CME Article #3

Interaction of Vinyl Chloride Monomer Exposure and Hepatitis B Viral Infection on Liver Cancer

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Learning Objectives

- Identify previously reported findings relating occupational vinyl chloride monomer (VCM) exposure to liver disease.
- Relate how – and to what extent – hepatitis B surface antigen (HBsAg) status and particular job-related tasks interact to increase the risk of hepatocellular carcinoma in workers exposed to VCM.
- Explain postulated mechanisms by which hepatitis B virus infection and VCM exposure may interact to cause liver cancer.

Abstract

Vinyl-chloride monomer (VCM), a human carcinogen, has caused angiosarcoma of the liver. Recent studies have shown that VCM exposure is associated with hepatocellular cancer. In Taiwanese studies, the majority of VCM-exposed workers with liver cancer had history of hepatitis B virus (HBV) infection. To determine the role of HBV on the development of liver cancer in the VCM-exposed workers, we conducted a case-control study from a previously established polyvinyl chloride (PVC) cohort consisting of 4096 male workers from six PVC polymerization plants. A total of 18 patients with liver cancer, and 68 control subjects matched for age and specific plant of employment were selected. Detailed history of the participants that included alcohol consumption status, cigarette use, occupation, and family history of chronic liver disease were obtained using an interviewer-administered questionnaire. When the HBV surface antigen (HBsAg)-negative subjects without history of tank-cleaning were used as the reference, the HBsAg-negative subjects with history of tank-cleaning demonstrated a 4.0-fold greater risk of liver cancer (95% confidence interval: 95% CI = 0.2–69.1). The HBsAg carriers without history of tank-cleaning revealed a 25.7-fold greater risk of liver cancer (95% CI = 2.9–229.4). Whereas the HBsAg carriers with history of tank-cleaning revealed the greatest risk (matched odds ratio (OR_m) 396.0, 95% CI = 22.6–∞) of developing liver cancer among subjects with different VCM-exposure status and HBsAg status categories. Further analysis showed the interaction term was significant (P < .01). Therefore, our results suggest an interaction between occupational VCM exposure and HBV infection for the development of liver cancer. (J Occup Environ Med. *2003;45:379–383*)

An association between occupational vinyl chloride monomer (VCM) exposure and angiosarcoma of the liver (ASL) has been demonstrated in previous studies.[1,2] Results of a previous study also showed hepatocellular carcinomas (HCC) in workers with occupational exposure to VCM.[3] Morbidity data of polyvinyl chloride (PVC) workers in Taiwan showed that they are at a higher risk of developing liver cancer than, for example, optical workers (morbidity odds ratio (MOR) 4.5) or motorcycle workers (MOR 6.5).[4] Our recent retrospective cohort study also revealed that Taiwanese PVC workers in Taiwan exhibited an elevated standardized mortality ratio for liver cancer as compared to the general male population.[5] In both studies conducted in Taiwanese PVC workers, a majority of the patients had hepatocellular cancer and experienced hepatitis B virus (HBV) infection.

Chronic HBV infection is common and presents in 15% to 20% of the Taiwanese population.[6,7] Epidemiological studies indicate that HBV infection exerts a synergistic interaction on the development of liver cancer with certain chemical exposures, such as aflatoxin[8,9] and alcohol.[10] However, it is not yet clear as to whether VCM and HBV exhibited an interaction in the development of liver cancer. Thus, we designed a case-control study based upon the above-mentioned study cohort in order to elucidate whether VCM exposure and HBV infection demonstrate

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This study was supported in part by IOSH 88-M101 and the Department of Health, Taiwan.

Tsun-Jen Cheng has no commercial interest related to this article.

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DOI: 10.1097/01.jom.0000063622.37065.fd

interaction on the development of liver cancer.

Study Design and Method

Study Cohort and Cases Identification

Polyvinyl chloride has been manufactured in Taiwan since the 1950s. We retrospectively established a cohort consisting of 4096 workers from six PVC manufacturing factories.[5] By linking cohort subjects with Taiwan's National Mortality Registry and National Cancer Registry systems, 25 cases of liver cancer were identified from 1985 through 1997. Medical records were successfully retrieved for 18 of these 25 workers in order to obtain information including HBV surface antigen (HBsAg) status, histopathological examination reports, and any available imaging results (sonography, and/or angiography, and/or computerized tomography). Among the 18 liver cancer subjects, five cases were confirmed to suffer from HCC by histopathological evidence. An additional five cases were also regarded as HCC due to extremely high serum levels of α-fetoprotein (>1000 μg/liter) and at least one positive image from angiography, sonography, liver scan, and/or from a computed tomography scan.[7,11] A further eight cases were diagnosed based upon the subjects' clinical manifestation and imaging studies.

