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Risk Factors of the Bladder Cancer

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ABSTRACT

Introduction and purpose: Bladder cancer [BC] is one of the most common cancers in the world. The number of cases of BC recorded in the National Cancer Registry has been approximately 7.5 thousand annually since 2013. The National Cancer Registry's "Cancer in Poland in 2021" report ranks BC as the 4 most frequent cancer in men in Poland. A deeper comprehension of the disease will aid in the creation of more effective preventative and therapeutic measures. Our effort aims to categorize and characterize risk factors [RF] for BC.

Review Methods: A systematic search of the ‘’PubMed’’ database was conducted, focusing on studies published within the last 5 years. The search strategy used relevant key words related to BC and RF. Studies were included if they provided information on RF associated with BC in the adult population. The articles most pertinent to the subject have been chosen.

State of knowledge: BC is recognized to have several RF. Current studies suggest that smoking is the most important RF. Other factors that increase the risk of BC include, for ex. occupational exposures to arsenic, toluene, rubber, petroleum products, agricultural chemicals, dyes, aromatic amines. BC development is also influenced by a positive family history of BC and

diesel exhaust emissions, certain dietary components, low physical activity, obesity, diabetes, male sex, and older age. Decreased risk of BC is observed in cases of higher consumption of MUFAs, plant-based oils, fish, some fruits and vegetables.

Summary: Variety of environmental, genetic and medical factors are considered with an increased risk of BC. Studies of RF for this disease may help in the development of prevention, enabling the implementation of proper screening programs and diagnostic procedures. More research on this subject is necessary to completely comprehend the etiopathology of BC, identify all RF, and determine whether they may be used in the process of treatment.

Keywords: bladder cancer; risk factors

1. Introduction

Bladder cancer (BC) is a significant social problem. The National Cancer Registry's " Cancer in Poland in 2021" report ranks bladder cancer as the fourth (6,3%) most frequent cancer in men in Poland. It was also the fourth leading cause of cancer deaths in men according to data from 2021 in Poland.[1] According to GLOBOCAN data, in 2022, there were over 614 298 new cases of bladder cancer and approximately 220 596 deaths due to this cancer. Bladder cancer is the most common malignant tumor of the urinary system.[2] Significantly more cases of the disease are observed among men.

Making up 90% of all cases, urothelial bladder carcinoma (UBC) is the most common histologic type of bladder cancer. The basal cell layer (carcinoma in situ, muscle-invasive urothelial cancer, and squamous cell carcinoma) or intermediate cells (noninvasive urothelial cancer) are the origins of bladder cancer. Bladder cancer is categorized according to the degree of tumor differentiation into: well-differentiated tumors with low malignancy potential (G1), tumors with an intermediate degree of malignancy (G2), poorly differentiated tumors with high malignancy (G3), undifferentiated, anaplastic G4 cancers and stage (muscle-invading or not). It can also be classified as flat (urothelial carcinoma in situ and invasive) or papillary (papilloma, low malignant potential, and papillary carcinoma) based on its form and route. The degree of invasion into the bladder wall and the cellular grade of the tumor are taken into

account when assessing prognosis and choosing treatment. Considering these factors, bladder cancer is divided into Non-muscle-invasive bladder cancer (NMIBC) (about 75%) and Muscle-invasive bladder cancer (MIBC) (about 25%). NMIBC is typically less aggressive.[3] Early BC is usually asymptomatic. This in turn translates to late diagnosis and worse treatment outcomes.

BC has many risk factors, including: smoking, male sex, increasing age, toxic substances, for example benzene products, aromatic amines, rubber, genetic factors, diesel exhaust emissions, obesity, lifestyle, low physical activity, diet.[4-42] It's a multifactorial disease that requires a thorough understanding of all risk factors, which would enable more effective prevention, early diagnosis and yield better treatment outcomes.

Objective: The aim of our study is to review currently available articles on PubMed about risk factors of bladder cancer to better understand the causes of bladder cancer.

2. State of knowledge:

Risk factors for bladder cancer are not fully known and are still the subject of much research. Finding appropriate risk factors appears to be essential for both early disease diagnosis and treatment.

