Mortality from liver cancer and leukaemia among polyvinyl chloride workers in Taiwan: an updated study

Hui-I Hsieh,[1,2,3] Pau-Chung Chen,[1] Ruey-Hong Wong,[4] Chung-Li Du,[1,5] Yu-Yin Chang,[1] Jung-Der Wang,[1,5] Tsun-Jen Cheng[1]

[1]Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei, Taiwan
[2]Department of Family Medicine, Cathay General Hospital, Taipei, Taiwan
[3]School of Medicine, College of Medicine, Fu-Jen Catholic University, Sinjhuang, Taiwan
[4]Department of Public Health, College of Health Care and Management, Chung Shan Medical University, Taichung, Taiwan
[5]Department of Occupational and Environmental Medicine, National Taiwan University Hospital, Taipei, Taiwan

Correspondence to
Tsun-Jen Cheng, Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, No. 17 Xu-Zhou Road, Zhongzheng District, Taipei 10055, Taiwan; tcheng@ntu.edu.tw

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ABSTRACT

Objectives To investigate types of cancer caused by occupational exposure to vinyl chloride monomer (VCM) and the temporal mortality trends of these cancers in workers from polyvinyl chloride (PVC) manufacturing factories in Taiwan, with follow-up of the cohort extended by 15 years, from 1980 to 2007.

Methods A retrospective cohort study of workers from six PVC factories in Taiwan was conducted. 3336 male PVC workers were enrolled and further linked with the National Mortality Registry and National Household Registry databases. Standardised mortality ratios (SMR) with 95% CIs were calculated and compared to the general Taiwanese male population. Cause-specific mortality between two study periods, 1980–1997 and 1998–2007, was compared. Six-year moving averages of the SMRs were calculated to examine mortality trends.

Results Liver cancer mortality increased during 1989–1994 (SMR 1.90, 95% CI 1.01 to 3.25), reached a peak during 1991–1996 (SMR 2.31, 95% CI 1.39 to 3.61) and became non-significant during 1994–1999 (SMR 1.42, 95% CI 0.80 to 2.34). Leukaemia mortality significantly increased during 1984–1989 (SMR 6.06, 95% CI 1.24 to 17.53), reached a peak during 1985–1990 (SMR 7.56, 95% CI 2.06 to 19.35) and became non-significant during 1991–1996 (SMR 3.24, 95% CI 0.39 to 11.69). The mortality trend for haemolymphopoietic cancer showed a similar pattern to that of leukaemia.

Conclusions VCM may increase the risk of liver cancer and leukaemia. When VCM exposure was controlled at worksites, mortality from these cancers returned to background levels.

What this paper adds

- Evidence of an association between vinyl chloride exposure and hepatocellular carcinoma, leukaemia and haemolymphopoietic cancer is less consistent than that for liver angiosarcoma.
- Our results support an association between vinyl chloride exposure and liver cancer, haemolymphopoietic cancer and leukaemia.
- Adequate control of exposure to vinyl chloride can result in a decrease in cancer mortality (especially liver cancer mortality).

INTRODUCTION

Vinyl chloride monomer (VCM, CAS No: 75–01–4) is classified as a group I (human) carcinogen by the International Agency for Research on Cancer (IARC).[1] The association between VCM exposure and liver angiosarcoma (LAS) has been established.[2–5] However, it is less clear whether VCM can also cause other malignancies such as hepatocellular carcinoma (HCC) and other primary liver cancers, leukaemia and other haemolymphopoietic cancers, cancers of the lung and respiratory system, cancers of the brain and central nervous system (CNS), cancers of connective tissue and soft tissue, and malignant melanoma.[6–15]

We have established a cohort with more than 3000 workers from six polyvinyl chloride (PVC, CAS No: 9002-86-2) manufacturing plants in Taiwan. A retrospective cohort study with a 13-year follow-up (1985–1997) indicated that PVC workers may have a higher risk of liver and haemolymphopoietic cancers.[12] However, because the number of cases was small, firm conclusions could not be drawn. The current updated study extended the follow-up period from 1997 to 2007. Further, follow-up in the previous study began from 1985 as personal identification numbers (IDNs) were not used in the National Mortality Registry (NMR) database before 1985. Through linkage with other government databases, the mortality database was reconstructed to extend backwards to 1980 in this study.[16] Thus, we are now able to investigate more thoroughly the mortality and time trends of specific cancers associated with VCM exposure.

