Research Article

Lung Cancer Disease and Arsenic: The Medical Geology as Key

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Abstract: Background Lung cancer is the most frequent cancer and the leading cause of cancer all around the world. Experimental data from Zanjan hospitals revealed a significant urinary arsenic content in lung cancer patients along with some anthropogenic aspects of lifestyle. In this study, the relationship between lung cancer and arsenic as well as other risk factors will be evaluated.

Methods In a descriptive-analytic and cross-sectional study performed from 10 January to 30 August 2020, 155 people, 65.2% men and 34.8 % women were selected for evaluation and the amount of arsenic in urine samples were determined with anodic stripping voltammetry method and chemtronics protocol No AN027v2.

Results Urinary arsenic concentration in lung cancer patients over 40 years old was 4 times, and in patients, 20-40 years old group was 3 times more than control groups. Urinary arsenic contents in lung cancer patients in all age categories are much lower by drinking Herbal Tea ($p <0.001$). A strong correlation between gender (male, $p <0.001$) and depression ($p <0.001$) with lung cancer was observed.

Conclusions The results of the current study reveal that arsenic is one of the main factors contributing to Lung cancer. Besides, statistical analysis showed that men are (3.5 times in a high-risk population), depression, asbestos exposure, working in mine are other significant factors which highly affected patients.

Keywords: Lung cancer, Urine arsenic levels, Environment, Geogenic, Health impacts

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Introduction

Arsenic (As) has long historical use by humans and its adverse health effects have been known for millennia. It has been used in both ancient and modern medicine and abused as a stimulant in people and animals such as in racehorse doping with potassic arsenic. Such malpractice

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occurs alongside other metals including cadmium, mercury, bismuth, gold and platinum chlorides. Significantly, arsenic appears synergistically to potentiate the adverse health impacts of these heavy metals. Arsenic is a highly toxic and carcinogenic metalloid. Exposure to arsenic in humans especially in foods and drinking waters, though nominal set by the WHO at 10 ppb is not safe [1-3].Widespread naturally, arsenic concentrates in certain geological formations such as sedimentary basins and their ground waters having emanated regionally from mineralized country rocks. Arsenic is widespread in the industrial and agricultural sectors, including animal feed used to control pathogens, weeds and pests, both aquatic and terrestrial. As occurs in low to high levels in many everyday food products such as rice, tobacco, drinking waters, and can attain very high levels in natural geological environments, including metal deposits, coal deposit and under the right geogenic conditions, sedimentary basins and their ground waters [4-6]. Given the synergistic effects of As, there are likely no safe limits to arsenic exposure.

Microbes play a critical role in arsenic species transformations, geogenic mobility, toxic species transformation, and environmental impacts of metal (loids). The biogeochemical mobilization of As in concert with sulfides in acidic environments and neutral to slightly alkaline environments should also be considered. As has no know essential functions in humans, though some microbes utilize arsenic in chemotropic reactions [6-13]. Many oxidoreductases, critical to normal biological functions, are sequestered by bacteria when confronted with xenobotics such as arsenic in terms of detoxification attempts *via* metalloid species transformation and mobilization. Class EC 1.20 reductases for instance act on phosphorous or arsenic, arsenates being able to participate in a competitive exchange with phosphates, one of the toxic modalities of arsenic in humans [9]. Excess environmental xenobiotics can also be used to derive energy from microbes *via* oxidation of iron, sulfur, manganese, and arsenic. Alternatively, the dissimilatory reduction of metals by some microorganisms also enables them to use metals as a terminal electron acceptor for anaerobic respiration, (and producing hydrogen sulphide). Oxyanions of As may be used in microbial anaerobic respiration as terminal electron acceptors, also well known for oxyanions of chromium, selenium and uranium [10- 11].

