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MICROBIAL ANTI-CANCER THERAPY AND PREVENTION (Y YAMAUCHI, SECTION EDITOR)

Prostate Cancer Microbiome: A Narrative Review of What We Know So Far

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Abstract

Purpose of review The role of the microbiome in mediating the pathogenesis of prostate cancer has been suggested to have a role in the carcinogenesis process. This review aimed to explore the potential role of the prostate, urinary, and gut microbiomes in prostate cancer development.

Recent Findings Current literature indicates that the discovery of microbes, potentially associated with prostate cancer, raises more questions about whether their presence was merely coincidental or due to contamination. Studies have discovered bacteria and viruses in the prostate, urinary tract, and gastrointestinal tract. However, whether there is a prostate microbiome is still unclear due to the study design limitations and small sample size.

Summary Even though the link between the specific microbiome and prostate cancer has not been established, findings suggest that chronic inflammation and immune system modulation associated with the microbiome are the underlying mechanisms increasing the risk of prostate cancer development.

Keywords Prostate cancer · Microbiome · Prostate microbiome · Genitourinary microbiome · Gut microbiome · Cancer

Introduction

The human body contains more than 38 trillion microbes, coexisting with our cells [1]. Microbes consisting of bacteria, viruses, archaebacteria, protista, and fungi mostly live in the aerodigestive tract and other areas of the body, including the urinary tract [2]. The definition of 'microbiota; refers to a collection of microorganisms, consisting of bacteria; eukaryotes; and viruses, existing in an environment, which are found in all multicellular organisms [3]. The term 'microbiome' refers to the interaction of a particular microbe with a disease, obtained from processing microbial DNA [4]. Several studies even suggest that the microbiome is heritable as a polygenic trait [5]. These microbes play a major role in many health and disease processes, in which they are believed to maintain a symbiotic relationship with the human body in metabolism, immune response, and reproduction [6, 7]. Research in the human microbiome as a part of ecological research has been conducted for decades; however, the role of the microbiome in certain diseases has only been studied in recent years [8]. Diseases such as obesity, psoriasis, inflammatory bowel disease (IBS), and colorectal carcinoma have been linked to the microbiome [9, 10, 11, 12]. Cancer is a multifactorial disease, involving genetic, immune, environmental, and psychological factors causing its management to be difficult [13, 14]. Knowledge regarding factors influencing cancer development and progression has increased dramatically in the past two decades [15]. A specific approach for each type of malignancy has produced many studies evaluating tumor genome, epigenome, and microenvironment [16, 17]. Approximately 20% of a malignancy's etiopathogenesis is related to the role of a microorganism, including the manipulation of a microbe on the stimulation or suppression of cancer cells [18]. Many studies

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have explored how microbiota works in mediating the pathogenesis of several solid tumors based on the thorough investigations in several studies, including its potential for diagnosis and risk stratification [19, 20, 21]. Prostate cancer is the second most commonly found malignancy in men. Based on the data published by the GLOBOCAN database, it is the second most commonly found cancer and the fifth leading cause of cancer-related death among men in 2020, as shown in Figure 1 [22•]. The organ is responsible for producing fluid to give nutrition and facilitate sperm transport during ejaculation [23]. In recent years, studies investigating the role of inflammation and prostate carcinogenesis have been published, reporting many chronic inflammatory cells found in the histopathological examination of the prostate cancer tissue, especially in the peripheral zone [24, 25]. Proliferative inflammatory atrophy (PIA) are inflammatory lesions that exist in many glandular tissues with basal and secretory cells. These lesions are abundant in the peripheral zone of the prostate, thus the lesions are believed to be a precursor to prostate cancer cells [24].

Bacteria have been thought to cause chronic, low-grade inflammation which could induce neoplasia [4]. The interaction of some microbes with the prostate can be explained both directly and indirectly. Direct interaction involves the microbiome in the urinary tract and prostatic tissue, whereas indirect interaction involves the gut microbiome, including oral and fecal microbiomes [26, 27]. Microbiomes have been suggested to have a role in the entire carcinogenesis process from initiation to progression, thus affecting the consequences of a particular treatment [28]. Some bacteria are able to produce toxins that could increase the risk of malignancy, such as colorectal cancer, gastric cancer, and bile cancers, such as *Salmonella typhi*, *Escherichia coli*, and *H. pylori* [29, 30]. Prostate cancer is the second-highest leading cause of cancer-specific mortality in the world, thus a thorough understanding regarding the risk and diagnosis for prevention, as well as management strategy for prostate cancer is necessary [31, 32]. Theoretically, natural microbiotic changes can increase the risk of prostate cancer development [33]. Chronic infection, the involvement of a genetic structure of a virus, and metabolic production can influence the prostatic carcinogenesis [34].

