RRPC89100971 (23.P)

行政院國家科學委員會補助專題研究計畫成果報告

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Follow-up study on health effects induced by air pollutants and arsenic among residents in Lanyang Basin

計畫編號：NSC-89-2318-B-038-001-M51
執行期間：87 年 8 月 1 日至 90 年 7 月 31 日
主持人：邱弘毅　執行機構及單位：台北醫學大學公共衛生學系

一、中文摘要

爲探討飲水砷與麩胺基硫轉移酵素 M1、T1 及 P1（GSTM1、T1、P1）基因多型性對頸動脈粥狀硬化的危險性。本研究共選取 605 位蘭陽盆地居民參加體檢，以結構式問卷標準化家戶訪視，以獲得研究資料包括菸、酒、飲水史及家族疾病史。火焰式原子吸光譜儀加氫化器，用來測定井水砷濃度。PCR-RFLP 用來判定 GSTM1、T1 及 P1 的基因型。頸動脈粥狀硬化係由神經內科醫師判定。邏輯斯蒂複迴歸分析用以計算年齡、性別調整之危險對比值及其百分之九十五信賴區間。具有 GSTM1 無效基因者，隨著飲水砷濃度增加，與罹患頸動脈粥狀硬化的危險性呈現劑量效應關係，其年齡性別調整之危險對比值，飲水砷濃度介於 50.1-99.9 mg/L 和 >=100 mg/L 兩組分別爲 2.7 及 3.3。對於飲用水砷濃度屬於兩組的研究對象，具 GST1 無效基因者，年齡性別調整之危險對比值分別爲 5.3 及 3.6，均達統計顯著水準。而對於具 GSTP1 W/V 或 V/V 基因型者，年齡性別調整之危險對比值分別爲 4.1 和 3.2。結論：本研究顯示具有 GSTM1、T1 無效基因型，以及 GSTP1 W/V 或 M/V 基因型者與飲水砷濃度的增加，會使其罹患頸動脈粥狀硬化的危險性顯著增加。

關鍵詞：砷、動脈粥狀硬化、麩胺基硫轉移酵素多型性

Abstract

In order to evaluate the synergistic effects of arsenic exposure through drinking water and genetic polymorphisms of GST M1, T1, and P1 on the risk of carotid atherosclerosis, a total of 605 residents in Lanyang Basin were recruited as study subjects. A standardized personal interview based on a structured questionnaire was carried out to obtained study informations including duration of well water consumption as well as personal and family history of hypertension, diabetes and cerebrovascular disease. Hydride generator combined with flame atomic absorption spectrometry was used to determine arsenic concentration. PCR-RFLP was used for genotyping GSTM1,T1and P1. Carotid atherosclerosis was diagnosed by medical doctor based on data of intimal-medial thickness (IMT) of arterial wall and plaque score. Logistic regression analysis was used to estimate age-sex-adjusted odds ratio and 95 % confidence interval. A significant dose-response relationship was observed between arsenic concentration in well water and risk of carotid atherosclerosis among study subjects with null genotype of GSTM1, T1, and P1. The age-sex-adjusted odds ratios of carotid atherosclerosis were 2.7 and 3.3 for arsenic concentrations in well water of 50.1-99.9 and ≧100 ug/L. Significant odds ratios of carotid atherosclerosis for study subjects with null-genotype of GST T1 were 5.3 and 3.6. Study subjects with W/V or V/V genotype of GSTP1 had 4.1 and 3.2 fold risks for the development of carotid atherosclerosis. In conclusion, a significant effect on the risk of carotid atherosclerosis were observed among study subjects with arsenic exposure and with null genotype of GSTM1, T1 and genotypes of W/V and V/V of GSTP1

key words : Arsenic, glutathione S-transferase , atherosclerosis

二、Background and Purposes

The atherogenic effects of arsenic has been well documented. Ingested inorganic

arsenic through drinking water has been related to the development of peripheral vascular disease in Poland, Chile, Mexico, Argentina, Japan and Xinjiang, China (1-8). Current studies have also reported long-term exposure to arsenic in drinking water was significantly associated with risk for development ischemic heart disease, cerebrovascular disease and peripheral vascular disease in Taiwan, showing a dose-response relationship(9-13). In addition, the association between ingestion arsenic through drinking water and hypertension and diabetes mellitus has also been reported in Taiwan and Bangladesh (14-17).

