Original Article

The Effect of Smoking and Opium on Bladder Cancer in Yazd Province: A Case - Control Study

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Received: 2016/01/05 **Accepted:** 2016/05/14

Abstract

Introduction: Bladder cancer is regarded as the most common urinary malignancy in the world. As other cancers, its incidence has increased in recent years. Hence, the present study was conducted to investigate the relationship between smoking and opium and bladder cancer in residents of Yazd province.

Materials and Methods: This case-control study was performed on 200 patients with bladder cancer and 200 matched healthy individuals in Yazd province. Research data was gathered through interview and administration of a researcher-made questionnaire. Furthermore, chi-square and regression tests were carried out with SPSS software (version 18).

Results: The mean and standard deviation of age in case and control groups were reported to be 61.54 ± 13.61 and 61.45 ± 13.3 respectively. Education level, type of oil consumed, weekly frequency of smoking and fried foods, white meat, red meat consumption involve the predictive factors for bladder cancer; as consumption of hydrogenated fats, animal fats, fried foods more than 4 times per week and red meat had (OR=1.31;95% CL,0.63-2.71), (OR= 6.32;95% CL,2.03-19.8), (OR=2.86;95% CL,1.2-6.8) and (OR=51.18;95% CL,14.78-177.03) times greater risk for bladder cancer respectively and also low education level. White meat intake had a protective effect. Moreover, in line with increasing number of cigarettes per day, the risk of bladder cancer increased.

Conclusion: The findings of the present study revealed that smoking and opium are risk factors of bladder cancer. Thus, appropriate training and intervention program need to be taken into account in order to prevent the cancer.

Keywords: Bladder cancer; Case-control; Opium; Smoking; Yazd province

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Introduction

Cancer is a general term for a large group of diseases that can affect any part of the body, also known as the neoplasm or malignancy. Cancer is the rapid growth of abnormal cells which can spread to different organs [1]. Today, cancer is a health problem in many countries around the world. As a matter of fact, currently cancer is the second leading cause of death in the developed countries and is the third in the developing countries[2]; so as in America a quarter of deaths is caused by cancer[3]. In Iran, after cardiovascular diseases and accidents, cancer is the third leading cause of death [4]. Due to its rapid growth, cancer is posed as a major health problem regarded as a priority in the healthcare [5]. In the developing countries, burden of cancer is increasing because of infectious diseases control and increased aging. In this regard, between 1990-2010, the number of cancer cases was reported to be 30% and 71% in the developed and developing countries respectively [6].

Bladder cancer is the most common urinary malignancy in many areas of the world [7] .Transitional epithelium cells cover from renal pelvis to ureter, bladder and two-thirds of urethra. Although cancers may occur anywhere, 90% of malignancies are in bladder [8]. Men more than women are at risk of bladder cancer [9, 10]. The incidence of bladder cancer in men is 2.5-4 times higher than that of women [11]. More than 12 million new cases of bladder cancer occur worldwide per year, and nearly 145,000 people die from this disease [12].There were 72,570 new cases of bladder cancer in 2013 with 15,210 related deaths in the United States [13]. In 2009, age-standardized cancer incidence rate in Iran was 12.59 and 3.28 for men and women respectively_ in Yazd, as the third-most common cancer city of Iran, the age-standardized cancer incidence rate was 17.05 [14]. Bladder cancer has a high mortality rate and statistics in Iran indicates that it is considered as an important disease, since its incidence is increasing [15]. In Iran, survival of patients with bladder cancer has been reported to be less than cancers in other regions [6]. According to findings of various studies, the most important risk factors of this cancer involve smoking, occupational exposure, genetic factors, gender and some fruits and vegetables intake [16, 17]. Due to different risk factors, the incidence and mortality rate of bladder cancer varies in different regions [15].so that may be up to 15 times difference. The age-standardized incidence rate is different from 21 per hundred thousand men in Eastern Europe to 1.5 per hundred thousand men in Central Africa [18].

