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ORIGINAL ARTICLE

Pattern of Cancer Presentation from Arsenic Affected Areas of Sindh- Analysis of A Decade -2008 to 2018

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ABSTRACT

OBJECTIVE: To evaluate the pattern of cancer in the arsenic contaminated belt of interior Sindh.

METHODOLOGY: The observational study includes cancer patients diagnosed and receiving treatment at Liaquat University of Medical & Health Sciences and National Institute of Medicine and Radiotherapy (NIMRA) from 2008 till December 2018. Non probability convenient sampling technique was used and cases were collected by using Institutional database containing demographic characteristics and basic information of the cancers.

Water samples data was retrieved from water testing laboratory which was collected from ten districts across the belt of high arsenic contamination. The patients who did not receive treatment at NIMRA were not included in the study. Water samples which showed presence of other toxic metals in a significant amount apart from arsenic were also excluded from the study.

Data was analyzed by using SPSS version 21. Percentages were calculated for each district and graphs were developed in Microsoft Office word.

RESULTS: A total of 22289 cancer patients reported from the identified districts. Highest rate of oral cancer was found in almost all areas followed by breast cancer, hematological cancers, laryngeal and lung cancers. The oesphageal and colorectal cancers were also among top ten cancers. Variation in the pattern of cancer was observed in arsenic contaminated districts of Sindh.

CONCLUSION: There appears to be an influence of arsenic on cancer pattern in the areas with high concentration. Further studies are required to explore the pathogenesis involved in arsenic associated carcinogenesis.

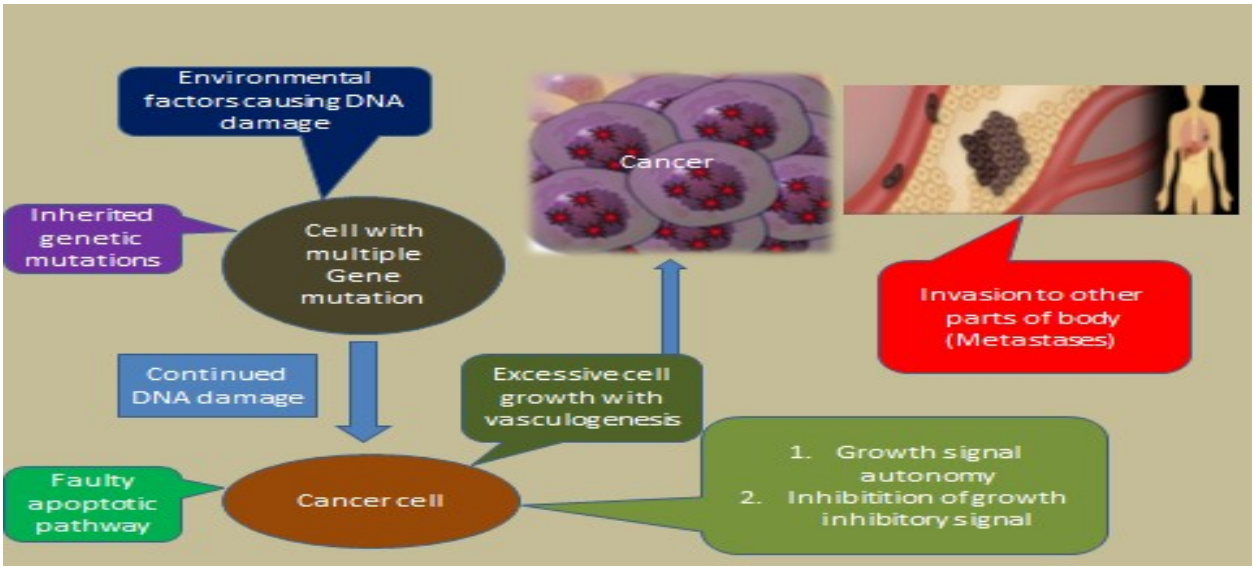
KEY WORDS: Arsenic, cancer, water, Sindh, Oral cancer, arsenic induced cancers

