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Review

Urinary microbiota and lower urinary tract disorders

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Abstract

In over fifty countries, the second leading cause of death after cardiovascular disease is cancer. Indeed, the 10thmost diagnosed cancer worldwide is bladder cancer, with half a million new reported cases and fifty percent of deaths per year. While cancer is primarily regarded because of host genetics and environmental influences, microorganisms are linked to 20% of human cancers. The microbiota of each individual is unique, undergoing development in childhood and adulthood and inhabiting the human body in various sites exposed to the external environment, including the gastrointestinal tract, oral cavity, genitourinary tract, and skin. The composition of the urinary microbiota can function as a host protection mechanism, preventing infections when the physiological balance is maintained or allowing infection and colonization by pathogens when the balance is disturbed by factors related to the host or the environment. It was previously assumed that healthy individuals had sterile urine using culture-based methods. However, using high-throughput DNA sequencing and improved culture techniques, numerous microorganisms are discovered in the urine of healthy people, many of which are not detectable by standard culture techniques. So, the symbiotic relationship between humans and commensal microbiota has become a topic of interest in both basic and clinical fields all over the world. This review will discuss the epidemiology and external risk factors of bladder cancer, as well as the association between urinary microbiota, urinary tract disorders, and bladder cancer, besides their role in treatment.

Keywords: Urinary microbiome, Microbiota, Bladder cancer, Risk factors, Urinary dysbiosis.

.1. Introduction

The intricate network of symbiotic microorganisms, including parasites, viruses, bacteria, and fungi, residing within the human body, influences the host's health and physiology through their interactions with one another and with the host **[1]**. In the past decade, the symbiotic relationship between humans and microbes has become a topic of interest for many researchers in both basic and clinical fields. This interaction involves the participation of

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microbes in essential host functions, including reproduction, defense, and metabolism, which contribute to our normal physiology and susceptibility to disease **[2]**. In the clinical vocabulary, the terms of microbiome and microbiota have been recently incorporated. Although they have distinct meanings, they are frequently used interchangeably. The microbiome pertains to the complete assembly of microbial genomes, encompassing pathogenic, symbiotic, and commensal microorganisms that reside within a designated anatomical site, while the microbiota denotes the microorganisms that inhabit a particular ecosystem **[3]**.

Commensal microbial communities are commonly found on internal surfaces, such as the gastrointestinal (GI) and vaginal epithelium. Human health benefits from the microbiomes, which are believed to eliminate defective immune cells and prevent pathogenic infections **[4]**. Moreover, the detoxification of dietary substances, the anti-inflammatory effects, and the modulation of host cell development and division are also attributed to the gut microbiota **[5]**.

There exists a close association between the immune system and the human microbiome, which plays a significant role in cancer-related mechanisms, including metabolism and cell proliferation **[6, 7]**. Several cancers, especially those in the GI tract, have been linked to the microbiome, which has been well-studied in this region. Animal studies have shown that carcinogens can be activated or produced by the gut microbiome and affect the GI tract or other organs **[4]**.

The gut microbiome participates in the occurrence of genetic and epigenetic alterations and abnormal pathways that lead to colorectal cancer **[6]**. As an example, the combination of FadA, a virulence factor found in *Fusobacterium nucleatum*, and E-cadherin stimulates b-catenin signaling, which leads to an increased incidence of colorectal cancer **[4]**.

Helicobacter pylori has been identified as a microorganism that is commonly associated with cancer. The bacterium is known to cause gastric ulcers and infects approximately 50% of the world's population. This infection can lead to the development of stomach cancer through the production of two specific toxins: vacuolating cytotoxin (VacA) and cytotoxin-associated gene A. The risk of stomach adenocarcinoma in H. pylori-infected individuals depends on environmental factors, host immune responses, and strain-specific components, but only a few develop cancer **[4]**. The role of *H. pylori* in the development of gastric cancer stimulates the search for microbial involvement in the development of other cancers **[8]**.

Cancer-causing infections, such as human papillomavirus (HPV) and hepatitis, are responsible for approximately 30% of cancer cases in low- and lower-middle-income countries **[9]**. Moreover, the association of schistosomiasis with squamous cell carcinoma (SCC) has

been established, whereas the involvement of microorganisms in bladder cancer (BC) remains uncertain **[4]**.

The existence of specific microorganisms in the microbiome of patients who respond to immunotherapy has been discovered by recent studies, opening a new era of precision medicine **[10]**. As such, the discovery that bacteria play a role in human carcinogenesis presents exciting opportunities for the development of potential biomarkers for disease prognosis **[6]**. From previous studies, the relationship between humans and microbes has advantages and disadvantages, and several studies are required to be able to prevent their harmful effects and improve their vital roles.

This review aimed to elucidate how the microbiota of the urinary tract (UT) influences the pathogenesis of various functional disorders affecting the lower UT (LUT) and summarize the existing literature on the urinary microbiome (UM) in relation to urothelial cell carcinoma (UCC).

2. Bladder cancer

Globally, cancer is the 2nd leading cause of mortality after cardiovascular disease, and it's the leading cause of death in over 50 countries [11].There were an estimated 19.3 million new cases of cancer and almost 10.0 million deaths from cancer worldwide in 2020 [12].It's estimated that, globally, cancer cases will increase from 19 million in 2020 to nearly 29 million by 2040. Globocan estimates that cases will increase by 96% between 2020 and 2040 among low Human Development Index (HDI) countries, compared with an increase of only 32.2% in remarkably high HDI countries [11]. In Egypt, cancer has an impact on individuals and healthcare systems. It was estimated that there were134,632 new cases and 89,042 in 2020 **[13]**.

