Case-Control Study of Hepatocellular Carcinoma, Occupation, and Chemical Exposures

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The relation of hepatocellular carcinoma (HCC) to occupation and chemical exposures was evaluated in a case-control study. The study included 80 cases and 146 matched hospital controls on whom a work history was obtained.

No persuasively positive association between HCC and any particular occupation, industry, or chemical exposure was found. However, the relative rate (RR) of HCC for persons employed in highway construction compared with those never so employed is 5.0 with 95% confidence limits (CL), 1.0 to 26. The RR for farming occupations, 1.4 (95% CL, 0.7 to 2.9), is also slightly elevated. The RR for persons exposed to pesticides compared with those not exposed is 2.4 (95% CL, 0.9 to 6.5). Asphalt exposures are associated with a RR of 3.2 (95% CL, 0.9, 11). These findings are compared to the results of other epidemiologic studies.

A recently completed case-control study examined the roles of cigarette smoking, the hepatitis B virus (HBV), alcohol consumption, occupation, and other factors in the etiology of hepatocellular carcinoma (HCC). This paper presents the results pertaining to occupational factors and to chemical exposures encountered at work or in leisure time activities. The findings for cigarette smoking, the HBV, and alcohol have been described elsewhere.[1]

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Methods

A detailed description of the methods has been presented.[1] Briefly, this is a case-control interview study. Eligible cases were persons aged 18 through 84 with HCC hospitalized at one of five participating study centers (the University of Alabama at Birmingham, Duke University, the University of Miami, the University of Pennsylvania, and the Harvard School of Public Health).

Of the 86 cases included, 80 were confirmed histologically. The diagnosis of HCC was established clinically for the remaining six. The median age of cases is 63; 60 are men; 66 are white, 19 are black, and 1 is Oriental.

Two hospital controls were sought for each case. Patients admitted to the hospital for cancers of the lung, oral cavity, esophagus, larynx, bladder, or pancreas; for chronic bronchitis; or for emphysema were ineligible as controls because a purpose of the study was to evaluate the relationship between cigarette smoking and HCC. Patients admitted for a primary liver disease also were excluded. The controls were matched to cases on gender, age (plus or minus 5 years), race (white, black, Oriental), and study center. Furthermore, because most HCC cases had been diagnosed recently, controls were restricted to patients whose current hospital admission was for a condition diagnosed within 3 years of the interview. This restriction reduces the proportion of controls who may have recently modified their habits as a result of a chronic disease.

A total of 161 controls are included in the study. There are 75 matched triplets and 11 matched pairs. The median age of controls is 62; 110 controls are men; 126 are white, 33 are black, and two are Oriental.

Subjects were asked about any job that they had held for 6 months or longer in their lifetime. Jobs were classified according to industry by the *Standard Industrial Classification Manual, 1972*[3] and according to occupational title by the *Standard Occupational Classification Manual, 1977*.[3] The distribution of subjects according to a two-digit classification of industry and occupation was examined. Adjacent categories of industry and occupation were combined if it seemed likely that these jobs would have entailed similar exposures. Any category with at least ten exposed subjects was selected for presentation. For occupational classifications, three-digit codes also were presented if at least ten subjects had worked in that occupation.

A subject is considered "exposed" to a particular industry or occupation if he had worked in that industry or occupation for at least 6 months and "unexposed" if he had not. Results in this report are presented as the relative rate (RR); that is, the rate of HCC among the exposed divided by the rate among the unexposed.

The RRs were obtained after accommodating the matching in the analysis through logistic regression models using conditional likelihood procedures to obtain maximum likelihood estimates.[4,5] For a dichotomous exposure with no adjustment for additional confounding factors, this procedure yields the usual maximum likelihood estimate of the RR derived from the analysis of matched triplets and pairs.[6]

Our previous report indicated that alcohol consumption and chronic infection with the HBV are risk factors for HCC.[1] Therefore, the RRs for selected industries and occupations were adjusted for alcohol habit and chronic HBV status (carrier *v* noncarrier) through conditional likelihood regression models which incorporated these factors. There was, however, little difference between any of the adjusted and unadjusted RRs, so that only the unadjusted RRs are presented in this paper. The statistical significance of relationships between RRs and duration of employment in a particular industry or occupation was evaluated by including in a logistic regression model a single ordinal exposure variable denoting years of employment. All reported *P* values are two-tailed.

