ORIGINAL ARTICLE

An increased standardised mortality ratio for liver cancer among polyvinyl chloride workers in Taiwan

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Aims: To determine the standardised mortality ratio (SMR) corresponding to different causes of death in workers from polyvinyl chloride polymerisation factories in Taiwan.
Methods: Retrospective cohort study of workers from six polyvinyl chloride polymerisation factories in Taiwan. A total of 3293 male workers who had been employed for at least one year during the period 1 January 1950 to 31 December 1992, and were alive on 1 January 1985 were included for analysis. Using data acquired from Taiwan's National Mortality Registry, it was found that 144 of these workers died during the period 1985–97. The follow up rate was 99% with a total number of person-years at risk of 40 557.
Results: SMR for all causes of death was 0.78, indicating a possible "healthy worker" effect. The SMR for liver cancer decreased with increasing age of first exposure to vinyl chloride monomer. This association was more prominent for workers who were first employed in the industry prior to 1970 (SMR 4.82). Medical records indicated that most liver cancers in this study were hepatocellular carcinoma.
Conclusions: Polyvinyl chloride workers may experience a higher risk of developing liver cancer, particularly hepatocelluar carcinoma.

The polyvinyl chloride (PVC) polymerisation process has become one of the major industries in Taiwan, with an annual PVC production of more than one million tons.[1] Since the first production in the late 1950s, many workers have been exposed to high concentrations of vinyl chloride monomer (VCM), which has been reported to cause liver cancer, particularly angiosarcoma of liver (ASL).[2–6]

VCM has thus been classified by the International Agency for Research on Cancer (IARC) as a group I carcinogen.[7] While there appears to be considerable evidence about the relation between occupational exposure to VCM and ASL,[2–6] the association between exposure to VCM and hepatocellular cancer (HCC) is not so clear. Some studies reported small numbers of VCM exposed workers with HCC[8 9]; however, the data appear somewhat limited. Data from Wong and colleagues[10] in the USA indicate that there is an excess risk for HCC in VCM exposed workers. In all cohort studies of liver cancer in workers exposed to VCM, primary HCC is not clearly delineated from ASL. Furthermore, the nature of liver cancer in most studies is not available. In Taiwan, Du and Wang[11] reported that PVC workers showed an increased risk of developing liver cancer compared to optical workers and motor workers with a morbidity odds ratio (MOR) of 4.5 and 6.5, respectively. As liver cancer is the leading cause of cancer elicited death in Taiwan,[12] there exists a sufficiently large sample size of such cancer related deaths to provide the opportunity and statistical discriminatory power for us to evaluate the association between VCM exposure and liver cancer in a cohort of PVC workers.

Furthermore, several studies also reported that exposure to VCM may be associated with brain tumours,[10] and malignancies of the lymphatic and haematopoietic system.[10 13] We report the results of a retrospective cohort study to determine the mortality pattern of PVC workers in Taiwan.

METHODS

Establishment of the PVC cohort

The original cohort consisted of 4096 workers from six PVC polymerisation plants. The participant name list was collected from the Bureau of Labor Insurance (BLI), where workers' details, including personal identification number (ID), date of birth, gender, and dates of new and change of employment, and retirement are stored. As every factory that employs more than five workers is required to join the National Labor Insurance (NLI) by law, inclusion of our cohort of PVC workers should be representative of PVC workers in general.

Eligibility criteria for analysis

As the number of female workers was small (n = 85), and all were office workers, they were excluded from the study. Furthermore, 80 workers whose ID numbers were not available from BLI were also excluded. To be eligible for this cohort, employees at six separate plants had to meet the following criteria: male workers exposed to VCM for a period of at least one year in the period 1950–92. Thus 468 workers who were employed before 1992 and had VCM exposure less than one year were excluded; 128 workers who were employed after 1992 were also excluded from analysis. As the personal ID number scheme in the National Mortality Registry (NMR) that was used as a linkage "key" has only been available since 1985, the study group was further restricted to men who were known to have been alive on 1 January 1985. Thus a further 42 workers were excluded because their vital status could not be established by 1985. A total of 3293 subjects were therefore included for estimation of the standardised mortality ratio (SMR).

