Arsenic levels in drinking water and mortality of liver cancer in Taiwan

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A B S T R A C T
The carcinogenic effect of arsenic is well documented, but epidemiologic data on liver cancer were limited. To evaluate the dose–response relationship between arsenic in drinking water and mortality of liver cancer, we conducted a study in 138 villages in the southwest coast area of Taiwan. We assessed arsenic levels in drinking water using data from a survey conducted by the government and reviewed death certificates from 1971 to 1990 to identify liver cancer cases. Using village as the unit, we conducted multivariate regression analyses and then performed post hoc analyses to validate the findings. During the 20-year period, 802 male and 301 female mortality cases of liver cancer were identified. After adjusting for age, arsenic levels above 0.64 mg/L were associated with an increase in the liver cancer mortality in both genders, but no significant effect was observed for lower exposure categories. Post hoc analyses and a review of literature supported these findings. We concluded that exposures to high arsenic levels in drinking water are associated with the occurrence of liver cancer, but such an effect is not prominent at exposure levels lower than 0.64 mg/L.

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1. Introduction
Arsenic is widely distributed in the natural environment and often transported by water [1]. Excess exposures to arsenic from drinking water have been found in Taiwan [2], China [3], Japan [4], Bangladesh [5], Thailand [6], Mexico [7], Argentina [8], Chile [9], Hungary [10], Romania [11], Italy [12], the United States [13], and many other countries [1,14–17]. In fact, the health effects of arsenic in drinking water have become a global crisis, and it was estimated that more than 80 million people were at risk from arsenic in drinking water and in food crops in Bangladesh alone [5,18], with 30 million drinking water containing five times the quality guideline of 0.01 mg/L proposed by World Health Organization (WHO) [5]. Acute and chronic arsenic exposures were found to have dermal, respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, neurological, developmental, reproductive, immunologic, genotoxic, mutagenic, and carcinogenic effects on humans [14,16,19]. The diseases and conditions of the liver observed in previous studies included proliferation of Kupffer cells, granulomas, fibrosis, cirrhosis, and portal hypertension [20–23]. In addition, the carcinogenic effect of arsenic has been documented for more than a century [24].

Over the years, the data from epidemiology studies in the blackfoot disease (BFD) endemic area in Taiwan [25,26] have been serving as a major basis of the regulatory standards of WHO and United States Environmental Protection Agency (USEPA).
BFD is an obstructive peripheral vascular disease characterized by the black discoloration due to gangrenous changes of lower extremities [30,31], and it was most prevalent in four townships in the southwest coast region in Taiwan, which is generally referred to as the “BFD endemic area” [30,32]. In this area, many artesian wells that were used by residents as sources of drinking water had high levels of arsenic, and it is generally believed that BFD was caused by arsenic in drinking water because dose–response associations between the arsenic level in drinking water and prevalence of BFD were reported [30,33]. The argument was supported by the fact that skin changes caused by arsenic intoxication, including skin cancer, were also prevalent in this area [30,33]. As more and more studies showed that arsenic in drinking water might also cause internal cancers, data collected by a study in the BFD endemic area [26] were adopted as a major scientific basis of justifying the revisions of regulatory standards of arsenic due to excess risks of lung and urinary cancers [25,34].

In addition to cancers of skin, lung, and urinary bladder, liver cancers were also observed among patients of arsenic intoxication since the 1950s [35]. However, epidemiologic data are quite limited, especially those on the dose–response relationship. An ecological study in the BFD endemic area categorized the 42 villages into three exposure groups and found a positive dose–response relationship between arsenic levels and mortality of liver cancer in men (but not in women) [26], but no obvious dose–response relationship was observed when Morales et al. [34] broke down the villages further into eight exposure groups. A study in Denmark enrolled 56,378 persons with arsenic levels in drinking water between 0.05 and 25.3 μg/L observed no dose–response relationship between arsenic exposure and liver cancer [36]. Likewise, a study in Idaho, USA observed no such dose–response relationship in the dose region from 0.1 to 950 μg/L [37]. To evaluate the association between arsenic levels in drinking water and occurrence of liver cancer further, we conducted a study including both the BFD endemic area and other areas in Taiwan.