INTRODUCTION

Arsenic is a naturally occurring metalloid (chemical symbol: As, atomic number 33 found in the soil, water, industrial waste, plants and animals. It can be found in pure form and also in combination with other elements such as Sulfur. The acceptable level of arsenic in drinking water is0.010 parts per million (ppm) as suggested by U.S. Environmental Protection Agency (EPA)which is equal to 10 µg/L. It is widely used in making of car batteries and ammunition industry. It is also used in pesticides, insecticides and herbicides. Human beings exposed to toxic levels of arsenic from drinking water, and food sources of plants and meat[1]. People are at high risk when they live in endemic areas of the arsenic toxicity or they work in the industry of copper smelting, in agriculture with the use of fertilizers and pesticides[2].

Medicinal uses of arsenic were relatively common in the past centuries where it had been used as antibiotic for syphilis and anticancer agent[3]. Recently arsenic-72 has been introduced to be used in Positron Emission Tomography (PET Scans), which produces clearer images as compared to the conventional radio-isotope scanning[4]. However International Agency for Research on Cancer (IACR) labeled arsenic as carcinogenic for human beings.[1,2] There has been enough evidence to link arsenic with lung, urinary bladder, skin, kidney, liver and prostate cancer[5–8]. For other cancers the evidence was not enough. The proposed mechanism of development of cancer by arsenic is given in Figure I. The arsenic is one of the environmental factors causing cancer. The exposure causes DNA damage resulting in genetic mutations. These genetic mutations then lead to the development of cancer. However exact mechanism of the development of cancer from exposure to arsenic is not yet well explored.

FIGURE I: POTENTIAL MODEL FOR CARCINOGENESIS FROM ARSENIC POISONING



The initial report from observational studies dates back to 1978 when patients treated with arsenic were reported to have malignant neoplasms. The interesting finding was the topical application of a small dose producing systemic malignant diseases[9]. The risk was observed to be

high in patients with arsenic keratosis. Similarly results from 1982 showed that exposure to arsenic, Sulfur dioxide and asbestos exposure are linked with the risk of lung cancer exceeded the risk associated with cigarette smoking, however the exposure to arsenic and sulfur dioxide could not be separated completely[10]. The same year study showed that the people from Tacoma, Washington with low exposure showed 1.5fold risk of dying from lung cancer while with high exposure the risk was 2.5 folds. Another study reported the high rate of malignant neoplasm's after medicinal use of arsenic but there was no significant high mortality of these cancers[3]. The appearance of the malignant neoplasms was linked with the appearance of signs of arsenosis[3]. The reports have also linked arsenic with the development of urinary bladder, kidney, skin, liver, prostate, oral cavity and rectum[11].

Sindh region of Pakistan has been shown to have high arsenic levels in most areas. This mainly involves the agriculture and industrial belt around the whole path of the river Indus[12]. A recent review on the situation of aqueous contamination showed that the main source of contamination of arsenic was found in the well water at the depth of 10-150 feet. Arsenic contamination was not found in the wells deeper than 150 feet[12]. Thus, main sources of the arsenic contamination in Sindh are possibly the industrial and agricultural waste.

This study was conducted to evaluate pattern of cancer occurrence in arsenic contaminated areas of Sindh.

METHODOLOGY

This observational study was part of a project on evaluation of effect of arsenic on human health, being conducted at Liaquat University of Medical & Health Sciences (LUMHS), Jamhsoro. Baseline information data was collected from National Institute of Medicine and Radiotherapy (NIMRA) after approval from institutional research and ethical committee. The study includes consecutive series of cancer patients diagnosed and receiving treatment at LUMHS and NIMRA from 2008 till December 2018. Non probability convenient sampling technique was used and cases were collected by using Institutional database containing demographic characteristics and basic information of the cancers. The patients included in the database belonged to the catchment area of the LUMHS and NIMRA including Hyderabad, Jamshoro, Tando Mohammad Khan, Badin, Dadu, Mirpurkhas, Matiari, Mithi/Umerkot, Thatta&Sujawal, and TandoAllahyar. Data was collected for all cancers coming from these districts regardless of age and gender. The patients who did not receive treatment at NIMRA were not included in the study. Water samples which showed presence of other toxic metals apart from arsenic were also excluded from the study.

