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Relationship between Grades of Bladder Cancer with the Level of Arsenic in Drinking Water

B M Saiduzzaman[1], AKM Khurshidul Alam[2], Mominul Haider[3], Md. Shaleh Mahmud[4], Md. Mominul Islam[5], Mohammad Manirul Islam[6]

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Abstract

Background: *Arsenic is a heavy metal and it is considered carcinogenic to humans. In Bangladesh, most of the people consume arsenic polluted water above the nationally accepted level. Several studies have demonstrated that the ingestion of arsenic in drinking water is a strong risk factor for several malignancies including urothelial carcinoma. Clinicopathological features of bladder cancer are related to the amount of arsenic exposure and duration of arsenic exposure into the urinary tract and other risk factors. Aim of the study was to see the relationship between grades of bladder cancers with the level of arsenic in drinking water.*

Objective: *To see the relationship between the grades of bladder cancer with the level of arsenic in drinking water.*

Materials and Methods: *This was a retrospective cross-sectional study done in the department of urology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka. In this study, a total of 72 histopathologically proven urothelial bladder carcinoma and history of at least 10 year underground water consumption patients were enrolled. Among them 12 patients were excluded from the study because no arsenic was found in sample underground drinking water. So, 60 patient was participants for this study. Sample of participant's drinking water was collected by a selective non-reactive container. The level of arsenic level in microgram/Liter was measured by standard kit method and the level of arsenic was recorded.*

Results: *Arsenic exposure 30 years or more was regardless of the amount of arsenic consumption in drinking water was found high-grade cancer. No significant statistical difference was found in the grading of carcinoma with the level of arsenic in drinking water.*

Conclusion: *Arsenic exposure amount is not related to the grades of bladder cancer rather the duration of arsenic exposure in drinking water is related to the grades of bladder cancer.*

Keywords: Arsenic, Bladder cancer, Grading

1. Assistant Registrar, Department of urology, Shaheed Suhrawardy Medical college Hospital, Sher-E-Bangla Nagar, Dhaka.
2. Professor, Department of urology, Bangabandhu Sheikh Mujib medical University, Dhaka.
3. Registrar, Department of urology, Shaheed Suhrawardy Medical college Hospital, Sher-E-Bangla Nagar, Dhaka.
4. Registrar, Department of urology, MAG Osmani Medical College Hospital, Sylhet.
5. Assistant registrar, department of urology, Kurmitola General hospital,
6. Resident Surgeon, Department of urology, Shaheed Suhrawardy Medical college Hospital, Sher-E-Bangla Nagar, Dhaka.

Correspondences: Dr. BM Saiduzzaman, Assistant Registrar, Department of Urology, Shaheed Suhrawardy Medical College, Dhaka, Bangladesh. Phone- +8801723888996 Email- dr.sayedsujon@ gmail.com

Introduction

Bladder cancer is the second most common cancer of the genitourinary tract[1]. It is the 10th most common cancer in the world[2] .Worldwide approximately 550,000 new cases are diagnosed annually[3]. It is the 13th most common cause of death accounting for 145,000 deaths worldwide[4]. Male are 3 to 4 times more likely to develop cancer than females, presumably because of an increased prevalence of smoking and exposure to environmental toxins[5]. About 47% of the cancers are high grade and 53% are low grade at diagnosis[6].Bladder Cancer type is determined by postoperative histopathology examination of the transurethral resection of the bladder tumor (TURBT) specimen[7]. World Health Organization (WHO) has determined that the term urothelial cancer is preferable to the term transitional cell cancer (TCC). The WHO also recommends that malignant tumors be classified as low grade or high grade, regardless of invasion status[8]. Inorganic arsenic is one of the few substances that have been shown to cause cancer in humans through consumption of drinking-water. Cancer usually takes more than 10 years to develop. Arsenic can cause cancers of the skin, bladder and lungs, and there is limited evidence that it may also cause cancers of the kidney, liver and prostate. The International Agency for Research on Cancer (IARC) has classified arsenic and arsenic compounds as carcinogenic to humans. The organic arsenic compounds are the active ingredients of some herbicides and are metabolites of inorganic arsenic[9-11]. It is estimated that of the 125 million inhabitants of Bangladesh are at risk of drinking arsenic contaminated water. Maximum concentration of arsenic permitted in Bangladesh: 50 microgram/L[12]. About 53% of the ingested arsenic is excreted through urine. Urine is maximum time is hold in the urinary bladder[12]. Several studies reported an increased prevalence of bladder cancer in populations exposed to arsenic in their drinking water. Study suggested that the cancer risk from drinking water containing arsenic at 50ìg/ liter may be as high as one in 100[13]. Arsenic directly damages human cell DNA. Changes in gene methylation status, mediated by arsenic, have been proposed activate oncogene expression or silence tumor suppressor genes, leading to long-term changes in activity of genes controlling cell transformation. Bladder tumors in patients with higher levels of arsenic exposure showed higher levels of chromosomal instability. Most of the chromosomal alterations associated with arsenic exposure were also associated with tumor stage and grade, raising the possibility that bladder tumors from arsenic-exposed patients may behave more aggressively than tumors from unexposed patients[14]. So, arsenic related changes maximum in the bladder urothelium and arsenic exposure amount or duration may have association with the formation of different grades of urothelial cancer. Since there is little information on the cancer grades of bladder cancer and level of arsenic in drinking ground water. More epidemiologic evaluations are needed to characterize the dose response relationship for arsenic-associated bladder cancer. So, aim of the study was to assess cancer grades and arsenic level in drinking ground water relationship.