2. Experimental

2.1. Collection of data

The current study includes the four hyper-endemic townships of BFD and six nearby townships. Original measurement reports from a census survey of wells conducted by the Taiwan Provincial Institute of Environmental Sanitation [32] were available for 138 villages in the study townships. Most of the measurements were made between 1974 and 1976, and a follow-up survey applying the same method to test a part of the wells found that the results were highly correlated [38,39]. According to the standard solutions used in the survey [32] and results from previous studies [40,41], we grouped arsenic levels into six categories: below 0.05 mg/L, 0.05–0.08 mg/L, 0.09–0.16 mg/L, 0.17–0.32 mg/L, 0.33–0.64 mg/L, and above 0.64 mg/L. As there were a total of 6103 wells in these 138 villages, each village had 44.2 wells on average.

In Taiwan, there is one household registry office in each township, and timely reporting of deaths to those offices is mandated by law. We reviewed death certificates filed to the ten household registry offices in the study townships between January 1, 1971 and December 31, 1990 to identify cases of liver cancer. In addition, we obtained data on residents in each village from the household registry offices and divided the residents into four age groups: 0–29, 30–49, 50–69, and >70 years old. The study villages had a total population of around 235,000. As there were a total of 6103 wells in the study villages, the estimated average number of people using a particular well was 38.5.

2.2. Data analysis

The data were analyzed by multivariate linear regression using village as the unit population. Data on men and women were analyzed separately, and the independent variables included the percentage of wells in each arsenic exposure category of each village. Because arsenic levels were divided into six categories, five variables were used in this model to estimate rate differences (RDs) between the reference exposure category (below 0.05 mg/L) and each of the five higher exposure categories (0.05–0.08 mg/L, 0.09–0.16 mg/L, 0.17–0.32 mg/L, 0.33–0.64 mg/L, and above 0.64 mg/L). This approach derives estimates of unit RDs (incremental mortality rates for a one-unit increase in independent variables) and can generate unbiased estimates from ecological data even when the dose–response relationship is not linear [42]. To adjust for effects of age, we also included percentages of residents in different age groups to the regression models as independent variables [43,44]. Likewise, three variables were used for four age groups.

The original regression model can be expressed as the following:

\[ R = \alpha + \beta_1 X_1 + \cdots + \beta_5 X_5 + \gamma_1 A_1 + \cdots + \gamma_3 A_3 \]  \hspace{1em} (Model 1)

where for each village, \( R \) is the mortality rate of liver cancer, \( X_i \) is proportion (expressed as percentage) of wells with arsenic levels in category \( j \), and \( A_p \) is proportion of residents in age group \( p \). \( R \) was calculated by dividing the number of liver cancer deaths by the estimated total number of person-years observed in a given village. In this case, \( \alpha \) (intercept) is the estimated background risk, and \( \beta_j \) indicates the RD associated with each 1% increase in wells in category \( j \). Furthermore, the data were weighted with the total population in each village as the weight, and weighted regression models were applied to account for the different weights of data contributed by different villages.

On the basis of results obtained through Model 1, we conducted post hoc analyses to confirm the findings. In addition to regression analyses, stratified analyses were applied. All statistical analyses were conducted using the SAS software, and all statistical tests were performed at the two-tailed significant level of 0.05.

3. Results

3.1. Associations between arsenic level in drinking water and mortality of liver cancer

Over the 20-year study period, 802 male and 301 female liver cancer deaths were identified in the study villages. After adjusting for age, arsenic levels above 0.64 mg/L in drinking water were associated with a statistically significant increase in the mortality of liver cancer in both genders. As shown in Model 1 and Table 1, a 1% increase in the proportion of wells in this category (arsenic levels above 0.64 mg/L) was associated with an increase of 0.21 per 100,000 persons per year in the mortality of liver cancer in men, and 0.09 per 100,000 persons per year in women. No significant difference in the mortality of liver cancer was found to be associated with any of the other four arsenic levels.