The geo-microbiological and ancillary biochemical reactions (for example microbial reduction) are important in the mobility and toxicity of arsenic species, but oxidation of As (III) to less toxic As (V) arsenates, or conversion to arsenopyrite or adsorption of such arsenates by oxyhydroxide of iron for arsenic stability is important environmentally [12-16]. Methylation for example is important in both the environment and within human's bodies. These offer a mechanism of arsenic loss in humans and soils by converting arsine to volatile species. Remediation of environmental arsenic is topical, being problematic. Chemical and biological remediation such as phytoremediation of soil or phyto-exclusion to crops has been considered, along with microbial remediation.

Isolation and breeding of bacteria to remove arsenic from the contaminated water have been one approach in the remediation of contamination. Genetic engineering of Corynebacterium glutamicum strains resistant up to 60 mM arsenite had generated efficient strains for As removal [12].

Arsenic occurs in solid solution within metal mineral species such as arsenical pyrite, or as a primary arsenical minerals species, most commonly arsenopyrite. Weathering of species such as arsenopyrite, and secondary alteration species such as realgar (As_4S_4) and orpiment (As_2S_3), begin the process of remobilizing arsenic geochemically and with subsequent leaching and runoff, arsenic enters soil and waterways, including groundwater's[17]. Pyrite is the most common sulphide mineral. Some of the arsenical gold mineralization in NW of Iran, such as from epithermal gold deposits have replete realgar, and orpiment, and of concern for groundwater pollution and surface distribution during occasional wet periods as these arsenic species are easily remobilized. It is itself used as a weed, insect, and vermin toxin, also in fireworks and in ancient times used as a red pigment [18]. Orpiment was used as a fly poison and medicine in China and preservative in herbal formulations, white-out, and decorations. Apart from low-temperature alteration produce in the aforementioned hydrothermal veinlets, realgar and orpiment's are also common in volcanic sublimations and hot springs[19]. Arsenopyrite is itself a higher temperature mineral deposited in very hot hydrothermal veining and as disseminations, generally in accompaniment with other metal (loids) which may be 'zoned' temperature depend, well out from deposit centers, that may themselves be disseminated and clustered widely, even regionally [20]. This may impact soil arsenic distribution widely, directly through residual soil weathering overlying such wide mineralization and laterally with the dispersion of these soils and arsenic through seep waters and ground water reaching surface further afield.

In Asia, the presence of As in the groundwater of Bangladesh, Cambodia, China, India, Japan, Myanmar, Nepal, Pakistan, Thailand, Vietnam and Iran has been reported [21, 22]. In Iran, As in nature is responsible for contaminating drinking water. Kurdistan, the western province of the country in Iran, has the most problems in this regard [23, 24].

Cancer is one of the diseases that are affected by environmental factors and its incidence varies in different geographical areas. After road accidents and cardiovascular diseases, cancer is the third leading cause of death among Iranians in recent years [25-27]. There are many reports regarding cancers in Iran. According to the reports by the Iranian Ministry of Health and Medical Education of Iran the lung cancer represents the second and third cause of cancer mortality among Iranian men and women, respectively [28]. However, lung cancer has been served as the second largest cause of cancer mortality among women in the world [29]. Interestingly, there are positive relations between provinces and special kinds of cancer while according to the report presented by Malekzadeh, Yazd, Zanjan and West Azarbaijan have the highest cancer rates amongst Iranian provinces [30, 31]. These differences are related to unique environmental exposures, dietary habits, and population genetics of the people of the mentioned regions. It should be noted that cancer registries are valuable research tools in the etiology, diagnosis, and treatment of the disease, and collecting data on cancer incidence also plays a significant role in planning screening schemes as well as preventing the disease [32, 33]. Gathering information about cancer epidemiology is normally considered the first step in controlling the disease. Due to the high rate of cancer, the plan for control and prevention of cancers must be a high priority for health policy in Iran as well as it is suggested that earlier screening is need for high-risk population and the dominant aim of the current study is to determine discussed in detail the main risk factors of lung cancer resulting from arsenic in Zanjan province.

