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Research Article

Association between smoking and urinary bladder cancer (BC): case-control study in Minia, Egypt

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Abstract

Background: Bladder cancer (BC) accounts for an estimated 500 000 new cases and 200 000 deaths worldwide each year in 2019. **Aim:** To find out the most revealing risk factors and BC development and to determine the relation between smoking and development of BC in patients attending Minia Oncology centre and compare them with their control. **Methods:** Study included 100 BC patients attending Minia oncology centre and 100 control subjects matched by age and sex. Subjects participating in the study filled in a questionnaire including questions about socio-demographic data, medical history and dietary and lifestyle factors. **Results:** Our results showed that studied BC cases had higher smoking index with mean of 7.77±3.76 compared to controls 3.08±1.88 (P <**0.001**). Mean duration of years since quitting smoking was significantly higher in studied controls than in BC cases with mean of 12.8±2.9 and 9.1±2.1 respectively. Smoking index was a risk factor for BC with (OR= 1.29). The most predictable risk factors for BC were recurrent urinary tract infections (OR=7.6), followed by BC family history (OR=6.1), urinary stones history (OR =5.04), schistosomal infection history (OR =4.92), wait long hours to use toilet (OR =2.25), drink coffee (OR =1.32), smoking index (OR= 1.29) and soft drinks (OR=1.08). **Conclusion:** BC is a common malignancy. Recurrent urinary tract infections, BC family history, urinary stones history, schistosomal infection history, wait long hours to use toilet, drink coffee, smoking index and soft drinks were related to BC risk.

Keywords: BC, Minia, Egypt

Introduction

Bladder cancer accounts for an estimated 500 000 new cases and 200 000 deaths worldwide. In the United States, bladder cancer is the sixth most common cancer with more than 80000 new cases and 17000 deaths each year in 2019[(1)]. The high incidence and prevalence of cancer of urinary bladder are seen in the sixth decade of life, especially its peak in the seventh and eighth. So is it mainly disease of elderly. Several studies found that median age at diagnosis for urinary bladder cancer, was 60 (range: 40-80 years[(2)].

According to WHO cancer country profiles, 2014 reports of Egypt, it was reported that bladder cancer incidence in men came in the second rank after liver cancer incidence and responsible for 8.6% deaths of total men cancer deaths and came in eighth rank according to most common cancer sites in female[(3)]. As reported by Minia cancer registry 2009, Transitional cell carcinoma was the most predominant histological type, constituting 66.4%, followed by squamous cell carcinoma (26.4%) and Adenocarcinoma (4.8%) and undifferentiated carcinoma (3.1%)[(4)]

Tobacco smoking has been widely acknowledged to be the most important risk factor for bladder cancer accounting for approximately 50–65% of new cases each year. Smoking has been shown to increase the risk of bladder cancer by three to four times [(5)]. Tobacco smoke contains known carcinogens such as beta-naphthylamine and polycyclic aromatic hydrocarbons and these particles promote inflammation, and their metabolism, in the bladder and throughout the body and permanent genetic mutation. Such mutations can activate oncogenes or suppress tumor suppressor genes, promoting carcinogenesis [(6)]

Previous studies indicate that the population attributable risk of bladder cancer for tobacco smoking is 50% to 65% in men and 20% to 30% in women and that current cigarette smoking triples bladder cancer risk relative to never smoking [(7)]. Because men smoke more than women, the percentage of cases attributable to smoking is higher in males than in females: 42.8% (males) versus 25.7% (females) in Europe, and 34.3% (males) versus 30.1% (females) in the United States [(8)]

Some studies reported that the relative risk of urinary bladder cancer appeared to vary according to dose, duration and type of tobacco smoked as it was found in previous studies that people who exclusively smoke unfiltered cigarettes had a 30 to 70% higher risk than those who smoke only filtered cigarettes[(9)]. 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 but other studies suggested that duration of smoking is the principle determinant in bladder cancer risk **(10)**

The older age of onset of bladder cancer suggests a latency period of approximately 30 years from the initiation of smoking to the cancer diagnosis and it was found that smoking cessation had been shown to reduce the risk of bladder cancer by approximately 40% within only 1–4 years, and complete return to baseline risk by 20 years [(11)]

Aim of the study:

1-To find out the most revealing risk factors and BC development among BC cases attending Minia oncology center comparing them with their controls.

