TOBACCO SMOKING, ALCOHOL CONSUMPTION AND THEIR INTERACTION IN THE CAUSATION OF HEPATOCELLULAR CARCINOMA

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During a 4-year period from January 1995 to December 1998, blood samples and questionnaire data were obtained from 333 incident cases of hepatocellular carcinoma (HCC), as well as from 360 controls who were hospitalized for eye, ear, nose, throat or orthopedic conditions in Athens, Greece. Coded sera were tested for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV) by third-generation enzyme immunoassays, and information on smoking habits and beverage consumption was obtained. We found a significant dose-response, positive association between smoking and HCC risk (≥2 packs per day, odds ratio: 2.5). This association was stronger in individuals without chronic infection with either HBV or HCV (≥2 packs per day, OR=2.8). Consumption of alcoholic beverages above a threshold of 40 glasses per week increased the risk of HCC (OR=1.9). We also found evidence of a strong, statistically significant and apparently super-multiplicative effect of heavy smoking and heavy drinking in the development of HCC (OR for both exposures=9.6). This interaction was particularly evident among individuals without either HBsAg or anti-HCV (OR for both exposures=10.9). Coffee intake was not positively associated with HCC risk, but the reverse could not be excluded for the subgroup of chronically infected individuals. In conclusion, tobacco smoking and heavy alcohol consumption are associated with increased risk of HCC, especially when these 2 exposures occur together. Int. J. Cancer 85:498–502, 2000.

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Hepatocellular carcinoma (HCC) is an important cancer globally, estimated to rank 4th in terms of mortality and 5th in terms of cancer incidence (Parkin et al., 1999). Although this cancer is relatively rare in the developed world, there are data to suggest that both the incidence and mortality are rising (Stuver and Trichopoulos, 1994). The overwhelming evidence that chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is an important cause of HCC is based on ecologic, case-control and cohort studies, as well as on clinical and laboratory investigations. A critical review up to 1994, published by the International Agency for Research on Cancer (IARC, 1994), concluded that both viral agents are definite human carcinogens. Although most cases of HCC worldwide can be attributed to HBV and HCV, there are many areas in the world where these infections are relatively rare and where a greater proportion of HCC may be attributable to other risk factors. Consumption of alcoholic beverages and tobacco smoking are 2 such possible factors because of their potential to cause human cancer and their high prevalence of use (IARC, 1986, 1988).

Many epidemiologic studies have shown an association between excessive alcohol consumption and risk of HCC (La Vecchia et al., 1988; Tanaka et al., 1992, 1995; Adami et al., 1992). Indeed, the relation is considered causal (IARC, 1988). It has been hypothesized, however, that heavy alcohol consumption may lead to HCC only through the production of liver cirrhosis as an intermediate step (Adami et al., 1992). Alcohol may further promote the development of HCC by increasing tumor growth in people with cirrhosis or other chronic liver diseases (Mukaiya et al., 1998). An interactive effect of heavy smoking and heavy drinking on the progression of chronic liver disease to HCC (Mukaiya et al., 1998) has also been hypothesized.

Data on smoking and risk for HCC are contradictory. A number of studies found no statistically significant association or dose-response relation between tobacco smoking and HCC, although some elevation in risk was frequently noted (La Vecchia et al., 1988; Tanaka et al., 1992; Hadziyannis et al., 1995). Other studies reported a statistically significant positive relationship and a dose-response relationship between cigarette smoking and risk of HCC (Trichopoulos et al., 1987; Tanaka et al., 1995). This effect could be limited to people who are HBsAg-negative (Trichopoulos et al., 1987).

Coffee has been implicated in the carcinogenesis of a variety of tumors (IARC, 1991), possibly reducing the risk of colorectal cancer (Ekborn, 1999) and increasing the risk of bladder cancer (Donato et al., 1997a). The role of coffee intake in the carcinogenesis of HCC has not previously been investigated in epidemiologic studies. However, some animal data suggest that a protective effect of coffee is possible (Tanaka et al., 1990).

