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Urine microbiota and bladder cancer

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ABSTRACT

Urine analysis data obtained using modern microbiological methods and *16S rRNA* gene sequencing technology indicate that the urinary system has its own microbial ecosystem. Individual microbiota members can play a key role in the development of cancer. Certain bacterial taxa have been revealed in bladder urothelial carcinoma cells that can affect carcinogenesis, treatment response, and the development of relapses through various mechanisms. The studies are conducted to use not only vaccine strains, but also probiotic strains and oncolytic bacteria for the treatment and prevention of relapses.

Keywords: urine microbiota; microbiome; bladder cancer.

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Микробиота мочи и рак мочевого пузыря

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АННОТАЦИЯ

Данные по исследованию мочи, полученные с помощью современных микробиологических методов и технологии секвенирования гена *16S рРНК*, свидетельствуют, что мочевыделительная система имеет свою собственную микробную экосистему. Отдельные представители микробиоты могут играть ключевую роль в развитии рака. В клетках уротелия при карциноме мочевого пузыря найдены определенные таксоны бактерий, которые могут влиять на онкогенез, ответ на лечение и развитие рецидивов с помощью различных механизмов. Проводятся попытки использовать для лечения и профилактики рецидивов не только вакцинные, но и пробиотические штаммы и онколитические бактерии.

Ключевые слова: микробиота мочи; микробиом; рак мочевого пузыря.

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INTRODUCTION

Over the past decade, the incidence of bladder cancer (BC) in the Russian Federation has risen 1.4 times faster than the global incidence [1]. In St. Petersburg in 2021, the prevalence of bladder cancer was 87.8 per 100,000 population, which was the highest in Russia. The lowest rate (51.8 per 100,000 population) was recorded in the North Caucasus Federal District [2]. Bladder cancer accounts for 9% of all malignant neoplasms and is the third most common type of tumor after upper respiratory tract cancers and gastric cancers [3, 4]. More than 500,000 cases of BC are diagnosed worldwide each year, making it the ninth most common neoplasm [5, 6], with a mortality rate of approximately 200,000 per year [7]. In all countries, men are 3.4–3.7 times more likely to develop BC than women [6, 8]; in Russia, this difference is 5.7 times [1]. People over 60 years of age are significantly more likely to develop BC. Improved diagnosis over the past 10 years has led to early detection of BC: stage I BC was detected in 37.4% of patients in 2012 rising up to 56.7% in 2021 [2]. However, it progresses to muscle invasive BC in a quarter of patients. After surgery, relapses occur in 40%–80% of patients and requires repeated interventions. As a result, the treatment of BC is extremely expensive [3, 5].

A systematic search for current publications was performed in the PubMed, Medline, eLibrary, Web of Science, and Google Scholar databases using the keywords "microbiota," "microbiome," and "bladder cancer." Therefore, this article reviews literature sources including Russian and global fundamental reviews, meta-analyses, and original studies, published before June 2024.

ETIOLOGY OF BLADDER CANCER

Although the characteristics of BC vary from region to region [5], it is considered a well-studied disease. However, its etiology is not fully understood. Genetic mutations, tobacco smoking, certain chemicals (β-naphthylamines with the BC risk up to 86.7%, benzidine, 4-aminodiphenine, nitrates, nitrites) and pharmaceutical agents (analgesics, codeine, pioglitazone, chlornaphazine), chlorinated water, heavy metal ions, a diet rich in salty, fried meat, strong sweet coffee and low in vegetables, are found to have a carcinogenic effect on the bladder mucosa [3, 8–14]. The direct correlation between BC and chemical exposure explains the high incidence rate among workers involved in the production of aniline dyes, inorganic acids, gunpowder, rubber products, pesticides, as well as in the gas processing, electrode, coke-chemical, aluminum, petrochemical, rubber, and textile industries, and in slaughterhouses. The mechanism of action of aromatic amino compounds on the urothelium was discovered in the 1960s and involves conversion of amines to the active carcinogen 2-amino1-naphthol, which is inactivated in combination with sulfuric and glucuronic acids and excreted in the urine. Under the influence of urinary enzymes (β-glucuronidase, sulfatase), which play a leading role, these compounds are hydrolyzed with the release of active 2-amino1-naphthol, which has a carcinogenic effect on the urothelium. A 2-fold increase in β-glucuronidase activity is reported in the urine of patients with early BC. The proliferation of urothelial tissue with morphological evidence of atypical cells, is influenced by trace elements, such as nickel, and excessive use of pharmaceutical agents, such as phenacetin, analgin, acetylsalicylic acid, caffeine, codeine with the use of silicon-rich water [11, 15–17].

