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Environmental risk factors for bladder cancer

Środowiskowe czynniki ryzyka rozwoju raka pęcherza moczowego

Fryderyk Menzel [1 (a, b, c)], *Aleksandra Drabik* [2 (a, b, c)], *Paweł Hackemer* [1 (b, c)], *Anna Otlewska* [3 (b, c)], *Krystyna Pawlas* [4, 5 (c, d, e)]

[1] *Department of Urology and Oncological Urology, Wroclaw Medical University, Wroclaw, Poland*
[2] *Studenckie Koło Naukowe Zdrowia Środowiskowego i Epidemiologii, Wroclaw Medical University, Wroclaw, Poland*
[3] *Department of Endocrinology, Wroclaw Medical University, Wroclaw, Poland*
[4] *Department of Hygiene, Wroclaw Medical University, Wroclaw, Poland*
[5] *Institute of Occupational Medicine and Environmental Health, Sosnowiec, Poland*

[(a)] *design*
[(b)] *drafting the article*
[(c)] *compiling literature*
[(d)] *critical revision*
[(e)] *supervision and final approval of the version to be published*

ABSTRACT

Bladder cancer is a disease characterized by an abnormal growth of cells in the urinary bladder. Potentially, it can infiltrate nearby tissues and metastasize to distant organs. It affects more than 3 million people, with over 430,000 new cases a year. Environmental risk factors have significant impact on the development of bladder cancer, with tobacco smoke being the single most significant risk factor. Arsenic, nitrates, and chlorine in drinking water are also potentially associated with an elevated risk of this disease. In this paper, we review most significant environmental risk factors for primary bladder cancer and analyze prevention methods.

Key words: bladder cancer; environmental risk factors; etiology; epidemiology

STRESZCZENIE

Rak pęcherza moczowego jest schorzeniem charakteryzującym się nieprawidłowym wzrostem komórek w pęcherzu moczowym. Potencjalnie może naciekać okoliczne tkanki i dawać przerzuty do odległych narządów. Rak pęcherza moczowego dotyka ponad 3 miliony ludzi na świecie, a co roku diagnozowanych jest ponad 430 tysięcy nowych przypadków. Środowiskowe czynniki ryzyka mają znaczący wpływ na rozwój raka pęcherza. Dym papierosowy jest czynnikiem ryzyka o największym znaczeniu. Arsen, azotany i związki chloru zawarte w wodzie pitnej są prawdopodobnie związane z podwyższonym ryzykiem raka pęcherza moczowego. Celem tego artykułu jest przegląd środowiskowych czynników ryzyka pierwotnego raka pęcherza moczowego oraz analiza metod zapobiegania.

Słowa kluczowe: rak pęcherza moczowego, środowiskowe czynniki ryzyka, etiologia, epidemiologia

INTRODUCTION

Bladder cancer is a serious condition in which we observe an abnormal growth of tissue in the urinary bladder. The International Agency for Research on Cancer (IARC) estimates that worldwide, bladder cancer is the seventh most commonly diagnosed cancer in men [1]. Each year, almost 430,000 people are diagnosed with bladder cancer. The incidence of bladder cancer in men is 3 times higher compared to women. In Poland, according to Polish National Cancer Registry, bladder cancer is the fifth most commonly diagnosed cancer in male population [2]. It is responsible for more than 6400 deaths in Poland each year. The incidence and mortality rates vary significantly across countries. It is associated both with modifiable factors, such as differences in occurrence of risk factors, access

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to diagnostic procedures, and availability and quality of treatments specific for each country, and with genetic and ethnic background. Overall, 5-year survival including all stages in Poland is approximately 60–65%, while in the United States, it is over 80%. Unfortunately, in patients with advanced disease and distant metastases, it drops drastically to 8.1% [3].

Taking into consideration the high recurrence rate of the disease and still unsatisfactory treatment efficacy, primary prevention is essential. Environmental carcinogens contribute to the development of neoplasms. Therefore, we reviewed most significant environmental risk factors for primary bladder cancer and analyzed prevention methods.

