Cell Type Specificity of Lung Cancer Associated with Arsenic Ingestion

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Abstract

Arsenic is a well-documented human carcinogen. Previous studies on urinary bladder and skin cancers have shown that arsenic can cause specific cell types of malignancy. To evaluate whether this is also true for lung cancers, we conducted a study on 243 townships in Taiwan. We identified patients through the National Cancer Registry Program and compared the proportion of each major cell type between an endemic area of arsenic intoxication with exposures through drinking water, which includes 5 of the townships and the other 238 townships. To control for gender and age, we analyzed data on men and women separately and divided patients into four age groups. A total of 37,290 lung cancer patients, including 26,850 men and 10,440 women, was diagnosed between January 1, 1980 and December 31, 1999 in study townships. Patients from the endemic area had higher proportions of squamous cell and small cell carcinomas, but a lower proportion of adenocarcinomas. These findings were similar across all age groups in both genders, although the lack of data on smoking is a limitation of our study. The results suggested that the carcinogenicity of arsenic on lungs is also cell type-specific: squamous cell and small cell carcinomas appeared to be related to arsenic ingestion, but not adenocarcinoma. Whereas data in the literature are limited, the association between adenocarcinoma and arsenic exposures through inhalation appeared to be stronger than that of squamous cell carcinoma. Therefore, we speculate that arsenic may give rise to different mechanisms in the development of lung cancers through different exposure routes. (Cancer Epidemiol Biomarkers Prev 2004;13(4):638–643)

Introduction

The association between arsenic ingestion and skin cancer was first documented more than a century ago (1). Such an association has also been observed in an area along the southwest coast of Taiwan since the early 1960s (2, 3). In addition to skin cancer, the association between arsenic ingestion and internal cancers, including cancers of the bladder, kidney, lung, liver, and colon has also been documented (4–7). Among the internal cancers found to be associated with arsenic ingestion, bladder cancer has the highest relative risk (RR) (4–7). A nationwide study in Taiwan has found that associations between arsenic ingestion and urinary cancers are cell type-specific; specifically, an association was observed in transitional cell cancer, but not in renal cell cancer (8). The association between transitional cell carcinoma and arsenic ingestion has also been supported by reports from other countries (9–12) and confirmed by another study in Taiwan (13). In the skin, the arsenic level in drinking water is associated with the incidence of squamous cell and basal cell carcinomas, but not with the incidence of malignant melanoma (14).

An increased incidence of lung cancer has been noted among patients of arsenic intoxication since the 1950s (15). Nonetheless, data on the pathological cell types are quite limited, and most studies are on exposures through inhalation. In fact, lung cancer is more common and more fatal than skin and bladder cancers, and therefore, it is of greater concern from the point of view of both clinicians and public health practitioners. In 2001, the U.S. Environmental Protection Agency (EPA) lowered the maximum contaminant level (MCL) of arsenic in drinking water from 0.05 to 0.01 mg/l (16); the associations between arsenic levels in drinking water and mortalities of lung and bladder cancers observed in Taiwan (17) have constituted an important scientific basis of the revision. The objective of this study was to evaluate whether lung cancer associated with arsenic ingestion also had cell type specificity, which might provide new insights for further studies.

Methods

We identified patients with lung cancer using data collected through the National Cancer Registration Program operated by the Taiwanese government. The analyses covered 243 townships in which data on arsenic in drinking water from a nationwide survey conducted

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by the government (18) were collected in a previous study on urinary cancers (8). We included patients who were diagnosed with lung cancer between January 1, 1980 and December 31, 1999. The year 1999 was the latest year on which registry data were available for analysis. The computerized database of the National Cancer Registration Program contained information on gender, date of birth, township of residence, date of diagnosis, and clinical and pathological diagnoses of each patient. Both clinical and pathological diagnoses were coded with the International Classification of Diseases for Oncology codes (19). All pathological classifications were made by board-certified pathologists. Considering the stability of estimates, we analyzed data on major pathological cell types only, which was defined as a cell type having at least 243 cases (at least 1 per township on average) of each gender during the 20-year study period.

