Original Article

Association between Arsenic Concentration of Groundwater and Mortality from Leukemia and Urological Cancers in the Northwest of Iran

Alireza Rahmani[1], Samira Khamutian[1], Amin Doosti-Irani[2], Mohammad Javad Shokoohizadeh[3], Roya Ahmaddoost Razdari[4], Sharareh Niksiar[5]

[1]Department of Environmental Health Engineering, School of Public Health, Research Centre for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran, [2]Department of Epidemiology, School of Public Health, Research Center for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran, [3]Department of Environmental Health Engineering, School of Public Health, Research Center for Environmental Determinants of Health, Kermanshah University of Medical Sciences, Kermanshah, Iran, [4]Department of Biostatistics, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran, [5]Deputy of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

Abstract

Aim: The present study aims to determine the relationship between arsenic (As) concentration in groundwater and mortality rates due to urological and leukemia malignancies in Hamadan, as a hotspot of As concentration. **Materials and Methods:** The inverse distance weighting method in ArcGIS 10.8 software was used to show spatial patterns of As concentration. A total of 370 samples of tap water from urban and rural areas in all nine countries of the Hamadan province were collected by grab method. Poisson regression analysis was performed for comparing Kabudarahang region (As exposed) with the rest of the countries in Hamadan province during 2016–2020, for leukemia (ICD-10 code C90-95), bladder (ICD-10 code C67-67.9), and kidney (ICD-10, code C64-65) cancers. **Results:** Regarding leukemia, both Poisson regression and dose-response analysis supported an association between As concentration in drinking water and the risk of death. However, based on Poisson regression, no statistically significant association was observed for As levels and the mortality rates due to bladder and kidney cancers. In the linear regression fitting, for each unit increase of As concentration in groundwater, the mortality rates of leukemia increased by an average of 0.33 (P = 0.03), and according to the Poisson regression, leukemia mortality was elevated for Kabudarahang region comparing with the rest of the Hamadan province (relative risk = 1.91, 95% confidence interval = 1.24–2.92, P = 0.003). **Conclusion:** Therefore, due to the toxic and carcinogenic properties of As species, to reduce the related health risks, some managing programs, including screening, community education, and intervention, should be developed in the As-contaminated areas.

Keywords: Arsenic, cancer, mortality

Introduction

Arsenic (As) is one of the most important toxic elements in the environment and considered a challenging threat to human health. The Earth's crust contains approximately 4×10^{16} kg of As, and it is present in more than 200 minerals, in the form of sulfides, oxides, arsenate, and arsenite.[1] Human resources of As include agricultural chemicals such as insecticides and herbicides, mining, manufacturing, coal burning, and preservatives of wood. This element is released by natural or industrial processes, and then it circulates in the environment and easily reaches plants and agricultural products and eventually enters the human body.[2]

Inorganic forms of As, such as trivalent arsenite (As III) and pentavalent arsenate (As V), are the most widespread and toxic forms in groundwater; however, food contains both organic and inorganic forms of As. Arsenic with the capacity (3+) that

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Address for correspondence: Dr. Samira Khamutian, Department of Environmental Health Engineering, School of Public Health, Research Centre for Health Sciences, Hamadan University of Medical Sciences, Hamadan, Iran.
E-mail: skhamutian@gmail.com

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makes arsenite, can be very toxic when it reacts with sulfide groups in proteins and enzymes, and it constantly reacts with oxygen inside the cell, leading to cell destruction.[3] In total, arsenite disrupts the activity of 200 important enzymes by deforming the genes and DNA of the cells. Another component of As is arsenate, which due to its structure can replace in the phosphorus-containing compounds of the body such as the bones.[4]

People in the different parts of the world are exposed to high levels of As mainly through contaminated groundwater. In Asia, exposure to As through drinking water has affected more than 200 million people. Bangladesh, Argentina, Chile, China, Hungary, India, Mexico, Taiwan, Vietnam, the United States, Romania, Pakistan, Iran, and some other parts of the world are contaminated with As.[5] In 1993, the WHO established the threshold for As in drinking water at 0.01 μg/L.[6] According to the the Environmental Protection Agency, more than 50 million people in the United States use water with a concentration of more than 0.025 μg/L.[7,8]

In Bangladesh and India, more than 100 million people are exposed to more than 0.01 μg/L of As. In West Bengal, 55% of the samples were reported to have higher than standard As. In Iran, the most important As-contaminated areas include West Azerbaijan (Takab), East Azarbaijan (Hashtrood), Kurdistan (Qorveh and Bijar), Kerman (the Rayen plain), Hamadan (Kabudarahang), Khorasan (Kashmar), Sistan and Baluchestan (Khash), and Fars province (Maharloo).[9-11]

As is absorbed through water, air, contaminated food, skin, respiratory system, and digestive system and then is widely manifested in the bloodstream and spreads in tissues and causes various diseases. Increasing acute and chronic effects of As on human health have led to the classification of this element as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer.[12]