METHODS

Establishment of the PVC cohort

The methodology for the establishment of the study cohort has been described in our earlier study.[12] A list of the names of workers from six PVC plants was obtained from the Bureau of Labour Insurance (BLI). Further information, including date of birth, gender, personal IDN and employment history, was also retrieved from this database. In the current study, PVC workers not retrieved from the BLI database were added based on company records. Thus the number of workers in this cohort increased from 4096 to 4294.

Exclusion criteria for study cohort

The exclusion criteria and number of workers excluded are shown in figure 1. Female workers

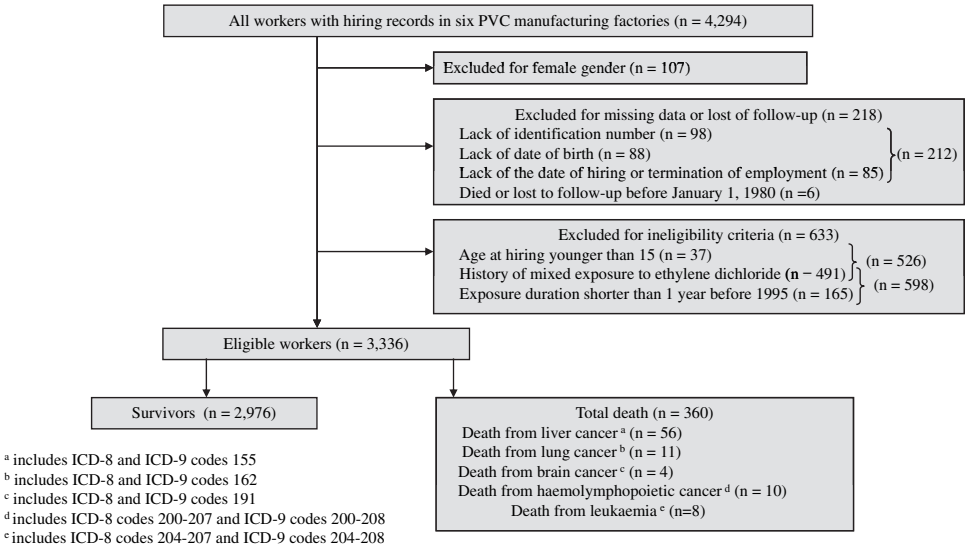

Figure 1 Exclusion criteria and worker selection process for establishing the study cohort.

were excluded from the study because there were relatively few of them (N=107, 2.5%), and all were clerical workers with minimal VCM exposure. Workers (N=212) whose personal information and/or employment history were missing were excluded. Workers who had died or were lost to follow-up before 1 January 1980 (N=6) were also excluded, because the personal IDN used for linkage in the NMR was only introduced in 1980. Employees at the six plants who met the following criteria were also excluded: (1) less than 15 years of age at hiring, (2) with a history of exposure to 1,2-dichloroethane (EDC, CAS No: 107-06-2) or (3) duration of VCM exposure less than 1 year before 1995. EDC is a known carcinogen (IARC group 2B), and some workers were exposed to it when they were employed in plants where EDC was used to produce VCM.[17] Finally, 3336 subjects were enrolled in the study.

Determination of individual vital status and cancer diagnosis

Subjects were followed from 1980 through 2007. Deaths were identified through linkage with the NMR, which maintains a digitised file of all death certificates, with only one underlying cause recorded for each death. In Taiwan, a population registration system, known as the National Household Registration System (NHR), continuously traces changes in households, including migration, births and deaths. The accurate rates of the NHR reached 99% in the five population censuses from 1970 and 2000.[18] If it could not be ascertained whether a subject was dead or alive through either the NHR or the NMR, the last date of a subject's successful follow-up was defined as the last observation date. A total of 360 deaths were found.

Statistical analysis

Analysis was performed using the NIOSH life table analysis system for the Windows environment (http://www.cdc.gov/niosh/ltas/default.html), with the general Taiwanese population as reference. Death certificates were coded with the eighth and ninth revisions of the International Classification of Diseases (ICD) for underlying cause. Mortality was calculated using the person-year method. Each cohort member accumulated person-years at risk (PYAR) beginning on 1 January 1980 or on the date when exposure duration to VCM for the subject accumulated more than (was equal to) 1 year, whichever was later. Person-time ended at the date of death, the date when the worker was lost to follow-up or the end date of the study, whichever was earliest. The PYAR was first stratified into 5-year intervals by age and calendar time. Each PYAR stratum was then multiplied by the appropriate gender- and cause-specific mortality to calculate the expected number of deaths. The standardised mortality ratio (SMR) was calculated as the ratio of the number of observed cases divided by the number of expected cases first from all causes (ICD-9 codes 001–999), then from all cancers (ICD-9 codes 140–208), liver cancer (ICD-9 code 155), lung cancer (ICD-9 code 162), brain cancer (ICD-9 code 191), haemolymphopoietic cancer (ICD-9 codes 200–208) and leukaemia (ICD-9 codes 204–208). The 95% confidence intervals (95% CI) and significance test for SMR were based on Byar's approximation of the exact Poisson test.[19]

