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Letter to the Editor

Correspondence re: Harland Austin *et al.* A Case-Control Study of Hepatocellular Carcinoma and the Hepatitis B Virus, Cigarette Smoking, and Alcohol Consumption. Cancer Res., *46:* 962–966, 1986[1]

In light of the negative findings of Austin *et al.* (1) on cigarette smoking and PHC,[2] we reanalyzed our 2 case-control studies of PHC (2, 3) with respect to cigarette smoking and alcohol consumption in an attempt to provide direct comparisons between the findings of these three studies. Table 1 presents the smoking and drinking habits of our PHC cases and controls in Los Angeles (2), using measures as defined by Austin *et al.* (1). Heavy drinkers (>65 drink-years of cumulative alcohol consumption) exhibited a 2-fold increased risk of PHC relative to nondrinkers (95% confidence limits=0.8, 5.1), and risk of PHC showed a significant dose-response relationship with increasing pack-years of cigarette smoking (2-sided *P* for trend test=0.02). The RRs associated with the various categories of cumulative alcohol consumption remained relatively unchanged after we adjusted for pack-years of cigarette smoking. Similarly, the RRs associated with the various categories of pack-years of cigarette smoking were almost unchanged after we adjusted for cumulative alcohol consumption (Table 1). The distribution by pack-years of smoking among PHC cases in Los Angeles was similar to that among the cases in Austin *et al.* (1). However, there were considerably more 50+ pack-year smokers among the hospital controls in Austin *et al.* (1) than among our neighborhood controls in Los Angeles (23 *versus* 4%). There is some evidence that the smoking habits of our PHC controls are representative of those of the general population in Los Angeles of similar sex and age. In a large case-control study of pancreas cancer (490 cases and 490 controls) which used the same questionnaire and whose controls were distributed similarly in sex and age as those of the PHC study (4), we observed that 9% of controls were 50+ pack-year smokers. On the other hand, 20% of the controls in Austin *et al.* (1) were admitted to the hospital for cardiovascular diseases, conditions that are known to be related to cigarette smoking. Besides, cigarette smoking is associated with illness (and therefore hospitalization) in general (5–7), suggesting that long-term heavy smokers might be over-represented among the controls of Austin *et al.*(1).

Austin *et al.* (1) raised the question of whether the relative risk associated with current, >1 pack/day smokers in Los Angeles (Table 1 of Ref. 2) remained elevated after adjustment for the 3 levels of alcohol consumption (0–9, 10–79, and 80+ g/day of ethanol intake). Indeed, there was an almost 2-fold excess risk of PHC among current, >1 pack/day smokers after we adjusted for alcohol consumption (adjusted RR=1.9). Similarly, drinkers of 80+ g of ethanol/day possessed a RR of 3.3 after we adjusted for the 4 levels of cigarette smoking (non-, ex-, current ≤1 pack/day, current > 1 pack/day smokers).

Table 2 presents the smoking and drinking habits of our hepatitis B surface antigen-negative PHC cases and controls in Hong Kong (3). Due to smaller numbers, drinkers were grouped into 2 (instead of 3) categories and smokers were grouped also into 2 (instead of 3) categories. Interestingly, the RRs associated with the various levels of drinking and smoking in Hong Kong were quite comparable to those observed for the corresponding levels of drinking and smoking in Los Angeles. Our 2 studies suggest that cigarette smoking and alcohol consumption are both risk factors for PHC.

Table 1 *Smoking and drinking habits of white and black PHC cases and controls in Los Angeles*

	No. of cases	No. of controls	Relative risk[a]	Adjusted relative risk	Relative risk from Austin *et al.* (1)
Cumulative alcohol consumption					
Nondrinkers	26	27	1.0	1.0[b]	1.0[c]
<18 drink-yr	13	17	0.7	0.8	1.4
18–65 drink-yr	10	16	0.7	0.8	2.5
>65 drink-yr	22	11	2.0	2.4	3.3
Pack-yr of cigarette smoking					
Nonsmokers	30	37	1.0	1.0[d]	1.0[e]
1–24	12	17	1.0	1.0	0.9
25–49	18	13	1.8	1.9	2.6
50+	10	3	8.7	7.0	0.8

[a] Computed from conditional logistic regression method for matched (on age, sex, race) sets.
[b] Adjusted for pack-years of cigarette smoking.
[c] Computed from all matched sets.
[d] Adjusted for cumulative alcohol consumption.
[e] Restricted to hepatitis B surface antigen-negative cases and controls, and adjusted for alcohol consumption.