The continued use of contaminated groundwater for drinking and irrigation can trigger to several health manifestations in the human body, commonly called arsenicosis. As toxicity also causes cancers of various organs, neurological dysfunction, cardiovascular disease, and immune-related disorders. According to the previous studies, the most common cancers associated with As contamination are neoplasms of the bladder and kidneys (with a global incidence of 7.4 and 5.5/100.000), liver (11/100.000), prostate (36/100.000), lung (28.3/100.000), and breast (58.5/100.000) and leukemia (6.1/100.000).[13] In a previous ecological study in Chile, the association between As levels in drinking water and mortality rates due to various cancers has been evaluated using Poisson regression. According to the results, As concentration in the study areas decreased from 600 to 20 μg/L during the 1960s and 2010. However, the adverse effects of As were observed for 40 years even after the reduction of As levels.[14]

According to the GLOBOCAN, the estimated mortality rates for combined bladder and leukemia in Iran and both sexes were 7.7 in 100,000 in 2020. In the world, leukemia and bladder cancer were the 11th and 14th leading cause of cancer mortality worldwide, accounting for 311,594 and 212,536 cancer deaths, and the age-standardized mortality rate (ASR) of 3.3/and 1.9/100,000. In Iran, they were the 8th and 13th leading cause of cancer mortality worldwide with 4634 and 1760 cancer deaths, and 5.5/100,000 and 2.1/100,000 (ASR), respectively.[15] It is estimated that 70%–90% of mineral As is absorbed by the gastrointestinal tract after consumption and is widely distributed through the blood to various organs, mainly the liver, kidneys, lungs, and bladder and second to muscle and nerve tissue. Then, it accumulates in the organs, especially in the liver, and is excreted mostly in the urine. As kinetics depend on the duration of exposure, route of administration, physicochemical properties of the compound, and the biological species damaged.[16]

Hamadan province, that is located along the belt of Tertiary volcanic rocks, is considered one of the most important As hotspots in the world. Considering the importance of the known effects of exposure to arsenic through drinking water, the present study aims to evaluate the concentration of As in nine counties of Hamadan province, and in addition, to determine the relationship between the concentration of As in the groundwater of Hamadan province and the mortality rate due to urological and leukemia malignancies.

Materials and Methods

The sampling locations in the study include Asadabad, Bahar, Famenin, Hamadan, Malayer, Nahavand, Razan, Tuyserkan, and Kabudarahang. Hamadan Province situated between latitudes 33º59′ N and 35º48′ N and longitudes 47º34′ E and 49º36′ E, with approximately 19,546 km^2. Its population is around 1,758,268 people.[17] The climate of Hamadan Province is extremely variable due to the existence of high mountains. It also has mild summers and snowy and cold winters. The average annual temperature of the province is 11.3°C. The annual precipitation is estimated to be 317.7 mm. The groundwater level varies from 180 to 300 m.[18]

In this study, mortality data due to leukemia (ICD-10, code C90-95) and urological (ICD-10, code C64-67.9) malignancies in all countries of the Hamadan province in 2021 were received from the Deputy of Health of Hamadan University of Medical Sciences. These data include age, gender, place of residence, and cause of death (based on ICD Codes).

A total of 370 samples of tap water from urban and rural areas in all nine countries of the Hamadan province was collected by grab method and were covered all water resources of Hamadan [Figure 1]. The sampling areas were as follows: Asadabad (7 sites: two cities and five villages), Bahar (13 sites: four cities and nine villages), Famenin (8 sites: two cities and six villages), Hamadan (10 sites: three cities and seven villages), Malayer (15 sites: five cities and ten villages), Nahavand (13 sites: four cities and nine villages), Razan (12 sites: four