Cause-specific mortality was calculated for the periods 1980–1997, 1998–2007 and 1980–2007. Six-year moving averages of the SMR were also calculated to examine mortality trends over time. Furthermore, age at death from cancers of interest was compared between cohort members and two control groups from the general Taiwanese population, one matched by birth year and the other by birth year and registered residence at death. A non-parametric test was used to test the significance of the difference in age at death or hiring between workers who died from liver cancer and haemolymphopoietic cancer. The statistical analyses were performed using SAS V. 9.1.3. All statistical tests in this study were two-sided with a significance level of 0.05.

RESULTS

Descriptive statistics

A total of 3336 male workers contributing 81 840 PYAR were included in the study. With 15 additional years of follow-up, 216 additional deaths and 41 263 PYAR were observed. Vital status at the end of the follow-up period could not be ascertained for 65 participants and thus a successful follow-up rate of 99.9% was achieved. Cohort demographics and employment characteristics are summarised in table 1. The characteristics of the subjects in this study were similar to those in our previous study.[12] Cohort participants were most frequently born between 1940 and 1959, and only 12.7% were born after 1960. All participants were hired before 1994, and 36.9% were hired before 1976, when VCM air concentrations at the worksite were still relatively high. Most participants (81.8%) were aged 19–35 when hired, and only 6.5% were hired after the age of 40. Most participants (82.8%) had been employed for more than 10 years, and only 6.4% were employed for less than 5 years. The median duration of

Table 1 Demographic and exposure characteristics of 3336 male workers hired during 1950–2007 by causes of death

Characteristic	All workers	All deaths	All cancers	Liver cancer	Lung cancer	Brain cancer	Haemolymphopoietic cancer	Leukaemia
ICD-8 codes		001–999	140–207	155	162	191	200–207	204–207
ICD-9 codes		001–999	140–208	155	162	191	200–208	204–208
Number of workers	3336	360	130	56	11	4	10	8
Mean year of birth (median)	1950 (1951)	1944 (1944)	1943 (1942)	1942 (1942)	1942 (1943)	1947 (1949)	1949 (1950)	1950 (1950)
Mean year of hire (median)	1978 (1978)	1975 (1975)	1974 (1975)	1974 (1973)	1975 (1972)	1974 (1973)	1977 (1978)	1977 (1978)
Mean year of death (median)		1997 (1998)	1997 (1998)	1996 (1996)	1997 (1998)	1998 (1999)	1994 (1991)	1992 (1991)
Mean±SD age at first exposure (range), years	27.5±6.7 (15.1–58.8)	31.0±8.7 (15.5–58.8)	31.7±9.5 (15.5–58.8)	32.4±10.3 (15.5–58.8)	33.8±10.2 (22.3–51.3)	27.1±6.1 (22.6–36.1)	28.1±7.6 (17.0–42.6)	27.8±8.5 (17.0–42.6)
Mean±SD age at death (range), years		53.8±11.3 (25.4–81.6)	54.4±10.9 (25.4–80.4)	54.6±10.5 (31.9–75.7)	55.5±10.0 (41.0–71.6)	51.4±7.2 (41.9–59.4)	44.4±13.6 (28.9–69.4)	42.7±13.4 (28.9–69.4)
Mean±SD follow-up period (range), years	28.9±7.9 (1.4–57.8)	22.8±9.9 (1.4–48.7)	22.7±9.9 (2.0–43.5)	22.2±10.4 (2.0–43.5)	21.7±5.0 (14.1–28.2)	24.3±10.1 (15.7–35.7)	16.3±11.2 (2.1–34.4)	14.9±11.1 (2.1–34.4)
Mean±SD employment duration (range), years	17.0±7.5 (1.0–42.5)	17.6±8.2 (1.2–38.5)	17.9±8.1 (1.2–36.4)	17.4±8.5 (1.2–34.8)	17.7±6.1 (8.7–26.8)	20.2±5.1 (15.7–24.8)	12.9±7.3 (2.1–26.5)	12.1±7.7 (2.1–26.5)
Number of workers with more than 10 years of exposure (%)	2763 (82.8%)	296 (82.2%)	110 (84.6%)	47 (83.9%)	10 (90.9%)	4 (100.0%)	8 (80.0%)	6 (75.0%)

