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REVIEW

Human microbiome and prostate cancer development: current insights into the prevention and treatment

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Abstract **The huge communities of microorganisms that symbiotically colonize humans are recognized as significant players in health and disease. The human microbiome may influence prostate cancer development. To date, several studies have focused on the effect of prostate infections as well as the composition of the human microbiome in relation to prostate cancer risk. Current studies suggest that the microbiota of men with prostate cancer significantly differs from that of healthy men, demonstrating that certain bacteria could be associated with cancer development as well as altered responses to treatment. In healthy individuals, the microbiome plays a crucial role in the maintenance of homeostasis of body metabolism. Dysbiosis may contribute to the emergence of health problems, including malignancy through affecting systemic immune responses and creating systemic inflammation, and changing serum hormone levels. In this review, we discuss recent data about how the microbes colonizing different parts of the human body including urinary tract, gastrointestinal tract, oral cavity, and skin might affect the risk of developing prostate cancer. Furthermore, we discuss strategies to target the microbiome for risk assessment, prevention, and treatment of prostate cancer.**

Keywords microbiome; prostate cancer; prevention; treatment; molecular pathological epidemiology (MPE); biomarker

Introduction

Prostate cancer has been reported as a worldwide important kind of cancer. Based on the reports of Cancer Research UK, this neoplasm is the most common form of non-skin cancer among men. It has been reported that 1 276 106 new cases were added to the prostate cancer patients all over the world [1]. The prevalence of prostate cancer is increasing worldwide, even in Asian countries including Iran [2–5].

Cancer is a complex multifactorial disease that involves multiple genetic, immunological, environmental and physiologic factors, leading to the complexity of the treatment. There are several risk factors considered for prostate cancer such as age, ethnicity, family history and environmental factors (diet and lifestyle), as well as microbial (viral and bacterial) infections and inflammation. Current reports suggest that prostate infections and bacterial communities within the host are associated with chronic inflammation and immunological responses, leading to prostate carcinogenesis [6,7].

There are 10 trillion to 100 trillion microbial cells in the human body including bacteria in the gut and the genes they harbor, which are called microbiota and microbiome, respectively [8]. The human-associated microbiota and its effect on the development of cancer is an interesting topic. The microbiome imposes an effect on the entire process of carcinogenesis from initiation to progression and even therapeutic consequences. This effect may be direct, such as the role of *Helicobacter pylori* in gastric cancer or indirect, through changes in metabolism and/or immune system settings. For example, a pathogenic shift in the intestinal microbial content may increase the risk of diseases, such as obesity, diabetes, and cancer via affecting the hormones [9–12].

In this review, we discuss recent data about how the microbes colonizing different parts of the human body including urinary tract, gastrointestinal tract, oral cavity, and skin might affect the risk of prostate cancer development. Furthermore, we discuss strategies to target the microbiome for risk assessment, prevention, and treatment of prostate cancer.

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Microbes and genome instability

Specific microbes cause genome instability and have a serious effect on tumorigenesis through the production of tumor-promoting metabolites such as hydrogen sulfide and superoxide radicals and some microbial toxins including colibactin, *Bacteroides fragilis* toxin and cytolethal distending toxin (CDT). CDT is produced by numerous species associated with colorectal cancer, gastric cancer, and gallbladder cancer, such as *Salmonella typhi*, *Escherichia coli*, and *H. pylori* [13,14]. Moreover, some bacterial species including *Campylobacter jejuni*, *Shigella dysenteriae*, *Hemophilus ducreyi*, *Helicobacter hepaticus*, and *Salmonella enterica* can produce CDT, which has DNase activity and causes DNA double-strand breaks and apoptosis. The superoxide radicals produced by *Enterococcus faecalis* are also known to be involved in colorectal cancers by creating double-strand DNA breaks [15–17].

Microbes and immune response

Infiltration of different immune cell populations, including neutrophils, macrophages, dendritic cells (DCs), adipose cells, T cells, B cells and natural killer (NK) cells is increased in tumor microenvironment. Leukocytes comprise more than 50% of tumor masses [18].

Microbes have been shown to regulate immunity processes. For example, *Fusobacterium nucleatum* and *H. pylori* can suppress the activity of T cells. The presence of T cells in cancerous tissues is associated with an increased overall survival among patients and a more effective response to treatment [19]. Microbes may cause tumor growth by changing the expression of growth hormones. For example, *E. coli* strains produce genotoxin colibactin which causes tumor growth by increasing production of growth factors [20]. Otherwise, some infectious agents such as the influenza A virus, *Staphylococcus aureus*, and *Streptococcus* Group A induce growth of tumor cells and metastases by utilizing transforming growth factor β (TGF-β) [21–23]. TGF-β is a multifunctional regulatory cytokine controlling several aspects of cellular function, including differentiation, cellular proliferation, migration, apoptosis, angiogenesis, immune surveillance, and survival. It also has tumor suppressor role by inhibition of epithelial cell proliferation. However, loss of autocrine TGF-β activity may cause malignant progression of some epithelial cells, suggesting a prooncogenic role for TGF-β in addition to its tumor suppressor role [24].

The normal human prostate tissue contains various types of immune cells including lymphocytes, which are either stromal or intraepithelial. Immune effector cells such as DCs and macrophages are also present in the prostate. Other immune cells including basophils, neutrophils, and eosinophils are rare in healthy prostate tissue but increased in inflamed regions [25–27]. Inflammatory changes in the prostate microenvironment accompanied by prostate infection cause epithelial barrier disruption and consequent progression of prostate cancer. It has also been shown that urinary tract microbiome alteration could lead to prostate infection. Several studies have looked at the role of inflammation and infection in the development of prostate cancer. Generally, the prostate tumor microenvironment is rich in inflammatory cells. It seems that with the progression of prostate tumors, number of anaerobic bacteria is increased due to the oxygen depletion [28,29].

Microbes and inflammation

Relationship between inflammation and cancer was hypothesized by Virchow over 150 years ago upon his discovery of leukocytes in cancerous tissues [30]. Up to 10%–20% of cancers are attributed to chronic inflammation involving microbes [31]. Inflammation can contribute to development of cancer in various organs, including liver, colon, bladder, lung, pancreas, and prostate [30]. Current molecular evidences from animal and human studies implicated the regulatory role of chronic inflammation in prostate cancer development and progression to advanced metastatic disease [30–33].

Microbes colonize the human body shortly at birth [34] and are involved in homeostasis, immunity education, and host defense. Each organ favors the survival and growth of specific collection of microbes [32]. Microbiome have an important immunoregulatory role in healthy individuals. Activation of myelopoiesis in the bone marrow by commensal bacteria has been shown more than three decades ago, suggesting the role of microbiota in the induction of host immune system [35]. For instance, *in vitro* experiments have shown that the deficiency of bone marrow resident myeloid cell populations make them susceptible to *Listeria* infections. Re-colonization of germ-free mice with microbiota restores the immunity against *Listeria* [36].

Homeostasis depends on the integrity of the epithelial barrier colonized by the commensal microflora protecting the host. The balanced symbiotic relationship between the host and its microbiome could be distracted due to environmentally induced dysbiosis [37]. An altered microbiota, termed dysbiosis, could lead to loss of epithelial barrier integrity [38].

