RESEARCH COMMUNICATION

Prominent Bladder Cancer Risk Factors in Iran

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Abstract

Several risk factors have been suggested for transitional cell carcinoma (TCC) of the bladder (BC). Since it seems that some factors have more prominent role over the others in our region, we conducted the present case-control study with 692 bladder cancer (BC) patients versus 692 healthy controls (262 women versus 1,122 men in total) matched on the basis of gender and age (±5 years). The enrolled cases had confirmed TCC of bladder. To gather data, we exploited a questionnaire filled up in face-to-face interviews. We classified different factors in four categories as follows: 1-dietary factors; 2-history of underlying diseases; 3-lifestyle; and 4-occupational/ chemical exposures. Among dietary factors, pickles (P= 0.04) and vegetables (P= 0.001) had protective effects. In the second group, histories of all evaluated diseases were accompanied by increased risks for BC. Among life style factors, cigarette smoking (P= 0.0001), opium use (P= 0.0001), history of excessive analgesic use (P= 0.0001) and hair dye use (P= 0.02) had significant correlations with BC. However, none of the occupational exposures was associated with BC. One may conclude that some factors such as opium use may have a more important role in developing BC in our region. Nonetheless, we should categorize occupations based on their definite exposure to chemicals for conducting further studies.

Keywords: TCC bladder - case-control study - risk factors - diet - lifestyle - opium - Iran

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Introduction

Bladder cancer (BC) is the most prevalent malignancy in genitourinary system. This malignancy is usually discovered in older patients and the median age at the time of diagnosis is 69 for men and 71 for women. (Daneshmand and Becker, 2009). While the rate of BC is high in the United States, Canada and Australia, the lowest incidences have been reported from Southeast Asia. Considerably, the incidence of BC seems to be moderate in Iran (Ferlay et al., 2004).

Based on the reports presented in 2005 by the Cancer Office at the Non-communicable Deputy of the Iranian Center for Disease Control and Prevention, BC accounts for 7.04% of all cancers in Iran. According to this report, the age-specific incidence rate of BC in Iran is 11.30 in males versus 2.86 in females in a population of 100,000. Surprisingly, in some areas of Iran the incidence of this cancer reaches to as high as 15.9 in a population of 100,000 (Mousavi, 2005-2006).

The relationship between BC on one hand and smoking, occupational exposure to aromatic hydrocarbons, and chronic infections on the other is quite likely (Cohen et al., 2000; Colombel et al., 2008; Hosseini et al., 2008). Among these, tobacco smoking and occupational exposures have been suggested as two major risk factors responsible for bladder tumors. Noticeably, tobacco smoking could be considered as the most important risk factor (Colombel et al., 2008).

To our knowledge so far, the number of studies carried out on BC risk factors in Iran seems to be limited, considering that compared with other countries, some particular risk factors such as opium use may play an important role in the development of BC as well as chronic infections (Colombel et al., 2008; Kantor et al., 1984). The high use of opium as well as morphine-derived substances in our country has been reported by United Nations Office on Drugs and Crime (UNODC) (2008).

The burden of BC as well as its various non-confirmed risk factors in Iran, prompted us to carry out a comprehensive study to demonstrate the relationship between some specific risk factors and BC. Consequently, we will be able to identify the high risk groups for BC that can assist us in early detection of such patients.

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Materials and Methods

In this population-based case-control study the eligible cases were defined as those who were newly registered as BC at Iranian cancer registry system based on pathologic findings in 2006. Reportedly, all the cases were live patients with TCC of bladder.

The patients were selected randomly from the areas and provinces that had been predicted to have high incidences of BC that in addition were capable of participating in the study considering their medical facilities. The selected provinces included Tehran, Khorasan, Khoozestan, Isfahan and East Azarbayjan. In this study, each patient of the case group was matched with a similar healthy subject but free from BC in the control group according to two factors of age (±5 years) and gender in the neighborhood of the BC patient. The addresses of cases had been recorded previously by Iranian Cancer registry system. Thus for selecting the individuals for control group, according to the address of each BC patient's home, that had been recruited as a case, we referred to the right-door neighbor to find a properly matched individual. If we could not find an appropriate control at that location then we would check the next right-door neighbor to find an individual.

