Smoking and urinary bladder cancer: A case-control study in Basrah

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ABSTRACT

Background: The primary and well established risk factor for urinary bladder cancer is cigarette smoking.

Objective: The purpose of the present study was to evaluate the association between cigarette smoking and the development of urinary bladder cancer in Basrah.

Methods: A case control study was conducted to examine the association between the risk of urinary bladder cancer and various characteristics of smoking: the smoking status (current or ex-smoker), smoking intensity (cigarette per day), duration, total exposure (pack-years), type of cigarette (filtered or unfiltered), inhalation, and environmental tobacco smoke exposure. The study population composed of 87 patients with newly diagnosed bladder cancer cases and 357 controls. Cases and controls were matched for age, sex, and residence.

Results: An increased risk of urinary bladder cancer was found for both current and ex-smoker (for current smoker OR = 2.98; 95% CI = 1.68-5.28 and for ex-smoker OR = 4.05; 95% CI = 2.19-7.48). The study also revealed a significant positive trend in urinary bladder cancer risk with smoking intensity, pack-years, and environmental tobacco smoke.

Conclusion: The results of the present study are consistent with the findings of the previous epidemiological studies and confirm that smoking is a major risk factor for urinary bladder cancer and preventive strategies should be directed toward smoking as risk factor for urinary bladder cancer in Basrah.

Key word: Smoking, urinary bladder cancer

التدخين وسرطان المثانة: دراسة مقارنة بالعين الضابطة في محافظة البصرة

خلفية البحث: يعد التدخين من عوامل الخطورة الرئيسية والمعروفة لسرطان المثانة ، وكان هدف الدراسة الحالية هو لتقييم الاقتران بين التدخين والاصابة بسرطان المثانة في محافظة البصرة.

طرق العمل: تم اقامة دراسة مقارنة بالعينة الضابطة لفحص الاقتران بين خطورة الاصابة بسرطان المثانة ومختلف حالات التدخين (التدخين الحالي والتدخين السابق، شدة التدخين ،طول فترة التدخين ، التعرض الكلي للتدخين، نوع السكائر ، طريقة الاستنشاق والتدخين السلبي). شملت الدراسة 87 مريضا مشخصين حديثا كمصابين بسرطان المثانة و357 شخصا كعينة ضابطة متوافقة مع المرضى من خلال العمر والجنس ومحل الاقامة.

النتائج:وجدت الدراسة زيادة في خطورة الاصابة بسرطان المثانة لدى المدخنين الحاليين والسابقين (للمدخنين الحاليين OR = 2.98; 95% CI = 1.68–5.28 والمدخنين السابقين OR = 4.05; 95% CI = 2.19–7.48 كما اظهرت الدراسة علاقة معنوية ايجابية بين خطر الاصابة بسرطان المثانة وشدة التدخين والتعرض الكلي والتدخين السلبي.

الاستنتاجات:

كانت نتائج الدراسة الحالية متوافقة مع الدراسات الوبائية السابقة مؤكدة كون التدخين عامل خطورة رئيسي لسرطان المثانة وان الاجراءات الوقائية يجب ان توجه للأخذ بعين الاعتبار ان التدخين عامل خطورة مهم للإصابة بسرطان المثانة في محافظة البصرة.

INTRODUCTION

Urinary bladder cancer (UBC) is the most common cancer of the urinary system, and is ranked the ninth in worldwide cancer incidence. It is the seventh most common malignancy in men and seventeenth in women. The incidence rate was 20.2/100,000 for economically developed countries and 6.8/100,000 for economically developing countries.[1] Worldwide differences in exposure to risk factors were suggested to be largely responsible for the observed variability in occurrence. [2,3] Cigarette smoking is the most common and well established risk factor for