Five provinces of Iran with highest incidence of bladder cancer are Yazd, Fars, Gilan, Isfahan, and Khorasan [19]. Smoking is a strong risk factor for bladder cancer in the both sexes [20]. In smokers, the risk is 2-4 times higher than non-smokers and with increasing of intensity or duration of smoking, the risk increases, as well. After1-4 years and 25 years of quitting, the risk is reduced more than 30% and 60% respectively, yet it never reaches the

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risk of non-smokers [21]. Cigarette smoking has been observed in 50-60% of men and 20-30% of women suffering from this cancer. Smoking may be carcinogenic with two mechanisms: 1.metabolites like nitrosamine and naphthyl amine released into the bloodstream through the lungs and 2. Increased urinary excretion of tryptophan metabolites [22]. The results of different studies have demonstrated that global burden of bladder cancer will be increased in the future, especially in the developing countries, which is mainly related to the significant prevalence of continuous smoking [15]. Since prospective cohort or case-control studies in Yazd province has not been conducted yet this study aimed to determine the relationship between smoking and opium with the bladder cancer prevalence within people living in the Yazd province.

Materials and Methods

This case-control study was conducted on patients suffering from bladder cancer in Yazd province. According to significance level of 5%, power of 80% and odds ratio of 2.5 for risk factors and using statistical software, total sample size was400, 200 patients in each. (n=200 in case and n=200 in control group).

Inclusion criteria were patients whose bladder cancer was proven, and pathologically confirmed between 2009-2013 in Yazd Cancer Center. Sampling was done through consensus. Moreover, address and phone number of patients were taken. After describing the study, information needed to be collected in person or by phone. The controls were selected from their neighbors, which were matched with the study group in regard with age, sex and location. Age matching was done via frequency matching; thus, the control subjects were matched for 2 ± years. Previous studies have shown that bladder cancer is more common in men than women which increases with age. Hence, in order to figure out the role of other causes, three variables including age, sex and residence were adjusted.

The study questionnaire consists of 6 parts:(1)Social–demographic characteristics (age, gender, religion, marital status, family size, location, blood group), (2) socio-economic factors (education, occupation, income, home ownership status and insurance coverage), (3) lifestyle related factors (smoking, hubble-bubble and pipe smoking, opium, alcohol, physical activity and diet), (4) family history related factors, taking drugs such as painkillers and cyclophosphamide, (5)factors related to history of systemic disease, chronic recurrent infections in urinary tract, kidney and bladder stones and Schistosomiasis, and (6) factors related to radiation exposure of lower body, exposure to chemicals or use of hair color. For validation, the questionnaire was substantiated by a team of specialists.

This study was approved by the Shahid Sadoughi University of Medical Sciences Research Ethic Committee (No:17/1/8257). In order to analyze the study data, SPSS software (version 18), SPSS Inc., Chicago IL) was used applying chi-square test in order to find the relationship between bladder cancer and its

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risk factors .Using forward logistic model, effects of confounding factors were eliminated and the most effective factors were detected. Significant level of test was set at 0.05 and the variables with significant level of ≤0.2 in univariate analysis, were entered into logistic regression model.

Results

In the present study, 400 patients participated (case=200 and control=200). In both groups, 12.5% were females and 87.5% were males and the mean and standard deviation of age in cases and controls were 61.54 ± 13.61 and 61.45 ± 13.3years respectively, between which no significant differences were observed (p= 0.86).In the case group, 4% of patients were under 30, 39% were between 30 -60 and 57%were over 60 years of age. In the control group, 3.5%, 40.5% and 56%, were under 30, 30-60 and above 60 years old respectively. Most patients in both groups were married and Shia. Table 1 illustrates the demographic characteristics of both groups.

Table 1. Demographic characteristics in case & control groups

Variable		Case Frequency (%)	Control Frequency (%)	OR(95% CI)	P-value
Education	Illiterate	47(23.5)	17(8.5)	3.3(1.73-6.27)	<0.0001
	Primary and secondary	86(43)	103(51.5)	0.99(0.64-1.53)	
	Above Diploma	67(33.5)	80(40)	1*	
Total family income	<1000000	127(66.8)	90(45.5)	2.32(1.20-4.49)	<0.0001
	1000000-1500000	46(24.2)	80(40.4)	0.94(0.46-1.91)	
	>1500000	17(8.9)	28(14.1)	1*	
Family size	≤4	42(21)	56(28)	1*	<0.0001
	5-6	73(36.5)	98(49)	0.99(0.6-1.64)	
	≥7	85(42.5)	46(23)	2.46(1.44-4.21)	
Blood groups	A	46(26.7)	66(37.9)	0.96(0.47-1.97)	<0.0001
	B	21(12.2)	53(30.5)	0.55(0.25-1.21)	
	O	87(50.6)	30(17.2)	4.02(1.93-8.39)	
	AB	18(10.5)	25(14.4)	1*	

*Reference category.

