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 the National Institute of Medicine and Radiotherapy (NIMRA) from 2008 till December 2018. A convenient non-probability sampling technique was used, and cases were collected using an institutional database containing demographic characteristics and basic cancer information.
Water samples data were retrieved from the water testing laboratory and collected from ten districts across the belt of high arsenic contamination. The patients who did not receive treatment at NIMRA were excluded from the study. Water samples that showed the 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. Each district's percentage was calculated, and graphs were developed in Microsoft Office Word.
RESULTS: Total 22289 cancer patients were reported from the identified districts. The highest rate of oral cancer was found in almost all areas, followed by breast, haematological, laryngeal and lung cancers. Oesophageal and colorectal cancers were among the top ten cancers. Variation in the pattern of cancer was observed in arsenic-contaminated districts of Sindh.
CONCLUSION: Arsenic appears to influence cancer patterns in areas with high concentrations. Further studies are required to explore the pathogenesis involved in arsenic-associated carcinogenesis.

KEYWORDS: 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 combined with other elements, such as Sulfur. The acceptable level of arsenic in drinking water is 0.010 parts per million (ppm), as suggested by the U.S. Environmental Protection Agency (EPA), which equals 10 µg/L. It is widely used in the making of car batteries and ammunition industry. It is also used in pesticides, insecticides and herbicides. Humans are 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 arsenic toxicity or work in the copper smelting industry in agriculture using fertilizers and pesticides[2]. Medicinal uses of arsenic were relatively common in the past centuries, where it had been used as an antibiotic for syphilis and an anticancer agent[3]. Arsenic-72 has been introduced to be used in Positron Emission Tomography (PET Scans), which produces clear images compared to conventional radio-isotope scanning[4]. However, the International Agency for Research on Cancer (IACR) labelled 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, the exact mechanism of cancer development from exposure to arsenic is not yet well explored.

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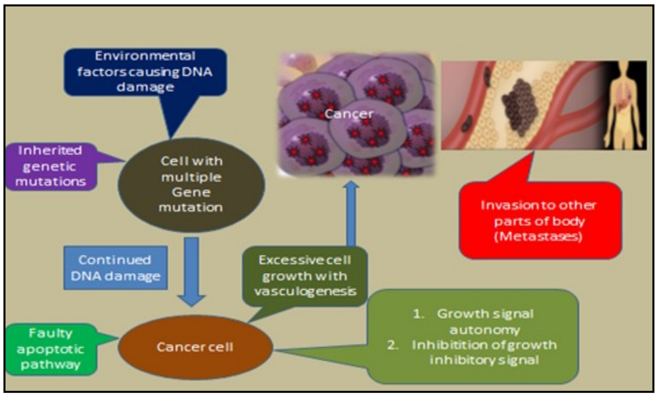
Figure I: Potential model for carcinogenesis from arsenic poisoning



The initial report from observational studies dates back to 1978 when patients treated with arsenic were reported to have malignant neoplasms. The exciting 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 a 1.5-fold risk of dying from lung cancer, while with high exposure, the risk was 2.5-fold. Another study reported a high rate of malignant neoplasm after the medicinal use of arsenic but no significant high mortality of these cancers[3]. The appearance of the malignant neoplasms was linked with 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].

The 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 Indus[12]. A recent review of aqueous contamination showed that the primary source of arsenic contamination was the well water at a depth of 10-150 feet. Arsenic contamination was not found in the wells deeper than 150 feet[12]. Thus, the primary sources of arsenic contamination in Sindh are possibly industrial and agricultural waste.

This study evaluated the pattern of cancer occurrence in arsenic-contaminated areas of Sindh.

METHODOLOGY

This observational study was part of a project on the effect of arsenic on human health conducted at Liaquat University of Medical & Health Sciences (LUMHS), Jamhsoro. Baseline information data was collected from the National Institute of Medicine and Radiotherapy (NIMRA) after institutional research and ethical committee approval. The study includes a consecutive series of cancer patients diagnosed and receiving treatment at LUMHS and NIMRA from 2008 till December 2018. A convenient non-probability sampling technique was used, and cases were collected using an institutional database containing demographic characteristics and basic cancer information. 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 from these districts regardless of age and gender. The patients who did not receive treatment at NIMRA were excluded from the study. Water samples that showed other toxic metals besides arsenic were also excluded from the study.

Water sample results for the districts included in the study were retrieved from the water testing laboratory. The water samples were analyzed at the water testing laboratory of the Community Medicine& Public Health Department, Liaquat University of Medical & Health Sciences, Jamshoro.