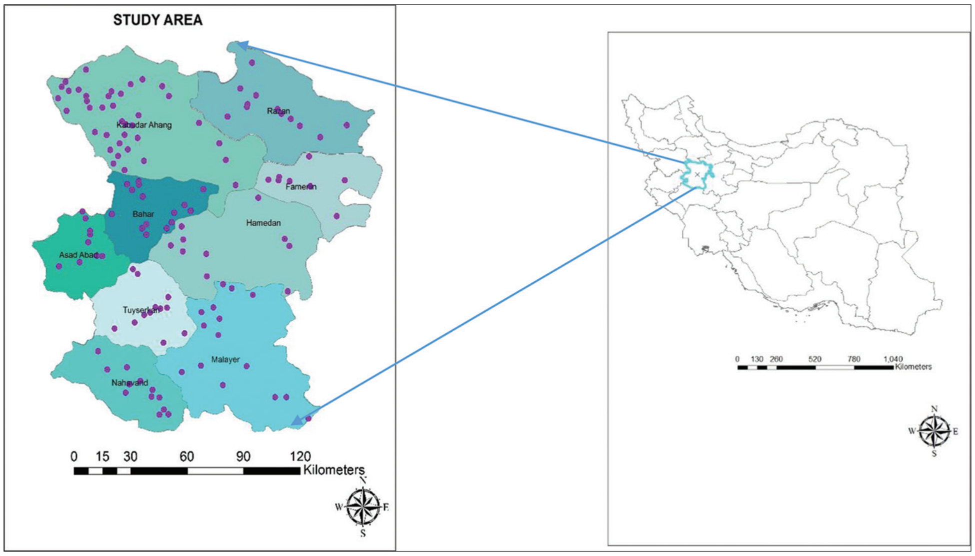

Figure 1: Map of the sampling locations

cities and eight villages), Tuyserkan (12 sites: three cities and nine villages), and Kabudarahang (46 sites: three cities and 43 villages). Sampling was performed for 5 years (2017–2021). The samples were collected in clean polyethylene bottles and labeled for easy identification. All of the samples were immediately transferred to the reference laboratory for further analysis under the cold box. In the laboratory, the samples were filtered using a 0.45 µm membrane filter. Then, samples were stored at 4°C in the refrigerator until the measurement was taken.

To prepare the As working standards, 1000 µg/L concentrated stock solutions were diluted with ultrapure water. Solutions and reagents with the analytical grade were provided by Merck Company (Darmstadt, Germany).

The analysis of the samples to determine the concentration of As was carried out by a Metrohm 797 VA Computrace Voltammograph (Metrohm, Switzerland) equipped with a volumetric cell.

Poisson regression analysis was performed for comparing Kabudarahang region (As exposed) with the rest of the countries in Hamadan province and determining the incidence rate ratios (IRRs) during 2016–2020, for leukemia (ICD-10 code C90-95), bladder (ICD-10 code C67-67.9), and kidney (ICD-10, code C64-65) cancers.

In addition, linear regression was applied to investigate the dose-response relationship between As levels and mortality due to mentioned cancers in the study area. Descriptive statistics including skewness, Kurtosis, mean, and standard deviation were used to describe and summarize the data. SPSS software (v. 21) and Stata 11 (Stata Corp, College Station, TX) were applied for analyses, and all the tests were performed at the 95% confidence level.

ArcGIS 10.8 software was used to show spatial patterns of As concentration. X, Y coordinate data of all sampling points were entered into ArcGIS. All these points were then projected by the Global Geodetic System (WGS) 1984 data to the Global Transverse Mercator (UTM). The inverse distance weighting method was also used to estimate the unknown points.

Ethical clearance

Ethical approval for this study (Ethical Committee IR.UMSHA.REC.1400.710) was provided by the Ethical Committee Hamadan University of Medical Sciences, Iran on 11 December 2021.

Results

According to the results, the concentration of As in Kabudarahang was higher than the recommended limit offered by the WHO ($P < 0.05$). Table 1 shows the summary of the results of the As concentration during 5 years. In rural regions of Kabudarahang, including Qapaqtapeh-ye Kord, Churmaq, Quhurd-e Olya, Qohurd-e Sofla, and Jaganlu, the concentration of As in groundwater was obtained at 91.73 ± 19.81, 100.45 ± 20.3, 185.4 ± 69.05, 180.5 ± 31.2, and 160.75 ± 41.64, respectively.

Table 2 shows the number of mortality rates due to leukemia and urological cancers for each country. Figure 2 shows the spatial variability map of As and the distribution of urological and leukemia cancer in the study area.

Based on the Poisson regression and the values of IRRs, no statistically significant association was observed for As levels, and the total mortality rates from 2016 to 2020 due to bladder and kidney cancers ($P < 05$) [Table 3]. In addition, according to the dose-response analysis using linear regression, there was no significant relation between As levels and the mortality rates due to bladder and kidney cancers separately ($P < 05$) [Table 4]. However, a little dose-response association was observed between As levels and the mortality rates of urological cancers (the bladder and kidney

Table 1: The summary of statistics for concentrations of arsenic in the water samples collected from 9 counties of Hamadan

Counties	Min (ppb)	Max (ppb)	Mean (ppb)	Std. deviation	Skewness		Kurtosis	
					Statistic	Std. Error	Statistic	Std. Error
Kabudarahang	0.00	185.40	40.1	50.72	1.83	0.37	2.52	0.74
Tuyserkan	0.00	1.67	0.28	0.600	1.98	0.63	2.51	1.23
Razan	0.00	0.65	0.14	0.260	1.47	0.63	0.390	1.23
Nahavand	0.00	29.81	6.1	10.32	1.77	0.61	1.97	1.19
Malayer	0.00	102.80	13.10	30.057	2.55	0.58	5.99	1.12
Hamadan	0.00	0.00	0.00	0.000	.	.	.	.
Famenin	0.00	1.41	0.36	0.59	1.37	0.75	0.050	1.48
Bahar	0.00	12.25	2.05	3.64	1.94	0.58	3.47	1.12
Asadabad	0.00	1.60	0.36	0.57	1.65	0.71	1.97	1.40

Table 2: The number of deaths and mortality rates due to leukemia and urological cancers

Counties	Population	No. of deaths Leukemia	Mortality rates (per 100000)	No. of deaths urological cancer	Mortality rates (per 100000)
Bahar	60251	3	4.979	1	1.65
Kabudarahang	101029	11	10.887	5	4.94
Malayer	100446	5	4.977	5	4.97
Tuyserkan	45453	3	6.600	3	6.60
Razan	80541	5	6.208	2	2.48
Famenin	25151	1	3.975	0	0
Nahavand	85333	2	2.343	1	1.17
Hamadan	98643	6	6.082	1	0.101
Asadabad	42158	0	0	1	2.37

cancers in total) ($P = 0.038$), and for each unit increase of As concentration in the groundwater, the mortality rate due to these cancers increases by an average 0.01 unit. Based on the linear regression fitting, the data were scattered around a straight line with a positive slope [Figure 3].

