RESEARCH ARTICLE

Can Reproductive Characteristics Predict Bladder Cancer in Women with Haematuria?

Ali Yavuzcan[1]*, Mete Caglar[1], Muhammet Ali Kayıkcı[2], Ekrem Basaran[2], Ali Tekin[2], Enver Ozdemir[2], Serdar Dilbaz[1],Yusuf Ustun[1], Haydar Kamil Cam[2]

Abstract

Background: Among women with haematuria, defining individuals under high risk for bladder cancer based on reproductive factors prior to cystoscopy would be of great benefit in the management of this condition. The aim of this study was to compare age and reproductive factors such as menopausal status, parity, age at first delivery and age at the last delivery between women who have haematuria with or without bladder cancer. Materials and Methods: A total of 463 patients underwent diagnostic cystoscopy in Düzce University Faculty of Medicine between 1 June 2008 and 1 June 2013. Female patients who presented with persistent microscopic or macroscopic haematuria and underwent standard evaluation for haematuria including urinalysis, urine culture, urine cytology, urinary tract imaging with excretory urography or computerized tomography with contrast enhancement and endoscopic evaluation of the urethra and bladder were included in this study. Exclusion criteria were tobacco use and high risk occupations for bladder cancer such as textile, dry cleaning, painting and etc. Forteen women had hematuria due to benign conditions, and 18 due to bladder cancer. Data were retrospectively retrieved from the medical records of Duzce University Hospital. Results: Patients with haematuria due to benign reasons did not significantly differ from patients who were found to have bladder cancer in terms of age (p=0.28), menopausal status (p=0.29), mean parity (p=0.38), being nulliparous (p=0.57), parity ≥3 (p=0.22), age ≤18 years at first delivery (p=1.00), age ≥30 years at last delivery (p=0.26), age ≥35 years at last delivery (p=0.23) and percentage of the patients with advanced age (≥65 years) (p=0.18). Conclusions: It is difficult to predict a high risk for developing bladder cancer in women with haematuria based solely on reproductive factors.

Keywords: Age - bladder cancer - haematuria - menopause - reproductive factors

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Introduction

Bladder cancer ranks ninth among the other malignancies in women. The incidence is 4-fold higher in men than in women. Around 13000 people each year are estimated to die from bladder cancer (Jamal et al., 2009). Smoking severity, exposure to occupational diesel or fuel combustion fumes and NAT1 genotype are presented as independent predisposing risk factors for bladder cancer (Kobeissi et al., 2013). Schistosomiasis infection is also a predisposing factor for bladder cancer (Badawi et al., 1995).

Bladder cancer symptoms often manifest as intermittent or persistent microscopic/macroscopic haematuria. Painless macroscopic hematuria is usually the first symptom of bladder cancer especially in the group of women 50 years or older (Khadra et al., 2000). Compared to men, urinary symptoms such as dysuria and pain as presenting symptoms are less often in women, which is thought to be one of the reasons for diagnosis at higher stages in women than in men. Male-to-female ratio was reported to be 4.8:1 (Mishriki et al., 2012)

The gold standard for diagnosis of bladder or urothelial cancer is via cystoscope or ureteroscope with biopsy (Ho et al., 2013). Several methods have been employed for noninvasive diagnosis of bladder cancer at an early stage. Urinary survivin and UroVysion FISH technique are used to diagnose patients with bladder cancer (Ho et al., 2013; Srivastava et al., 2013). Even though initial diagnostic methods may fail to demonstrate any pathological findings, recent studies have provided clear evidence that 11.6% of patients with recurrent haematuria eventually develop malignant pathology in the following years (Mishriki et al., 2012).

Human and animal studies indicated that oestrogen and progesterone exert significant physiological effects on the lower urinary tract. Sex steroids cause symptomatic and functional alterations in the bladder (McGrath et al., 2006; Huang et al., 2009). The prevalence of detrusor instability, urinary incontinence and recurrent urinary

*[1]Department of Obstetrics and Gynaecology, [2]Department of Urology, Düzce University Faculty of Medicine, Düzce, Turkey *For correspondence: draliyavuzcan@yahoo.com*

tract infections that cause chronic inflammation may vary depending on the specific reproductive phase of female patient (Hextall, 2000; Aikawa et al., 2003). Studies exist suggesting that different incidence rates for bladder cancer in male and female patients could be associated with menopausal status and hormonal factors (McGrath et al., 2006; Huang et al., 2009). Among women with persistent haematuria, prediction of high risk patients for developing bladder cancer based on the reproductive factors prior to cystoscopy would be of great benefit in the management of this neoplasm.