Materials and Methods

Study Area Geology

Geological arsenic sources are ubiquitous in rocks, sediments, soil and water, even air from volcanoes and aerosol arsenic from fumarolic vents. Low crustal abundances around 1 ppm As may reach levels around 50 ppm As or more regionally, reach very levels surrounding metal ore deposits of copper, lead, iron and particularly gold that may have percentage levels of arsenic. Arsenic weathered, eroded and leached out from such geologies may be adsorbed on iron oxy hydroxide in soils and sediments and with dissolution under anoxic geogenic conditions continue remobilization, together with mass and fluvial transport, into sedimentary basins and deltas and ingress their soils, ground waters, food bowls and ecosystems. A time perspective helps to understand this, over millions of years, the subsurface mineralized orogenic belts, including metal deposits have been worn away into sedimentary basins and fluvial valise and delta. This substantial arsenic remobilization process is globally underappreciated, under reported. The true levels of chronic arsenic exposure and acute intoxication may therefore far exceed 150 million known globally.

The study area of Zanjan regions includes the juxtaposition of two major magmatic belts emanating mineralization: the SE trending **Zagros Magmatic Mineral Belt,** closest to the subduction margin and the EW trending Alborz Magmatic Belt. These two belts and particularly their "intersection or conjunction in the study area is pertinent to Medicinal Geology. Regionally in the inspection of these two major organic methanolic belts epithermal-gold-silver occurs along with arsenical mineralization in the form of orpiment and realgar, along with stibnite. There are three main belts in Iran which surround the triangular Central East Iranian Micro continental plate (CEIM), a remnant from Gondwanaland. The Cimmerian orogenesis was largely responsible for mineralization as the Arabian plate accreted the CEIM onto Eurasia. The other two mineral belts impacting Medical Geology within Iran include the eastern sector borders with Pakistan and Afghanistan (Changi metallogene) and the Northern regions bordering Turkmenistan, Caucasus and Afghanistan to the north [28]. These orogenies were accompanied by volcanism which introduced the mineralization. Medical Geology in orogenic belts with physiographic-geogenic mobility of metal (loids) including arsenic into adjacent agricultural basin communities and ground waters is concerning. Such metallogene belts have developed from evolving calc-alkaline to alkalic Cenozoic magmatism and fault fracture networks during orogenesis and evolving sialic crust within island arcs to continental margins and deeper back arc continental environments during subduction of oceanic crust, in this case the former Tethys Oceanic crust. The northern belt conforms to the back arc environment in relation to subduction of the Arabian plate. More geological details are given to the spatual character of mineralization in relation to the spatual relationships of the metallogenic belts and geological implications to Medical geology in previous studies [1, 8].

Study Population

Current research is a population-based cross-sectional study initiated in the central zones of Zanjan (all patients have been coming to hospitals located in Zanjan city and its main hospital which provide health services and act as an educational tool to compare the effect of diet, smoking habits and lifestyle on the incidence of Lung Cancers (stages I to III; as Stage III is divided into subcategories known as IIIA, IIIB, and IIIC.) in a total study population of 89 Lung Cancer patients in different subgroups of the <40year; 40-60 and the last group>60 years old. Participated along with 63 men and 26 women in the control group at the same time, and also in the control group in the same central zones in Zanjan province, with incident invasive lung Cancer identified. This is a descriptive-analytic and a cross-sectional study performed from 10 January 2019 to 30 August 2020. The study population consisted of 1 hospital affiliated to Zanjan University of Medical Sciences and the hospital was educational hospital.

Sample Preparation

Spot urine samples were collected from most of the participants from 10 January 2019 to 30 August 2020 after face to face interviews. Women and men with missing information on adjustment variable(s) were included in the analysis in a separate category for adjustment. No single variable had data missing for more than 18% of participants. In sensitivity analyses, the reports were repeated including only women/men with complete information on all variables.

Data collection

Face-to-face interviews based on structured and food frequency questionnaires were utilized to obtain demographic lifestyle and dietary information by trained staff at the time of study enrolment. Food-Frequency Questionnaires (FFQ) are designed to assess dietary patterns by collecting information regarding the frequency with which specific food items are consumed over a specified reference period. It should be noted that the FFQ was designed based on the local community foods, especially for young and older adults living in Zanjan province. The participation proportions; the percentage of participants eligible to participate in the population-based Lung cancer parent study, who completed the interview, was 85% for case participants and 67% for control participants. Of those who completed the meeting and agreed to participate in the metal sub-study, a participation proportion of 63% was achieved for urine specimen returns for both case and control participants.