Based on Table 1, education, monthly household income and blood group were significantly associated with the bladder cancer so as people who had lower education, lower income, who lived in large families showed greater risk of disease.

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Table 2 shows smoking and opium use in the both groups. Smoking status, smoking duration, number of cigarettes smoked per day and the age of starting smoking, were significantly associated with the risk of bladder cancer. The results of the present study revealed people with a history of opium use, had 3.01 times more risk of bladder cancer. no statistically significant difference was observed between the type of opium used in the case and control group, and in both groups us of opium was dominant

Table 2. The ORs between bladder cancer and using cigarette derivatives opioid and alcohol

		Case	Control		
		Frequency (%)	**Frequency (%)**	**OR(95% CI)**	**P-value**
Cigarette smoking	No (do not use)	74(37)	129(64.5)	1*	
	yes	98(49)	54(27)	3.16(2.04-4.9)	<0.0001
	quit smoking	28(14)	17(8.5)	2.87(1.47-5.59)	
Smoking duration	1-9 years	7(5.6)	11(15.9)	1*	
	10-20 years	26(20.8)	33(47.8)	1.23(0.42-3.63)	<0.0001
	21-30 years	45(36)	20(29)	3.53(1.19-10.45)	
	31 years≤	47(37.6)	5(7.2)	14.77(3.93-55.41)	
The number of cigarettes smoked per day	10<	22(17.6)	52(75.4)	1*	
	20-11	47(37.6)	10(14.5)	11.10(4.77-25.86)	<0.0001
	30-21	24(19.2)	4(5.8)	14.18(4.4-45.69)	
	31>	32(25.6)	3(4.3)	25.21(6.98-91.05)	
Age of smoking onset	20<	57(45.6)	8(11.6)	18.52(5.2-65.92)	
	30-21	51(40.8)	23(33.3)	5.76(1.83-18.07)	<0.0001
	40-31	12(9.6)	25(36.2)	1.24(0.36-4.31)	
	41<	5(4)	13(18.8)	1*	
Exposed to cigarette smoke	yes	80(40.6)	47(23.5)	2.22(1.44-3.43)	<0.0001
	No	117(59.4)	153(76.5)	1*	
Opium History	yes	52(26.1)	21(10.5)	3.01(1.73-5.23)	<0.0001
	No	147(73.9)	179(89.5)	1*	
History of Hubble bubble and pipe	yes	45(22.6)	20(10)	2.63(1.48-4.64)	0.001
	No	154(77.4)	180(90)	1*	
History of alcohol	yes	17(8.5)	7(3.5)	2.57(1.04-6.35)	0.034
	No	182(91.5)	193(96.5)	1*	

*Reference category _ Frequency distribution of cigarette derivatives opioid and alcohol related variables and odds ratio and the 95% reliability interval in bladder cancer

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Table 3. Comparison of physical activity and nutrition status in case and control groups with crude odds ratios.

Variable		Case Frequency (%)	Control Frequency (%)	OR(95% CI)	P-value
Physical activity	Regularly	17(8.5)	31(15.5)	1*	
	Rarely	28(14)	46(23)	1.11(0.56-2.36)	0.002
	No Physical activity	155(77.5)	123(61.5)	2.29(1.21-4.34)	
Type of the consuming oil	Liquid oil	54(27)	97(48.5)	1*	
	Solid oil	114(57)	85(42.5)	2.4(1.55-3.72)	<0.0001
	Animal oil	32(16)	18(9)	3.19(1.64-6.21)	
Fried food intake (per week)	1≥	36(18)	69(34.5)	1*	
	2-3	78(39)	90(45)	1.66(1-2.75)	0.09
	4≤	86(43)	41(20.5)	4.02(2.32-6.95)	
Red meat intake	1≥	34(12)	62(31)	1*	
	2-3	100(50)	103(51.5)	2.5(1.45-4.32)	0.05
	4≤	76(38)	35(17.5)	5.61(3.02-10.41)	
White meat intake	1≥	57(28.5)	62(39)	0.49(0.26-0.91)	
	2-3	106(53)	78(39)	0.73(0.41-1.31)	<0.0001
	4≤	37(18.5)	97(48.5)	1*	

*Reference category

According to the Table, in terms of physical activity, a significant difference was observed between case and control group. Type of physical activity was not significantly different between the two groups; which most prevalent type of activity was walking. In terms of physical activity level per week, no significant differences were observed between the two groups. In addition, no difference was observed in smoked food intake between the two groups (p=0.24). Weekly consumption of red meat, white meat, frequency of fried food consumption and type of oil showed a significant difference between the two groups.

