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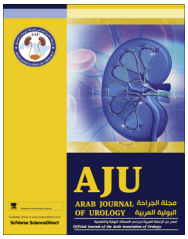

ONCOLOGY/RECONSTRUCTION

ORIGINAL ARTICLE

Evaluation of grade and stage in patients with bladder cancer among smokers and non-smokers

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KEYWORDS

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Abstract ***Objectives:*** To evaluate the role of smoking as a risk factor for higher stages and grades of bladder cancer, for although smoking is considered to be one of the most important risk factors for bladder cancer, its relationship to grade and stage is not clear.

Patients and methods: In all, 300 patients diagnosed with bladder cancer were studied to compare the grade and stage and bladder cancer between non-smokers, low-dose, moderate-dose and high-dose smokers.

Results: The smokers and non-smokers had no significant difference in tumour grade or stage ($P = 0.702$ for grade and 0.166 for stage) but the high-dose group had significantly higher grades and stages than the other groups ($P = 0.026$, odds ratio 4.8, 95% confidence interval 1.2–19.1 for grade, and 0.037, 10.91 and 1.16–102.6, respectively, for stage).

Conclusion: Smoking has a potential dose-dependent effect on the grade and stage of bladder cancer, with high-dose smokers having more aggressive disease. The equality in the aggressiveness of the cancer between smokers in general and non-smokers might be a result of the hazardous effect of passive smoking in countries where smoking is a common habit.

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Introduction

TCC of the bladder is one of the most common urological malignancies worldwide. Bladder cancer is an increasingly common disease, and is estimated to be-

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come more prevalent as the population ages. There is a strong association between cigarette smoking and bladder cancer. While specific industrial chemicals have been linked to the development of this disease, 60% of bladder cancers are estimated to result from smoking [1]. Therefore cigarette smoking is the most important risk factor for the development of TCC of the urinary bladder [2].

Experimental evidence suggests that nitrosamines, 2-naphthylamine and 4-aminobiphenyl might be the bladder carcinogens in cigarette smoke [3]. These amines cause oxidative DNA damage in the normal urothelium and induce bladder cancer [4].

The association between bladder cancer and smoking has been studied and evaluated from different aspects, especially in relation to gender [5–7], intensity and duration of smoking [8,9], ceasing smoking [8], environmental tobacco smoking [6,9], and cigarettes vs. other types of smoking [6,10].

It is not clear whether smoking contributes to the development of higher grades and stages of bladder cancer. Studies assessing this issue are few and have given conflicting results. In the present study we tried to evaluate the role of smoking, as a separate risk factor, in higher stages and grades of bladder cancer.

Patients and methods

We reviewed the records of the last 300 patients in our hospital who had undergone transurethral resection of a bladder tumour and were diagnosed with bladder cancer. We documented their cigarette smoking habit, and patients were categorised into two groups accordingly, i.e. smokers (defined as smoking of $\geqslant$10 cigarettes/day for the last 3 years), and non-smokers, who had no previous history of cigarette smoking. The first group was subdivided arbitrarily into three groups, i.e. low-, moderate- and high- dose smokers, defined as smoking 10–29, 30–59 and $\geqslant$60 cigarettes/day, respectively. We then compared the stage and grade of cancer among these groups. Grade 1 tumours were considered as low-grade and if grade $\geqslant$2 as high-grade; for stage, tumours of $\leqslant$T1 were considered as low-stage and $\geqslant$T2 as high-stage tumours.

The statistical analysis included descriptive statistics and logistic regression to calculate the odds ratio and 95% CI, with $P < 0.05$ considered to indicate significance.

Results

The mean (range) age of the patients was 47 (30–80) years; 285 were men (95%) and 15 were women (5%). Of the 300 patients, 240 (80%) were smokers and 60 (20%) were non-smokers. The female to male ratio in the smoker group was 1:39 (6/234 patients). In the smoker group, only 21 patients (8.7%) were low-dose smokers, with 202 (84.1%) moderate-dose and 17 (7.1%) high-dose smokers.

The smokers and non-smokers had no significant difference in mean age and tumour grade or stage ($P = 0.702$ for grade and 0.166 for stage; Table 1).

Comparing the high-, moderate- and low-dose smokers, the high-dose group had significantly higher grades and stages than the other groups (Table 1). The difference between moderate- and low-dose smokers was not significant for grade or stage (Table 1).

Discussion

Tobacco smoking is the main known cause of TCC in humans. In most populations, over half of cases in men and an important proportion in women are attributable to this habit. Epidemiological studies conducted in different populations have shown a linear relationship between the intensity and duration of smoking and the risk of developing a bladder cancer [6].