To evaluate the possible cell type specificity of the carcinogenic effect of arsenic on lung, we compared the proportion of each major cell type of lung cancer between an endemic area of arsenic intoxication, generally known as the ''blackfoot disease (BFD) area,'' and the other areas in Taiwan. The BFD area covered 5 of the 243 townships in our study and is known for its high prevalence of BFD, a peripheral vascular disease that may lead to gangrenous changes of extremities, especially in feet (3). This area had high arsenic levels in drinking water, and it is generally believed that BFD is caused by exposure to arsenic from drinking water. The study that led to the revision of the MCL (17) was conducted in the BFD area, so was the study that justified the previous MCL (3). According to the nationwide survey (18), the 5 townships in the BFD area had an average arsenic level of 0.22 mg/l in well water, and the other 238 townships had an average arsenic level of 0.02 mg/l. Data from the Department of Interior showed that the BFD area had a population around 145,000, and the rest of the study areas had around 11 million.

To evaluate the possible cell type specificity of the carcinogenic effect of ingested arsenic on the lung, a RR was defined as the ratio of the proportion of a given cell type of lung cancer in patients from the BFD area to that proportion in patients from the other areas. Because it is possible that arsenic leads to increases in the incidence rates of all cell types (a lack of specificity), this ratio of the relative frequencies (proportions) among lung cancer patients in the two study populations is a more direct indicator of cell type specificity. Differences in the proportions were evaluated by χ^2 test or Fisher's exact test at the two-tailed significant level of 0.05. We used the SAS package to conduct all statistical analyses.

Results

Through the national cancer register, we identified 37,290 lung cancer patients, including 26,850 men and 10,440 women, in the 243 townships during the 20-year study period (Table 1). The BFD area had a higher overall crude incidence rate in both men (39.8 *versus* 22.3 per 100,000 person-year, $P < 0.01$) and women (20.8 *versus* 9.4 per 100,000 person-year, $P < 0.01$). In addition, the BFD area had higher overall incidence rates in all age groups, except for men under 30 years of age—no case of lung cancer was observed in this age group in the BFD area.

Overall, 80.7 % of male patients and 74.8% of female patients had pathological diagnoses, and there were

Table 1. Comparison of distributions of pathological cell types of lung cancer patients between the blackfoot disease area and the other areas in Taiwan

Cell type	Other areas				Blackfoot disease area					
	Cases	Incidence (10^{-5} per year)	[%][a]	[%][b]	Cases	Incidence (10^{-5} per year)	[%][a]	[%][b]	RR	[95% CI][c]
Men[d]										
Squamous cell	8,124	6.9	[31.0]	[38.3]	207	13.4	[33.6]	[42.8]	1.1	[1.0, 1.2]*
Adenocarcinoma	7,419	6.3	[28.3]	[35.0]	120	7.7	[19.5]	[24.8]	0.7	[0.6, 0.8]**
Small cell	2,713	2.3	[10.3]	[12.8]	77	5.0	[12.5]	[15.9]	1.2	[1.0, 1.5]*
Others	2,936	2.5	[11.2]	[13.9]	80	5.2	[13.0]	[16.5]	1.2	[1.0, 1.5]
Subtotal, with pathology	21,192		[80.8]	[100.0]	484		[78.6]	[100.0]		
No pathology	5,042		[19.2]		132		[21.4]			
Total	26,234		[100.0]		616		[100.0]			
Women[e]										
Squamous cell	1,466	1.4	[14.5]	[19.4]	90	6.2	[29.9]	[36.7]	1.9	[1.6, 2.2]**
Adenocarcinoma	4,692	4.3	[46.3]	[62.0]	89	6.2	[29.6]	[36.3]	0.6	[0.5, 0.7]**
Small cell	270	0.2	[2.7]	[3.6]	20	1.4	[6.6]	[8.2]	2.3	[1.5, 3.5]**
Others	1,135	1.0	[11.1]	[15.0]	46	3.2	[15.3]	[18.8]	1.3	[1.0, 1.6]
Subtotal, with pathology	7,563		[74.6]	[100.0]	245		[81.4]	[100.0]		
No pathology	2,576		[25.4]		56		[18.6]			
Total	10,139		[100.0]		301		[100.0]			

