Liver Fibrosis in Asymptomatic Polyvinyl Chloride Workers

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This study was designed to determine whether vinyl chloride monomer (VCM) exposure is associated with liver fibrosis. A total of 347 workers with occupational exposure to VCM were systemically examined using liver ultrasonography and routine liver function tests. Vinyl chloride monomer cumulative dose (ppm-month) was estimated by summing the products of air VCM concentration levels and months of employment. Liver fibrosis was defined in subjects with precirrhosis and cirrhosis of liver diagnosed using ultrasonography. Significantly increased risks of developing liver fibrosis were found in workers who had history of high exposure jobs (odds ratio 5.5, 95% confidence interval 1.7–25.4) when compared with workers who did not have history of high exposure jobs. We concluded that there was an increased risk of developing liver fibrosis in PVC workers who had high exposure to VCM. (J Occup Environ Med. *2004;46:962–966*)

According to the results of epidemiological studies, angiosarcoma of the liver has been associated with vinyl chloride monomer (VCM) exposure.[1] Thus, VCM has been classified as a group I carcinogen by International Agency for Research on Cancer.[2] However, the association between VCM exposure and liver cirrhosis is less clear. Cases of liver cirrhosis have been reported in PVC workers with high doses of VCM exposure.[3,4] Recently, PVC workers were found to have an increased risk of liver cirrhosis as compared with control subjects.[5] However, the effects of hepatitis viral infection on liver cirrhosis could not be separated from the VCM exposure in previous studies. Because the number of cirrhosis was small, we further included precirrhotic fibrosis of liver in this study to investigate whether VCM exposure leaded to liver fibrotic change, which consisted of precirrhosis and cirrhosis[6] as diagnosed by liver ultrasonography.

Liver function tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transpeptidase (GGT) have been widely used in medical surveillance on those who are exposed to hepatic toxins. Liver function has been less reliable in detecting chronic liver diseases particularly for liver cirrhosis and liver cancer than other methods of diagnosis. Thus, we also compared the prevalence of abnormal results on liver function tests between individuals with and without liver fibrosis diagnosed using results of liver ultrasonography.

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Materials and Methods

After informed consent was obtained from each subjects, we performed liver ultrasonographic examinations on 382 workers from five polyvinyl chloride (PVC) manufacturing plants from 1994 through 1997. All these workers had no symptoms of liver disease and were currently working in the plants. Considering the induction period of chronic liver disease, we excluded the workers with working history of polyvinyl chloride production of less than 1 year. Female workers were also excluded because of small number. Thus, a total of 347 male workers were included for analysis.

Each worker completed an interviewer-administered questionnaire with questions that pertained to history of alcohol consumption, tobacco smoking, medicine, and work environment. We used air vinyl chloride concentrations as determined by Du et al[7] in 1995 to ascertain the association between VCM exposure and abnormal liver function. Briefly, personal samplings were performed to calculate median TWA concentrations of VCM for each category of work. If personal sampling was not available, data of area sampling were used. The VCM levels ranged between less than 1 ppm to 80 ppm. To further determine the association between cumulative VCM exposure and liver fibrosis, several exposure indices were used. Cumulative VCM exposure doses (ppm-month) for the study subjects were calculated by summing the product of air VCM concentration levels, as previously determined, and months of employment.[7] Because the above methodology may underestimate the exposure dosage of early years, history of high VCM-exposure jobs, including reaction tank cleaning, PVC unloading, and catalyst adding, also were used as exposure indices. The median of cumulative exposure dose among those workers with the history of high exposure jobs was approximately 2400 ppm-month. Thus, those with history of high-exposure jobs were further divided into high- and moderate-exposure groups using 2400 ppm-month as the cutoff point, whereas the low cumulative VCM exposure group was defined as having never been involved in the high-exposure jobs. The median of duration of employment for those with history of high exposure jobs was 40 months. Again, we divided those with the history of high-exposure jobs into two groups using 40 months as the cutoff point.