We utilized a questionnaire that was devised by a urologist, an occupational-disease specialist, and an epidemiologist. To signify the reliability of the questionnaire, concerning the inter-item consistency of the questions related to the different risk factors, Cronbach's alpha was measured approximately 0.5. Face-to-face interviews in both the case and the control groups were performed to fill up the questionnaires by the staff of the health center in each province that had been previously trained for this purpose. The overall response rate was over 80% for both the case and the control groups. With respect to responding to the questions, some 418 (62%) of cases and 494 (77%) submitted their answers to the interviewer by themselves. The remaining questionnaires were filled up by proxy interviews with the close relatives of the both the cases and the controls.

To fill the questionnaires, those who would smoke cigarettes and take opium at the time of the study, and also those who had been ex-smokers and opium users, were considered as cigarette smokers and opium users. Yet about exposure to hair dye, those who had used hair dye once or more in a year were considered as hair dye users. Moreover, some other variables such as drinking tea or coffee (cups of tea or coffee per day), previous history of any disease, family history of BC, occupational exposures to chemicals, excessive use of analgesics, herbal medications for weight loss and oral contraceptive pills consumption were asked too. With regards to exposure to chemicals, we classified occupations into nine discrete categories as follows: 1- without exposure, 2- with probable exposure, 3- paint (painters, printers), 4- petroleum products (oil company workers, truck drivers), 5- leather (shoemakers), 6- beauticians and hairdressers, 7- general chemicals, 8- electrical workers, and 9- weavers. In addition, questions about education and marital status (such as being married, unmarried, widowed or divorced) were asked from the participants of the study too.

The collected data were presented to a computer through Access database. Afterward and by utilizing the Stata software (version 8), the data were analyzed and edited; the absolute and relative frequencies and also means and standard deviations were measured for data description. The averages of numerical variables were compared between the case and the control groups by using the paired-t test. To evaluate the relationship between different exposures and the BC occurrence, the conditional logistic regression models were exploited.

To quantify the effects of exposures, odds ratio and 95% confidence interval were measured. A p-value of lower than 0.05 was considered as statistically significant. From the ethical point of view, written informed consents were obtained from all participants after reassuring the patients about the aim of the study as well as the confidentiality of the collected data. The present study was approved by the Ethical Committee of the Urology and Nephrology Research Center of Shahid Beheshti University of Medical Sciences.

Results

According to the data gathered through questionnaires, some 692 BC cases and another 692 controls were included in our study (262 women versus 1,122 men in total). Male to female ratio was 4:1. The mean age were 64.67 years old (standard error= 0.47) and 65.64 (standard error= 46) in the controls and the cases, respectively (P= 0.17). The maximum number of questionnaires was from the Tehran province (34%). In this study, 610 (88%) of the controls and 581 (84%) of the cases were married (P= 0.08). The average years of education were 5.75 years (standard deviation= 5.37) in the control, and 5.90 years (standard deviation= 5.57) in the case groups, respectively.

Table 1. Dietary Factors and their Impacts on Bladder Cancer in Iran

Food category	Cases				Controls				Odds ratio (95% CI)	P
	Max*	Min*	SE	Average	Max*	Min*	SE	Average		value
Sausage	3	0	0.01	0.15	3	0	0.02	0.16	0.98 (0.70-1.34)	0.85
Ham	3	0	0.02	0.15	3	0	0.01	0.13	1.24 (0.87-1.78)	0.24
Smoked fish	3	0	0.01	0.08	3	0	0.01	0.09	0.78 (0.50-1.20)	0.26
Can	3	0	0.02	0.19	3.5	0	0.02	0.21	0.80 (0.60-1.07)	0.13
Pickles	7.5	0	0.07	1.06	8	0	0.08	1.27	0.93 (0.88-0.99)	0.04
Fruits	21	0	0.17	4.47	21	0	0.18	4.73	0.97 (0.94-1.00)	0.06
Vegetables	21	0	0.13	3.06	21	0	0.15	3.58	0.93 (0.89-0.97)	0.001