[a]Percentage in all patients, including 92 without data on age, rounded off to the first decimal digit.
[b]Percentage among those with pathological diagnoses, rounded off to the first decimal digit.
[c]RR: relative risk defined as the ratio of the proportion of a given cell type of lung cancer in patients from the BFD area to that proportion in patients from the other areas; CI: confidence interval.
[d]$P < 0.001$ for χ^2 tests of differences in distributions of all cell types between male patients from the blackfoot disease area and those from other areas.
[e]$P < 0.001$ for χ^2 tests of differences in distributions of all cell types between female patients from the blackfoot disease area and those from other areas.
*$P < 0.05$.
**$P < 0.01$.

three major pathological cell types: squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. In general, the BFD area also had higher crude and age-specific incidence rates for all three major cell types of lung cancer in both genders (Tables 1 – 3).

Both male and female patients from the BFD area had higher proportions of squamous cell carcinoma (RR = 1.1, 95% confidence interval [CI]: 1.0–1.2 in men, and RR = 1.9, 95% CI: 1.6–2.2 in women) and small cell carcinoma (RR = 1.2, 95% CI: 1.0–1.5 in men, and RR = 2.3, 95% CI: 1.5–3.5 in women) but had a lower proportion of adenocarcinoma (RR = 0.7, 95% CI: 0.6–0.8 in men, and RR = 0.6, 95% CI: 0.5–0.7 in women). These findings generally held when the patients were broken down by gender and age (Tables 2 and 3). The exceptions were the groups with no patient observed in the BFD area, including all three cell types in men under 30 years of age (Table 2) and adenocarcinoma and small cell carcinoma in women under 30 years of age (Table 3). Although the differences were not statistically significant in some gender-age groups for squamous cell carcinoma and small cell carcinoma, the proportions were higher in the BFD area in all these groups, which was consistent with the overall findings (Tables 2 and 3). In addition, when we stratified the data by 10-year intervals to compare the data from the first half of the study period to those from the second half, we also found that in the BFD area, the relative proportions of squamous cell and small cell carcinomas were higher and that adenocarcinomas were lower in different time periods, which is consistent with results from pooling all the data together.

Discussion

Since the 1950s, an increased incidence of lung cancers has been noted among arsenic-intoxicated patients (15). Whereas lung cancers associated with inhalation of arsenic have been frequently reported, very limited data on the association between ingested arsenic and lung cancer are available (20), and most of these data are from Taiwan (4–6). A review of studies in Taiwan revealed a consistent association between exposure to arsenic in drinking water and lung cancer (7). A study on users of Fowler's solution (containing potassium arsenite) has found an increased risk of bladder cancer, but not cancers of respiratory system (21). Nonetheless, Moselle wine growers with exposure to arsenical pesticides through drinking alcoholic beverages and spraying pesticides were found to have an excess risk of lung cancer (22). In addition, studies in Japan (12, 23), Chile (24), Argentina (25), and China (26) on populations exposed to arsenic through drinking water have also found an association between exposure to arsenic in drinking water and lung cancer. Overall, there is adequate evidence to argue that arsenic ingestion may cause lung cancer.