Prostate cancer management has advanced rapidly in the use of chemotherapy, androgen deprivation therapy, surgery, radiotherapy, and immunotherapy in recent years [35]. In the era of specific management strategies for each malignancy, a deep understanding of the specific microbiome for prostate cancer will be beneficial to increase the quality of management of prostate cancer patients [36]. With the introduction of novel therapies such as immunotherapy and the field of metagenomics and next-generation sequencing, the microbiome is expected to be the foundation of future therapeutic strategies for prostate cancer management [37].

Prostate Microbiome in Prostate Cancer Patients

There are only a few studies evaluating the prostate tissues of both healthy people and prostate cancer patients, in contrast with the abundant studies evaluating the microbiome of various parts of the body [38••, 39••]. Even though some

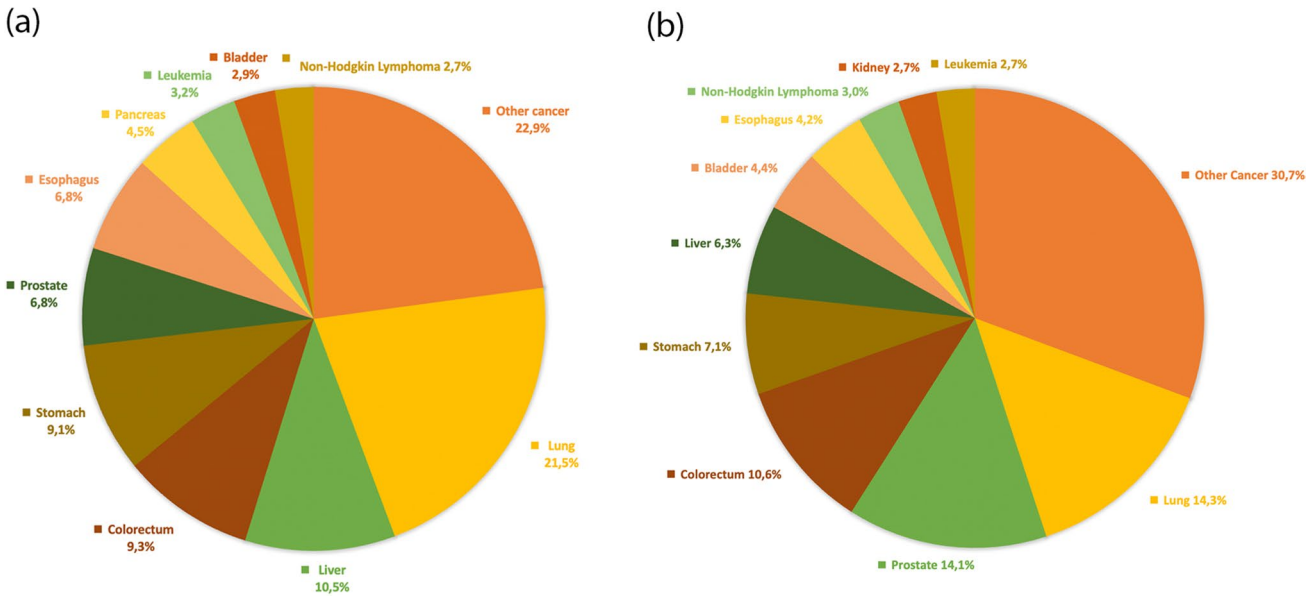

Figure 1 The cumulative risk of prostate cancer (**a**) incidence and (**b**) death in men aged up to 74 years old in 2020

studies have reported the presence of microbiome in prostate cancer tissue, whether there is a prostate microbiome is still unclear [28].