Water Sample Collection Procedure:

As mentioned, water samples were collected from the districts' hand pumps and motor pumps. Water flowed for 3-5 minutes for each sample collection. Water samples were collected in clean 0.5L polystyrene bottles after rinsing three times in running water.

Arsenic Determination:

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

Data was analyzed using a Statistical package for social sciences (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Each district's percentage was calculated, 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. The minimum level in some areas was 0.005 within allowable levels but higher than the permitted values in most areas. 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 lung and bronchus cancer followed by prostate, urinary bladder, colorectal, melanoma skin, non-Hodgkin's lymphoma, leukaemia, pancreas, kidney and stomach as top ten malignancies in the interior Sindh region. Breast cancer was the most frequently reported cancer among females, followed by colorectal, lung & bronchus, pancreas, non-Hodgkin's lymphoma, urinary bladder, leukaemia, melanoma skin, uterus and ovary.

The ten districts showed differing patterns of cancer. However, oral cancers remained at the top, followed by breast, 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 shown in the Thatta & Sujawal area with 27.5%, followed by Hyderabad and Tando Mohammad Khan at 24%, and lowest in Mirpurkhas and Jamshoro with 15%. Breast cancer remained at the second highest rank, with the highest number from Hyderabad district at 18.1% and the lowest in Mithi and Umerkot with 7.0%. The highest rate of hematological malignancies has been observed in Mithi and Umerkot (8.7%) and the lowest in Mirpurkhas, with a rate of 4.5%. Lung and laryngeal cancer remains in the middle ranking in all districts. Cervical cancers in females were seen at a 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**.

Figure II: Overall pattern of cancer (percentage) from the arsenic-contaminated area of interior Sindh, Pakistan

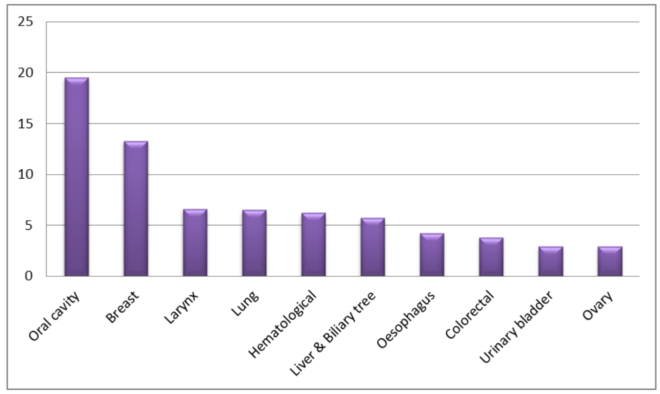


Table I: District-wise presentation of the top ten cancers in the affected belt of interior Sindh

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)