2-To determine the relation between smoking and development of BC

Subjects and Methods

Study Design: Case Control Study

Administrative and ethical consideration: An approval was obtained from a manager of Minia oncology center to attain data about number of BC patients attending the centre and to facilitate data collection through a questionnaire.. A verbal consent had been taken from each subject after explanation of the objectives of the study.

Study Population

-Selection of cases:

Inclusion criteria –. Primary BC patients receiving treatment (ie, surgery, chemotherapy, radiotherapy, or combination of these therapies) in Minia oncology center during period from December 2018 to February 2020.

Exclusion criteria – Patients with a primary cancer rather than BC, severely ill patients and cases who refuse interview.

- Selection of control:

- Criteria of inclusion: Age and sex matched with cases and community based during the period between July 2019 to February 2020

- Criteria of exclusion: Individuals who are relatives for cases and diagnosed as BC before Collection of data: Data were collected through a questionnaire about socio-demographic characteristics, medical data (presentation); and life style factors concerning smoking included type and duration of smoking, smoking index, i.e. total number of cigarettes per day multiplied by the duration of smoking, passive smoking, quitting smoking , years since quitting smoking and dietary history.

Statistical methods:

The analysis of the data was carried out using the IBM SPSS 28.0 statistical package software. Student *t*-test was used for comparison between two independent groups for parametric data, and analysis of variance (ANOVA) was used to compare

more than two means followed by post-hoc test to assess intergroup differences. The *Chi square test or Fisher's exact test* were used to compare categorical variables. A binary and multinomial logistic regression model was used to evaluate the predictive value of the different variable. A p-value less than 0.05 was considered significant

Results

Age of studied subjects ranged between 53-83 years in both cases and controls. 77% of cases were males and 23% were females and matched with controls (table 1)

56% of studied BC patients versus 31% of controls were current smokers and 42% of controls versus 35 % of BC cases were non smokers and this difference was statistically significant (P **<0.001**). Studied BC cases had higher smoking index with mean of 7.77±3.76 compared to controls 3.08±1.88 (P **<0.001**). Mean duration of smoking years was higher in BC cases with mean of 17.6±5 than in controls 13±3.3 and this difference was statistically significant (P **<0.001**). It was found that exposure to second smoke was positive in (84.1%) in BC cases versus controls (40.6%) with (P **<0.001**). Mean duration of years since quitting smoking was significantly higher in studied controls than in BC cases with mean of 12.8±2.9 and 9.1±2.1 respectively (Table 2).

Smoking index mean for 3 groups (Transitional cell carcinoma (TCC), Squamous cell carcinoma (SCC) and controls) was 4.28± 4.41, 5.05±5.24 and 1.63±2.06 respectively and this was statistically significant difference. It was found that mean number of cigarettes /day was significantly higher among TCC and SCC groups compared to controls with P **<0.001**. Mean number of smoking years was higher among TCC and SCC groups (16.8± 4.7 and 18.5±6.1 respectively) than among controls (13±3.3) and this difference was statistically significant. As regard mean number of years since quitting smoking, it was found that it was significantly higher among controls than TCC and SCC groups (12.8±2.9, 7.5± 2.1 and 10.4±1.1 respectively) with P=0.002. 82.1%, 84.6% and 40.6% among TCC, SCC groups and controls respectively had positive history of second smoke exposure and this was significantly difference (Table 3).

Most predictable risk factors for bladder cancer were recurrent urinary tract infections (Adjusted OR=7.6), followed by BC family history (Adjusted OR=6.1), urinary stones history (Adjusted OR =5.04), schistosomal infection history (Adjusted OR =4.92), wait long hours to use toilet (Adjusted OR =2.25), drink coffee (Adjusted OR =1.32), smoking index (Adjusted OR= 1.29) and soft drinks (Adjusted OR=1.08) (Table 4).