Water sample results for the districts which were included in the study were retrieved from water testing laboratory. The analysis of the water samples was carried out at the water testing laboratory of the department of Community Medicine& Public Health, Liaquat University of Medical & Health Sciences, Jamshoro.

Water Sample Collection Procedure:

Water samples were collected from both hand pumps and motor pumps from all above mentioned districts. For each sample collection, water was allowed to flow for 3-5 minutes. Water samples were collected in clean 0.5L polystyrene bottles after rinsing 3 times in running water.

Arsenic Determination:

The arsenic was evaluated by using MERCK test kit (low range 0.005-0.5 mg/L (Merck, Germany) by using manufacturer manuals described previously.[13] Briefly, the test generates arsenic hydride at first, then analytical strip provides mercury bromide. The reaction of the arsenic hydride and mercury bromide produces arsenic mercury halogenide (which is yellow in color). Finally, the scale of color fields is taken by visual comparison of the reaction zone.

Data was analyzed by using Statistical package for social sciences (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Percentages were calculated for each district and graphs were developed in Microsoft Office word.

RESULTS

Water was tested from ten districts of Sindh. The level of the arsenic was much higher than the permissible value of 0.01 ppm. Minimum level in some areas was 0.005 within permissible levels but in majority areas it was higher than the permissible values. A summary of the results is given in Table I.

Overall there were 22289 cancer patients reported during the said period. Out of which 50.1% were males and 49.9% were females. In general males had the highest number of lung and bronchus cancer followed by prostate, urinary bladder, colorectal, melanoma skin, Non-Hodgkin's lymphoma, leukemia, pancreas, kidney and stomach as top ten malignancies in the interior Sindh region. The breast cancer was the most frequently reported cancer among females followed by colorectal, lung & bronchus, pancreas, non-Hodgkin's lymphoma, urinary bladder, leukemia, melanoma skin, uterus and ovary.

The ten districts showed differing pattern of cancer. However oral cancers remained at the top followed by breast cancer, larynx, lung, hematological malignancies, liver & biliary tree, oesophagus, colorectal, urinary bladder and ovary (Figure II). The district wise pattern of cancers is presented in Table I. The highest rate of oral cancers was presented from Thatta & Sujawal area with 27.5% followed by Hyderabad and Tando Mohammad Khan with 24%, being lowest in Mirpurkhas and Jamshoro with 15%. Breast cancer remained at the second highest rank with highest number from Hyderabad district at 18.1% and lowest in Mithi and Umerkot with 7.0%. Highest rate of hematological malignancies has been observed in Mithi and Umerkot (8.7%) and lowest in Mirpurkhas with a rate of 4.5%. Lung and laryngeal cancer remain in the middle ranking in all districts. Cervical cancers in females was seen in high rate in Jamshoro (3.7%), Matyari (3.6%), Mirpurkhas (3.7%) and TandoAllahyar (3.5%). A summary of the top cancers is presented in Table I.