3. Epidemiology

3.1. Incidence and Mortality

With over 573,000 new cases and 213,000 deaths each year, bladder cancer is the tenth most often diagnosed disease globally. Males are more likely to contract it than females are, with incidence and death rates of 9.5 and 3.3 per 100,000, respectively, which are almost four times higher than those for females worldwide. As a result, the illness is more prevalent among males, where it is the ninth most common cause of cancer mortality and the sixth most widespread cancer overall. Both the male and female incidence rates are highest in Southern Europe (Greece has the highest incidence rate globally among males), Western Europe (Belgium and the Netherlands), and North America; however, the highest rates worldwide are for women in Hungary **[14]**. In 2020, Egypt ranked third in incidence and mortality. It was estimated that 10,655 new cases, among males, were 8,410 out of the total new cases and 6,170

deaths **[13]**. It is obvious that bladder cancer is one of the most common cancers worldwide, and incidence and mortality rates differ among sexes and countries due to differences in exposure to risk factors.

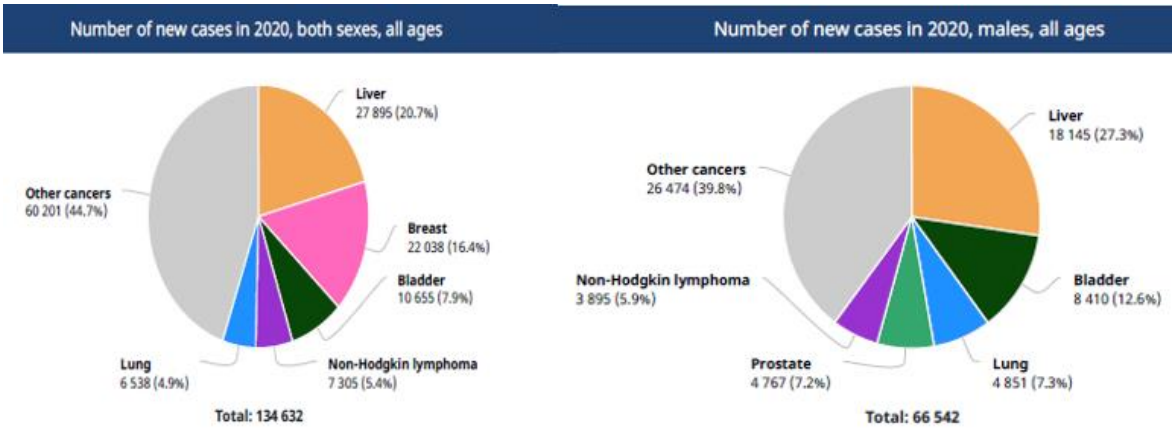

Figure: Number of new cases in 2020 in Egypt

3.2. Survival

The number of people who have urinary bladder cancer (UBC) at a given time is called prevalence. It depends on how many people get the disease and how long they live with it. We can use this formula to find the prevalence:

$$\text{Prevalence} = \text{incidence} \times \text{duration}$$

Duration is influenced by survival rates as well as the duration that an individual with a prior UBC diagnosis is regarded as having the disease. A common measure of the number of patients who survive for a certain time (typically 5 or 10 years) after being diagnosed is partial prevalence. In 2018, the worldwide partial prevalence for five years was about 1,650,000, with around 1,300,000 men and 350,000 women **[15]**.

4. Types of bladder cancer

Urothelial carcinomas, which originate from the epithelial cells lining the bladder's interior, account for around 90% of BCs. About 75% of these are non-muscle-invasive. Considering the World Health Organization (WHO) classification system, there are three types of BCs that do not invade the muscle (non-muscle invasive bladder cancers, or NMIBCs): Ta (papillary tumors that do not grow into other tissues), Tis (cancer cells that stay on the surface of the bladder), and T1 (cancer cells that penetrate the tissue below the surface/lamina propria). These types make up about 70%, 10%, and 20% of NMIBC cases, respectively.

According to **[16]**, Ta and Tis tumors are localized within the urothelium and do not extend beyond the basal membrane. These tumors typically manifest as low-grade lesions, particularly in the case of Ta tumors, and can often be effectively managed through conservative approaches. On the other hand, T1 tumors are usually high-grade and have the potential to invade the muscle and metastasize outside the bladder.

As **[17]** pointed out, BCs that do not grow into the muscle (NMIBCs) have an effective treatment outcome, with up to 90% of patients surviving for five years. On the other hand, BCs that invade the muscle have a worse outlook, with only 30% to 70% of patients surviving for five years.

5. Symptoms and diagnosis

The primary symptom observed in the majority of BC patients upon diagnosis is painless, visible blood in the urine, known as macroscopic hematuria. Additionally, storage symptoms related to lower UT dysfunction, including dysuria (painful urination), increased frequency, or urgent urination, can also be identified, particularly in cases of carcinoma in situ (CIS). Advanced tumors may cause obstruction in the upper UT and result in pain. To accurately diagnose BC, a comprehensive physical examination, cystoscopy, and transabdominal ultrasound should be conducted on patients exhibiting these symptoms. Urinary cytology, performed during cystoscopy, could also be considered. If a suspicious lesion is observed during cystoscopy, scheduling a transurethral resection of the bladder tumor is necessary to verify the diagnosis and assess the extent of the disease **[18]**.

Differentiating between non-invasive (Ta) and invasive (T1) BCs is of utmost importance for clinicians to develop an appropriate and timely treatment plan for patients. Ta and T1 cancers cannot be correctly staged by any molecular markers. Therefore, histological assessment is still an essential tool for telling apart T1 disease from Ta disease **[17]**.

6. The severity of bladder cancer

Most bladder cancers are diagnosed at an early stage when they are highly treatable. However, about 25% of bladder cancers are diagnosed at later stages **[19]**. Despite advances in immunotherapy, early detection, and robotic surgery, BC remains a significant and increasing cause of cancer-related morbidity globally, particularly in industrialized countries **[20]**. Urothelial cell BC, a subtype of the disease, is significantly linked to chemical exposure, including those encountered in certain occupations or through tobacco use, due to the direct contact of the urothelium with these substances. This type of cancer can spread beyond the urothelium and infiltrate the submucosa, muscles, lamina propria, and serous layers of the bladder wall. It can also extend to nearby pelvic organs such as the vagina, urethra, uterus, and

prostate. Lymphatic metastasis can occur through the presacral, obturator, and para-aortic lymph nodes. Hematogenous dissemination typically leads to metastases in the bones, adrenal glands, lungs, and liver and is related to a poor prognosis **[20, 21]**.

