Journal of Nephropathology

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Opium and grade of urothelial bladder cancer

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ARTICLE INFO

ABSTRACT

Background: Bladder cancer is a serious global problem. Although the risk factors of bladder cancer have been found through many studies, the effect of them on the grade of this cancer has not been focused previously.
Objectives: This study was conducted to evaluate the association of some risk factors of urothelial bladder cancer on its grade.
Patients and Methods: The patients with proved diagnosis of urothelial carcinoma of bladder were enrolled in this study. They were divided into case group (those with high-grade bladder cancer) and control group (those with low-grade bladder cancer). Each of case and control groups contained 103 patients. Age, gender, place of residence, cigarette smoking state, opium consumption state, occupation, previous exposure to poisons or chemicals, and family history of bladder cancer were compared between the case and control groups.
Results: Eighty-two patients (79.6%) of the case group and 87(84.5%) of the control group were male. The mean age of the case group was significantly higher than control group (66.1 ± 11.8 and 61.7 ± 14.2, respectively; $P = 0.003$). The results of this study showed that ever usage of opium was significantly higher in the case group (OR = 2.97; 95% CI: 1.64- 5.38; P <0.001). Although mean pack-years of cigarette smoking of case group was significantly higher than control group in univariate analysis ($P = 0.009$), it was omitted from regression models when multivariate analysis was applied.
Conclusions: High grade urothelial bladder cancer has been significantly associated with opium usage and older ages.

Original Article

Implication for health policy/practice/research/medical education:
Bladder cancer, as the first most common cancer of genitourinary system, is still a serious global problem. Opium, after tobacco, is the second most abused drug in the world. Unfortunately, there is a wrong traditional opinion that it is useful for health. Based on our results, opium is associated with high grade bladder cancer. Hence, it is necessary that opium use prevention be as a part of health policy making. opium users should be educated about bladder cancer and its clinical manifestations for early diagnosis and prevention of disease progression.
Please cite this paper as: Zeighami S, Azizzadeh E, Tabatabaee HR, Adib A, Babaei AH, Ariafar A. Opium and grade of urothelial bladder cancer. J Nephropathol. 2018;7(2):69-73. DOI: 10.15171/jnp.2018.17.

1. Background

Bladder cancer accounts for the first most common cancer of genitourinary system (1). Although the diagnosis and management of bladder cancer have been progressed, it is still a serious global problem.

Around 74 000 new cases and 16 000 deaths of bladder cancer have been estimated in the United States in 2015 (2). It has a mortality rate of about 8 per 100 000 person-years in the Middle-East and it occurs more in men than women (3).

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Cigarette smoking accounts for the most important risk factor of bladder cancer. Also, some other factors like occupational exposure to carcinogens, genetic susceptibility, chronic cystitis, and immunosuppression have been proved to be associated with bladder cancer (4,5). In some societies, opium consumption has been found to be associated with affliction with bladder cancer (6).

Hematuria is the most common clinical manifestation of bladder cancer. Cystoscopy has been the gold standard, but invasive, method for its diagnosis. Voided urine cytology is a non-invasive method which contributes to its diagnosis (7).

Grading of bladder cancer is useful for determining its treatment and prognosis. Currently, according to the World Health Organization (WHO) grading system in 2004, it has been classified into papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade (L-G) and high-grade (H-G) (8). Although the risk factors of bladder cancer have been investigated through several studies, their effects on the grade of this disease have not been focused previously.

2. Objectives

The aim of this cross-sectional study was to investigate the association of some of the risk factors of urothelial bladder cancer on the grade of this disease.

3. Patients and Methods

3.1. Study population

The patients who were diagnosed as urothelial carcinoma of bladder in Shahid Faghihi and Ali Asghar hospitals (Shiraz, Iran) from September 2012 to March 2014 were enrolled in this study. Their cancer was histologically confirmed by an expert pathologist, through cystoscopy and transurethral resection of bladder tumor (TURB). Urothelial carcinoma must be the first and the only cancer diagnosed in these patients. Those who had adenocarcinoma, squamous cell carcinoma, or concurrent cancers in other organ or metastasis from another organ to bladder were excluded from our study. According to the WHO classification and after pathological documentation, the patients were divided into PUNLMP, L-G and H-G. The patients with H-G bladder cancer were regarded as the case group. The patients with PUNLMP bladder cancer and L-G bladder cancer were considered as the control group. Each of case and control groups contained 103 patients.