The number of women smoking tobacco is estimated to have increased worldwide, but the incidence of BC in women is significantly lower than in men [6, 8]. This is explained by the fact that carcinogenic metabolites of tryptophan (3-hydroxyanthranilic acid, 3-oxykynurenic, xanthurenic, and 8-oxyquinolinic acids), which are found in the urine of 60% of patients with BC, are periodically present in the urine of women, depending on hormone levels. Chronic urinary retention caused by benign prostatic hyperplasia should also not be underestimated, as it contributes to prolonged urothelial contact with urinary carcinogens and urothelial malignancy [11].

In addition to the BC mechanisms described above, biocarcinogens such as *Schistosoma haematobium*, human papillomavirus, and herpesviruses play an important role in the malignant transformation of the urothelium [8, 18–20]. Carcinogenesis is thought to be triggered by the accumulation of free radicals during the schistosomiasis-induced inflammation. As early as the 19th century, Virchow associated the high incidence of BC with schistosomiasis and found lymphocytes in a malignant tumor [21]. *S. haematobium* also stimulates bacterial coinfection, particularly Salmonella [20], and contributes to changes in the counts of *Fusobacterium* spp., *Sphingobacterium* spp., and *Enterococcus* spp. [3, 22, 23], which are proven to be involved in carcinogenesis. Studies of individual human papillomavirus genotypes are ongoing, and five high-oncogenic risk genotypes are found in 20% of patients with BC. Human papillomavirus type 16 has been isolated from 95.5% of histologic tumor specimens [8, 18, 19]. Herpes simplex virus type 2 is detected significantly more often in bladder tissue, and antibodies to this virus are found in serum of patients with BC compared to patients with cystitis and healthy individuals [19].

URINE MICROBIOTA OF HEALTHY INDIVIDUALS

The first hypotheses about the bacterial nature of cancer appeared in the 18th century, when the relationship between tuberculosis and lung cancer was suggested [21]. However, diagnostic microbiology and human microbiome research later revealed that urine of a healthy person is not sterile in the bladder and can contain several dozens of bacteria [6, 8, 24, 25], depending on sex, age, and co-morbidities [23]. Four species such as *Firmicutes, Actinobacteria, Proteobacteria, and Bacteroidetes* were present in more than 94% of the urine samples, with the predominance of *Streptococcus, Veillonella* [26, 27], *Bifidobacterium, Lactobacillus, Actinomyces* [26] found in all samples, and *Corynebacterium* [27]. Actinomycetes, especially *Actinotignum massiliense, Actinotignum urinale,* and *Actinotignum timonense*, which are opportunistic bacteria, were isolated much less often in the urine of healthy people, but were more often associated with urinary tract infections [6]. For example, *A. massiliense* was isolated in women with cystitis [28], and *A. timonense* was isolated in women with end-stage renal disease [29].

Men and women have different bacterial urine compositions. Most papers describe the correlation between the vaginal and urinary microbiota in women. However, papers published in the last 10 years have evaluated a wider range of microorganisms. *Mycobacterium, Bacteroides* [3], *Lactobacillus, Prevotella* and *Gardnerella* [30] are significantly more common in women, while *Opitutales, Klebsiella* [3] and *Corynebacterium* [30] are more common in men. In women, one of the Lactobacillus species, *Lactobacillus mulieris*, was found only in urine and was not present in the vagina [31]. Considerably fewer publications describe age-related differences in microbiota; some study groups included only one participant. However, some age-related differences in bacterial composition were found. *Gardnerella, Lactobacillus*, and *Streptococcus* predominated in women aged 20–49 years. *Peptinophilus, Parvimonas, Streptococcus, Lactobacillus, Fastidiosipila*, and *Escherichia, Shigella, Actinotignum*, and *Williamsia* were more common in women aged 50–69 years. *Streptococcus, Lactobacillus*, and *Corynebacterium* were more common in women over 70 years of age. In men, *Anaerococcus, Corynebacterium, Peptoniphilus, Staphylococcus, and Streptococcus* were the predominant species regardless of age [27, 32]. Hormonal changes in the body most likely explain age-related changes in the microbiota in women.