Table (1): BC cases and controls according to their socio demographic characters, Minia governorate, December 2018 to February 2020:

Variable		BC cases (100) N (%)	Control (100) N (%)	p value
Age	**(Range)**	53-83	53-83	0.347
	Mean±SD	70.8±8	69.7±8	
Sex	**Male**	77 (77%)	77 (77%)	<0.99
	Female	23 (23%)	23 (23%)	
Residence	**Rural**	45 (45%)	45 (45%)	>0.99
	Urban	55 (55%)	55 (55%)	
Occupation	**Professional**	31 (31%)	29 (29%)	0.208
	Clerk	28 (28%)	41 (41%)	
	Manual	26 (26%)	21 (21%)	
	Unemployed	15 (15%)	9 (9%)	

SD= standard deviation

Table (2): smoking and bladder cancer among cases and controls, Minia governorate, December 2018 to February 2020:

Variable		BC cases N (%)	Control N (%)	p value
Smoking status	**Current smoker**	56 (56%)	31 (31%)	<0.001*
	EX- smoker	9 (9%)	27 (27%)	
	Non smoker	35 (35%)	42 (42%)	
		N=100	N=100	
Smoking index	**Range**	0.55-17.50	0.45-8.55	<0.001*
	Mean±SD	7.77±3.76	3.08±1.88	
		N=65	N=58	
Smoking type	**Cigarettes**	52 (80%)	51 (87.9%)	0.123
	Shisha	4 (6.2%)	5 (8.6%)	
	Both	9 (13.8%)	2 (3.4%)	
Smoking years	**Range**	9-28	2-22	<0.001*
	Mean±SD	17.6±5	13±3.3	
		N=65	N=58	
Second smoke	**Exposed**	37 (84.1%)	28 (40.6%)	<0.001*
	Not exposed	7 (15.9%)	41 (59.4%)	
		N=44	N=69	
Years since quitting smoking	**Range**	5-12	7-19	0.002*
	Mean±SD	9.1±2.1	12.8±2.9	
		N=9	N=27	

***** *statistically significant*

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation

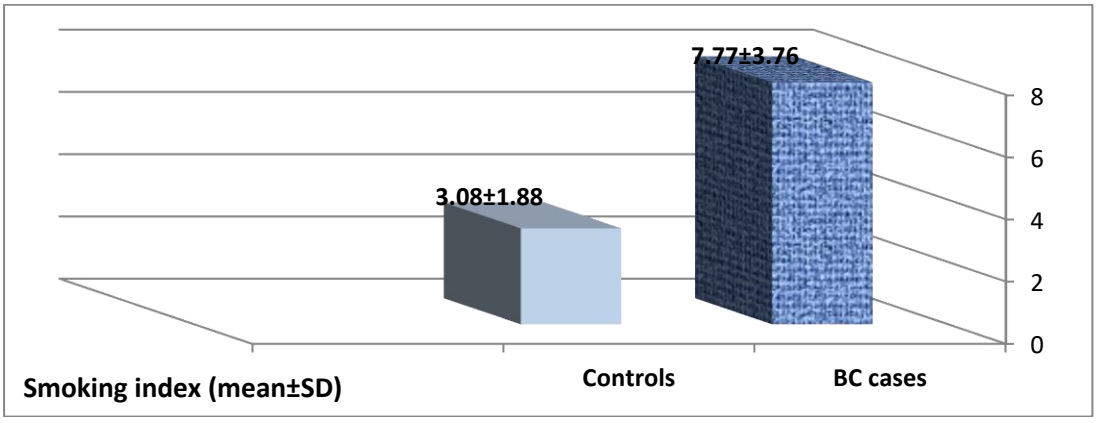

Figure (1): Smoking index among studied subjects, El-Minia governorate, December 2018 to February 2020:

This figure showed that studied BC cases had higher smoking index with mean of 7.77±3.76 compared to controls 3.08±1.88 and this is statistically significant (P=**<0.001**)