After selection of the patients, their files were reviewed for data gathering. Age, gender, place of residence, cigarette smoking state, opium consumption state, occupation, previous exposure to poisons or chemicals, and family history of bladder cancer were compared between the case and control groups. High risk jobs were considered working in the chemical, dye, rubber, petroleum, leather and printing industries. Cumulative use of cigarette was reported as pack year. Data of opium were reported as ever use of opium and duration of consumption.

3.2. Ethical issues

The research followed the tenets of the Declaration of Helsinki. Our study protocol was approved by the ethics committee of Shiraz University of Medical Sciences (ethics code #EC-91-6222). The patients' medical records were used for data gathering and this process was secret.

3.3. Statistical analysis

Chi-square test, Fisher's exact test, independent t test, and Mann-Whitney U test were used. Additionally, univariate analysis and logistic regression models were used for multivariate analysis. Multivariate models were adjusted for significant and near significant ($P < 0.25$) factors in univariate analysis. The association of the factors and grade of bladder cancer were reported using odds ratio and 95% CI, and P values. Additionally, P values less than 0.05 were regarded as significant. Data were analyzed using SPSS (IBM SPSS, version 13).

4. Results

Eighty-two patients (79.6%) of the case group and 87 (84.5%) of the control group were male. There was no significant difference between the gender of the case and control groups. The mean age of the case group was significantly higher than the control group (66.1 ± 11.8 and 61.7 ± 14.2, respectively).

The amount of cigarette smoking was 24.8 ± 22.39 pack-year for the case group and 16.8 ± 23.28 pack-year for the control group which was significantly higher in the case group. Sixty-three (61.2%) patients in the case group and 40 (38.8%) of the control group had a history of ever opium use that was significantly different. Duration of using opium was significantly higher in the case group than the control group (Table 1).

There was no significant difference between the case and control groups regarding the place of residence, job state, cancer recurrence, exposure to poisons or chemicals, and family history of bladder cancer (Table 1).

Multivariate models were adjusted for age, place of residence, recurrence of bladder cancer, cigarette smoking state (pack-year), and opium use (ever versus

Table 1. Risk factors and elements of bladder cancer has been compared between case and control groups

Variable	Control group	Case group	OR (95% CI)	*P* value
Sex, No. (%)				
Male	87 (84.5)	82 (79.6)	1.39 (0.68-2.8)	0.36
Female	16 (15.5)	21 (20.4)		
Place of residence, No. (%)				
Urban	69 (67)	81 (78.6)	0.55 (0.29-1.03)	0.06
Rural	34 (33)	22 (21.4)		
Age, mean ± SD	61.7±14.2	66.1±11.8		0.02
Smoking				
Smoker, No. (%)	57 (55.3)	75 (72.8)	2.16 (1.2-3.87)	0.009
Non-smoker, No. (%)	46 (44.7)	28 (27.2)	-	
Pack-years, mean ± SD	16.8±23.2	24.8±22.3	-	0.003
Family history of bladder cancer, No. (%)				
Yes	10 (9.7)	8 (7.8)	0.78 (0.29-2.07)	0.6
No	90 (90.3)	95 (92.2)		
Opium				
Ever use, No. (%)	40 (38.8)	63 (61.2)	2.48 (1.4-4.3)	0.001
Never, No. (%)	63 (61.2)	40 (38.8)	-	
Years of opium consumption (mean ± SD)	5.7±9.3	9.4±9.6	-	0.001
Exposure to poisons or chemicals, No. (%)				
Yes	61 (59.2)	58 (56.3)	0.88 (0.51-1.54)	0.67
No	42 (40.8)	45 (43.7)		
Cancer recurrence, No. (%)				
Yes	74 (71.8)	83 (80.6)	1.62 (0.84-3.11)	0.14
No	29 (28.2)	20 (19.4)		
Job, No. (%)				
Low risk	102 (99)	100 (97.1)	3 (0.31-30)	0.31
High risk	1 (1)	3 (2.9)		

never). Just opium usage and age remained in the regression models. Overall, ever use of opium was significantly higher in the case group (odds ratio [OR] = 2.97; 95% CI: 1.64-5.38; *P* < 0.001). High grade bladder cancer was associated with older ages (OR = 1.035; 95% CI: 1.011-1.059; *P* = 0.003).