ICD, the International Classification of Diseases.

employment for the entire cohort was 16.9 years. Almost 80% of workers who died from cancers of interest had been employed for more than 10 years. In addition, workers who died from leukaemia were significantly younger when they were first hired or when they died as compared to workers who died from liver cancer ($p<0.05$).

Cause-specific mortality analysis

SMRs for selected causes of death and stratified by different periods are presented in table 2. Overall, mortality from all causes (168 deaths; SMR 0.78, 95% CI 0.67 to 0.91) was significantly less than expected. Mortality from all cancers (65 deaths; SMR 1.33, 95% CI 1.03 to 1.70), liver cancer (33 deaths; SMR 1.93, 95% CI 1.37 to 2.79) and leukaemia (six deaths; SMR 3.93, 95% CI 1.44 to 8.54) was significantly higher in the period 1980–1997. However, liver cancer and leukaemia deaths became non-significant in the period 1998–2007. Mortality from haemolymphopoietic cancer (SMR 2.27, 95% CI 0.91 to 4.67) increased in the period 1980–1997, but not significantly. Four deaths were observed and there was no statistically significant increase in mortality from brain cancer (SMR 2.29, 95% CI 0.62 to 5.86) in the period 1980–2007. Mortality from lung cancer was lower than for the general population during the different follow-up periods. Finally, no subjects died due to soft-tissue sarcoma (ICD-9 code 171) or malignant melanoma (ICD-9 code 172) and only two cases of non-Hodgkin's lymphoma (ICD-9 code 200) were found in the period 1980–2007.

Since there were significant differences in the causes of death in the two time periods, we further examined trends in mortality. Six-year moving averages were calculated for the specific causes of deaths of interest (figure 2). Liver cancer mortality increased during 1989–1994 (SMR 1.90, 95% CI 1.01 to 3.25), reached a peak during 1991–1996 (SMR 2.31, 95% CI 1.39 to 3.61) and then became non-significant during 1994–1999 (SMR 1.42, 95% CI 0.80 to 2.34). Leukaemia mortality became significant during 1984–1989 (SMR 6.00, 95% CI 1.24 to 17.53), reached a peak during 1985–1990 (SMR 7.56, 95% CI 2.06 to 19.35) and became non-significant during 1991–1996 (SMR 3.24, 95% CI 0.39 to 11.69). The trend for leukaemia occurred about 5 years before that for liver cancer, while that for haemolymphopoietic cancer mortality was the same as that for leukaemia.

DISCUSSION

We observed increased mortality for liver and haemolymphopoietic cancer as well as leukaemia. These findings are generally consistent with our previous study.[12] However, our results cannot confirm that the excess mortality from brain cancer is related to VCM exposure due to the limited sample size. Additionally, this study did not show an excess risk for lung cancer. Moreover, as we were unable to reconstruct an individual's cumulative exposure dose of VCM, an exposure–response analysis was not performed.

The results of this updated study are consistent with our previous work with respect to liver cancer.[12] However, a lack information on the histological types of most of the liver cancer deaths prevents us from drawing a firm conclusion about the

Table 2 Observed deaths and standardised mortality ratios for selected causes of death

Underlying cause of death (ICD-9 codes)	Study period											
	1980–1997				1998–2007				1980–2007			
	O/E	SMR	95% CI		O/E	SMR	95% CI		O/E	SMR	95% CI	
All causes (001–999)	168/215.71	0.78	0.67 to 0.91	**	192/267.95	0.72	0.62 to 0.83	**	360/483.66	0.74	0.67 to 0.83	**
All cancers (140–208)	65/48.79	1.33	1.03 to 1.70	*	65/91.40	0.71	0.55 to 0.91	**	130/140.19	0.93	0.77 to 1.10	
Liver cancer (155)	33/16.64	1.93	1.37 to 2.79	**	23/25.68	0.90	0.57 to 1.34		56/42.35	1.32	1.00 to 1.72	*
Lung cancer (162)	4/6.34	0.63	0.17 to 1.61		7/15.61	0.45	0.18 to 0.92	*	11/21.95	0.50	0.25 to 0.90	*
Brain cancer (191)	2/0.77	2.59	0.29 to 9.36		2/0.98	2.05	0.23 to 7.40		4/1.75	2.29	0.62 to 5.86	
Haemolymphopoietic cancer (200–208)	7/3.09	2.27	0.91 to 4.67		3/4.08	0.73	0.15 to 2.15		10/7.17	1.39	0.67 to 2.56	
Leukaemia (204–208)	6/1.53	3.93	1.4 to 8.54	**	2/1.53	1.31	0.16 to 4.73		8/3.06	2.62	1.13 to 5.16	*