Arsenite is methylated mainly in liver to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) (18) . The methylation process may be recognized as a detoxification mechanism since the methylated metabolites are, in comparison with inorganic arsenic, less reactivewith tissue constituents, less toxic, and more readily excreted in the urine (19-23). Many studies have suggested that GSH might be involved in the initial reduction of arsenate to arsenite and the subsequent oxidative methylation. GSH is necessary enzyme for arsenic methylation, perhaps through the formation of arsenite that is the preferred arsenic form for methylation, or through conjugation with arsenic (24-26). Glutathione (GSH) S-transferases (GST) are detoxification enzymes that catalyze the conjugation of reduced glutathione to a wide spectrum of hydrophobic and electrophilic compounds. There are four subclasses of GST in mammalian cells, namely alpha, mu, pi and theta (27). The null genotype of GSTM1 has a decreased detoxification capability. It has been linked with an increased risk of cancers of the lung, bladder, breast, colon, multiple skin, meloma, and oral (28-30). The null genotype of GSTT1 was reported to be associated with an increased cancer risks of the brain and colorectal (29-31). The GSTPi is the most ubiquitous of the human GST family, being express in different tissues. Current study also reported that GSTP1 genotype may play a role in risk for oral cancer particular among lighter smokers (32). Humans with null genotypes of GSTM1, T1, and P1 have been considered to be a high risk group of cancers due to their GSH deficiency. The specific aim of this study is to evaluate the synergistic effects of arsenic exposure through drinking water and genetic polymorphisms of GST M1, T1, and P1 on the risk of carotid atherosclerosis.genetic polymorphisms of GST M1, T1, and P1 on the risk of carotid atherosclerosis.

三、Results and Discussion

A total of 605 study subjects included 289 men and 316 women were recruited in this study. The distribution of study subjects by various age groups were 18.2%, 42.6% AND 39,2% for age less than < 55 , 55- 64.9, and ≧ 65 years old. Among them, 37.2% were cigarette smokers and 18.7% had history of alcohol drinking. In addition, 13.2% and 6.3% of them affected with hypertension and diabetes mellitus, respectively.

Table 1 shows age-sex-adjusted odds ratios of carotid atherosclerosis for various arsenic exposure groups in different exposure indices of arsenic through drinking well water. A significant age-sex-adjusted odds ratios of risk of carotid atherosclerosis were observed both in exposure groups with arsenic concentration in well water greater than 100 and ranged from 50.1 to 99.9 ug/L. Moreover, study subjects with cumulative arsenic exposure greater than 1.0 mg/L-year also had significant age-sex-adjusted risk of developing carotid atherosclerosis.

The risks of carotid atherosclerosis for genetic polymorphisms of GSTM1, T1, and P1 were illustrated in Table 2. A significant higher age-sex-adjusted odds ratio of 2.0 for the development of carotid atherosclerosis was observed among study subjects with

genotypes of W/V and V/V. However, study subjects with null genotype of GSTM1 and T1 did not have higher risk of carotid atherosclerosis.

The cross-tabulation of various exposure of arsenic and genotype of GSTM1, T1, and P1 was shown in Table 3. A significant dose-response relationship was observed between arsenic concentration in well water and risk of carotid atherosclerosis among study subjects with null genotype of GSTM1,T1, and P1. The age-sex-adjusted odds ratios of carotid atherosclerosis were 2.7 and 3.3 for arsenic concentrations in well water of 50.1-99.9 and ≧100 ug/L. Among them, significant risks of carotid atherosclerosis were also found for cumulative arsenic exposure of 1.0-6.9 and ≧ 7.0 mg/L-year, showing odds ratios of 2.6 and 3.6, respectively. Significant odds ratios of carotid atherosclerosis were 5.3 and 3.6 for arsenic concentrations in well water of 50.1-99.9 and >100 ug/L among study subjects with null genotype of GSTT1. Among them, significant risks of carotid atherosclerosis were also found for cumulative arsenic exposure of 1.0-6.9 and ≧ 7.0 mg/L-year, showing odds ratios of 2.2 and 2.5, respectively. Study subjects who drank well water contained arsenic level of 50.1-99.9 and ≧100 ug/L , and with W/V or V/V genotype of GSTP1 had 4.1 and 3.2 fold risks for the development of carotid atherosclerosis.