CI, confidence interval; *times per week

Table 2. History of Disease Associations with Bladder Cancer

History of disease	Cases (No %)		Controls (No %)		Odds ratio (95% confidence interval)		P value
Renal failure	65	9.4	35	5.1	1.87	(1.21-2.89)	0.001
Bladder stone	124	17.9	34	4.9	4.14	(2.76-6.21)	0.001
Neurogenic bladder	127	18.4	34	4.9	5.90	(3.63-9.61)	0.001
Spinal cord paralysis	11	1.6	1	0.1	11.0	(1.42-85.2)	0.02
Recurrent urinary tract infections	229	33.1	59	8.5	5.23	(3.73-7.35)	0.001
Diabetes mellitus	115	16.6	87	12.6	1.41	(1.03-1.92)	0.03
Family history of bladder cancer	85	12.3	54	7.8	1.77	(1.19-2.62)	0.01

Table 3. Lifestyle and the Bladder Cancer Risk Factors

Risk factor	Group Response	Cases				Controls				Odds ratio (95% CI)	P value
		Yes (N %)		No (N %)		Yes (N %)		No (N %)			
History of cigarette smoking		241	34.8	158	22.8	158	22.8	469	67.8	2.00 (1.51-2.64)	0.00
Having smoker colleagues		193	27.9	185	26.7	185	26.7	451	65.2	1.25 (0.94-1.47)	0.12
Having smoker in house		126	18.2	103	14.9	103	14.9	582	84.1	1.36 (1.00-1.84)	0.05
Current opium consumption		85	12.3	34	4.9	34	4.9	631	91.2	2.88 (1.84-4.50)	0.00
History of opium consumption		67	9.7	20	2.9	20	2.9	583	84.3	3.50 (2.41-8.41)	0.00
History of excessive analgesic use[a]		203	29.3	162	23.4	162	23.4	517	74.7	1.52 (1.16-1.99)	0.00
History of herbal medications use		162	23.4	149	21.5	149	21.5	528	76.3	1.17 (0.88-1.55)	0.28
Tea drinking		334	49.5	311	46.2	311	46.2	362	53.8	1.26 (0.96-1.66)	0.10
Hair dye use[b]		80	8.3	60	8.7	60	8.7	505	73.0	1.81 (1.08-3.06)	0.02

CI, confidence interval; [a]Constant use of analgesics for more than one year; [b]More than once a year

(P=0.23).

The risk factors could be summarized into four categories as follows: 1) dietary factors; 2) history of underlying diseases; 3) life style (including cigarette smoking and/or opium consumption); and 4) occupational/ chemical exposures.

Table 1 includes the studied dietary factors. The results showed that other than pickles and vegetables that had protective effects, the impact of other kinds of food on the development of BC was not statistically significant in both the cases and the controls.

Table 2 reveals the history of different chronic diseases. Notably, all these conditions seem to increase the risk of BC according to the analyzed data.

Table3 contains factors that are related to the individuals' life styles. Concerning the cigarette smoking at the time of the study, the mean numbers of cigarettes used per day were 5.52 (standard error= 0.41) and 3.39 (standard error= 0.34) among the cases and the controls, correspondingly (P= 0.0001). In addition, the mean cigarette smoking years were 4.25 years (standard error= 0.46) and 3.4 years (standard error= 0.43) among the cases and the controls, respectively (P= 0.20). For ex-smokers, the mean numbers of cigarettes used per day among the cases and the controls were 16.17 (standard error= 0.81) and 14.88 (standard error= 0.98), respectively (P= 0.003). Furthermore, the mean years of cigarette smoking among the cases and the controls were 28.07 years (standard error= 1.25) and 24.30 (standard error= 1.44), accordingly (P= 0.05).

In current habitual opium users, 55 individuals were among the cases and 9 individuals were among the controls (P= 0.0001). Moreover, 67 of the cases and 20 of the controls had the previous history of opium consumption (P=0.001).

Table-4 shows the exposures to the important chemicals in different occupations. Seemingly, based on these findings no statistically significant correlation was established between BC and any chemical exposure.