Results

The occupational analysis is restricted to those 80 cases and their 146 controls for whom a work history was obtained. The distribution of cases and controls according to industries in which at least 10 subjects had worked is presented in Table 1. Of the 25 industries investigated, the RR is at or below the null value (RR = 1) for 11, whereas for 14 the RR exceeds unity. None of the RRs displayed in Table 1 is statistically significant at a two-tailed level of 5%.

The highest RR in Table 1 is 2.0 for employment in the nonbuilding construction industry. This elevated RR is a result of employment in highway and street construction (code 161) with five exposed cases and two exposed controls (RR=5.0, 95% CL, 1.0, 26). The five cases had been employed in highway construction for a mean of approximately 11 years, whereas the two controls had been so employed for 8 years.

The distribution of cases and controls according to occupations in which at least 10 subjects had worked is displayed in Table 2. Of the 23 occupations investigated, the RR is at or below the null value for 12, whereas for 11 the RR exceeds unity. The RRs are highest for persons employed as teachers and in clerical occupations. The RR is also elevated for persons employed as mechanics and repairers. However, the mean years of employment as mechanics and repairers were approximately the same for cases and controls.

The RR for persons employed in the agricultural industry is 1.1 compared with those never so employed. The RR for employment in livestock agriculture compared with no such employment is 1.5 (95% CL, 0.4 to 5.6). The RRs pertaining to farming occupations are the same (approximately 1.4) for persons who were farm managers and owners and for those who were farm workers. There is, however, no consistent trend (*P* value = 0.22 for trend test) between years of farming and HCC risk.

Chemical Exposures

Subjects were asked whether they had been exposed to any of 26 substances for at least 3 hours per week for at least six months in their work or in their leisure time. The matched RRs and their confidence limits were obtained for those substances to which at least 10 subjects had been exposed. Those substances were benzene, gasoline, other solvents, paints, dyes, grease, tar, asphalt, welding materials, glues, lacquer, asbestos, fertilizers, herbicides, and pesticides.

The RRs are elevated for exposure to fertilizers, herbicides, and pesticides (1.7, 1.5 and 2.4, respectively). However, the relationships between fertilizer and herbicide exposures and HCC are confounded by pesticide exposure. An indicator variable for each of these substances was included in a conditional logistic regression model, and the RRs for fertilizer and herbicide exposures were reduced to 1.1 and 1.0, respectively. However, the RR for pesticides remained elevated (RR = 2.1, 95% CL, 0.6, 6.9). Three cases and two controls had been exposed to pesticides in farming prior to 1970 when pesticides were made predominantly from organochlorine chemicals. These three cases had been exposed for 51, 50, and 23 years, whereas the two controls had been exposed for 3 and 28 years. The remaining exposed subjects (eight cases, nine controls) had been exposed because of home gardening, monthly pest extermination in their home, or residence near fields that had been sprayed with pesticides. Both cases and controls had been exposed to pesticides for a median of 11 years.

TABLE 1
Exposed Cases and Controls, the Relative Rates and Confidence Limits by Industry (80 Cases, 146 Controls)