The atherogenic effects of ingestion inorganic arsenic through drinking water have been well documented. A serious studies carried out in Taiwan have reported the significant association between long-term exposure to arsenic in drinking water and the risk for the development of atherosclerotic vascular diseases such as ischemic heart disease, cerebrovascular disease, and peripheral vascular disease, showing a dose-response relationship(9-13). Atherosclerosis is a pathological condition that underlies several important disorders including coronary artery disease, cerebrovascular disease, and diseases of the aorta and peripheral arterial circulation. Multiple risk factors included diabetes mellitus and hypertension predispose to the development of atherosclerosis. (33). Prevalence of atherosclerotic vascular diseases were significantly increased among individual with diabetes mellitus and hypertension (34). Significant dose-response relationships between long-term exposure to arsenic through drinking well water and risks of hypertension and diabetes mellitus were reported in Taiwan (14-15,35). A dose-response relationships between risk of carotid atherosclerosis and various exposure indices of arsenic were not observed. In addition, a significant dose-response relationship between age and risk of carotid atherosclerosis was observed. It might be implied that age was a major risk factor of carotid atherosclerosis. Many studies have suggested that GSH might be involved in the initial reduction of arsenate to arsenite and the subsequent oxidative methylation. GSH is necessary enzyme for arsenic methylation, perhaps through the formation of arsenite that is the preferred arsenic form for methylation, or through conjugation with arsenic (24-26, 36). In this study, a significant high risk of developing carotid atherosclerosis was observed among study subjects with W/M or M/M genotypes of GSTP1, showing an odds ratio of 2.0. Humans with null genotypes of GSTM1, T1, and P1 have been considered to be a highest risk group of carotid atherosclerosis due to their GSH deficiency. However, there were not significant differences in risks of carotid atherosclerosis between study subjects with various genetic polymorphisms of GSTM1, T1, and P1 within same exposure level to arsenic. It might be due to that there were many genes of GST family and many genetic polymorphism sites in each GST gene needed to be examined. In order to evaluate the synergistic effects of genes with arsenic

exposure on the atherogenesis of arsenic, more genes need to be examined in future studies.

四、Study Evaluation

This study has given a solid data for the synergistic effects between arsenic and genetic polymorphisms of GATM1, T1, and P1 on risk for development of carotid atherosclerosis. We have recruited the promised number (605) of study subjects in this study. In addition, genetic polymorphisms of GST M1, TI, and P1 among study subjects have also been typed. Significant association between risk for the development of atherosclerosis and null genotype of GSTM1, T1, and W/V or V/V genotype of GST P1 were observed in this study. It is important evidences in supporting of atherogenic effects of arsenic observed through epidemiological studies. However, significant synergistic effects between arsenic and various GST genes were not observed in this study. It might be due to that there were many genes of GST family and many genetic polymorphism sites in each GST gene needed to be examined. In order to evaluate the synergistic effects of genes with arsenic exposure on the atherogenesis of arsenic, more genes need to be examined in future studies based on many new technologies of molecular biology developed in post era of Human Genome Project. There were two master thesis and one paper published based on the support of this study (37-39). Some papers are prepared now and will be submitted in the near future.

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Table 1 Age-sex-adjusted odds ratio (OR) and 95% confidence interval (CI) of carotid atherosclerosis by various arsenic exposure indices

Variable	Case	Control	OR (95%CI)[a]	OR (95%CI)[b]
	No(%)	No(%)		
Arsenic concentration in well water (μg/L)				
≤50	50 (17.9)	115 (35.4)	1.0	1.00
50.1-99.9	92 (32.9)	84 (25.8)	2.5 (1.6-3.9) ***	2.13 (1.04-4.32) ***
100+	138 (49.2)	126 (38.8)	2.5 (1.02-4.02) ***	2.13 (1.04-4.32) ***
Cumulative arsenic exposure mg/L-year)				
<1.0	58 (20.7)	101 (31.1)	1.0	1.0
1.0-6.9	150 (53.6)	156 (48.0)	1.7 (1.1-2.5) **	1.8 (1.2-2.8) **
7.0+	72 (25.7)	68 (20.9)	1.8 (1.2-2.9) **	1.9 (1.1-3.0) **

a: crude odds ratio b:age-sex-adjusted odds ratio

§: 0.05<p<0.1 * :0.01<p<0.05 **: 0.001<p<0.01 *** :p<0.001

Table 2 Age-sex-adjusted odds ratio (OR) and 95% confidence interval (CI) of carotid atherosclerosis by genetic polymorphisms of GSTM1, T1 and P1

Variable	Case No(%)	Control No(%)	OR (95%CI)[a]	OR (95%CI)[b]
GSTM1				
Non-null	136 (48.7)	139 (42.8)	1.0	1.0
Null	143 (51.3)	186 (57.2)	0.8 (0.6-1.1)	0.9 (0.5-1.0)
GSTT1				
Non-null	134 (48.0)	133 (40.9)	1.0	1.0
Null	145 (52.0)	192 (59.1)	0.8 (0.5-1.0) §	0.7 (0.5-1.0) §
GSTP1				
W/W	178 (63.8)	248 (76.4)	1.0	1.0
W/V [c]	95 (34.1)	71 (21.8)	1.8 (1.3-2.6) **	2.0 (1.4-3.0) ***
V/V	6 (2.1)	6 (1.8)		

a: crude odds ratio b: age-sex-adjusted odds ratio c: W: wild type; V: variant type