Current alcohol drinking was defined as having consumed greater than or equal to one drink per week. Total amount of alcohol consumed for each worker also was calculated. Current tobacco smoking was defined as having at least one cigarette per day. Number of pack-years of cigarette smoking was also calculated for each worker. Obesity was defined as body mass index (BMI) greater than or equal than 25.[8] Liver enzymes of AST, ALT, GGT, and HBsAg and Anti-HCV were determined at the National Taiwan University Hospital (NTUH). Abnormalities of AST, ALT, and GGT were defined as having values greater than the reference ranges at NTUH, and positivity of HBsAg and anti-HCV was determined according to the manufacturers' recommendation. Ultrasonographic examinations of liver and spleen also were performed in each worker (Toshiba, model SAL-38B equipped with a 3.75 MHz convex-type transducer) by three hepatologists at NTUH, who were blind to the exposure status of these workers and applied the same criteria to make the diagnoses of liver fibrosis, fatty liver, and splenomegaly.[6,9] Liver fibrosis includes precirrhosis and cirrhosis, both of which have heterogeneous echo patterns. Liver cirrhosis, a more advanced form of liver fibrosis, was diagnosed in the presence of coarse echo patterns with and without irregular surface outlines. Fatty liver was recognized by increased liver echogenicity.

Statistical analysis was performed using SAS (SAS Institute, Cary, INC) edition 6.12. Analysis of variance was used to compare the continuous variables, and chi-square test or the Fisher exact test was used to compare the interval variables among different exposure groups for abnormal liver functions and liver fibrosis. Subsequently, multiple logistic regression models were used to assess whether VCM exposure, hepatitis viral infection, body mass index, alcohol consumption, and tobacco smoking were associated with abnormal liver enzymes and liver fibrosis.

Results

The basic characteristics of the 347 study subjects are shown in Table 1. The average age of the workers was 41 ± 10 (mean ± SD) years. The median cumulative dose of VCM exposure for the workers was approximately 2400 ppm-month. The average BMI was 24.0 ± 2.6. Sixty-one (17.6%) workers consumed alcohol regularly. Positive results for HBsAg were found in 73 (21.0%) workers. The subjects were not tested for Anti-HCV before 1995. Among the 290 workers who had anti-HCV data, eight (2.8%) workers tested positive. The prevalence of abnormal AST, ALT, and GGT were 6.3%, 10.7%, and 13.5%, respectively. Results for ultrasonographic examinations among different exposure groups are compared in Table 2. Twenty subjects (5.8%) were diagnosed with liver fibrosis and seven (2.0%) with cirrhosis of the liver. Among these 20 workers with liver fibrosis, only 10 had at least one abnormality in liver function tests. Proportion of liver fibrosis was significantly higher in the high-exposure group as compared with the low-exposure group. Splenomegaly was found in 32 (9.2%) workers. The association between splenomegaly and VCM exposure was not significant. Fatty liver was observed in 135 (38.9%) workers, which was the most common ultrasonographic find-

TABLE 1
Basic Characteristics of Study Subjects According to Type of Exposure Groups

	Cumulative Dose†			
	High	Moderate	Low	Total
Numbers	97	97	153	347
Age (years)**	43 ± 9‡	38 ± 9	42 ± 10	41 ± 10
Working duration (years)**	18.4 ± 8.9	12.9 ± 8.9	17.1 ± 10.2	16.3 ± 9.7
Body mass index (BMI)	24.4 ± 2.6	23.6 ± 2.7	23.9 ± 2.6	24.0 ± 2.6
Current alcohol drinking*	25 (25.8%)	15 (15.5%)	21 (13.7%)	61 (17.6%)
Current tobacco smoking	14 (14.4%)	22 (22.7%)	34 (22.2%)	70 (20.2%)
HBsAg (+)	28 (28.9%)	16 (16.5%)	29 (19.1%)	73 (21.0%)
Anti-HCV (+)	3 (3.7%)	1 (1.3%)	4 (3.0%)	8 (2.8%)¶

† High, workers who had history of high exposure jobs and the cumulative dose of exposure equal to or greater than 2400 ppm-month (median 4316, range, 2402–20413); moderate, workers who had the history of high exposure jobs and the cumulative dose of high exposure jobs less than 2400 ppm-month (median 963; range, 88–2361); low, workers who never had high exposure jobs (median 147; range, 2–3498).