In the current study, both regressions supported an association between As levels in drinking water and the risk of death from leukemia [Tables 3 and 4]. Based on the linear regression fitting, for each unit increase of As concentration in groundwater, the mortality rate of leukemia increases by an average of 0.34 ($P = 0.033$), and according to the Poisson regression, leukemia mortality was elevated for the Kabudarahang region comparing with the rest of Hamadan province for 2016–2020 (relative risk = 1.91, 95% confidence interval = (1.24–2.92), $P = 0.003$).

According to the results, the minimum age of mortality from bladder cancer was 54 years old for men and 75 years old in women, and the maximum age of mortality from bladder cancer was 92 years old in men and 78 years old in women. Overall, the range of mortality rate from bladder cancer is 54–92 years old.

In the current study, the minimum and maximum age of mortality due to leukemia among men were 1 and 82 years old, respectively, and among women these values were 4 and 81 years old, respectively.

Based on the results, in the rural areas of Kabudarahang, the concentration of As in drinking water and the mortality rate due to bladder and leukemia cancers were significantly higher than in other countries. However, among the countries of Hamadan, in Tuyserkan, the rate of both bladder and leukemia cancers was high, but the average concentration of As in this area was less than the allowable limit [Table 1]. Therefore, it can be said that there are other reasons for the high rate of cancers in this field, which need more studies.

Discussion

The spatial modeling showed the highest concentration of As in Kabudarahang country. In addition, in some areas of Malayer and Nahavand, the As concentration ranged from 1.7 to 10 times higher than standard values. The As sources in this region were related to specific geological conditions, volcanic rocks, and sulfide compounds.[19,20] In Kabudarahang, the bottom layer of the earth's crust consists of slate/phyllite rocks, which, among the various rocks (such as peaty soils and mudstones/marine shales), has the maximum concentration of As.[8] The most of the natural As contamination in Iran has occurred along the belt of tertiary volcanic rock that stretches from Turkey to Pakistan.[9] In a study by Barzegar in East Azarbaijan (the northwest of Iran), the mean concentration of As in groundwater was obtained at 150 ppb.[21]

According to the meteorological data released, climate change has appeared in the Hamadan province with the increase in temperature, reduction of rainfall in the past two decades, so that in Hamadan-Bahar plain in years 1991 and 2011, the

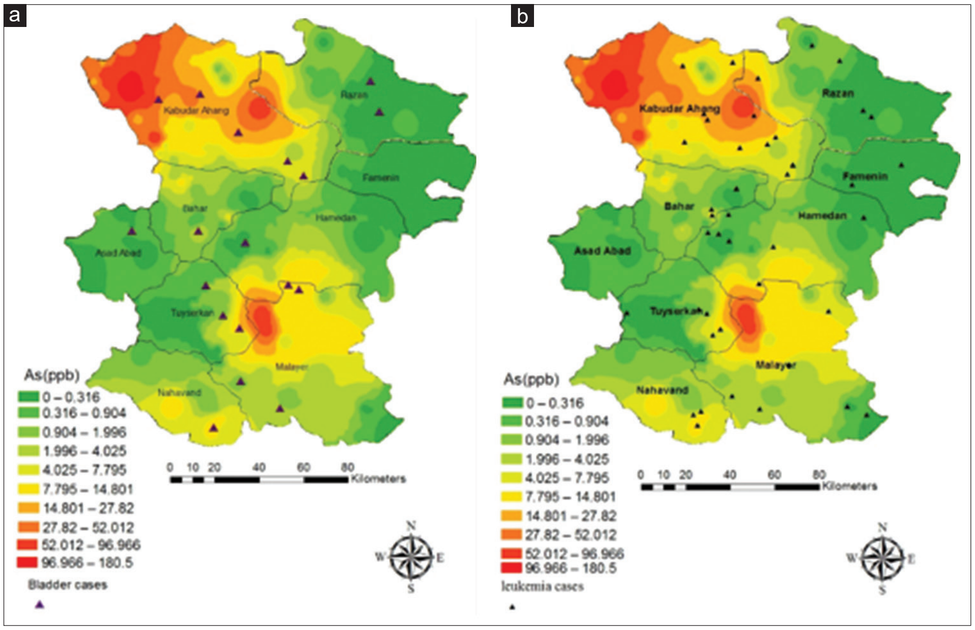

Figure 2: Spatial variability map of arsenic and the distribution of bladder (a) and leukemia (b) cancers in the study area