§: 0.05<p<0.1 * :0.01<p<0.05 **: 0.001<p<0.01 *** :p<0.001

Table 3 Age-sex-adjusted odds ratio (OR) and 95% confidence interval (CI) of carotid atherosclerosis by genetic polymorphisms of GSTM1, TI, and P1 by various arsenic exposure indices

Variable	GSTM1 Null	GSTT1 Null	GSTP1 W/V[b] or V/V
	OR[a](95%CI)	OR[a](95%CI)	OR[a](95%CI)
Arsenic concentration in well water (μg/L)			
≤50	1.0	1.0	1.0
50.1-99.9	2.7(1.4-5.3) **	5.3(2.6-10.8) ***	4.1(1.-10.0)**
100+	3.3(1.8-6.2) ***	3.6(1.9-7.0) ***	3.2(1.4-7.1)**
Cumulative arsenic exposure (mg/L-year)			
<1.0	1.0	1.0	1.0
1.0-6.9	2.6(1.4-4.8) **	2.2(1.2-4.1) *	2.4(1.1-5.4)*
7.0+	3.6(1.7-7.6)	2.5(1.2-5.2) *	2.1(0.8-5.1)

a: age-sex-adjusted odds ratio b: W: wild type; V: variant type

§: 0.05<p<0.1 * :0.01<p<0.05 **: 0.001<p<0.01 *** :p<0.001

行政院國家科學委員會補助國內專家學者出席國際學術會議報告

90 年 7 月 10 日

附件三

報告人姓名	邱弘毅	服務機構及職稱	臺北醫學大學 公共衛生學系
會議時間地點	7.1.2001-7.5.2001 South Molle Island, Queensland, Australia	本會核定補助文號	NSC-89-2318-B-038-001-M51
會議名稱	(中文)金屬與類金屬環境毒理國際會議 (英文)International Conference on the Environmental Toxicology of Metals and Metalloids		
發表論文題目	(中文)臺灣蘭陽盆地居民井水各種金屬含量與全癌症相關性分析 (英文)Risk of all cancer sites combined and various elements ingestion through well water among residents of Lanying Basin in Taiwan		

報告內容應包括下列各項：

一、參加會議經過

金屬與類金屬環境毒理國際會議於民國九十年七月一日至七月五日在澳洲 South Molle Island 的飯店舉行。此會議是國際毒理學會的衛星會議，由澳洲國家環境毒理研究中心與昆士蘭大學合辦。參加會議人士來自美國、瑞典、荷蘭、日本、泰國及各地醫師、專家、學者，共計約 100 人與會。

本人與本校醫學系公共衛生學科薛玉梅教授於六月二十九日搭乘長榮班機，經雪梨，六月三十日抵達 Hamilton Island 機場，再搭乘渡輪約三十分鐘到達 South Molle Island 飯店投宿。七月一日在 South Molle Island 飯店會議中心報到後，隨即領了會議議程日程表、會議摘要論文集後由會議主席主持開幕儀式及晚間舉辦歡迎晚會。本次會議內容針對砷、鎘、鉛與鋁對人類之環境暴露與健康效應，毒性與作用機轉，預防與治療等領域分別進行討論。

本人於七月二日下午四點二十分以口頭發表論文，題目為" Risk of all cancer sites combined and various elements ingestion through well water among residents of Lanying Basin in Taiwan" 論文發表時，與會多位學者極表興趣，並與本人進行廣泛討論與交換意見。此外，本人亦於七月三日下午"Toxicity and Mechanism-Arsenic" section 擔任主持人。七月五日晚間大會舉辦晚宴感謝與會學者，氣氛熱鬧感性並相約後會有期。本人於七月六日飛抵雪梨，因班機關係轉往布理斯班，於七月九日上午搭乘長榮飛機返國，於晚間七點鐘左右安全返抵國門。

二、與會心得

參加本次金屬與類金屬環境毒理國際會議，使筆者有機會與世界各國從事砷、鎘、鉛與鋁研究的知名學者專家討論及交換意見，對未來研究工作有極大的助益。此次會議中以臺灣的學者所發表有關砷之論文最受重視，且可說在世界各國居領先地位。在此會議中發現美國為了飲用水中砷的安全閾值規定，非常注意臺灣已發表或正在進行的無機砷對人類之環境暴露量與健康效應之流行病學結果。本人所發表的論文，對於井水中是否存在其他主要會致癌或與砷拮抗的金屬，以致於修正砷的致癌性，提出重要數據，引起與會學者諸多討論。