7. Etiology

External risk factors are linked to the majority of BC cases. Up to 50% of patients with urothelial carcinoma have a family history of cancer, and 4.3% of all BC patients have a first-degree relative who has BC **[22-24]**.The following risk factors for BC have been deemed to have adequate supporting data by the International Agency for Research on Cancer (IARC): tobacco use, several workplace hazards (such as those associated with the manufacture of rubber, aluminum, paint, and firefighting equipment), dyes [magenta and auramine] or dye intermediates [4-aminobiphenyl]), environmental exposures (such as arsenic and X radiation or gamma radiation), and Schistosoma infection **[12, 25]**. Therefore, the key to prevention is developing a thorough understanding of these risk conditions **[22]**.

7.1. Smoking

BC incidence is attributable to tobacco smoking, which represents 50-65% of new cases every year. Smoking enhances the probability of having BC by three to four times. Among all cancers, BC mortality associated with smoking is only surpassed by lung cancer mortality, the main global cause of cancer death **[26]**. Polycyclic aromatic hydrocarbons and beta-naphthylamine represent carcinogenic substances in tobacco smoke that can trigger inflammation. They are metabolized in the bladder and elsewhere in the body, resulting in DNA adducts and irreversible genetic changes. These changes can turn on oncogenes or turn off tumor suppressor genes, thus facilitating the growth of cancer **[20]**.

7.2. Environmental and occupational exposure

Occupational exposure to carcinogenic substances, including polycyclic aromatic hydrocarbons, chlorinated hydrocarbons, and aromatic amines, is the second most frequent BC risk factor for industrialized countries **[22]**. Workers involved in manufacturing rubber, textiles and leathers, dyes, paints, plastics, mining and metals can regularly come into contact with important levels of bladder-cancer-causing chemicals such as aromatic amines. **[27]** suggested that people working in these industries could be at increased risk of developing occupational bladder cancer compared to the general population. The substances in a cloud of smoke that firefighters are exposed to include benzene, toluene, ethylbenzene, acetaldehyde, formaldehyde, and sulfur dioxide **[22, 28]**. According to a general estimate, 18% of BC cases are caused by occupational exposures.

Environmental exposure as a natural metalloid that is present in air, water and soil, X radiation or gamma radiation and arsenic, may also raise the likelihood of BC, as indicated by a large prospective study conducted in Chile **[20]**.

7.3. Gender

The occurrence of BC worldwide is fourfold lower in women than in men, and a comparable trend is observed in the death rate **[29]**. Although much of this difference can be explained by the varying prevalence of tobacco use between genders, the incidence rate remains lower in women (2.4) than in men (3.0) **[13]**. The incidence of BC among women is especially high in countries where female smoking is prevalent in the culture. Lebanon, which has the highest global rate of this disease among women, is one such country **[29]**. For both genders, current smokers have an earlier onset of BC by about 6 years compared to non-smokers **[20]**.

In Egypt, there is a strong male predominance of the disease with 4:1 male-to-female ratio. This may be due to higher rates of *Schistosomiasis hematobium* among male farmers who are more exposed to the Nile water **[30]**.

7.4. Age

Age-related risk accumulation for cancers is the cause of the considerable rise in cancer incidence. In addition to the general risk accumulation, ageing people tend to have less efficient cellular repair systems **[9]**. BC is primarily diagnosed in older individuals, with 90% of cases occurring in people over the age of 55 and 80% in those over 65 in the United States. BC is usually diagnosed at an older age (73 on average) than most other cancers (65-70 on average) **[31]**. This implies that BC requires prolonged time to develop after being exposed to substances that can damage DNA, as the cells' defenses against tumors are slowly overcome. BC can also affect children and young adults, but it is rare and usually not aggressive or invasive **[20]**.

7.5. Red meat

[32] conducted a meta-analysis and found that the consumption of red meat and processed meat was associated with a 17% and 10% higher risk of BC, respectively. However, **[33]** reported a 22% higher risk for processed meats but no significant difference for red meats. This inconsistency may be related to how high meat consumption was defined. Nitrosamines, which are derived from nitrates in processed meats, have been shown to directly induce bladder tumor development in rodents **[34]**. A high diet of organ meat was associated with an increased risk of developing bladder cancer, according to a pooling analysis of 11 cohort research studies (which involved 518,545 people) **[35]**.

7.6. Obesity

[36] performed a meta-analysis of 15 cohort studies and reported that the risk of BC was 7% and 10% higher for pre-obese and obese individuals, respectively. The study found a direct link between body mass index (BMI) and BC risk, with a 4.2% higher risk for every 5 kg/m^2 increase in weight, regardless of other factors such as physical activity, diet, alcohol consumption, or smoking. The production of insulin and insulin-like growth factor-I can be increased by obesity, which can affect angiogenesis, apoptosis and cell proliferation **[37]**. Additionally, obesity can promote chronic inflammation by altering cytokine levels, triggering an immune response that can lead to carcinogenesis **[38]**.

7.7. Genetic factors

According to **[39]**, about 7% of BC cases are influenced by genetic factors. The FGFR growth factor receptor has somatic mutations in up to 20% of relapsed BC patients, as reported by **[40]**. This resulted in the approval of erdafitinib, a tyrosine kinase inhibitor, as a therapeutic option for advanced stages.