TOBACCO SMOKE

Smoking is considered to be the main known cause of bladder cancer and results in an incidence rate even five times higher than that seen in non-smokers [4, 5]. Tobacco smoke includes over 60 known carcinogens, which belong to multiple chemical classes, such as aromatic amines, N-nitrosamines, aldehydes, polycyclic aromatic hydrocarbons (PAHs), and volatile organic hydrocarbons. Especially aromatic amines are considered to be associated with bladder cancer development [6].

A number of studies have proved that the risk is dose-relate. In general, the risk increases with the duration of smoking and number of cigarettes smoked per day [5]. Typically, the risk partially decreases in former smokers in comparison to current smokers; however, it is still significantly higher when compared to never-smokers. Usually, there is a long latency period of even 20–30 years before developing symptoms.

The influence of environmental tobacco smoke exposure, including passive and household smoking, has been investigated in a number of studies, but the results are still inconclusive, and additional research is required to determine the correlation. However, several studies have indicated a strong association between second hand smoking (SHS) and developing various types of cancer [7, 8].

Patients' awareness regarding the relationship between smoking and urinary bladder cancer is low and insufficient [9]. The majority of patients diagnosed with non-muscle invasive bladder cancer is not aware of that association and of the importance of smoking cessation for recurrence prevention [10]. That suggests that there is a need for better cancer education concerning urinary tract neoplasms.

CARCINOGENS IN DRINKING WATER

Substances and elements such as arsenic, chlorine, chloramine, or nitrates contained in drinking water are potentially associated with a higher risk of developing bladder cancer [11]. Identification of hazardous and toxic compounds might result in better prevention and hence reduce the number of people exposed to these carcinogens.

Arsenic is a chemical element classified as metalloid. Toxic levels of arsenic result in epigenetic changes, such as hypermethylation of tumor suppressor genes p53 and p16, which promotes carcinogenesis. Inorganic arsenic is the most prevalent form and has been confirmed as a carcinogen which might promote lung, skin, prostate, and bladder cancer. Furthermore, inorganic compounds tend to be more toxic than organoarsenicals [12]. In a number of countries, including Bangladesh, China, Hungary, and India, arsenic can be found at high concentration both in ground water and surface soil. Exposure to high doses of arsenic is related to a higher incidence rate of bladder cancer and high mortality rates even 20 years later [13, 14].

There are several studies analyzing the association between bladder cancer and nitrate in drinking water, although their results are inconsistent. There is some evidence that elevated nitrate levels might correlate with a higher risk of death from bladder cancer [15]. By contrast, studies from the United States and the Netherlands showed no association between nitrate exposure and the risk of bladder cancer [16, 17].

Water chlorination is a common method of disinfection, especially often used for swimming pool sanitation. While chlorination is definitely effective in killing bacteria and microbes, there are certain serious drawbacks of this method. Chlorine can react with organic compounds, which results in the production of disinfection by-products, such as trihalomethanes (THMs) and haloacetic acids. Chlorination by-products are a potential risk factor for the development of bladder cancer [18].

OCCUPATIONAL RISK FACTORS

Certain industries (chemistry and construction) and professions, such as painters, leather manufacturer workers, petrochemical workers, or plastic welders, are exposed to a high risk of bladder cancer. Occupational exposure may account for 5-25% of bladder cancer cases [19].

Occupational exposure to aromatic amines, such as 4-aminobiphenyl, is considered important in

bladder cancer development. Currently, most of the developed countries have limited the use of aromatic amines in the industries due to their carcinogenic activity. However, in the past, they were widely used to produce dyes, pesticides, fungicides, and pharmaceuticals. Occupational exposure to these carcinogens is associated with an elevated risk of urinary bladder cancer and higher mortality even 50 years later [20]. A study carried out among rubber manufacturing workers has shown that o-toluidine exposure is associated with an increased relative risk of bladder cancer compared to the general population [21].

Firefighters are particularly exposed to a number of contaminants including polycyclic aromatic hydrocarbons (PAHs). Those substances can be absorbed by inhalation or dermally. Many combustion products can be classified as carcinogens. Several studies have shown that they have significantly elevated the risk for numerous neoplasms, including melanoma, leukemia, lung, brain, prostate, kidney, and bladder cancer [22, 23].

