				
<25 cigarettes/d	6	44	1.5	(0.5–4.6)
≥25 cigarettes/d	3	5	7.2	(1.1–46.6)
χ_1^2 trend			3.2; $P = .07$	
Ex-smokers	7	33	2.2	(0.8–6.2)

*Estimates from logistic regression equations, including terms for study center, age, sex, and education.

†Reference category.

‡One control subject who smoked a pipe only and two control subjects who smoked an unknown number of cigarettes are not included.

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NOTES

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