However, most reports on arsenic in drinking water and lung cancer do not provide information on pathological cell types. In fact, none of the previous studies in Taiwan presents such data. A Japanese study (12) on a population exposed to drinking water contaminated by king's yellow (arsenic trisulfide) observed nine lung cancer patients and obtained pathological diagnoses on seven, including three small cell carcinomas, two

Table 2. Pathological cell types of male lung cancer patients by age; comparisons between the blackfoot disease area and the other areas in Taiwan

Cell type	Other areas			Blackfoot disease area				
	Cases	Incidence (10^{-5} per year)	[%][a]	Cases	Incidence (10^{-5} per year)	[%][a]	RR	[95% CI][b]
<30 years old								
Squamous cell	16	0.03	[13.3]	0	0	[0.0]	NA	
Adenocarcinoma	55	0.09	[45.8]	0	0	[0.0]	NA	
Small cell	9	0.01	[7.5]	0	0	[0.0]	NA	
Others	40	0.07	[33.3]	0	0	[0.0]	NA	
30–49 years old								
Squamous cell	384	0.8	[23.5]	23	3.4	[52.3]	2.2	[1.7, 3.0]**
Adenocarcinoma	838	1.7	[51.4]	13	1.9	[29.6]	0.6	[0.4, 0.9]**
Small cell	129	0.3	[7.9]	5	0.7	[11.4]	1.4	[0.6, 3.3]
Others	280	0.6	[17.2]	3	0.4	[6.8]	0.4	[0.1, 1.2]
50–69 years old								
Squamous cell	4829	27.9	[38.9]	132	60.1	[39.2]	1.0	[0.9, 1.2]
Adenocarcinoma	4275	24.7	[34.5]	93	42.3	[27.6]	0.8	[0.7, 1.0]**
Small cell	1686	9.7	[13.6]	54	24.6	[16.0]	1.2	[0.9, 1.5]
Others	1614	9.3	[13.0]	58	26.4	[17.2]	1.3	[1.0, 1.7]*
>69 years old								
Squamous cell	2883	96.9	[41.2]	52	113.4	[52.0]	1.3	[1.0, 1.5]*
Adenocarcinoma	2241	75.3	[32.0]	12	26.2	[12.0]	0.4	[0.2, 0.6]**
Small cell	883	29.7	[12.6]	18	39.3	[18.0]	1.4	[0.9, 2.2]
Others	991	33.3	[14.2]	18	39.3	[18.0]	1.3	[0.8, 1.9]

[a]Percentage among those with pathological diagnoses, rounded off to the first decimal digit.
[b]RR: relative risk defined as the ratio of the proportion of a given cell type of lung cancer in patients from the BFD area to that proportion in patients from the other areas; CI: confidence interval. NA: not applicable.
*$P < 0.01$.
**$P < 0.05$.

Table 3. Pathological cell types of female lung cancer patients by age; comparisons between the blackfoot disease area and the other areas in Taiwan

Cell type	Other areas			Blackfoot disease area				
	Cases	Incidence (10^{-5} per year)	[%][a]	Cases	Incidence (10^{-5} per year)	[%][a]	RR	[95% CI][b]
<30 years old								
Squamous cell	11	0.02	[11.6]	3	0.4	[75.0]	6.5	[2.9, 14.3]**
Adenocarcinoma	49	0.09	[51.6]	0	0	[0.0]	NA	
Small cell	5	0.01	[5.3]	0	0	[0.0]	NA	
Others	30	0.05	[31.6]	1	0.1	[25.0]	0.8	[0.1, 4.4]
30–49 years old								
Squamous cell	272	0.6	[20.6]	9	1.5	[36.0]	1.7	[1.0, 3.0]
Adenocarcinoma	815	1.8	[61.8]	7	1.2	[28.0]	0.5	[0.2, 0.9]**
Small cell	47	0.1	[3.6]	1	0.2	[4.0]	1.1	[0.2, 7.8]
Others	185	0.4	[14.0]	8	1.4	[32.0]	2.3	[1.3, 4.1]*
50–69 years old								
Squamous cell	822	6.4	[20.4]	60	25.9	[36.6]	1.8	[1.5, 2.2]**
Adenocarcinoma	2461	19.3	[61.1]	58	25.0	[35.4]	0.6	[0.5, 0.7]**
Small cell	146	1.1	[3.6]	16	6.9	[9.8]	2.7	[1.6, 4.4]**
Others	601	4.7	[14.9]	30	12.9	[18.3]	1.2	[0.9, 1.7]
>69 years old								
Squamous cell	359	10.9	[17.1]	18	31.6	[34.6]	2.0	[1.4, 3.0]**
Adenocarcinoma	1352	40.9	[64.4]	24	42.2	[46.2]	0.7	[0.5, 1.0]**
Small cell	71	2.2	[3.4]	3	5.3	[5.8]	1.7	[0.6, 5.2]
Others	317	9.6	[15.1]	7	12.3	[13.5]	0.9	[0.4, 1.8]