The aim of this study was to compare age and reproductive factors such as menopausal status, parity, age at first delivery and age at the last delivery between female patients having haematuria with or without bladder cancer.

Materials and Methods

A total of 463 patients underwent diagnostic cystoscopy in Düzce University Faculty of Medicine between 1 June 2008 and 1 June 2013. Written informed consents were obtained from all patients prior to operation. Exclusion criteria were being male, tobacco use and high risk occupations for bladder cancer such as textile, dry cleaning, painting and etc. Thirty-two women with persistent microscopic or macroscopic haematuria underwent standard evaluation for haematuria including urine analysis, urine culture, urine cytology, urinary ultrasonography and excretory urography or computerized tomography with contrast enhancement (Mishriki et al., 2012). Patients' data were retrospectively retrieved from the medical records of Düzce University Hospital. Biopsy specimens obtained during diagnostic cystoscopy were evaluated by the Department of Pathology in Düzce University Faculty of Medicine. In our study, women whose periods have stopped for complete one year, and women above 55 years of age and who do not remember the date of their last period were considered menopausal. Parity was determined according to the number of pregnancies that have resulted in birth greater than 20 weeks of gestation or greater than 500 grams birth weight. Age at first delivery and age at last delivery were determined for patients who delivered at 37-42 weeks.

We compared the women with haematuria due to benign reasons and women with haematuria due to bladder neoplasm in terms of age, age being above 65 years, menopausal status, rate of nulliparous women and parity (≥3) in our study. Furthermore, we evaluated the proportion of patients with age ≤18 at first delivery, age ≥30 at last delivery and age ≥35 at last delivery.

Mean, standard deviation, proportion and frequency were used in descriptive statistics. The distribution of data was tested using Kolmogorov Simirnov Test. Independent sample T-Test and Kruskal-Wallis test were used in the analysis of quantitative data. Chi-square test was used to analyse qualitative data and Fischer's exact test was used where the conditions for using Chi-square test were not met. SPSS 21.0 package software was used in the analyses. p values <0.05 were considered statistically significant.

Results

Mean age of the study participants was 68±15 years (range 28-98). Of the patients, 14 (44%) had haematuria due to benign reasons, 18 (56%) were diagnosed with bladder cancer. Fourteen patients (44%) were below 65 years and 18 patients (56%) were at or above 65 years. Four patients (13%) were premenopausal and 28 patients (88%) were menopausal. Parity was 3 or above in 13 (41%) patients and 3 patients (9%) never had a delivery. Demographic characteristics of the patients were presented in Table 1.

Patients with haematuria due to benign reasons did not significantly differ from patients who were found to have bladder cancer in terms of age, age at or above 65 years, menopausal status, parity, rate of nulliparous women, age ≤18 years at first delivery, age ≥30 years at last delivery, and age ≥35 years at delivery (p=0.28; p=0.18;

Table 1. Demographic Characteristics of the Patients

		N %
Age (years)*		67.78±15.30
Benign lesions	Chronic cystitis	7 (21%)
	Polypoid cystitis	3 (9.3%)
	Cystitis cystica	3 (9.3%)
	Follicular cystitis	1 (3.1%)
	Mullerinosis	1 (3.1%)
Cancer Histological Type	Urethelial cell carcinoma	16 (21%)
	Adenocarcinoma	1 (3.1%)
	Sarcoma	1 (3.1%)
Age	<65 years	18 (56.2%)
	≥65 years	14 (43.8%)
Menopausal	Pre-menopausal	4 (12.5%)
	Menopausal	28 (87.5%)
Mean Parity*		2.56±1.54
Nulliparous		3 (9.3%)
Parity	<3	16 (50%)
	≥3	13 (40.6%)
Age at delivery	≤ 18 years	3 (9%)
	≥ 30 years	18 (56.2%)

