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MINI REVIEW

Bladder cancer: A mini review

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Abstract

Bladder cancer is the fourth most common cancer in the West, after prostate, breast, lung, and colorectal cancer. Between the ages of 60 and 70, it reaches its highest occurrence. Bladder cancer is 2.5 times as common in men than in women. According to the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) data, an additional 573,000 cases of bladder cancer were detected in 2020. This accounts for about 3% of new cancer diagnoses. Tobacco is the leading known cause of bladder cancer, accounting for 30-40% of all cases of urothelial carcinoma and up to two-thirds of all bladder cancers. The increase in the incidence of urothelial and squamous bladder cancer has been associated with mutations in the tumor suppressor gene phosphatase and tensin homolog (PTEN) and DNA mismatch repair gene MutS homolog 2 (MSH2) seen in Cowden and Lynch syndromes. In this review, our goal was to review the epidemiology, etiology, and main risk factors of bladder cancer.

Keywords: Bladder cancer, smoking, urology.

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Introduction

Following prostate, breast, lung, and colorectal cancer as the most prevalent malignancies in the Western world is bladder cancer (1). Its prevalence rises directly with age, peaking between the ages of 60 and 70. (2). Men are 2.5 times as likely than women to have bladder cancer.

Aromatic amines are the main bladder carcinogens. Several etiological variables affect the formation of bladder tumors (eg chronic infections, radiation, chemotherapy, occupational exposure to aromatic amines). But now, smoking is the most significant risk factor (3). Urothelial cell carcinomas make up more than 90% of bladder cancer cases (UCC). Squamous cell carcinoma (6–8%) and adenocarcinoma (1-2%) are similar histological forms. Squamous cell carcinoma used to be the most prevalent histological subtype in Egypt and other nations where endemic schistosomiasis has expanded. In the bladder, UCCs are most often found. Less than 10% of carcinomas are ureteral, renal pelvis, and urethral cancers (1–3).

Micro or macroscopic hematuria is the main sign that raises the possibility of a bladder tumor. Hematuria is often painless and intermittent, which delays diagnosis rather frequently (1).

Frequent urination, urgency, or discomfort in the bladder might be indications of a bladder tumor or carcinoma in situ (1). Urinary cytology and endoscopic urethroscopy (UCS) are used to diagnose UCC (UC). To see the kidneys and upper urinary system (renal pelvis and ureters), an intravenous urogram, CT scan, or ultrasound is needed (4). An exophytic bladder lesion may be directly seen with UCS. Diagnoses of high-grade squamous carcinoma, namely carcinoma in situ, may be made with the use of UC (CIS). Transurethral resection (TUR) or biopsy is scheduled for histological diagnosis in the event that UCC in the bladder is suspected (3,4).

In this study, we aimed to review the epidemiology, etiology, and main risk factors of bladder cancer.

Epidemiology

According to the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) data, an additional 573,000 cases of bladder cancer were detected in 2020. This accounts for about 3% of new cancer diagnoses. Most countries with a high incidence of bladder cancer are located in Southern and Western Europe and North America. Worldwide, men have the most significant incidence of bladder cancer in Greece, while women have the most in Hungary (5). Southern Europe has the most significant incidence of bladder cancer among the global population, with approximately 26.6 per 100,000 men and 5.8 per 100,000 women diagnosed with bladder cancer each year. Regions with the lowest prevalence of bladder cancer are Central Africa, South Central Asia, and West Africa, which are largely composed of countries with a below-average development index as a result of reduced exposure to chemicals in manufacturing and limited access to tobacco (5-7).

An estimated 12,400 cases of bladder cancer were diagnosed in the UK in 2020, accounting for 2.7% of all cancer diagnoses. Therefore, bladder cancer is the ninth most common cancer in the UK. Due to the greater prevalence of smoking and an older population, the bladder cancer prevalence rate has continued to rise in many European countries, including Germany, and is expected to increase further. However, a few countries have achieved significant success in prevention, with New Zealand's incidence decreasing by roughly 10% over the previous decade (5).

Bladder cancer is about four times more common in men than women, with incidence rates of 9.5 per 100,000 men and 2.4 per 100,000 women worldwide. Bladder cancer is the sixth most common and ninth most deadly tumor among men. This disparity is most likely linked to gender disparities in smoking, which could possibly explain why cancer rates are rising among women in industrialized countries (8).

While bladder cancer is the tenth most common malignancy in the world, it was the thirteenth most deadly cancer with an estimated 212,536 deaths in 2020. This accounts for 2.1% of all cancer deaths. Mortality rates follow incidence rates related to gender imbalance, with a death rate of 3.3 per 100,000 men almost four times higher than the worldwide mortality rate of 0.9 per 100,000 women (4,5,8,9).