The p53 gene, which is frequently mutated in various cancers, has also been involved in BC initiation and may predict the outcome **[20]**. Additionally, slow acetylation by the enzyme N-acetyltransferase, which is associated with the metabolism of aromatic amines, may also contribute to BC development **[41, 42]**.

7.8. Pathogens

Approximately 5% of BC cases worldwide are attributed to squamous cell origin, with a higher incidence observed in Africa. This increased occurrence can be attributed to the presence of schistosomiasis, a protozoal infection known to induce inflammation **[43]**. Squamous cell carcinoma (SCC) is the main type of BC that is linked to schistosomiasis infection in areas where the infection is or was common, especially in Egypt. SCC was the predominant type of BC in these regions in the past. However, notable shifts have been observed over the past few decades, with an increase in the proportion of urothelial carcinoma (UC) cases and a decline in SCC cases, which decreased from 78% in 1980 to 27% in 2005 **[39]**.

These changes can be attributed to various factors, including public health interventions and the construction of the Aswan Higher Dam in the Nile Delta during the 1960s. The implementation of public health measures and infrastructure development led to the replacement of *Schistosoma haematobium*, a known risk factor for BC, with *Schistosoma mansoni*, which does not pose the same risk for urothelial BC (UBC). Consequently, from 74% in 1935 to only 4% in 1983, *S. haematobium* infection was significantly decreased **[44]**.

Bladder infection caused by schistosomiasis has been associated with the occurrence of coinfections with N-nitrosamine–forming bacteria (i.e., *Pseudomonas*, *Proteus* and *Escherichia coli*) that are thought to act synergistically in BC initiation **[22, 45]**. Moreover, the infection induces inflammation, which can lead to the internal production of N-nitrosamines and the generation of free oxygen radicals that damage DNA **[43]**. It has been observed that the progression of this disease is more rapid compared to the effects caused by exposure to tobacco or chemicals. Fortunately, the use of praziquantel, an anti-helminthic medication, can effectively control the parasite and prevent this disease's progression **[46]**. Similarly, **[47]** suggested a metabolic link between polycyclic aromatic hydrocarbon (PAH) degraders (i.e., *Acinetobacter, Micrococcus and Pseudomonas*) and BC oncogenesis through potent PAH intermediates formed by the bacteria.

Concisely, it is extremely important to manage the risk factors of bladder cancer to reduce the incidence of the disease as there is a notable number of individuals who do not have a good response to the initial therapeutic approaches and the disease progresses to advanced stages.

8. Urinary microbiota

The microbial population inhabiting the human body surpasses the human cells, with commensal relationships established in various body sites exposed to the external environment, including the gastrointestinal tract, oral cavity, genitourinary tract, and skin. Each of these sites hosting microbial ecosystems exhibits distinct microbial compositions and metabolic functions **[48]**. The microbiome of everyone is unique, undergoing rapid development during early childhood and displaying varying rates of variability in adulthood **[48, 49]**.

The association between cancer and microorganisms is intricate. While cancer is primarily regarded as a result of host genetics and environmental influences, microorganisms are linked to 20% of human cancers, on average **[50]**. Microbes living in mucosal areas can be part of the tumor microenvironment in cancers of the airway and digestive tract, and microbes inside tumors can have different effects on cancer growth and spread **[5, 51]**.

Numerous elements, including genetic and environmental features including exposure to toxins or carcinogens, diet, environment, geographic location, and hormonal impacts, affect the variety of microbial makeup within the human body. Many studies have shown that a specific microbial community, called the urinary microbiota, exists in the urinary tract (UT), which has been involved in UT problems **[52]**. In addition, studies investigating the genitourinary microbiome's potential role in the development of genitourinary malignancies,

such as prostate, kidney, and BC, have been inspired by the recent discovery of a genitourinary microbiome in humans **[45]**.

Intravesical BCG (bacillus Calmette-Guerin immunotherapy), which uses an attenuated strain of the bacterium *Mycobacterium bovis*, has been used by urologists for more than 40 years to manipulate the bladder microbiota **[53]**. The success of this therapy, combined with observations made in other types of malignancies, shows that the bladder microbiome can influence the pathophysiology of urothelial carcinoma (UCC). It may function as a noninvasive biomarker for the disease and impact the response to therapy **[4]**.

Further evidence supporting the function of *Lactobacillus* in Bladder Cancer prevention has come from studies looking into the differences in microbial populations in Bladder Cancer **[22, 54]**. In fact, most of the research on the urine microbiome in bladder cancer has found that these numerous genera are lost in bladder cancer **[55]**. Although *Lactobacillus* species themselves are lethal to human Bladder Cancer cell lines in vivo **[56]**, it's probable that a higher *Lactobacillus* abundance in healthy patients is indicative of urinary microbiome homeostasis and probiotics protective effects **[57]**.

In sum, human cells have a commensal relationship with their own microbiome which is affected by several factors. This microbiota may cause urinary tract infection and bladder cancer or bladder cancer prevention.

8.1. Human Microbiome Project

The National Institutes of Health (NIH) launched the Human Microbiome Project (HMP) in 2008 as an international and interdisciplinary project. Its primary objective is to comprehensively describe the human microbiome and examine its significance in relation to human health **[3, 58]**. The development of DNA sequencing technologies has been significant in enabling the identification of bacteria without relying on traditional culture methods. Rather than analyzing the genome of a single bacterial strain grown in a lab, the metagenomic method used by the HMP looks at the combined genetic material from microbial communities living in their original habitats **[3].**

The HMP has focused on investigating microbial communities residing in several regions of the human body, such as the vagina, GI tract, skin, nasal and oral cavities. Furthermore, the project aims to elucidate the roles played by these microorganisms in maintaining human homeostasis as well as their involvement in various pathological conditions **[59]**.The UT was not initially explored in the Human Microbiome Project (HMP) due to the traditional belief that it was a sterile environment, especially in the proximal regions near the

urethra**[59, 60]**.This notion was backed by the absence of observable cultivable cells using common urine culture methods in healthy individuals **[61,62]**.