[a]Percentage among those with pathological diagnoses, rounded off to the first decimal digit.
[b]RR: relative risk defined as the ratio of the proportion of a given cell type of lung cancer in patients from the BFD area to that proportion in patients from the other areas; CI: confidence interval; NA: not applicable.
*$P < 0.01$.
**$P < 0.05$.

squamous cell carcinomas, one large cell carcinomas, and one with both small cell and squamous cell carcinomas. In another study in Japan (27) on a population with both environmental and occupational arsenic exposures (through both ingestion and inhalation), 9 of the 11 cases of lung cancer had pathological diagnoses, including 7 squamous cell carcinomas and 2 adenocarcinomas. No data on a nonexposed population was provided in this study for comparison. A review of pathological cell types of lung cancer in autopsy cases in Japan from 1958 to 1997, however, shows that in both genders, the predominant cell type is adenocarcinoma, followed by squamous cell carcinoma (28).

The major exposure route of arsenic among Moselle wine growers is by drinking ''Haustrunk,'' a wine substitute made from pressed grapes, although inhalation exposure through spraying insecticides containing arsenic is also suspected (22). A post-mortem study found that 37.6% of lung cancers among Moselle wine growers were squamous cell carcinomas, a proportion higher than those observed in three of the four reference populations. Moreover, the proportion of adenocarcinoma (3.5%) was lower than those observed in all four reference populations (22). These findings were also comparable with those in our study.

Some of the previous studies on lung cancers related to arsenic exposure through inhalation have included their pathological cell types (Table 4). Because the classification of small cell cancers varies among the published reports (some include oat cell cancers and some do not), we focus our subsequent discussion on squamous cell carcinoma and adenocarcinoma. In a study on U.S. copper smelter workers with occupational exposures to arsenic, two comparison groups are used: the copper miners with low level of occupational exposure and the general population (29). As a result, the proportion of adenocarcinoma increases as the arsenic exposure level increases, but the three groups show similar proportions of squamous cell carcinoma. On the other hand, a study on Swedish copper smelter workers observed 8 squamous cell carcinomas (44.4%) and 2 adenocarcinomas (11.1%) among the 18 cases of lung cancer in exposed workers, but 3 adenocarcinomas (50%) and no squamous cell carcinoma among the 6 cases in unexposed workers (30). Whereas the findings of those two U.S. and Swedish studies may appear contradictory, the number of cases is too small to yield stable estimates, especially for unexposed workers. Neither of these two studies, however, controlled for the effects of smoking.

Some studies on inhalation arsenic exposures have controlled for smoking (Table 4). A study on U.S. copper smelter workers found a significant increase in the proportion of adenocarcinoma among exposed workers (38.1% *versus* 11.9%, $P < 0.05$) but a lower proportion of squamous cell carcinoma in controls matched for smoking status and dates of birth and death (31). Another study on Swedish copper smelter workers controlled smoking through stratification and observed an increased proportion of adenocarcinoma and a decreased proportion of squamous cell carcinoma among exposed workers in the smoker group (32). In nonsmokers, a lower proportion of adenocarcinoma and a higher proportion of squamous cell carcinoma were observed among exposed workers, but the number of cases was small. Overall, previous studies on lung cancer-associated arsenic inhalation have suggested a higher proportion of adenocarcinoma and a lower

Table 4. Pathological diagnoses in the literature on lung cancer patients associated with arsenic exposures through inhalation