Our present study is one of the largest case-control investigations of the etiology of HCC and the largest undertaken outside of Asia (studies reviewed by Donato et al., 1998). We used third-generation immunoassays to determine HBV and HCV status of the study participants. Special attention was paid to the control of selection and information bias, based on the experience gained from several independent case-control studies of HCC previously undertaken in Greece (Trichopoulos et al., 1978, 1987; Hadziyannis et al., 1995).

MATERIAL AND METHODS

During a 4-year period between January 1995 and December 1998, 374 incident cases of HCC were admitted to 3 teaching hospitals in Athens (Hippokration, Western Attica and Laiko General Hospital). Forty-one (11%) of the HCC cases identified in these hospitals during the study period were not enrolled for various reasons. For the 333 cases included in the study, confirmation of their HCC diagnosis was based on biopsy (n=157), elevated alpha-fetoprotein level (n=159) or echography and/or other methods (n=14); for 3 cases, details concerning diagnostic confirmation was missing. Since a diagnosis of cirrhosis was not histologically determined for all subjects, this information was not considered sufficiently reliable to be taken into account in the analysis.

Controls were patients hospitalized for injuries or for eye, ear, nose or throat conditions, that is, patients with non-cancer disor-

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orders usually requiring minor surgery and considered unrelated to smoking, alcohol intake or coffee consumption. For each case with HCC, we attempted to select 1 control patient from the same hospital, matching for gender and age (± 5 years). There were 25 refusals in the control series (6%), and a properly matching control could not be identified for some HCC cases. Eventually, 360 control subjects were included in the analysis.

Sera, which had been obtained from each subject and stored at −25°C for 1–4 years, were transferred on dry ice to internationally certified Biomedicine Laboratories in Athens, Greece, for serologic testing. Coded samples were tested for hepatitis B surface antigen (HBsAg), the marker for HBV infection, using the Auszyme monoclonal enzyme immunoassay (EIA) kit (Abbott, Chicago, IL). The presence of antibodies to HCV (anti-HCV) was determined with the Abbott HCV EIA 3.0. The anti-HCV assay detects antibodies to the H-C34 (core), H-C31 (NS3 and NS4), c100–3 (NS3 and NS4) and NS5 antigens. Results were interpreted according to the manufacturer's instructions. Both the HBsAg and anti-HCV assays are considered third-generation tests.

All HCC patients and hospital controls were interviewed in the hospital. Data concerning demographic, socioeconomic and medical variables were recorded, and detailed histories of smoking habits and alcoholic beverage and coffee consumption were taken. Current smokers were classified according to the daily number of cigarettes smoked before the onset of HCC or a corresponding date in the controls. Those who had stopped smoking within the 3 years prior to disease diagnosis were considered current smokers. Those who had stopped smoking more than 3 years before the onset of disease were considered former smokers. Former smokers were also classified according to the daily number of cigarettes smoked in the past. Total daily alcohol consumption was expressed as number of glasses per week, summing over all categories of alcohol. One glass of an alcoholic beverage contains 10 g of ethanol (IARC, 1988). Total daily coffee consumption was expressed as number of cups per week, summing over all categories of coffee.

As estimates of relative risk, odds ratios (OR) with 95% confidence intervals (CI) for the risk of HCC were generated by stratified analysis and unconditional logistic regression modeling (Breslow and Day, 1980). Because individual matching was impossible for some HCC cases, it was necessary to conduct unconditional, rather than conditional, logistic regression modeling, with adjustment for the matching factors. The likelihood ratio test, which is the difference between the maximized log-likelihood statistics, was used to assess the significance of additional covariates in the model (Breslow and Day, 1980).

RESULTS

Table I shows the distribution of HCC cases and hospital controls by demographic characteristics and serologic evidence of chronic infection with HBV, infection with HCV or both. Cases and controls were balanced with respect to age, gender and years of schooling. As expected, there were striking differences in the prevalence of the markers of infection with HBV and HCV, given that these are the dominant viral causes of HCC.