Bacteria Microbiome

One of the earliest prostate microbiome studies conducted in the year 2000 evaluated the specimens of prostate tissue taken from healthy, benign prostatic hyperplasia, and prostate cancer patients. They discovered bacteria in the radical and simple prostatectomy specimens performed on prostate cancer and BPH patients respectively, but not in the prostate tissue of healthy subjects [40••]. Folate and arginine metabolism pathways are associated with the presence of *Bacteroidetes* and *Streptococcal* species, which are enriched among prostate cancer patients [4]. Golombos et al. discovered an enrichment in Bacteroidetes in the stool of 12 prostate cancer patients and *Eubacterium* and *Faecalibacterium* in eight BPH patients. They reported enrichment of metabolically active pathways in patients with BPH compared to patients with cancer [38••]. Cavaretta et al. discovered that *Cutibacterium acnes* was present in the tumor, peri-tumor, and non-tumor tissue of prostate cancer patients undergoing radical prostatectomy [41••]. Several studies have linked the development of prostate cancer with the bacteria in an animal model [42]. However, the results of the study could be biased due to the possible specimen contamination, as *Cutibacterium acnes* is a common contaminant [43••]. There was a higher proportion of *Streptococcaceae* in non-tumor tissue compared to peri-tumor tissue. A higher proportion of *Staphylococcaceae* bacteria was found in tumor and peri-tumor tissue [41••]. The presence of *Streptococcaceae* in normal tissue may indicate the normal microbiome of a healthy prostate tissue as the bacteria are speculated to help maintain an ecosystem for the host environment [44]. However, the results may also be biased as both bacteria are frequent contaminants [45]. In another study, Feng et al. identified over 40 bacteria, with *Eschericia, Acinetobacter, Pseudomonas,* and *Propionibacterium* being the most prominent, taken from the frozen radical prostate specimens of 65 Chinese patients [46••]. Banerjee et al. managed to isolate mostly gram-negative bacteria from the formalin-fixed tissue of 50 prostate cancer patients [47••]. One of the major findings is the presence of *Helicobacter pylori* in more than 90% of prostate cancer tissue. They suggest that *Helicobacter pylori* might play a role in prostatic cancer development [47••]. However, other studies also find the bacteria in BPH specimens and non-tumor tissues [48•]. The studies evaluating the presence of microbes in tumor and non-tumor tissue from formalin-fixed tissue reported similar microbiota characteristics between both tissues [41••, 46••]. The results of these studies could not be concluded as to whether the bacteria's presence is merely due to contamination could not be ruled out [49]. One of the most commonly associated bacteria with bacteria is *Mycoplasma genitalium*, as it can induce oncogenic transformation in both in vitro and in vivo studies [50]. In a study evaluating prostate cancer and BPH patients for various sexually transmitted infection (STI) bacteria, *Mycoplasma genitalium* was discovered to be independently associated with prostate cancer [51]. *Chlamydia trachomatis* has also been suggested to be a potential cause of prostate cancer [13]. A screening trial also suggested that the odds of developing prostate cancer are higher if a person is infected with sexually-transmitted bacteria [52]. Another study by Yu et al. investigated the presence of microbes in the seminal and prostatic fluids in men with BPH and prostate cancer due to the less invasive method of studying the prostate microbiome [53••]. Prostate cancer specimens had a significantly higher presence of *Alphaproteobacteria, Firmicutes, Bacteroidetes, Ochrobactrum, Propionicimonas, Sphingomonas,* and *Lachnospiraceae* bacteria, but a much lower presence of *Eubacterium* and *Defluviicoccus* bacteria compared to BPH tissue specimens [53••]. The variety of bacteria found in many studies increases more questions whether there are many bacteria with the role of inducing prostate cancer progression or there isn't any bacterial microbiome responsible for prostate cancer carcinogenesis and their presence was merely coincidental or due to contamination.

Viral Microbiome

Viral etiologies have been proposed for prostate cancer for years [54, 55]. A study managed to isolate viruses from 80% of the evaluated prostate tissue, in which 40% were tumorigenic viruses including Human Papilloma Virus (HPV) with high-risk strains (16 and 18) and cytomegalovirus (CMV) [47••]. Viruses can prevent clearance from the host through immune tolerance by downregulating the stimulator of the interferon genes (STING) pathway [56]. Viral infections due to polyomavirus, HPV, and CMV have been found to be able to infect the prostate and have a higher prevalence in people with prostate cancer [34]. Some viruses can shut down the STING pathway from destroying the affected cells, including tumor cells, allowing further progression and proliferation to take place [57].