3.2. Post hoc data analysis

Post hoc stratified analyses were conducted according to two features of the dose–response relationship observed using Model 1: (1) no significant effect below 0.64 mg/L and (2) a significant positive effect above 0.64 mg/L. Accordingly, two post hoc multiple regression models were applied to validate the observations. The first one combined all exposure between 0.05 and 0.64 mg/L as one predictor variable—\( X_{14} \), as the following:

\[ R = \alpha_1 + \beta_1 X_{14} + \beta_5 X_5 + \gamma_1 A_1 + \cdots + \gamma_3 A_3 \]  \hspace{1em} (Model 2)

...
Table 1

<table>
<thead>
<tr>
<th>Arsenic level (mg/L)</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rate difference [95% CI]</td>
<td>Rate difference [95% CI]</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05–0.08</td>
<td>−0.06 [−0.29, 0.18]</td>
<td>−0.03 [−0.14, 0.08]</td>
</tr>
<tr>
<td>0.09–0.16</td>
<td>−0.03 [−0.23, 0.17]</td>
<td>−0.03 [−0.07, 0.12]</td>
</tr>
<tr>
<td>0.17–0.32</td>
<td>0.00 [−0.18, 0.30]</td>
<td>0.02 [−0.09, 0.13]</td>
</tr>
<tr>
<td>0.33–0.64</td>
<td>−0.11 [−0.39, 0.18]</td>
<td>0.01 [−0.13, 0.05]</td>
</tr>
<tr>
<td>0.64</td>
<td>0.21 [0.04, 0.37]</td>
<td>0.09 [0.01, 0.16]</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05–0.64</td>
<td>0.02 [−0.13, 0.09]</td>
<td>0.01 [−0.04, 0.06]</td>
</tr>
<tr>
<td>0.64</td>
<td>0.21 [0.05, 0.38]</td>
<td>0.09 [0.01, 0.17]</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
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<tr>
<td>0.64</td>
<td>0.22 [0.06, 0.38]</td>
<td>0.09 [0.01, 0.16]</td>
</tr>
</tbody>
</table>

*Confidence interval.
*p < 0.05.
**p < 0.01.

and the results showed that this new variable (X_{14}) was not a significant predictor of the mortality of liver cancer. This model is to examine whether there is a significant effect of levels between 0.05 and 0.64 mg/L. Under the assumption of no significant effect of arsenic in drinking water below 0.64 mg/L, the second model had only one indicator for arsenic exposure (for levels above 0.64 mg/L), as the following:

\[ R = a_2 + b_5 X_5 + \gamma_1 A_1 + \ldots + \gamma_3 A_3 \]  

(Model 3)

Both Models 2 and 3 generated point estimates for the increases in liver cancer mortality associated with arsenic levels above 0.64 mg/L similar to the full model (Table 1).

In post hoc stratified analyses, we validated the observed dose–response relationships further by dividing the 138 villages into the following three groups: the Group A consisted of 29 villages with all the 291 wells containing less than 0.05 mg/L of arsenic, Group B consisted of 74 villages with 30.6% of the 4286 wells containing more than 0.05 mg/L of arsenic but none with arsenic levels above 0.64 mg/L, and Group C consisted of 35 villages with 12.4% of the 1526 wells containing more than 0.64 mg/L of arsenic. If conclusions drawn on the dose–response relationship from regression analyses hold, Group C should have the highest mortality among the three, and Groups A and B should have similar mortality rates. The first projection that Group C has the highest mortality rate was generally true in all but two groups—men below 29 years of age and women between 50 and 69 years old, and the difference between Group C and the group with the highest mortality were not statistically significant in either case (Table 2). The second projection was supported by the facts that Group A and Group B had similar liver cancer mortality in four of the eight gender-age groups and that all the differences between Groups A and B were not statistically significant except for women between 50 and 69 years old. In other words, results of stratified analyses confirmed the dose–response relationships projected by the regression analyses.

4. Discussion

4.1. Literature on the association between arsenic ingestion and liver cancer

The occurrence of liver cancer in patients of arsenic intoxication has been documented since about half a century ago [35]. Many of the earliest case reports were on patients taking medicines containing arsenic such as Fowler’s solution [21,45–49], and cases attributable to environmental and occupational exposures were also reported [9,20,45,50,51]. The relatively high frequency of angiosarcoma was the focus of most case reports [9,21,45–47,49,51,52]. Epidemiologic studies on such populations, however, are very limited. A follow-up on 478 patients taking Fowler’s solution found only one case of liver cancer and obtained a standardized mortality ratio (SMR) of 1.23 (95% confidence interval [CI]: 0.04–7), while a statistically significant increase in bladder cancer was observed (SMR = 3.07) [53]. Whereas the early literature has provided sufficient evidence to argue an association between arsenic ingestion and liver cancer, for hepatic angiosarcomas at least, data on the dose–response relationship were quite limited.