The cumulative probability of dying from bladder cancer between birth and age 74 is 0.3% in men and 0.08% in women. Geographical and temporal trends of bladder cancer incidence globally tend to reflect the prevalence of tobacco use. However, infection with Schistosoma haematobium and exposure to other chemicals can contribute significantly in some populations, such as Egypt. Table 2.1 summarizes the number of deaths by country (10).

Etiology and risk factors

The bladder wall consists of four components: mucosa, submucosa, muscularis, and serosa. The typical urothelium of the mucosa consists of seven-celled thick layered, non-squamous, homogeneous cells with large umbrella cells on top. Tumors arising from urothelial cells endanger most bladder cancers, with an estimate of roughly 90%. Other non-urothelial bladder malignancies that may occur include squamous cell carcinoma (SCC), small cell carcinoma, adenocarcinoma, and other tumors with mixed histology (11,12). Because of urothelial direct exposure, the urothelial subtype is strongly associated with exposure to chemicals such as exposed workers or tobacco smoking. On the other hand, examples of the squamous cell subclass are more common in Africa, perhaps due to schistosomiasis, a protozoal disease that causes bladder irritation and inflammation (13).

Smoking

Tobacco is the leading known cause of bladder cancer, accounting for 30-40% of all cases of urothelial carcinoma and up to two-thirds of all bladder cancers. There are more than 1 billion active smokers worldwide, and smokers have a two to three more chance of developing bladder cancer. Tobacco smoke contains carcinogens, including beta-naphthylamine and polycyclic aromatic hydrocarbons (14). The metabolism of these particles in the bladder and throughout the system results in the formation of DNA inserts and permanent genetic mutation. These mutations can activate oncogenes or inhibit tumor suppressor genes and promote carcinogenesis (15). Certain inherited genotypes associated with defective detoxification enzymes have been shown to increase susceptibility to cancer in smokers. Although smoking is the most common tobacco product associated with the incidence of bladder cancer, pipe and cigar consumption is also associated with the development of urothelial carcinoma (16). One study showed that quitting smoking reduces the risk of urothelial carcinoma. Those who quit for 1-3 years had a relative risk of 2.6 compared to 1.1 for those who quit for more than 15 years (17).

Gender

As previously noted, about three-quarters of bladder cancer cases occur in men, with a higher incidence rate than women (5). Various theories have been proposed to explain the increased incidence of bladder cancer in men. First, smoking is much more common among men than women worldwide. Although exposure to carcinogens does not account for differences between the sexes, the physiological distribution of carcinogens may be different. Enzymes involved in aromatic amine degradation and foreign matter detoxification have been associated with bladder cancer-related carcinogen metabolism. It has been shown that these enzymes are expressed differently in men and women (18,19). In addition, differences in sex steroid synthesis and receptor expression underlie gender disparities. Age at menarche greater than 15 years, parity compared to women who have not given birth, and the use of estrogen or progestin drugs were associated with a lower risk of bladder cancer in women, suggesting that exposure to sex steroids reduces the risk of bladder cancer (20). From a tumor biology perspective, the androgen receptor (AR) is linked to the occurrence and progression of bladder cancer. AR expression appears to be downregulated in bladder cancer immunohistochemistry studies, and this downregulation tends to increase with increasing tumor stage and grade. In both men and women, smokers develop bladder cancer six years earlier than non-smokers (21).

Genetic factors

Although studies have failed to identify important germline genetic factors that favor sporadic bladder cancer, genome-wide correlation studies have identified several genetic loci with a small correlation with genetic susceptibility to bladder cancer. Among them, the deletion of N-acetyltransferase 2 (NAT2) and glutathione S-transferase (GSTM1) is associated with the ability to metabolize aromatic amines and thus plays an important role in the subset of individuals exposed to environmental carcinogens (22). Also, both seem to have a cancer-causing relationship with cigarette smoking. Although first-degree relatives of bladder cancer patients are twice as likely to develop urothelial bladder cancer, it is extremely rare in families at high risk of bladder cancer. The absence of a Mendelian inheritance pattern in hereditary bladder cancer renders traditional family tree linkage analyzes ineffective. The possibility supports a complex explanation that certain genes amplify environmental stressors. The increase in the incidence of urothelial and squamous bladder cancer has been associated with mutations in the tumor suppressor gene phosphatase and tensin homolog (PTEN) and DNA mismatch repair gene MutS homolog 2 (MSH2) seen in Cowden and Lynch syndromes (22,23).

Age

One of the hallmarks of bladder cancer is its tendency to affect the elderly population. In the United States, more than 90% of people diagnosed with bladder cancer are over the age of 55, with an average age of diagnosis of 73. Aging puts people at risk for numerous more malignancies (24). This suggests a disease progression that takes decades after exposure to toxins to override cellular tumor suppressor systems (25).

Conclusions

Bladder cancer is seen very frequently in genetically predisposed male smokers. In addition, advancing age should be kept in mind as a serious risk factor.

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