2.1 Smoking

Cigarette smoking is one of the main risk factors for bladder cancer Masaoka's et al. analysis of 10 Cohort Studies in Japan showed that in men, the HRs of current and past smokers were 1.47 and 1.96, respectively, when compared to those who had never smoked. In women, the risk was higher for present smokers than for never-smokers, while the risk was higher for past smokers but not statistically significant. The risk of the disease increased linearly with increasing years of smoking in men. As men's years of stopping smoking increased, their risk went down. When compared to never-smokers, former smokers who had been smoke-free for more than ten years did not exhibit a markedly elevated risk.[4] Also, waterpipe smoking is a risk factor for bladder cancer. Hadżi et al. in their study emphasized that exclusive waterpipe smoking was associated with a significantly increased risk of bladder cancer (OR = 1.78; 95% CI, 1.16–2.72). Additionally, they noticed that multiuse of other things, such as opium, cigarettes, and/or nass (OR = 7.48; 95% CI, 5.77–9.712) and combined usage of waterpipe and other products (OR = 2.55; 95% CI, 1.79–3.65) were more strongly associated with bladder cancer. However, those who began smoking water pipes before the age of twenty had a larger chance to get bladder cancer. Jee et al. also showed that there was more than doubled risk of bladder cancer in the groups that smoked the most. The risk of bladder cancer remained elevated even after long-term cessation of smoking, according to dose-response meta-analyses that

revealed a plateau for smoking intensity. According to the meta-analysis, the group that stopped smoking had a 1.83-fold increased risk of bladder cancer when compared to those who never smoked.[6] Abdolahinia et al. also emphasize that those who had a 20 pack-year history of smoking (AOR: 3.4; 95% CI = 1.3, 8.9) and those persons had an over 20 pack-year history of smoking (AOR: 15.8; 95% CI = 5.9, 42.4) had a higher risk of bladder cancer than those who never smoked. In their analysis the groups who smoked up to 20 pack-years had a 3-fold increased chance of bladder cancer and those who smoked more than or equal to 20 pack-years had a 15-fold increased chance of bladder cancer. [7] Much evidence points to the huge contribution of cigarette smoking to the development of bladder cancer. Researchers have also shown that smokers with certain genetic variants have a higher risk of getting bladder cancer. Such a relationship they showed especially for the NAT2 genotype. It is a tobacco smoke metabolism gene. Specifically, people with the NAT2 genotype with slow acetylation by ever smoking had a much higher risk of aggressive bladder cancer.(HR, 5.00 [95% confidence interval, 2.67-9.38]). Additionally, it was discovered that smoking raised the incidence of lethal urotherial cancers, especially in those with the NAT2 slow acetylation genotype (rs1495741).[8] It has also been demonstrated that quitting smoking is a crucial part of preventing bladder cancer. Gaffney et al. found that after smoking cessation, the risk decreases after 1-3 years, and approaches that of non-smokers after about 15 years. They presented data that the risk of current smokers is HR 4,1 (95% CI 3,7–4,5), while former smokers: HR 2.2 (95% CI 2.0–2.4).[9] The key to reducing the incidence of this cancer may lie in promoting measures to reduce cigarette smoking among the population.

2.2 Sex and age

According to the Polish National Cancer Registry, over 98% of bladder cancer cases occur in men over the age of 45. It is three times more common in men than in women. [1] Researches by other scientists around the world have also identified this relationship. Luo et al. in their study emphasized that those who were older and male were at a significantly higher risk. [10] In the article ,, Epidemiology of Bladder Cancer in 2023: A Systematic Review of Risk Factors" emphasized that in 2018 it was the sixth most prevalent type of cancer in men. GLOBOCAN reports that men accounted for more than three-quarters of newly diagnosed BC cases in 2020 in the world. The incidence ratios of ASRs for males and females (per 100,000 people) range from 6:1 to 2:1 depending on the location. The incidence ratios for men and women in West Asia and East Africa are 15 and 2.6, respectively (a ratio of 6:1) and 4.2 and 2.4, respectively (a ratio of 2:1), for example in West Asia, the incidence ratios for men and

women is 15 versus 2.6 for men versus women (ratio of 6:1).[11] Richters et al. in their article have noted that lifetime risk is 1.2% for women and 3.9% for males in the US. Both males and females aged 80 have the highest risk of this disease. Most BC patients receive their diagnosis when they are 60 years of age or older in the US.[12]