URINE AND UROTHELIA MICROBIOTA IN BLADDER CANCER

The midstream portion of urine is usually the most accessible material for *16S rRNA* sequencing. *Firmicutes* (33%) were predominant in the urine samples, followed by *Proteobacteria* (29%), *Actinobacteria* (23%), *Bacteroidetes* (4%) [5, 26, 27, 33], and *Cyanobacteria* (7%) [27]. When comparing the bacterial species in the urine of patients with BC and healthy individuals, most studies emphasize the differences between the samples (beta diversity) [3, 5, 34–38]. Others find no significant differences [34, 39] or find them only in male patients [22, 40].

The most common bacteria found in urine from patients with BC included *Acinetobacter* [3, 8, 27, 34, 41, 42], *Sphingobacterium* [3, 8, 27, 34, 41], *Anaerococcus* [3, 8, 22, 27, 34], *Fusobacterium* [8, 34], *Rubrobacter, Atoposites* [27], *Geobacillus* [27, 41], *Actinomyces* [26, 35], *Achromobacter, Brevibacterium* [35], *Brucella* [35, 41], *Actinobaculum, Facklamia, Bacteroides, Faecalibacterium* [3], *Veillonella* [5, 43], *Varibaculum* [5], *Cupriavidus, Anoxybacillus, Pelomonas, Ralstonia* [41], *Pseudomonas* [22], and *Enterobacteriaceae* such as *Klebsiella [*6, 22], *Enterobacter* [6], *Tepidimonas* [40], *Escherichia-Shigella* [41, 43], *Streptococcus*, *Enterococcus*, *Corynebacterium*, *Fusobacterium* [44] and a decrease in counts is reported for *Serratia, Proteus* [3, 6, 8, 34], *Roseomonas* [3, 8, 34], *Prevotella* [3, 41, 40, 43], *Massilia* [3], *Lactobacillus, Ruminococcaceae* [41], *Veillonella* [40].

Species associated with BC include *Fusobacterium nucleatum*, found in 26% of patients with BC [45], and *Actinomyces europaeus* which is positively correlated with BC [3, 8, 26] and is independent of sex, smoking, and disease stage [26]. However, higher counts of other Actinomyces species in healthy tissue samples are associated with a lower incidence of BC in women, suggesting a protective role of Actinomyces [36]. In contrast, another study highlighted the difference in counts of *Bacteroidaceae, Erysipelotrichales, Lachnospiraceae, and Bacteroides* in the urinary tract of smokers with BC, who had significantly higher counts compared to non-smokers with a similar diagnosis [14]. This study contradicts the study by Moynihan et al. who found no difference between smokers and non-smokers with BC [39].

In catheterized urine, the counts of *Veillonella* [6, 44], *Acinetobacter, Actinomyces, Aeromonas, Anaerococcus, Pseudomonas, Roseomonas, Tepidomonas* [6], *Corynebacterium* [44], *Fusobacterium, Actinobaculum, Facklamia*, and *Campylobacter* [27] were higher in patients with BC compared to the controls, while the counts of *Lactobacillus* [6] and *Ruminococcus* [44] were lower.

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The study by Hrbacek et al. [43] in 49 male patients showed that the bacteria counts differed significantly in the first-catch and mid-stream voided urine, as well as in catheterized urine samples. Bladder resident species (*Corynebacterium glucuronolyticum, Enterococcus faecalis*, and *Staphylococcus epidermidis*) were always detected in voided urine [43]. Oresta et al. [44], comparing bacteria in catheterized and mid-stream urine, found a single taxon (*Corynebacterium*) with significantly increased counts in patients with BC compared to the controls.