Selection of Controls

A 1:4 ratio of cases to control subjects was used in this study. The control subjects were matched individually to the cases on age (±5 years) and specific plants of employment. Control subjects were selected randomly from a pool of eligible workers who underwent detailed questionnaires, whose HBsAg status was known, and who were free from any evidence of chronic liver disease. However, two patients ended up with incomplete matching. Overall, 18 male case examples and 68 male control subjects were included in the analysis conducted herein.

Epidemiological Information and Hepatitis Virus Infection Status

Information pertaining to personal characteristics was collected for PVC workers using interviewer-administered questionnaires during the medical surveillance period. Informed consent was obtained from all participants. For the study subjects who had died during the study, interviews were conducted with their immediate relatives. In order to reduce the effects of recall bias, this information was further verified by questioning the coworkers of the deceased, and especially any industrial hygienists. The structured questionnaire contained questions that covered demographic characteristics, life styles including habits of cigarette smoking and alcohol consumption, detailed occupational history as well as personal and family history of chronic liver diseases. The subject's smoking history included the number of cigarettes smoked daily and the duration of the subject's smoking habit. Because the amount of alcohol consumed by Taiwanese people is low, habitual alcohol drinking was defined as alcohol consumption on at least one occasion weekly and consuming more than 80 g of alcohol weekly. Family history of chronic liver disease was defined as chronic liver disease within the first-degree relatives of the test subjects. The HBsAg status, determined using radio-immunoassay (RIA; Abbott Laboratories, Chicago, IL) or enzyme-linked immunosorbent assay (ELISA; Austrial-II, Abbott Laboratories), was also obtained from medical surveillance records.

Assessment of VCM Exposure

To determine the association between VCM exposure and liver cancer, several exposure indices were used. Because cumulative doses of VCM exposure could not be calculated for some cases due to the lack of detailed work history, we chose to use job titles as exposure indices (tank cleaning, yes versus no; high exposure job, yes versus no). In the processes of PVC polymerization, VCM along with catalysts, stabilizers, emulsifiers, and additives were administrated into a polymerization tank. The mixture was heated under pressure and the polymerization took place. After polymerization, the tanks were opened and cleaned manually. Thus, workers involved in the tank cleaning were exposed to the highest concentrations of VCM compared with other workers. In addition to tank cleaning, workers involved in PVC unloading and catalyst adding were also exposed to relatively high levels of VCM.[12] Thus, high-exposure jobs in this study included tank cleaning, PVC unloading, and catalyst adding.

Statistical Analysis

Comparisons between the case group and control group for age, proportion of HBV infection, smoking behavior, alcohol consumption status, and family history of chronic liver disease were conducted using the *t* test for continuous variables and χ^2 test or Fisher's exact test for discrete variables. Again, comparisons between the case group and control group for various indices of VCM exposure were performed. Subsequently, a conditional logistic model was employed to obtain the matched odds ratio (OR_m) and 95% confidence interval (95% CI) for each variable. Likelihood ratio χ^2 tests were also used to test the interaction between HBV infection and VCM exposure with respect to the risk of liver cancer. All *P* values were calculated using two-tailed statistical tests.

Results

Basic characteristics and potential risk factors for odds ratios of liver cancer in the 18 cases and 68 matched control subjects are presented in Table 1. The mean age of the subjects was 56.7 ± 8.8 (SD) years. Twenty eight (32.6%) subjects

TABLE 1
Basic Characteristics and Matched Odds Ratios of Liver Cancer in Liver Cancer Cases and Controls

	Cases (n = 18)	Controls (n = 68)	Matched odds ratio[a]	
			OR_m	95% CI
Age (years)	57.2 ± 8.5[b]	56.6 ± 9.0		
HBsAg-positive status	16 (88.9%)**	13 (19.1%)	15.7	3.6–68.4
Smokers	2 (11.1%)*	26 (38.2%)	0.3	0.1–1.1
Habitual alcohol drinkers	0 (0.0%)	6 (8.8%)		
Family history of chronic liver disease	1 (5.6%)	2 (2.9%)	1.6	0.2–12.2
Exposure indices				
History of tank-cleaning	10 (55.6%)**	12 (17.6%)	3.6	1.4–9.2
History of high VCM-exposure jobs	10 (55.6%)**	16 (23.5%)	2.9	1.1–7.3

[a] Matched for age and specific plant of employment.
[b] Mean ± SD.
* $0.01 < P < 0.05$, ** $P < 0.01$, cases v controls.

were smokers, six (7.0%) were habitual drinkers, and only three (3.5%) had family history of chronic liver diseases.

