eters *(1)*. Any one of these devices can be combined with the transjugular intrahepatic portal vein catheter technique. This hypothesis seems to us worthy of testing in clinical trials.

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Re: Alcohol Dehydrogenase 3 Genotype and Risk of Oral Cavity and Pharyngeal Cancers

Recently, Harty et al. *(1)* reported in the Journal that alcohol dehydrogenase type 3 (ADH_3), a polymorphic enzyme that metabolizes ethanol to acetaldehyde, modified the risk of development of oropharyngeal cancers in a cohort of Puerto Ricans who had high levels of alcohol consumption.

We investigated whether these findings could be reproduced in another population, from part of a hospital-based, case–control study performed in France among Caucasians *(2)*. In our study, only case subjects (n = 165) with histologically confirmed squamous carcinoma of the oral cavity and pharynx were included. Control subjects (n = 234) were individuals without a history of cancer and were frequency matched for sex, age, and hospital.

The main conditions diagnosed among control subjects were rheumatologic (n = 74; 32%), infectious and parasitic (n = 24; 10%), respiratory (n = 21; 9%), cardiovascular (n = 19; 8%), and digestive (n = 14; 7%) diseases as well as traumatic injuries (n = 12; 5%). Severe liver diseases were exclusion criteria for both case subjects and control subjects.

ADH_3 genotypes were determined with the use of a polymerase chain reaction DNA amplification assay *(3)* for 68 patients with oral cavity cancer, 51 patients with pharyngeal cancer, and 167 control subjects. Genotype determinations were performed by investigators who were blinded to the source of the specimens.

Lifetime use of tobacco (cigarettes, cigars, or pipe) and alcohol consumption were recorded during a personal interview conducted by seven trained interviewers. Alcohol beverages were converted into grams of pure ethanol, and the average daily consumption was calculated by dividing the cumulative lifetime consumption by the overall duration of drinking. Odds ratios (ORs) were calculated by unconditional logistic regression, including sex, age, and smoking as confounding factors. The interaction between ADH_3 genotype (ADH_3^{1-1} versus ADH_3^{1-2} or ADH_3^{2-2}) and levels of daily alcohol consumption was studied to test the equality of the effect of ADH_3 genotypes across the drinking levels *(4)*. To this end, the average daily consumption of alcohol was divided according to the approximated quartile distribution observed among the control subjects.

The risk of oropharyngeal cancer associated with the ADH_3^{1-1} genotype, compared with the ADH_3^{1-2} and the ADH_3^{2-2} genotypes combined, was slightly, although not significantly, increased (OR = 1.4; 95% confidence interval = 0.8–2.3) (Table 1). The risk of cancer rose significantly with increased daily consumption of alcohol (χ^2 two-

Table 1. Number of case and control subjects* and odds ratios† (95% confidence intervals) of oropharyngeal cancer according to ADH_3 genotypes and alcohol consumption‡

	Average consumption of ethanol§				
ADH_3 genotype	⩽40 g/day	41–80 g/day	81–120 g/day	>120 g/day	Total§,‖
ADH_3^{1-2} and ADH_3^{2-2}	1 (referent) 6/26	2.3 (0.8–7.0) 18/35	3.4 (1.0–10.9) 13/19	5.8 (1.9–17.6) 29/22	1 (referent) 66/102
ADH_3^{1-1}	1.7 (0.5–5.5) 10/23	3.4 (1.1–10.9) 14/19	5.3 (1.3–21.6) 8/7	6.3 (1.8–21.4) 17/11	1.4 (0.8–2.3) 49/60
Total¶	1 (referent) 16/49	2.2 (1.0–4.6) 32/54	3.2 (1.3–7.5) 21/26	4.8 (2.2–10.7) 46/33	

*Data on smoking (cigarettes, cigars, pipe) and/or alcohol exposure were missing for four case subjects and five control subjects.

†Odds ratios are adjusted for sex, age, and exposure to smoking (cigarettes, cigars, or pipe).

‡Interaction test between ADH_3 genotypes and levels of alcohol consumption: χ^2 two-sided test for homogeneity = 0.4 for 3 degrees of freedom, $P = 0.94$.

§Values in columns for each group = *top line:* odds ratio (95% confidence interval); *bottom line:* number of case subjects/number of control subjects.

‖Also adjusted for daily consumption of ethanol.

¶Also adjusted for ADH_3 genotype.

sided test for trend; $P<.0001$). No interaction was found between ADH_3 genotype and alcohol consumption; i.e., the effect of ADH_3 genotype was the same in each category of alcohol consumption and vice versa. Similar results were observed when the same cut points for the number of alcoholic drinks per week used by Harty et al. *(1)* were analyzed.