Table II shows the distribution of HCC cases and hospital controls by smoking habits, habitual consumption of alcoholic beverages of any type and regular intake of coffee of any type. The distributions are gender-specific on account of the expected differences in the prevalence of these activities by gender. Based on adjustment for age and gender, there is evidence that smoking and excessive alcohol drinking but not coffee consumption are associated with an increased risk of HCC, but mutual confounding precludes valid etiological inferences.

Table III shows the multiple regression-derived, mutually adjusted OR (and 95% CIs) for the association of HCC with consumption patterns of cigarettes, alcoholic beverages and coffee. Because latency for a possible tobacco smoking-HCC association has not been determined, we opted to study the effect of usual number of cigarettes smoked daily irrespective of current or former smoking status. Data are shown for all subjects and after stratification by serologic evidence of infection with HBV and/or HCV. We found a dose-response, positive association between smoking and HCC risk. In contrast, for consumption of alcoholic beverages, there appears to be a threshold for an association with increased risk of HCC at about 40 glasses per week. With respect to smoking, the association with HCC risk is stronger among individuals who have no chronic viral infection than among those with either infection. The opposite relationship was observed for an effect of alcohol intake, according to viral infection status. Finally, there is no indication that coffee intake is associated with HCC risk.

We also evaluated whether the apparent effect of smoking depends on alcohol consumption levels. Table IV presents data assessing the interaction between tobacco smoking and alcohol consumption. Because drinkers of fewer than 20 glasses per week and those consuming 20–39 glasses per week did not appear to have an elevated risk for HCC, these 2 categories were combined with non-drinkers into a group of non- and light-alcohol consumers to simplify data presentation. We found a strong, statistically significant ($p = 0.0001$) and apparently super-multiplicative interaction between heavy smoking and heavy drinking in the causation of HCC. Because few controls had HBsAg or anti-HCV (Table I), we examined the possible interaction of heavy smoking and heavy drinking in the data set restricted to those cases and controls without infection with HBV or HCV. As expected, the pattern of interaction remained the same (Table IV).

Table III indicates that the effect of tobacco smoking is stronger among individuals negative for HBsAg and anti-HCV than among individuals positive for either of these seromarkers. To assess whether tobacco smoking alone or in combination with high alcohol intake is indeed more important, in relative terms, for HCC cases positive for chronic hepatitis virus infection than for HCC cases positive for infection, we performed a case-case analysis to compare the 2 case series for prevalence of cigarette and alcohol consumption (Table V). HCC cases without evidence of chronic infection with either HBV or HCV were considered the study series, whereas HCC cases infected with either virus were considered the comparison series. The OR and 95% CI produced by a case-case comparison give an estimate of the departure from multiplicative joint effect of the exposures of interest, in this instance cigarette and alcohol consumption, and viral status on risk of HCC. There is again evidence that in relative terms both smoking and heavy drinking and, in particular, the interaction of heavy smoking and heavy drinking are substantially more impor-
tant for the development of HCC among individuals without chronic infection with either HBV or HCV than among individuals with hepatitis virus infection (OR for both heavy smoking and heavy drinking $= 5.6$, 95% CI $= 1.7–19.0$).

**DISCUSSION**

The present case-control study was large and relied on state-of-the-art biochemical assays. The study protocol was developed by taking into account the experience of the investigators from past studies conducted on the etiology of hepatocellular carcinoma (Trichopoulos et al., 1978, 1987; Hadziyannis et al., 1995). Reporting of alcohol consumption and cigarette smoking may be more accurate in the Greek population than in many others, since wine drinking is common and smoking continues to be culturally acceptable. Misclassification of exposure is therefore likely to be both minor and non-differential with respect to disease status. The hospital controls were selected from ophthalmology, ear, nose and throat and orthopedic departments, and the corresponding diagnostic categories were either unrelated or, at most, weakly positively related to the exposures under study. Thus, selection bias, if any, could lead only to a mild underestimation of the reported associations with alcohol consumption and tobacco smoking. Since hepatitis B and C viruses are established causes of HCC (IARC, 1994), the potential confounding effects of these viruses has been appropriately controlled for the analysis.