HBsAg carrier status (OR_m 15.7, 95% CI = 3.6–68.4), former/current tank cleaning occupation (OR_m 3.6, 95% CI = 1.4–9.2), and history of high exposure job (OR_m 2.9, 95% CI = 1.1–7.3) were significantly associated with liver cancer. However, smoking, habitual drinking, and family history of chronic liver disease were not associated with liver cancer.

Stratified analyses were further conducted to explore the interaction between VCM exposure status and HBsAg status categories upon liver cancer (Table 2). When the subjects that were HBsAg negative without history of tank cleaning were used as the reference, the HBsAg-negative subjects with history of tank cleaning demonstrated a 4.0-fold greater risk of liver cancer (95% CI = 0.2–69.1). The HBsAg carriers without history of tank cleaning revealed a 25.7-fold greater risk of liver cancer (95% CI = 2.9–229.4), whereas the HBsAg carriers with history of both tank cleaning revealed the greatest risk (OR_m 396.0, 95% CI = 22.6–∞) of developing liver cancer among different VCM exposure status and HBsAg status categories. Similar relationships were observed when history of high-VCM-exposure jobs replaced history of tank cleaning in the analysis. When the subjects that were HBsAg negative without history of high-exposure job were used as the reference, the HBsAg-negative subjects with history of high-exposure job demonstrated a 2.9-fold greater risk of liver cancer (95% CI = 0.2–50.0). Those HBsAg carriers without history of high-exposure job revealed a 26.1-fold greater risk of liver cancer (95% CI = 2.9–235.1), whereas the HBsAg carriers with history of high-exposure jobs revealed the greatest risk (OR_m 184.5, 95% CI = 15.0–∞) of developing liver cancer. Furthermore, interaction between HBsAg status and either VCM exposure status on the risk of liver cancer was significant ($P < .01$).

Discussion

The results of our study demonstrated an interaction between VCM exposure and HBsAg status upon the risk of liver cancer. The relationship between ASL and VCM exposure has been established.[1,2] However, we did not observe any case of ASL in our current study. Because tissue proof has been relatively uncommon for liver cancer in Taiwan, a diagnosis of ASL may not be convincingly made.[13] ASL has accounted for more than half of liver cancers in previous studies.[1,2] The lack of ASL in our cohort was probably due to the much lower levels of VCM exposure in our study subjects as compared to those in Western workers. The PVC industry began in 1958 in Taiwan, which was two to three decades later than that in Western countries. It has been estimated that in the early years, workers in Western countries might have been exposed to as high as 1000–2000 ppm of VCM prior to 1960.[14] A job exposure matrix model developed by Du et al[15] in 2001 revealed that VCM exposure for Taiwanese workers was about 500 ppm in the 1960s. Furthermore, the p53 mutation in liver cancer cells and serum oncoprotein p53 were observed in VCM-exposed workers.[16,17] The prevalence of serum oncoprotein p53 in Taiwanese PVC workers was much lower than that in Western workers.[16–18] This suggests that the levels of VCM exposure in Taiwanese workers were not as high as those in Western workers.

An association between VCM and hepatocellular cancer has been demonstrated in Taiwanese PVC workers.[5] During the current study, we observed an increased risk of liver cancer with VCM exposure. The association was not significant probably due to the rather small sample size ($n = 18$) for liver cancer. Although a recent follow-up study in European VCM-exposed workers suggest a link between hepatocellular cancer and VCM exposure,[2] the association between VCM exposure and hepatocellular cancer in Western VCM-exposed workers has been less demonstrated. This in part may be explained by the fact that the HBV, one of major risk factors for hepatocellular cancer, is less prevalent in Western countries. With the interaction between HBV and VCM exposure, VCM-exposed workers tend to have higher risk of HCC in the area where HBV is prevalent.