TABLE I: DISTRICT-WISE PRESENTATION OF TOP TEN CANCERS IN ARSENIC AFFECTED BELT OF INTERIOR SINDH

District	Arsenic range	1	2	3	4	5	6	7	8	9	10
Sujawal and Thatta (n=846)	0.005-0.5	Oral cavity (27.5)	Breast (8.9)	Larynx (7.3)	Lung (6.1)	Oesophagus (5.1)	Molar pregnancy (4.6)	Hematological (3.9)	Ovary (3.3)	Liver & Biliary (3.0)	Uterus (3.0)
Badin (n=1993)	0.005-0.5	Oral cavity (17.2)	Breast (10.0)	Larynx (9.9)	Lung (9.2)	Hematological (6.9)	Oesophagus (5.2)	Liver & Biliary (3.7)	Urinary bladder (3.3)	Colorectal (3.1)	Molar pregnancy (2.9)
Tando Mohammad Khan (n=1006)	0.005-0.5	Oral cavity (24.3)	Breast (10.4)	Larynx (7.7)	Lung (7.0)	Liver & Biliary (6.2)	Oesophagus (5.5)	Hematological (4.8)	Molar pregnancy (4.4)	Colorectal (3.5)	Ovary (3.0)
Hyderabad(n=4656)	0.005-0.25	Oral cavity (24.8)	Breast (18.1)	Lung (5.4)	Hematological (5.2)	Larynx (5.0)	Liver & Biliary (4.9)	Oesophagus (3.4)	Colorectal (3.2)	Ovary (3.1)	Bone & SKM(2.6)
Jamshoro (n=1950)	0.005-0.5	Oral cavity (15.3)	Breast (13.2)	Liver & Biliary (8.4)	Hematological (7.0)	Larynx (5.4)	Lung (5.1)	Oesophagus (4.1)	Colorectal (3.9)	Cervix(3.7)	Urinary bladder (3.5)
Matyari (n=1321)	0.005-0.5	Oral cavity (18.7)	Breast (13.0)	Larynx (6.4)	Lung (6.1)	Liver & Biliary (6.0)	Hematological (5.9)	Oesophagus (4.3)	Colorectal (4.2)	Cervix(3.6)	Urinary bladder (3.3)
Dadu (n=3019)	0.005-0.25	Oral cavity (21.7)	Breast (14.6)	Hematological (6.9)	Lung (5.7)	Larynx (5.0)	Liver & Biliary (4.7)	Colorectal (4.1)	Ovary (3.5)	Oesophagus (3.1)	Uterus (3.0)
Mithi&Umarkot (n=588)	0.005-0.5	Oral cavity (16.0)	Hematological (8.7)	Larynx (8.7)	Urinary bladder (7.3)	Breast (7.0)	Colorectal (6.1)	Lung (5.1)	Oesophagus (4.4)	Bone & SKM(3.4)	Liver & Biliary (2.9)
Mirpurkhas (n=1184)	0.005-0.25	Oral cavity (15.3)	Breast (14.0)	Larynx (7.9)	Lung (7.5)	Oesophagus (5.7)	Liver & Biliary (5.6)	Colorectal (4.6)	Hematological (4.5)	Cervix(3.7)	Urinary bladder (3.0)
TandoAllahyar(n=1083)	0.005-0.5	Oral cavity (18.0)	Breast (11.4)	Lung (8.7)	Larynx (7.6)	Liver & Biliary (6.3)	Oesophagus (5.4)	Hematological (5.1)	Colorectal (5.0)	Cervix(3.5)	Ovary (2.9)