Table (3): Comparison between different histopathological types of studied BC cases and controls regarding their smoking history, El-Minia governorate, December 2018 to February 2020:

Variable		TCC (1) N=69	SCC (2) N=31	Control (3) N=100	p value
Smoking index	Mean±SD	4.28± 4.41	5.05±5.24	1.63±2.06	**<0.001***
	(Range)	0-14.3	0-14.85	0-8.55	**1vs2 >0.99** **1vs3 <0.001*** **2vs3 <0.001***
Smoking type	Cigarettes	34 (75.6%)	11 (84.6%)	51 (87.9%)	
	Shisha	3 (6.7%)	1 (7.7%)	5 (8.6%)	**0.1**
	Both	8 (17.8%)	1 (7.7%)	2 (3.4%)	
Number of cigarettes/ day	Mean±SD	8.4±3.3	9.7±2.6	4.9±2.7	**<0.001*** **1vs2 0.5** **1vs3 <0.001***
	Range	1-15	4-15	1-10	**2vs3 <0.001***
Smoking years	Mean±SD	16.8± 4.7	18.5±6.1	13±3.3	**<0.001*** **1vs2 0.6**
	Range	(9-27)	(10-28)	(2-22)	**1vs3 <0.001*** **2vs3 <0.001***
Second smoke	Exposed	23 (82.1%)	11 (84.6%)	28 (40.6%)	**<0.001*** **1vs2 0.8**
	Not exposed	5 (17.9%)	2 (15.4%)	41 (59.4%)	**1vs3 <0.001*** **2vs3 0.004***
Number of years since quitting	Mean±SD	7.5± 2.1	10.4±1.1	12.8±2.9	**0.002*** **1vs2 0.3**
	Range	(5-10)	(9-12)	(7-19)	**1vs3 0.003*** **2vs3 0.2**

***** *statistically significant*

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation

TCC (Transitional cell carcinoma)

SCC (Squamous cell carcinoma)

Table (4): Association of selected factors with BC, Minia governorate, December 2018 to February 2020:

Variable	crude OR	95% CI	P value	adjusted OR	95% CI	p value
Recurrent UTI history	7.21	3.61-15.13	<0.001*	7.63	3.72-15.67	<0.001*
Family history of BC	5.88	3.18-10.89	<0.001*	6.1	2.05-18.14	0.001*
Urinary stones history	5.04	2.6-9.79	<0.001*	5.04	1.67-15.25	0.004*
Schistosomal infection history	5.02	2.5-15.19	0.004*	4.92	1.59-15.19	0.006*
Wait long hours to use toilet	2.25	1.66-3.97	<0.001*	2.25	1.28-3.97	0.005*
History of repeated urinary catheter	1.92	0.83-5.21	0.1	1.99	0.76-5.21	0.1
Coffee	1.28	1.13-1.44	<0.001*	1.32	1.05-1.67	0.02*
Processed meat	1.36	1.17-1.59	<0.001*	1.31	1-1.71	0.05
Smoking index	1.27	1.16-1.4	<0.001*	1.29	1.11-1.51	0.001*
Red meat	1.1	0.79-1.9	0.5	1.1	0.71-1.7	0.6
Soft drinks	1.06	1.18-1.31	<0.001*	1.08	1.02-1.14	0.006*
Tea	0.88	0.83-0.94	<0.001*	0.88	0.79-0.98	0.015*
Vegetables	0.88	0.89-0.99	<0.001*	0.88	0.82-0.94	<0.001*
Yogurt	0.76	0.67-0.85	<0.001*	0.87	0.75-1.01	0.07
Milk	0.73	0.63-0.85	<0.001*	0.82	0.69-0.98	0.027*
Number of water cups/day	0.64	0.56-0.74	<0.001*	0.78	0.63-0.96	0.017*
Fruits	0.66	0.57-0.77	<0.001*	0.77	0.63-0.95	0.013*

c OR: crude odds ratio; a OR: adjusted odds ratio ;CI: confidence interval
p value < 0.05 was considered statistically significant
R^2=0.572