The University of Zanjan, Educational hospital subjects Committee approved this study. Oral consent was obtained for the interview and written informed consent was obtained for the urine specimen collection.

Determination of Arsenic

The Anodic Stripping voltammetry (ASV) method for arsenic is employed, utilizing the PDV6000+ analyzer (Manufactured B3 Electronics, Perth Australia) configured with a solid gold electrode for total as analyses. The instrument uses a platinum counter electrode and silver /silver chloride reference electrode. 1M KCl is injected into the counters electrode cell, separated from the sample with a frit, soaked in distilled water overnight. The silver electrode is plated with 1M KCl in an electric cell with power supply provided, for no longer than 5min., achieving an even brown or black coat of silver chloride after first cleaning the silver rod with fine white emery if degraded [2]. Chemtronics Protocol No AN027v2 is employed, the instrument connected to a PC running the VAS software supplied. After a voltammogram is achieved, The Standard Comparison (SC) technique is suitable for most samples that have low organic content, such as a clean river, lake, and seawater. With interferes, standard additions overcome some of the matrix effects. For excessively dirty samples, digestion of the matrix is carried out before. Analysis with VAS software and standard addition LDL of approximately 2ppb, As is achieved with5% coefficient of variation over 5 clean samples at 50 ppb in solution. Arsenic (III) Standard (20 ppm) is employed.

The sample is run on linear sweep parameters as follows; Rest potential, 500 mV; condition time 30s; Mix potential, 500mV; Deposit potential, -900mV; Hold potential, -200mV; Hold time 15s; measure start potential, -5mV; measure stop potential,400mV; Sweep rate, 500mV/s, Clean time 10s, range 100uA. AV conditioning parameters are as follows; conditioning potential, 0mV; alternate potential, 800mV; alternating duty cycle, 50; cycle period 0.2s; sweep start potential -200mV, sweep stop potential 600mV; step size 1mV; step duration 2ms, sample time 1550us, samples per step 16. Blanks were run in of 0.5M M HCL three times to ensure electrodes are clean after polishing. Samples are then run with single comparison, or if metric effects are experiences, noted by suppressed or double peaks, standard additions are employed in the Peaks are observed between +50mV to +300mmV, dependent on matrix. If necessary, electrode conditioning was employed utilizing 1ppm as standard in 0.1M electrolyte, run as a standard a few times to increase the sensitivity of the gold electrode. Interferes may be experienced with high Cu due to peak overlap. This has had previously been established at 50 ppb As, 20% peak drop at ppb: Cu 50, Pb100, Zn200, Ag250, Hg, 500, Fe2000. 20ml sample cups. Continuous analysis of solutions containing Selenium (Se) can gradually foul the electrode. In this case, Clean Potential of +750mV minimizes a reduction as a response.

Data analysis method

Multivariate logistic regression models were used to assess the effects of urinary Total Arsenic levels on Lung Cancer risk, controlling for age and for suspected or established risk factors (age, weight, height, BMI, education levels, family history of Lung Cancers, history of other cancers in the family, marital status, family history, occupational status, Smoking duration and Initial smoking Age (years), physical activity, living and working in mine, dietary habits such as Drinking Herbal Tea; consuming bio-engineering foods in the weekly diet, Occupational in mine and exposure to As, Chronic Pulmonary diseases, Exposure to cooking fumes, Exposure to Asbestos and feeling depression (Depression was defined as the feeling of unhappy sustained for over 3 days every week and existed for more than 1 year).

Moral considerations

According to the codes approved by the National Ethics Committee in Medical Sciences Research, all information taken from patients, it remains confidential, and the results of the research will be published in general and in the form of details of the study group and the individual results will be presented without mentioning the name and personal information.