Determination of individual vital status

For each cohort subject, through data linkage to Taiwan's National Health Insurance, information was collected to

Abbreviations: AFP, α fetoprotein; ASL, angiosarcoma of liver; BFD, blackfoot disease; BLI, Bureau of Labor Insurance; CT, computed tomography; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular cancer; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; ID, identification number; MOR, morbidity odds ratio; NLI, National Labor Insurance; NMR, National Mortality Registry; PVC, polyvinyl chloride; SMR, standardised mortality ratio; VCM, vinyl chloride monomer

ascertain the cohort's vital status. Furthermore, the NMR was also contacted in order to identify the occurrence of any deaths of cohort members. The NMR has maintained a computerised file of all death certificates issued in Taiwan since 1971. The underlying cause of death has been systematically coded according to the ninth revision of the International Classification of Diseases (ICD9).

The period of observation of this study was within the period 1985–97. A total of 144 deaths of cohort members occurred during the follow up period, with a successful follow up rate of 99%.

Statistical analysis

The SMR was estimated by counting person-years at risk, which were accumulated into five year age groups beginning at the age of 15, and five year calendar periods commencing in 1985. Person-years calculation for a subject begins on 1 January 1985 or on the date when the subject accrued one year of exposure, whichever was later. Subsequently, the observed mortality number was divided by the expected number of deaths, computed from the general male population of Taiwan during the period 1985–97. The age and calendar period adjusted SMR were established and the corresponding 95% confidence intervals (95% CI) calculated using Poisson distribution.[14] SMR analysis was also performed for the different classifications of exposure variables, including duration of VCM exposure, age and calendar year of first exposure, and duration of latency. Latency is the total length of time between the start of work and the end of follow up.

RESULTS

Descriptive statistics

A total of 3293 male workers met the enrolment criteria. By the end of the study, 3146 (95.5%) members of the cohort were still alive, 144 (4.4%) had died, and three (0.01%) had an unknown status. The total number of person-years at risk was 40 577 (table 1).

The majority of the cohort members were born between the period 1940–59, and only 12.5% were born after 1960. Over half (58.5%) of the cohort participants commenced employment before 1980. Most of the cohort (72.6%) were hired before the age of 30, although 6.3% were hired after the age of 40. Virtually half of the cohort (49.1%) had been employed for more than 10 years, and only 34.5% had remained employed for less than five years. The median duration of employment for the entire cohort was 9.0 years.

Cause specific mortality analysis

Table 2 summarises the observed and expected death by cause specific SMR for the whole cohort. The 144 observed deaths in the cohort resulted in an overall SMR of 0.78 (95% CI: 0.65 to 0.91) in comparison to normal Taiwanese male mortality. Mortality from cancer of all sites combined in PVC workers was higher than the expected number based on normally expected male Taiwanese mortality (57 observed *v* 43.7 expected). The excess deaths in our study group were caused mainly by liver cancer (25 observed *v* 14.1 expected), and lymphatic and haematopoietic cancer (7 observed *v* 2.6 expected). There were no excess deaths for any other category of cause of death. There was a significant reduction in mortality from all diseases of the circulatory system (12 observed *v* 35.0 expected), which were mainly from cerebrovascular disease. There were also significant decreases in deaths from all diseases of the digestive system (12 observed *v* 23.3 expected), caused mainly by chronic liver disease and cirrhosis (7 observed *v* 16.4 expected).

Analysis by duration of exposure, age, calendar year of first exposure, and latency for mortality

The data were further analysed by duration of exposure, age, and calendar year of first exposure, as well as for different latency periods (table 3). Longer duration of exposure did not seem to be a significant determinant of increased mortality for all causes and all cancers including liver cancer.

