

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

In their recent brief communication, Talamini et al. (1) reported on the risk of developing cancer of the oral cavity and pharynx in nonsmokers who drink alcohol and in nondrinkers of alcohol who smoke tobacco. Although the data were quite sparse (60 never-smoking and 32 never-drinking case subjects), the authors concluded that there was a statistically significant increased risk of cancer in these sites associated with heavy alcohol intake in nonsmokers and with heavy tobacco smoking in nondrinkers. In this letter, we present solid evidence that the same conclusion holds true for esophageal cancer. The results shown in Table 1 were gathered from a pooled analysis of five hospital-based case-control studies of squamous cell carcinoma of the esophagus conducted from 1986 through 1992 in the following four countries in South America: Brazil (2),

Uruguay (3), Argentina (4), and Paraguay (5). These studies were coordinated by the International Agency for Research on Cancer (Lyon, France), and they were carried out with the same research protocol and data collection procedures, thus making the studies suitable for a pooled analysis. Overall, the pooled data included a total of 830 incident case subjects with esophageal cancer and 1779 control subjects. Control subjects were individually matched to the case subjects with respect to the admitting hospital, age ( $\pm 5$  years), and sex.

There were 144 case subjects and 630 control subjects who described themselves as being life-long nonsmokers and 179 case subjects and 776 control subjects who reported themselves as being life-long nondrinkers of alcohol. Table 1 shows the estimated odds ratios (ORs) and 95% confidence intervals (CIs) of esophageal cancer linked to alcohol intake among nonsmokers and linked to cigarette smoking among nondrinkers. All logistic regression models were adjusted by age group, sex, admitting hospital, and years of schooling.

Consistent with the brief communication by Talamini et al. (1), for nonsmokers who drank alcohol, the OR was not markedly increased for a consump-

**Table 1.** Odds ratios and 95% confidence intervals of squamous cell carcinoma of the esophagus for alcohol drinking in nonsmokers and cigarette smoking in nondrinkers participating in five case-control studies in South America (1986-1992)

Exposure	No. of subjects		OR (95% CI)*
	Case	Control	
Alcohol consumption among nonsmokers, mL of pure ethanol per day			
Never	91	423	1.0 (referent)
Ever	53	207	1.76 (1.12-2.79)
Amount for ever drinkers			
1-24	14	65	1.43 (0.72-2.84)
25-49	12	43	1.61 (0.75-3.48)
50-149	14	69	1.77 (0.85-3.67)
$\geq 150$	9	18	5.70 (2.11-15.44)
Unknown	4	12	
<i>P</i> for trend (two-sided)			.002
Cigarette smoking among nondrinkers, number of cigarettes per day			
Never	91	423	1.0 (referent)
Ever	88	353	2.22 (1.45-3.41)
Amount for ever smokers			
1-7	21	120	1.45 (0.81-2.60)
8-14	15	62	2.57 (1.23-5.36)
15-24	32	98	3.39 (1.89-6.06)
$\geq 25$	16	62	2.49 (1.23-5.36)
Unknown	4	11	
<i>P</i> for trend (two-sided)			<.001

\*Odds ratios (ORs) were adjusted for hospital, age group, sex, and years of schooling. CI = confidence interval.

tion of pure ethanol that was less than 150 mL per day, but it increased almost sixfold for amounts exceeding 150 mL or more of ethanol per day. The trend in risk was highly statistically significant ( $P = .002$ ). It is interesting that this effect was much stronger among males than it was among females. Among males, the ORs (95% CIs) were 1.78 (0.42–7.54), 3.27 (0.57–18.78), 5.49 (1.82–16.57), and 12.62 (3.37–47.16) for 1–24 mL, 25–49 mL, 50–140 mL, and 150 mL or more of pure ethanol per day, respectively ( $P$  for trend  $<.001$ ). For females, the association with alcohol intake was weak and not statistically significant.

For nondrinkers who smoked cigarettes, the OR was increased almost threefold for smoking as few as eight to 14 cigarettes per day, 3.4-fold for smoking 15–24 cigarettes per day, and 2.5-fold for smoking 25 cigarettes or more per day, also with a highly statistically significant trend in risk ( $P <.001$ ). As with alcohol, this association was stronger among males in whom the corresponding ORs (95% CIs) were 1.22 (0.39–3.80), 3.75 (1.44–9.79), 5.03 (2.05–12.31), and 3.73 (1.39–10.02) ( $P$  for trend  $<.001$ ). Among females, the association with cigarette smoking was weak, and the trend did not reach statistical significance.