The presence of a urine microbiome has been understudied in the scientific literature due to the conventional belief that urine from healthy individuals is sterile. However, new research has shown that people with a variety of benign urological diseases have an innate commensal community in their urine **[63, 64]**. This discovery presents an opportunity to investigate the distinct urine microbiome in patients with malignant bladder tumors, potentially enhancing our understanding of the complex nature of this disease **[6]**. Recent studies have verified that the bladder is not a germ-free place, but the consequences of this discovery in the disease process and treatment of UCC are still unclear. UCC may originate and grow in part due to the bladder microbiome, which may also serve as a urine biomarker that can be altered and discovered without surgery. It is crucial for researchers to continue refining techniques for characterizing this intriguing field of human health **[4]**. Although the development of several malignancies has been related to the human microbiome, little is known about the microbiome of those who have BC **[6]**. Hence, a thorough comprehension of the functions of the microbiota and microbes in disease requires a holistic view**[5]**.

9. Urine is not sterile

Using culture-based methods, it was previously assumed that healthy individuals had sterile urine. For over six decades, urine culture was the main technique for detecting the causative agents of UTIs **[41, 65]**. However, using approaches such as 16S rRNA gene sequencing and expanded quantitative urine culture (EQUC) methods, new findings have emerged. They have discovered that there are numerous microorganisms in urine samples, many of which are not detectable by standard culture techniques **[66]**. Researchers have been able to see microorganisms in the urine of healthy persons and find bacteria that would have been labeled as culture-negative using high-throughput DNA sequencing and improved culture techniques **[67]**. As a result, a varied colony of microorganisms residing in the UT has been discovered **[41, 65, 66]**. These findings support the emerging concept that the bladder harbors its indigenous microbiome. Further research has revealed that the bladder microbiome has a protective role and Disturbances in these microorganisms (known as dysbiosis) can contribute to lower UT dysfunction **[4]**.

Novel molecular assays have provided valuable insights into the vast diversity, functional capabilities, and age-related dynamics of the human microbiota present in the UT. These microbial communities influence the maintenance of the homeostasis of the UT via different mechanisms. For instance, the urinary microbiota has the capacity to generate

molecules which can interact with the nervous system, potentially influencing the regulation and integrity of epithelial junctions. Furthermore, commensal bacteria in the UT can establish a barrier within the uroepithelium, effectively outcompeting uro-pathogens and producing antimicrobial compounds or degrading harmful substances **[59]**. Additionally, these bacteria can influence the normal development of the UT, including the uroepithelium, as well as the immune and peripheral nervous systems **[3]**.

In recent decades, understanding the genetic information of microbes and hosts has advanced with the development of next-generation sequencing (NGS). In the "omics" era, numerous fields have been discovered, including genomics, proteomics, transcriptomics, metabolomics, phenomics, and metagenomics. Metagenomics has among them led to a remarkable development of the number of findings pertaining to the microbial world. There are two types of metagenomics: amplicon and shotgun. It is a culture-independent technique. In contrast to shotgun metagenomics research, which focuses mostly on mining functional genes and metabolisms, amplicon metagenomics investigations often study microbial diversity.**[68]**. Therefore, the results of metagenomic studies enhance the detection of species that were thought to be un-culturable, which has improved our knowledge of the physical and pathological aspects of different urologic disorders and highlighted the significant role played by this unique microbial community in overall urological health **[68,69, 70]**.

It is crucial to study the typical microbial communities in the lower UT of healthy individuals to recognize the microbial changes linked to abnormal lower UT symptoms, and it has the potential role to radically alter how these disorders are treated **[52, 71]**. To illustrate, insights gained from investigations into the gut microbiota indicate that the excessive, prolonged, or inappropriate utilization of antibiotics can disrupt microbial equilibrium, making the host more susceptible to colonization by pathogenic bacteria like *Clostridioides difficile* (formerly *Clostridium difficile*) **[72]**.

Although the urinary microbiota literature lacks a comparable body of compelling evidence, a possible explanation for why antibiotic treatment for asymptomatic bacteriuria dramatically raises the risk of recurrent UT infections in young women is that a similar event happens**[67, 73]**.The administration of oral and parenteral antibiotics for the management of acute and recurrent UT infections (UTIs) may lead to a decline in the presence of advantageous bacteria that inhibit the pathogenic bacteria. Consequently, comprehending the composition of the typical urinary microbiota has the potential to revolutionize our approach to treating bladder disorders. Rather than prioritizing the eradication of pathogenic bacteria through antibiotic use, which invariably causes harm to the normal microbiota, a paradigm shift towards rebuilding a

resilient microbiome could be pursued. This approach aims to reduce the host's susceptibility to pathogenic bacteria by focusing on the restoration of a healthy and diverse microbiota **[52, 74]**.

10. Urinary microbiota and urinary tract disorders

The composition of the UM can act as a host protection mechanism, preventing infections when the physiological balance is maintained, or allowing infection and colonization by pathogens when the balance is disturbed by factors related to the host or the environment **[70]**.

Although extensive research has been conducted on the gut microbiome, the exploration of the UM is a recent development **[4]**. Current investigations primarily focus on elucidating potential causal relationships and understanding the disease mechanisms mediated by the urinary microbiota. The primary objective is to enhance our comprehension of these mechanisms, with the ultimate aim of devising novel therapeutic and preventive approaches for diverse disorders. Recent investigations have shown a correlation between chronic urological problems and dysbiosis, which is characterized by disturbances in the composition and functionality of the urine microbiota **[3]**.

It is still unknown how the urine microbiome affects both healthy individuals and those who have urogenital diseases. Asymptomatic bacteriuria, which means bacteria in urine samples from people who do not have any signs or symptoms of a UTI, is common in the general population, including people who do not have any known UT disorders **[75]**.