三、考察參觀活動(無是項活動者省略)

大會於七月四日安排至大堡礁(Great Barrier Reef)參觀，此為世界七大景觀之一，讓與會者浮潛參觀壯觀的珊瑚礁與五彩繽紛的魚群，瞭解大自然的奇妙。

四、建議

過去數十年台灣烏腳病盛行地區無機砷健康危害研究，有關癌症危害結果備受國際重視，美國環境保護局並以台灣的研究結果訂定水質標準。全世界尚有許多國家如美國、中國大陸、日本、德國、阿根廷、墨西哥、印度、孟加拉、智利等國有相同問題。然而目前臺灣東北蘭陽盆地含砷地下水問題及居民是否受到砷引發之癌症與心臟血管疾病等健康危害?政府應更應廣泛深入調查、研究，期使該地區居民不再重遭西南沿海砷中毒地區居民的噩夢。同時政府更應大力支持無機砷致病機制的研究，俾使台灣地區在此一領域的研究能傳承過去癌症流行病學研究之光榮的歷史領先其他國家。並以臺灣經驗分享於世界其他國家，進而對世界各地日益增多地下水砷污染及砷誘發之疾病健康危害事件有實質的幫助。

五、攜回資料名稱及內容

1.會議議程日程表

2.會議摘要論文集

六、其他

Risk of all cancer sites combined induced by arsenic and various elements ingestion through well water among residents in Taiwan

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ABSTRACT

In order to evaluate the various elements exposure from drinking well water among residents in Lanyang Basin located in the northeastern arseniasis-endemic area in Taiwan, a total of 1349 well water samples were collected randomly from study area to examine concentration of arsenic (As), zinc (Zn), chromium (Cr), sodium (Na), manganese (Mn), iron (Fe), beryllium (Be), magnesium (Mg), calcium (Ca), strontium (Sr), barium (Ba), boron (B), copper (Cu), and cadmium (Cd). Inductively coupled plasma-atomic emission spectrophotometry (ICP-AES) was used to determine Zn, Cr, Na, Mn, Fe, Be, Mg, Ca, Sr, Ba, B, Cu, and Cd; As were examined by ICP-AES with hydride generation. A total of 2253 residents whose household well water was collected were interviewed personally based on a structured questionnaire. Information obtained from the interview included duration and volume of well water consumption. The cumulative exposure level of each study subject to various elements was derived from concentration of each element in well water of the household, duration of drinking well water and volume of well water consumption. The concentrations of these elements in well water, except arsenic, were significantly different among four study townships in Lanyang Basin. The log transformed concentrations of Ca, Fe, Cr and Ba were positively correlated with As significantly. However, significantly correlation of Mn, Mg and Be with As were also observed. Compared with low Mn and Cu exposed group, those who drank well water contained high concentration of Mn and Cu had significant low risk of all cancer sites combined after adjustment for age, sex, cigarette smoking, and alcohol drinking.

INTRODUCTION

Arsenic is a ubiquitous element widely distributed in nature and mainly transported in the environment by water. Humans are exposed to arsenic through water, air, food and beverages. Arsenic in sea food is high and predominantly in its organic forms which are considered less toxic than inorganic arsenic. Sources of high exposure to arsenic through ingestion included drinking water with an elevated level of inorganic arsenic, some drugs used to treat leukemia and psoriasis, and arsenic-contaminated wine. Workers from industries of smelting and refining copper, producing and using arsenic-containing agricultural chemicals, and manufacturing glass, semiconductor and various pharmaceutical substances may have an increased occupational exposure to air-borne arsenic[1,2]. The maximum contaminant level (MCL) for arsenic in drinking water set by the US Environmental

Protection Agency is 50 ug/L[3]. In the United States, it has been estimated that about 350,000 people may drink water containing arsenic higher than this level[4].