These results add precision to the estimates by Talamini et al. (1) and further indicate that, in nondrinkers, even moderate exposure to tobacco smoking significantly increases the risk of esophageal cancer. These findings complete the epidemiologic picture of the independent etiologic role of alcohol drinking and tobacco smoking in the development of cancers of the upper aerodigestive tract.

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## NOTES

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## RESPONSE

We thank Drs. Castellsagué and Muñoz for their interest in our work (1) and take this opportunity for reconsidering, as they have done, the risk of esophageal cancer in nonsmokers who drink alcohol and alcohol abstainers who smoke tobacco; we use the combined dataset of two case-control studies on esophageal cancer conducted in the greater Milan area (2–4) and the Pordenone province (5) of northern Italy.

Overall, the dataset included 410 case subjects (343 men and 67 women) with incident, histologically confirmed esophageal cancer who were admitted to major teaching and general hospitals of the study areas from 1984 through 1992. Control subjects were admitted to the same network of hospitals as case subjects for acute, non-neoplastic conditions. Diseases related to tobacco use or alcohol abuse were excluded as causes of hospital admission but not as comorbidities. Fifty-five case subjects (20 men and 35 women) and 275 control subjects (100 men and 175 women) described themselves as life-long never smokers, and 40 case subjects (22 men and 18 women, all from Milan) and 151 control subjects (79 men and 72 women) described themselves as alcohol abstainers. These subgroups are the subject of the present communication.

We used a validated (6) questionnaire, including information on smoking status, number of cigarettes and/or pipe and cigars habitually smoked per day, age at smoking initiation, duration of smoking, and time since smoking cessation for exsmokers. Total alcohol consumption was defined as the mean number of alcoholic beverages consumed per week. One drink corresponded to approximately 120 mL of wine, 330 mL of beer, and 30 mL of spirits (i.e., about 12 g of ethanol). Odds ratios (ORs) and corresponding 95% confidence intervals (CI) were computed by unconditional multiple logistic regression, including terms for

**Table 1.** Odds ratios of esophageal cancer and corresponding 95% confidence intervals for alcohol-drinking nonsmokers and tobacco-smoking nondrinkers in Italy, 1984–1992\*

	No. of subjects		OR (95% CI)
	Case	Control	
Alcohol consumption among nonsmokers, drinks/week			
Never drinkers	12	76	1.0 (referent)
<21	21	116	1.2 (0.5–2.6)
21–34	10	51	1.6 (0.6–4.3)
35–55	5	18	2.0 (0.6–7.2)
≥56	7	14	5.5 (1.4–21.3)
$\chi^2_{\text{trend}} \dagger = 5.20, P = .02$			
Smoking status among nondrinkers			
Never smokers	12	76	1.0 (referent)
Current smokers, cigarettes/day			
<20	5	26	1.3 (0.4–4.2)
≥20	20	22	7.5 (2.7–20.4)
$\chi^2_{\text{trend}} \dagger = 15.31; P <.001$			
Exsmokers	3	27	0.8 (0.2–3.4)

\*OR = odds ratio, CI = confidence interval. Estimates from multiple logistic regression equations, including terms for center, age, sex, and years of education. All  $P$  values are two-sided.

†Chi-square for trend, one degree of freedom.

study center, age, sex, and educational years.

For nonsmokers who drank alcohol, the OR increased significantly ( $P = .02$ ) with the increase in alcohol consumption and was 5.5 (95% CI = 1.4–21.3) for 56 drinks or more per week compared with nondrinkers (Table 1). The risk increase seemed steeper for women (OR for  $\geq 35$  drinks/week = 5.5; 95% CI = 1.0–30.7) than for men (OR for  $\geq 56$  drinks/week = 1.7; 95% CI = 0.3–10.0), but consumption ranges varied substantially and the risk estimates were not statistically heterogeneous between sexes (data not shown).

For never drinkers who were current smokers of fewer than 20 cigarettes per day, the OR was 1.3 (95% CI = 0.4–4.2); however, for never drinkers who were heavy tobacco smokers, the OR rose to 7.5 (95% CI = 2.7–20.4) (Table 1). ORs for smokers of 20 cigarettes per day or more were similar for the two sexes (i.e., OR = 8.1 [95% CI = 1.8–7.0] for men and OR = 6.3 [95% CI = 1.4–29.0] for women [data not shown]).

Our present findings thus confirm and further quantify the observation that, in developed countries, alcohol is the most important risk factor for esophageal cancer in nonsmokers, and to-

bacco is most important in alcohol abstainers (7).

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## NOTES

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