Earlier epidemiological studies have demonstrated that HBV infection is the most important risk factor for liver cancer in Chinese.[8,19] Chen

TABLE 2
Odds Ratio of Liver Cancer in Related Risk Factors Stratified by HBsAg Status[a]

	HBsAg status					
	HBsAg negative			HBsAg positive		
	Cases/Controls	OR	95% CI	Cases/Controls	OR	95% CI
History of tank-cleaning						
Yes	1/11	4.0	0.2–69.1	9/1	396.0	22.6–∞
No	1/44	1.0	Reference	7/12	25.7	2.9–229.4
	Test for interaction: $\chi^2 = 16.8$ (1 df); $P < 0.01$					
History of high VCM-exposure jobs						
Yes	1/14	2.9	0.2–50.0	9/2	184.5	15.0–∞
No	1/41	1.0	Reference	7/11	26.1	2.9–235.1
	Test for interaction: $\chi^2 = 16.6$ (1 df); $P < 0.01$					

[a] Adjusted for family history of chronic liver diseases.

and Sung[20] in 1978 reported that the prevalence of HBsAg was 82.7% among Taiwanese hepatoma patients. In the present study, workers suffering from liver cancer also demonstrated a high prevalence (88.9%) of the presence of HBsAg.

Several researchers have reported the synergistic effects of HBV infection and some chemical exposure to alcohol[10] and aflatoxin[8,9] in producing liver cancer. Nonetheless, to the best of our knowledge, any interaction between HBV and VCM upon liver cancer has not been previously reported. Here, we observed an interaction of HBsAg and VCM exposure on the risk of liver cancer when different exposure indices were used.

The mechanism of interaction between HBV infection and VCM exposure in the etiology of liver cancer remains unclear. One possibility is that liver cells infected with HBV exist in an inflammation state leading to the depletion of glutathione.[21] The electrophilic intermediate metabolites are conjugated with glutathione to be detoxified.[22] Thus, liver cells infected with HBV may accumulate more active metabolites of VCM and be more readily susceptible to challenges with chemical carcinogens. A study has shown that HBV X (HBx) can bind to the p53 tumor-suppressor protein and inhibit its DNA binding.[23] Results of recent studies have revealed that HBx may inhibit cellular DNA repair.[24] Thus, HBV infection may impair the capacity of hepatocytes to correct DNA damage elicited by chemical carcinogens. This hypothesis appears to be supported by a study of a transgenic mouse model, in which the expression of HBx enhanced the frequency of aflatoxin B1-induced p53 mutation.[25] Another possible explanation for the association between VCM exposure and HBV infection upon the liver cancer is that HBV influences the hepatic expression of metabolizing enzymes[26] and leads to a state of increased DNA damage. Studies have reported that VCM is metabolized into active chloroethylene oxide and chloroacetaldehyde by cytochrome P450 enzymes.[27,28] Thus, the modification of the metabolic enzymes may affect the DNA damage elicited by exposure to VCM.

In addition to HBV infection, many other possible etiological factors have been implicated in the development of chronic liver damage, including hepatitis C virus (HCV) infection,[10,29] arsenic exposure,[30,31] aflatoxin exposure,[8,9] alcohol consumption,[10,19] and family tendency toward chronic liver disease.[19] In our study, we carried out record linkage of our study subjects with those from the Blackfoot Disease cohort in Taiwan,[30,31] the study of which focused upon identifying the possible association between arsenic exposure and certain cancers, although none of our study subjects were present in the Blackfoot Disease cohort list. In our study, the association between liver cancer with habitual alcohol drinking, smoking, and a family history of chronic liver disease in VCM-exposed PVC workers was not demonstrated. The number of subjects with history of alcohol drinking, smoking, and family history of chronic liver disease was small. These may explain why the purported risk factors do not explain the risks of liver cancer for VCM-exposed workers. Because techniques for the detection of anti-HCV antibody in Taiwan became available after 1992, HCV infection status was not included in our analysis. Our recent study reported that 2.4% of VCM-exposed PVC workers had anti-HCV antibody.[32] Apparently, HCV infection did not affect the results in the present study.

Our results showed a potential interaction between HBV and VCM exposure on liver cancer. However, this study had the limitation of small number of subjects, especially subjects with liver cancer. Thus, this association might be attributable to chance or other factors including diagnostic criteria for liver cancer. Further follow-up is warranted to confirm the findings in this study.

Acknowledgment

We would like to thank the Bureau of Health Promotion and Protection, the Office

of Statistics, Department of Health, and Dr Chien-Jen Chen for their assistance in data linkage. We are grateful to Ms Chia-Hui Hsu, Ms Shih-Yi Lee, and Ms Hsiao-Die Chiang for their management of the cohort data. We are also indebted to Dr Jing-Shiang Hwang for his statistical assistance and Dr Fung-Chang Sung for his helpful comments.

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