2.3 Toxic chemical exposure

Exposure to toxic chemicals is one of the main factors that increase the risk of bladder cancer. Such substances include, for example arsenic, nitrosamine, rubber, aromatic amines and hydrocarbons, benzene products and many others. The link between diesel exhaust fumes exposure and BC risk was presented by Koutros et al. A higher risk of BC was linked to cumulative respirable elemental carbon (REC) exposure. Participants who having a cumulative REC greater than 396 μg/m3-years have an increased risk of cancer (Odds ratio (OR) = 1.75 (95% CI, 0.97–3.15) in the U.S. and OR = 1.54 (95% CI, 0.89–2.68) in Spain). Particularly exposed to this danger are for example heavy railroad workers, truck drivers and mechanics.[13] Another social group with an increased risk is the petroleum industry workers. The study of Shala et al. underlined that workers who had ever been exposed to benzene had a 25% higher risk of bladder cancer than those who had not (HR = 1.25, 95% CI: 0.89–1.77). Those with ≥18.8 years of benzene exposure showed the biggest relative risk (HR = 1.89, 95% CI: 1.14–3.13; p-trend = 0.044).[14] Occupational exposure to organic solvents was performed by Xie et al. Occupational groups exposed to solvents include, for example, rubber workers, painters, the dry cleaning industry workers to name a few. Those who had ever been exposed to xylene (OR = 1.67, 95% CI: 1.13–2.48), toluene (OR = 1.60, 95% CI: 1.06–2.43), and benzene (OR = 1.63, 95% CI: 1.14–2.32) separately had higher risks of bladder cancer. Furthermore, the research revealed a significantly increased risk for concurrent exposure to toluene, xylene, and benzene.[15] In the Be-Well Study researchers found consistently higher odds of developing advanced-stage non-muscle-invasive bladder cancer NMIBC for asbestos at all levels of exposure duration (with ORs of 1.46 (95% CI, 1.04-2.05) for less than five years, 1.48 (95% CI, 1.00-2.16) for five to twenty years, and 1.39 (95% CI, 0.88-2.17) for over twenty years). This suggests a saturation effect. Asbestos has also been linked to an increased incidence of advanced-stage NMIBC (OR = 1,43; 95% CI, 1,11-1,84).[16] Men who worked with silica for ≥27 years had 1.41 (95%CI: 1.01-1.98) times increased the risk of bladder cancer compared to those who were not exposed as demonstrated in the study Latifovic et al. They also reported a 67% (OR: 1.67, 95%CI: 1.06–2.62) higher risk of BC when workers were exposed to silica and asbestos at the same time.[17]

2.4 Diet

The study BLEND showed that whereas a higher intake of total cholesterol was linked to an increased risk of BC, particularly in men, and also a higher consumption of MUFAs reduced the risk of BC particularly in women. There was an reduced BC risk when consumption of plant-based oils and sunflower oil was big, but excessive consumption of animal fats was linked to an elevated risk of BC.[18] In the study of Dianatinasab et al. the review of many publications was performed. The mediterranean diet (MD) has a protective effect on BC risk, but Western diet (WD) have negative impact. The main ingredients of the MD include dietary fiber, whole grains, fruits, and vegetables, legumes, fish, moderate milk, dairy products and wine consumption and low meat consumption. In turn, the main WD components are red meat, a lot of processed foods and high-fat meat and products high in sugar.[19] Another study assessed the association between meat and fish consumption and BC risk. In general consuming a lot of organ meat was related to an increased risk of BC. [20] Teng et al. have evaluated the relationship between the dietary inflammatory index (DII) score and the risk of BC. A pro-inflammatory diet and an increased risk of BC were linked to high DII scores, which were positively correlated with an increased risk of BC. In particular, by causing oxidative stress and influencing DNA repair processes, this may encourage the development of BC.[21] Analysis studies performed by Boot et al. shows that the risk of bladder cancer is lower for those with the biggest fruit consumption ($OR_{men} = 0.83$; 95% CI 0.71–0.95 and $OR_{women} = 0.60$; 95% CI 0.40–0.80). Eating particular groups of fruits - citrus, pome fruits, tropical fruits - also had a protective effect. A higher intake of vegetables overall, and shoot vegetables in particular, related to a lower risk of BC.[22] Wigner et al. summarized role of fruits in BC prevention. Citrus fruits, pomegranates, cranberries, apples, and cactus pears may all successfully lower the chance of developing BC. These fruits are a source of many compounds that may exhibit anticancer effects, such as flavonoids, anthocyanidins, quercetin. Nevertheless, additional clinical research is required to validate current theories. [23] In the study of Al-Zalabani et al. [7] the review of many publications was achieved. A higher amount of tea drinking was connected with reduced the BC risk. All degrees of tea consumption showed a statistically significant inverse relationship with BC as compared to not drinking any tea. Among men, this decreased risk was clinically meaningful.[24] As you can see, dietary choice is an important factor in health and can both increase the risk of disease and have a protective effect.