‡ Mean ± SD.

** $P < 0.01$, ANOVA test; * $P < 0.05$, chi-square test.

¶ Anti-HCV data available in 290 workers.

TABLE 2
Abnormal Ultrasonographic Findings of Different Cumulative VCM Exposure Groups

	Cumulative Dose			
	High	Moderate	Low	Total
Number	97	97	153	347
Liver fibrosis**	12 (12.4%)	5 (5.2%)	3 (2.0%)	20 (5.8%)
Precirrhosis*	8 (8.3%)	3 (3.1%)	2 (1.3%)	13 (3.8%)
Cirrhosis	4 (4.1%)	2 (2.1%)	1 (0.7%)	7 (2.0%)
Splenomegaly	11 (11.3%)	11 (11.3%)	10 (6.6%)	32 (9.2%)
Fatty liver	36 (37.1%)	38 (39.2%)	61 (39.9%)	135 (38.9%)

* $P < 0.05$, ** $P < 0.01$, chi-square test.

Numbers in parentheses indicate percentages.

ing among these workers. However, fatty liver was not associated with VCM exposure. Eight subjects had small hemangiomas. However, we did not observe any focal lesion, which was consistent with either angiosarcoma of liver or hepatocellular cancer.

Multiple logistic regression models revealed that VCM exposure was not associated with fatty liver, and overweight was the only factor associated with fatty liver (OR 5.1, 95% CI = 3.1–8.6). Table 3 summarized the results of analysis, which observed that subjects with abnormal AST were associated with viral hepatitis (OR 7.3, 95% CI = 2.8–20.4) and habitual drinking (OR 3.1, 95% CI = 1.1–8.4). Subjects with abnormal ALT were associated with viral hepatitis (OR 3.0, 95% CI = 1.4–6.4) and overweight (OR 2.6, 95% CI = 1.2–5.5). Furthermore, subjects with abnormal GGT were associated with habitual drinking (OR 3.9, 95% CI = 1.9–8.0). Although those with VCM exposure greater than 10 ppm tended to have higher risk of abnormal ALT and AST as compared with those with VCM less than 10 ppm, the relationship was not statistically significant.

Logistic regression models were further used to analyze the association between VCM exposure and liver fibrosis (Table 4). Workers with history of high exposure jobs had an OR of 4.5 to develop precirrhosis (95% CI = 1.1–30.1) compared with workers without history of high-exposure jobs. Similar results were also obtained for those with cirrhosis (OR 5.8; 95% CI = 0.9–116.8). When we combined precirrhosis and cirrhosis together as liver fibrosis, workers with history of high-exposure jobs had higher risk of developing liver fibrosis (OR 5.5; 95% CI = 1.7–25.4). Viral hepatitis B and/or C infections and overweight were also found to be independent risk factors for liver fibrosis in these models. Three different exposure indices were further used to test the association between cumulative VCM exposure dose and liver fibrosis. Workers with history of high-exposure jobs were divided into high and moderate cumulative VCM exposure groups. These groups had odds ratios for liver fibrosis of 5.9 (95% CI = 1.7–28.2) and 4.6 (95% CI = 1.0–25.5), respectively, as compared with the workers without history of high-exposure jobs. Workers with history of high-exposure jobs were also divided by the duration of work. Those with longer duration of high exposure jobs had OR of 3.7 (95% CI = 1.0–18.3) and those with shorter duration had OR of 6.3 (95% CI = 1.6–33.1) as compared with those without history of high exposure.