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UBC, contributing to an estimated 35 to 50% of UBC cases, causing about 50 to 65% of male cases and 20 to 30% of female cases.[4] The alleged carcinogenic constituents of tobacco smoke include arylamines, particularly the potent 4-aminobipheny[1], polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, heterocyclic amines and various epoxides.[5] Cordier and coworkers[6] reported that the relative risk of UBC appeared to vary according to dose, duration and type of tobacco smoked. People who exclusively smoke unfiltered cigarettes have a 30 to 70% higher risk than those who smoke only filtered cigarettes.[7] Inhalation of tobacco smoke moderately increases the risk compared with no inhalation.[8] A number of investigators have highlighted the importance of dose relationship between increasing number of cigarettes smoked per day and increasing risk of bladder cancer. [9,10] However, Brennan et al [11] reported a threshold between 15-20 cigarettes per day, and suggested that duration is the principle determinant in UBC risk with respect to smoking. They reported that 100% increment of increased risk of UBC for every ten years of smoking; from 100% increased risk after twenty years of smoking, to 500% increased risk after sixty years of smoking. A case control study was conducted to investigate and to gain more insight on the role of smoking as a risk factor associated with UBC in Basrah.

MATERIALS AND METHODS

The study is a case-control study: cases were newly diagnosed incident cases of UBC. Admitted to the urology ward in Basrah General Hospital during the period extending from 1st of October 2010 to the 31st of March 2012. All cases were histopathologically confirmed UBC patients, did not receive systemic chemotherapy or radiotherapy prior to enrollment. There were no recruitment restrictions based on age, gender, or cancer stage, however, cases included in the study were restricted to inhabitants of Basrah

governorate only. Eighty-seven cases fulfilling the criteria of inclusion in the study were included The controls were attendants of 9 selected primary health care centers in Basrah governorate (6 from the city center and 3 from Basrah districts). Controls were patients attending for any cause unrelated to the urinary tract and they were clinically free from UBC at the time of the study. Four controls matched for age, sex and residency were selected for each case. The first 4 attendants matching the case for age and sex were selected. A total of 357 controls were included in the study. Controls were enrolled during the period from the 1st of January 2011 to the 1st of March 2013. A detailed questionnaire, especially designed to obtain information about smoking history among patients and controls was used including: smoking status at inclusion (current smokers, ex-smokers and non-smokers). For current and ex-smokers; type of tobacco (cigarettes, cigars, pipe and water pipe); average number of cigarettes smoked per day; duration of smoking; age of starting; filtered or unfiltered cigarettes; inhalation of smoke or not; and for ex-smokers the time since quitting smoking. The data were analyzed in the computer by using SPSS "Statistical Package for Social Sciences program" version 17. Chi-squared test and logistic regression analysis were used to find out the significant differences and associations between different variables. A p-value of < 0.05 was considered to be significant. The basic model for logistic regression analysis included the following terms: exposure to generators, cigarette smoking, type of fat (saturated fat), history of Belhariziasis, history of urinary stones, red meat consumption, intake of non-steroidal anti-inflammatory drugs, education, risky occupations, fried foods consumption, fruits consumption, vegetables consumption, pesticides use, exposure to bombing, exposure to war remnants, family history of cancers, and participation in wars.

RESULTS

The distribution of bladder cancer patients and controls according to age, sex and place of residence is presented in (Table-1). The distribution of cases of UBC and controls according to smoking characteristics is presented in (Table-2). Cases of UBC showed a significantly higher percentage of current smokers (39.1%) and ex-smokers (32.2%) than controls (26.3% and 16% respectively; P < 0.001). In comparison to non-smokers, current smokers had about three times higher risk and ex-smokers had a four times higher risk of developing UBC (OR 2.98; 95% CI 1.68-5.28 and OR 4.05; 95% CI 2.19-7.48 respectively). The risk of UBC significantly increased with the increase in the number of cigarettes smoked per day and pack-years of smoking; P < 0.001. On the other hand, although the association between duration of smoking and the risk of UBC was statistically significant (P < 0.001), the risk of UBC as measured by odds ratio decreased with the increase in the duration of cigarette smoking; (Table-2).