2.5 Body Mass Index and Obesity

Excessive body fat accumulation is referred to as obesity, and it is closely connected to the onset of several diseases. Indicators of obesity can be BMI, body fat percentage, waist circumference. A person's height and weight are used to calculate their BMI. The BMI, which is measured in kilograms per square meter, is calculated by dividing the body mass by the square of the body height. High BMI and increased waist circumference have shown an association with increased risk of BC. Qiu et al. in their study underlined that obesity increased BC risk. They emphasizes the value of screening obese people for BC early and encouraging weight loss to reduce the prevalence of BC.[25] In the study of Tzelves et al. the review of many publications was achieved. In summary, their meta-analysis found that males who are overweight, males who are obese, females who are obese, and males who had central obesity had a higher risk of BC. Men over 50 years old experienced a more noticeable effect.[26]

2.6 Hyperlipidemia

Shih et al. in their study emphasized that the hyperlipidemia group had a considerably greater incidence of BC than the non-hyperlipidemia cohort (0.6% [217/33555] vs. 0.4% [143/33555], P<.001;). According to subgroup analysis, males in the hyperlipidemia cohort were much more likely compared to those in the non-hyperlipidemia cohort to have BC in the future (adjusted HR = 1.36, P =.040). Compared to men without hyperlipidemia, young men (ages 20 to 39) who have it have a 5.45-fold higher risk of bladder cancer. According to this population-based cohort study, those with hyperlipidemia had a 37%–51% higher risk of bladder cancer than those without hyperlipidemia. Men have been particularly impacted by this danger.[27] High triglyceride level is connected with bladder cancer (P = 0.042, OR = 1.001, 95% CI = 1.000–1.002), independent of the effects LDL and HDL levels and smoking, according to the Xi's et al. study.[28]

2.7 Diabetes

The effect of diabetes on the risk of BC is still being studied. And more research is needed to systematize this correlation. Participants with Type 2 diabetes (T2DM) had a 57% higher incidence of invasive BC than those without DM in a large prospective trial of Dutch men and women aged 55 to 69. Those with a T2DM diagnosis less than 5 years prior to baseline showed larger beneficial associations. Participants with type 2 diabetes who took antidiabetic drugs were more likely to develop invasive BC than those who did not.[29] In the study "Interethnic Differences in Bladder Cancer Incidence and the Association between Type 2 Diabetes and Bladder Cancer in the Multiethnic Cohort Study" performed by Bogumil et al. it

has been demonstrated that in the multiethnic population, the risk of bladder cancer was 1.15 (95% CI, 0.99–1.33) times higher among individuals with T2D than among those without, with minimal evidence of ethnic group-to-ethnic relationship heterogeneity. Because T2D is more common in Native Hawaiians, lowering its prevalence could significantly reduce the incidence of bladder cancer in this population. Regardless of T2D status, European Americans have a high absolute risk of bladder cancer, suggesting that variables other than T2D may be responsible for this group's increased risk. The causes of this variation in occurrence must be investigated in future research.[30] Further work on this connection may help prevent BC more effectively.