*mean±standard deviation

Table 2. The Comparison of Age and Reproductive Factors between the Control Group and Patients with Bladder Cancer

			Bladder Cancer Group (Mean±S.D.)	Control Group (Mean±S.D.)	p value
Age			64.43±17.93	70.39±12.83	0.281
(years)	<65		8 (57.1%)	6 (33.3%)	0.178
	≥65		6 (42.9%)	12 (66.7%)	
Premenopausal			3 (21.4%)	1 (5.6%)	0.295
Menopausal			11 (78.6%)	17 (94.4%)	
Parity			2.29±1.54	2.78±1.56	0.380
	≥3	Yes	10 (71.4%)	9 (50.0%)	0.221
		No	4 (28.6%)	9 (50.0%)	
Age at the first delivery					
	≤18	Yes	11 (91.7%)	15 (88.2%)	1.000
		No	1 (8.3%)	2 (11.8%)	
	≥30	Yes	6 (50.0%)	5 (29.4%)	0.260
		No	6 (50.0%)	12 (70.6%)	
	≥35	Yes	9 (75.0%)	9 (52.9%)	0.228
		No	3 (25.0%)	8 (47.1%)	
Nulliparous	Yes		12 (75.0%)	17 (75.0%)	0.568
	No		2 (75.0%)	1 (75.0%)	

*p<0.05 were considered statistically significant: **Independent sample t-test / Chi-square test (Fischer's test) were used

p=0.30; p=0.38; p=0.57; p=0.22; p=1.00; p=0.26; p=0.23, respectively) (Table 2).

Discussion

Patients with macroscopic or microscopic haematuria requires detailed evaluation with urine cytology, upper and lower urinary tract imaging, and when necessary, should undergo cystoscopy due to the risk of bladder cancer (Mishriki et al., 2012). Benign causes of haematuria in women include urinary tract infections, foreign bodies (bladder, ureter or renal calculi) and renal tubular pathologies. Significant proportion of patients with persistent haematuria eventually develops malignant disease in later periods of their lives. Cystoscopic follow-up of patients should be continued unless a benign lesion is clearly identified as the underlying aetiology (Nabi et al., 2004; Mishriki et al., 2012). Haematuria is a less common symptom in women than in men (Mishriki et al., 2012) and bladder cancer is often characterized by more progressive disease in women (Chamie et al., 2013). It is, therefore, assumed that clinical evaluation based on menopausal status and reproductive factors in patients with persistent haematuria would provide benefits in early diagnosis and follow-up frequency for bladder cancer in high risk patients.

The incidence of bladder cancer is increasing worldwide and the rise is 25% much higher in women than in men (Jamal et al., 2009). Bladder cancer will be one of the important threads that will negatively affect the women's life in the future. This might have been caused by the changes in the life styles of men and women in time, which, until today, is thought to have provided protection against bladder cancer in women. Besides, there is still no clear consensus on the protective effects of hormonal and reproductive factors in women (McGrath et al., 2006; Huang et al., 2009). In order to clearly indicate the effects of reproductive factors, we evaluated only non-smoker women who had not previously worked in high risk occupations for bladder cancer.

The incidence of bladder cancer increases after 65 years of age. Prolonged exposure to environmental carcinogens and accelerated neoplastic process with advancing age are thought to be associated with malignant transformation of bladder urothelial cells (Shariat et al., 2009). Furthermore, Krześlak et al. (2012) suggested that oestrogen produced by the ovaries play a protective role in women, and therefore, bladder cancer in women occurs in advanced ages when the oestrogenic effects are subsided. In our study, patients with haematuria in whom bladder cancer was detected did not significantly differ from control patients in terms of age (p=0.28). According to our findings, control group and bladder cancer group were similar with respect to the proportion of patients at or above 65 years of age (p=0.18). This study was conducted in a single centre and in a homogeneous group of patients. This is likely to account for the discrepancy between our results and the literature.