Study	Reference	Squamous cell (epidermoid)		Adenocarcinoma	
		Cases	[%]	Cases	[%]
Newman *et al*., 1976	29				
Copper smelter workers (exposed)		14	[56.0]	3	[12.0]
Copper miners (occupational controls)		33	[61.1]	5	[9.3]
Reference population		27	[60.0]	3	[6.7]
Axelson *et al*., 1981	30				
Exposed copper smelter workers		8	[44.4]	2	[11.1]
Unexposed workers		0	[0.0]	3	[50.0]
Wicks *et al*., 1981	31				
Exposed copper smelter workers		13	[31.0]	16	[38.1]
Unexposed matched controls		20	[46.7]	5	[11.9]
Pershagen *et al*., 1981	32				
Nonsmokers					
Copper smelter workers		6	[60.0]	1	[10.0]
Reference population		5	[27.8]	6	[33.3]
Smokers					
Copper smelter workers		34	[41.0]	12	[14.5]
Reference population		58	[49.1]	11	[9.3]

proportion of squamous cell carcinoma. Because more than three fourths of participants in the matched U.S. study are smokers, the suspected cell type specificity is very likely to be also true among smokers.

A study in Taiwan observed associations between smoking and lung cancer in a population with exposure to arsenic in drinking water (33), but we were unable to adjust for effects of cigarette smoking directly in the current study. The lack of data on smoking is a limitation of our study. Nevertheless, until recently, only a very small proportion of Taiwanese women were smokers, and therefore the association between arsenic exposure in drinking water and lung cancer observed in women in our study is unlikely to be affected remarkably by smoking as a confounder. Because the associations we observed in men are similar to those in women, the confounding effect of smoking on the association in men should be small, if existed. Furthermore, a previous study found the consumption of cigarettes in BFD endemic townships was similar to that in the rest of Taiwan (34), which supports that cigarette smoking is not likely to be a significant confounder in our study.

Because reporting of cancer cases to the cancer registry is not mandated in Taiwan, results of this study might be affected by possible incomplete case ascertainment. Nonetheless, such effects, if existed, were unlikely to be limited to certain cell types and thus were unlikely to account for the associations we observed. This argument could also be applied to other risk factors that were not controlled in our analyses. In addition, comparisons between studies based on cancer registry and studies based on death registry, to which case reporting is mandated by law in Taiwan, found the results were in fact quite compatible for skin and urinary cancers (35–37). Furthermore, in a study on urinary cancers in Taiwan, all cases identified through reviewing death certificates are also found in the tumor registry (13). For lung cancer, a higher mortality has been reported in the BFD area in both genders by previous studies on the basis of death registry (4–6), which is compatible to our observations.

In Taiwan, a substantial proportion of lung cancer patients did not have pathological diagnoses, which might have affected the results of our study. However, this did not seem to be a problem in men because the proportions of patients without pathological diagnoses were similar between the BFD area and the other areas (Table 1). Even though women in the BFD area had a lower proportion of patients without pathological diagnoses, there was no reason to expect that the undiagnosed rate might have occurred differentially by cell type, and therefore this factor was not likely to have had a significant effect on the study results. The fact that our analyses of data on women led to the same conclusions as those on men further supports this argument. Overall, patients from the BFD area had a slightly higher proportion in the ''other'' group, but the differences were not statistically significant (Table 1). Because this group included all the pathological diagnoses except the three major ones, it was not a homogenous group. Further studies are needed to determine whether there are other relatively rare cell types of lung cancer that are also related to arsenic ingestion.

In the current study, we made comparisons between an area with high levels of arsenic in well water (average = 0.22 mg/l) and the other 238 townships with low levels of arsenic (average = 0.02 mg/l). We were unable to obtain the exposure level for each individual and therefore could not assess the dose-response relationship, which is a limitation of this group-level exposure assessment approach. Furthermore, there were variations in the exposure levels within each of the two populations, which might lead to misclassifications—some people in the BFD area had relatively low exposure levels, and some people in the other areas had relatively high exposure levels. However, such misclassifications generally lead to a result closes to the null value (no difference), and because significant differences were observed in most comparisons and the results were similar across different age groups, the cell type specificity in the current study was not likely to be a result of misclassifications. In other words, our conclusions were not likely to be changed by such misclassifications.