Bacteria were also isolated from tissue samples after transurethral resection. Tissue samples contained *Firmicutes* (34%), *Actinobacteria* (23%), *Proteobacteria* (22%), *Bacteroidetes* (15%), and *Cyanobacteria* (8%). *Akkermansia, Bacteroides, Clostridium sensu stricto, Enterobacter* and *Klebsiella*, as "five suspect genera," were over-represented in tissue samples compared to the urine. In addition to the above, *Cupriavidus, Pelomonas, Acinetobacter, Anoxybacillus, Escherichia-Shigella, Geobacillus, Ralstonia, Sphingomonas* [27, 41], *Burkholderia* [33], *Barnesiella, Parabacteroides, Prevotella, Alistipes, Lachnospiracea, Staphylococcus* [36, 41], *Burkholderiaceae* [44] are found in the tumor tissue. A significant difference in bacterial counts, especially *Acinetobacter* spp., should be noted between tumor tissue and adjacent healthy mucosa, where bacteria are greater in both counts and diversity [33]. Some studies show that intratumoral and urinary microbiota are not completely equivalent [33], and DNA of *Fusobacterium, Cupriavidus, Pelomonas* was not detected in any tumor sample, but was always present in urine [27]. However, some publications provide data on the correlation between these two groups [46].

The bacterial diversity in the urine from patients with BC found in various studies indicates that there are no biocarcinogens among the bacteria. Conflicting data have been reported for some bacterial genera (Streptococci, Enterobacteria) [6, 8, 22, 34, 44]. To date, a reliable correlation between infections caused by *Streptococcus pyogenes* [6] and *Staphylococcus aureus* [34] and BC has only been identified for certain types of bacteria.

Current studies on the relationship between urinary microbiota and BC focus on predicting disease progression and outcome by changes in bacteria composition. Qiu et al. [37] showed that patients with recurrent BC had higher alpha diversity than non-recurrent patients. Many authors have found that *Enterococcus* spp. predominate in low grade tumors [33, 36]. However, attempts to find such markers in urine failed. Urine in patients at high risk for relapse and progression is reported to have higher diversity and counts of the following bacterial orders: *Lactobacillales, Corynebacteriales, Bacteroidales, Pseudomonadales*, and *Enterobacteriales*; Families: *Staphylococcaceae, Streptococcaceae, Corynebacteriaceae, Prevotellaceae* [22]; genera such as *Herbaspirillum, Porphirobacter, Bacteroides* [8, 33, 34, 38], *Gemella, Faecalibacterium, Aeromonas* [34], *Micrococcus, Brevibacterium* [3], *Veilonella* [33, 44], *Corynebacterium* [33, 37, 44], *Pseudomonas, Staphylococcus, Acinetobacter* [37]; species such as *F. nucleatum* [3]. No consensus is reached regarding the comparison of microbiota in muscle invasive and non-muscle invasive BC. Most publications report bacteria differences in recurrences of non-muscle invasive BC (increased counts of *Anoxybacillus, Massilia, Thermomonas, Brachybacterium, Micrococcus, Nocardioides* [33], *Campylobacter* [6], *Corynebacterium, Staphylococcus* [3, 6], *Acinetobacter* [3,] *Cupriavidus* [3, 35], *Herbaspirillum, Gemella, Porphyrobacter, Aeromonas Bacteroides, Faecalibacterium* [34]) and muscle invasive BC (*Haemophilus* [3, 6, 35], *Veillonella* [3, 35], *Bacteroides, Faecalibacterium* [33, 38]), whereas other authors found no differences in microbiota composition [27].

POSSIBLE MICROBIOTA-RELATED MECHANISMS OF CARCINOGENESIS

The superficial urothelial layer of the bladder consists of facet cells covered with an extracellular matrix of glycosaminoglycans. Chronic inflammation is thought to be the primary mechanism of tumorigenesis. However, this is only possible if bacteria adhere to the urothelium and form a biofilm, which is associated with all chronic infections and a higher risk of malignant degeneration of bladder facet cells [3]. In the population of more than 6,000 patients, a high correlation was reported between recurrent cystitis (three or more cases per year) and the development of BC in men and postmenopausal women. In addition, urinary tract infections not treated with antibiotics are more common in the history of patients with muscle invasive BC [47].