Using “arsenic” combined with “liver cancer” and “hepatoma” to search literatures in the PubMed, we found 19 English reports of epidemiologic studies on the association between arsenic ingestion and liver cancer [22,23,34,36,37,54–67]. A study found 5 cases amongst 258 wine growers with exposures through both ingestion and inhalation, but none in 159 non-exposed persons [22]. A study on 3141 deaths in Japan compared the mortalities before and after an episode of arsenic contamination of milk powder and found an increase in liver cancers [57]. The other studies were on the atherogenic and carcinogenic effects [23,34,36,37,54–56,58–67] of arsenic in drinking water.

4.1.1. Studies outside Taiwan

A study in Argentina divided the study areas into three groups and observed a non-significant dose–response relationship in both genders [64] (Table 3). However, the study did not report actual exposure levels, but obtained a “crude average” of 0.178 mg/L for the “high exposure” group using measurements ≥ 0.04 mg/L only (instead of using all measurements). This was an unusual and probably unreliable way to estimate the exposure level, especially when only about 20% of the population in this group might have been exposed to levels ≥ 0.04 mg/L.

In Chile, a study on a population with an average exposure up to 0.568 mg/L observed no increase in liver cancer (SMR = 1.1, 95% CI: 0.8–1.5) [60], but another study on a population with an average exposure up to 0.870 mg/L observed an increase in liver cancer mortality between ages 0 and 19 [54] (Table 3).

A study in Idaho, USA also observed no associations between arsenic exposure and liver cancer (RR = 0.02 per 100,000 for 1 μg/L increment in arsenic level) [36]. A study in Japan identified two cases among 113 persons with arsenic levels in well water above 1 mg/L (SMR = 7.17, 95% CI: 1.28–26.05), but none among 330 persons with lower exposure levels [55].

Overall, the observations in these studies support both our findings of an increased risk associated with exposures above 0.64 mg/L and no increased risk below 0.64 mg/L.

4.1.2. Studies in Taiwan

The other 11 studies were conducted in Taiwan. Two studies found a significant increase in mortality of liver cancer in both genders in the BFD endemic area but provided no data on the dose–response [23,58]. Two other studies also provided evidence supporting an association between arsenic ingestion and liver cancer but did not provide data on the dose–response [65,66]. Using the duration of consuming artesian well water (containing 0.35–1.14 mg/L of arsenic) as the exposure indicator, a study observed a dose–response trend (p < 0.01) among 65 cases and 368 controls [62], which supported our finding of an increased risk associated with high-level exposures.
Three of the remaining seven studies [34,61,63] were re-analyses of data from a previous study [26] (Tables 3 and 4). A preliminary report of that study gathered 42 villages into three groups (<0.30 ppm [mg/L], 0.30–0.59 ppm, and >0.60 ppm) according to the median arsenic levels in well water and reported a significant dose–response relationship in both genders [38,39] (Tables 3 and 4). When the full report excluded residents under 20 years of age, however, the dose–response relationship in women became not statistically significant [26] (Tables 3 and 4). The first re-analysis [61] divided the study population further into four exposure and four age groups (Tables 3 and 4) and identified all residents with liver cancers listed on death certificates as cases (the previous analyses only identified those with liver cancer as the major cause of death as cases) [26,38]. As a result, a significant dose–response relationship was observed in most age groups in both genders (Tables 3 and 4). Nonetheless, when the second re-analysis [34], broke down exposure levels further into eight groups, no dose–response relationship was observed (Tables 3 and 4). The third re-analysis [63] included 18 more villages with exposure data from another survey [67] and divided exposure levels even further into 11 groups. The researchers did not present actual risk estimates, but reported variations in the dose–response relationship and concluded no evidence of excess risk below 0.1 mg/L, which is compatible to our finding. Because the population was large and case number was large even when being broken down to groups, study power did not seem to be a problem in these analyses. Discrepancies among findings were probably attributable to the fact that the median arsenic level in each village was not a good exposure indicator. If our finding that the effect was much more prominent above 0.64 mg/L holds, the proportion of wells with arsenic levels above 0.64 mg/L will be a better exposure indicator, and it is reasonable that using the median exposure as the indicator, which is less reliable, may observe different dose–response relationships when different divisions of exposure levels were applied.