Results

This section analyzes the data based on the specific objectives of the research. Table 1 describes the mean urinary arsenic levels (u As) residents of in the central zones of Zanjan province (all patients have been coming to hospital located in Zanjan, the capital of the Province) to compare the effect of diet such as consuming engineering foods, smoking habits and lifestyle on the incidence of lung cancer (stages I to III Lung Cancer usually includes Chemotherapy and radiotherapy; as Stage III is divided into subcategories known as IIIA, IIIB, and IIIC.) in a total study population of 89 lung cancer patients in different subgroups including 63 men and only 26 women in different ages participated along with 76 persons: 53 men and 23 women in the control group at the same time in the same central zones in Zanjan province, with incident invasive lung Cancer identified. This is a descriptive-analytic and cross-sectional study performed from 10 January to 30 August 2020.

Table 1- Arsenic levels (ppm) in Lung Cancer Patients and control, males and females

Population	Sub -Group	N	Mean (ppm)	SD	SE	*P-Value*
Case Control	**Case**	89	0.0501	0.0037	0.0081	0.003
	Control	66	0.0103	0.0011	0.0014	
Gender	**Females**	54	0.0043	0.0062	0.0078	0.001
	Males	101	0.0711	0.0016	0.0032	

Table 2: demographic factors, background diseases, and lifestyle in 89 Patients by Lung Cancer disease and 76 persons in control group

Risk factor	Classification	Risk assignments	*p*-Value
Sex	**Male**	101	0.001**
	Female	54	0.054
Age (years)	<40	17	0.046
	40-60	108	0.001
	>60	40	0.041
Average daily cigarette consumption (cigarettes per day)	1-10	17	0.125
	11-20	87	0.089
	21-40	25	0.054

	>40	4	0.065
Smoking duration (years)	<20	21	0.044
	20-40	35	0.044
	<40	2	0.073
Drinking Tap water	(always)	128	0.879
Water purifier at home(yes)	In the last 5 years	23	0.076
Drinking Herbal Tea (NO) Times in a week	< 5	98	< 0.001**
Initial smoking Age (years)	≤15	6	0.058
	>15	67	0.032
Family History of Lung Cancer	Yes	17	< 0.001**
History of Cancer in Family (non-lung cancer)[a]	Yes	12	0.001***
Chronic Pulmonary diseases	Tuberculosis	10	0.001***
	Chronic bronchitis	13	0.001***
	Emphysemas	54	< 0.001**
Exposure to cooking fumes (plates per day [b]	<150	5	0.065
Years [c]	≥150	11	0.062
Taking bioengineered foods/ vegetables /crops per week	<5	3	<0.003***
	5-10	78	<0.001***
	>11	37	<0.001***
Years for working as a minor	1-10	17	0.001**
	10-25	13	0.001**
	25 >	38	0.001**
Exposure to Asbestos (years)	<20	11	<0.001***
	20-29	28	<0.001***
	30>	31	<0.001***
Depression [d]	Usually	65	<0.001***

a Family history of malignant tumors means malignant tumor patient in first-degree relatives

[b]Years The average daily cooking plates × cooking duration (years)

[c] Plates per day

[d] Depression was defined as the feeling of unhappy sustained for over 3 days every week and existed for more than 1 year

In a typical, multivariable-adjusted model (adjusted for all age group, smoking, daily regimen, exposure to asbestos and working in mine, urinary As Levels in all lung Cancer patients and control groups who used to drink herbal teas (more than 3 times in a week) were significantly ($p < 0.001$) lower than others.

Results from current study showed that the mean concentration of total Arsenic in the urine of Stage III patients was significantly much higher than the control group (0.087+0.011mg/L vs. 0.011+0.005 mg/L, $p < 0.003$).

It might be described as an association between U-As and anthropometric factors, that is considered in specified analyses. Urine Arsenic (UAs) levels in smokers: Although we found a significant difference between the mean U-As levels of recent active or passive smokers ($p = 0.044$).