Materials & Methods

This was a retrospective cross-sectional study. A total 60 patients were in included in this study from October, 2018 to January, 2020 in Department of Urology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, with histopathologically proven urothelial carcinoma and history of exposure of drinking underground water for at least 10 years. Ethical clearance for the study was taken from the Institutional Review Board (I.R.B.) of BSMMU prior to the commencement of this study. Exclusion criteria was Patients who are not exposed to underground water and secondary tumors involving urinary bladder. Patients were allocated into 2 groups by arsenic level in drinking water- Group 1: arsenic level in drinking water was 10-50 microgram/L & Group 2: arsenic level >50 microgram/L. Then semi quantitative arsenic level was measured by Hach EZ Arsenic test kit 2822800 (EZ arsenic) .Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0. Statistical significance between grades of bladder cancer and level of arsenic, duration of exposure and tobacco smoking status was tested by Fisher Exact test curve. $P<0.05$ was accepted as statistically signifi-cant.

Result

In this study the mean age of the patients was 60.47±10.73 years where minimum age was 35 years and maximum age was 90 years. Among the 60 patients 50 (83.3%) patients were male and 10 (16.7%) were female. The mean duration for exposed to arsenic contaminated water of the patients was 34.67±10.24 years where minimum duration was 12 years and maximum duration was 50 years. About 40% patient's exposure was 30-39 years (Table-7.1).

Table-I: Distribution of study subjects by Arsenic exposure time (n=60)

Arsenic Exposure time	Frequency (f)	Percentage (%)
10-19	6	10.0
20-29	4	6.7
30-39	24	40.0
40-49	19	31.7
50-59	7	11.7
Mean ± SD	34.67 ±10.24	
Range(min-max)	12-50 years	

In histopathology reports 51 (85.0%) patients had high grade urothelial carcinoma and 9 (15.0%) patients had low grade urothelial carcinoma. In this study 50 (83.3%) patients had Low arsenic level (10-50 microgram/liter) in their drinking water while 10 (16.7%) patients had high arsenic level (>50 microgram/liter) in their drinking water. 42 (84.0%) patients with Low arsenic level in their drinking water had high grade urothelial carcinoma; while 9 (90.0%) patients with high arsenic level (>50 microgram/liter) had high grade urothelial carcinoma. No significant statistical difference was found in grading of carcinoma regarding level of arsenic in drinking water as p value was 1.000 (obtained by Fisher Exact test). (Table-II)

In exposure time - 8 (80.0%) patients with 10-29 years had low grade urothelial carcinoma while 49 (98.0%) patients with e"30 years had high grade urothelial carcinoma. Highly significant statistical difference was found in grading of carcinoma regarding exposure time as p value was <0.001 (obtained by Fisher Exact test).

Table -II: Distribution of study subjects by level of arsenic in drinking water and grade of urothelial carcinoma (n=60).