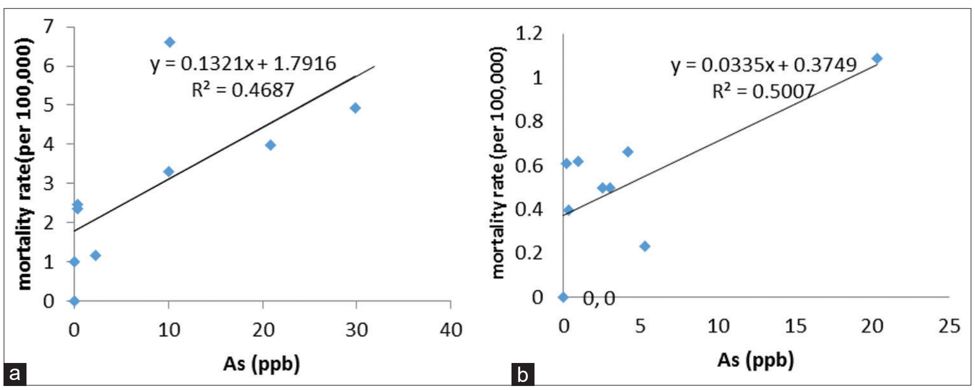

Figure 3: Distribution of arsenic levels and mortality rate due to urological cancers (a) and leukemia (b)

Table 3: Poisson regression analysis for comparing Kabudarahang area with the rest of the counties during 2016 to 2020, for leukemia, bladder, and kidney cancers

Type disease	Groups	IRR	*P*	[95% conf. Interval]
Kidney, renal pelvis, C64, C65	Kabudarahang	0.8	0.764	0.18-3.42
	Rest of the Hamadan P.	1	-	-
	Rural	0.0.57	0.046	0.98-0.33
	Urban	1	-	-
Bladder cancer, C67-C67.9	Kabudarahang	1.302326	0.517	0.58-2.89
	Rest of the Hamadan P.	1	-	-
	Rural	0.4	0	0.57-0.28
	Urban	1	-	-
Leukemia, C90.1-C95.9	Kabudarahang	1.91	0.003	2.92-1.24
	Rest of the Hamadan P.	1	-	-
	Rural	0.64	0	0.82-0.51
	Urban	1	-	-

rainfall has been 430 and 200 mm, and the temperature has been 8.2°C and 12°C.[22] In the Hamadan province, like other areas with arid and semiarid climates, to access more water resources, wells are drilled into deeper rocks which affects water quality in terms of As pollution. Based on the past works, there is a significant positive relationship between well depth and arsenic concentration.[21,23] In a study by Li *et al*., the maximum concentration of As was found in the depth of 25 m, and the estimated target cancer risk values at the depths of 25 m ranged from 1.32×10^{-4} to 5.87×10^{-2}, while at a depth of 10 m was obtained as 3.86×10^{-4}–1.04×10^{-4}.[23] In another study by Barzegar *et al*., the As concentration was measured in water samples from deep and shallow wells (8–150 m depth), and the highest concentration was obtained from a depth of 120 m.[21]

In accordance with the current work, some previous studies have shown a weak association between low As concentrations and mortality rates of bladder cancer.[24,25] For example, in a study conducted by Lamm *et al*. in Taiwan, there was little to no increase of health risk with rising As exposure at low levels (<150 μg/L).[24] In another study by Meliker *et al*., no convincing evidence was found regarding the association between low level (<10 μg/L) As exposure and bladder cancer.

Table 4: The summary of results of dose – response analysis using linear regression

Diseases	Parameters	Coefficient	Std. Error	Standardized coefficients	*t*	*P*
Bladder	Constant	1.58	0.58	-	2.73	0.02
	Arsenic	0.09	0.04	0.61	2.06	0.07
	R^2=0.38		F=4.26	Value=0.07		
Kidney	Constant	0.128	0.32	-	0.39	0.70
	Arsenic	0.028	0.02	0.39	1.12	0.29
	R^2=0.15		F=1.25	Value=0.29		
*Urological cancers	Constant	1.65	0.72	-	2.25	0.059
	Arsenic	0.13	0.05	0.69	2.55	0.038
	R^2=0.46		F=6.55	Value=0.038		
Leukemia	Constant	3.75	0.91	-	4.08	0.005
	Arsenic	0.33	0.13	0.71	2.65	0.033
	R^2=0.50		F=7.02	Value=0.033		

*Total mortality rates due to bladder and kidney cancers

According to their results, in cases where the concentration of As in drinking water was more than 10 µg/L, bladder cancer was elevated in people aged 30–55 whose daily water intake was above average.[25]

However, there are some other studies that reported exposure to high levels of As was significantly associated with the mortality rate of bladder cancer. For example, the results of a review study of 30 years of ecologic evidence by Saint-Jacques *et al*. supported an association between high levels of As in drinking water and the risk of death from bladder cancer, although, due to the limitations of epidemiological studies, the threshold level for exposure to As in drinking water without causing health effects has not yet been determined.[26] According to the previous studies, it seems that, in the case of mortality rates, if the average concentration of As was high, the relationship between mortality rates from urological cancers and the As levels would be significant though weak, but at lower concentrations, this relationship would not be statistically significant.[24-26]