GENETIC SUSCEPTIBILITY TO ENVIRONMENTAL TOXINS

In most cases, bladder cancer is not a hereditary condition, but the result of the accumulation of mutations in somatic cells. Mutations in chromosomal genes which play a role in preventing cells from dividing too rapidly, such as FGFR3, RB1, HRAS, TP53, TSC1, may result in abnormal growth of the tissue. Changes in genes located in chromosome 9 and 22 are a common cause of bladder cancer. Mutations in the core promoter of the telomerase reverse transcriptase gene (TERT) are currently considered to be the most common mutations in bladder cancer, occurring in 55% to 88% of cases [24]. The studies aimed to examine the role of mutations in p53 suppressor gene have shown that mutations in this gene occur much more frequently in high grade tumors than in low grade tumors, although the evidence is not sufficient to use it as a prognostic marker [25, 26].

Another important mechanism in the process of carcinogenesis is epigenetic modification, such as alteration in DNA methylation, histone modification, or microRNA gene silencing. These modifications can cause significant reduction in the expression of DNA repair genes, which are responsible for repairing the damage caused by endogenous causes, including reactive oxygen species, and exogenous ones, such as ultraviolet radiation, toxin, or viruses. In a number of studies, hypermethylation of various DNA repair genes, including COX2, MGMT, GSTP1, was identified in bladder cancer [27]. Studies conducted in Gdansk, Poland, investigating the expression of selected genes provided evidence that also MBD4, TDG, MLH1, and MLH3 play an important role in the pathogenesis of bladder cancer [28].

Moreover, there are a number of genes encoding proteins which are active in the metabolism of carcinogens and environmental toxins. Glutathione S-transferase Mu 1 (GSTM1) and N-acetyl transferase2 (NAT2) are well-studied examples of such genes. Polymorphisms in NAT2 gene result in variation in acetylation rate among human populations. Thus, we can distinguish rapid, intermediate, and slow acetylators. This variation might have severe consequences, as slow acetylators are more prone to carcinogens and toxins. Nuclear matrix protein 22 (NMP22) could be used as a diagnostic marker of bladder cancer in patients with genetic susceptibility (NAT2 slow acetylators) [29, 30].

URINARY SCHISTOSOMIASIS

Schistosoma haematobium is a parasite and an etiologic agent for urinary schistosomiasis and can be found in vast regions of Africa and the Middle East. Chronic infection is linked with urinary bladder cancer [31]. While in Europe and the United States over 90% of bladder cancer cases are transitional cell carcinomas, schistosomiasis is significantly associated with squamous cell carcinomas (SCC) [32].

PREVENTIVE FACTORS

The prevention of bladder cancer is important, especially among those at higher risk. While obesity seems to slightly increase the risk of bladder cancer, physical activity may protect against it [33]. Balanced diet composed of fruits and vegetables, rich in vitamins and microelements, may be beneficial in cancer prevention. Some studies suggest protective effect of vitamin C, vitamin E, selenium, and increased intake of fruits and vegetables [34]. Different diets including combinations of fruits, vegetables, meat, and dairy products were compared. Increased fluid intake, especially tea, seems to reduce the incidence rate of bladder cancer. Still, this might be associated with increased urine production and frequency of urination. However, due to limitations of the studies, there is no sufficient evidence and fur-

ther research is required [35]. While there is no strong evidence that a certain diet or type of food is an independent factor affecting the risk of cancer, balanced diet and physical activity indirectly decrease the risks.

CONCLUSIONS

Environmental risk factors have significant influence on bladder cancer pathogenesis. Due to the large amount of carcinogenic substances, tobacco smoke is considered the main known cause of transitional cell carcinoma. High concentration of arsenic in drinking water is also considered to be an important risk factor, especially in areas where soil and ground water are contaminated with its inorganic forms. The influence of nitrates and chlorine is still debatable and further studies are needed to clarify it. In recent years, occupational risk factors have been reduced, with limitations imposed on the use of aromatic amines in various industries.

Primary prevention might significantly reduce the incidence rate of bladder cancer. Smoking cessation is associated with a lower number of primary cancers and recurrence rate. Therefore, adequate cancer education and informing people about the harmful consequences of smoking might be beneficial for their health.

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Adres do korespondencji:
Fryderyk Menzel
Katedra i Klinika Urologii i Onkologii Urologicznej
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu
ul. Borowska 213, 50-556 Wrocław
tel.: 71 733 10 10
e-mail: fryderyk.menzel@student.umed.wroc.pl