The extracellular matrix (ECM) is a three-dimensional network of extracellular macromolecules, such as laminin, collagen, fibronectin, and proteoglycans, that provides structural and biochemical support to adjacent cells. It has a critical role in regulation of cell survival in normal and

tumorigenic growth through the regulation of cell communication, proliferation, differentiation, and survival [39].

Inflammatory cascade has an important effect on the tumor immune microenvironment. In chronic inflammation, several cytokines are produced by inflammatory cells, such as tumor necrosis factor (TNF), interleukin-7 (IL-7), interleukin-2 (IL-2), RANTES, and macrophage inflammatory protein-1b (MIP-1b). Moreover, chronic inflammatory cascade causes activation of growth factors including fibroblast growth factor (FGF) and TGF-β [40]. The release of soluble inflammatory mediators into the ECM results in activation of surrounding stromal cells and promotes formation of reactive stroma [41,42] (Fig. 1). The reactive stroma represents an inflammatory cytokine-rich microenvironment contributing to prostate tumor progression and is associated with poor outcome in clinically localized prostate cancer [42]. Generally, normal cells detached from the ECM are not able to survive and proliferate, and undergo a form of apoptosis termed anoikis. Anoikis is a variant of programmed cell death that occurs due to a lack of extracellular connections to the ECM and adjacent cells [43]. Following inflammation-mediated disruption of ECM, anoikis-resistant cells invade and migrate to distant sites and prostate cancer metastasis occurs [33].

Growth factors, DNA-damage-promoting agents, and a micro-environment rich in inflammatory cells are known as the other hallmarks of cancer. Host cells release several chemical signals in response to tissue damage, which stimulate activation and migration of leukocytes (neutrophils, monocytes, and eosinophils) to the damaged area [44]. Moreover, it was suggested that inflammation due to tissue injuries increases the proliferative capability of cells in the involved area, leading to carcinogenesis [45]. Neutrophils are the first leukocytes recruited to the sites of infection or tissue injury followed by monocytes [46,47]. Chemokines direct the recruitment of particular leukocyte effector cells, leading to the progression of the inflammatory response [44]. The dysregulation of cytokine/chemokine may result in chronic inflammation and subsequent subversion of cell death and/or repair programs and eventually, contributes to cancer pathogenesis [44]. Several chronic inflammatory diseases contributing to cancer, are due to either altered microbiome or the involvement of specific microbes [48]. Gut microbiota is capable of establishing a proinflammatory or antitumor milieu through the modulation of host physiology and

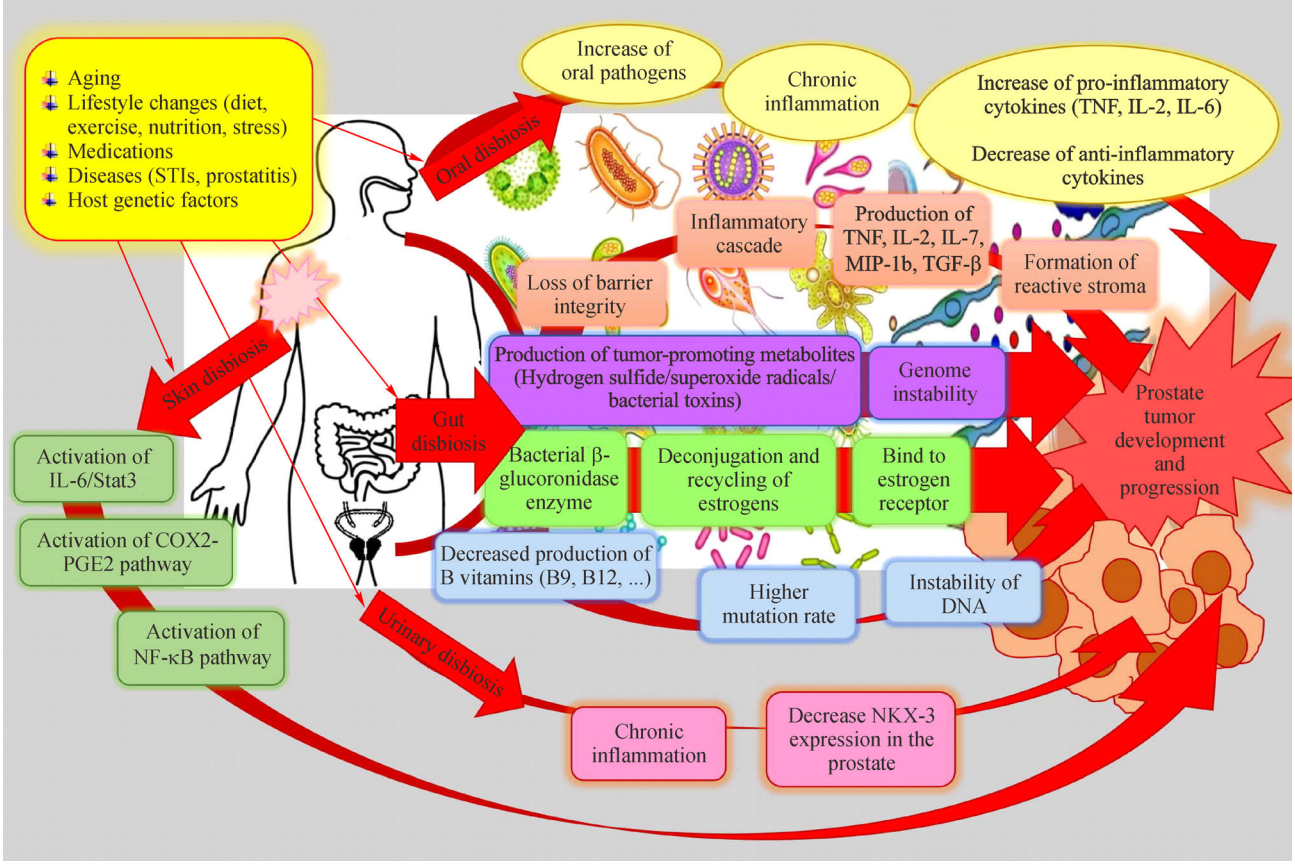

Fig. 1 Schematic representation of the effect of microbiome dysbiosis on prostate cancer development.

functioning of immune cells [49]. Recent evidence suggests a role for inflammation and tissue microbes in prostate cancer [28]. Generally, intraprostatic inflammation is detected in prostate biopsies [50]. In addition, chronic inflammation in benign prostate tissue is associated with high-grade prostate cancer [51]. The high prevalence of chronic inflammatory infiltrates in histopathological examination of the prostate from radical prostatectomy (RP) specimens, prostate biopsy, and transurethral resection of the prostate (TURP) suggests a potential link between chronic inflammation and prostate cancer [52]. Prostatitis can be caused by a variety factors including microbial pathogens such as non-sexually transmitted organisms (*E. coli* and *Propionibacterium acnes*) [53,54], as well as sexual transmitted organisms (*Neisseria gonorrhea* and *Chlamydia trachomatis*) [55,56]. Apart from the causative factors for prostatitis (specific pathogen or environmental factor), inflammation can be considered as a ubiquitous factor associated with increased incidence of prostate cancer among patients with prostatitis [57]. Inflammatory cells result in enhanced vascularity, DNA damage, and ECM degradation to form a nurturing growth microenvironment [46]. Chronic inflammation of the prostate can be caused by persistent infection. Thereby, DNA damage occurs due to constant production of oxygen and nitrogen species produced by leukocytes [58].