An ecologic analysis of 314 townships adopted the same source of exposure data [32] as in our study but used the mean arsenic level in each township as the indicator [59]. A significant positive association was observed in both genders, but when the analyses were limited to 170 southwestern townships, slightly higher incremental mortalities associated with each 0.1 mg/L increase in the arsenic level were obtained (Table 3). Because the exposure indicators were different, it is hard to compare the risk estimates with those from our study.

The remaining studies in Taiwan did not have data on arsenic level [65–67]. Overall, findings from previous studies in Taiwan are not incompatible with our observations.

### 4.2. Other epidemiologic evidence

The literature search also identified two studies of BFD patients with data on liver cancer, and both found an excess risk of liver cancer [30,56]. Because no BFD patients were identified among those who did not used water from artesian wells [68], some researchers treated BFD patients as a population whose exposure levels were above 0.35 mg/L—the lowest arsenic level detected in artesian well water in the endemic area of BFD [69]—in the risk assessment [62]. While this measure might not be entirely accurate, because a survey showed about one fourth of the artesian wells in that area had arsenic levels below 0.3 mg/L [67], it is true that BFD patients are a group of people exposed to high levels of arsenic in drinking water. Artesian wells in the endemic area of BFD should have an average arsenic level around 0.5–0.6 mg/L and a range around 0.010–1.752 mg/L [26,39,40,68,70,71]. Therefore, these two studies support our finding of an association between exposures to high levels of arsenic and liver cancer.

### 4.3. The dose–response

Besides a lack of effects at low-dose levels, there are other possible reasons for not observing positive associations between exposures to low levels of arsenic in drinking water and liver cancer in our and other studies. First, the excess risks associated with arsenic levels below 0.64 mg/L might be too small for the study to detect. In addition, un-controlled confounders might affect the observed dose–response curve. In particular, Taiwan is an endemic area of virus hepatitis B, which is also a risk factor of liver cancer. None of the previous studies controlled effects of hepatitis B, but its effects as a confounder in the our study is expected to be small, if any, because the prevalence of hepatitis B in the BFD endemic area is about the same as that in the rest of Taiwan [70] and not related to the arsenic level in drinking water [72].

On the other hand, some studies indicated that arsenic might be an essential nutrient with a safety level of ingestion, and therefore, a non-linear dose–response relationship between arsenic exposure and liver cancer is biologically plausible [28,73]. In addition, a study in Belgium found that a low to moderate level arsenic in drinking
Table 3
Epidemiologic studies on arsenic levels in drinking water and liver cancers using arsenic level as the exposure indicator.