Table 4. Occupational /Chemical Exposures

Occupational exposure	Odds ratio	95% CI	P value
Dye and similar substances	1.61	0.63- 4.11	0.32
Petroleum and its derivatives	0.49	0.20-1.21	0.12
Other chemical exposure	0.61	0.14-2.55	0.49
Without exposure	1.02	0.73-1.44	0.89

CI, confidence interval

Table 5. Effects of Factors on Bladder Cancer Adjusted for Cigarette Smoking

Risk Factor	Odds ratio	95% CI	P value
Opium consumption	2.57	(1.55-4.26)	0.0001
Hair dye consumption	1.99	(1.04-3.82)	0.04
Excessive analgesics use	1.41	(1.02-1.94)	0.04

Eventually, some risk factors have been adjusted for conditional logistic regression analysis with cigarette smoking to evaluate their main influence on BC in table-5. Considerably, the most important point of this table is the significant correlation of opium consumption with BC even after using logistic regression model by which the effect of smoking was excluded.

Discussion

According to the findings of the present study, it seems that there is a statistically significant difference between the cases and the controls for the development of TCC of bladder on one hand, and some risk factors such as tobacco smoking, opium consumption, recurrent UTIs, bladder stones, neurogenic bladder, spinal cord paralysis, DM, RF, hair dye consumption, excessive analgesics use, and positive family history for BC on the other. Moreover, it

has been demonstrated that pickles and vegetables possess protective effects.

Admittedly, one of the limitations of case-control studies is individual differences in responding to the questions. Additionally, individuals in the case and the control groups may not remember accurately their previous exposures and this could lead to recall bias. Nevertheless, considering that most of the risk factors assessed in this study had been the daily habits of the participants, the inability to remember was assumingly low.

Considerably, there are more than 60 identified carcinogens including reactive oxygen radicals in cigarette smoke. The potential role of 4-aminobiphenyl, polycyclic aromatic hydrocarbons, N-nitroso compounds, and unsaturated aldehydes in development of BC seems to be prominent.(Daneshmand and Becker, 2009) We found a positive relationship between tobacco smoking and the development of BC. There are many other studies that have supported this link. It is likely that cigarette smoking can cause development of BC among genetically susceptible individuals.(Strope and Montie, 2008)

With regards to opium the results of our study demonstrated that the opium use among the cases is approximately four times higher than the controls. Considering the fact that cigarette smoking is believed to be the main culprit in BC development and since most of the opium users are simultaneous cigarette smokers, by utilizing logistic regression model, we excluded the effect of cigarette smoking on opium consumption. Notably, even after excluding the impact of smoking the correlation of opium consumption with BC was statistically meaningful. In a study conducted by Hosseini et al. the same correlation between opium use and BC could be demonstrated. They have suggested some reasons for the impact of opium on BC according to the following: 1- opium has a post-smoking residue called dootle that has carcinogenic effects. 2- additionally, substituted hydroxyphenanthrenes in opium pyrolysates that has been proposed as a contributor in the development of esophageal cancer may also play a similar role in BC progression.(Hosseini et al., 2008) In a study conducted by Sadeghi et al., opium and especially its pyrolysis-derived substances had been suggested as carcinogens for BC in men. Owing to the low rate of opium addiction among females at the time, their results could not been generalized for both sexes (Sadeghi et al., 1979). One of the effects of the opium could be the compromising of the immune system and, therefore, the affected individuals would be susceptible to influences of other carcinogens too (Risdahl et al., 1998).

There is a debate on the effects of recurrent UTIs and their association with BC. Jhamb et al. (2007) have claimed that there is no correlation between UTI and BC.Surprisingly, Jiang et al. (2009) from USA have demonstrated a completely different protective impact of UTI. Nonetheless, Parsonnet (1995) has stated that the inflammation of chronic infections could facilitate the development of malignancy. Peluchi et al. (2006) have mentioned that chronic infections and urinary tract stones could damage mucosal membranes and culminate in malignancy in long term. Our study demonstrated a significant correlation between recurrent UTIs and BC. Particularly, this relation considered to be significant even after using logistic regression model. It seems that chronic irritation due to recurrent infections could theoretically initiate neoplastic changes in urinary bladder. One of the other limitations in our study was that we did not ask about the type and the duration of UTI involvements, bladder stones, and neurogenic bladder.

As it was stated above, urinary tract stones and, bladder calculi in particular, can cause mucosal injury, and in turn, neoplastic changes will ensue in long term. (Pelucchi et al., 2006) Our findings on bladder stones and TCC are in support of this theory.