Regarding cancer incidence, in some studies at low As concentrations, positive associations with cancer risk were reported.[27-29] A systematic review of forty studies showed a risk effect of 5.8 (2.9–8.7) for 140 µg/L and 2.7 for 10 µg/L for bladder cancer incidence.[27]

In another case–control study, Baris *et al*., also found an association between the incidence of bladder cancer and low As levels in drinking water.[28]

The results of the present study showed that, among the total population of Hamadan province, the risks of mortality of the urological cancer were 4.25/100,000 people and 1.28/100,000 people for men and women, respectively. In total, 20% of the mortality rates were related to women and 80% for men.

In a study by Chen and Ahsan conducted in Bangladesh, among the entire population, the mortality rate (per 100,000) for bladder and lung cancer obtained 0.3 and 23.1 for women and 5.4 and 159.1 for men, respectively. Thus, as can be seen, the rate of bladder cancer in men was recorded 16 fold higher than in women.[30] In contrast, in another work by Marshal *et al*., the mortality rates of bladder and lung cancer per 100,000 were 50 and 153 for men and women in region II (area with a high concentration of As), compared with 19 and 54 in other regions.[31]

According to the GLOBOCAN data, in 2018, nations with the highest rates of urological cancer were largely reported in Western and Southern Europe and North America. The highest rate of bladder cancer among women belonged to Lebanon, and in Greece, the highest rate was among men. Nevertheless, in the world, this type of cancer in males is fourfold higher than in females. Tobacco smoking, chemical exposure in workplaces, and low fruits and vegetable consumption are the strongest risk factors that are more common in men than women.[32] Only 7% of bladder cancer are predicted to rise from heritable genetic influence and 81.8% of cases could be attributed to environmental, occupational exposure, and lifestyle. Therefore, this cancer is an optimal candidate for public health prevention interventions.[33]

As mentioned in the results, it was found a positive association between As-contaminated water and the risk of death from leukemia. However, in previous studies, the association between As in water and the incidences of hematologic cancers, including leukemia and lymphoma, has not been completely investigated, and very limited studies, in recent years, have been conducted on the relationship between As in water resources and leukemia. While, in some works, a positive and significant relationship was observed, in a number of other studies, no relationship was reported, and even though in some surveys, these relations were negative.[34-37] Basu *et al*. in a cross-sectional biomarker study in West Bengal showed that chronic environmental exposure to As in groundwater causes genotoxic effects, and the micronuclei frequencies in the exposed group were significantly elevated to 5.33-fold over unexposed levels of lymphocytes.[36] In another study in Taiwan, Chen *et al*. were observed a positive association between leukemia and As in well water of the villages and townships (SMR for males: 1.42 (1.00–1.84).[37] In contrast, in an another study in Chile by Liaw *et al*., there was a little risk for increasing of leukemia, brain, and all childhood cancers; and the RR of leukemia, for those people their childhood was being exposed to high As concentration in drinking water was below 1.0 (95% CI) for both males and females.[35] In a study by Lin *et al*., the As levels in water sources were negatively associated with the leukemia incidence, both in men and women.[34]

One of the reasons of different results for the correlation of leukemia with As levels could be the dual properties of As, which has been recognized as both drug and poison for more than 2000 years for promyelocytic leukemia.[34,38]

According to the results, the average age of mortality due to leukemia was 44 years old, and the risk of leukemia cancer was 5.6/100,000 people overall, 4.56/100,000 for men and 6.76/100,000 for women, respectively. The total deaths attributed to leukemia were 41.6% and 58.3% for men and women, respectively. However, this difference in mortality rates between men and women is much smaller than the difference in mortality rates of bladder cancer.

Among environmental factors, obesity and body mass index have been identified as other risk factors for a variety of leukemia among adults and children.[39,40] So perhaps, one of the reasons for the higher mortality rate due to leukemia in women, along with other factors, is their higher BMI index. However, there are other factors that contribute to the development of leukemia, including smoking and exposure to chemicals as well as hereditary factors.[41] Globally, the mortality rate of leukemia in males was 4.2/100,000 compared to 2.8/100,000 in females. In Iran, the mortality rate due to leukemia was reported to be 4.4 in women and 6.6/100,000 in men.[15]

In a study by Mjali *et al*., the age of patients diagnosed with leukemia was reported to be between 1 and 90 years old, and 234 cases were males (58.2%) and 168 were females (41.8%). Among all leukemia cases, 22.6% ($n = 91$) were under 10 years, and the median age of diagnosis was 30 years for all cases.[42]

This study has two limitations: first, in the present study, the concentration of different types of As has not been determined separately, and therefore, it cannot be said which type of As has a significant association with mortality due to cancer. As mentioned earlier, there are several types of As, including $As^{3}+$, $As^{5}+$, MMA, and DMA, that adversely affects human health. Second, some disruptive factors such as diet, obesity, smoking, physical activity, and genetic factors were not controlled. Identifying cancer risk factors play an important role in preventing and controlling them in each region. In this regard, it is suggested that further studies are designed to consider all confounding factors and assess the health effects of the different types of As species.