5. Discussion

Grade of bladder cancer is one of the important prognostic factors for this disease. It is considered as an important item for decision making for treatment. TURB and intra-vesical therapies are the main treatments considered for non-muscle-invasive bladder cancer (NMIBC) (9). However, for high risk and treatment failure forms of NMIBC, radical cystectomy with regional lymph node dissection remains the best method of treatment (10). High grade superficial bladder cancer is the highest risk type of NMIBC (11). The results of this study showed that opium users had 2.97 times more chance of getting high grade bladder cancer (H-G in proportion to L-G and PUNLMP).

High grade bladder cancer is associated with older ages. Each year increase in age, can rise the chance of high grade bladder cancer 1.03 times more.

Opium, after tobacco, is the second most abused drug in the world (12). Opium consumption is mostly a problem of eastern countries; hence it is not an issue to be focused in Western literature. Iran accounts for the second most severe addiction to opium in the world (13). Unfortunately, there is a traditional positive attitude to opium use (14). This attitude as well as some other factors such as poverty, unemployment, urbanization, homelessness, and divorce, cause a high rate of opium usage in Iran (13).

Opium use, even in low dose, is associated with increased risk of death by 86% (15). It has been found to have a role in some cancers like esophagus, stomach, larynx, lung, and bladder cancers (16-18).

Akbari et al found that opium usage increases the occurrence of bladder cancer by 3.9 points. They have found a dose-related association of using opium and getting bladder cancer (16). The results of a study

conducted by Karbakhsh et al showed that opium consumption can decrease the age of getting bladder cancer (19). We found that high grade bladder cancer was associated with older ages. Mohseni et al and Yang et al investigated on the prognostic factors of bladder cancer. They found no association between age and grade of bladder cancer (20,21).

Although many studies have mentioned cigarette smoking and opium consumption as risk factors of bladder cancer, few researches have investigated their effects on the grade of this cancer. One was a study conducted by Hosseini et al. They have found increased risk of grade III (OR: 3.44; 95% CI: 2.82–8.28; $P = 0.001$) and grade IV (OR: 3.86; 95% CI: 2.14–10.16; $P = 0.001$) bladder cancer, by opium consumption (6). Results of our study did not show any significant association between cigarette smoking and grade of bladder cancer although it was significant in univariate analysis.

Results of a study conducted by Sturgeon et al, to investigate the association of risk factors on grade and stage of bladder cancer, revealed some similar paradoxical findings. They found that cigarette smoking was associated with higher risk of low grade bladder cancer than high grade tumor (22). In contrast, some studies have found that cigarette smoking is associated with higher grades of bladder cancer (23,24).

Jiang et al conducted an investigation on the association of smoking and subtypes of bladder cancer and found increased risk of invasive bladder cancer by cigarette smoking. The results of this study showed ORs associated with regular smokers 2.2(1.8–2.8) for L-G superficial, 2.7 (2.1–3.6) for H-G superficial, and 3.7 (2.5–5.5) for invasive tumors (25).

Van Roekel et al studied the relationship between smoking and clinical characteristics of bladder cancer. They found that smokers, compared to non-smokers, had higher T stage and higher grade. Overall, they found that smoking is associated with younger age at diagnosis and more malignant type of bladder cancer (26).

It seems that further studies are needed to investigate the association of cigarette smoking and grade of bladder cancer.

6. Conclusions

To conclude, getting higher grade bladder cancer has been significantly associated with opium usage. H-G bladder cancer was associated with older ages. Although cigarette smoking accounts for a powerful risk factor of bladder cancer, it did not increase risk of getting H-G bladder cancer.

Study limitations

We had some limitations in this study. There is not any standard scale for cumulative use of opium (as pack year for cigarette smoking). Therefore, we had to report data of opium use as ever use of opium and duration of consumption. This study must be repeated with larger sample size.

Authors' contribution

SHZ and AA made a substantial contribution to the conception and design of this study. Acquisition of data, analysis, and interpretation of data were done by EA, HRT, and AA. AA and AHB were involved in drafting the manuscript and revising it. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have not any conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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