Table 1 Exposure information for the PVC cohort members

Variable	Number (%)	Person-years at risk
Year of birth		
Before 1940	391 (11.9%)	4693
1940–60	2490 (75.6%)	31444
After 1960	412 (12.5%)	4420
Exposure duration (years)		
≥20	414 (12.6%)	5363
10–19	1203 (36.5%)	15369
<10	1676 (50.9%)	19825
Age at first exposure		
≥40	207 (6.3%)	2513
30–39	695 (21.1%)	8839
<30	2391 (72.6%)	29205
Calendar year of first exposure		
Before 1970	451 (13.7%)	5611
1970–79	1477 (44.8%)	18740
After 1980	1365 (41.5%)	16206
Latency period (years)		
≥25	877 (26.6%)	11499
15–24	1299 (39.5%)	16753
<15	1117 (33.9%)	12305
Total	3293 (100%)	40557

We analysed the cause specific SMR stratified by calendar year of first exposure. The SMR for liver cancer was 4.82 (11 observed *v* 2.3 expected, 95% CI: 2.41 to 8.63) for those first employed before 1970, 1.92 (8 observed *v* 4.2 expected, 95% CI: 0.83 to 3.79) for those employed between 1970 and 1979, and 0.78 (6 observed *v* 7.7 expected, 95% CI: 0.28 to 1.69) for those employed after 1980.

Subsequently, we analysed the data by stratifying the latency period into three groupings: less than 15 years, 15–24 years, and more than 25 years. The results also reflected an increased SMR value for liver cancer corresponding to the largest duration category (SMR 3.13; 10 observed *v* 3.2 expected, 95% CI: 1.50 to 5.75).

Analysis by age at first exposure in the categories less than 30 years of age, 30–39 years of age, and greater than 40 years of age was conducted. Mortality from liver cancer was inversely associated with age at first exposure. The SMR value for these three groups was 2.24 (10 observed *v* 4.5 expected, 95% CI: 1.07 to 4.12), 1.78 (6 observed *v* 3.4 expected, 95% CI: 0.65 to 3.88) and 1.43 (9 observed *v* 6.3 expected, 95% CI: 0.65 to 2.71), respectively. Further analysis was performed on SMR for liver cancer by latency and age at first exposure. In workers with latency greater than 25 years, SMR for liver cancer in those who had first exposure before 30 years of age was greater than that in those who had first exposure after 30 years of age (SMR 4.05, 95% CI: 1.48 to 8.82 *v* SMR 2.33, 95% CI: 0.63 to 5.95). In workers with latency less than 25 years, a similar relation was not observed.

We successfully obtained medical records in 18 of 25 cases of cohort members having died from liver cancer. Among 18 subjects who had medical records (as summarised in table 4), five workers were confirmed to have HCC by histology. An additional five workers with extremely high serum concentrations of α fetoprotein (AFP >1000 μg/l) and at least one positive image from angiography, sonography, liver scan, and/or a computed tomography (CT) scan, were regarded as having

Table 2 Observed and expected deaths by cause and SMR for all PVC cohort members

Cause of death (ICD9)	Observed	Expected	SMR (95% CI)
All causes (1–999)	144	185.9	0.78 (0.65 to 0.91)*
All cancers (140–209)	57	43.7	1.30 (0.99 to 1.69)
Cancer of lip, oral cavity, and pharynx (140–149)	4	6.6	0.60 (0.16 to 1.55)
Cancer of digestive system (150–159)	37	24.1	1.54 (1.08 to 2.12)*
Malignant neoplasm of stomach (151)	6	3.3	1.83 (0.67 to 3.99)
Malignant neoplasm of colon and rectum (153, 154)	3	2.8	–
Malignant neoplasm of liver (155)	25	14.1	1.78 (1.15 to 2.62)*
Malignant neoplasm of other GI sites† (150, 152, 157)	3	2.9	–
Cancer of respiratory system (160–165)	4	6.7	0.59 (0.16 to 1.52)
Cancer of genitourinary system (179–189)	2	1.2	–
Malignant neoplasm of brain (191)	2	0.7	–
Cancer of lymphatic and haematopoietic tissue (200–208)	7	2.6	2.71 (1.09 to 5.60)*
Lymphoid leukaemia (204)	2	0.2	–
Diabetes mellitus (250)	3	4.9	–
Diseases of the circulatory system (390–459)	12	35.0	0.34 (0.18 to 0.60)*
Ischaemic heart disease (410–414)	4	6.0	0.66 (0.18 to 1.69)
Cerebrovascular disease (430–438)	4	17.6	0.23 (0.06 to 0.58)*
Diseases of the digestive system (520–579)	12	23.3	0.52 (0.26 to 0.90)*
Diseases of liver and biliary tract (570–579)	11	21.4	0.51 (0.26 to 0.92)*
Chronic liver disease and cirrhosis (571)	7	16.4	0.42 (0.17 to 0.88)*
Diseases of the genitourinary system (580–589)	3	3.2	–
Unknown (797–799)	6	6.1	0.98 (0.36 to 2.13)
Injury and poisoning (800–999)	36	48.8	0.74 (0.52 to 1.02)