Conclusion

The results of this study could be an evidence for a strong positive association of As in drinking water and mortality rate of leukemia. In addition, when the total of bladder and kidney cancers were considered urological cancers, a little dose-response association was observed between As levels and the mortality rates of urological cancers. Therefore, due to the toxic and carcinogenic properties of As species, to reduce the related health risks, some managing programs, including screening, community education, and intervention, should be developed in the As-contaminated areas.

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Conflicts of interest

There are no conflicts of interest.

References

1. Chikkanna A, Mehan L, Sarath P, Ghosh D. Arsenic exposures, poisoning, and threat to human health: Arsenic affecting human health. In: Environmental Exposures and Human Health Challenges. IGI Global (Publisher of Timely Knowledge) 2019. p. 86-105.
2. de Souza AC, de Almeida MG, Pestana IA, de Souza CM. arsenic exposure and effects in humans: A mini-review in Brazil. Arch Environ Contam Toxicol 2019;76:357-65.
3. Chen T, Yuan X, Su Y. Impacts of petroleum exploitation activities on the speciation of inorganic arsenic in groundwater. Environ Forensics 2021;22:241-50.
4. Kumar R, Kumar S, Ghosh A. Current scenario of groundwater arsenic contamination in West Bengal and its mitigation approach. Arsenic Toxicity: Challenges and Solutions. Springer, nature master classes(Publisher); 2021:193-216.
5. Orosun MM. Assessment of arsenic and its associated health risks due to mining activities in parts of North-central Nigeria: Probabilistic approach using Monte Carlo. J Hazard Mater 2021;412:125262.
6. Ahmad A, Bhattacharya P. Arsenic in drinking water: Is 10 μg/L a safe limit? Curr Pollut Rep 2019;5:1-3.
7. Uppal JS, Zheng Q, Le XC. Arsenic in drinking water – Recent examples and updates from Southeast Asia. Curr Opin Environ Sci Health 2019;7:126-35.
8. Shaji E, Santosh M, Sarath K, Prakash P, Deepchand V, Divya B. Arsenic contamination of groundwater: A global synopsis with focus on the Indian Peninsula. Geosci Front 2021;12:101079.
9. Hamidian AH, Razeghi N, Zhang Y, Yang M. Spatial distribution of arsenic in groundwater of Iran, a review. J Geochem Explor 2019;201:88-98.
10. Radfard M, Yunesian M, Nabizadeh R, Biglari H, Nazmara S, Hadi M, et al. Drinking water quality and arsenic health risk assessment in Sistan and Baluchestan, Southeastern Province, Iran. Hum Ecol 2018;25(4): 949-65.
11. Sobhanardakani S. Health risk assessment of inorganic arsenic through groundwater drinking pathway in some agricultural districts of Hamedan, West of Iran. Avicenna J Environ Health Eng 2018;5:73-7.
12. Sinha D, Prasad P. Health effects inflicted by chronic low-level arsenic contamination in groundwater: A global public health challenge. J Appl Toxicol 2020;40:87-131.
13. Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, *et al.* The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer 2021;157:308-47.
14. Smith AH, Marshall G, Roh T, Ferreccio C, Liaw J, Steinmaus C. Lung, bladder, and kidney cancer mortality 40 years after arsenic exposure

