

RESEARCH COMMUNICATION

Epidemiologic Status of Bladder Cancer in Shiraz, Southern Iran

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Abstract

Background: Bladder cancer is the second most common malignancy of the genitourinary tract worldwide after prostate cancer. However, in Iran it is the most common cancer of the genitourinary system and the third most common cancer in males. The increasing trend in bladder cancer incidence in recent decades, along with the lack of research on this malignancy in Iran, make epidemiologic research important in light of its preventability through early recognition and limiting exposure to risk factors. The present study aimed to assess the epidemiology of bladder cancer in Shiraz, a large city in southern Iran, during a 2-year period. **Methods:** The data for this study were obtained from the population-based cancer registry of the Vice-Chancellery for Health Affairs of Shiraz University of Medical Sciences and Shiraz hospitals between March 1, 2007 and March 1, 2009. Demographic, clinical and pathological aspects of 216 patients with bladder cancer were investigated through careful review of their medical records. Statistical analyses were performed with SPSS software. P values less than 0.05 were considered statistically significant. **Results:** We analyzed data for 179 (82.9%) men and 37 (17.1%) women (mean age of 65.1±12.7 years). Tobacco and opium use were found in 109 (65.3%) and 44 (34.1%) patients, respectively. Cigarette smokers and water pipe smokers were mostly men (P=0.001 and P=0.04, respectively). The most common type of tumor was transitional cell carcinoma (95.7%) and most tumors were of low malignant potential grade (39.7%). Nearly half of the patients suffered recurrence. **Conclusion:** Comparisons with previous studies showed that bladder cancer tends to appear slightly more often in the elderly and that the tumors tend to have a higher grade of malignancy in our region. There is a need for more epidemiologic studies on the trends in the incidence and other epidemiologic indices.

Keywords: Bladder cancer - epidemiology - Iran, Shiraz - transitional cell carcinoma

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Introduction

Worldwide, bladder cancer is the fourth most common cancer in males and the ninth most common in females (Campbell, 2007; Scelo and Brennan, 2007; Yavari et al., 2009). It accounts for 7% of all new cancer cases in men and 2% in women (Carel et al., 1999). In 2009, approximately 71 000 new cases were detected in the USA, with 14 000 deaths. The crude incidence in the European Union was 19.5 in 100 000 with a mortality of 7.9 in 100 000 (Bellmunt and Guix, 2010). The highest incidences have been found in Western Europe and North America, while the lowest incidence is seen in Asia (Azizi et al., 2010). According to the World Cancer Report 2008, in the Eastern Mediterranean Region the second most common cancer is bladder cancer in men, after lung cancer (World Cancer Report, 2008). In the most recent national cancer report in Iran, the age-specific incidence rates for bladder cancer were 13.03 in males and 3.32 in females per 100 000 population (Report of National Cancer Registration Iran, 2008).

The overall incidence of bladder cancer has apparently increased during recent decades (Madeb and Messing, 2004; Villares da Costa et al., 2008). This increasing trend cannot be attributed to technological improvements in medicine, as bladder cancer has been diagnosed by cystoscopy and biopsy for about six decades (Madeb and Messing, 2004). However, the trend might be due to the latent effects of risk factors for bladder cancer, including tobacco, non-occupational and industrial carcinogens, and population aging (Villares da Costa et al., 2008).

The most important risk factor for bladder cancer is cigarette smoking (Scelo and Brennan, 2007; Konety and Carroll, 2008; Villares da Costa et al., 2008; World Cancer Report, 2008), which accounts for 50%-66% of new cases in men and 31% in women in industrialized countries (Scelo and Brennan, 2007; Konety and Carroll, 2008). According to studies in the Netherlands and Tehran, Iran, smokers were susceptible to a 2.9-fold to 3.8-fold increase in the risk for bladder cancer (Aliasgari et al., 2004; Zeegers et al., 2004). Similarly, it has been shown that opium consumption increases the incidence of

