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The Etiology of Bladder Cancer

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Abstract: Urothelial cancer of the bladder, known as bladder cancer, is one of the most common cancers in the world. The incidence is rising steadily particularly in developed nations where tobacco smoking is prevalent. With the development of accessible diagnostic modalities, enhanced surgical techniques, and improvement in novel immunotherapy regimes, overall survival rates are improving. Better understanding of the epidemiology and etiology of bladder cancer will lead to improved preventative strategies particularly modifiable risk factors like smoking.

Keywords: etiology of bladder cancer; genetics of bladder cancer; mortality in bladder cancer; schistosomiasis infection and bladder cancer; transitional cancer of the bladder

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INTRODUCTION

Bladder cancer is the 10th most diagnosed cancer worldwide, with 573,278 new cases diagnosed in 2020 (1). The major histological type of bladder cancer is transitional cell carcinoma (90%) which arises from urothelial cells in the bladder, while squamous cell carcinoma (due to Schistosomiasis infection and recurrent urinary tract infections) and adenocarcinoma are less common. Typical presentation for bladder cancer is mainly hematuria (either non-visible microscopic or frank macroscopic hematuria), irritative lower urinary tract symptoms, and less commonly, suprapubic pain. Increasingly, more patients have been referred for urological management in the event of non-visible (microscopic) hematuria based on easily accessible use of urine dipsticks. Once confirmed on urine microscopy for the presence of red blood cells, the patient will be subjected to renal tract imaging (either ultrasound of kidneys or computed tomogram urography) and flexible cystoscopy. Obvious frank visible hematuria will certainly trigger the same approach of imaging and flexible cystoscopy. Once a suspicious lesion is seen on imaging or in cystoscopy, resection in the form of transurethral resection of bladder tumor (TURBT) will be performed urgently to attain histopathological confirmation.

With the advancements in radiological imaging coupled with refined diagnostic flexible cystoscopes, bladder cancers are much more likely to be diagnosed at earlier stages. Therefore, most bladder tumors are superficial (without any invasion into deeper muscular layers) on first TURBT and this surgery, if completed successfully with no macroscopic lesion left behind, will usually be sufficient for disease control. Based on the histopathological grade and subtype of bladder cancer, a regimen of follow up involving check cystoscopies and upper tract renal imaging will be implemented to detect any recurrence. The advent of intravesical treatment of mitomycin and Bacillus Calmette-Guerin have proven to be effective in reducing the risk of recurrence and progression of bladder transitional cell carcinoma (TCC).

However, if there was muscle invasive TCC noted on first TURBT, the treatment regimen will then involve either radical radiotherapy to bladder or neoadjuvant chemotherapy followed by radical cystectomy. Muscle invasive TCC are more aggressive and lethal. Metastatic TCC of bladder often carry quite a poor prognosis as the response to cisplatin-based chemotherapy regimen is limited. However, in this new era of immunotherapy, various immune checkpoint inhibitors (programmed cell death protein, PD-1 and cytotoxic T cell antigen, CTLA-4) have provided some modest improvement in survival and bring hope to this cohort of patients with metastatic bladder cancer.

Bladder cancer is the 14th most common cause for cancer-related deaths worldwide with 212,536 deaths in 2020 which equates to 2.1% of all cancer deaths. In men, bladder cancer is the 6th most common cancer and the 9th leading cause of cancer deaths. The incidence of carcinoma of bladder have been rising, especially in Europe and North America, largely due to tobacco smoking. There is an overpowering male predominance in incidence and mortality rates. Elsewhere, in parts of Northern Africa, Schistosomiasis infections still account for bladder squamous cell carcinoma (SCC) cases. Bladder cancer typically presents in the older patients with 80% of diagnoses made in those who are above age 65 in the United States (2). This perhaps reflect the chronicity of carcinogenic exposure to overcome the urothelial tumor suppressor mechanisms leading to carcinogenesis (3).

MORTALITY

Bladder cancer is the 14th most common cause for cancer deaths worldwide with 212,536 deaths in 2020 and this equates to 2.1% of all cancer deaths. However, in men, bladder cancer is the 6th most common cancer and the 9th leading cause of cancer deaths (1). The age standardized rate (ASR) for mortality in men was 3.3 per 100,000 compared to ASR of 0.9 in women. This mortality rate of almost four times more in men than in women perhaps is reflective of the incidence rate disparity where incidence ASR in men is 9.5/100,000 compared to 2.4/100,00 in women (1). The mortality rates in regions with highest incidence (Europe and North America) is about 2.1–3.3 ASR per 100,000; however, the highest mortality rates in the world lies with Northern Africa with a mortality rate of 5.2/100000 (4, 5). The high mortality rates in Europe and North America are reflective of the influence of tobacco smoking whereas the highest incidence in Northern Africa is largely due to Schistosomiasis haematobium infections which causes squamous cell carcinoma of bladder.