When low-exposure workers with neither HBsAg nor anti-HCV were used as a reference group, risk of liver fibrosis was higher in low-exposure workers with HBsAg and/or anti-HCV and in high-exposure workers with neither HBsAg nor anti-HCV (OR 7.9 and 4.2, respectively). High-exposure workers with HBsAg and/or anti-HCV experienced the highest risk (OR 40.8). However, the interaction term between hepatitis infection and VCM exposure on liver fibrosis was not significant.

Discussion

Increased morbidity OR of liver cirrhosis among Taiwanese vinyl chloride monomer-exposed workers has been previously reported.[5] In this study, we further observed that high

TABLE 3
Multiple Logistic Regression Models of Abnormal Liver Function Tests in PVC Workers

	AST		ALT		GGT	
	Abnormal (n)	Odds ratio† (95% CI)	Abnormal (n)	Odds ratio† (95% CI)	Abnormal (n)	Odds ratio† (95% CI)
Current VCM exposure						
≥10 ppm (n = 61)	7	1.3 (0.4–3.9)†	12	2.0 (0.8–5.0)	9	1.1 (0.4–2.8)
1–10 ppm (n = 151)	6	0.7 (0.2–2.1)	13	1.1 (0.4–2.5)	23	1.5 (0.7–3.2)
<1 ppm (n = 135)	9	1.0	12	1.0	15	1.0
Viral hepatitis‡						
Yes (n = 79)	14	7.3** (2.8–20.4)	16	3.0** (1.4–6.4)	16	1.9 (0.9–3.9)
No (n = 268)	8	1.0	21	1.0	31	1.0
Body mass index						
≥25 (n = 111)	10	1.9 (0.7–5.0)	18	2.6* (1.2–5.5)	18	1.1 (0.5–2.1)
<25 (n = 236)	12	1.0	19	1.0	29	1.0
Current alcohol drinking						
Yes (n = 61)	9	3.1* (1.1–8.4)	10	1.5 (0.6–3.4)	19	3.9** (1.9–8.0)
No (n = 286)	13	1.0	27	1.0	28	1.0

† Adjusted for tobacco smoking and age.
‡ Viral hepatitis, HBsAg positive and/or Anti-HCV positive.
* $P < 0.05$, ** $P < 0.01$.

TABLE 4
Multiple Logistic Regression Models of Precirrhosis, Cirrhosis, and All Fibrosis Cases in PVC Workers

	Precirrhosis[a]	Cirrhosis[a]	Fibrosis[b]
	Odds Ratio† (95% CI)	Odds Ratio† (95% CI)	Odds Ratio† (95% CI)
Case Number	13	7	20
History of high exposure jobs			
Yes (n = 194)	4.5* (1.1–30.1)	5.8 (0.9–116.8)	5.5* (1.7–25.4)
No (n = 153)	1.0	1.0	1.0
Viral hepatitis‡			
Yes (n = 79)	8.8** (2.7–34.4)	9.2** (1.8–69.9)	10.7** (3.9–33.4)
No (n = 268)	1.0	1.0	1.0
Body mass index			
≥25 (n = 111)	2.9 (0.9–10.1)	2.5 (0.5–14.9)	3.1* (1.1–9.1)
<25 (n = 236)	1.0	1.0	1.0

† Adjusted for alcohol drinking, tobacco smoking, and age.
* $P < 0.05$, ** $P < 0.01$.
‡ Viral hepatitis, HBsAg positive and/or Anti-HCV positive.
[a] The case of precirrhosis diagnosed by ultrasonography.
[b] The sum of cases of precirrhosis and cirrhosis.