Inflammation of prostate, is characterized by an increased number of inflammatory cells in the prostate tissue [59]. The tumor microenvironment in prostate tumor frequently contains inflammatory cells. It has been suggested that inflammatory changes in the microenvironment of prostate along with infection of prostate infection are associated with epithelial barrier disruption and stimulation of prostate cancer development [28]. Numerous signaling factors and biological events influenced inflammation in the prostate microenvironment, linking inflammation to prostate cancer progression and metastasis. These associations provide promising potential therapeutic targets. Currently, several researches have suggested the association of antiinflammatory agents and reduced prostate cancer risk [33].

Microbial-induced inflammation contributes to cancer progression by stimulation of cytokine and chemokine production that stimulates cell proliferation and/or apoptosis inhibition [60]. Numerous studies have shown the association of microbiome composition with modulation of tumor-promoting inflammatory cytokines [61]. A diverse microbial flora in healthy individuals results in production of inflammatory cytokines including TNF-α, IL-6, IL-1β, interferon γ (IFNγ), IL-17, and IL-22 by myeloid and lymphoid cells [62]. Thereby, tumor progression is influenced by these cytokines through different mechanisms, including recruitment of suppressive immune cells into the tumor microenvironment via TNF-α, IL-6, IL-1β or tumor immune surveillance via IFNγ and IL-17 [61]. TNF is a cytokine involved in systemic inflammation [63]. It has been shown that TNF is a mediator of cancer-associated chronic inflammation and stimulates tumor growth and progression [63]. Nuclear factor κ B (NF-κB) is a protein that regulates transcription of DNA, cytokine production, and cell survival. It induces the expression of various proinflammatory genes involved in cell growth, angiogenesis, and metastasis [64]. Increased expression of NF-κB have been found in prostate tumor cells [64]. It may stimulate cell proliferation in prostate tumor cells by regulating the expression of genes involved in cell cycle controlling (such as c-myc, cyclin D1, and IL-6) [65]. In addition, NF-κB transcription factors regulate the expression of angiogenic factors, including vascular endothelial growth factor (VEGF) and IL-8 [65]. Constitutive NF-κB activation in prostate cancer cells has been associated with invasive behavior of prostate cancer tumors [64].

In the tumor microenvironment, immune cells respond to lipopolysaccharide (LPS), flagellin, and other bacterial components and products by producing several cytokines such as IL-23 and IL-17 [66]. LPS is a characteristic component of Gram-negative bacteria. It is a ligand for TLR4 and stimulates the production of proinflammatory cytokines [66]. In addition, it has proangiogenic effects [67]. It also stimulates myeloid cells to produce reactive oxygen species (ROS) which result in DNA damage and mutation leading to cellular transformation [68]. Moreover, other bacterial components including flagellin and peptidoglycan affect systemic inflammation through the ligation of TLR5 and TLR2, respectively [66,69]. Microbial metabolites such as hydrogen sulfide (H2S], N-nitroso compounds, and polyamines have also direct effects on DNA including microsatellite instability [70]. On the other hand, the microbial products have the potential to suppress cancer progression. For instance, it has been reported that 3-ethylbutyrolactone, kynurenic acid, and 3-methyladenine from *Lactobacillus johnsonii* decrease the gene damage and inflammation that is beneficial in cancer prevention [71].

In summary, the complex relationship between inflammation, the microbiome, and cancer is yet to be elucidated. Precise defining the roles of microbes and inflammation in cancer can offer unique opportunities for improved management and prevention of cancer in the future.

Microbiome and prostate cancer

Gut microbiome and prostate cancer

The microbiome and its inflammatory and carcinogenic effects are organ specific [72]. Gut microbiome make up about 99% of the total microbial mass of the human body and has local and distal effects. The gut microbiome is better known than microbiome of other parts of the body

[72]. The human is constantly exposed to microbiome as an environmental factor. Recent studies have shown the association between microbiome alteration and carcinogenesis in the colon, liver, and pancreas [38]. These carcinogenic alterations are due to mechanisms including stimulating inflammatory responses mediated by microorganism-associated molecular patterns (MAMPs) and genomic instability as described above. Inflammatory responses mediated by microbiota occur both locally and systemically via proinflammatory cytokines, such as IL-17, IL-23, TNF-α, and IFNγ [73].

The introduction of next generation sequencing (NGS) of bacterial 16S rRNA has led to better identification of gut microbiome particularly anaerobes that comprise the majority of the human gut microbiome. The human gut microbiome consist of 10^{13}–10^{14} organisms and 3×10^6 genes [74]. The bacterial microbiome has several functions and its content is dependent on the individual's diet, geography, initial infant colonization as well as the individual's immune system [75].

There are four phyla of bacteria predominantly comprising human gut microbiome including Firmicutes, Bacteroidetes, Proteobacteria, and Actinomycetes, of which, the first two constitute about 90% of total bacteria. Firmicutes are mostly Gram-positive anaerobic clostridia, streptococci and enterococci, and Bacteroidetes is composed of Gram-negative bacilli. *Bacteroides thetaiotamicron* and *Bacillus fragilis* are recognized as examples of this phylum with the ability to digest complex carbohydrates. Actinobacteria represent Gram-positive bacteria with a high G + C content in their DNA with the example of Bifidobacteria. They are the first microbes colonizing the human gastrointestinal tract and are known as probiotic organisms. In addition, Proteobacteria represent a diverse group of Gram-negative bacteria including *E. coli* and *Klebsiella* species [75,76].

Estrogens are considered as important agents for treatment or prevention of prostate cancer. First, the association of androgens with prostate cancer was shown by Huggins and Hodges [77]. Then it was shown that estrogen has an indirect antiandrogenic effect by feedback inhibition of hypothalamic luteinizing hormone (LHRH), stimulating the release of luteinizing hormone (LH) from pituitary [78]. Studies have shown that exogenous estrogens such as the non-metabolized diethylstilbestrol (DES) can inhibit telomerase, resulting in inhibition of prostate cancer cell division [79,80].

It has been suggested that gut microbiome via a group of gut bacteria whose products can metabolize estrogens (defined as estrobolome) have major influence on level of circulating estrogens, and consequent risk of developing estrogen-driven cancers, including prostate cancer [81–83]. Typically, circulating estrogens are hepatically conjugated via glucuronidation and producing glucuronides (conjugated estrogens), which do not bind to estrogen receptors (ERs). Dysbiosis of gut microbiome can promote deconjugation and recycling of estrogens via secretion of β-glucuronidase enzyme. Deconjugated estrogens (active forms) can bind to ERs, result in cell proliferation and tumor development [83–86] (Fig. 1).

Therefore, it is rational that patients with prostate cancer may have altered gut microbiome in comparison to healthy individuals. In this respect, it has been demonstrated that there is a significant variation of microbiota among different patient populations. In a recent study, *Bacteroides massiliensis* was more prevalent among prostate cancer patients, and *Faecalibacterium prausnitzii* and *Eubacterium rectale* were more prevalent in benign controls. The differences in the gut microbiota of prostate cancer patients compared to benign controls suggest an important role in the pathobiology of prostate cancer and need further investigation (Table 1) [87]. *B. massiliensis* is a member of the *Bacteroides* species [87]. *F. prausnitzii* is a Gram-positive, rod-shaped, anaerobic bacterium and belongs to the phylum Firmicutes utilizing acetate to produce butyrate [88]. *E. rectale* is a member of Firmicutes phylum and produces butyrate [89].