Consumption of food grown in arsenic-contaminated areas is another source of chronic arsenic exposure since agricultural products are cultivated using arsenic-contaminated groundwater. Many studies confirmed that contaminated groundwater used to grow vegetables and rice for human consumption probably lead to the significant pathway of arsenic ingestion. However, the type of arsenic species found in the foods was not investigated in this research, but we know that they are necessary to assess the risk among humans who ingest the diversity of foods. The consuming factors which impressively affected the results were:

Nevertheless, the results of the current study support the theory that food may be an important route of arsenic exposure in some regions and that these exposures may have long-term adverse health effects in humans but on the other hand, drinking endemic herbal teas and also consuming green pepper and mushrooms are a very essential role in preventing or treatment of breast cancer. Considering the widespread distribution of food, arsenic-contaminated food and the possible associated risks of disease should be regarded as a In current research , Asbestos exposure are emphasized although in most investigations they were considered as less priority in consumer safety assessments since they are wrongly assumed to have no important effect our health. Assessing the amount of dermal absorption from a single component in a cosmetic product is complex and depends on many factors such as the concentration of arsenic in the product, the amount of product applied, the length of time left on the skin and the presence of emollients and penetration enhancers in the asbestos materials and products. The results of exposure to these hazardous materials for years , shown the significant results ($p<0.001$) in all Patients by Cancer disease.

Discussion

As known as one of the most hazardous metalloid element present in air, water, and soil. It has organic and inorganic forms through various natural and anthropogenic sources with different oxidation states [34]. According to the International Agency of Research on Cancer (IARC); Arsenic is classified as a class-1 carcinogen that exhibits toxic effects depending on the type of exposure. The acute toxicity of As (LD_{50}) is related to its chemical form and oxidation state. Generally, inorganic arsenic species are more toxic than organic forms to living organisms, including humans and other animals. The oral LD_{50} for inorganic arsenic ranges from 11–150 mg (As) kg/body weight in the animal laboratory [35].. World Health Organization (WHO) states that the threshold level of As in drinking water is (10 μg/ L). However, different toxicity and genotoxic were reported regarding the organic form of As. By way of illustration in the mouse, the oral LD_{50} of TMAO (pentavalent organic arsenic) is 550 (mg As/kg) in the mouse [36].

Considering new evidence that As widely distributed in air, water, food, crops, and plants, it exposes to skin, brain, liver, kidney, lungs, heart, and blood. As a result, the risk of bladder, kidney (Mostafa and Cherry, 2013), skin (Mayer and Goldman, 2016), lungs (Steinmaus et al., 2014; Begum et al., 2015), and prostate cancer (García-Esquinas et al., 2013), along with diabetes and depression increase significantly. Also, the epidemiology evidence shows a correlation between As exposure and lung cancer especially human malignant lung tumors for nonsmokers [37].

Based on our study, there is strongly associated with lung cancer, and As exposure. Our study showed a significant correlation in urine arsenic concentration and lung cancer patients over 40 years old was 4 times, and in patients, 20-40 years old group was 3 times more than control groups. Arsenic intoxication may occur in association with other metal (loids), since co-exposure commonly occurs. Such confounding effects were not assessed in this study. Our previous study similar BC associations with cadmium from similar cohorts in the Shiraz region[38], and other health concerns within the wider region such as Zagros mountains mineralogical belts were found. along with other metallogeny regions have Medical Geology imperatives including Alzheimer's and diabetes [39].

Although it is clear that arsenic is a carcinogen, the mechanism of action in lung cancer is unknown. Some proposed mechanisms include promoting oxidative stress, genotoxicity, cell proliferation, altering DNA repairing, DNA methylation, and tumor promotion [40]. In detail, Arsenic-exposure produces dramatic cellular changes that may explain the rise of lung cancer cases in certain geographical regions. As was regarded as a kind of oncogenic promoter probably by inhibiting DNA repair and/or increasing cell proliferation [41, 42]. It has been proposed that even moderate levels of As, constitutively activate the EGFR signaling pathway. Also, As can stimulate c-Src activity, which can then activate EGFR. The mentioned process results in phosphorylation events on: Tyr845 and Tyr1101, leading to ligand-independent EGFR phosphorylation, constitutive activation, and increasing cell proliferation. As is capable of activating Rac1 GTPases resulting in downstream engagement of the JNK pathway and increased cell survival and proliferation [43].