VCM exposure jobs were associated with precirrhosis, cirrhosis, and liver fibrosis in asymptomatic workers. Data of anti-HCV were not available in 2 of 20 cases with liver fibrosis. Assuming the worst scenario that these two subjects had positive anti-HCV, VCM exposure remained associated with liver fibrosis. As we have already controlled alcohol drinking, hepatitis B and/or C infections and BMI in our multiple logistic regression models, we suspect that the association may be a causal one and deserves further attention. Recently, increased periportal fibrosis of liver diagnosed by ultrasonography was also reported in Italian workers.[10]

Although different exposure models consistently showed that workers with history of high-exposure jobs had an increased risk of liver fibrosis, the dose–response relationship was less prominent for cumulated exposure. Moreover, there was no such relationship in the analysis of work duration. Duration is not a sensitive indicator because it can't reflect the difference between current and remote exposure levels. The cumulative dose is also not sensitive enough, because the remote exposure is very likely under estimated. Thus, methodology of cumulated dose calculation needs to be improved.

Because our study was conducted in asymptomatic workers only, selection bias cannot be completely ruled out. Those with advanced liver cirrhosis may leave their job earlier. Because they tend to have high VCM exposure, the real risk of liver cirrhosis from VCM exposure may be underestimated. When these workers leave their job because of HBV or HCV status, the real OR may remain, given the VCM exposure status is evenly distributed in these workers. In fact, the proportion of positive HBsAg and anti-HCV in the current study was compatible with that in general population. Therefore, the true OR of liver fibrosis for VCM exposure may be higher.

In our study, hepatitis B and/or C viral infection carried an OR of 10.7 for liver fibrosis, which is consistent

with previous studies in Taiwan.[11–13] Model fitting also revealed that there was a potential multiplicative effect between viral hepatitis and VCM exposure on liver fibrosis. Because the number of subjects with liver fibrosis was small in our study, further verification is needed.

The other independent risk factor for developing liver fibrosis was obesity, or BMI $\geq$25, as shown in Table 4. In our present study, workers with liver fibrosis had higher BMI than those without fibrosis (25.9 ± 2.0 vs. 23.9 ± 2.6, Student's t test, $P < 0.001$). In a recent study by Ratziu et al[14] in 2000, 93 overweight patients without any known risk factors of liver damage had persistently elevated ALT levels. Among them, 28 patients (30%) had septal fibrosis including 10 subjects with cirrhosis. The possible mechanism was that the excess weight-induced nonalcoholic steatohepatitis via lipid peroxidation.[15,16] Although the progression from nonalcoholic steatohepatitis to liver fibrosis is slow, some study results showed that approximately 37% of patients with fatty liver had undergone this change.[17–19] Thus, body weight reduction program may be considered in future health promotion for workers with increased BMI.

William et al[20] in 1976 were among the first to use ultrasonographic examinations for monitoring chronic liver disease in PVC manufacturing workers. They detected abnormal findings of ultrasonography in 5 of 10 workers with normal liver function. However, they did not claim the finding to be a fibrosis probably because of the low resolution of the instrument, and they did not control other potential confounders for fibrosis. Because ultrasonographic machines with high resolution have become portable, liver ultrasonography should be considered in addition to traditional liver function tests in the medical surveillance for PVC workers, especially those with hepatitis viral infection. The high resolution of our machine also allowed us to differentiate heterogeneous and coarse echotexture of liver fibrosis from increased echogenicity, which was a sign of fatty liver. However, these might still be some misclassification if the diagnosis of fibrosis is based solely on ultrasonography. A previous study showed that the sensitivity and specificity of detecting liver fibrosis was 57% and 88%, respectively.[6] Because the hepatologists in our study performing the ultrasonographic examinations were blind to the VCM exposure status, the misclassification was assumed to be non-differential. Nonetheless, data analysis showed that the results were compatible with the prior knowledge that viral hepatitis infection, obesity and VCM exposure associated with liver fibrosis. We concluded that the accuracy of ultrasonography diagnosis is acceptable.

In our study, half of subjects with liver fibrosis diagnosed by ultrasonography could not be detected by traditional liver function tests. We suggest that ultrasonographic examination should be included in medical surveillance for PVC workers to detect chronic liver disease.

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