Butyrate is a type of fatty acid and has important benefits, including antiinflammatory and antitumorigenic properties. Butyrate functions as an antitumor agent by inducing apoptosis and inhibiting cell proliferation [90]. An *in vivo* study has demonstrated that *F. prausnitzii* resulted in a reduction in proinflammatory cytokine secretion (TNF-α, IL-12) and increase in antiinflammatory cytokine secretion (IL-10) [91]. Moreover, *Bacteroides* and *Faecalibacterium* sp. are harbor genes encoding β-glucuronidase, which is essential for estrogen metabolism. However, the *Eubacterium* sp. do not have these genes [92]. β-glucuronidase function leads to increase the circulating levels of free estrogens and react with the host's DNA and make mutations leading to prostate cancer [82] (Fig. 1).

Metabolic pathways of gut microbiome and prostate cancer

Life style is considered as one of the important factors associated with prostate cancer, which greatly affects the microbiota of the intestine. Reduction of the intestinal microbial diversity would make an increase in the number of the bacteria causing systemic inflammation and may lead to increased risk of tumorigenesis [93,94] (Fig. 1). Intestinal bacteria are well recognized for their important role in production of active biological agents including folate, riboflavin (vitamin B12), biotin (vitamin B7), and arginine, contributing in development and progression of cancer. Association of folate and the risk of prostate cancer is the most widely studied of these to date, followed by biotin and arginine [95,96].

Fecal microbiome is a reflection of the intestinal

microbiome. Some studies focused on the systemic effects of fecal microbiome, in order to examine their metabolic pathways and to achieve an appropriate diet for prostate cancer patients [28,29,97] (Table 1). Evaluation of microbiome metabolic pathways can provide an insight into the modifiable risk factors of prostate cancer. A study examined various bacterial components in fecal microbiome to consider the metabolic pathways associated with prostate cancer [98]. The analysis showed high frequency of bacteria associated with carbohydrate metabolism pathways and lack of bacteria producing B vitamins. Epidemiological studies have shown the protective effect of folate against cancers including intestinal and cervix cancers [98–101].

Table 1 Studies evaluating the microbiome in prostate cancer patients

Samples	Method	Findings
Pre-biopsy urine samples (before cancer diagnosis)	16S rDNA sequencing	A higher prevalence of proinflammatory bacteria associated with urogenital infections (prostatitis, bacterial vaginosis, and urinary tract infections) in biopsy proven prostate cancer men (*Streptococcus anginosus*, *Anaerococcus lactolyticus*, *Anaerococcus obesiensis*, *Actinobaculum schaalii*, *Varibaculum cambriense*, *Propionimicrobium lymphophilum*) [29]
Voided urine, EPS[1], seminal fluid of patients with prostate cancer and BPH[2]	16S rRNA gene sequencing with PCR-DGGE analysis	Significant microbial difference in EPS of patients with prostate cancer compared to BPH ones, suggesting the role of dysbiosis in the pathobiology of prostate cancer The prostate cancer group had a considerably increased number of Bacteroidetes bacteria, Alphaproteo bacteria, Firmicutes bacteria, Lachnospiraceae, Propionicimonas, Sphingomonas, and Ochrobactrum, and a decrease in Eubacterium and Defluviicoccus compared to the BPH group [155]
Rectal swab of patients prior to undergoing transrectal biopsy of prostate (before cancer diagnosis)	16S rRNA gene sequencing	Abundance of the proinflammatory species (*Bacteroides* and *Streptococcus*) in prostate cancer patients Bacteria associated with carbohydrate metabolism pathways in prostate cancer group were significantly higher than non-cancer groups, whereas bacteria associated with folate, biotin, and riboflavin were less abundant [98]
Tumoral, peritumoral, and non-tumoral prostate tissue after RP[3]	UDPS[4] of 16S rRNA	Microbial composition varies according to the nature of the tissue In all types of samples, the major phylum was Actinobacteria (dominant genera: *Propionibacterium*), followed by Firmicutes and Proteobacteria *Staphylococcus* spp. were more represented in the tumor/peri-tumor tissues [97]
Fecal samples of healthy male and men with localized, biochemically recurrent and metastatic prostate cancer	16S rDNA sequencing	Significant difference in alpha diversity in gut microbiome of prostate cancer patients compared to non-cancer individuals Significant difference in gut microbiome composition of patients receiving oral ATT[5] [246]
Fecal swab, voided urine (after prostatic massage) before performing the biopsy	16S rRNA NGS[6]	The urinary microbiome composition of prostate cancer patients differs from non-cancer patients An increased abundance of the *Veillonella*, *Streptococcus*, and *Bacteroides*, and a decreased abundance of *Faecalibacterium*, *Lactobaccili*, and *Actinetobacter* in cancer patients An increased abundance of *Bacteroides* in fecal samples of prostate cancer patients [195]
Prostate tumor tissue of prostate biopsy and post-RP tissue samples after RP	Host-derived whole-genome sequencing	Presence of a core, bacteria-rich, prostate microbiome (Enrichment of the Proteobacteria) [196]
RP tissue samples	Shotgun metagenomic sequencing	Non-sterile prostatic tissue in prostate cancer patients *Escherichia*, *Propionibacterium*, *Acinetobacter*, and *Pseudomonas* constituting the core of the prostate microbiome No significant difference between the microbiome and local progression of prostate tumor Correlated expression of *Pseudomonas* genes and human small RNA genes providing primary evidence that *Pseudomonas* infection may inhibit metastasis [197]
The Swedish Twin Registry	Data retrieving from national registries, between 1963 and 2004	Significant association of periodontal disease due to proinflammatory Gram-negative bacteria with an increased risk of prostate cancer [260]

(*Continued*)

Samples	Method	Findings
Prostatic fluid samples of prostate cancer patients and non-prostate cancer people	16S rRNA gene sequencing	Beneficial role of microbiome in maintaining the microenvironment stability of the prostate Significant difference of several species (genera *Alkaliphilus*, *Enterobacter*, *Lactococcus*, *Cronobacter*, *Carnobacterium*, and *Streptococcus*) between the cancer group and non-cancer group [198]
TURP[7] and/or RP specimens from prostate cancer patients and TURP specimen from BPH patients	PCR screening primer	Significant increase of *Mycoplasma genitalium* infection in prostate cancer patients in comparison with the BPH patients [261]
Prostate tissue from patients with prostate cancer or BPH	Immuno-histochemistry, PCR, and DNA sequencing	Presence of *H. pylori* DNA in prostatic tissue of prostate cancer and BPH [262]
Fecal swab from prostate cancer patients	DNA sequencing	Significant difference between gut microbiome of prostate cancer patients compared to controls Higher abundance of *Bacteriodes massiliensis* in prostate cancer patients in comparison with benign controls Higher abundance of *Faecalibacterium prausnitzii* and *Eubacterium rectalie* among controls compared to cancer patients [87]
Pre- and post transrectal biopsy urine, and fecal samples	16S rRNA gene NGS[5]	Alteration of urinary microbiome after prostate biopsy, suggesting introduction of fecal bacteria into the urinary tract through prostate biopsy [263]

[1]EPS, expressed prostatic secretions; [2]BPH, benign prostatic hyperplasia; [3]RP, radical prostatectomy ; [4]UDPS, ultradeep pyrosequencing ; [5]ATT, androgen receptor axis-targeted therapies; [6]NGS, next-generation sequencing; [7]TUR, transurethral resection of the prostate.