Urinary Microbiome in Prostate Cancer Patients

The role of a urinary tract is to excrete metabolism byproducts from the body's systemic circulation [58]. It is commonly believed that the urinary tract is sterile; however, several

studies have reported the presence of microbiome within the tract [59]. Even though both the gastrointestinal and urinary tracts' epithelial layers are exposed to bacteria, the density and type of microbes in both layers are vastly different [60]. The urinary tract is made specifically to filter, collect, and excrete the byproducts of metabolism without any leakage. Both kidneys receive 20% of the blood pumped by the cardiac with a 125 ml/minute filtration rate [61]. The gut microbes are the main source of metabolites. The metabolites will travel into the hepatic circulation and filtrated by the urinary tract [62]. This mechanism explains why bacteria residing in an area of the body could affect the bacteria in another location. The proximity between the urinary tract and prostate makes it easier for inflammatory pathogens to enter the prostatic duct via urinary reflux and cause infection [63]. Chronic inflammation occurring in the prostate or urinary tract could help provide a microenvironment that stimulates prostate carcinogenesis [64]. Some studies suggested that prostate cancer is with chronic prostatitis and chronic pelvic pain syndrome [65, 66]. Many basic science and clinical studies have attempted to investigate the microbiome of the prostate and urinary tract to determine its role in cancer development. The progress in contamination control techniques has allowed the identification of a natural tissue microbiome [67]. Currently, studies performed a 16S rRNA gene PCR on specimens to identify the presence of bacteria [68]. Theoretically, the occurrence of dysbiosis in the local tissue could lead to a chronic damage, slowly progressing into cancer development [69]. Several studies have investigated the presence of several bacteria and viruses residing in prostate cancer patients' urinary tract, which are not found in healthy patients [65]. The urinary microbiome of 135 prostate cancer patients undergoing a prostate biopsy was evaluated by Shresta et al. with interesting results. In both positive and negative biopsy results, *Staphylococcus, Streptococcus,* and *Corynebacterium* species were found in similar numbers. Other species, such as *Anaeroccous lactolyticus, Anaerococcus obesiensis, Actinobaculum schaalii, Varibaculum cambriense,* and *Propionimicrobium lymphophilum* were found to be higher in patients with a positive biopsy result [39••]. Another study discovered the presence of *Bacteroides, Streptococcus*, and *Veillonella* in the urine sample following a prostatic massage in prostate cancer patients. These bacteria were found to be higher compared to the results of BPH patients. However, it should be noted that the sample size was small [70••].

Gastrointestinal (Gi) Tract Microbiome in Prostate Cancer Patients

Studies investigating the role of the gut microbiome in prostate cancer patients are also small in number. The major component of gram-negative bacteria, lipopolysaccharide (LPS), is able to promote the upregulation of NF-κB and inflammatory cytokines release, which could increase the risk of prostate cancer metastasis in a rat animal model [71]. The increased signaling of NF-κB is also discovered in prostate cancer [72]. A study attempted to evaluate the fecal microbiome by performing rectal swabs in both prostate cancer patients and healthy subjects, in which overlapping presence of bacteria was found, but *Bacteroides* and *Streptococcal* bacteria were mostly found in prostate cancer patients [73]. Another study also discovered a higher proportion of *Bacteroidetes* among prostate cancer patients [74••]. A different result was reported by another study which found no difference in the bacterial results obtained via rectal swab between prostate cancer and BPH patients [70••]. One study attempted to analyze the association between the oral microbiome and prostatic fluid. In patients with mild chronic periodontitis, most of them also had one or more similar bacteria in their prostatic fluid. However, the small sample size and lack of a control group made the results less impactful [26].