*Significant at 5% level.
†Other gastrointestinal sites including oesophagus, small intestine, and pancreas.

Table 3 Observed and expected deaths and SMR for liver cancer by duration of exposure, age at first exposure, calendar year of first exposure, and latency

	Observed	Expected	SMR (95% CI)
Exposure duration (years)			
⩾20	2	3.2	–
10–19	10	5.7	1.76 (0.84 to 3.24)
<10	13	5.3	2.45 (1.30 to 4.19)*
Age at first exposure			
⩾40	9	6.3	1.43 (0.65 to 2.71)
30–39	6	3.4	1.78 (0.65 to 3.88)
<30	10	4.5	2.24 (1.07 to 4.12)*
Calendar year of first exposure			
Before 1970	11	2.3	4.82 (2.41 to 8.63)*
1970–79	8	4.2	1.92 (0.83 to 3.79)
After 1980	6	7.7	0.78 (0.28 to 1.69)
Latency period (years)			
⩾25	10	3.2	3.13 (1.50 to 5.75)*
15–24	7	4.8	1.46 (0.58 to 3.61)
<15	8	6.2	1.29 (0.56 to 2.54)

*Significant at 5% level.

HCC. Previous clinical observations indicated that an AFP concentration exceeding 400 μg/l with at least one positive image suggesting liver tumour, confirms the presence of HCC.[15 16] Most liver cancers among VCM exposed workers in this study were therefore HCC. However, we found no deaths caused by ASL.

DISCUSSION

In this study, we found that workers from PVC manufacturing plants, compared to the general male population in Taiwan, showed a higher mortality from digestive system cancers, especially liver cancer. The risk increase as a result of VCM exposure was almost five times greater than that for the general Taiwanese male population, if the first exposure occurred before 1970. We also observed that the risk of liver cancer increased in workers who were first exposed to VCM before age of 30.

The most compelling evidence for the carcinogenic potential of VCM in humans comes from the cluster of reports of a greater than expected incidence of angiosarcoma of the liver in workers occupationally exposed to VCM.[2–6] Angiosarcoma of the liver is considered to be a very rare type of cancer, and it has become apparent that workers exposed to VCM exhibit an exceptionally high incidence of this type of tumour.[2–6] In this study, we found no deaths caused by ASL. As tissue proof was relatively uncommon for liver cancer in Taiwan,[17] a diagnosis of ASL may not be convincingly made. In previous studies, ASL accounted for more than half of the liver cancers.[5 6] The lack of ASL in our cohort was probably a result of the much lower levels of VCM exposure in our study subjects compared to those in Western workers. The PVC industry began in 1958 in Taiwan, 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 concentrations as high as 1000–2000 ppm of VCM before 1960.[18] A job exposure matrix model developed by Du and colleagues[19] in 2001 revealed that VCM exposure for Taiwanese workers was about 500 ppm in 1960s. Furthermore, p53 mutation in liver

Table 4 Clinical information and reasons for diagnosis of liver cancer in male PVC workers