In order to find the pivotal and predictive factors of bladder cancer and to eliminate the confounding factors, variables that have a significant level of ≤0.2 in univariate analysis were entered into logistic regression model. As the results of the regression model is demonstrated in Table 4, education level, type of oil consumed, weekly frequency of fried foods consumption, white meat, red meat and smoking involve the predictive factors of bladder cancer.

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Table 4. Effects of risk factors using adjusted logistic regression models

	Variables	Adjusted OR	95% CI	P-value
Education	Illiterate	3.11	1.1-8.8	0.008
	Primary and secondary	0.62	0.29-1.32	0.032
	Above Diploma	1*	-	0.21
oil	Liquid	1*	-	0.006
	Soil	1.3	0.63-2.71	0.46
	Animal	6.32	2.03-19.8	0.001
Fried food (per week)	1≥	1*	-	0.005
	2-3	0.76	0.34-1.69	0.5
	4≤	2.86	1.2-6.8	0.01
Red Meat	1≥	1*	-	<0.0001
	2-3	6.82	2.56-18.11	<0.0001
	4≤	51.18	14.78-177.03	<0.0001
White meat	1≥	0.16	0.06-0.47	0.003
	2-3	0.35	0.13-0.94	0.001
	4≤	1*	1	0.039
The number of cigarettes smoked per day	Non-smoking	1*	-	<0.0001
	10<	0.37	0.14-0.92	0.03
	21-11	11.11	4.09-30.22	<0.0001
	30-21	19.47	4.7-80.68	<0.0001
	31>	44.65	8.03-248-14	<0.0001

*Reference category

Discussion

In this case-control study, the relationship between smoking and drugs with bladder cancer risk was examined in patients whose cancer was diagnosed in 2009 -2013 in Yazd province. In both groups, three variables including age, sex and location, were matched to eliminate the impact of these factors on the risk of bladder cancer. In univariate analysis, education and income were significantly correlated with the risk of bladder cancer, though after taking into account the effects of other variables, only education remained significant. As a result, as subjects who had higher education were less likely to develop bladder cancer and those who were on low income had 2.32 times higher chance of developing bladder cancer. In Aminian's study, education level was not significantly different between cases and controls [23]. Sheikh Salim et al. proposed that mean years of education in control and case groups were 5.75 ,5.90 years respectively, between which

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no statistically significant difference was observed [24], though in the present study, mean difference of education was statistically significant in the case (6.77 ± 5.49 years) and control (7.9 ± 5.21 years) group. Jhamb et al. revealed no significant difference in family income (p=0.882) and education (p=0.22) between the groups [25].

Ling Zhang et al. in a case-control study of bladder cancer and its risk factors showed that 92% of men and 97% of women in the case group, and, 79% of men and 92% of women in the control group had primary school or lower education level; and thus, a higher percentage of men had secondary school or higher education in the control group [26].

The difference between income and education level seen in studies is likely to be due to various classification criteria based on frequency, or different cultural and socio-economic status in regions. In the current study, the relationship between education and income with bladder cancer can be related to the high level of awareness among people with higher education levels leading to a healthy lifestyle. Moreover, high income may increase access to goods and services; which may protect the individuals against the disease.

Smoking, as the most important known risk factor of bladder cancer, was estimated as the cause of %50 of tumors; and thus, a pathophysiological link was observed between smoking and cancers. Cigarette smoke includes aromatic amines as B.naphthylamines and polycyclic aromatic hydrocarbons which is associated with the bladder cancer [17]. In this study, as the results of univariate analysis demonstrated, a positive relationship was revealed between smoking, hubble-bubble, drug use and alcohol intake with the bladder cancer. Furthermore, the results of the regression model showed that with increasing the number of smoked cigarettes, the risk of bladder cancer increases. Freedman's study demonstrated that the hazard risk in those who had history of smoking was 2.22 (2.03-2.44; CI =95%) and in those who were already smoker was reported 4.06 (3.66-4.50; CI= 95%) in comparison with those who had never smoked [20]. Univar ate analysis revealed results consistent with the findings of the present study, so that Odds ratio in smokers was 3.16 (2.04-4.9) and in those who had quit smoking was 2.87 (1.47-5.59) compared with those who had never smoked.