Industry	Codes	No. of Exposed Cases	No. of Exposed Controls	RR*	95% Confidence Limits
Agriculture	13–78	18	32	1.1	0.6, 2.3
Construction	15–17	13	21	1.1	0.5, 2.4
Building	15	5	8	1.1	0.3, 3.7
Other than building trade	16	5	5	2.0	0.6, 6.9
Trade	17	4	9	0.7	0.2, 2.5
Manufacturing					
Food, tobacco	20–21	8	11	1.5	0.5, 4.1
Textile, apparel	22–23	11	21	1.0	0.4, 2.2
Lumber, wood, furniture	24–25	6	9	1.2	0.4, 3.6
Chemicals, petrochemicals	28–29	6	7	1.7	0.5, 5.4
Primary metal	33	6	11	1.3	0.3, 5.4
Machinery	35–36	3	13	0.4	0.1, 1.5
Transportation equipment	37	3	11	0.5	0.1, 1.9
Transportation					
Motor freight	42	6	8	1.3	0.4, 3.8
Wholesale trade	50–51	5	8	1.1	0.3, 3.6
Retail trade	52–59	25	49	0.9	0.5, 1.6
General merchandise	53	5	11	0.7	0.2, 2.5
Food stores	54	4	13	0.5	0.2, 1.6
Automotive dealers and gasoline service stations	55	5	10	0.9	0.3, 2.5
Eating and drinking places	58	4	10	0.7	0.2, 2.8
Miscellaneous	59	5	8	1.2	0.4, 3.9
Finance service	60–67	8	8	1.9	0.7, 5.4
Services					
Hotels	70	5	7	1.3	0.4, 4.0
Business services	73	3	6	1.0	0.2, 4.3
Health services	80	4	15	0.5	0.2, 1.5
Educational	82	9	21	0.8	0.3, 1.8
National security	97	31	49	1.5	0.7, 3.2

* Matched relative rates.

Seven cases and five controls had been exposed to asphalt (RR = 3.2; P value = 0.07; 95% CL, 0.9, 11). One exposed case and one exposed control had worked in the road building industry for 55 and 14 years, respectively. Another exposed case had worked as a laborer for an asphalt company and had been exposed directly to asphalt for 10 years. Among the remaining five exposed cases and four exposed controls, the RR of HCC is 2.3 (95% CL, 0.5 to 10).

Discussion

The present study has found no persuasively positive or negative relationship between HCC and any industry or occupation. The RRs for those industries and occupations for which there were at least ten exposed subjects are dispersed more or less equally below and above the null value of unity. However, in interpreting the findings of this study, it must be borne in mind that the RRs are based on few exposed subjects and are therefore quite imprecise. Case-control studies not designed specifically to investigate the role of a particular occupation in the etiology of some disease typically suffer this limitation of imprecision and lack of statistical power. Despite this limitation, several findings have emerged which warrant discussion, particularly if they are interpreted in light of previous investigations of HCC and occupation.

Stemhagen et al[7] reported statistically significant elevated RRs for HCC for men employed in eating and drinking places or as bartenders, and for men employed in laundering, cleaning, and other garment services. As seen in Tables 1 and 2, the present study found RRs below 1.0 for employment in eating and drinking places (RR = 0.7) and for employment in food and beverage service occupations (RR = 0.9). Only four subjects in the present study, all of whom are controls, had been employed in the laundering and cleaning industry.

On the other hand, Stemhagen et al reported a non-statistically significant elevated RR (2.2) of HCC for men who had been employed in the highway construction industry. Although only seven subjects in the present study reported a history of such employment, the resulting RR of 5.0 is just statistically significant and is the highest RR obtained for any industry or occupation examined in the present study. Furthermore, of the 15 chemical substances to which at least ten subjects had been exposed, the RR is highest for asphalt exposure, and this RR is almost statistically significant. The association between asphalt and HCC is not secondary to employment in road building, because the positive as-

TABLE 2
Exposed Cases and Controls, the Relative Rates and Confidence Limits by Occupation (80 Cases, 146 Controls)

Occupation	Codes	No. of Exposed Cases	No. of Exposed Controls	RR*	95% Confidence Limits
Executive, administrative, and managerial	11–14	8	19	0.8	0.3, 1.9
Teachers	23	7	7	2.2	0.6, 7.2
Marketing and sales occupations	40–41	20	31	1.2	0.6, 2.2
Clerical occupations	45–47	23	32	1.6	0.8, 3.3
Service occupations					
Protective	51	4	6	1.3	0.4, 4.7
Food and beverage preparation	521	6	12	0.9	0.3, 2.9
Cleaning and building service	524	3	9	0.5	0.1, 2.1
Farming	55–56	20	31	1.4	0.7, 2.9
Construction	60–61	14	22	1.1	0.5, 2.5
Carpenters	612	3	7	0.7	0.2, 2.9
Transportation and material moving	63–65	12	23	0.9	0.4, 1.9
Transportation	64	11	19	1.1	0.5, 2.3
Motor vehicle operators	641	9	16	1.1	0.5, 2.3
Mechanics and repairers	66–67	20	26	1.6	0.8, 3.1
Vehicle mechanics	671	6	7	1.6	0.5, 4.9
Electrical repairers	675	5	5	1.7	0.5, 6.1
Production work	71–79	20	50	0.7	0.4, 1.3
Precision products	72	2	13	0.3	0.1, 1.2
Machine operators	75–76	12	26	0.8	0.4, 1.8
Textile operators	765	6	12	0.9	0.3, 2.5
Fabricators, assemblers, and hand workers	77	2	9	0.4	0.1, 2.1
Production inspectors	78	3	8	0.7	0.2, 2.9
Material handlers, equipment cleaners	82	5	12	0.7	0.7, 2.4