Discussion

The age of studied subjects ranged between 53-83 years in both cases and controls. 77% of cases were males and 23% were females and matched with controls. About 55% of BC patients were from urban areas and 31%were professionals. The majority (69%) of histopathology of BC studied cases was transitional cell carcinoma while 21% was squamous cell carcinoma. Majority of studied cases (54%) presented with painless hematuria. The mean age of studied TCC BC cases was 70.3± 8.3, SCC BC cases was72.7±5.9 and among controls was 69.7±8 but this difference was statistically non-significant. Males constitute 55% of TCC cases, 15% of SCC cases and 77% among controls but not significantly different. There was no association between sociodemographic data and bladder cancer.

In contrary to our results, the study reported that among the confirmed cases, there were 689 SCC (35%), 1,197 TCC (60%), and 102 other type of primary bladder cancer cases (5%). Among cases, the ratio of women to men was 1:6, 1:3, and 1:5 for TCC, SCC, and all cases, respectively. The mean ages for SCC were significantly younger than that for TCC ($P < 0.01$) [12]

However, in the study of Kyritsi et al., they included 2,523 cases and confirmed 2,325 to be primary bladder cancer. There were 1,402 TCC (60.3%), 784 SCC (33.7%), 77 adenocarcinomas (3.3%), and 62 (2.7%) cases of other types of primary bladder cancer. The mean age at diagnosis of bladder cancer was higher for men than that for women (57.2 years versus 53.4 years, p value < 0.0001; 61.2 years versus 59.2 years, p value 0.01) for SCC and TCC, respectively [13].

Also, Krimphove study stated that with an average age of 73 years at diagnosis, bladder cancer exhibits four times higher incidence in males compared to females. Female patients with non-muscle invasive bladder cancer (NMIBC) generally present late with more advanced tumor stages than males, and often suffer early recurrences [14].

One explanation for the differential behavior of TCC between genders has related to sex steroids and their receptors. An epidemiological study showed that postmenopausal women have a greater risk of developing TCC than premenopausal women. Animal studies showed that the incidence of spontaneous and chemically induced TCC is significantly greater in male than in female rats, and treatment of male rats with androgen deprivation reduce the development of chemically induced TCC. In humans, the androgen receptor (AR) has been detected in normal bladder epithelium and in bladder tumours from men and women. Only a few authors found no AR expression in the rat and human urinary bladder. Moreover, experiments using AR antagonists, small interfering RNA against the AR, and androgen deprivation suggested the importance of the AR signalling pathway in the development and progre-ssion of TCC. However, mechanisms that regulate the activity of the AR in TCC cells remain unknown. Moreover, the prognostic significance of AR expression in human TCC needs further investigation [15]

Smoking is a well-known risk factor of chronic lung disease, heart disease and various types of cancer including bladder cancer [12]

The current study showed that 56% of studied BC patients versus 31% of controls were current smokers and 42% of controls versus 35% of BC cases were non smokers and this difference was statistically significant (P=<0.001). Studied BC cases had higher smoking index with mean of 7.77±3.76 compared to controls 3.08±1.88 (P=<0.001). As regard number of cigarettes per day, it was significantly higher in BC cases compared to controls with mean of 8.8±3.2 and 4.9±2.7 respectively. Mean duration of smoking years was higher in BC cases with mean of 17.6±5 than in controls 13±3.3 and this difference was statistically significant (P=<0.001). It was found that exposure to second smoke was positive in (84.1%) in BC cases versus controls (40.6%) with (P=<0.001). Mean duration of years since quitting smoking was significantly higher in studied controls than in BC cases with mean of 12.8±2.9 and 9.1±2.1 respectively.

Smoking is the most important risk factor for BC with an attributable risk of approximately 50%. Tobacco is a rich source of known carcinogenic compounds such as aromatic amines and N-nitroso compounds. These compounds result in DNA damage in the form of double-stranded breaks, base modifications, and bulky adduct formation. Such genomic events are implicated in gene-smoking interactions [16, 21] .