Although arsenic is a well-documented human carcinogen, animal models have not been well established, probably because susceptibility to the carcinogenic effect of arsenic is different in experimental animals in comparison with human beings. Therefore, the advancement of knowledge on the carcinogenicity of arsenic mainly relies on epidemiological studies and studies on human cell lines. The possibility that different cell types of lung cancer can be induced through different routes of exposure to arsenic is, therefore, intriguing and suggests that different mechanisms of carcinogenicity may be involved. If this is true, further studies on those differences may lead to a better understanding of the carcinogenicity of arsenic.

Whereas bladder cancer has the highest RR associated with arsenic ingestion among all internal cancers (7), lung cancer is more common and more fatal than bladder cancer. Even a small increase in the incidence of lung cancer may lead to a substantial number of excess deaths. Because arsenic is widely distributed in the ground, water, and soil, lung cancer associated with arsenic ingestion is an important issue that calls for more research and prevention efforts. Findings in the current study, particularly the cell type specificity, may cast some light on the direction for further studies.

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References

1. Hutchinson J. Arsenic cancer. Br Med J, 1887;2:1280–1.
2. Yeh S. Relative incidence of skin cancer in Chinese in Taiwan: with special reference to arsenical cancer. Natl Cancer Inst Monogr, 1963;10:81–107.
3. Tseng W-P, Chu H-M, How S-H, Fong J-M, Lin C-S, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst, 1968;40:453–63.
4. Chen C-J, Kuo T-L, Wu M-M. Arsenic and cancers. Lancet, 1988;1:414–5.
5. Wu M-M, Kuo T-L, Hwang Y-H, Chen C-J. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol, 1989;130: 1123–32.
6. Chen C-J, Wang C-J. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. Cancer Res, 1990;50:5470–4.
7. Guo H-R, Chen C-J, Greene HL. Arsenic in drinking water and cancers: a descriptive review of Taiwan studies. In: Chappell WR, Abernathy CO, Cothern CR, editors. Arsenic: exposure and health. Northwood: Science and Technology Letters; 1994. p. 129–38.
8. Guo H-R, Chiang H-S, Hu H, Lipsitz SR, Monson RR. Arsenic in drinking water and incidence of urinary cancers. Epidemiology, 1997;8:545–50.
9. Besuschio SC, Prez Desanzo AC, Croci M. Epidemiological association between arsenic and cancer in Argentina. Biol Trace Elem Res, 1980;2:41–55.
10. Koh E, Kondoh N, Kaihara H, Fujioka H, Kitamura K. Ureteral tumor with multiple Bowen's disease forty-two years after exposure to arsenic. Eur J Urol, 1989;16:398–400.
11. Nomura Y, Nojiri A, Kudo S. Two cases of transitional cell carcinoma of urinary tract in patients with chronic arsenic poisoning. J Kumamoto Med Sci, 1986;60:13–24.
12. Tsuda T, Babazono A, Yamamoto E, et al. Ingested arsenic and internal cancer: A historical cohort study followed for 33 years. Am J Epidemiol, 1995;141:198–209.
13. Chiou H-Y, Chiuo S-T, Hsu Y-H, et al. Incidence of transitional cell carcinoma and arsenic in drinking water: a follow-up of 8,102 residents in an arseniasis-endemic area in northeastern Taiwan. Am J Epidemiol, 2001;153:411–8.
14. Guo H-R, Yu H-S, Hu H, Monson RR. Arsenic in drinking water and skin cancer: cell-type specificity. Cancer Cause Control, 2001;12: 909–16.
15. Sommers SC, McManus RG. Multiple arsenical cancers of skin and internal organs. Cancer, 1952;6:347–59.