These findings do not support the conclusion of a greater effect of ADH_3^{1-1} genotype among the group of subjects within our study group who had the highest level of alcohol consumption. This discrepancy between the conclusions of the two studies might be due to mere chance, selection bias, or differences in the populations studied. Our results are consistent, however, with those of Coutelle et al. *(5)*, who reported a slightly positive but not statistically significant association between ADH_3^{1-1} and the risk of oropharyngeal cancer among French Caucasian alcoholics. The ADH_3 allele frequencies among our control subjects (0.57 for ADH_3^1 and 0.43 for ADH_3^2) were quite similar to those reported for subjects in this other French population (0.55 and 0.45, respectively) *(5)*, but they were slightly different from those observed in the cohort of Puerto Rican subjects (0.62 and 0.38, respectively) studied by Harty et al. *(1)*. A limitation of our study would be the use of hospital control subjects, especially if there are any associations between ADH_3 genotypes and diseases diagnosed. Nevertheless, the distribution of ADH_3 genotypes was not significantly different among the disease groups, although the power to detect such differences is low. Further studies are needed to understand better the role of ADH_3 in susceptibility to alcohol-related cancers.

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Response

We thank Bouchardy et al. for bringing to our attention their new data regarding the relationship of alcohol drinking, alcohol dehydrogenase 3 (ADH_3) genotype, and oral cancer. However, the limited information they provide makes comparisons between the two studies difficult. Details are missing regarding subjects' age and sex; the anatomic subsites of the tumors; whether incident or prevalent cases were studied; the method used to calculate alcohol intake; the types of alcoholic beverages consumed; the distribution of alcohol intakes by case–control status, by ADH_3 genotype, and by disease category for the control subjects; the risks observed with the use of a non-drinker referent group; and the risks associated with each of the following three ADH_3 genotypes: ADH_3^{1-1} (homozygous for the fast-metabolizing ADH_3^1 allele), ADH_3^{1-2} (heterozygous), and ADH_3^{2-2} (homozygous for the slow-metabolizing ADH_3^2 allele).

In our study *(1)*, we observed an adjusted risk for oral cancer of 1.3 (95% confidence interval [CI] = 0.8–2.4) among subjects with the ADH_3^{1-1} genotype compared with subjects with the ADH_3^{1-2} or the ADH_3^{2-2} genotype, quite similar to the risk observed by Bouchardy et al. (odds ratio [OR] = 1.4; 95% CI = 0.8–2.3). However, Bouchardy et al. did not observe an increased risk associated with the ADH_3^{1-1} genotype among consumers with the highest alcohol intakes, in contrast to our study *(1)*. We note that the alcohol-related risk of oral cancer was higher for heavy drinkers ($\geq$57 drinks/week) in Puerto Rico (OR = 13.1; 95% CI = 3.9–44.2) *(1)* than for heavy drinkers (>120 g/day [approximately >70 drinks/week]) in France (OR = 4.8; 95% CI = 2.2–10.7), which may be due to the use of different referent groups (0 drinks/week in our study; $\leq$40 g/day [approximately $\leq$23 drinks/week] in the study by Bouchardy et al.), differences in alcohol use (i.e., amounts, patterns of use, or beverage types), or misclassification in the exposure assessment. Like Bouchardy et al., we *(1)* observed no additional risk associated with the ADH_3 genotype at intakes associated with risks up to OR = 4.7 (95% CI = 1.6–14.4).

A particular concern is that individuals with severe liver disease were excluded from the study by Bouchardy et al. but not from our study *(1)*. The relationships between ADH_3 genotype, liver damage, alcohol intake, and ADH activity are unresolved *(2–6)* and potentially complex. If liver damage and ADH_3^{1-1} genotype are positively associated, excluding subjects with severe liver disease will undersample heavy drinkers with the ADH_3^{1-1} genotype. While details regarding the exclusion criteria are not given by Bouchardy et al., case–control differences could have biased the results toward the null.

We interpret the only other study *(6)* of ADH_3 genotype, alcohol intake, and oropharyngeal cancer as suggesting that heavy drinkers with the ADH_3^{1-1} genotype may have an elevated risk of upper aerodigestive tract cancers compared with those with the ADH_3^{1-2} or the ADH_3^{2-2} genotype. Coutelle et al. *(6)* reported a 2.6-fold (95% CI = 0.7–10.0) higher risk of oropharyngeal cancer and a 6.1-fold (95% CI = 1.3–28.6) higher risk of laryngeal cancer associ-