Folate plays a significant role in the synthesis of nucleotides and DNA methylation. *In vivo* studies have shown that folate deficiency causes substitution of uracil with thymine in DNA, the instability of DNA, and the higher mutation frequency [100]. According to a research report, folate producer microbiota is more abundant in non-cancer than in cancer patients [98]. It seems that folate supplements source increases the risk of prostate cancer, but natural sources of folate have protective effects. Therefore, it has been suggested that men with high-grade prostate cancer use probiotics instead of supplements. Furthermore, although riboflavin has received less attention than folate, it is a cofactor of methylenetetrahydrofolate reductase and there is a synergy between the protective function of folate and riboflavin [98,102]. Mammalian cells are not capable of producing biotin and are dependent to the gut microbiome. The deficiency of this vitamin has been reported in men with prostate cancer. LASSO analysis has shown a lack of biotin-producing microbiome among patients with prostate cancer that can indicate the importance of this vitamin [102]. *In vitro* studies have shown that biotin supplementation enhances mRNA encoding cytochrome P450 1B1 (CYP1B1) in human lymphocytes, and may have similar effects on non-lymphoid cells [103]. Therefore, it should be noted that, like other B group vitamins, supplementation with a highly concentrated biotin can have adverse effects [103].

Oral microbiome and prostate cancer

There are more than 700 different bacterial species in the human oral cavity recognized as oral microbiome [104]. Recent studies have shown that inadequate oral hygiene has led to a destruction of the oral microbial population, resulting in an increase in the number of oral pathogens [105] (Fig. 1). The association of oral pathogens with various diseases including cardiovascular diseases [106,107], preterm birth [108], as well as pancreatic cancer [105] has been shown previously. The important question is that how oral bacteria get to the prostate. And how can they contribute to inflammation or carcinogenesis? As mentioned, chronic inflammation could be a risk factor for prostate cancer. In addition, prostatitis is an inflammatory status for the prostate. Several studies have shown the spread of pathogenic bacteria from the oral cavity to other parts of the body in a variety of diseases, including prostatitis. Etiopathogenesis is similar in chronic prostatitis and periodontitis. Periodontitis is a chronic inflammation and is caused by oral pathogens and causes the loss of soft tissue attached to the teeth [109,110]. Some prostatitis categories, as well as periodontitis, are due to Gram-negative bacteria, increased proinflammatory cytokines, and decreased antiinflammatory cytokine [111,112]. Several systemic diseases are associated with periodontitis, including blood disorders and atherosclerosis [113,114].

The relationship between periodontitis and systemic diseases might be due to the dissemination of bacteria and their toxins throughout the body or immune deficiency [10]. For example, the presence of oral bacteria was shown in synovial fluid of patients with rheumatoid arthritis. Moreover, several studies have shown the association of periodontitis with increased prostate-specific antigen (PSA) [115,116]. There is also a correlation between PSA levels and coexistence of chronic prostatitis and periodontitis [115]. Higher levels of serum PSA may also be associated with aggressiveness of prostate cancer [117,118].

Oral infectious diseases can cause inflammation throughout the body by increasing C-reactive protein (CRP) as well as proinflammatory cytokines such as TNF, IL-1, and IL-6, which may accordingly cause prostate inflammation [119]. In addition, inflammatory responses may destroy the integrity of the prostate epithelium and result in release of PSA to the blood stream [115]. Detection of oral bacterial DNA in prostatic secretions of men with both prostatitis and periodontitis conditions, indicates an association between these diseases and the potential role of inflammatory processes [120]. Thus, elimination of the oral infection foci is an essential prostate health priority [116]. *Porphyromonas gingivalis* was prevalently isolated from prostatic secretions. This bacterium has the ability to produce Arg-gingipain to destroy collagen [121]. This bacterium can enter into epithelial cells through binding to erythrocytes [122]. The association of *P. gingivalis* with pancreatic cancer has already been shown [109,123]. *P. gingivalis* has also the potential to invade the human immune system via destroying signaling pathways [124,125].

To date, no study have addressed the relationship between oral microbiome and prostate cancer risk that warrants further research. However, oral microbiome might be associated with prostate cancer, or at least inflammatory condition which increases the risk of prostate cancer.

Urinary microbiome and prostate cancer

For a long time it was thought that the urinary tract is sterile [126]. Recent studies indicated a typical urinary microbiome, which is distinctive from the gut microbiome [127–129]. One of the concerns about urinary microbiome was the possibility of sampling contamination. To rule out this concern, highly advanced molecular techniques such as 16S rDNA sequencing were used [127].

The recent discovery of the existence of urinary tract microbiome has highlighted the role of the microbiome in prostate cancer [126]. Since the urinary tract is very close to the prostate and can contaminate it, urinary microbial studies are important in identifying prostate diseases [130,131]. Several studies have reported the isolation of various microbial strains, including *Corynebacterium*, *Streptococcus*, *Veillonella*, *Prevotella*, *Anaerococcus*, *Propionibacterium*, *Finegoldia*, and *Staphylococcus*, from the urine of adult males [132–134]. *P. acnes* is one of the most commonly isolated bacteria from male urine, and is a proinflammatory bacterium. Association of *P. acnes* with prostatitis in animal models as well as human prostate cancer has been studied previously [29,53,135–139]. Chronic prostatitis is most commonly caused by uropathogenic strains of *E. coli* and enterococci [140]. Prostatitis due to *E. coli* and *P. acne* strains may cause morphologic changes and hyperplasia. These changes have also been associated with decreasing the expression of tumor suppressor NKX 3.1 in the prostate [53]. According to studies, proinflammatory bacteria such as *Streptococcus anginosus*, *Anaerococcus lactolyticus*, *Varibaculum cambriense*, and *Propionimicrobium lymphophilum* have been found to be more common in patients with cancer [141,142], which suggests that inflammatory bacteria are likely to cause prostate inflammation for the development or progression of prostate cancer [28].

Using advanced molecular techniques such as polymerase chain reaction (PCR) and 16S rRNA sequencing, it has been suggested that some unchangeable host factors such as the expression of specific receptors, and the mother-to-child bacterial transmission during the first few months of life are contributed to the colonization and survival of these bacteria in urinary tract without causing infection [143–146]. Although studies are different in terms of sample collection, inclusion criteria, methodology, etc., all of them have shown that human urinary microbiome vary according to age, sex, and disease [128,129,134]. The male urinary microbiome is mainly composed of the genus *Corynebacterium*, *Staphylococcus*, and *Streptococcus* [29,129,147]. Urinary microbiome alteration may occur for various reasons, including puberty, type of sexual behavior, urinary incontinence, and antimicrobial agents of prostatic secretions [145,146]. Dysbiosis affects immune molecules as well as response to treatment of urinary tract infections [148,149]. In this regard, changes in the frequency and diversity of microbiome have been shown in individuals with neurogenic bladder dysfunction (NBD), interstitial cystitis (IC), urinary incontinence, and sexually transmitted infections (STIs) [132–134,144,148,150]. It is also possible that difference between urinary microbiome of men and women is responsible for the difference in the incidence and survival rate of bladder cancer between the sexes [151].