**TABLE II** – GENDER-SPECIFIC DISTRIBUTION OF HCC CASES AND HOSPITAL CONTROLS BY SMOKING HABITS AND CONSUMPTION OF ALCOHOLIC BEVERAGES AND COFFEE INTAKE, WITH ODDS RATIOS AND 95% CONFIDENCE INTERVALS

| Smoking status (packs per day) | HCC cases (n = 333) | Hospital controls (n = 360) | Odds ratio$^1$ (95% CI) |
|--------------------------------|--------------------|-----------------------------|------------------------|
|                                | Men (n = 283)      | Women (n = 50)              |                        |
|                                |                    |                             |                        |
| Never smoker                   | 61 (21.6%)         | 37 (74.0%)                  | 74 (24.8%)             | 52 (83.9%) | 1.0 |
| Current smoker                 |                    |                             |                        |
| $< 2$                          | 103 (36.4%)        | 9 (18.0%)                   | 111 (37.2%)            | 6 (9.7%)  | 1.2 (0.8–1.9) |
| $\geq 2$                       | 36 (12.7%)         | 2 (4.0%)                    | 31 (10.4%)             | 1 (1.6%)  | 1.6 (0.9–2.3) |
| Former smoker                  |                    |                             |                        |
| $< 2$                          | 61 (21.6%)         | 2 (4.0%)                    | 63 (21.1%)             | 3 (4.8%)  | 1.2 (0.7–1.9) |
| $\geq 2$                       | 22 (7.8%)          | 0 (0%)                      | 19 (6.4%)              | 0 (0%)    | 1.5 (0.7–3.0) |

| Alcoholic beverages (glasses per week) | HCC cases (n = 333) | Hospital controls (n = 360) | Odds ratio$^1$ (95% CI) |
|----------------------------------------|--------------------|-----------------------------|------------------------|
|                                        | Men (n = 283)      | Women (n = 50)              |                        |
|                                        |                    |                             |                        |
| Non-drinkers                           | 96 (33.9%)         | 39 (78.0%)                  | 90 (30.2%)             | 47 (75.8%) | 1.0 |
| Drinkers                               |                    |                             |                        |
| $< 20$                                 | 63 (22.3%)         | 8 (16.0%)                   | 88 (29.5%)             | 14 (22.6%) | 0.7 (0.5–1.0) |
| $20–39$                                | 46 (16.3%)         | 0 (0%)                      | 64 (21.5%)             | 1 (1.6%)  | 0.7 (0.4–1.0) |
| $\geq 40$                              | 78 (27.6%)         | 3 (6.0%)                    | 56 (18.8%)             | 0 (0%)    | 1.4 (0.9–2.1) |

| Coffee (cups per week) | HCC cases (n = 333) | Hospital controls (n = 360) | Odds ratio$^1$ (95% CI) |
|------------------------|--------------------|-----------------------------|------------------------|
|                        | Men (n = 283)      | Women (n = 50)              |                        |
|                        |                    |                             |                        |
| Non-drinkers           | 31 (11.0%)         | 5 (10.0%)                   | 26 (8.7%)              | 7 (11.3%)  | 1.0 |
| Drinkers               |                    |                             |                        |
| $< 20$                 | 191 (67.5%)        | 39 (78.0%)                  | 194 (65.1%)            | 43 (69.4%) | 0.9 (0.5–1.5) |
| $\geq 20$              | 61 (21.6%)         | 6 (12.0%)                   | 78 (26.2%)             | 12 (19.4%) | 0.7 (0.4–1.2) |

$^1$Adjusted for age and gender.