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bladder cancer significantly, with an odds ratio of 3.9 to 6.2 (Aliasgari et al., 2004; Zeegers et al., 2004). Another risk factor is occupational exposure, which accounts for 15%-35% of the cases in men and 1%-6% in women (Konety and Carroll, 2008). The best known risk factor is exposure to aromatic amines (Carel et al., 1999). Workers exposed to chemicals (odds ratio (OR): 6.2, 95% CI: 2.2-18.0), dye, rubber, petroleum or leather, and who work in printing industries and foundries, are at increased risk (Carel et al., 1999; Vineis, 1994; Gaertner and Theriault, 2002; Konety and Carroll, 2008). Patients who have received cyclophosphamide (relative risk (RR): 5.0 to 9.0), analgesics that contains phenacetin (RR: 2.4 to 6.0), and those exposed to pelvic irradiation are also at increased risk (Madeb and Messing, 2004; Konety and Carroll, 2008; Report of National Cancer Registration Iran, 2008; Villares da Costa et al., 2008; World Cancer Report, 2008; Azizi et al., 2010; Bellmunt and Guix, 2010). Physical trauma to the urothelium induced by calculi (OR: 11.0, 95% CI= 1.4- 84.5), instrumentation-induced infections and infections such as schistosomiasis or chronic cystitis also increase the risk of this kind of malignancy (Carel et al., 1999). In addition, bladder cancer is associated with the human papilloma virus (Eslami et al., 2008). Fruit and fluid consumption might serve as a protective factor against bladder cancer (Zeegers et al., 2001; Kellen et al., 2006; Eslami et al., 2008; Report of National Cancer Registration Iran, 2008; Villares da Costa et al., 2008; Buchner et al., 2010;), by reducing the exposure of the bladder epithelium to toxins through dilution and reducing the contact time of urine in the bladder (Report of National Cancer Registration Iran, 2008; Villares da Costa et al., 2008).

In Iran, a developing country in southwest Asia, an epidemiologic transition is underway from communicable to noncommunicable diseases (Report of National Cancer Registration Iran, 2008; Azizi et al., 2010). As the third most common cause of death (Kolahdoozan et al., 2010), cancer is a major public health problem in Iran. Bladder cancer is the third most common cancer among Iranian males and the ninth most common among females (Ahmad et al., 2003; Yavari et al., 2009). The risk for bladder cancer in Iran based on a male-to-female ratio of 3.9:1 is considered intermediate, (Ahmad et al., 2003). To the best of our knowledge, few studies have reported the epidemiological characteristics of bladder cancer in Iran (Sedghi, 1994; Soofi Majidpour et al., 2001; Safaie, 2002; Ahmad et al., 2003; Farahmand et al., 2009; Yavari et al., 2009). The present study aimed to assess the epidemiology of this malignancy in a 2-year period in Shiraz, southwestern Iran.

Materials and Methods

Patients

This retrospective, cross-sectional study involved the population of Shiraz, the center of Fars province, Iran. The data for this study were obtained from the population-based cancer registry of the Vice-Chancellery for Health Affairs of Shiraz University of Medical Sciences and Shiraz hospitals between March 1, 2007 and March 1,

2009. Demographic, clinical and pathological data for 216 patients with bladder cancer including sex, age, residency, past history of other cancers except bladder cancer, presenting symptoms, histological type of tumor, history of smoking and opium use, treatment modalities used, tumor recurrence, and tumor grade were obtained from their medical records. Tumor grading followed the World Health Organization and International Society of Urological Pathology grading system (WHO/ISUP 2004). The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences.

Statistical Analysis

Statistical analyses were done with SPSS software (Chicago, IL, USA, Version 16). In addition to the descriptive statistics obtained for each variable, the chi-squared test was used to compare qualitative data, and Student's t-test was used for quantitative data. P values less than 0.05 were considered statistically significant

Results

Data from a total of 216 patients (179 men [82.9%], 37 women [17.1%], a mean age 65.1±12.7 years) were analyzed. The male/female ratio was 4.8:1. There was no significant difference in age between sexes (P<0.05). Among the various age groups (Figure 1), the largest proportion of patients (86 cases, 39.8%) was more than 70 years old. Ninety-five cases (62.9%) were from the city of Shiraz, located in the center of the province.