16. Environmental Protection Agency. National primary drinking water regulations; arsenic and clarifications to compliance and new source contaminants monitoring; Final rule. Fed Reg, 2001;66: 6976–7066.
17. Morales KH, Ryan L, Kuo T-L, Wu M-M, Chen C-J. Risk of internal cancers from arsenic in drinking water. Environ Health Perspect, 2000;108:655–61.
18. Lo M-C, Hsen Y-C, Lin B-K. Second report on the investigation of arsenic content in underground water in Taiwan. Taichung, Taiwan: Taiwan Provincial Institute of Environmental Sanitation; 1977.
19. World Health Organization. International classification of diseases for oncology, 1st ed. Geneva, Switzerland: World Health Organization; 1976.
20. Bates MN, Smith AH, Hopenhayn-Rich C. Arsenic ingestion and internal cancers: a review. Am J Epidemiol, 1992;135:462–76.
21. Cuzick J, Sasieni P, Evans S. Ingested arsenic, keratoses, and bladder cancer. Am J Epidemiol, 1992;136:417–21.
22. Lüchtrath H. The consequences of chronic arsenic poisoning among Moselle wine growers. J Cancer Res Clin Oncol, 1983;105:173–82.
23. Nakadaira H, Endoh K, Katagiri M, Yamamoto M. Elevated mortality from lung cancer associated with arsenic exposure for a limited duration. J Occup Environ Med, 2002;44:291–9.
24. Ferreccio C, Gonzalez C, Milosavjlevic V, Marshall G, Sancha AM, Smith AH. Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology, 2000;11:673–9.
25. Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. Int J Epidemiol, 1998;27:561–9.
26. Luo FJ, Luo ZD, Ma L. A study on the relationship between drinking water with high arsenic content and incidence of malignant tumour in Heihe Village, western part of Huhehot, Inner Mongolia. Chin J Epidemiol, 1995;16:289–91.
27. Hotta N. Clinical aspects of chronic arsenic poisoning due to environmental and occupational pollution in and around a small refining spot. Jan J Cons Med, 1989;53:49–70.
28. Morita T. A statistical study of lung cancer in the annual of pathological autopsy cases in Japan, from 1958 to 1997, with reference to time trends of lung cancer in the world. Jpn J Can Res, 2002;93:15–23.
29. Newman JA, Archer VE, Saccomanno G, et al. Histological types of bronchogenic carcinoma among members of copper-mining and smelting communities. Ann NY Acad Sci, 1976;217:260–8.
30. Axelson O, Dahlgren E, Jansson C-D, Rehnlund SO. Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. Br J Ind Med, 1978;35:8–15.
31. Wicks MJ, Archer VE, Auerbach O, Kuschner M. Arsenic exposure in a copper smelter as related to histological type of lung cancer. Am J Ind Med, 1981;2:25–31.
32. Pershagen G, Bergman F, Klominek J, Damber L, Wall S. Histological types of lung cancer among smelter workers exposed to arsenic. Br J Ind Med, 1987;44:454–8.
33. Chiou H-I, Hsueh Y-M, Liaw K-F, et al. Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. Cancer Res, 1995;55:1296–300.
34. Tsai S-F. Ecological correlation study on major risk factors of various malignant neoplasms in Taiwan; 1972–1983 [Master Thesis]. National Taiwan University; 1987.
35. Guo H-R. Arsenic in drinking water and skin cancer: comparison among studies based on cancer registry, death certificates, and physical examinations. In: Abernathy CO, Calderon RL, Chappell WR, editors. Arsenic: exposure and health effects. London: Chapman & Hall; 1997. p. 243–59.
36. Guo H-R. Dose-response relation between arsenic in drinking water and mortality of bladder cancers. Chin J Public Health (Taipei), 1999; 18:s134–9.
37. Guo H-R, Tseng Y-C. Arsenic in drinking water and bladder cancer: comparison between studies based on cancer registry and death certificates. Environ Geochem Health, 2000;22:83–91.

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