McGrath et al. (2006) reported increased risk of bladder cancer in postmenopausal women. Hormone replacement therapy during menopause and menopause occurring at or above 48 years of age has been shown to be protective against bladder cancer (McGrath et al., 2006; Prizment et al., 2007). Although Prizment et al. (2007) reported increasing risk of bladder cancer with decreasing ovulatory years in women's life, we did not observe an increased incidence of bladder cancer in postmenopausal period (p=0.30). Our study is limited by the sample size; however, similar to our study, Huang et al. (2009) studied the association between bladder cancer and reproductive factors in Spanish women and did not report an increased risk of bladder cancer in association with menopausal status. During menopause, many factors such as obesity, eating habits and androgen levels in peripheral circulation affect the levels of oestrogen derivatives in the circulation (Aubertin-Leheudre et al., 2011). In our opinion, these factors need to be taken into consideration while evaluating the association between bladder cancer and the menopausal status.

During pregnancy, capacity and the compliance of urinary bladder changes in consequence of elevated oestrogen and progesterone levels (Blakeman et al., 2000; Rodriguez et al., 2004). Oestrogen and progesterone receptors have been identified in bladder and bladder cancer cells (Blakeman et al., 2000). Shen et al. (2006) provided evidence that growth of bladder cancer cells is stimulated in vitro by oestrogens and this effect is inhibited in the presence of antioestrogens such as 4-hydroxy-tamoxifen. IOWA study evaluating the risk factors for bladder cancer in women found no relationship between parity and bladder cancer (Prizment et al., 2007). In our study, the proportion of nulliparous women (p=0.57) or those with a parity ≥3 (p=0.22) was not significantly different between the patients with bladder cancer and the control group. Among patients with persistent haematuria, mean parity also did not differ between patients with and without bladder cancer (p=0.38). In contrast to our findings, there are numerous studies suggesting that the risk of bladder cancer is higher in nulliparous women and the risk of bladder cancer decreases with increasing parity (Prizment et al., 2007; Huang et al., 2009). A recent study demonstrated 30% reduction in the risk of bladder cancer in multiparous compared to nulliparous women (Dietrich et al., 2011). The fact that studies have yielded differing results regarding the association of bladder cancer with nulliparity and parity could be attributed to varying levels of progesterone and estetrol during each pregnancy the levels of which rise with oestrogen. Progesterone and estetrol, an oestrogen derivative produced by the foetal liver through hydroxylation and inactivation of the oestrogens, possess anti-oestrogenic activity in pregnancy (Coelingh et al., 2008). Furthermore, the association of hormones such as beta human chorionic gonadotrophin, human placental lactogen and prolactin, the levels of which rise during pregnancy, with bladder cells and bladder cancer still remains unknown.

Several studies have previously investigated the effects of first or last pregnancy in early (age ≤21 years), mid (21-35 years) and late (age ≥35 years) reproductive periods on the risk of developing bladder cancer (McGrath et al., 2006; Huang et al., 2009 ; Davis-Dao et al., 2011; Dietrich et al., 2011). Wolpert et al. (2010) claimed that delivering

the first child after 18 years of age has been associated with reduced total amount of exposure to oestrogens in a life time and with an increased prevalence of bladder cancer. Cantor et al. (1992) suggested that delivering the first child in later ages is associated with decreased risk of bladder cancer. Among patients with persistent haematuria in our study, the proportion of patients ≤18 years at first delivery did not differ between patients with or without bladder cancer (p=1.00). Similar to our results, many other studies have failed to demonstrate an association between the age at first delivery and the risk of bladder cancer (McGrath et al., 2006; Huang et al., 2009; Dietrich et al., 2011). Studies evaluating the association between age at last delivery and the risk of bladder cancer are very scarce. The proportion of patients with age above 30 or 35 at the last delivery did not differ between patients with haematuria due to benign reasons and those with bladder cancer in our study (p=0.26 and p=0.23, respectively). Similar to our study, Huang et al. (2009) also reported no association between age at last delivery and the risk of bladder cancer.

Lifelong exposure to oestrogen has been the focus of studies evaluating reproductive factors and bladder cancer. Our study and current literature suggest that the exact effects of other biologically active oestrogen derivatives together with androgens and progesterone-like hormones during both in pregnancy and menopause on malignant transformation of bladder lining remain still unknown.

According to this study; it is difficult to define female individuals with haematuria who are at high risk for developing bladder cancer based on reproductive factors. Therefore, cystoscopy should not be ignored or postponed according to the reproductive factors of these patients.

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