For adhesion to the cell surface, Gram-negative bacteria have at least 15 adhesins located on fimbriae and pili, which are particularly expressed in *E. coli* and *Klebsiella pneumoniae*. In Gram-positive bacteria (*Staphylococcus saprophyticus*, Anaerococci, and *E. faecalis*), the role of adhesins is performed by surface proteins of the cell wall. The enzymes such as collagenase, hyaluronidase, and elastase facilitate bacterial invasion through the extracellular matrix and deep into the urothelium. Bacterial invasion triggers an inflammatory process in cells that is initiated by the release of proinflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)-6 and IL17, granulocyte colony-stimulating factor [30, 48, 49]. In addition, some bacteria, such as

F. nucleatum, maintain chronic inflammation by cleaving type 1 cadherin [50, 51], inhibit apoptosis by hyperstimulating Toll-like receptor (TLR)-2 and TLR4-mediated inflammation [33, 51, 52], and stimulate proliferation of cancer cells (*F. nucleatum, Streptococcus gallolyticus*) [36, 50]. As a result, reparative processes in cells are exhausted, while TLR4 activation promotes tumor cell survival in nutrient-poor conditions and induces the expression of a vascular endothelial growth factor [53]. In addition to inflammation, Anaerococci cause extracellular matrix remodeling and re-epithelialization [34], resulting in continuous regeneration of bladder epithelial cells causing genomic instability and increasing the likelihood of mutation [33]. *Acinetobacter* can promote tumor metastasis [3, 42]. Chronic inflammation triggers the production of intracellular reactive oxygen species that cause DNA breaks, inhibit DNA damage repair, suppress the expression of related RNAs and proteins, and promote angiogenesis in the microenvironment. In addition, the intracellular signaling pathway is disrupted, particularly the signal transducer and activator of transcription 3 (STAT3). This protein plays a critical role in BC as one of the messenger proteins that mediate the cell's response to signals received through interleukin and growth factor receptors [33].

Urea-splitting microorganisms such as *Proteus mirabilis* and *Ureaplasma urealyticum* increase urinary pH, leading to the crystallization of calcium, magnesium, and phosphate in the urine and the formation of struvite (infection) concrements [54].

Mechanisms of direct damage to cellular DNA have been described in addition to the bacterial ability to cause chronic inflammation. For example, enterobacteria use colibactin to form interchain cross-links by alkylating adenine fragments on opposite DNA strands, resulting in DNA damage [51, 55], epithelial-mesenchymal transition, and metabolic reprogramming [3]. A carcinogenic mechanism is described for cyanobacterial microcystin [56]. Bacteria are suggested to play a role in the development of BC because they are found in 7% of urine samples and 8% of tumor tissue [27]. Ceramides and sphingophospholipids from *Sphingobacterium spiritivorum* can induce DNA fragmentation, activate caspase3, induce morphological changes, and shorten the cell cycle [34, 57]. *E. faecalis* is known to produce high levels of extracellular superoxide, causing damage to cellular DNA [58]. *Eubacterium* culture in bladder tissue induced tumor cell proliferation via the ECM1/ERK1/2/MMP9 phosphorylation pathway [33]. This is one of the most important and well-understood signaling pathways involved in the regulation of endothelial cell transcription and proliferation during angiogenesis.

Mycoplasmas may promote abnormal growth and transformation of host cells by activating oncogene expression, increasing growth factor production, inactivating tumor suppressors, promoting tumor cell migration, and modulating apoptosis. In addition to these mechanisms, their enzyme binds polymerase, which plays a critical role in the detection and repair of DNA damage, thereby reducing its catalytic activity. Long-term persistence of *Mycoplasma genitalium* and *Mycoplasma hyorhinis* in normal BPH1 cells resulted in malignant transformation of human epithelial cells [59–64].

Metabolites produced by the gut microbiota, including tryptophan derivatives, bile acids, trimethylamine N-oxide, and short-chain fatty acids, may also influence the inhibition or development of BC. Indoleamine 2,3-dioxygenase 1, a key enzyme in tryptophan metabolism, enhances antitumor immunity and inhibits angiogenesis in BC. The study showed that plasma tryptophan levels were significantly decreased and urinary tryptophan levels were increased in patients with BC [65, 66]. Concentrations of bile acids, including chenodeoxycholic, glycursodeoxycholic, and glycochenodeoxycholic acids, are elevated in urine samples of patients with BC compared to healthy controls. Farnesoid X receptor (a nuclear receptor that can be activated by binding to bile acids) inhibits migration, invasion, and angiogenesis of BC cells *in vitro* [33]. He et al. [13] found dysbacteriosis of the intestinal microbiota in patients with BC, expressed by lower *Clostridium* and *Prevotella* counts, lower concentrations of butyrate, and impaired structural integrity of the intestines, which was associated with limited fruit in the diet [13].