reduction. J Natl Cancer Inst 2018;110:241-9.
15. Bispo JA, Pinheiro PS, Kobetz EK. Epidemiology and etiology of leukemia and lymphoma. Cold Spring Harb Perspect Med 2020;10:a034819.
16. Palma-Lara I, Martínez-Castillo M, Quintana-Pérez JC, Arellano-Mendoza MG, Tamay-Cach F, Valenzuela-Limón OL, *et al.* Arsenic exposure: A public health problem leading to several cancers. Regul Toxicol Pharmacol 2020;110:104539.
17. Halimi L, Bagheri N, Hoseini B, Hashtarkhani S, Goshayeshi L, Kiani B. Spatial analysis of colorectal cancer incidence in Hamadan Province, Iran: A retrospective cross-sectional study. Appl Spat Anal Policy 2020;13:293-303.
18. Aleseyyed SB, Rafati L, Heidarimoghadam R, Khodabakhshi M, Zafarmirmohammadi SA, Heidari S. Investigation of residual concentration of organochlorine, organophosphorus, and carbamate pesticides in Urban drinking water networks of hamadan province, Iran. Avicenna J Environ Health Eng 2021;8:9-16.
19. Nadiri AA, Aghdam FS, Khatibi R, Moghaddam AA. The problem of identifying arsenic anomalies in the basin of Sahand dam through risk-based 'soft modelling'. Sci Total Environ 2018;613:693-706.
20. Mosaferi M, Nemati S, Armanfar F, Nadiri A, Mohammadi A. Geogenic arsenic contamination in northwest of Iran; role of water basin hydrochemistry. J Environ Health Sustain Dev 2017;2:205-16.
21. Barzegar R, Asghari Moghaddam A, Kazemian N. Assessment of heavy metals concentrations with emphasis on arsenic in the Tabriz plain aquifers, Iran. Environ Earth Sci 2015;74:297-313.
22. Mosavi SH, Soltani S, Khalilian S. Coping with climate change in agriculture: Evidence from Hamadan-Bahar plain in Iran. Agric Water Manag 2020;241:106332.
23. Li R, Kuo YM, Liu WW, Jang CS, Zhao E, Yao L. Potential health risk assessment through ingestion and dermal contact arsenic-contaminated groundwater in Jianghan Plain, China. Environ Geochem Health 2018;40:1585-99.
24. Lamm SH, Robbins SA, Zhou C, Lu J, Chen R, Feinleib M. Bladder/lung cancer mortality in Blackfoot-disease (BFD)-endemic area villages with low (<150 μg/L) well water arsenic levels – An exploration of the dose-response Poisson analysis. Regul Toxicol Pharmacol 2013;65:147-56.
25. Meliker JR, Slotnick MJ, AvRuskin GA, Schottenfeld D, Jacquez GM, Wilson ML, *et al.* Lifetime exposure to arsenic in drinking water and bladder cancer: A population-based case-control study in Michigan, USA. Cancer Causes Control 2010;21:745-57.
26. Saint-Jacques N, Parker L, Brown P, Dummer TJ. Arsenic in drinking water and urinary tract cancers: A systematic review of 30 years of epidemiological evidence. Environ Health 2014;13:44.
27. Cumberbatch MG, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, *et al.* Epidemiology of bladder cancer: A systematic review and contemporary update of risk factors in 2018. Eur Urol 2018;74:784-95.
28. Baris D, Waddell R, Beane Freeman LE, Schwenn M, Colt JS, Ayotte JD, *et al.* Elevated bladder cancer in Northern New England: The role of drinking water and arsenic. J Natl Cancer Inst 2016;108.
29. Saint-Jacques N, Brown P, Nauta L, Boxall J, Parker L, Dummer TJ. Estimating the risk of bladder and kidney cancer from exposure to low-levels of arsenic in drinking water, Nova Scotia, Canada. Environ Int 2018;110:95-104.
30. Chen Y, Ahsan H. Cancer burden from arsenic in drinking water in Bangladesh. Am J Public Health 2004;94:741-4.
31. Marshall G, Ferreccio C, Yuan Y, Bates MN, Steinmaus C, Selvin S, *et al.* Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. J Natl Cancer Inst 2007;99:920-8.
32. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. Med Sci (Basel) 2020;8:15.
33. Al-Zalabani AH, Stewart KF, Wesselius A, Schols AM, Zeegers MP. Modifiable risk factors for the prevention of bladder cancer: A systematic review of meta-analyses. Eur J Epidemiol 2016;31:811-51.
34. Lin MH, Li CY, Cheng YY, Guo HR. Arsenic in drinking water and incidences of leukemia and lymphoma: Implication for its dural effects in carcinogenicity. Front Public Health 2022;10:863882.
35. Liaw J, Marshall G, Yuan Y, Ferreccio C, Steinmaus C, Smith AH. Increased childhood liver cancer mortality and arsenic in drinking water in Northern Chile. Cancer Epidemiol Biomarkers Prev 2008;17:1982-7.
36. Basu A, Ghosh P, Das JK, Banerjee A, Ray K, Giri AK. Micronuclei as biomarkers of carcinogen exposure in populations exposed to arsenic through drinking water in West Bengal, India: A comparative study in three cell types. Cancer Epidemiol Biomarkers Prev 2004;13:820-7.
37. Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: High-arsenic artesian well water and cancers. Cancer Res 1985;45:5895-9.
38. Wang QQ, Hua HY, Naranmandura H, Zhu HH. Balance between the toxicity and anticancer activity of arsenic trioxide in treatment of acute promyelocytic leukemia. Toxicol Appl Pharmacol 2020;409:115299.
39. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: A population-based cohort study of 5·24 million UK adults. Lancet 2014;384:755-65.
40. Mazzarella L, Botteri E, Matthews A, Gatti E, Di Salvatore D, Bagnardi V, *et al.* Obesity is a risk factor for acute promyelocytic leukemia: Evidence from population and cross-sectional studies and correlation with FLT3 mutations and polyunsaturated fatty acid metabolism. Haematologica 2020;105:1559-66.
41. Censin JC, Peters SAE, Bovijn J, Ferreira T, Pulit SL, Mägi R, *et al.* Causal relationships between obesity and the leading causes of death in women and men. PLoS Genet 2019;15:e1008405.
42. Mjali A, Al-Shammari HH, Abbas NT, Azeez ZD, Abbas SK. Leukemia epidemiology in Karbala province of Iraq. Asian Pac J Cancer Care 2019;4:135-9.