**TABLE III** – MULTIPLE REGRESSION-DERIVED MUTUALLY ADJUSTED ODDS RATIOS (AND 95% CONFIDENCE INTERVALS) FOR THE ASSOCIATION OF HCC WITH SMOKING HABIT AND CONSUMPTION OF ALCOHOLIC BEVERAGES AND COFFEE, BY HBsAg AND/OR ANTI-HCV STATUS

| Smoking (packs per day) | All subjects OR (95% CI) | Subjects with HBsAg and/or anti-HCV OR (95% CI) | Subjects without both HBsAg and anti-HCV OR (95% CI) |
|------------------------|--------------------------|-----------------------------------------------|--------------------------------------------------|
| Never smokers          | 1.0                      | 1.0                                           | 1.0                                               |
| Ever smokers           |                          |                                               |                                                  |
| $< 2$                  | 1.6 (0.8–2.9)            | 1.3 (0.3–5.6)                                | 1.8 (0.9–3.6)                                     |
| $\geq 2$               | 2.5 (1.1–5.5)            | 2.1 (0.3–17.1)                               | 2.8 (1.1–6.9)                                    |
| $p$ for trend          | 0.03                     | 0.48                                          | 0.03                                              |
| Alcoholic beverages (glasses per week) | All subjects OR (95% CI) | Subjects with HBsAg and/or anti-HCV OR (95% CI) | Subjects without both HBsAg and anti-HCV OR (95% CI) |
| Non-drinkers           | 1.0                      | 1.0                                           | 1.0                                               |
| Drinkers               |                          |                                               |                                                  |
| $< 20$                 | 0.8 (0.4–1.4)            | 1.0 (0.2–4.1)                                | 0.7 (0.3–1.3)                                     |
| $20–39$                | 0.7 (0.3–1.5)            | 1.4 (0.3–7.9)                                | 0.6 (0.2–1.4)                                     |
| $\geq 40$              | 1.9 (0.9–3.9)            | 5.4 (0.6–50.3)                               | 1.6 (0.8–3.4)                                    |
| $p$ for trend          | 0.13                     | 0.14                                          | 0.33                                              |
| Coffee (cups per week) | All subjects OR (95% CI) | Subjects with HBsAg and/or anti-HCV OR (95% CI) | Subjects without both HBsAg and anti-HCV OR (95% CI) |
| Non-drinkers           | 1.0                      | 1.0                                           | 1.0                                               |
| Drinkers               |                          |                                               |                                                  |
| $< 20$                 | 1.1 (0.5–2.6)            | N/A$^2$                                      | 1.9 (0.6–5.9)                                     |
| $\geq 20$              | 0.9 (0.4–2.5)            | N/A$^2$                                      | 1.7 (0.5–5.9)                                     |
| $p$ for trend          | 0.75                     | N/A$^2$                                      | 0.66                                              |

$^1$Also controlling for age, gender, years of schooling and HBsAg and/or anti-HCV status, as appropriate. $^2$The multivariate model did not converge because there were no controls who did not drink coffee.
**TABLE IV**  - EVALUATION OF INTERACTION BETWEEN EXCESS ALCOHOL DRINKING (≥40 GLASSES PER WEEK) AND TOBACCO SMOKING IN THE CAUSATION OF HCC, WITH ODDS RATIOS AND 95% CONFIDENCE INTERVALS

| Alcohol consumption | Smoking status       | All subjects | Non and light drinkers (<40 glasses per week) | Heavy drinkers (≥40 glasses per week) | Subjects without HBsAg or anti-HCV | Non and light drinkers (<40 glasses per week) | Heavy drinkers (≥40 glasses per week) |
|---------------------|----------------------|--------------|---------------------------------------------|---------------------------------------|------------------------------------|---------------------------------------------|---------------------------------------|
|                     | Never smoker         | 1.0          | 1.0 (0.9–3.2)                                | 2.0 (1.0–5.9)                         | 1.0 (0.7–3.6)                      | 4.2 (0.7–25.9)                              | 2.4 (0.9–6.9)                          |
|                     | Moderate smoker      | 1.7          | 6.2 (2.6–15.3)                               | 7.2 (2.7–20.5)                       | 2.1 (0.9–5.3)                      | 4.7 (0.7–34.5)                              | 10.9 (3.5–33.8)                       |
|                     | Heavy smoker         | 1.5          | 1.5 (0.6–4.0)                                | 3.2 (1.0–11.0)                       | 1.7 (0.4–4.0)                      | 7.5 (0.7–75.0)                              | 10.9 (3.5–33.8)                       |

1Also adjusting for age, gender, years of schooling, coffee drinking and HBsAg and/or anti-HCV status, as appropriate.