2.8 Lifestyle

Lifestyle and physical activity can also affect the development of the disease. In women who had never smokedand moderate (HR 0.63, 95% CI 0.39-1.00) and the most physically active (HR 0.47, 95%CI 0.20-1.08) had lower risks than the sedentary, however the latter was not statistically significant as Hektoen et al. stated. Moderately active people were considered those who walking or bicycling less than four hours per week, however active persons practiced competitive sport regularly or light sport and gardening for minimum four hours per week. It was discovered that in men, the incidence of BC rose as systolic blood pressure (SBP) (HR 1.04, 95% CI 1.01-1.07) and diastolic blood pressure (DBP) (HR 1.07, 95% CI 1.02-1.12) levels increased. Elevated DBP (≥90mmHg) was associated with a higher risk than normal (HR 1.21, 95% CI 1.08-1.36). Furthermore, they observed that DBP and BC were more strongly correlated among never-smokers, with substantially higher HR (1.57, 95% CI 1.15-2.14) for DBP hypertension (≥90mmHg) than for normal DBP levels. However, there was no correlation between current and past smokers.[31] In a population-based prospective cohort analysis An et al. proves that for those who participated in recreational sports for 1-2 hours per week, 3-4 hours per week, and 5 hours or more per week, the HRs (95% CI) of BC were 0.67 (0.38-1.20), 0.79 (0.36-1.74), and 0.28 (0.09-0.89), respectively (p for trend=0.017). Standing and walking as part of occupational physical activity were linked to a decreased risk of BC than mostly sitting at work. Walking hours per day did not correlate with risk. It was more obvious that males who participated in leisure sports and who stood and walked at work had a lower risk of BC.[32] As research shows, a healthy lifestyle and adequate physical activity have a beneficial effect on the functioning of the body, and it is important to emphasize this role to prevent cancer.

2.9 Genetic factors

Genetic factors also contribute to the risk of bladder cancer. Often a combination of genetic predisposition and exposure to carcinogens, environmental influences, behaviors, lifestyle choices have a big impact on the risk of BC. Koutros et al. underlined that future bladder cancer screening tests and prevention actions may be influenced by a combination of lifestyle risk factors, like smoking, and genetic risk factors. They discovered new genetic markers which shed light on the molecular underpinnings of BC. They summarized that there are currently 24 independent markers of genome-wide significance ($p < 5 \times 10\text{-}8$), including several new bladder cancer risk loci (6p.22.3, 7q36.3, 8q21.13, 9p21.3, 10q22.1, and 19q13.33) and enhanced signals in three existing sites (4p16.3, 5p15.33, and 11p15.5). They also assessed that interactions between smoking status and genetic polymorphisms at 8p22, 8q21.13, and 9p21.3 raised the risk of BC.[33] Another study found an association between *CYP2C8* polymorphisms (rs1934951 and rs17110453 were strongly connected with a higher risk of BC, but rs1934953 and rs2275620 had protective effects). In various studies, we can see both protective and negative effects of genetic changes on bladder cancer risk.[34] Genetic polymorphisms of the MTTR gene in combination with risk factors also increase the risk of bladder cancer.[35] Also LIG1 is a possible risk biomarker that increases proliferation, invasion, and other critical processes, all of which contribute to the malignant course of bladder cancer.[36] N-acetyltransferase2 (NAT2) gene is an enzyme that breaks down drugs and aids in the detoxification of several carcinogens and xenobiotics. Some NAT2 SNPs (single nucleotide polymorphism) were linked to BC and changed the way that smoking was linked to BC. Elsalem et al. have demonstrated the relationship between two NAT2 variants and smoking with BC. BC is 6.15 times more likely to occur in patients with the TC genotype.[37] The study of et He al. underlined that even for those with a high genetic risk, maintaining a healthy lifestyle could significantly lower the risk of BC across all genetic strata. In their research a higher risk of BC was substantially correlated with higher PRS (polygenic risk score) (HR 1.20, 95% CI 1.13–1.29 per SD increment). Patients with intermediate and high PRS were more likely to get BC incidentally than those with low PRS. In every genetic strata, an optimal lifestyle was linked to a roughly 50% lower incidence of BC than a unhealthy lifestyle. The risk of bladder cancer was 3.6 times higher for persons with a high genetic risk and a bad lifestyle than for persons with a lower genetic risk and a healthy lifestyle.[38] Teleka et al. examined the weighted genetic risk score (wGRS) of 18 genetic variants of BC, blood pressure and their connection to the risk of urothelial carcinoma. Aggressive UC risk was positively correlated with SBP. As the wGRS