Several pathways of bacterial carcinogenesis are described, such as barrier disruption, inflammation, induction of gene mutations, manipulation of intracellular signaling, direct and indirect DNA damage. However, long-term asymptomatic bacteriuria prevents BC recurrence by activating the immune system. Studies reported recurrence of non-muscle invasive BC in 40% of patients without bacteriuria and only in 25% of patients with latent bacteriuria [3, 33]. The balance between the microbiota and the immune system is critical; immunosuppressive therapy in renal transplant patients increases the risk of BC100-fold [11].

ROLE OF BACTERIA IN THE TREATMENT OF BLADDER CANCER

Historically, the Bacille Calmette-Guérin (BCG) vaccine has been used to prevent recurrence of non-muscle invasive BC. The attenuated vaccine strain of *Mycobacterium bovis* colonizes the bladder wall and interacts with the urothelium, urothelial bacteria, and the immune system cells [33, 67–70]. A key role in the interaction

between the epithelium and *M. bovis* is played by integrin alpha5 (a membrane protein, a glycoprotein of the integrin superfamily), which induces tumor cell cycle arrest, and fibronectin, which promotes tumor destruction by NK cells. BCG also induces proliferation and differentiation of $CD4^+$ receptor-bearing T-cells [3] and decreases levels of the proinflammatory cytokine IL1β over six months [71]. Although the BCG effects on immune cells are well understood, the relationship between bladder microbiota and *M. bovis* response remains controversial. Even the same authors in different publications give conflicting information about changes in *Corynebacterium* counts in BCG responders and non-responders with BC recurrence. A positive effect after vaccination has been reported with higher urinary counts of *Lactobacillus, Serratia, Brochothrix, Negativicoccus, Escherichia-Shigella, Pseudomonas* [3, 6, 33, 35], *Ureaplasma*, and an increase in *Aerococcus* counts in case of recurrence [33].

A long history of intra-bladder BCG instillation reports local and systemic side effects such as cystitis, decreased bladder capacity, and systemic inflammation [67]. Patient age may also affect vaccine effectiveness, which decreases with age [72]. All of these factors, including the cost of vaccination, are driving the search for new ways to prevent BC recurrence. Another vaccine strain (anti-typhoid vaccine) is one of the candidates under consideration. In a mouse model, intra-bladder injection of Ty21a was shown to control BC via dendritic cells and a T cell-dependent mechanism [73].

It should be noted that endogenous bacteria found in urine have protective properties, such as *Mycobacterium* and *Bacteroidetes* isolated from the female urinary tract [3]. Experiments show the ability of *Lactobacillus gasseri*, typical of type II vaginal microbiota and present in the bladder in inflammation [74], to inhibit cancer cells [75]. *L. mulieris* isolated from the urine of patients with recurrent UTI, secrete biosurfactants that directly destruct the pathogenic biofilm [76]. This is why lactobacilli have been used as probiotics since the 1990s to prevent the BC recurrence. Gram-positive bacteria, which include *Lactobacillus casei* and *Lactobacillus rhamnosus*, have a good adsorption for carcinogenic substances (heavy metals, cadmium, pesticides) due to the structural characteristics of their cell wall [8]. Patients with BC who received chemotherapy and a probiotic containing *L. casei* had a 15% lower recurrence rate than those who received chemotherapy alone, and *L. casei* was superior to BCG in reducing tumor growth in mice [22]. Significant protective effects against BC recurrence were also observed with another probiotic based on *Bifidobacterium, Lactobacillus* and *Veillonella* [26]. Another study found that a product based on *Butyricicoccus pullicaecorum*, which produces butyrate, increased the anti-inflammatory potential of cells. Butyrate is shown to mediate antitumor effects on bladder urothelial cells in BC cell lines and mouse models [3]. Mechanistic studies of probiotic strains provide conflicting data on their effects. It should be noted that lactobacilli may aggregate with *E. coli*, which is considered a form of symbiosis that gives *E. coli* the ability to survive and reproduce [76]. Higher counts of these bacteria may be unfavorable because *E. coli* has beta-glucuronidase, which is elevated in the urine of patients with early-stage BC.