FIGURE II: OVERALL PATTERN OF CANCER (PERCENTAGE) FROM THE ARSENIC CONTAMINATED AREA OF INTERIOR SINDH, PAKISTAN

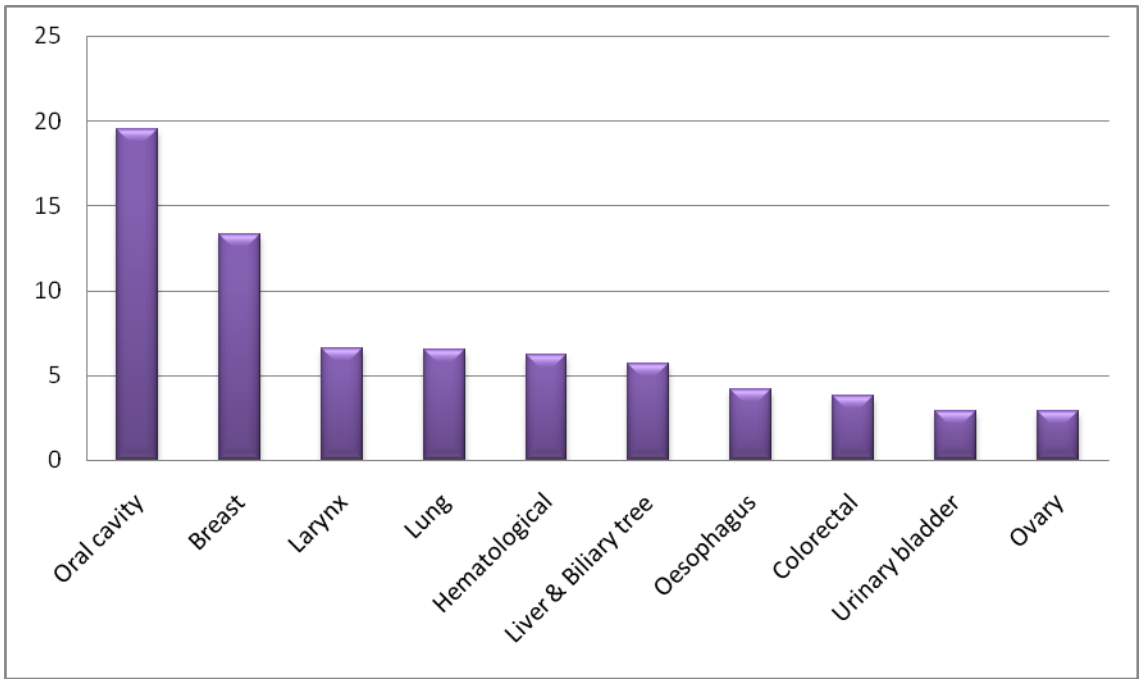


FIGURE III-(A): GLOBOCAN 2020: PATTERN OF CANCERS WORLDWIDE

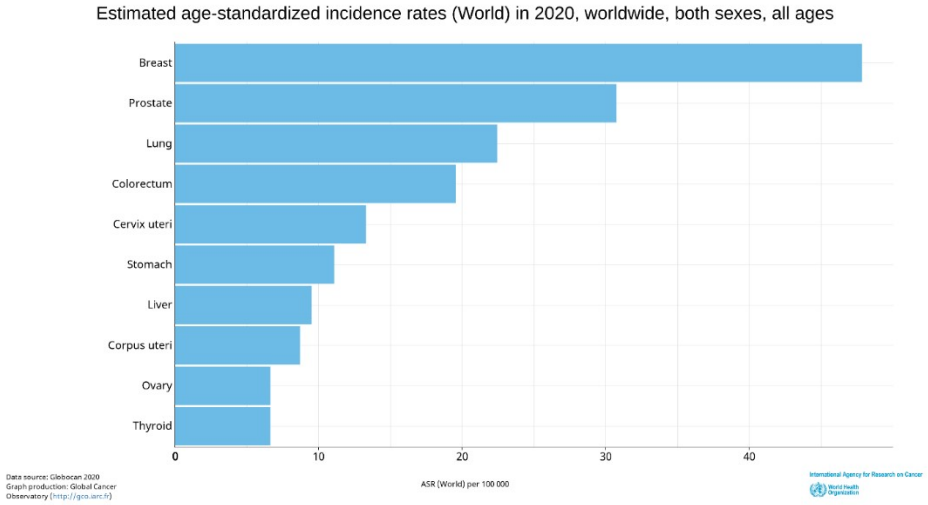


FIGURE III-(b): GLOBOCAN 2020: PATTERN OF CANCERS IN ASIA

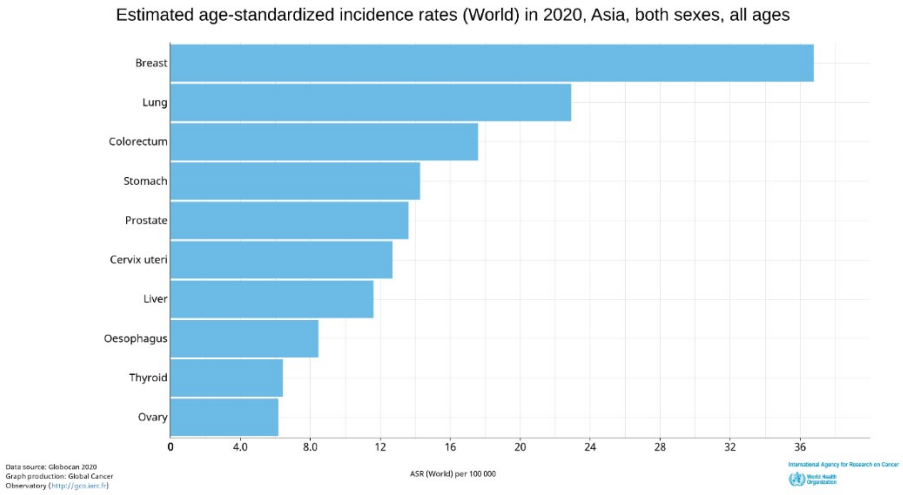
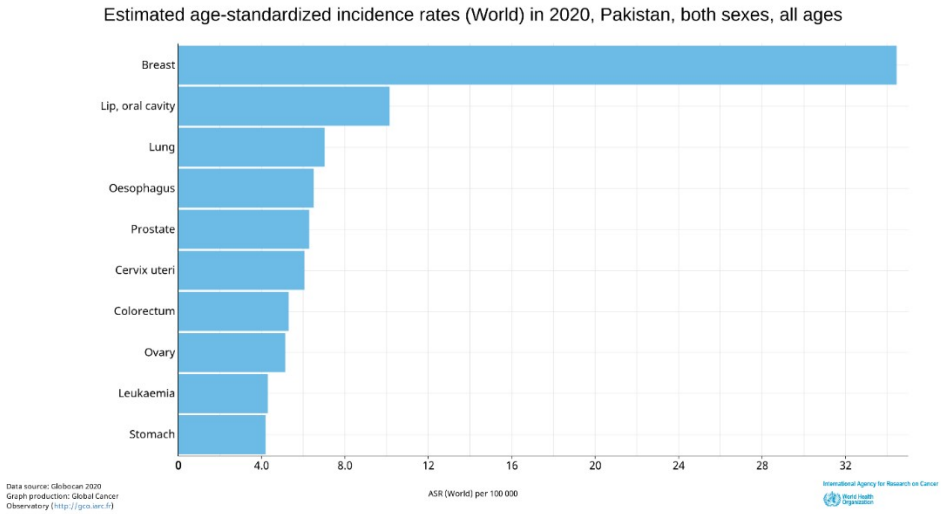


FIGURE III-(c): GLOBOCAN 2020: PATTERN OF CANCERS IN PAKISTAN



DISCUSSION

Arsenic level in well water found to be high in most parts of interior Sindh. The cancer showed varying pattern among the districts with reportedly high arsenic levels in drinking water. However oral cancers, breast cancer, lung, larynx and hematological cancers remain at the top. Figure III presents pattern of cancer worldwide (III-a), in Asia(III-b) and Pakistan(III-c). There is clearly high ranking of oral cancers, larynx and urinary bladder among arsenic affected areas. Hemtaological malignancies also appear to be higher then reported in the rest of the country.

The arsenic has been known to be a carcinogen for a long time. The initial reports received from the skin cancer treated patients who received arsenic topically. Later on systemic malignancies were observed in the arsenic exposure from water and also from occupational use of arsenic products. Arsenic is present in the air, water and soil thus transferred to human body by breathing, eating and drinking. The risk of cancer associated with the route and dose of exposure. At the high dose it cause cancers while at low dose chronic exposure again cause cancer. Through inhalation it causes cancer of respiratory system while with eating and drinking it is more likely to cause cancer in internal organs.