Regular consumption of dairy products, red meat, and high fat is believed to be associated with prostate cancer occurrence [75]. Several carcinogenic metabolites are produced by gut microbes, including polyamine, ammonia, and N-nitroso components [76]. The excessive production of polyamine could cause a toxic effect via polyamine catabolism resulting in many free radicals [77]. Several studies reported the role of spermine polyamine in urine as a biomarker for prostate cancer [78]. However, it is difficult to determine whether the spermine was produced by bacteria or the patient's own metabolism. Several types of antibiotics are suggested to cause dysbiosis, which can increase the risk of pathogenic bacteria translocation and chronic inflammation of the prostate [79]. The risk of prostate cancer seems to increase with the use of quinolones, tetracyclines, sulfonamides, and penicillin [80]. Several chemotherapeutic drugs, such as cyclophosphamide may also cause shortening of the gut intestinal wall villi, causing microbes to cross and enter the systemic circulation [81]. Several gram-positive bacteria such as *Enterococcus hirae Lactobacillus murinus,* and *Lactobacillus johnsonii*, were also discovered to be necessary for mediating the cyclophosphamide stimulation of response from type 17 T helper (TH17) cells and type 1 T helper (Th1) cells [82].

Clinical Application

The microbes residing in the GI tract are involved in drug metabolism and pharmacokinetics [83, 84]. The alterations of the gut microbiota composition in both BPH and prostate cancer patients receiving a specific pharmacological treatment have been reported in recent years [85]. Several studies noticed the effects of androgen deprivation therapy

(ADT) on the gut microbes in an animal model [86]. Sfanos et al. discovered a higher diversity of microbes based on the rectal swab of BPH patients compared to prostate cancer patients undergoing ADT [87••]. There is an increase of *Akkermansia muciniphila* and *Ruminococcaceae* among patients consuming abiraterone acetate (AA) and enzalutamide, as opposed to patients taking gonadotropin-releasing hormone agonist and antagonist. Several species of bacteria are capable of steroid and hormone biosynthesis, which could influence treatment response. However, the clinical significance of this finding is unclear [87••]. Another study attempted to further elaborate on this finding. They reported that the administration of sole ADT or ADT and AA might reduce *Corynebacterium* species relying on androgens while increasing the population of *Akkermansia muciniphila.* These findings suggested that AA could be used as a fuel for the bacteria in prostate cancer patients. In the GI specimens of these patients, vitamin K2 biosynthesis-related pathways were increased [88]. As an anti-cancer agent, capable of inhibiting tumor growth in prostate cancer animal models, vitamin K2 role is important. The efficacy of AA for treating castration-resistant prostate cancer (mCRPC) may be supported by the increase of vitamin K2 synthesis by the bacteria [89]. Regarding immunotherapy, the presence of *Akkermansia muciniphila* in the gastrointestinal tract is suggested to influence response to anti-PD-1 immunotherapy. However, since the use of immunotherapy in prostate cancer is still limited, studies evaluating immunotherapy and microbiome in prostate cancer patients are less relevant [90•]. The therapy has not been effective for prostate cancer, which contains scarce tumor infiltrating lymphocytes. However, a recent animal model study has demonstrated the use of a uropathogenic *Eschericia coli* isolated from the prostatic secretions of chronic prostatitis patients, to induce infiltration by anti-tumor immune cell types, increase immunogenicity of the tumor, and decrease the immunosuppressive cells in the tumor microenvironment. The processes resulted in a strong clinical benefit in combination with the programmed cell death protein 1 (PD-1) blockade [91].

Future Studies

Before planning or conducting future studies, most current studies agreed that it is essential to standardize the procedures and techniques for sample collection. With a standard procedure, the results from various studies would be less biased and comparable to make a definite conclusion [92]. The variety of findings in currently available studies made it difficult to determine whether the discovered microbes do have a role in prostate carcinogenesis or are merely coincidental. However, we can't deny that the abundant findings of studies indicate that the potential discovery of a prostate cancer microbiome exists and remains to be seen. Additionally, a study evaluating the carcinogenic role of bacterial products instead of the presence of the bacteria themselves should be performed in the future as the microbiome of the prostate becomes fully understood.

Conclusions

The role of either prostate, urinary, or GI microbiome is still being investigated with no definite conclusion as of the conduction of this review as the currently available studies present various conflicting results with a huge potential for bias. Standardized methods of sampling and analysis with proper prevention measurements for risk of contamination should be determined. Nevertheless, the currently available studies have shown that prostate cancer specimens contain bacterial DNA, not found in healthy prostate tissue. Even though the link between the specific microbiome and prostate cancer has not been established, findings suggest that chronic inflammation and immune system modulation associated with the microbiome are the underlying mechanisms increasing the risk of prostate cancer development.

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Declarations

Conflict of Interest Yudhistira Pradnyan Kloping and Lukman Hakim declare that they have no conflicts of interest.

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