Inorganic arsenic has been well documented as a human carcinogen of skin and lung[1,2,3,5]. It is also involved in the development of several other cancers in humans without showing any organotropism. Two studies had shown an increased mortality from lung cancer due to occupational exposures to airborne arsenic through inhalation among copper smelter workers in Anaconda [6-8] and Tacoma [9-11]. Significant associations between ingested inorganic arsenic and risk from cancers of the lung and bladder have been observed in patients treated with Fowler's solution, in Moselle vintners exposed to arsenic pesticide-contaminated wine, and in persons exposed to inorganic arsenic from artesian well water [12-16]. Inhaled inorganic arsenic has also been found to be associated with an increased mortality from bladder cancer among workers in the USA and Japan [12,13]. Excess mortality from kidney cancer has also been observed among copper smelter workers and patients treated with Fowler's solution [15]. A significantly increased mortality from stomach cancer has been reported among Swedish copper smelter workers and Moselle vintners [15-17]. In our previous studies, an increased mortality from cancers of the all sites combined, lung, liver, bladder, kidney, skin, and prostate gland has been observed among residents in the endemic area of blackfoot disease (BFD) in Taiwan [16-18]. A significant dose-response relation between the long-term exposure to inorganic arsenic through drinking water and the incidence from cancers of the all sites combined, lung, and bladder has also been reported in our recent cohort follow-up study [19].

Zn, Cu and Mn were essential elements which could reduce carcinoghenicity of arsenic through inhibition free radical induced by arsenic[20,21] . While, some elements such as Cd, Be, Cr and Fe have been well-documented human carcinogen for their specific species[4]. The elements examined their concentration in well water were selected based on some reasons including carcinogenicity or toxicity of these elements and having synergistic effects with arsenic on developing cancers.

Though the dose-response relationship between arsenic exposure through water consumption and risk on development of various cancers were observed in previous studies carried out in BFD endemic area and in Lanyang Basin located in the northeastern Taiwan, there were only 1% of study subjects affected with arsenic-related cancers. In addition, there were on any solid evidences from

animal experiments to support the carcinogenicity of arsenic. In order to elucidate whether arsenic was the only major exposure source in well water for the high cancer risk groups of Lanyang Basin, the specific aim of this study was to assess the exposure of elements including Zn, Na, Ca, Cu, Fe, Mn, Mg, Cr, Sr, Ba, Cd, Be, and B in well water among residents in Lanyang Basin and to evaluate the synergistic interaction between these elements and arsenic on the development of internal cancers.

MATERIALS AND METHODS

Study Area

A total of eighteen villages in four townships of Lanyang Basin were included in the present study. The area included four villages in Chiaohsi Township, seven villages in Chuangwei Township, three villages in Wuchieh Township and four villages in Tungshan Township. Because of the abundance of underground water, residents in Lanyang Basin used shallow well water (< 40 m in depth) since 1940s for more than 50 years. Although the implementation of tape water system started in study area from early 1990s, some residents are still drinking well water. The variation in arsenic levels in well water of study area was much more striking than those in artesian well water of the southwestern arseniasis-endemic area [22]. The main source of exposure to inorganic arsenic among residents in both areas was through drinking well water.

Recruitment of Study Cohort and Determination of Element Contents in Well Water

The recruitment of study subjects as the study cohort has been described previously [23]. In brief, residents aged forty years or above were recruited into the cohort under their informed consent. A total of 2753 study subjects were selected randomly from the study cohort in this study. Information of history of well water consumption, residential history, sociodemographic characteristics, cigarette smoking, alcohol consumption, physical activities, history of sun light exposure, as well as personal and family history of hypertension, diabetes, cerebrovascular disease, heart disease, and cancers were obtained from structured questionnaire carried from October 1992 through September 1994[23]. A total of 1349 well water samples were selected randomly from -20℃ water bank. Inductively coupled plasma atomic emission spectrometry (ICP-AES) was used to determine element concentrations of Zn, Na, Ca, Cu, Fe, Mn, Mg, Cr, Sr, Ba, Cd, Be, and B in these samples.

Follow-up of Cancer Incidence

The occurrence of cancer of study subjects was followed-up by annual interview and data linkage with community hospital records and national death certification and cancer registry profiles. The vital status and causes of death for all subjects in the study cohort during the entire follow-up period from initial recruitment to December 31, 1996 were verified. A total of 170 newly diagnosed cancer cases (ICD9=140-208) including various cancer sites occurred during follow-up period.

Data Analyses and Statistical Methods

The mean and standard error were used to express the concentration variation of study elements in well water by various study townships. Pearson correlation coefficient was used to assess to correlation between study elements and arsenic. In order to evaluate the association between study elements and incidence of all cancer sites combined , Cox's proportional hazards regression analysis was used to estimate the multivariate-adjusted relative risk (RR) and its 95% confidence interval (CI) for each element which was significantly correlated with arsenic[24,25]. The statistical significance of a multivariate-adjusted RR was examined by the significance test for regression coefficient. The synergistic interacton on all cancer sites combined between cumulative arsenic exposure and Mn were also evaluated through Cox's proportional hazards regression model.