Study on global burden of metal toxicities showed that the ingestion of arsenic was associated with high risk of cancer[14]. A study calculated the measurements of the arsenic in drinking water and concluded that 100µg/L has been linked with increased risk of cancer[15]. In 1985 Chen CJ et al showed the high rate of urinary bladder, kidney, skin, liver and colon cancer among individuals living in arsenic toxicity endemic area, the rate of cancers was even higher in those drinking well water[8]. Similar findings were observed from the Blackfoot disease endemic area of Taiwan. Blackfoot is a chronic vascular disease caused by arsenic toxicity[16]. The updated data from 1995 showed that arsenic exposure not only associated with respiratory cancers but also shown link with other cancers including oral cavity, rectum and kidney. After 33 years follow-up of the exposure group including 454 individuals who had exposure for five years showed risk of dying from cancers of lung and urinary tract. However for lung cancer arsenic and smoking cause synergistic effect. A study from Palma- Lara including people exposed to arsenic contaminated environment, and showed that the arsenic toxicity is dose and duration of exposure related[17].

A collective review of literature was conducted focusing on the association of inorganic arsenic with the development of prostate cancer.[18] The results showed a positive link. An Italian cohort study including 1467 fertilizer and plastic workers showed that the arsenic exposure was associated with cancer of pleura, bone and melanoma[19]. The study from Bengladesh showed that the arsenic toxic well water consumption put the population at high risk of cancer. The exact dose of arsenic linked with cancer is not yet exploredx[20]. A meta-analysis including 10 studies showed no additional risk of lung and urinary bladder cancer at low level of arsenic in drinking water,[6] which was in contrast to the individual studies showing risk of bladder and lung cancer with arsenic toxicity.

A study evaluated association of elevated serum levels of 18 metals in serum in gallbladder cancer and gallstone disease and compared it with controls from populations [21]. Twelve out of 18 studied metals including arsenic showed significant positive correlation with gallbladder cancer while negative association with gallstone disease[22]. This is an interesting finding that arsenic can even cause gallbladder cancer without gall stones. This needs further evaluation in prospective setting.

Spanish study evaluated trace elements including arsenic in patients with pancreatic duct adenocarcinoma with and without KRAS mutations. The results suggested statistically non-significant association with Odds ratio of 3.37 [23].
There is evidence available showing association of arsenic exposure in 528 cases and comparing with 533 healthy controls and showed a link between arsenic exposure and shortening of telomere lengths and increased risk of basal cell carcinoma of skinx[24].
A large prospective study including 58,406 people exposed to arsenic via well water showed young deaths and a great majority was associated with cancers, having exposure to >138.7 level of arsenic. There is established link between skin cancer and arsenic. The study from Chile suspected influence of arsenic exposure with the development of oral cancers. Arsenic not only linked with the arsenic toxicity in adult life but also there is evidence from Chile to link arsenic exposure in utero and later life development of cancer[25]. There was a local study which compared arsenic level in manchar, lake and that in the blood, hair and nails of the people using manchar water. The results showed toxic levels of arsenic in the water, blood, hair and nails[26].
This is first study including a large series of patients with different cancers in the area of high arsenic levels. However, this study has limitation of not assessing arsenic levels in the blood and toe nails to confirm rise of arsenic in the patients. Further studies are required to confirm the causal relationship of the arsenic in cancer development as well as carcinogenesis of arsenic induced cancers.

CONCLUSION

The oral cancers are the top malignancy observed in the region with change in the presentation of other cancers including hematological, lung, larynx gastrointestinal and urinary system. There appears to be an influence of arsenic toxicity with changing pattern of cancers in arsenic affected areas of Sindh. There is limited evidence to suggest mechanisms of arsenic causing cancer and particular types of cancers. Further studies are required to explore it in detail. The mechanism to limit or stop arsenic exposure are also required to be developed in particular water purification mechanism at large scale needs to be developed.

DISCLAIMER

This study is part of an international consortium collaboration study under auspices of Asian Consortium on Arsenic Research.

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AUTHOR CONTRIBUTIONS

Syed BM: Principal investigator
Mangi FA: Manuscript writing
Sushel C: Data collection, manuscript writing
Memon F: Data collection, manuscript writing
Sheikh TA: Data collection, manuscript writing
Ghani A: Data collection, manuscript writing
Memon N: Data collection, manuscript writing

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