Significantly, there exists evidence indicating that bacteria within the UT may influence in modulating the pathogenesis of urgency urinary incontinence (UUI), at least in a subset of women. Studies employing EQUC and 16S rRNA gene sequencing have identified altered bacterial communities in women with UUI **[76]**. These investigations provide support for the notion that symptoms associated with overactive bladder (OAB), such as UUI, might be affected by changes in the UM. However, it is important to mention that these studies had significant differences in characteristics between their UUI and control groups, such as age, hormonal status, and BMI, which may all affect the composition of the urinary microbiota. Furthermore, the studies considering the UM remains limited, emphasizing the urgent need for further research in this area **[66]**.

The findings reported by **[66]** demonstrate the presence of a polymicrobial community within the female bladder, observed in both healthy individuals and women affected by UUI. These results show that alterations in the normal composition of the bladder microbiome can lead to a substantial effect on the pathophysiology of UUI. The researchers were able to

successfully extract and sequence bacterial DNA from 95% of the urine samples collected. After data analysis, it became clear that there were significant variations between the control group and the UUI group in the relative abundance of 14 bacterial species. In particular, women with UUI had statistically significant changes in the relative amount of some bacteria compared to the control group. Furthermore, the study demonstrated that a decrease in microbial diversity was linked to greater severity of symptoms in women affected by UUI. These findings provide evidence supporting the notion that the UMaffects UUI development and underscore the potential correlation between reduced microbial diversity and the clinical severity of the condition.

Research conducted by **[77]** employed high-throughput 16S rDNA pyrosequencing to investigate the UM of a female patient diagnosed with OAB. Two urine samples were collected one year apart. The first sample showed the presence of *Streptococcus* through standard urine culture, and the patient was treated with antibiotics. One year subsequent to the initial study, the standard urine culture yielded negative results, yet the patient continued to experience urinary symptoms. Analysis of 16S rDNA in both urine samples indicated the presence of fastidious and anaerobic bacteria, with minimal fluctuations in microbial diversity over the course of a year. These outcomes show a plausible association between OAB and the urinary microbiota, as evidenced by the consistent composition of the microbiome and the existence of urinary symptoms despite antibiotic treatment.

In a study conducted by **[78]**, the potential contribution of urinary microbiota to urge UUI was investigated. In order to isolate live bacteria from urine samples taken via transurethral catheter from female patients with OAB with UUI (OAB wet) as well as a control group of women without LUTS, the researchers combined 16S rRNA gene sequencing and an EQUC protocol. The findings indicated discernible dissimilarities in the UMs between the two groups, as observed through both culture and sequence analysis. Specifically, the 16S rRNA sequencing revealed that patients with UUI exhibited elevated levels of *Gardnerella* and reduced levels of *Lactobacillus*when compared to the control group. Additionally, the EQUC technique identified nine genera (*Aerococcus, Arthrobacter,Oligella, Staphylococcus, Corynebacterium,Streptococcus, Gardnerella,Actinobaculum, and Actinomyces*) that were more frequently detected in the urine samples of OAB wet patients.

In a comparative analysis of the two groups, *Lactobacillus* was found to be present in both. Nevertheless, at the species level, variations were observed, with a higher prevalence of *Lactobacillus gasseri* in patients with UUI and *Lactobacillus crispatus* in the control group. Comparing the results of culture and sequencing analyses, it was found that 58% (30 out of 52)

of the urine samples evaluated positive for bacteria using both techniques. In contrast to the EQUC study, which discovered bacterial DNA in only 6% of the urine samples that evaluated negative, the sequencing analysis revealed bacterial growth in 7% of the urine samples. In all, bacteria were found in 90% (47 out of 52) of the specimens using one or both methods, with only 10% of the samples being bacterially negative (5 out of 52).

[78] Compared urine samples using these two methods and found a high degree of similarity in the bacteria they detected, implying that many of the genera they sequenced were alive. They also discovered that women who suffered from UUI had more *Actinomyces, Aerococcus, and Gardnerella* in their urine, while *Lactobacillus* was less common than in women without LUTS. A plausible reason for this is that the LUT microbiome is disturbed in UUI patients, leading to the emergence of storage symptoms. This theory is supported by the observation that each genus connected to the UUI group contained at least one species that was known to cause disease. The UMs of women with and without UUI show considerable variances, and these findings may have an impact on how this disorder is prevented, identified, and treated.

11. Urinary microbiota and bladder cancer

The UM's influence on urologic cancers has been explored by few studies **[4]**. The bacteria in urine or tissue samples from patients with BC are still poorly understood **[41,79-81]**.

According to **[5]**, the microbiota of a host can either increase, decrease, or have no effect on cancer susceptibility. Finding out the causal effects of specific microbes and microbiotas on cancer, studying the interactions between host-microbiota and environmental factors in cancer development, and using this knowledge for cancer diagnosis and treatment are all active research topics. According to **[79]**, bladder microbiota changes could serve as markers for BC, potentially assisting in disease monitoring and screening.

The interaction between microorganisms and their hosts is complex, and there are numerous molecular mechanisms through which they can influence oncogenesis, tumor progression, and response to anticancer therapy **[82, 83]**. For instance, bacteria have the capability to directly harm the host's DNA by producing genotoxins like colibactin, which is produced by specific strains of *Escherichia coli*. Indirectly, bacteria can lead to DNA damage via the generation of reactive oxidative species. The Wnt/β-catenin pathway, which is known to be changed in several types of cancer, is just one example of the host signaling pathways that some pathogenic microbes are capable of manipulating to promote cell growth. Additionally, the microbiota found in the gastrointestinal tract has the ability to cause persistent

inflammation, creating an environment that is favorable for tumor growth. Additionally, it may cause immunosuppressive reactions that interfere with cancer immunosurveillance systems. Additionally, bacterial metabolism of metabolites derived from the host, dietary components, or xenobiotics can lead to the production of harmful compounds that may contribute to tumorigenesis, even in distant regions of the body.