Inter-individual variation in urinary microbiome composition affects susceptibility to infection with STIs such as *C. trachomatis* and *N. gonorrhoeae* [133]. Studies also have shown the elevated PSA levels associated with STIs, which could be a sign of prostate involvement [152,153]. The history of inflammatory STIs can increase the risk of developing prostate cancer [57]. Moreover, the association

between male urinary microbiome and prostate problems including prostatitis, benign prostatic hyperplasia (BPH) as well as prostate cancer has been explored previously [29,154,155]. Additional studies are needed to investigate the effect of urinary microbiome composition on progression of prostate cancer.

Prostate microbiome

There are many studies on the microbial composition of various parts of the body [156–159], but little studies have been done on microbiome of healthy tissue of prostate as well as prostate tumor tissues [136,160]. It has not yet been elucidated whether there is prostate microbiome. Using the 16S rDNA PCR has not shown any bacteria in a healthy prostate. Some studies have shown the presence of bacteria in prostate cancer tissues [97,136,160–162]. One of the concerns about the presence of microbiome in the prostate is treatment of false positive results due to contamination, which must be minimized by using aseptic methods, as well as negative controls [163,164].

In the study of Sfanos *et al*., in which negative control was also used, bacterial DNA of various species has been isolated from prostatectomy tissues. In this study, tissue cores of prostate were negative for bacterial DNA. Hence, it was concluded that there is no flora in the prostate and microorganisms in the focal regions are likely to be associated with prostate inflammation and are bacterial remnants within the macrophages. Using 16S sequencing, most of the strains were related to the normal flora of urethra (*Acinetobacter* spp., *Prevotella* spp., *Actinomyces* spp., *Streptococcus* spp., *Pseudomonas* spp.) or urinary tract infections (UTIs) (*Escherichia* spp., *Pseudomonas* spp., and *Enterococci* spp.) that highlighted the theory of colonization of the prostate by urine flora [136].

As mentioned above, inflammation plays an important role as stimulant for carcinogenesis. A change in bacterial populations, may lead to an increase of cancer risk by increasing inflammatory responses [53,135,165]. Some bacteria are known to have potential for creating inflammation in the prostate, including Enterobacteriaceae, such as *E. coli* and *Pseudomonas*, as well as the bacteria causing STIs [166,167].

In another study using ultradeep pyrosequencing (UDPS), the microbiome associated with the nontumor, peri-tumor, and tumor tissue of prostate was evaluated [97]. In that study, existence of prostate specific microbiome was reported and the dominant isolated bacterium was *P. acne*. Moreover, nontumor regions of prostate were considered as healthy prostate samples, and thus there were no confounding factors such as diet and lifestyle. High prevalence of Lactobacillales in nontumor regions as a normal microbiome of prostate was reported, which may play a role in maintaining the health of the prostate [97].

In summary, considering the antibacterial properties of prostatic fluid [168,169], and the impact of the urinary microbiome as well as skin and gut microbiome on the prostate, and finally according to all studies that have been done so far, there is no evidence to prove the definite existence of prostate microbiome. In all the studies that have been done so far, there are limitations that make it difficult to interpret their results. Further studies are needed in order to gain insight into characterization of the prostate tumor microenvironment.

Skin microbiome and prostate cancer

P. acnes is an anaerobic Gram-positive bacterium found in sebaceous follicles of the human skin, and its strains cause inflammatory diseases through their hemolytic, cytotoxic, and immunostimulatory activities. This bacterium was abundantly isolated from patients with prostate cancer [135,170]. It has been reported that *P. acnes* strains involved in prostate cancer were different in surface properties from strains associated with skin disorders. Studies have shown a powerful inflammatory activity of *P. acnes* in prostate tissue. *In vitro* studies on RWPE1 cells infected with *P. acnes* showed activation of NF-κB, the IL-6-Stat3, and the COX2-PGE2 pathways and increased transcriptional activation of IL-8, VEGF genes [171]. *P. acnes* infection results in the continuous degradation of IκBα (major NF-κB inhibitor) and subsequent activation of NF-κB, leading to positive regulation of genes involved in development and progression of prostate cancer [171–174]. Furthermore, increased level of IL-6 in the serum of prostate cancer patients is associated with advanced metastases. IL-6 activates the JAK/STAT signaling pathway. Persistent activation of Stat3 transcription factor contribute to increase tumor growth and proliferation. VEGF and COX-2 are also important molecules in angiogenesis [172–174].

Molecular pathological epidemiology (MPE) in the context of prostate cancer

MPE is a discipline combining epidemiology and pathology. The goal of pathology and epidemiology is clarifying etiology of disease, and MPE intends to achieve this aim at molecular, individual, and population levels. Generally, MPE employs tissue pathology resources and data available in epidemiological studies. Molecular epidemiology includes MPE and conventional molecular epidemiology as well as traditional disease designation systems [175]. In MPE, interrelationships between exposures including environmental, dietary, lifestyle and genetic factors; cellular or extracellular molecules alterations (molecular signature of disease); and evolution and progression of disease are evaluated [176].

Application of molecular signatures to improve the value of standard clinical-pathological parameters has affected clinical practice in several cancer types including prostate cancer. The molecular signatures indicative of disease grade and predictive of subsequent behavior could expedite the optimal treatment choice for prostate cancer. In this context, genome, immunity, and microbiome can be analyzed to identify new biomarkers for potential clinical utilities. The concept of MPE in clinical medicine is equivalent to precision medicine and personalized medicine [177]. Epidemiology provides analytical frameworks to evaluate the association of exposure (endogenous or exogenous factor) and incidence of a disease or its outcome [178]. It aims to identify patterns and determinants of health and disease conditions [178]. Conventional epidemiological researches comprise quantitative and qualitative study designs and examine association of an exposure and a disease entity in population-based cohorts. For example, genome-wide association studies (GWAS) implicate scanning markers across the genomes of numerous people to find genetic variations associated with a specific disease [178]. Currently, due to the emerging of molecular diagnostic tests in the field of infectious disease, molecular pathology has become a major subfield of pathology. Therefore, MPE has been emerged as an interdisciplinary integrative scientific discipline which analyses complex interplay between molecular pathological signatures, environment, lifestyle factors, disease occurrence and progression, by using large populations [178–180]. MPE can be considered as the next step of GWAS, termed "GWAS-MPE approach." It has demonstrated to be a promising approach to identify biomarkers for precision medicine [179,180].

As mentioned before, dysbiosis can have carcinogenic effects. Therefore, analyses of the microbiome in various body sites as well as pathologically transformed tissue (tumor) provide a basis for better understanding the cancer etiologies and their population impact. These analyses should be integrated into MPE, which is recognized as microbiology-MPE [178,181]. Microbiology-MPE affords a valuable approach to evaluate the interpersonal heterogeneity of the carcinogenic process related to the dysbiosis and to provide evidence for the role of microbiome in the processes of tumor development and progression [181].