In the present study, a statistically significant correlation has been presented between BC and the cord paralysis as well as neurogenic bladder. Although we can consider the neurogenic bladder as a consequence of the cord paralysis, these conditions can put the patient at the risk of recurrent UTIs and ultimately development of bladder TCC. Pannek (2002) has shown the same findings concerning the mentioned circumstances. In a survey in Sweden, completed by Larsson et al (2008) it has been claimed that DM has no correlation with BC.In contrast, the same author joined with another team in a meta-analysis has considered DM as a risk factor for BC.(Larsson et al., 2006) Our findings supported the latter correlation regarding diabetes and BC too. The impact of DM on developing BC may be attributed to immunosuppressive state that occurs through the course of the disease.

Chronic renal failure is another condition that a person's immunity is in jeopardy dramatically. Therefore, the probability of BC development increases. Chen CH. et al. (2008) from Taiwan have found an association between ESRD and BC, especially among females. In another survey in Taiwan, it has been suggested that chronic kidney disease and ESRD may have roles in the development of urothelial cancers (Chen et al., 2007). Our results revealed that there is a significant association between RF and BC similar to the other aforementioned chronic conditions.

The association between hair dye use and BC is also controversial.(Huncharek and Kupelnick, 2005; Kelsh et al., 2008) In the current study, we found a statistically significant difference between the cases and the controls regarding the use of hair dyes. However, if the effect of hair dye use assessed separately among female and male participants, owing to the reduction in the sample size among females and the low rate of hair dye use among males, this correlation would not be significant statistically. One of the other limitations of our study was that we did not ask about the type of used hair dye.

Another probable risk factor is the excessive analgesics use. Different authors have come up with various results about analgesics overuse. Genkinger et al. 2007) have demonstrated no overall correlation between the use of aspirin, ibuprofen, acetaminophen, and the NSAIDs, and the risk of BC. Fortuny et al. (2007) have reported that aspirin use may be accompanied by reduced BC risk. In contrast, their results have supported the previous findings about carcinogenicity of phenacetin-containing

medications. Our data showed that there is a positive association between the excessive use of the analgesics and BC risk. Nonetheless, in our study the type of analgesics has not been asked distinctly, and we merely focused on both their constant use and the duration of analgesics consumption.

The role of genetic predisposition implicated in BC is still controversial. A clear genetic pattern has not been recognized yet; though the familial aggregation has been stipulated in many studies (Bermejo et al., 2009; Kiemeney and Schoenberg, 1996). In contrast, Mueller et al. (2008) in their review have stated that familial TCC of bladder is very uncommon.Nevertheless, our findings on positive family history in BC occurrence represented that this factor might be responsible for the development of BC too.

In addition, we found two protective factors among evaluated dietary items. Frequent use of vegetables and pickles had been found to possess protective impacts on BC. However, Chyou et al. (1993) have claimed that frequent use of pickles might increase the risk. Yet, La Vecchia et al. (1996) have suggested vegetables as protective factors.

Ultimately, we did not find a statistically significant difference between the cases and the controls regarding the occupational exposures and the development of BC. Admittedly, according to this finding we cannot ignore the role of occupational exposures in the development of BC in our region. In contrast, we should explain why this relationship has been found to be insignificant. First of all, obviously the exposures of different occupations to various chemicals have not been identified clearly in Iran. Furthermore, the occupations have not been categorized according to the exposure factors. Additionally, this insignificant association may arise from our data collection method. In other words, owing to this point that within questionnaires we asked about individuals' occupations instead of their definite chemical exposures, we could not identify desirable findings for the occupational exposures (this type of query inside questionnaires, however, was inevitable because of insufficient awareness of participants regarding their exact chemical exposures).

It could be concluded that opium might play an important role in the development of BC in our region considering its relatively prevalent use among Iranian addicts. Certain other factors concerning individuals' life styles, however, were involved in the pathogenesis of bladder TCC. In our study, the other surprising finding was the insignificant relationship between the occupational chemical exposures to BC in spite of completely different results in other parts of the world; though this finding might be attributable to the unclear exposures of different occupations to certain chemicals. Thus, more investigations for categorizing the occupations, and further classifications based on the exact chemical exposures, seem to be required.

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