E, expected number of deaths; O, observed number of deaths; SMR, standardised mortality ratio.
*$p<0.05$; **$p<0.01$ by Byar's approximation of the exact Poisson test.

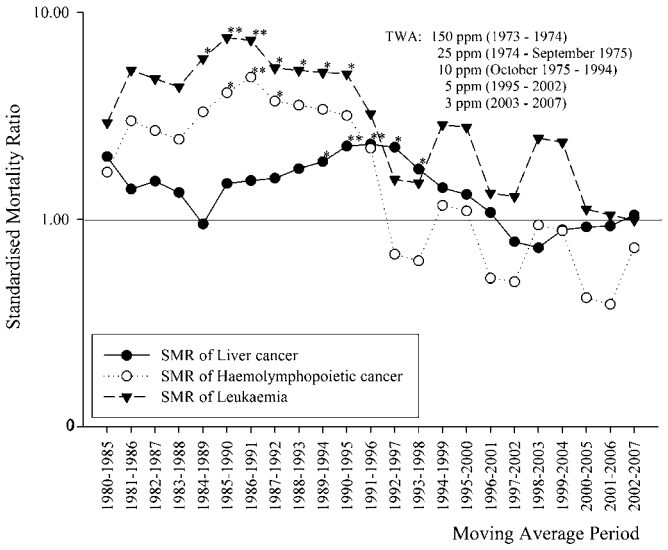

Figure 2 Time trends of mortality from liver cancer, haemolymphopoietic cancer and leukaemia among male PVC workers in the period 1980–2007. (Statistical significant, *p < 0.05 and **p < 0.01, of the standardized mortality ratio by selected cause-of -death during the study period is shown above the points; TWA: permissible 8-hour time weighed average levels during different points.

association between VCM exposure and HCC. According to information in the Taiwan Cancer Registry (TCR) Annual Reports 2002–2006, among 48 102 cases of primary liver cancers, 41 835 (87.0%) and 36 (0.1%) are classified as HCC and LAS, respectively.[20] Furthermore, 99% of liver cancers which could not be specified as either primary or secondary liver cancer (ICD-9 code 155.2) in the NMR were coded as primary liver cancer (ICD-9 code 155.0) in the TCR using combined data from the NMR and TCR from 1979 to 2005 for adult male deaths. Further, HCC constitutes over 87% of incident adult male cases of primary liver cancer with histological confirmation in the TCR. Thus, as other epidemiological studies describe, HCC is the most common liver cancer in Taiwan.[21 22] Therefore, it is expected that future research on the histological types of liver cancer could provide further information on the association between VCM exposure and the development of HCC.

Epidemiological studies have shown that chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the most important causes of HCC in Taiwan and accounted for approximately 70–80% and 10–30% of HCC, respectively.[23 24] In addition to HBV and HCV, tobacco smoking and alcohol drinking are also associated with HCC.[25] As discussed in our previous studies, the study subjects did not have a higher prevalence of HBV and HCV infection, tobacco smoking or alcohol consumption than the general population (HBsAg 17–20% vs 15–20%, anti-HCV 2–4% vs 1–5%, current smoking 17–35% vs >20%, and habitual drinking 3–11% vs 18%, respectively), and so these potential confounders would not have made a significant contribution to the high liver cancer mortality.[25–31]

LAS is a rare cancer and is usually diagnosed by the histological findings. No case of LAS was confirmed among the Taiwanese PVC workers. It is possible that some cases were not identified because histological findings were only available for about 35% of liver cancers in the TCR. However, it is notable that no claim for worker's compensation was made even though 32 adult males with LAS were registered in the TCR. One study reported 26 cases of LAS in Taiwan from 1981 to 1999, but none were ever employed in the PVC plants.[32] Another explanation for the lack of LAS cases in Taiwan is that the exposure dose for individual PVC workers was relatively low compared to that of Western workers because the manufacturing plants were established a few decades later in 1960.[12 33]