Table 1. Distribution of urinary bladder cancer cases and controls according to age, sex and residency

Variable	Cases		Controls	
	No.	*%*	*No.*	*%*
Age(years)				
<30	2	2.3	8	2.2
30-39	2	2.3	8	2.2
40-49	7	8.0	28	7.8
50-59	20	23.1	86	24.2
60-69	27	31.0	107	30.0
70-79	24	27.6	100	28.0
≥80	5	5.7	20	5.6
X^2= 0.075	df= 6		P = 1	
Sex				
Males	74	85.1	301	84.3
Females	13	14.9	56	15.7
X^2= 0.029	df= 1		P = 0.864	
Residency(in Basrah)				
City center	29	33.4	120	33.6
South	7	8.0	29	8.2
East	1	1.1	4	1.1
West	26	29.9	104	29.1
North	24	27.6	100	28.0
X^2= 0.021	df= 4		P = 1	
Total	87	100%	357	100%

Table 2. Distribution of urinary bladder cancer cases and controls according smoking status

Variable	Cases		Controls		Odd ratio	95% confidence interval
	No.	*%*	*No.*	*%*		
Smoking status						
Current	34	39.1	94	26.3	2.98	1.68 - 5.28
Ex-smoker	28	32.2	57	16.0	4.05	2.19 - 7.48
Non smoker	25	28.7	206	57.7	1*	
X^2= 24.84			**df= 2**			**P<0.001**
Number of cigarettes/day						
≤10	5	5.8	15	4.2	2.75	0.92 - 8.2
11-20	22	25.3	72	20.2	2.52	1.34 - 4.74
21-40	25	28.7	48	13.4	4.29	2.27 - 8.12
> 40	10	11.5	16	4.5	5.15	2.11 - 12.57
Non smoker	25	28.7	206	57.7	1*	
X^2= 28.34			**df = 4**			**P < 0.001**
Duration (years)						
≤10	5	5.7	11	3.1	3.75	1.20 - 11.66
11-20	9	10.3	21	5.9	3.53	1.64 - 8.55
> 20	48	55.3	119	33.3	3.32	1.95 - 5.67
Non smoker	25	28.7	206	57.7	1*	
X^2= 23.59			**df = 3**			**P < 0.001**
Pack-years						
<40	20	23.0	81	22.7	2.01	1.07 - 3.86
40-79	21	24.1	44	12.3	3.93	2.02 - 7.65
≥ 80	21	24.1	26	7.3	6.65	3.27 - 13.53
Non smoker	25	28.8	206	57.7	1*	
X^2= 36.73			**df = 3**			**P < 0.001**
Total	87	100	357	100		

1*= reference group

Furthermore, type of cigarettes smoked and smoke inhalation pattern significantly affected the risk of UBC among smokers; the risk of UBC among smokers using filtered cigarettes was nearly three times that of non-smokers (OR=2.91; 95% CI=1.56-5.43), this increased to about four times for those using both filtered and unfiltered cigarettes (OR=3.77; 95% CI=2.14-6.64); (Table-3). While contrary to expectation, smoke inhalers showed a lower risk of UBC than non-inhalers; (Table-3).

Finally, exposure to passive smoking was found to be significantly associated with an increase in the risk of UBC (P < 0.001), the risk increased with the increase in the number of smokers among family members; (Table-4).

Table 3. Distribution of urinary bladder cancer cases and controls according to inhalation pattern and type of cigarettes

Variable	Cases		Controls		Odd ratio	95% confidence interval
	No.	%	No.	%		
Type of cigarettes						
Filtered	24	27.6	68	19.0	2.91	1.56 - 5.43
Mixed	38	43.7	83	23.3	3.77	2.14 - 6.64
Non smoker	25	28.7	206	57.7	1*	
X^2= 24.46	df = 2			P < 0.001		
Smoke inhalation						
Yes	55	63.2	144	40.3	3.15	1.87 - 5.29
No	7	8.1	7	2.0	8.24	2.67 - 25.43
Non smoker	25	28.7	206	57.7	1*	
X^2= 27	df = 2			P < 0.001		
Total	87	100	357	100		

1= reference group*

Table 4. Distribution of urinary bladder cancer cases and controls according exposure to passive smoking