The elimination of chemical carcinogens from the body depends not only on genetic factors, but also on the interactions with biochemically active microbes. For instance, bacteria that produce nitrate can facilitate the formation of N-nitrosamines, which are carcinogenic **[45]**. The kidneys play a crucial role in filtering out various toxins, including polycyclic aromatic hydrocarbons, pesticides, ochratoxins, heavy metals, and other environmental pollutants, from the bloodstream. Nevertheless, the presence of these substances in the bladder can affect the microbiota, resulting in the production of metabolites that could either increase or decrease the likelihood of developing BC **[41]**. This finding provides further evidence to support the idea that variations in the urinary microbiota may lead to the onset, advancement, and reappearance of BC **[65, 84]**.

Tobacco smoking is the major risk factor for BC, but other carcinogenic risks include exposure to aromatic amines or arsenic in drinking water. These factors also have an impact on microbiota development **[41, 85]**. On the other hand, several factors contribute to the variation in the occurrence and advancement of BC between men and women. One of them is the influence of male hormones on the kind of BC that a patient may develop, as reported by **[86]**. Another one is the difference in the urinary microbiota between women and men **[87]**.

The urinary microbiota composition differs between genders due to the anatomical and hormonal differences, which also result in higher female UT infections. Female BC incidence is much lower than male bladder oncogenesis, and this could be explained by the different microbiota **[4, 41,88]**. A fascinating observation was made in a study examining the UM of aging males, which showed a notable decline in the overall bacterial count as men grew older. However, an increase was observed in the number of different bacterial genera present **[87]**. This shows that the male UM may undergo a decrease in size while becoming more diverse with age.

In addition, a different study that concentrated on men discovered a link between the intensity of LUT symptoms and the amount of bacteria in urine obtained during transurethral catheterization, also referred to as the male bladder microbiome **[4, 89]**. This suggests that the severity of LUT symptoms may be related to the presence of bacteria in the male bladder microbiome.

The host microbiome has been implicated in cancer susceptibility in various systems, but not much is known about the UT **[90]**. The majority of the research has focused on the connection between gastrointestinal tract malignancies and intestinal flora. However, the UM of urothelial cancer (UC) patients has been scarcely investigated and its role in BC remains unclear **[91]**. Using 16S sequencing, **[92]** reported variations in the urine microbiome of UC patients (n = 8) and healthy controls (n = 6), such as an increased abundance of the genus Streptococcus in the urine of patients.

In a study conducted by **[80]** using 16S sequencing of midstream voided urine, it was discovered that male patients with UCC had elevated levels of the genera*Sphingobacterium, Anaerococcus,* and *Acinetobacter* compared to healthy individuals. The study involved 31 UCC patients and 18 healthy controls. The researchers also noticed that *Herbaspirillum, Bacteroides,* and *Porphyrobacter* levels were higher in UCC patients who were at considerable risk of progression and recurrence. These findings suggest that these genera could serve as potential biomarkers for assessing the risk of UCC.

Similar to this, **[41]** discovered notable variations in the urine microbiome between those with bladder cancer and healthy people. Patients with bladder cancer had greater concentrations of specific bacterial genera in their urine samples. In particular, "five suspect genera" that were more common in tissue samples than in urine were found as being *Enterobacter, Bacteroides, Clostridium sensu stricto, Akkermansia,* and *Klebsiella.*

[82] used 16S sequencing to compare the urine of 12 UCC patients and 11 controls, and found that *Fusobacterium*, a genus linked to colorectal cancer, had significantly higher levels in UCC patients than in non-cancer patients. Additionally, it was observed that healthy urine samples exhibited a higher prevalence of three operational taxonomic units (OTUs) belonging to the genera *Veillonella*, *Streptococcus*, and *Corynebacterium*. The findings suggest that there were distinct variations in the urine microbiota between the group of individuals with BC and the control group. **[93]** also noticed variations in the urine microbiome between patients who experienced recurrent superficial UT infection and those who did not. According to **[94]**, the least prevalent genera in the human UM were*Staphylococcus* (6.9%), *Actinomyces* (6.9%), *Streptococcus* (11.9%), *Corynebacterium* (14.2%), and*Lactobacillus* (15%).

[95] mentioned that the bladder microbiota and the vaginal microbiota have similar genomic and functional features, which are different from those of the gastrointestinal microbiota. The researchers also demonstrated that the bacterial strains obtained from both the vagina and bladder of women are remarkably alike. Examples of these strains include*Lactobacillus iners, Streptococcus anginosus,Escherichia coli*and *Lactobacillus*

crispatus. This outcomeshows a close relationship between the microbial communities in the female urogenital tract, encompassing not just harmful bacteria but also beneficial ones associated with good health.To improve the diagnosis and management of the condition, more research is required to support the link between the urine microbiota and BC **[65]**.

12. Urinary microbiota and treatment of bladder Cancer

By avoiding risk factors and using currently available evidence-based preventive techniques, between 30 and 50% of malignancies may now be avoided. By abstaining from tobacco use, keeping a normal body weight and consuming a balanced diet containing fruit and vegetables, BC can be decreased. Moreover, limiting occupational exposure to ionizing radiation and carcinogenic compounds, as well as avoiding ultraviolet radiation exposure to and assuring safe and proper use of radiation in healthcare (for diagnostic and therapeutic purposes). Early cancer identification and adequate cancer therapy and patient care may both minimize the burden of the disease. several cancers have a good chance of recovery if caught early and adequately treated **[9]**.

Transplantation of fecal microbiota, Symbiotic microbiota consortia, microbiota-derived proteins and metabolites, engineered symbiotic bacteria and prebiotics have all been investigated for microbiome-based therapies **[96]**.Additionally, certain metabolites, such as fatty acids of short-chain, have a role in the microbiome's processes **[97]**.The microbiome may have a role in the genesis and management of genitourinary cancers, according to mounting evidence **[45, 98, 99]**.