RESULTS

Table 1 shows the concentrations of study elements in well water in four townships. The concentrations of study elements in well water are significantly different in various study townships. However, the arsenic content in well water does not have an significant difference in these township. In other words, all the study townships had high arsenic level in well water.

As shown in Table 2. seven study elements which were significantly correlated with arsenic were further used to examine the association with incidence of all cancer sites combined through regression analysis. A significant regression coefficient, which indicate the increase of the risk pre 100,000 person-year for development of all cancer sites combined for every 1 ug/L increment in Mn were observed. While, significant reversed regression coefficient were observed for Fe and Cr.

The multivariate-adjusted RR of development all cancer sites combined with 95% CI for various risk factors are shown in Table 3. A significant reversed dose-response relationship between

concentration of Mn and risk of development of all cancer sites combined was observed after adjustment for age, sex, cigarette smoking, and alcohol drinking. Compared with the first tripletile level of Mn in well water as the referent group, the multivariate-adjusted RR with 95%CI of the second and the third tripletile level of Mn in well water were 0.6 (0.4-0.9) and 0.5 (0.4-0.8), respectively.

DISCUSSION

Significant associations between ingested inorganic arsenic and various cancers have been reported in our previous studies carried out in the southwestern arseniasis-endemic area in Taiwan. These case-control and ecological studies showed that long-term inorganic arsenic exposure through water consumption increases the risk of cancers of all sites combined, lung, liver, bladder, kidney, prostate gland and skin [13,16,18,26,27]. Dose-response relations between incidence rates of cancers of all sites combined, lung, and bladder and cumulative arsenic exposure were also observed in a cohort follow-up study [19]. Because there were only few wells shared be residents lived in villages of the southwestern arseniasis-endemic area in Taiwan, median arsenic levels in well water of study villages were used to derived the individual exposure to ingested inorganic arsenic in these studies. In other words, the cumulative arsenic exposure was estimated in a less precise way which might result in a non-differential misclassification of individual exposure. In the arseniasis-endemic area in northeastern Taiwan, each household had its own well for drinking water. Because the arsenic content in wells of a given village had a striking variation, residents lived in the same village had very similar socioeconomic status, lifestyles and medical care facilities with a significant difference in exposure to ingested inorganic arsenic through consumption of well water. This natural experiment circumstances was considered most appropriate for the assessment of cancer risk associated with ingested inorganic arsenic. In previous study carried out in the northeastern arseniasis-endemic area, we found a significantly increased risk of developing cancers of all sites combined, colon and rectum, skin and urinary organs. The finding was consistent with those reported previously in the southwestern arseniasis endemic area [16,18,19,26,27].

Arsenic seems to be a well-documented human carcinogen of skin and several internal organs. However, limited evidence shows the carcinogenicity of inorganic arsenic in experimental animals [28-30]. In addition, arsenic is inactive or extremely weak to induce gene mutations at specific loci [4,31], The possible modes of action for inorganic arsenic carcinogenicity might include induction of

chromosome abnormality, inhibition of DNA repair, induction of oxidative stress, and increase of cell proliferation [32]. The genotoxicity of arsenic includes changes in chromosome structure and number, increases in sister chromatid exchanges and micronuclei, gene amplification, cell transformation, and aneuploidy [15,31-35]. The role of inorganic arsenic in the carcinogenesis has been hypothesized as a co-carcinogen such as promoter or progressor rather than an initiator [30,31].

Because the evidence was far from adequate to draw a definite conclusion on the exact mechanism of inorganic arsenic to induce various cancers in humans, it is essentially to reevaluate the carcinogenic effects of arsenic. This study aims to assess the synergistic interaction between many elements and arsenic in well water. These elements include Zn. Na, Ca, Cu, Fe, Mn, Mg, Cr, Sr, Ba, Cd, Be, and B. Some elements such as Cd, Be, Cr, Fe, Ni have been well-documented human carcinogen for their specific species[4]. However. the other elements included Zn, Mn, and Cu have been recognized as essential trace elements of antioxidant enzyme-superoxide dismutase (SOD) and also involved in antioxidant process [20,21]. The prevalence of cerebrovascular diseases among residents in Lanyang Basin were higer than general population in Taiwan and Na seemed to be a risk factor of these diseases [23]. Mg, Sr, B, and Ba would have toxic effects on enzymatic function, skeletal and blood vessel system [36]. Our study found that there were seven elements significantly correlated with arsenic in well water. However, only Mn had significant protect effects on the development of cancer. According our finding, arsenic exposure through water consumption should be the major risk factor of developing various cancers among residents in Lanyang Basin.