Case no.	Age at death	Age at first exposure	Year of first exposure	Exposure (years)	Latency (years)	HBsAg/ anti-HCV	Major clinical finding
1	44	30	1980	4.0	13.8	+/NA	CT: 2 cm right lobe hepatoma, cirrhosis
2	55	37	1977	14.3	17.5	+/–	CT and angiography: caudate lobe tumour, portal vein thrombi, AFP >100000 μg/l, cirrhosis
3	42	25	1973	16.6	16.6	+/NA	CT: multiple hepatoma, cirrhosis, cytology: HCC
4	53	45	1984	4.9	8.1	+/–	Sonography: right lobe tumour, portal vein thrombi, AFP 7590 μg/l, cirrhosis
5	58	46	1983	6.0	11.7	+/NA	Sonography: 13 cm right lobe tumour, portal vein thrombi, cirrhosis, cytology: HCC
6	40	37	1986	3.3	3.3	+/NA	Sonography: 1.2 cm mass hepatoma, cirrhosis
7	40	25	1979	1.5	14.8	NA/NA	NA
8	47	24	1967	17.4	22.6	+/NA	CT and angiography: right lobe hepatoma, portal vein thrombi, AFP 7700 μg/l, cirrhosis
9	51	25	1965	25.3	25.5	+/–	CT and angiography: right lobe hepatoma, portal vein thrombi, cirrhosis
10	51	26	1968	16.6	25.3	+/NA	CT: tumour mass with central necrosis, metastasis post wedge resection, pathology: HCC
11	53	26	1969	4.3	27.0	+/–	CT: right lobe tumour, portal vein thrombi, AFP >12000 μg/l
12	55	28	1969	14.4	26.9	+/–	1.7 cm mass, portal vein thrombi, AFP 1485 μg/l, cirrhosis
13	62	35	1969	4.3	27.2	NA/NA	NA
14	63	47	1977	8.1	16.4	+/NA	CT: multiple hepatoma over right lobe, AFP 16698 μg/l, pathology: HCC
15	64	51	1984	6.0	12.8	NA/NA	NA
16	67	39	1967	17.3	28.3	NA/NA	NA
17	67	59	1983	1.3	8.4	+/NA	Sonography: hepatoma
18	74	47	1969	4.3	26.8	NA/NA	NA
19	47	39	1978	8.3	8.3	+/NA	Angiography: hepatoma, portal vein thrombi, cirrhosis
20	53	23	1966	25.7	30.3	–/–	Sonography: 5.9 cm mass, ascites, splenomegaly, cirrhosis
21	40	17	1979	9.0	23.0	NA/NA	Sonography: hepatoma, cirrhosis
22	39	22	1976	10.0	10.0	NA/NA	NA
23	52	33	1973	15.3	19.3	+/NA	Liver scan: multiple space occupying lesion, portal vein occlusion
24	55	30	1969	18.0	25.2	NA/NA	NA
25	61	46	1969	12.2	15.3	NA/NA	NA

NA, data unavailable.

cancer cells and serum oncoprotein p53 were observed in VCM exposed workers.[20 21] The prevalence of serum oncoprotein p53 in Taiwanese PVC workers was much lower than that in Western workers.[22] This also suggests that the levels of VCM exposure in our workers were not as high as those in Western workers.

Epidemiological studies suggest that hepatitis B virus (HBV) infection is the most important cause of liver cancer in Taiwan, with more than 80% of liver cancer patients carrying hepatitis B virus surface antigen (HbsAg),[23 24] and 30–50% being anti-HCV positive.[25 26] This has suggested that the increased risk of liver cancer might be a result of confounding by hepatitis virus infection. Although we had no data pertaining to HCV infection prior to 1992, our recent cross sectional study has revealed the prevalence of 19.9% for HBsAg and 2.4% for anti-HCV in this cohort.[27] This level was comparable to that for the general Taiwanese population (HBsAg 15–20%,[23] anti-HCV 1–4%,[28] respectively). In this study, we observed that PVC workers exhibited almost a twofold greater risk of developing liver cancer than the general male Taiwanese population. The magnitude of such a risk could not be explained completely solely by hepatitis B or C virus infection. Whether there is a synergistic interaction between VCM exposure and hepatitis virus infection in the development of liver cancer, however, needs to be further investigated.