In addition to probiotics, oncolytic bacteria may be useful in the treatment of cancer [77]. In the future, using data on the tropism of individual bacteria for tumor cells and novel genomic technologies, it will be possible to program the delivery of recombinant bacteria encoding cytotoxic molecules directly into the tumor to achieve its lysis [3].

Immune checkpoint inhibition therapy is a new approach in the treatment of BC. This therapy inhibits the programmed cell death protein, but is effective in no more than 30% of patients. One of the reasons for these failures is thought to be the bladder microbiome, where *Leptotrichia, Roseomonas*, *Propionibacterium* [33, 34], and gut-dwelling *Bifidobacterium pseudolongum, Lactobacillus johnsonii, Olsenella* [33] are thought to play a critical role in response to immunotherapy.

ISSUES WITH EVALUATING THE RELATIONSHIP BETWEEN MICROBIOTA AND BLADDER CANCER

When reviewing publications on microbial associations with BC, the most striking thing is the inconsistency of the obtained data, even when comparing taxa such as phyla, classes, and families. There is no consensus on three of the four divisions at the level of higher taxa: *Actinobacteria*, *Bacteroidetes*, and *Pseudomonadota* [2, 33, 41]. Of 17 families, only two (*Corynebacteriaceae* and *Streptococcaceae*) are mentioned by different authors, but some discrepancies are reported [33, 46]. More interestingly, urinary bacteria in patients with BC were analyzed at the genus level, even though the samples were diverse with respect to sex, age (often not reported), and BC characteristics (see Table 1).

There are several reasons for this diversity of genera and differences in data:

1. Not enough samples. The sample cannot be considered representative, as most of the data was obtained from a few patients (five patients with BC). This explains the fact that in the same condition, a different composition and quantity of bacteria can be found in the urine.

2. Not all studies report the sex, age, or ethnicity of patients. Sex may be an important factor, as the urinary

microbiota of healthy men and women and of patients with BC differ in terms of species composition. Most studies were conducted in Asia and North America, and fewer in Europe and Africa. Recent experiments in a mouse model have shown that tumorigenesis induced by exposure to chemical carcinogens alters the microbiota differently in young and old animals [72]. The observed heterogeneity of urinary microbiota among individuals, regardless of sex and possibly age and race, does not allow identification of the BC-associated microbiota.

3. Testing of urine samples collected by different methods. The ability of urinary microbiota to reflect tumor tissue microbiota is currently a controversial issue. Therefore, it is important to evaluate the intra-tumoral microbiota in BC to assess its metabolic activity and functional significance. The characteristics of bacterial

Table 1. Changes in the number of bacteria isolated from the midstream urine of patients with bladder cancer compared to healthy individuals
Таблица 1. Изменение численности бактерий, выделенных из средней порции мочи больных раком мочевого пузыря (РМП), по сравнению со здоровыми пациентами

Genus	Changes in bacterial counts	No. of patients with bladder cancer	Reference
Acinetobacter	Increased	31	[34]
		10	[27]
		24	[42]
		22	[41]
		40	[37]
Actinobaculum	Increased	12	[45]
	Decreased	32	[36]
Actinomyces	Increased	29	[26]
Akkermansia	Increased in the bladder	10	[27]
Anaerococcus	Increased	8	[78]
		31	[34]
Anoxybacillus	Increased in the bladder	10	[27]
	Increased	62	[22]
			[41]
Atopostipes	Increased	31	[34]
Bacteroides	Increased during recurrence	31	[34]
	Increased in the bladder	10	[27]
	Increased	38	[38]
Bifidobacterium	Decreased	29	[26]
Brachybacterium	Increased	62	[22]
Brochothrix	Increased in non-muscle invasive BC	43	[35]
Campylobacter	Increased	12	[45]
Clostridium	Increased in the bladder	10	[27]
Corynebacterium	Increased	24	[42]
		51	[44]
	Increased	24	[42]
		40	[37]
	Decreased	12	[45]
Cupriavidus	Increased in non-muscle invasive BC	43	[35]
	Increased	22	[41]
Enterobacter	Increased in the bladder	10	[27]
Enterococcus	Increased	24	[42]
		51	[44]
Escherichia–Shigella	Increased in the bladder	10	[27]
	Increased in non-muscle invasive BC	43	[35]
	Increased	22	[41]
Eubacterium	Decreased	31	[34]
Facklamia	Increased	12	[45]
Faecalibacterium	Increased	38	[38]