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Study design (study period)</th>
<th>Study area</th>
<th>Cases</th>
<th>Arsenic level (mg/L)</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al. [26]</td>
<td>Ecologic analysis (1973–1986)</td>
<td>42 villages, Taiwan</td>
<td>&gt;20 Men 54 42</td>
<td>&lt;0.3</td>
<td>47.78/100,000 py</td>
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<td>27 0.3–0.59</td>
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<td>25 &lt;0.005</td>
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<td>16 0.3–0.59</td>
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<td></td>
<td></td>
<td></td>
<td>10 ≥0.6</td>
<td></td>
</tr>
<tr>
<td>Chen and Wang [59]</td>
<td>Ecologic analysis (1972–1983)</td>
<td>314 townships, Taiwan</td>
<td>All Men NR</td>
<td>1 mg/L increase</td>
<td>RD = 6.8/100,000 py</td>
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<td>Women 1 mg/L increase</td>
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<td></td>
<td>Men 1 mg/L increase</td>
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<tr>
<td>Smith et al. [60]</td>
<td>Ecologic analysis (1989–1993)</td>
<td>8 cities, Chile</td>
<td>≥30 Both Men 48</td>
<td>0.568</td>
<td>SMR = 1.1</td>
</tr>
<tr>
<td>Liaw et al. [54]</td>
<td>Ecologic analysis (1950–2000)</td>
<td>2 regions, Chile</td>
<td>0–19 Men 7</td>
<td>0.870</td>
<td>RR = 8.9</td>
</tr>
<tr>
<td>Bastrup et al. [36]</td>
<td>Ecologic analysis (1993–2003)</td>
<td>56,378 persons</td>
<td>50–64 Both Men 35</td>
<td>1 μg/L increase</td>
<td>RR = 0.97</td>
</tr>
<tr>
<td>Han et al. [37]</td>
<td>Ecologic analysis (1991–2005)</td>
<td>All 44 counties in Idaho, USA</td>
<td>All Both 477</td>
<td>1 μg/L increase</td>
<td>RD = 0.02/100,000</td>
</tr>
<tr>
<td>Tsuda et al. [55]</td>
<td>Cohort study (1959–1992)</td>
<td>454 patients, Japan</td>
<td>All Both 0</td>
<td>&lt;0.05</td>
<td>SMR = 0</td>
</tr>
<tr>
<td>Hopenhayn-Rich et al. [64]</td>
<td>Ecologic analysis (1986–1991)</td>
<td>24 counties, Argentina</td>
<td>≥20 Men 186</td>
<td>Low</td>
<td>SMR = 1.54</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>142 Medium</td>
<td>SMR = 1.80</td>
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<td></td>
<td>98 High (0.178 mg/L)</td>
<td>SMR = 1.84</td>
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<td></td>
<td></td>
<td>125 Medium</td>
<td>SMR = 1.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90 High (0.178 mg/L)</td>
<td>SMR = 1.92</td>
</tr>
</tbody>
</table>

* All studies were on mortality.
+ Person-years.
^ Not reported.
¢ Incremental rate difference.
^ Standardized mortality ratio.
° Relative risk.
* A “crude average” estimated using all measurements ≥0.04 mg/L cancers of biliary passage and liver.
(1) * p < 0.05 for trend test.
(2) * p > 0.05 for trend test.
(3) p < 0.05 for comparison with the reference population.

water does not affect causes of mortality, suggesting non-linearity of the dose–response relationship for arsenic and cancer [74].

Whereas angiosarcoma seems to be a type of liver specific to arsenic exposure [45–49,75,76], the occurrence of this cancer is rare and thus has little effect on the dose–response relationship. On the other hand, a previous study found the carcinogenic effect of ingested arsenic on liver was not specific to hepatocellular carcinoma [66,67], and therefore the increase in liver cancer observed in the present study should be due to an over-all increase in all types of liver cancer.

4.4. Strengths and limitation of the current study

Timely and accurate reporting of deaths is mandated by law in Taiwan, and therefore the mortality registry we used in this study is reliable and complete. Some studies have been conducted in Taiwan to assess the dose–response relationship between arsenic level in drinking water and mortality of liver cancer, but the results were not consistent even when the same exposure data were categorized in different ways. In fact, even in the same study, the dose–response relationship might be different between the two genders [26,34]. Since the gender difference was only observed in one study, we believe the gender difference observed by Wu et al. in 1989 [26,34] was most likely due to the statistical approach. In comparison with previous studies in Taiwan, the current study had a much larger study population (40 of the 42 villages most frequently studied villages were included in our study) and longer study period (Table 3), and therefore the results should be more reliable. Furthermore, the current study had more exposure categories than most of the previous studies and thus should be able to describe the dose–response relationship more precisely.

Because the present study used ecologic data, its results might be affected by “ecological fallacy” as well as other common limitations of ecological studies, such as misclassification of exposure, the lack of ability to address exposure duration, and effects of
population mobility. Further studies with exposure data on individuals and the ability of adjusting for effects of other confounders such as hepatitis B and C infection, liver cirrhosis, social-economic status, and alcohol consumption are necessary to confirm findings in this study.

5. Conclusions

In conclusion, we found exposures to high arsenic levels in drinking water are associated with the occurrence of liver cancer, but such an effect was not prominent at low exposure levels. These findings suggest that both the Joint FAO/WHO Expert Committee on Food Additives guidelines for lung cancer (3.0 μg/kg bw per day; 2–7 μg/kg bw per day) and the new U.S. EPA arsenic standards for drinking water (0.1 mg/L) may provide sufficient protection against the carcinogenic effect of arsenic on liver.

Acknowledgements

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