In epidemiology, the term "exposure" designates any factor that may (or may not) associate with cause, prevent, or influence an outcome of interest [178]. In microbiology-MPE study, the microbial profile can be considered as an exposure or outcome variable. For instance, in cancer research, the microbial profile in non-cancerous tissue or biospecimen obtained before cancer diagnosis can be evaluated as an exposure associated with disease incidence as an outcome [178]. However, the detection of a certain microorganism may show either causal association with the tumor or can occur as a result of tumor development [178]. There are microbiology-MPE studies that have evaluated microbiome profile in prostate cancer patients and provided new insights into prostate cancer etiologies (See previous sections). Several studies have reported the association of microbial agents with prostate tumors (Table 1). In these studies, the composition of microbiome of different parts of human body, their interactions with the host and effects on host health have been widely considered. These studies have been carried out using advanced molecular techniques such as PCR-based targeted detection, sequencing and qPCR, and pyrosequencing. Their findings indicated differences in the diversity and abundance of microbes in healthy individuals and cancer patients [132,150,155,182,183]. Studies related to microbiome of different parts of the body associated with prostate cancer are discussed in their respective sections in this article (Table 1).

A current study used an array-based metagenomic analysis to define the prostate tumors microbiome in comparison with non-cancerous prostate tissues [184]. They defined the microbiome signatures associated with prostate cancer. They also suggested increased recombination activity in the tumor showing the viral and bacterial sequences integration into the somatic chromosomes of tumor cells. These integrations may affect host genes related to oncogenic activities in tumor cells [184]. Moreover, they compared the microbiome of cancerous prostate tissue with tissue from BPH patients and reported diverse and distinct prostate tumor microbiome in comparison with that of the controls [184]. Viral signatures including oncogenic human papillomavirus 18 (HPV18), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), and JC virus (JCV) in prostate cancers, were also reported previously [182,185,186].

Target the microbiome for risk assessment, prevention and treatment of prostate cancer

Cancer is a complex disease influenced by an interplay between host genetic diversity, immunology, and environmental factors. Despite genetic factors being involved in cancer, several studies have shown the influence of microorganisms on cancer biology [187]. In addition to metabolism-related genetic profiles, gut microbiome and its related metabolic properties also can potentially be important in cancer risk including prostate cancer [188]. There are some comprehensive review articles available on interactions between intake and species of gut microbes [189,190].

A biomarker is indicative of the severity or the presence of a particular disease, or pharmacologic responses to a therapeutic intervention [191]. A cancer biomarker refers to either a biological molecule secreted by a tumor or it can

be a particular response of the body that is a sign of the presence of cancer. Cancer biomarkers are used as diagnostic markers to detect the presence of cancer, and prognostic markers to anticipate how well the body responds to a treatment [192]. Some of these markers have created paradigm shifts in personalized treatment of cancer [192]. Theranostics is a newly defined field of study intended to combine particular targeted therapy based on specific targeted diagnostic tests. It provides an evolution from conventional medicine to a contemporary personalized and accurate medicine approach. Today's biomarker will be tomorrow's theranostics for risk-stratification and treatment personalization [193]. Current researches are focused on the human microbiome as a potential early detection biomarker for diseases [194]. Some metagenomic markers have also potential for cancer diagnosis. Current evidences suggest that carcinogenesis proceeds by microbial factors. Therefore, several studies have examined the probability of profiling microbiome for cancer diagnosis [29,97,98,138,155,195–198]. These studies have brought much hope in the possibility of microbiome manipulation to improve treatment efficacy and to reduce side effects (Table 1). Despite promising preliminary data, clinical use of these metagenomic markers needs to be supported by further studies [192].

Several factors including aging, lifestyle changes (in diet, exercise, nutrition, and stress), medications, and gastrointestinal pathogens can affect the microbiome composition with consequent change of inflammatory and pathophysiological states of various organs and tissues [199]. Lifestyle factors may influence prostate cancer susceptibility [200]. Consumption of meat [201], dairy products [202], eggs [203], and fish oil [204] has been studied in relation to prostate cancer risk. However, few studies have been performed on the interactions between how intake and metabolic factors influence cancer risk [188]. The performed studies are mostly limited to the characterization of genetic variation effect on metabolism or intake [205–207]. For instance, previous studies examined the effect of a single-nucleotide polymorphism (rs4988235) on the lactase (LCT) gene and the effect of arachidonic acid metabolism gene polymorphisms on prostate cancer risk [206,207].

Microbiome composition exists in a precise balance that, if disrupted, dysbiosis occurs which has been considered as etiology of several cancers, including prostate cancer [208]. During dysbiosis, a decrease of Lentisphaerae, *Bacteroides*, and Parabacteroides has been seen. This condition can cause an increase in the serum levels of TNF-α, IL-8, IL-1β, and CRP [209].

Antibiotics cause the death of pathogens as well as the death of commensal bacteria that modulate gut microbiota composition [210]. The microbiome alteration depends on the antibiotic class, dose, and duration of antimicrobial exposure, their pharmacological action, and targeted bacteria [210]. There are some evidences that antibiotic-caused dysbiosis can increase the frequency of some cancers including prostate cancer which is increased by using penicillin, suggesting a link between the microbiome and carcinogenesis [211].

Moreover, gut microbiome metabolism impacts on digestion of dairy product, affects the composition of bioactive fatty acids in adipose tissue of host [212], and contributes to the production of carcinogenic metabolites and inflammation [213]. There are several metabolic pathways encoded among various microbes. These pathways may encode some rare functions including specific nutrient exploitation, antibiotic resistance, heavy metal utilization/resistance and the production of hormones, such as androgens [214,215]. Since our diet contains atypical compounds, the microbiome capable of utilizing them are rapidly enriched [216]. This microbial composition shift could have significant consequences for the host; for instance, intended medications may be modified or inactivated by the microbiome or may become toxic to the host [216].

Gut microbiome affects the host's digestive process by enzymatic actions [188]. Some gut microbes contribute to the digestion of phenolic compounds from tea, coffee, and other plant-based diet sources into biologically active metabolites. Resveratrol belongs to a class of polyphenolic compounds and has potential antiinflammatory effects by modification of eicosanoid synthesis and inhibiting cytokines such as PTGS2, IL6, and TNF [217]. Hepatically conjugated estrogens excreted into the intestinal tract by bile can be deconjugated by bacterial β-glucuronidases, which leads to their reabsorption into the circulation [218,219]. A previous study showed that the intestinal microbial richness and alpha diversity affects the total urinary estrogen levels as well as risk for estrogen-related conditions [218]. Therefore, it was suggested that the gut microbiome should be considered as a biodynamic system interacting with its living environment and associates with disease risk [220].

In addition, gut microbiome can impact prostate cancer risk due to the presence of isoflavone-metabolizing, equol-producing bacteria. Equol, a nonsteroidal estrogen, may influence prostate cancer susceptibility. *Slackia* sp. strain NATTS, classified in the Coriobacteriacea family, belonging to the *Slackia* genus, is a newly identified human intestinal bacterium with a high equol-producing activity. It is capable of degrading one of the daidzeins in soy isoflavones into equol with high efficiency [221]. These can emphasize the role of microbiome in prostate cancer risk [221]. The first step to determine the influential role of gut microbiome in prostate cancer development is to evaluate key differences in the microbial profiles of men who do and do not progress aggressive disease [188]. Chemoprevention of prostate cancer has gained great interest in recent years. It has been suggested that

incapability to convert daidzein to equol in the intestine due to lack of equol-converting bacteria in the intestinal environment can be considered as a risk factor for prostate cancer susceptibility. Therefore, using the NATTS strain bacteria to improve the intestinal environment as well as administration of S-equol-containing supplement can be considered as preventive options for prostate cancer [220].