Slightly more than half of the patients (103, 52.5%) had a positive history of urinary tract infection with no significant differences between sexes (P<0.05). The history of tobacco use was positive in 109 (65.3%)

Table 1. Pathological Characteristics of the Tumors in our Patients with Bladder Cancer

Characteristic	Total	Males	Females	p value
Tumor status (n, %)				
Cases	116 (53.7%)	94 (52.9%)	22 (59.4%)	
Single	52 (44.8%)	43 (45.7%)	9 (40.9%)	0.8
Multiple	64 (55.2%)	51 (54.3%)	13 (59.1%)	
Muscular invasion (n, %)				
Cases	128 (59.2%)	100 (55.9%)	28 (75.5%)	0.9
Yes	69 (53.9%)	55 (55.0%)	14 (50.0%)	
Histological grade (n, %)				
Cases	141 (65.3%)	113 (80.1%)	28 (19.9%)	0.05*
Papilloma	1 (0.7%)	1 (0.9%)	0 (0.0%)	
Low	56 (39.7%)	47 (41.6%)	9 (32.1%)	
Mod	40 (28.4%)	35 (31.0%)	5 (17.8%)	
High	44 (31.2%)	30 (26.5%)	14 (50.1%)	
Histological type (n, %)				
Cases	186 (86.1%)	153 (85.5%)	33 (89.2%)	
TCC	178 (95.7%)	147 (96.1%)	31 (93.9%)	0.4**
AC	2 (1.1%)	0 (0.0%)	2 (6.1%)	
SCC	1 (0.5%)	1 (0.6%)	0 (0.0%)	
Mixed*	5 (2.7%)	5 (3.3%)	0 (0.0%)	

TCC ,transitional cell carcinoma; AC, adenocarcinoma SCC, squamous cell carcinoma; *transitional and squamous as the most common types in mixed carcinoma;**Significance level between transitional cell carcinoma group and nontransitional cell carcinoma group; *Patient with papilloma was included in the low malignant potential category

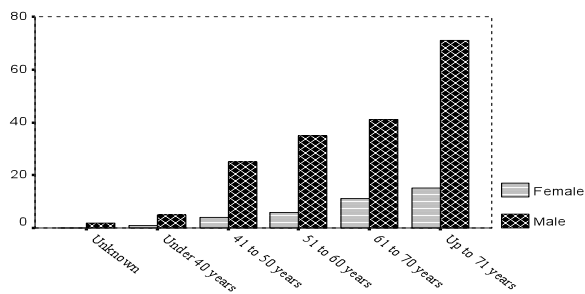


Figure 1. Distribution of Bladder Cancer Incidence by Age and Sex

patients, 85 (78.0%) of whom were cigarette smokers and 24 (22.0%) of whom were water pipe smokers. Most cigarette smokers ($P=0.001$) and water pipe smokers ($P=0.04$) were men. About one third of the patients were opium users (44, 34.1%); all of them were men.

Of the 216 cases of bladder cancer, 183 (84.7%) had a history of hematuria with no significant differences in age distribution between sexes ($P<0.05$). Based on available information regarding surgical treatment (193 patients, 89.4%), transurethral resection (TUR) was done in 142 (73.6%) and radical cystectomy was done in 51 (26.4%) patients. Based on the pathology reports, 95.7% of the patients (178 cases) had transitional cell carcinoma (TCC), 1.1% (2 cases) adenocarcinoma, and only one case (0.5%) had squamous cell carcinoma (SCC). Muscular invasion was seen in 69 (53.9%) patients. The grade of malignancy in our sample was low in 56 cases (39.7%), most of whom were men (47, 83.9%). High-grade malignancy was found in 44 patients (31.2%), and 68.2% of these were men ($P=0.02$). Details of the pathologic characteristics of tumors in our sample are shown in Table 1.