Level of arsenic (microgram/L)	Grade of urothelial carcinoma			Test statistics
	Low	High	Total	
10-50	8(16.0%)	42 (84.0%)	50(100.0%)	p=1.000
>50	1(10.0%)	9 (90.0%)	10(100.0%)	

Table- III: Distribution of study subjects by exposure time and grading of carcinoma (n=60)

Exposure time(in years)	Grade of urothelial carcinoma			Test statistics
	Low	High	Total	
10-29	8 (80.0%)	2 (20.0%)	10(100.0%)	**p<0.001**
≥30	1 (2.0%)	49 (98.0%)	50(100.0%)	

Discussion:

This study was carried out with an aim to see the relationship between grades of bladder cancer with level of arsenic in drinking water. This study also assess the relationship with duration of arsenic exposure with grades of bladder cancer.

In this study, it was observed that mean age of the patients was 60.47±10.73 years where minimum age was 35 years and maximum age was 90 years. Horstmann et al (2008) showed that mean age of bladder cancer in male is 62 years and female is 67 years. Higher mean age and age range found in some studies due to geographical variations, racial, ethnic differences, and genetics[15].

This study showed that 50 (83.3%) patients were male and 10 (16.7%) were female which indicates that bladder cancer is more common in male subjects in this study. Similar observations regarding the male predominance were also observed by many investigators[16-18].

In this study, it was observed that the mean duration for exposed to arsenic contaminated water of the

patients was 34.67±10.24 years where minimum duration was 12 years and maximum duration was 50 years (Table-1).

In this study, it was observed that 51 (85.0%) patients had high grade carcinoma and 9 (15.0%) patients had low grade carcinoma which means that arsenic exposed patients are more prone to develop high grade urothelial carcinoma (Table-2). Chow et al (1997) showed that patients arsenic exposed group had a significantly higher histological grading (P = 0.04) than those in the non-arsenic exposed group; which support with the present study[19]. Another study showed that ingestion of inorganic arsenic in drinking water is indeed a cause of bladder cancer. It was estimated that arsenic might account for 7% of all deaths among those aged 30 years and over[20].

This study shows that 50 (83.3%) patients had 10-50 microgram/liter arsenic in their drinking water while 10 (16.7%) patients had >50 microgram/liter arsenic in their drinking water indicates that all the bladder cancer patients consumed drinking water above the safety range of WHO and 16.7% patients above the national acceptable range.

In this current study, 42 (84.0%) patients with 10-50 microgram/liter arsenic in their drinking water had high grade carcinoma while 9 (90.0%) patients with >50 microgram/liter arsenic in their drinking water had high grade carcinoma.(Table-3). No statistical difference was found in grading of carcinoma regarding level of arsenic in drinking water as p value was 1.000 (obtained by Fisher Exact test). Bates et al (2004) showed that there was no association of bladder cancer with either measure; however, among smokers, but not among nonsmokers, positive trends in risk were found for exposures estimated for decade-long time periods. Exposures were in the range 0.5-160 microgram/liter. The data raise the possibility that smoking potentiates the effect of arsenic on risk of bladder cancer. However, the risk estimates obtained are much higher than predicted on the basis of the results of the Taiwanese studies, raising concerns about bias or the role of chance[21]. This study results supports the current study.

Chen C-H et al (2010) showed that the highly exposed (>100 ìg/L), the relative risks (RR) were >5-fold, whereas the risk was elevated but not significant for low exposure (<100 ìg/L). Relative to the arsenic concentration <10 ìg/L, those who drank well water with higher concentration from birth still drank and drank for >50 years had a significantly increased risk of urinary bladder cancer[22]. When restricted to urothelial carcinoma, all risk estimates including concentration and characteristics of well water consumption were higher. So, long exposure of arsenic may produce this finding.

This study showed that 8 (80.0%) patients with low exposed time 10-29 years had low grade carcinoma while 49 (98.0%) patients with high exposed time e"30 years had high grade carcinoma. Highly significant statistical difference was found in grading of carcinoma regarding exposure time as p value was <0.001 (obtained by Fisher Exact test). High time exposure may contribute more changes in urothelium and caused high grade tumor. Nathalie Saint-Jacques et al (2014) showed that exposures more than 50 ìg/L, there was an 83% probability for elevated incidence of bladder cancer; and a 74% probability for elevated mortality. This elevated mortality due to high grade and invasiveness of bladder cancer[23].

Conclusion

From this study, it can be concluded that long duration arsenic exposure irrespective of amount per day above normal range causes high-grade urothelial carcinoma.

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