Based on the other mechanism, Arsenic can also induce activation of Ras, Raf, Mek, and ERK through ROS in lung epithelial cells. Oxidative stress due to the production of ROS leads to the instability of the mitochondrial DNA [43, 44]. Acute exposure to As can stimulate the PI3K/AKT phosphorylation cascade release of vascular endothelial growth factor (VEGF), inducing cell migration, and proliferation[45].

Some reported that the nuclear factor erythroid-derived factor 2–related factor 2 (NRF2) induce cytoprotective proteins and preclude cancer. Interestingly NRF2 has dual behavior. Exposure to low doses of As can stimulate the activity of the NFR2 pathway and protect the cell during acute/short-term exposure. On the other hand, chronic As activates the NRF2 pathway which may result in detrimental cellular effects associated with arsenic-induced pathogenesis [46]. Furthermore, constitutive activation of the NRF2-KEAP1 pathway results in resistance to chemotherapy and radiotherapy, worsening disease prognosis which induces specific alterations and pathways in lung cancer. Arsenic-exposure produces dramatic cellular changes that may explain the rise of lung cancer cases. Various studies confirmed that both hypomethylation and hypermethylation of DNA in human lung cells was seen after exposure to arsenite for several weeks [47]. The evidence suggests that the molecular mechanisms driving lung cancer in smokers are similar, not identical; however, mutations in the KRAS gene is seen which result in increased TGF-α as the ligand of EGFR and activate Ras and the PI3K–AKT signaling pathway. The evidence suggests that *in vitro* and *in vivo* lung cancer studies showed hypermethylation of several tumor suppressor genes such as p53, CDKN2A, Ink4/Arf, p16 and RASSF1A [48].

Some studies have focused on occupational risks to As exposures as measured by DNA damage and oxidative stress in exposed workers by also assaying nail, hair and blood levels of As and heavy metals. One study of n = 50 industry against the background of 200 controls in Pakistan revealed brick kiln, furniture, and welding industries risk. Results showed arsenic exposures associated with DNA fragmentation in a brick kiln, furniture, and welding industries and differences in age and exposure[12].

Considering the medical geology of arsenic in natural, rural and urban environments, As exposure was concluded to be a key factor inducing lung cancer; however, the environmental biogeochemical analysis was not performed in this study. Various combined effects were not evaluated such as various multiple metalloid ratio exposures. Western cultures and many developing nations have compounded factors of high body mass afflicted inflammation and consequent DNA and epigenetic damage. Cultural differences have different impacts on cancer risks. Regarding the fact that mostly Iran is non-alcohol consumer with high smoking culture, important cofactors include diets and environmental risks should be considered. The contribution of genetics and family history to the development of lung cancer is well documented in various studies and textbooks [49-51]. Our follow-up results showed that family history of lung cancer (p-value <0.001), family history of non-lung cancer (p-value <0.001), and chronic pulmonary diseases (p-value <0.001), are important factors related to lung cancer. Similar to our study, in the comprehensive Detroit Research on Cancer Survivors (ROCS) cohort study performed on 1500 participants, 71% reported at least 1 first-degree relative or grandparent with cancer with a p-value of 0.003 for lung cancer [52]. The other formal evaluation stated significant crossover family history of any other type of cancer will increase the risk of lung cancer; however, the exact mechanism of family history of specific cancer over another on lung cancer risk is still unknown [53].