Recurrence was seen in 81 patients (43.8%), 64 (79.0%) of whom were men and 17 (21.0%) of whom were women. There was no significant difference in the rate of recurrence between sexes ($p<0.05$). During the 2-year study period, 18 cases (8.3%, all men) died of bladder cancer. The causes of death were obstructive uropathy, uremic encephalopathy and respiratory distress in 3 patients each (16.7%), and sepsis in 1 patient (5.5%).

Discussion

This cross-sectional study analyzed the epidemiologic features of 216 patients with bladder cancer during a 2-year period in Shiraz, Fars province, Iran. Mean age of this group was 65.1 ± 12.7 years, and there was no significant difference in mean age between men and women. Some research in Pakistan reported a mean age of 55.5 years (Badar et al., 2009). However, the results of comparable studies in Kurdistan and Tehran, Iran reported lower mean ages of 62.5 ± 13.0 and 61.9 years, respectively (Soofi Majidpour et al., 2001; Yavari et al., 2009). A previous study in Shiraz reported that the mean age of patients with bladder cancer was 61.0 ± 12.7 years (Ahmad et al., 2003). The proportion of our patients older than 71 years was higher than in previous studies in Shiraz (Ahmad et al., 2003; Farahmand et al., 2009). Compared to one earlier study of the incidence of bladder cancer,

the age when this malignancy first appears seems to have increased (Ahmad et al., 2003).

Worldwide, the male-to-female ratio in the incidence of bladder cancer is 3.3:1.0. However, this ratio varies around the world and has been reported as 1.1:1.0 in Eastern Africa, 2.1:1.0 in South Africa, 5:1 in Northern Africa and 5.1:1.0 in several areas of southern Europe (Scelo and Brennan, 2007; Yavari et al., 2009). In our sample, this ratio (4.8:1) was similar to the figures reported in previous research in Iran and Pakistan (Sedghi, 1994; Soofi Majidpour et al., 2001; Safaie, 2002; Ahmad et al., 2003; Badar et al., 2009; Yavari et al., 2009). Greater exposure to tobacco, opium, and occupational carcinogens in men may account for the difference in the incidence of bladder cancer between men and women (Samanic et al., 2006).

Cigarette smoking is the most common risk factor for bladder cancer. Recently, several epidemiologic studies and reviews have shown that cigarette smoking significantly increases the risk of this malignancy (Aliasgari et al., 2004; Zeegers et al., 2004; Scelo and Brennan, 2007; Konety and Carroll, 2008; Villares da Costa et al., 2008). Alpha-naphthylamin and beta-naphthylamin may be the specific etiologic agents (Scelo and Brennan, 2007; Konety and Carroll, 2008). In our sample, 65.3% had a positive history of tobacco use (78.0% as cigarette smokers and 23.0% as water pipe smokers). In addition, 34.1% of the patients we analyzed were opium users. Some studies in Iran have found that opium consumption can increase the risk of bladder cancer (Behmard, et al., 1981; Aliasgari et al., 2004; Nourbakhsh et al., 2006; Hosseini et al., 2010). Hematuria was the presenting symptom in 85%-90% of these patients. This symptom can be macroscopic or microscopic, and intermittent or constant (Konety and Carroll, 2008). There was a history of hematuria in 84.7% of our patients.

About 90% of all bladder cancer patients have TCC, which usually appears as papillary and superficial lesions. Fewer than 2% are diagnosed as having adenocarcinoma, which is commonly localized although muscle invasion is usually seen. Between 5% and 10% of the patients have SCC, which frequently presents as a nodular, invasive and poorly differentiated lesion and is often associated with a history of chronic infection, calculi, chronic catheter use, infection due to *Schistosoma haematobium*, and pelvic irradiation. SCC accounts for 60% of all bladder cancer cases in Egypt, parts of Africa, and the Middle East (Konety and Carroll, 2008; Villares da Costa et al., 2008). Fewer than 2% of these cancers are undifferentiated, aggressive and metastatic. A small proportion of all bladder cancers (4% to 6%) comprise mixed carcinomas that commonly contain a combination of transitional and squamous elements (Konety and Carroll, 2008). In our study sample, 95.7% of the cases had TCC, 1.1% had adenocarcinoma and 0.5% had SCC. In previous studies, TCC was seen in 95% to 98% of all bladder cancer patients in Iran (Soofi Majidpour et al., 2001; Safaie, 2002; Ahmad et al., 2003). However, studies of populations in Tehran and Shiraz, (both in Iran) and Pakistan have reported a frequency of TCC of 85% among bladder cancer patients (Sedghi, 1994; Badar et al., 2009; Yavari et al., 2009).