The management of bladder cancer is governed by specific guidelines, and the stage and grade of cancer are the most important factors influencing these guidelines. As the grade and stage of bladder cancer are the most important prognostic factors, any link between other variables (e.g. gender, tumour volume and tumour multiplicity) and these two factors should also be addressed.

The link between smoking and grade or stage, as a sole risk factor, has not been examined in sufficient detail. Mohseni et al. [11] found that smoking was not only the most important risk factor for TCC of the urinary bladder, but was also associated with higher grades of the tumour. Also, Marsit et al. [12] reported that smoking not only induced bladder cancer, but also, once developed, it could increase the grade of the tumour,

Table A comparison of smokers and non-smokers, and intensity of smoking, for tumour grade and stage. G1 tumours are considered low-grade, and $\geqslant$G2 as high-grade. Ta and T1 tumours are considered low-stage, and $\geqslant$T2 as high-stage.

Group (*n*)	Grade, *n* (%)		Stage, *n* (%)	
	High	Low	High	Low
Smokers (240)	70 (29)	170 (71)	65 (19)	175 (81)
Non-smokers (60)	16 (26)	44 (74)	11 (17)	49 (83)
P	0.702		0.166	
Odds ratio	1.132		1.655	
95% CI	0.599–2.14		0.811–3.38	
Dose				
High (17)	12 (71)	5 (29)	6 (35)	11 (65)
Moderate (202)	51 (25)	151 (75)	12 (6)	190 (94)
Low (21)	7 (33)	14 (67)	1 (5)	20 (95)
P	0.026		0.037	
Odds ratio	4.8		10.91	
95% CI	1.2–19.1		1.16–102.6	

resulting in a worse prognosis. In these two studies the relationship of smoking with tumour stage was not discussed. Thompson et al. [13] reviewed the records of 386 patients diagnosed with TCC of the bladder, to determine any correlation between smoking history and stage, grade and number of recurrences of TCC. There was a significant association between the smoking history and all three variables.

Fleshner et al. [14] conducted a retrospective cohort study to assess the influence of tobacco exposure, at the time of diagnosis, on the disease-related outcomes of superficial TCC. They tried to define the relationship of various smoking habits with the disease recurrence rate and TCC-related adverse events. They found that there were no significant differences among ex-smokers, those who had smoked, and continuing smokers in terms of stage, grade, tumour size, multifocality, immediate BCG therapy, or the median duration of the follow-up.

Using data from 1860 patients with bladder cancer and 3934 population-based controls from the National Bladder Cancer Study, Sturgeon et al. [15] examined the relationship between suspected bladder cancer risk factors and tumour stage and grade. They found that cigarette smoking increased the risk of both non-muscle-invasive and muscle-invasive bladder tumours, but the effect of smoking was more obvious in the higher stages (heavy smokers had a relative risk of 3.0 for non-muscle-invasive disease but had a relative risk of 5.2 for muscle-invasive tumours). This association was not seen with grade.

The present study was conducted in the authors' oncological hospital, which is the only one in the Syria specialising in the management of malignancies. The large number of patients with bladder cancer (300) were from all regions in Syria, with no racial or ethnic discrimination. There was no significant difference between smokers and non-smokers in grade or stage, but the high-dose smokers had significantly more aggressive cancer ($P < 0.05$).

Although it remains to be determined whether the non-smokers had other risk factors that might contribute to the induction of high-grade and high-stage bladder cancer, the insignificant difference between the groups could also be explained by the fact that smoking is a very common habit in Syria and thus even non-smokers are commonly exposed to cigarette smoke. Our conclusion that high-dose smokers had a more aggressive cancer not only supports this explanation, but also again shows the dose-dependent relationship between smoking and bladder cancer, although there were only 17 heavy smokers of the 240 smokers, which restricted the value of the statistical analyses.

Thus from our results we strongly advise heavy smokers to stop smoking, or at least to smoke fewer cigarettes per day, as we found that a greater dose of smoking was associated with the higher grades of bladder cancer.

In conclusion, smoking has a potential dose-dependent effect on the grade and stage of bladder cancer, with high-dose smokers having more aggressive disease. The equality in the aggressiveness of the cancer between the low- to moderate-dose smokers and the non-smokers in the present population might be a result of the effect of passive smoking, in a country where smoking is a common habit, or it might be the result of other risk factors. To answer these questions, a population-based study is needed, with more patients and studying all environmental factors, including smoking.

Conflict of interest

None of the authors have conflicts of interest that are relevant to this study.

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