* Matched relative rates.

sociation is evident among persons who had never worked in road construction. These observations could be chance findings. On the other hand, these findings may indicate that employment in occupations that entail considerable exposure to asphalt or to substances used in conjunction with asphalt may increase a person's risk of developing HCC. However, we are not aware of any other epidemiologic study that has implicated either road building or asphalt in the etiology of liver cancer. An excess of lung cancer was found in a retrospective follow-up study of roofers and waterproofers who were exposed to pitch and asphalt, but no mention of liver cancer is made in this report.[8]

Stemhagen et al[7] also reported a statistically significant association among men between employment in agricultural industries and HCC. Their RRs ranged from a low of approximately 1.3 for farm owners and managers to a high of 1.7 for men employed in the agricultural industry. The present study has also found a weakly positive relationship between farming and HCC, although our RRs are not statistically significant. Furthermore, a causal interpretation of our findings is diminished by the lack of a consistent relationship between years of farming and HCC. Other epidemiologic studies generally have not reported an excess of liver cancer among farmers.[9–12] For example, Milham[9] reported 69 liver cancer deaths among male farmers compared with an expectation of 68 in a proportionate mortality study in Washington state. The present study provides slight support to the inference that farming is weakly associated with HCC. However, it can reasonably be concluded from all the epidemiologic evidence that HCC is either not, or only weakly, related to farming.

The present study found a positive, although not statistically significant, association between pesticide exposure and HCC. This finding could be a result of recall bias; that is, a propensity for cases to more readily recall their exposures to pesticides than controls did. However, this type of bias presumably did not affect the RRs pertaining to the majority of the other chemicals, since most are in the vicinity of unity. Furthermore, there is no positive association between HCC and either herbicides or fertilizers after adjustment for pesticide use. Thus, it seems unlikely that recall bias would affect pesticide exposures and not other substances, particularly herbicides and fertilizers.

There is some biologic credibility to the hypothesis that pesticides are a cause of HCC. Many of the organochlorine pesticides induce liver tumors in rodents, particularly mice. For example, chlordane and heptachlor produce HCC in mice[13,14]; dichlorodiphenyltrichloroethane (DDT) causes benign and malignant liver tumors in mice and rats[14,15]; and dieldrin and toxaphene cause liver cancer in mice, but not in rats.[13,14,15] On the

other hand, the organophosphate pesticides such as malathion, methyl parathion, and parathion whose use increased considerably in the 1970s are not carcinogenic in animals.[16]

Two retrospective follow-up studies of pesticide applicators[17,18] and two of workers engaged in the manufacture of pesticides[19,20] found no excess of liver cancer deaths, although they do not, together, rule out an increase as large as twofold. In the four studies combined, the total number of observed liver cancer deaths is only four *v* an expectation of 4.2. The corresponding standardized mortality ratio (SMR) is 95 with 95% confidence limits, 26 to 244.

The lack of a consistent dose-response relationship between years of pesticide exposure and HCC suggests that our finding does not reflect a causal relationship. Furthermore, a causal interpretation is diminished by the observations that the study is small and that the elevated RR is explained, in part, by exposures of an intermittent and ill-defined nature, some of which probably involved organophosphate compounds. Thus, although the results suggest a positive association between pesticide exposures and HCC, this finding is not persuasive.

In summary, the present study has found no persuasively positive or negative association between HCC and any occupational or chemical exposures. However, the findings suggest that pesticides and exposures sustained in road construction, particularly asphalt, may increase HCC risk.

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