Table 1 (continued) / Окончание таблицы 1

Genus	Changes in bacterial counts	No. of patients with bladder cancer	Reference
Fusobacterium	Increased	12	[45]
		51	[44]
Geobacillus	Increased	31	[34]
		22	[41]
	Increased in the bladder	10	[27]
Haemophilus	Increased in muscle invasive BC	43	[35]
Herbaspirillum	Increased during recurrence	31	[34]
Klebsiella	Increased in women	49	[46]
	Increased	10	[27]
Lactobacillus	Decreased	29	[26]
	Increased	22	[41]
			[42]
Methylorubrum	Increased	34	[5]
Micrococcus	Increased	62	[22]
Negativicoccus	Increased in non-muscle invasive BC	43	[35]
Pelomonas	Increased	22	[41]
Porphirobacter	Increased during recurrence	31	[34]
Prevotella	Decreased	22	[41]
		22	[40]
Proteus	Decreased	31	[34]
Pseudomonas	Increased	8	[78]
		40	[37]
	Increased in non-muscle invasive BC	43	[35]
Ralstonia	Increased in the bladder	10	[27]
	Increased	22	[41]
Roseomonas	Decreased	31	[34]
Rubrobacter	Increased	31	[34]
Ruminiclostridium	Decreased	31	[34]
Ruminococcus	Decreased in catheterized urine	51	[44]
	Decreased	22	[41]
Serratia	Decreased	31	[34]
	Increased in non-muscle invasive BC	43	[35]
Sphingobacterium	Increased	31	[34]
Sphingomonas	Increased in the bladder	10	[27]
	Increased	22	[41]
Staphylococcus	Increased	24	[42]
		40	[37]
Stenotrophomonas	Increased	24	[42]
Streptococcus	Decreased	12	[45]
		29	[26]
	Increased	8	[78]
		24	[42]
		51	[44]
Tepidimonas	Increased	22	[40]
Ureaplasma	Increased	24	[42]
Varibaculum	Increased	34	[5]
Veilonella	Decreased	12	[45]
		29	[26]
	Increased	34	[5]
	Increased in muscle invasive BC	43	[35]
	Increased, including in the bladder	51	[44]

DNA in the first-catch and mid-stream voided urine and catheterized urine are shown to differ significantly, and bacterial DNA in the latter case has a similar profile compared to that of suprapubic puncture urine. It is recommended that urine microbiota and microbiome studies should be conducted using catheterized urine, as it is in direct contact with the urothelium.

4. The number of taxonomic units identified for individual urine samples varies significantly (20 to 500), which is explained by the research methods used. Current methods for urinary tract microbiota profiling are primarily based on sequencing the variable region of the *16S rRNA* gene, which does not allow differentiation between live and dead bacteria or detection of micromycetes, viruses, and protozoa. Short-read technology (generation 2 sequencing) does not allow identification beyond the *16S rRNA* gene, so taxonomic identification of samples is usually limited to the genus or even family level. Bacterial species within a genus are known to have different sets of virulence factors, enzymes, etc. Therefore, mapping of specific microbes may be required to establish a precise correlation between individual members of the urinary microbiota and BC, similar to the study of the gut microbiota in colorectal cancer. It is impossible to select probiotic candidates among bacteria without identifying them to the species level.

CONCLUSION

Identification of the precise role of specific microbes in causing BC remains a major challenge. Therefore, the choice of treatment strategies and recurrence prevention cannot be based on prognostic biomarkers, as they do not allow differentiation of patient groups and long-term prognosis.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: D.N. Maistrenko, D.A. Granov, S.Yu. Rumyantseva — concept of the study, analysis of literary data, editing the text of the manuscript; I.Yu. Lisitsyn, O.E. Molchanov, O.E. Punchenko — search and analysis of literary data, writing the text of the manuscript, editing the text of the manuscript.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Личный вклад каждого автора: Д.Н. Майстренко, Д.А. Гранов, С.Ю. Румянцева — концепция исследования, анализ литературных данных, редактирование текста рукописи; И.Ю. Лисицын, О.Е. Молчанов, О.Е. Пунченко — поиск и анализ литературных данных, редактирование текста рукописи, написание текста рукописи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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