Moreover, in a meta-analysis study, relative risk of bladder cancer for all smokers was 2.58 (2.37-2.80; CI=95%), and for those who had history of smoking was 2.04 (1.85-2.25) [27]. In another study, Chen concluded that quitting smoking can reduce the recurrence rate of muscle invasive bladder cancer [28]. In a case-control study, Hosseini showed a significant association between bladder cancer and drug use OR= 4.6 (3.53- 6.28).Those with a longer history OR= 5.42 (4.12-7.28) were at a greater risk than those with a shorter history OR=3.65 (2.76-4.76).Individuals who smoke heavily and take drugs were 6 times more at risk; and the risk of bladder cancer was significantly associated with duration of drug addiction (r=

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0.74, p= 0.001), type of narcotic (r=0.65 , p=0.001) and concurrent smoking (r= 0.74, p=0.0001) [29].

In Ketabchi's study, the amount, duration, and way of opium use have been demonstrated to be effective in carcinogenic effects of opium in incidence of bladder cancer in the addicted patients [30]. In the present study, a significant relationship was detected between the duration of cigarette smoking, drug abuse and alcohol consumption with the risk of bladder cancer. However, no statistically significant difference was observed between the type of opium used in the case and control group, and opium was dominant in both groups.

A study carried out in Japan showed that the incidence of bladder cancer in both sexes within smokers was about 6 years earlier than non-smokers(6.1 years in men and 5.9 years in women). At the time of diagnosis, tumor stage in smokers was significantly higher and tumor size was also larger[31]. Due to the design of case-control study, the age of disease onset in smokers and non-smokers was not clear; however, the mean age of starting smoking was lower in the case group and the duration or number of cigarettes smoked was higher than the control group. Jiang et al. showed that cigarette smoke was associated with the higher risk of bladder cancer in the both groups (case and control) who were not smokers. .Moreover, they proposed a long time exposure of cigarette smoke can be a risk factor for the bladder cancer progression in women [32]. Ling Zhang et al. proposed that within men, smoking was associated with an increased risk of urothelial cancer OR= 1.8 (1.4-2.2; CI 95%). In addition, a significant relationship was detected with squamous cell carcinoma OR= 1.8 (1.2-2.6; CI=95%). Therefore, non-smoker men and women exposed to cigarette smoke are at increased risk of urothelial cancer as well [26]. In univariate analysis, subjects exposed to cigarette smoke at work or home had 2.22 times more risk of developing the disease.

In univariate analysis, significant differences were revealed in regard with physical activity between the two groups, while it was not observed in the logistic model. There was no significant difference with respect to duration and type of physical activity between groups, which walking was the dominant physical activity in this study. Although results of a meta-analysis study showed that physical activity reduces the risk of bladder cancer [33], in some studies no relationship was reported [34, 35]. Insignificancy of physical activity in these studies seems to be due to the effects of other variables such as smoking. Based on the present study findings, red meat and weekly frequency of fried food consumption was positively related with the, whereas an inverse relationship was observed between bladder cancer and consumption of white meat. After entering variables in a multiple logistic regression model, a statistically significant relationship was demonstrated. In both univariate and multiple logistic regression analysis, the type of oil used for cooking, was significantly associated with the risk of bladder cancer; hence, risk of cancer with use

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of hydrogenated fats was 1.31 times and use of animal fats was 6.34 times more. JW Wu et al. found that consuming processed meats is associated with the bladder cancer (OR= 1.28) and a stronger association for red meat consumption was expressed, as well [36]. Mirsafa showed that meat and butter were positively and olive oil was negatively associated with the risk of bladder cancer [19]. In a meta-analysis study, Fei Li showed that, in general for all studies, relative risk of red meat consumption was 1.15 (0.97-1.39; CI= 95%) [37]. yet, some studies found no relationship between red meat consumption and bladder cancer [38, 39].

The present study suffers from some limitations; some questions may have been answered incorrectly due to social and cultural reasons. In addition, some patients did not cooperate in answering

Conclusion

Education level, type of oil consumed, weekly frequency of fried foods consumption, white meat, red meat and smoking had significantly been associated with the bladder cancer. As a result, low education level, consumption of hydrogenated and animal fats, fried foods, red meat and smoking status were identified as risk factors for the bladder cancer. Therefore, proper training and intervention programs seem to be effective in reducing the incidence of this type of cancer.

Acknowledgments

We are grateful to all who helped us in conducting this study especially patients with bladder cancer as well as health department staff.

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