Table 2 *Smoking and drinking habits of hepatitis B surface antigen-negative PHC cases and controls in Hong Kong*

	No. of cases	No. of controls	Relative risk[a]	Adjusted relative risk
Cumulative alcohol consumption				
Nondrinkers	10	53	1.0	1.0[b]
≤65 drink-yr	4	23	0.9	0.8
>65 drink-yr	5	12	2.0	1.6
Pack-yr of cigarette smoking				
Nonsmokers	3	32	1.0	1.0[c]
1-24	7	32	1.9	1.9
25+	9	24	2.5	1.9

[a] Adjusted for sex and age (<50, 50+).
[b] Adjusted for sex, age (<50, 50+), and cigarette smoking (nonsmokers, smokers).
[c] Adjusted for sex, age (<50, 50+), and alcohol consumption (nondrinkers, regular drinkers).

Smoking and drinking are highly correlated variables, and the possibility of subjects underreporting alcohol consumption because of social stigma toward heavy drinking makes untangling the effects of both factors even more difficult. The case-control studies that have examined the roles of cigarette smoking and alcohol consumption were all limited by small sample sizes. Larger studies are needed to further evaluate the roles of these 2 possible risk factors in the etiology of PHC.

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[2] The abbreviations used are: PHC, primary hepatocellular carcinoma; RR, relative risk.

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Reply

We concluded in our paper (1) that an overall evaluation of the epidemiological evidence indicates a weakly or moderately positive relationship between cigarette smoking and HCC.[1] In reaching this conclusion, we considered Yu and Henderson's two case-control studies (2, 3) as providing some evidence that cigarette smoking is a cause of HCC. However, we suggested that the relationship between cigarette smoking and HCC in their case-control studies was overestimated because of confounding by alcohol consumption. They, on the other hand, suggest that our study underestimates the effect of heavy smoking on HCC risk because of our use of hospital controls.

The data in their letter support our concern that the relative risks pertaining to smoking and HCC in their studies were spuriously high because of confounding by alcohol consumption. In the Los Angeles study the excess HCC risk for persons smoking more than a pack per day is diminished by 44%, while in the Hong Kong study the excess HCC risk for persons with 25 or more pack-years of smoking is reduced by 40% after adjustment for alcohol consumption. Furthermore, the adjustment for alcohol habit in the Hong Kong study was made by use of only 2 categories (nondrinkers, regular drinkers), even though HCC risk was elevated only among heavy drinkers in this study. Adjustment that makes use of a more appropriate categorization of alcohol habit would presumably further reduce the apparent excess.

We too were concerned that the absence of a positive relationship between cigarette smoking and HCC in our study was the result of selection bias because of our use of hospital controls. However, we noted in our paper that the exclusion of the controls with cardiovascular disease had little effect on the matched relative risks relating HCC and cigarette smoking. It is more difficult for us to evaluate the possibility that the smoking habits of our remaining controls are elevated because cigarette smoking is a determinant of hospitalization in general. To some extent this type of selection bias may exist and our study may have underestimated the effect of heavy smoking on HCC risk. However, hospital controls also were used in the study by Trichopoulos *et al.* (4) and they found a strong relationship between HCC risk and heavy smoking. Thus, it is unlikely that selection bias resulting from the use of hospital controls is serious enough to mask a strong relationship between heavy smoking and HCC.

Yu and Henderson argue in their letter that the smoking habits of the controls in their HCC study are representative of those of the general population of Los Angeles of the same sex and age. Their implication seems to be that the smoking histories of their controls are valid whereas those of ours are not. As a matter of general principle, however, the objective of the control series in a case-control study is to provide a valid estimate of the exposure frequency among persons who would have been included in the study as cases had they developed the disease (5). Whether or not the controls are representative of the entire nondiseased population is not germane. The HCC cases in our study were obtained from several large referral hospitals and therefore were not representative of all cases. Our selection of controls from the same hospitals was motivated by the objective of the control series as described above and not by the pursuit of broad representativeness. Our cases, and therefore our controls, lived predominantly in the Southeast, were older, and included proportionately more men and more blacks than did Yu and Henderson's controls. These demographic differences between the subjects in the two studies could account for the observation that heavy smoking was more prevalent among our controls than among theirs. A comparison of the smoking habits of their controls to those of ours therefore does not bear on the validity of our study.

Finally, an overall assessment of the relationship between smoking and HCC should incorporate the findings of both positive and negative studies considering the strengths and limitations of each. Based upon all the information available we concluded that the evidence indicates a weakly or moderately positive relationship. Despite the inevitable differences in results from study to study, some of which have no obvious explanation, the conclusions of Yu and Henderson on the question are similar to our own.

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[1] The abbreviation used is: HCC, hepatocellular carcinoma.

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