DEMOGRAPHY AND GENDER

The highest incidence rates among both sexes are in Southern Europe (ASR 15.3/100,000), Western Europe (ASR 13/100000) and North America (ASR 10.9/100000), while the lowest rates are from South Central Asia (ASR 1.9/100000) and Middle Africa (ASR 1.6/100000). Greece has the highest incidence rates among men in the world while Hungary has the highest incidence rates among women (4). As mentioned above the incidence and mortality rates in males are approximately 4 times higher compared to females. This marked discrepancy may be largely attributed to patterns of cigarette smoking where men are more likely to smoke longer than women. However, in United States, there has been a rising trend among women smokers with 39% of bladders cancers among women were attributed to smoking in 2014 as compared to 49% among men (6). Another theory for this male predisposition is due to the likelihood of further occupational chemical exposure when working in chemical, dyes, and paints industries.

GENETICS AND HEREDITARY

Genome wide association studies have identified potential genetic loci that has some association with the development of bladder cancers. Some of the genes identified include NAT2 (slow acetylator which detoxifies aromatic amines) (7) and GSTM1 (enzyme which detoxifiers environmental carcinogens) (8), with NAT2 and GSTM1 having been shown to have synergistic effect with tobacco smoking (9). Certain hereditary syndromes like Lynch syndrome and Cowden's syndrome can predispose an individual to develop bladder cancer. In Cowden's syndrome, there is a defect in the tumor suppressor gene PTEN which predisposes to various tumors including TCC (10). In Lynch syndrome, there is development of non-polyposis colorectal cancer with an increased risk of bladder cancer due to defect in DNA mismatch repair (11).

SMOKING

The most significant modifiable risk factor for bladder cancers is tobacco smoking. Smoking has been shown to increase the risk of developing bladder cancer by up to four times, with mortality from bladder cancer due to smoking is only second to lung cancer due to smoking (12). The well-known carcinogens in tobacco smoke include beta-naphthylamine and polycyclic aromatic polycarbons. These carcinogens promote inflammation, and metabolizes in the bladder leading to DNA-adduct formation and permanent genetic mutations which either suppress tumor suppressor genes or activates oncogenes (3). Another study showed that there exists a difference in types of smoking, with pure tobacco cigarette smokers were at greater risk compared to pure pipe smokers or pure cigar smokers (13). A meta-analysis also revealed that passive second-hand smokers unfortunately develop a 22% increased risk of bladder cancer when compared to unexposed non-smoking individuals (14).

OCCUPATIONAL EXPOSURE

Another important modifiable risk factor for bladder cancer is exposure to hazardous environmental and/or occupational compounds found in dye, paint, rubber, petroleum, and metal industries. These compounds usually contain carcinogens which includes aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons (15). Other professionals who might carry an increased risk due to exposure to such carcinogens include firefighters, hairdressers, and farmers using fungicides. These carcinogens have been estimated to cause about 18% of bladder cancers, usually decades after exposure (16).

SCHISTOSOMIASIS INFECTION

A less common but aggressive bladder cancer is SCC of bladder which is caused by *Schistosomiasis haematobium*. This trematode is endemic to the Middle East and North Africa and has resulted in bladder SCC to become the second most form of cancer in those regions after hepatic cancer (17). The infection in the bladder caused by Schistosomiasis leads to generation of carcinogens like N-nitroso compounds and also enhances inflammation which induces free oxygen radicals and N-nitrosamines (18). The development of SCC seems to be at a much quicker pace compared to tobacco or hazardous chemicals exposure.

OBESITY

Obesity has been long associated with various forms of cancers including bladder cancers. One meta-analysis showed that obesity is an independent risk factor which increases the risk of bladder cancer by 10%. There is a 4.2% increased risk

of bladder cancer for every increase in 5 kg/m^2 weight (18). Well-established mechanisms linking obesity to bladder cancers include promotion of chronic inflammation with cascading cytokines, production of insulin like growth factors, and adipokines, which can affect angiogenesis and apoptosis, leading to carcinogenesis (19, 20).

CONCLUSION

The incidence of urothelial carcinoma of bladder have been rising especially in Europe and North America largely due to tobacco smoking. There is an overpowering male predominance in incidence and mortality rates. In parts of Northern Africa, Schistosomiasis infections still account for bladder SCC cases. The modifiable risk factors in bladder cancers include tobacco smoking, occupational exposure to carcinogenic chemicals and obesity. In Schistosomiasis endemic regions, better water disinfection, avoiding freshwater swimming and mass treatment of praziquantel can help decrease the risk of bladder SCC. Prevention strategies aimed at modifiable risk factors like smoking cessation will continue to reduce the incidence rates. Earlier detection of superficial localized bladder cancers will also lead to improvement in cancer survival rates.

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