In addition to HBV and HCV infection, aflatoxin exposure, arsenic exposure, and alcohol consumption may also play important roles in the development of liver cancer. We carried out a data linkage between our cohort and another cohort in Taiwan, the blackfoot disease (BFD) cohort, which investigated the association of arsenic exposure and cancer.[29 30] Only one subject from our cohort was present in the BFD cohort list; that person remained healthy at the end of follow up. Moreover, our data also showed that only two cases of liver cancer death reflected a history of excessive alcohol consumption. Thus, arsenic exposure and alcohol drinking could not explain the twofold increase in the risk of SMR shown in this study.

Some previous studies have reported that PVC workers experienced a greater risk of developing cancer of the brain[10] and/or the lymphatic/haematopoietic systems.[10 13] In our study of PVC workers, we also observed a significantly higher risk of developing a cancer in the lymphatic and haematopoietic systems, although the number of deaths from lymphatic and haematopoietic system cancer was too small to draw a conclusion. Further follow up may shed light on this relation. By contrast, we observed no increased mortality from brain tumours, although this result was similar to previous studies from the USA and Europe.[5 6]

A reduced overall mortality risk compared to the general population was also observed in our study, which was generally recognised as the so called "healthy workers" effect. Such a phenomenon could be explained by significant deficits in mortality arising from diseases of the circulatory system and digestive system among cohort members, although as cancer mortality was less likely to be influenced by the initial and subsequent selection of the healthiest individuals for work purposes, the effect might be less great.[31] Even if such an effect existed in this Taiwanese cohort, it might lead to a null result. In addition, we also observed a reduced mortality risk for chronic liver disease and cirrhosis (ICD9 = 571) in this study. This was caused either by the healthy workers effect or the fact that these PVC workers had better medical care provided by NLI. These workers thus had a better chance to survive chronic liver disease or cirrhosis compared to the general population. It was also likely that VCM caused p53 mutation, which might promote neoplastic transformation of liver cirrhosis by means of increased proliferation of liver cells and reduced DNA damage.

Longer duration of exposure did not seem to be a significant determinant for increased cancer mortality. A possible explanation is the higher turnover for workers involved in high

Main messages

- Hepatocellular cancer is associated with vinyl chloride exposure.
- Vinyl chloride exposure before the age of 30 may increase the risk of liver cancer.

Policy implications

- Hepatocellular cancer may be considered to be one of the occupational cancers caused by vinyl chloride.

exposure activities compared to other workers who were not directly exposed to VCM. The other explanation is that those with diseases tended to leave the job earlier, which was consistent with the observation that SMR increased with shorter duration of exposure for all causes and all cancers. In this study, the available historical exposure data were deemed to be sparse for quantitative estimation of (historical) cumulative exposures. Thus, the cumulative dose of VCM exposure was not used in the analysis. However, it was interesting to observe that workers with VCM exposure prior to 1970 had higher mortality for liver cancer. PVC workers tended to be exposed to higher levels of VCM before 1981 when worksite VCM permissible exposure levels had not been set. Further analysis indicated that workers who had a latency greater than 25 years also had a higher risk of liver cancer. It may take more than two decades for liver cancer to develop from the beginning of exposure to death. Because the 10 deaths caused by liver cancer with latency greater than 25 years included nine deaths with first exposure prior to 1970, it is difficult to separate the effect of exposure prior to 1970 on liver cancer from latency. We also found that mortality from liver cancer increased inversely with age at first exposure after controlling for the effect of latency. In animal studies, induction of preneoplastic hepatocellular lesions in rats by vinyl chloride was restricted to young animals.[32 33] Thus the early period of life may be a sensitive period for developing tumours related to VCM exposure.

Another limitation of this study was that some of our cohort members might have died before 1985. Unfortunately, we were unable to carry out the data linkage on our computerised NMR prior to 1984 because of an absence of personal ID numbers in this file. We are exploring the possibility of linking the NMR with other government databases to increase the completeness of available data; until we can do this, an underestimation of occupationally influenced mortality among PVC workers appears likely.

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