DISCUSSION

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

Figure III-(A):
Globocan 2020: pattern of cancers worldwide

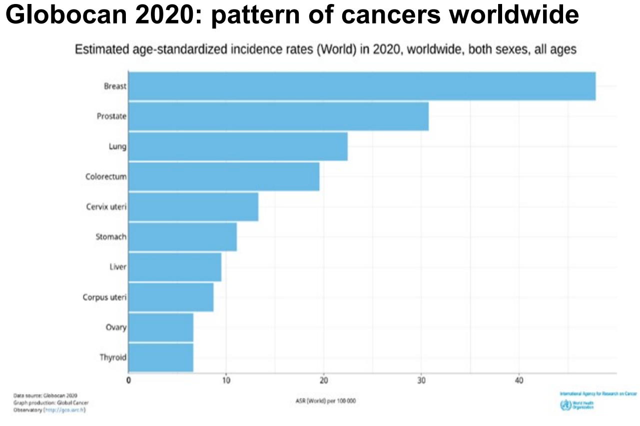


Figure III-(b):
Globocan 2020: pattern of cancers in Asia

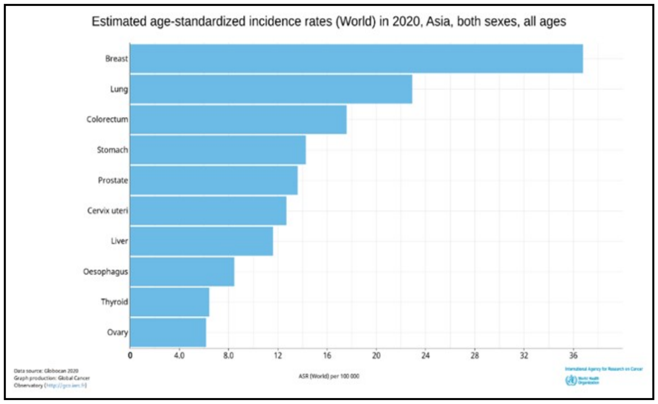
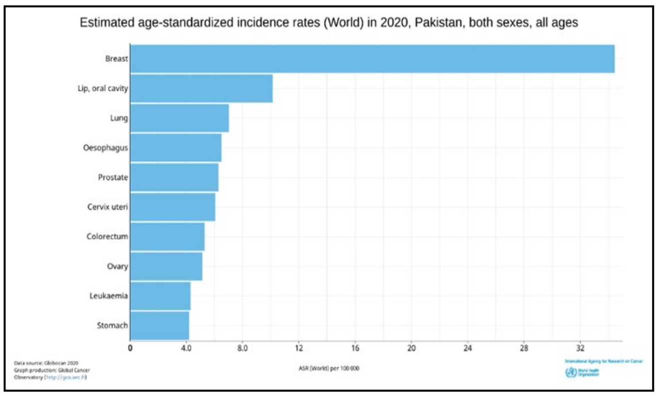


Figure III-(c):
Globocan 2020: pattern of cancers in Pakistan



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

A study on the global burden of metal toxicities showed that ingesting arsenic was associated with a 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 an increased risk of cancer[15]. In 1985, Chen CJ et al. showed a high urinary bladder, kidney, skin, liver and colon cancer rate among individuals living in arsenic toxicity endemic areas; 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 is not only associated with respiratory cancers but also linked with other cancers, including the oral cavity, rectum and kidney. After 33 years, follow-up of the exposure group, including 454 individuals who had exposure for five years, showed the risk of dying from lung and urinary tract cancers. However, for lung cancer, arsenic and smoking cause synergistic effects. A study from Palma-, including people exposed to an arsenic-contaminated environment, showed that the arsenic toxicity is dose and duration of exposure related[17].

A collective review of the literature focused 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 arsenic exposure was associated with cancer of pleura, bone and melanoma[19]. A study from Bangladesh showed that arsenic-toxic well water consumption puts the population at high risk of cancer. The exact dose of arsenic linked with cancer has not yet explored[20]. A meta-analysis including ten studies showed no additional risk of lung and urinary bladder cancer at low levels of arsenic in drinking water,[6] which was in contrast to the individual studies showing the risk of bladder and lung cancer with arsenic toxicity.

A study compared the association of elevated serum levels of 18 metals in serum in gallbladder cancer and gallstone disease with controls from populations [21]. Twelve out of 18 studied metals, including arsenic, showed a significant positive correlation with gallbladder cancer and a negative association with gallstone disease[22]; this is an exciting finding that arsenic can even cause gallbladder cancer without gallstones. This needs further evaluation in a prospective setting.

Spanish study evaluated trace elements, including arsenic, in patients with pancreatic duct adenocarcinoma with and without KRAS mutations. The results suggested a statistically non-significant association with Odds ratio of 3.37 [23].

Evidence shows an association of arsenic exposure in 528 cases, compared with 533 healthy controls, and a link between arsenic exposure and shortening of telomere lengths and increased risk of basal cell carcinoma of skinx24 was established.

A large prospective study including 58,406 people exposed to arsenic via well water showed young deaths and a great majority were associated with cancers, having exposure to >138.7 levels of arsenic. There is an established link between skin cancer and arsenic. The study from Chile suspected the influence of arsenic exposure on the development of oral cancers. Arsenic is not only linked with 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]. A local study compared arsenic levels in manchar and lake and the blood, hair, and nails of people using manchar water. The results showed toxic levels of arsenic in the water, blood, hair and nails[26]. This first study includes an extensive series of patients with different cancers in the area of high arsenic levels. However, this study has a limitation in that it does not assess arsenic levels in the blood and toenails to confirm the rise of arsenic in the patients. Further studies are required to verify the causal relationship of arsenic in cancer development and carcinogenesis of arsenic-induced cancers.

CONCLUSION

Oral cancers are the top Malignancy observed in the region, with changes in the presentation of other cancers, including hematological, lung, larynx, gastrointestinal and urinary systems. There appears to be an influence of arsenic toxicity with the 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 must also be developed. In particular, a large-scale water purification mechanism needs to be developed.

DISCLAIMER

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

Ethical permission: Liaquat University of Medical & Health Sciences ERC Letter No. LUMHS/REC/-879.

Conflict of Interest: The authors have no conflict of interest to declare

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically.

AUTHOR CONTRIBUTION

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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