Previous studies suggest that VCM exposure may increase the risk of HCC.[10 11 15] Recently, Mastrangelo *et al* and Wong *et al* reported a significant risk of HCC in VCM-exposed workers after controlling for potential confounders.[14 34] Furthermore, dose–response trends were observed between VCM exposure and liver cirrhosis (the preneoplastic condition of HCC).[11 14 35] Our previous studies also found that VCM could interact with HBV infection for the development of liver fibrosis and, furthermore, liver cancer.[34 36] These studies provide support for the association between VCM exposure and HCC. Although the evidence on the association between VCM exposure and HCC was seen as insufficient in two reviews, the IARC listed VCM as an established risk factor for HCC.[37–39]

Some previous studies reported that PVC workers experienced a greater risk of developing cancers of the haemolymphopoietic system, leukaemia or non-Hodgkin's lymphoma, although other studies did not.[8–12] Recently, a working group of the IARC concluded that there was no strong epidemiological evidence supporting an association between VCM exposure and cancers of the haemolymphopoietic system.[40] Although our previous study observed a significantly higher risk, the association between VCM exposure and such cancers cannot be confirmed due to the small number of cases. In this updated study, we observed an increased risk of haemolymphopoietic cancer as well as leukaemia during 1984–1995. The relationship between VCM exposure and leukaemia and haemolymphopoietic cancer thus needs further study.

Our study found no evidence of increased mortality from lung cancer. Some earlier studies reported an association between VCM and lung cancer, but most cohort studies did not observe this relationship.[3 4 6 9–11 15 41] Interestingly, an excess lung cancer risk was found to be associated with exposure to PVC dust, but not with exposure to VCM among Italian workers.[42] Recently, the working group of IARC concluded that there was no evidence supporting the association between VCM exposure and lung cancer.[40]

Our study found four cases of brain cancer and no evidence of increased mortality from brain cancer. Some studies reported an association between VCM and cancers of the brain and CNS (ICD-9 codes 191–192), but several cohort studies did not observe this relationship.[6 9–11 13] Recently, the working group of IARC concluded that there was no evidence supporting an association between VCM exposure and brain cancer.[40]

In this study, we observed increased mortality for liver cancer and haemolymphopoietic cancer or leukaemia. Moreover, the increase in haemolymphopoietic cancer or leukaemia mortality occurred earlier than that of liver cancer. Although factors affecting the induction period of carcinogenesis include age, genetic susceptibility, exposure dose and general health conditions, cancers of epithelial origin usually take longer to develop than cancers of non-epithelial origin.[43 44] Our results are consistent with these observations.

A reduced overall mortality risk compared to the general population was also observed in this updated study, which is likely due to the healthy worker effect. Among our subjects, the SMRs for diseases of the circulatory system (SMR 0.71, 95% CI 0.54 to 0.93) and non-malignant diseases of the digestive system (SMR 0.57, 95% CI 0.39 to 0.80) were significantly lower than expected in the period 1980–2007. Since cancer mortality was less likely to be influenced by pre-employment selection and the

protective effect declined with extension of the follow-up period, the healthy worker effect on cancer mortality would thus be limited.

The major limitation of this study is the lack of information on histological findings and potential confounders, which was discussed above. The other limitation is that the cumulative exposure dose for each study subject was not clear. Records of personal exposure status were not available for most of the study subjects. This deficit prevented us from analysing the dose–response relationship between VCM exposure and different types of cancer deaths. Future study on the reconstruction of exposure dose is required before a firm conclusion can be drawn.

CONCLUSION

These results are consistent with our previous study of this cohort which reported significantly elevated mortality from liver cancer and leukaemia. This study also found that the risk of liver cancer and leukaemia decreased among VCM-exposed workers in Taiwan during the updated study period, which was probably the result of successful control of ambient VCM exposure at worksites. In the current study, we observed an inverted U-shaped mortality trend for leukaemia and haemolymphopoietic cancer, although the number of deaths from leukaemia or haemolymphopoietic cancer was still too small to draw a firm conclusion. Clearly, the association between VCM exposure and leukaemia and haemolymphopoietic cancer requires further study.

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Competing interests None.

Ethics approval The study was approved by the Institutional Review Board of the College of Public Health, National Taiwan University.

Provenance and peer review Not commissioned; externally peer reviewed.

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