Early carcinogenesis is seldom triggered by the immune system, however immune detection of tumor interstitial feedback loops, inflammation, or malfunction may encourage tumor growth **[100]**. There is growing evidence that the microbiota, along with their bioactive metabolite, has immunomodulatory properties and may play a role in controlling the immunological microenvironment of solid tumors, including bladder cancer **[70, 101]**. In 28 individuals with NMIBC, **[102]** looked at the connection between the urine microbiota and PD-L1 expression. Nine patients with PD-L1 positivity were shown to have a higher species abundance in their urinary microbiome. The number of PD-L1-positive cells was gradually correlated with an increase in the diversity of microbial species. *Roseomonas, Propionibacterium* and*Leptotrichia* were all part of the amplified microbiota. The researchers also saw a decrease in *Prevotella*and*Massilia* abundance at the same time. According to this finding, microbiota enrichment and PD-L1 expression in NMIBC are significantly correlated.

In 149 patients with MIBC, **[103]** looked at the impact of antibiotics on the effectiveness of immunotherapy. The findings indicated that using antibiotics at the same time

as immunotherapy medications was linked to decreased rates of full response and relapse-free survival. These findings also obliquely indicate the contribution of microbiota to BC immunotherapy. Therefore, prospective research using larger sample sizes should be conducted.

13. Future respective

The bladder microbiome is a recent discovery that challenges the current understanding of various urologic diseases. However, the UM and UCC have been scarcely explored **[4]**. In the coming years, urologists might need to consider the possibility of urinary dysbiosis as a potential contributor to various functional LUT disorders. According to **[3]**, this may have significant effects on how these illnesses are diagnosed and treated. Additionally, **[4]** suggestion to look into the bladder microbiome's relationship with urothelial carcinoma of the bladder (UCC), which is a prominent cause of cancer-related death among urologic patients, could be extremely helpful for its diagnosis and treatment.

The bladder microbiome is a promising area for further research. By analyzing the microbial communities in the bladder of UCC patients, causal links between UCC and the microbiome could be established, and novel diagnostic markers could be identified. The use of the microbiota to improve UCC diagnosis and treatment has great potential advantages. Researchers should persist in refining methods for exploring this fascinating aspect of human health **[4]** and the role of microbes and the microbiota in modulating carcinogenesis, therapeutic responses, and cancer-related complications **[5]**. The development of suitable screening or monitoring approaches may be made possible by a more precise identification of microbiota changes during BC advancement **[41]**.

14. Conclusion

The of bladder cancer is a worldwide burden. While cancer is primarily regarded because of host genetics and environmental influences, microorganisms are linked to 20% of human cancers. By using high-throughput DNA sequencing and improved culture techniques, current evidence supports that the urinary tract is inhabited by a variety of microorganisms that were previously not detectable by standard culture techniques. the link between the urinary microbiome and bladder cancer and urinary tract disorders might be critical to establish the novel strategies and consequently improve diagnosis, treatment and prevention of them. So, the bladder microbiome is a promising area for further research to more understanding of various urologic diseases.

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16. Conflict of Interests

The authors clarify that they have no conflicts of interest. None of the data provided in this paper has ever been published or is being considered elsewhere. Prior to submission, the manuscript's final version was reviewed and approved by all authors.

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الملخص العربى

ميكروبيوتا المسالك البولية وإضطرابات المسالك البولية السفلية

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الملخص العربى

يعد السرطان السبب الرئيسي الثاني للوفاة بعد أمراض القلب والأوعية الدموية في أكثر من خمسين دولة. ويحتل سرطان المثانة المرتبة العاشرة بين أكثر أنواع السرطان تشخيصًا على مستوى العالم، حيث يتم الإبلاغ عن نصف مليون حالة جديدة وخمسين بالمائة من الوفيات سنويًا. بالرغم من أن مرض السرطان يتأثر في المقام الأول بالعوامل الوراثية والبيئية، إلا أن الكائنات الحية الدقيقة تساهم في ٢٠٪ من أمراض السرطان. وتعد الكائنات الحية الدقيقة لكل شخص فريدة من نوعها، حيث تمر بالتطور في مرحلة الطفولة والبلوغ وتتواجد في جسم الإنسان في الأماكن المعرضة للبيئة الخارجية كالجهاز الهضمي، وتجويف الفم، والجهاز البولي التناسلي، والجلد. فقد وجدوا أن ميكروبيوتا المسالك البولية تعمل كآلية حماية للإنسان عن طريق منع العدوى في حالة التوازن الفسيولوجي،أو السماح بالعدوى بواسطة مسببات الأمراض عند إضطراب هذا التوازن بسبب العوامل المرتبطة بالإنسان أو البيئة. في الماضي ، كانوا يعتقدون بأن عينات البول من الأفراد الأصحاء تكون معقمة وخالية من الكائنات الحية الدقيقة وذلك عن طريق إستخدام الطرق التي تعتمد على زراعة الميكروبات على البيئات الغذائية. ومع ذلك، بإستخدام تقنيات تسلسل الحمض النووي عالي الإنتاجية وزراعة الميكروبات المتطورة، تم اكتشاف كائنات حية دقيقة في بول الأفراد الأصحاء، والتي لم يتم اكتشاف العديد منها بواسطة الطرق التقليدية لزراعة الميكروبات. لذلك، أصبحت العلاقة التكافلية بين الإنسان والميكروبات الحيوية المتعايشة محل إهتمام في كلاً من المجالات الأساسية والسريرية في جميع أنحاء العالم. وبالتالي سيتم مناقشة الدراسات الوبائية وعوامل الخطر الخارجية لسرطان المثانة، بالإضافة إلى الإرتباط بين ميكروبيوتا المسالك البولية، وإضطرابات المسالك البولية وسرطان المثانة، إلى جانب دورها في العلاج.