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Table 1 Township-specific concentrations of study elements in well water of Lanyang Basin (ug/L)

Township / Element	Chuangwei		Tungshan		Chiaohsi		Wucheih		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	p
Zn	23.36	3.18	338.01	66.95	129.65	11.32	114.94	3.46	0.0001
Na	54373.08	2578.80	24992.00	1259.61	35226.20	1552.21	25238.53	1156.75	0.0001
Ca	15313.64	476.82	26726.13	560.77	12367.75	393.43	26801.59	880.92	0.0001
Cu	147.26	2.22	317.93	8.87	417.59	8.62	526.71	2.83	0.0000
Fe	335.60	23.32	1320.13	191.71	831.43	71.44	1290.88	123.39	0.0001
Mn	140.30	7.74	98.84	10.67	99.91	5.08	98.54	8.63	0.0015
Mg	19723.97	1252.40	10621.42	283.20	9786.00	290.43	15962.54	563.52	0.0001
Cr	167.11	3.78	956.73	116.36	874.99	12.14	1055.37	6.46	0.0001
Sr	278.58	9.04	218.65	4.86	157.40	4.42	256.71	7.64	0.0001
Ba	17.35	0.51	57.93	0.90	92.22	2.46	112.31	1.01	0.0000
Cd	8.20	0.34	35.92	0.85	57.57	0.98	79.12	0.24	0.0001
Be	0.03	0.02	0.06	0.01	1.31	0.05	3.04	0.03	0.0000
B	294.67	3.52	243.14	8.52	540.45	12.06	571.80	18.08	0.0001
As	195.49	10.79	318.61	19.57	293.52	30.51	178.92	26.59	0.1260

* water sample were 1349

Table 2. Regression analysis of incidence rates from all cancer sites combined and various elements level in well water in four townships of Lanyang Basin in Taiwan

	All sites combined [140~208]			
	Mean (ug/L)		Median (ug/L)	
Elements	β[a]	SE	β	SE
Ca	-0.009	(0.006)	-0.009	(0.004)
Fe	0.75	(0.34)	-0.49	(0.06)*
Mn	4.34	(1.00)*	3.32	(0.54)*
Mg	0.01	(0.01)	-0.003	(0.02)
Cr	-0.23	(0.03)*	-0.20	(0.08)
Ba	-1.81	(0.95)	-1.89	(0.82)
Be	-37.38	(38.72)	-35.59	(38.50)

* $0.01<P<0.05$

[a] regression coefficient indicating the increase the risk for development of all cancer sites combined in incidence/100,000 person-year for every 1 ug/L increase in study elements level in well water

elative risk (RR) and 95% confidence interval (CI) of elements significantly correlated with arsenic all cancer sites combined among residents of Lanyang basin in Taiwan

Ca	Fe	Mg	Cr	Ba	Be	Mn
-1.1)***	1.1(1.0-1.1)***	1.1(1.0-1.1)***	1.1(1.0-1.1)***	1.1(1.0-1.1)***	1.1(1.0-1.1)***	1.1 (1.0-1.1)***
	1.0	1.0	1.0	1.0	1.0	1.0
.6-1.7)	1.0 (0.6-1.7)	1.0 (0.6-1.7)	1.0 (0.6-1.7)	1.0 (0.6-1.7)	1.0 (0.6-1.7)	1.1 (0.7-1.8)
	1.0	1.0	1.0	1.0	1.0	1.0
.8-2.1)	1.3 (0.8-2.1)	1.3 (0.8-2.1)	1.3 (0.8-2.1)	1.2 (0.8-2.1)	1.3 (0.8-2.1)	1.2 (0.7-2.0)
	1.0	1.0	1.0	1.0	1.0	1.0
8-1.8)	1.2 (0.8-1.8)	1.2 (0.8-1.8)	1.2 (0.8-1.8)	1.2 (0.8-1.8)	1.2 (0.8-1.8)	1.1 (0.7-1.7)
	1.0	1.0	1.0	1.0	1.0	1.0
8-1.8)	0.9 (0.6-1.4)	0.9 (0.6-1.3)	1.4 (0.9-2.3)	1.6 (1.0-2.4)*	1.2 (0.8-2.0)	0.6 (0.4-0.9)*
8-1.7)	0.8 (0.5-1.2)	0.8 (0.5-1.1)	1.2 (0.7-1.9)	1.3 (0.9-2.0)	0.9 (0.6-1.4)	0.5 (0.4-0.8)***

<P<0.01 , *** P<0.001