**TABLE V**  - COMPARISON OF HCC CASES WITHOUT HBsAG OR ANTI-HCV TO HCC CASES WITH EITHER MARKER, WITH RESPECT TO TOBACCO SMOKING AND ALCOHOL CONSUMPTION, WITH ODDS RATIOS AND 95% CONFIDENCE INTERVALS

| Alcohol consumption | Smoking status       | Never smoker | Moderate smoker (<2 packs per day) | Heavy smoker (<2 packs per day) |
|---------------------|----------------------|--------------|-----------------------------------|-------------------------------|
| Non and light drinkers (<40 glasses per week) | 1.0 (0.7–3.6) | 1.6 (0.7–3.6) | 1.0 (1.0–5.9) | 1.2 (0.4–4.0) |
| Heavy drinkers (≥40 glasses per week) | 1.0 (0.2–5.8) | 1.0 (0.5–4.1) | 5.6 (1.7–19.0) | 1.0 (0.4–4.0) |

1Also adjusting for age, gender, years of schooling and coffee drinking.

Animal data have indicated that coffee consumption may reduce the risk of HCC (Tanaka et al., 1990), and epidemiological data imply that high coffee consumption may retard the progression to alcoholic cirrhosis (Klatksy and Armstrong, 1992). Our data cannot reject this hypothesis, particularly among individuals with HBsAg or anti-HCV, for whom the point estimate for coffee drinkers was essentially zero (Table III), but neither do they provide any direct evidence to support such a role.

Our results indicate that heavy alcohol consumption (more than 40 glasses per week), but not moderate to light consumption, increases the risk for HCC. This observed association is in agreement with those of most previous studies on this topic (La Vecchia et al., 1988; Tanaka et al., 1992, 1995; Adami et al., 1992). The finding is also biologically plausible, since ethanol is not a mutagen but likely acts as a promoter or growth enhancer, probably through liver cirrhosis (Adami et al., 1992). In agreement with other studies (Donato et al., 1997b), the apparent effect of ethanol intake on the risk of HCC was stronger among individuals infected with HBV or HCV.

Our results are compatible with an important role of tobacco smoking in the etiology of HCC. Although null studies have been reported (Tanaka et al., 1992), several investigations have suggested that smoking is causally related to HCC (Trichopoulos et al., 1987; Tanaka et al., 1995). An effect of smoking on the development of HCC is biologically plausible, given the carcinogenic potential of several compounds in tobacco smoke and the role that the liver plays in their metabolism (Stare et al., 1997). The association of tobacco smoking with HCC risk appears to be more evident among individuals without chronic infection with HBV or HCV. This observation is compatible with an additive role of chronic viral infection and tobacco smoking in the etiology of HCC, since the effect of tobacco smoking in those cases with HBsAg and/or anti-HCV is concealed by the extremely strong carcinogenic effect of HBV and HCV.

Previous studies have suggested the possibility of an interaction between heavy drinking and heavy smoking in the development of HCC (Mukaiya et al., 1998). Our data convincingly demonstrate a super-multiplicative, interactive effect of heavy smoking and heavy drinking in the development of HCC. Again, this interaction is more pronounced among individuals without chronic infection with either HBV or HCV. The interaction is biologically plausible because tobacco smoke contains several mutagenic initiating agents as well as potential promoting agents, and heavy alcohol drinking is likely to have a promoting or growth-enhancing effect via the process of cirrhosis. Thus, smoking and alcohol could act together along the same pathway of hepatocarcinogenesis.

In conclusion, we have found evidence that tobacco smoking is an important cause of HCC among individuals who are not chronically infected with either HBV or HCV. In addition, we have documented a strong interaction between heavy drinking and heavy smoking in the development of this form of cancer. Because most HCC cases in developed countries, including those in North America and northern Europe, do not occur against a background of chronic infection with HBV or HCV, tobacco smoking in conjunction with heavy drinking could be responsible for the largest fraction of HCC cases in these parts of the world.

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