The other risk factor of lung cancer in this study was exposure to asbestos with a p-value of <0.001. Since the industrial revolution asbestos has been used as an insulating material due to its special criteria including strengthening, resistance to heat and chemicals, and electrical insulators. Asbestos refers to six occurring silicate minerals specifically chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite [54]. Evidence about the carcinogenicity of asbestos has been accumulating in this century [55]. Results were reported in cohort study showed more than 10-fold excess of lung cancer among British asbestos textile worker [56]. Analyses done on 115 pulmonary cancer cases showed the average age of death was 40.8 years with 10.4 years of average exposure to asbestos [57]. Although the concentration of asbestos , fibers in air, type of asbestos, and size of fibers must be considered for potential health risks. Collectively all forms of asbestos are carcinogenic and result in cancers of the lung, larynx and ovary [58], An updated evaluation on asbestos confirmed that every 20 tons of asbestos produced kill a person somewhere in the world [59]. Asbestos inhalation has been found to increase direct mechanical injury, activate oncogenes, loss of tumor suppressor genes, chromosomal, and DNA alteration [60].

According to our study, a statistically significant increase in lung cancer was observed in male gender compare to the female (p-value <0.001). The evidence of association shows a complex relationship between males and exposure to As. The major causes of higher rates in male-lung cancer may be due to Iranian culture about working. Generally, males are more likely to work out (in this case as minor in Zangan) and probably a greater prevalence to As exposure. On the other hand, women contribute more effort to household chores and childcare and less effort to the workplace with fewer exposure to As. However, further support should be performed to longstanding this claim.

Herbal tea plant traded in the traditional Zanjan markets comprise of *Hibiscus sabdariffa*, *Camellia sinensis*, *Mentha piperita and Echium Borage.* The common bioactive substances found in *Camellia sinensis* include flavan-3-ols, proanthocyanidins and flavonols which have anti-inflammatory, and anti-cancer activities [61]. *Hibiscus sabdariffa* contains organic acids (citric acid and ascorbic acid), phytosterols, polyphenols and anthocyanins. *H. sabdariffa* shows antioxidant, anti-hypertension, anti-hyperlipidemia, antimicrobial and anti-cancer activity in both human and animal studies [62, 63]. It was suggested that *Mentha piperita* is rich in flavonoids such as eriocitrin, narirutin, hesperidin, rosmarinic acid with antimicrobial, antiviral, anti-inflammatory, and anti-carcinogenic activity [64, 65]. Several studies confirmed the high potency of *Echium Borage* for its neuroprotective, anti-inflammatory, and immunomodulatory activities. This therapeutic potency may be due to a high amount of secondary metabolites especially polyphenols and alkaloids [66, 67]. Interestingly, combining different herbs with various bioactive constituents tend to be significantly more effective than the sum of the individual effects of each known compound. Mentioned combined tea may result in preventive of therapeutic synergistic effects intended for oral aqueous consumption. Our evidence stated explicitly that consumption of mentioned local herbal tea used as hot beverages decrease the risk of lung cancer (P value <0.001). A number of studies published support longstanding this claim [61].

Controversy exists whether daily cigarette consumption or duration of smoking have a statistically significant correlation with lung cancer or not. Our studies in 155 cases depicted that smoking had no significant risk related to lung cancer although positive associations were seen. It seems that a reliable population, as well as more factors (exp., increase time period of evaluation), should be closely monitored

This investigation considers various risk factors and lifestyle that may have contributed to lung cancer. Yet they have the highest aging accumulation of metal(loids) concentration, even from 'normal' exposures, let alone acute or chronic xenobiotic circumstances. This leads us to the question; what is chronic xenobiotic exposure with standards? Should its criterion change with patient age and include synergistic impacts of all metal (loids)?

Conclusion

Our study contributes to the evidence that exposure to various sources of As and Asbestos increases the risk of lung cancer. Also, significant correlation was detected between gender (male) and lung cancer. Interestingly, the consumption of mixed herbal tea can reduce the risk of lung cancer. However constant program should be applied to ban asbestos use and improve safety coverage to reduce Arsenic exposure especially for miners. On the other hand environmental friendly method to removing arsenic from different sources including air, water and solid should be performed. Further objective research should include the development of screening tests and strategies that identify patients at higher risk of lung cancer.

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Conflict of Interests

It is declared that the authors neither have any financial gain nor conflict of interests regarding this paper.

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