Variable	Cases		Controls		Odd ratio	95% confidence interval
	No.	%	No.	%		
Exposure to passive smoking						
Yes	32	36.8	64	17.9	2.66	1.60 - 4.45
No	55	63.2	293	82.1	1*	
X^2= 14.67	df= 1			P < 0.001		
Number of smokers						
0	55	63.2	293	82.1	1*	
1	19	21.8	51	14.3	1.99	1.09 - 3.62
≥ 2	13	15.0	13	3.6	5.33	2.34 - 12.12
X^2= 20.96	df= 2			P < 0.001		
Total	87	100	357	100		

1= reference group*

When logistic regression analysis was carried out, a strong independent association was found between smoking and bladder cancer (Adjusted odd ratio 3.710; 95% CI of odd ratio (1.184-11.619).

DISCUSSION

The results of the present study confirms the strong independent association between smoking and bladder cancer, a positive trend was observed in the risk of UBC among former and current smokers as compared to non-smokers. These findings are consistent with the results of several case control and cohort studies.[12-14] A pooled analysis of results from case control studies indicated an approximately 3.5 folds elevated risk among ever smokers as compared to never smokers in both men and women. [12] While two cohort studies indicated a twofold or greater risk of UBC among current smokers as compared with never smokers. The risk in former smokers was intermediate between the risks of current and never smokers.[13,14] In the present study, the risk of UBC among former smokers was higher than that among current smokers, may be due to differences in intensity and duration of smoking between the two groups. In addition, the results of the present study revealed statistically significant dose response relationship in risk of UBC for smoking intensity and pack-years but not for duration of smoking. This finding is consistent with previous studies which also revealed such relationship.[11,15,16] However, although the risk of UBC have been reported by numerous studies to be increased with increasing duration and intensity of smoking, the risk levels off at higher intensity but not at high duration.[17,18] In addition, other studies reported that there was a little change in risk from moderate to heavy smoking levels.[16, 19] This finding was attributed to different inhalation patterns associated with smoking intensity.[18] Heavy smokers may inhale proportionately less than light smokers causing leveling off of exposure and the relative impact of an additional cigarette would be expected to decline at higher intensity; this may explain the negative association between smoke inhalation and the risk of UBC which was found in the present study. Alternative explanation is that

variation in the genetic factor that affects carcinogen activation, detoxification, or saturation of key metabolic activation process occurs at high levels of tobacco smoking exposure.[17] The inhalation pattern had no influence on the smoking related risk of UBC in some studies, while other studies reported that smokers who inhaled deeply may have a greater risk than those who did not. [8, 20] In fact the effect of inhalation of cigarette smoke as risk factor for UBC is difficult to assess due to differences in ascertainment and subjective assessment of inhalation.[15] Furthermore, exposure to environmental tobacco smoke, also known as secondhand cigarette smoke or passive smoke has been shown to increase the risk of UBC. [8,21-23] As with active cigarette smoke, environmental tobacco smoke contains arylamines, which are established bladder carcinogens. The dose of exposure to carcinogens from environmental tobacco smoke is less than that from active cigarette smoking, however, such low dose of carcinogens has been found to make a large contribution to bladder carcinogenesis.[24] The association between environmental tobacco smoke and UBC is further strengthened by the fact that the urine of environmental tobacco smokers contains invariable quantities, of cigarette smoke carcinogens, which indicated that carcinogens from environmental tobacco smoke come into direct contact with urinary bladder.[25] The results of the present study showed that the risk of UBC was positively associated with environmental tobacco smoke and also the risk increased when number of smokers among family members increased. This finding is similar to those reported by several other studies [8, 21-23], but other studies reported controversial results. [15, 26, 27]

In conclusion, the results of the present study provide confirmation that cigarette smoking is a strong risk factor for UBC. A significant trend in risk was observed among former and current

smoker. Also the dose response relationship was more prominent for smoking intensity and pack-years than for duration. In addition to that environmental tobacco smoke was significantly associated with increased UBC risk.

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