Compared to the current study, the distribution of papillomas, tumors with low malignant potential, low-grade carcinomas, and high-grade carcinomas showed some variations. In a study of new patients with bladder cancer in the USA from 1998 to 2000, 25.7% of the tumors were of low malignant potential, 34.3% were low-grade, 22.6% were high-grade and 15.6% fell into other categories (Schned et al., 2008). In a study of patients with a diagnosis of primary noninvasive TCC of the bladder in the Netherlands between 1979 and 2000, papilloma accounted for 5% of the cases, low malignant potential tumors for 36%, low-grade carcinomas for 44%, and high-grade carcinomas for 14% (Oosterhuis et al., 2002). In another study between 1995 and 2000 in Australia, papillomas accounted for 0% of the tumors, low malignant potential tumors for 14%, low-grade carcinomas for 63%, and high-grade carcinomas for 23% (Yin and Leong, 2004). However, a previous study in Shiraz that used WHO grading criteria reported that among patients with bladder cancer, 45% had grade I lesions, 45% grade II, 8.3% grade III, and 1.7% grade IV (Ahmad et al., 2003).

Although in our study women had high-grade carcinomas significantly more frequently than men, another study in the USA from 1998 to 2000 found that the percentage of women with low malignant potential lesions was significantly larger than for other categories (Schned et al., 2008). Women with bladder cancer were more likely to be diagnosed with higher stages and to have lower survival rates, so mortality in women is higher than mortality than in men (Madeb and Messing, 2004). However, during the period we studied, all of the patients who died from bladder cancer (8.3%) were men. This finding probably reflects the small number of women in our sample.

Although treatment modalities are based on tumor stage and grade, TUR is the primary form of treatment for all bladder cancers (Konety and Carroll, 2008). In this survey, TUR was done for the majority of patients (73.6%). This operation was sometimes followed by intravesical chemotherapy, radiotherapy, chemotherapy, and partial or total cystectomy.

The natural history of bladder cancer is characterized by tumor recurrence and progression, leading to considerable morbidity for patients (Konety and Carroll, 2008). In this study, 43.8% of the patients had recurrences; likewise, previous studies reported recurrence rates of 41.7% in Shiraz (Ahmad et al., 2003), and 34% in Kurdistan (Soofi Majidpour et al., 2001). A long-term follow-up study between 1985 and 2006 in Japan showed that 49.4% of the patients with bladder cancer experienced tumor recurrence (Tanaka et al., 2011). In the majority of superficial papillary TCCs, the tumor recurs after endoscopic resection (Campbell, 2007). Recurrence is more likely in patients with high-grade tumors. Surveillance strategies for bladder cancer recurrence are based on the diagnostic combination of cystoscopy and urinary cytology (Campbell, 2007).

Because this was a retrospective study, some data were not accessible so we could not assess tumor staging. Despite this limitation, we were able to evaluate the overall picture of bladder cancer in our setting. In

conclusion, comparisons between our study and previous reports regarding bladder cancer in Shiraz show that this malignancy presents slightly more frequently in the elderly, and that tumor grade is higher in our region than before. There is a need for more epidemiologic studies of trends in the incidence of this disease identify high-risk groups and obtain data for other epidemiologic indices in our region. The population-based cancer registry system is a potentially rich source of data for such research. The findings will help identify risk factors for bladder cancer, facilitate the early detection of high-risk groups, and support the development of preventive measures. Additional cohort studies to evaluate high-risk groups in industrial centers would also yield useful data.

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