The strongest support for the association of tobacco use and BC is a meta-analysis of 83 studies conducted by Cumberbatch et al, in which the pooled relative risk (RR) for current versus never smokers was 3.47 (95% confidence interval [CI] 3.07–3.91) and for ex-smokers 2.04 (95% CI 1.85–2.25). The lower rate for former smokers suggests that smoking cessation may reduce the risk for BC development. The meta-analysis also found that disease-specific mortality (DSM) is greater in current smokers versus ex-smokers. Limitations cited by the authors of the meta-analysis were the heterogeneity with which smoking histories were obtained and the cut points used for stratifying smoking intensities and durations. This is important, as there is

strong evidence that smoking duration and intensity are positively correlated with an increased risk of BC [17,18]

In the study of Zheng et al., among men, the prevalence of cigarettes smoking was 77% for TCC cases, 69% for SCC cases, and 65% for controls. Those who reported ever smoking cigarettes had a significant association with increased risk of TCC, with an adjusted OR of 1.8 [95% confidence interval (CI), 1.4–2.2]. This behavior was not significantly associated with an increased risk of SCC. Importantly, smokers who smoked both cigarettes and water pipe had a significantly elevated risk of both TCC and SCC, with an OR of 2.9 (2.1–3.9) and 1.8 (1.2–2.6) for TCC and SCC, respectively. Among the cigarette smokers, current smokers had significantly elevated risk of TCC, with an OR of 2.0 (95% CI, 1.6–2.5) [12].

Significant dose–response relationships between the number of cigarettes smoked per day and risk of TCC ($P < 0.01$), between years smoked and risk of TCC ($P< 0.01$), and between pack-years and risk of TCC ($P< 0.01$) were observed in study of Zheng et al. Among the current smokers, heavy smokers who smoked >2 packs per day had a much higher risk of TCC (OR = 4.4; 95% CI, 2.5–7.7) than never smokers. Among former cigarette smokers, no significant dose–response relationships between the risk of TCC and number of cigarettes smoked per day, duration of smoking, or pack-years were observed. They observed a statistically significant trend between years of quitting and a decreased risk of TCC among former smokers, 1–5 years quitting (OR = 2.3; 95% CI, 1.5–3.5), 5–10 years quitting (OR = 1.2; 95% CI, 0.7–1.9), 10–20 years quitting (OR = 1.8; 95% CI, 1.2–2.7), ≥20 years quitting (OR = 1.3; 95% CI, 0.8–2.0; P = 0.04, where never smokers were the reference) [12].

The older age of onset of bladder cancer suggests a latency period of approximately 30 years from the initiation of smoking to the cancer diagnosis. However, smoking cessation has been shown to reduce the risk of bladder cancer by approximately 40% within only 1–4 years, and complete return to baseline risk by 20 years, suggesting a non-linear relationship between incidence and pack-years [19]**.** A meta-analysis of 14 studies by Yan et al showed that there was 22% increased risk of bladder cancer for lifetime secondhand smoking exposure in nonsmoking patients compared with unexposed nonsmoking population [8, 20, 21]

Conclusion

BC is a common malignancy. Recurrent urinary tract infections, BC family history, urinary stones history, schistosomal infection history, wait long hours to use toilet, drink coffee, smoking index and soft drinks were related to BC risk but eating fruits, drink high number of water cups/day, drink milk, eating vegetables and drink tea were protective factors against BC development.

Recommendations:

1) There is a need to increase community awareness about BC through health education message that should be provided about its risk factors, its serious consequences' and methods of BC prevention by educational programs applied to all people in the form of mass media campaigns and public lectures.
2) Giving importance to smoking cessation program, its benefits and how it contribute to bladder cancer prevention and other diseases.
3) Increase awareness about importance of rapid treatment of urinary tract infections and stones and avoid neglecting these diseases as they are common and contribute to BC risk.
4) Detection of high risk groups and regular counseling especially those with BC family history and giving importance for conducting regular urine test as screening tests for early detection of microhematuria.
5) Develop programs for nutrition education and should be integrated though the health promotion and preventive activities of school program.

Conflict of interest:

The authors declare no conflict of interest.

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