level grew, the probability of both overall and non-aggressive UC increased gradually. When comparing the upper 50% of the wGRS combined to the counterpart group, the HR of aggressive UC was 1.72 (95% CI 1.03-2.87) for SBP ≥ 140 mmHg. Furthermore, the low SBP/low wGRS group had a 20-year risk of aggressive UC of 0.78%, while the high SBP/high wGRS group had a risk of 1.33%. These results lend support to a possible additive relationship between the wGRS and SBP and aggressive UC in men.[39] Avirmed et al. in their research, they look into the genetic variations of N-acetyltransferase 2 (NAT2) and glutathione S-transferase M1 (GSTM1) as risk factors for bladder cancer in the Mongolian population, both alone and in conjunction with tobacco use. This study shows that the highest risk of BC in the Mongolian population is found among tobacco smokers who have the GSTM1 null genotype and the NAT2 low acetylator phenotype. The risk of bladder cancer was about 3.35 times higher for those with the NAT2 low acetylator phenotype. The risk of bladder cancer was five times greater for smokers with the GSTM1 null genotype and twenty times higher for those with the NAT2 low acetylator phenotype.[40] There are several genetic changes that increase the risk of bladder cancer. More of such mutations have been discovered. This is evidence of an association of disease risk from genetic changes. Many studies show a link between genetic factors and lifestyle, indicating the important role of promoting a healthy lifestyle, urging smoking cessation, and can be used in the prevention of BC.

Another aspect is still family history and genetic susceptibility. Many studies indicate an approximately two-fold increase in the risk of bladder cancer among people with a family history. Pemov et al. in the analysis of the familiar BC cases identified a number of biologically plausible genes that could be connected to the pathogenesis of BC, suggesting to a complex polygenic character of genetic susceptibility to this cancer. However, these genes grouped together in a small number of BP, including cellular metabolism (*IDH1* and *ME1*), DNA repair (*MLH1* and *MSH2*), and cilia formation, despite the significant variety among them. The percentage of pathogenic and possibly pathogenic mutations was substantially greater in cases in the familial BC group than in controls (P =.003).[41] Yi-Wen You et al. in their study discovered a positive correlation between first- and second-degree relatives' family history and bladder cancer, with tobacco smoking being a contributing factor. According to the findings, having a first-degree or second-degree relative with BC increases the chance of developing BC (OR, 2.72; 95% CI, 1.55-4.77 and OR, 1.71; 95% CI, 1.22-2.40, respectively).[42] Studies show that a family history of bladder cancer increases the risk of the disease in close relatives. People

at risk should have screening tests and get advice on avoiding factors that increase the risk of the disease for example smoking cessation.

3. Conclusions

Numerous medical, genetic, and environmental variables are related to a higher risk of bladder cancer. By understanding and fully knowing all risk factors of BC, it is possible to introduce appropriate, diagnostic processes, prevention, screening programs and more effective treatment. It seems that there are several contributing factors to this cancer. The etiopathogenesis of BC is still unknown in spite of several studies and diligent scientific efforts. The main risk factors for BC are: smoking and toxic chemical exposure. A diet high in red meat, consumption of processed foods, high fat meat and high sugar products, as well as a high BMI, obesity, diabetes, low physical activity have also been suggested as a risk factors for BC. Additionally, it is noted that BC is more common in older men, indicating a correlation between age and sex and the cancer's incidence. Further research on the risk factors is necessary to fully understand the carcinogenesis of BC. The role of known modifiable factors is very important, as adherence to a healthy lifestyle can minimize the risks associated with genetic and environmental exposure factors for bladder cancer. For example, reducing the burden of bladder cancer can be achieved by quitting smoking, avoiding exposure to toxic compounds, limiting red meat consumption, playing sports, and reducing body weight. Appropriate preventive interventions and introduction of early screening diagnosis in patients with a genetic predisposition would help reduce morbidity and mortality due to bladder cancer.

Author's contribution Statement

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