Nowadays, immunotherapy is one of the successful treatment options for metastatic diseases. The main focus of cancer immunotherapy is on the modulation of T cells that are present in normal and cancerous prostate tissues [222,223]. Evidences suggest that the gut microbiome composition can have a significant effect on modulation of immunotherapy response and toxicity. Therefore, re-educating and/or diversifying the gut microbiome through using probiotics and prebiotics before or in combination with immunotherapies can lead to a better response rate [224–226].

Current studies have reported that some bacteria might increase the effect of some traditional anticancer drugs and immunotherapy drugs. Local and systemic effects of gut microbiome on cancer is through various mechanisms that involve the innate and adaptive immunity, endocrine and neural pathways, bacterial products and toxins, modulation of the systemic inflammation, and the oxidative stress [199]. Since the extensive effect of microbiome on human health, microbiome composition differences between patients can be considered as a factor to decide who would benefit from a specific treatment modality [187]. In addition, the presence or absence of particular bacteria as well as their metabolites may affect the prevalence, severity, and treatment of a tumor and can serve as prognostic biomarkers [187]. In the foreseeable future, gut microbiome may be used as a biomarker to segregate healthy and cancer patients. Currently, cellular targets for improving chemotherapies and targeted therapies are the matters of interest. Therefore, microbial drug targets have the potential to improve the harmful side effects of chemotherapy as well [187].

Studies on animal models have shown that the gut microbiome has effect on antitumor activity of agents, such as cyclophosphamide [224] as well as anti-PDL1 [226] and CTLA-4 blockade immunotherapies [141]. Furthermore, animal model studies have shown that apoptotic activity of platinum-based antineoplastic compounds in the tumor cells is decreased in the absence of commensal microbes [224,227].

Human microbiome can affect a patient's response to immune checkpoint inhibitors (ICIs) that mainly target the immune system rather than the patient's tumor [216]. ICIs, such as programmed cell death protein (PD-1), have been reported effective in patients with advanced melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC). The use of ICIs, such as monoclonal antibodies targeting PD-1 and its ligand (PD-L), promotes the memory T lymphocyte-mediated immune responses via suppressing the interaction of T inhibitory receptors with cognate ligand on tumor cells [228,229]. PD-1/PD-L1 ligand belongs to the superfamily of CD28/B7 and PD-1/PD-L1 signaling pathway inhibits the T cell mediated immune responses [230,231]. Studies have shown that the agents targeting PD-1 are useful in men who have received androgen deprivation therapy (ADT) with androgen receptor antagonist (enzalutamide) [232]. One study reported that antibiotic treatment before anti-PD-1 therapy had reduced the survival of patients compared to those who had not received antibiotics [28]. Antibiotic administration can also impair therapeutic outcomes of some chemotherapy drugs such as cyclophosphamide, highlighting the importance of the microbiome in patients' response to these immune modulating agents [233].

A study on metastatic melanoma patients showed that the patients who responded to anti-PD-1 therapy had more diverse gut microbiome than non-responders [189]. Fecal microbiota transplantation (FMT) from healthy donors with a diverse microbiome profile could improve patient's response to anti-PD-1 therapy. Moreover, antibiotic treatment for common infections including dental, pulmonary, and urinary has been shown to reduce significantly progression-free survival (PFS) and overall survival in patients treated with ICIs [228].

Microbes play an important role in pharmacokinetics, toxicity, and mechanism of action of chemotherapy as well as local and systemic immune responses. For example, *Mycoplasma hyorhinis* converts Gemcitabine into its deaminated inactive form [234]. Currently there is no approved second-line therapy for metastatic hormone-refractory prostate cancer (MHRPC) after docetaxel failure [235]. Metronomic administration of the cyclophosphamide has been shown preclinically to be an effective inhibitor of angiogenesis [236], and induces a decrease in circulating regulatory T cells, leading to the restoration of NK cell cytotoxicity, and proliferation of peripheral T cells [237]. Human clinical trials (Phase II) showed that cyclophosphamide administered in metronomic schedule has significant activity in HRPC [238–240]. In addition, data from a study that assessed the efficacy and tolerance of metronomic cyclophosphamide administration in HRPC, suggested that metronomic cyclophosphamide/prednisolone chemotherapy might be advantageous for patients with docetaxel-resistant HRPC [235].

Cisplatin is a platinum (II) compound that represents clinical activity against several solid tumors, and was shown to have potential in management of castration-resistant prostate cancer (CRPC) [241]. The efficacy of alkylating antineoplastic agents (cyclophosphamide and cisplatin) can be affected by the microbiome. The efficiency of these compounds has been shown a great decrease in germ-free mice [242]. This efficacy reduction

was also shown in other animal models receiving antibiotics to eradicate bacteria in the gut [243]. Moreover, chemotherapy can damage the diversity and health of gut microbiota by reducing the abundance of advantageous bacteria (e.g., Lactobacilli and Bifidobacteria), while increasing pathogenic bacteria (e.g., Clostridia and Enterobacteriaceae) [226]. Diversity is identified as an important factor for a healthy microbiome. Studies have shown that gut microbiome could be changed by castration or pelvic radiotherapy [183,244].

Abiraterone acetate (trade name: Zytiga) and enzalutamide (trade name: Xtandi) are antiandrogen medications used in the treatment of prostate cancer. Abiraterone acetate targets the biosynthesis of testosterone and enzalutamide directly binds to the androgen receptor (AR). Both of them are administered orally and have poor solubility, so they are in exposure of gut microbiome for a considerable time. This maximizes the probability of microbial modification. The acetate portion of abiraterone acetate can be a source of carbon for microorganisms [216].

There are two important pathways of drug metabolism. First, the drug may be modified into more active form or into inactive form by microbiome. Second, the microbiome may produce metabolites to decrease the drug's efficacy, such as the regulation of testosterone in prostate cancer. In the absence of endogenous production of testosterone, this may act as a harmful mechanism in the context of prostate cancer patients. A previous study showed that a human gut bacterial species (*Clostridium scindens*) converts glucocorticoids into androgens. The implication is that not only the host endocrine system but also gut microbiome, may be the source of androgens [214].

Although the most microbiome studies have been done on the gut, chemotherapeutic agents may also affect microbial population of other sites of the human body [220].

Soy bean-derived products are considered as factors for reducing prostate cancer risk. Among these products, soy isoflavones and their interaction with gut microbiome has gained more attention [220]. Animal studies suggest that the gut microbiome is affected by circulating androgen levels and castration [244]. A previous study assessed the compositional profile of the gut microbiome in men with and without prostate cancer and with and without treatment with androgen receptor axis-targeted therapies (ATT) [29]. They reported that alpha diversity of the gut microbiome in men without prostate cancer is greater than the men with a prostate cancer diagnosis. They also found that men taking oral ATT had a different gut microbiome composition than men taking GNRH agonists/antagonists alone [29]. Studies of rodent models have shown that chemotherapy- and immunotherapy-caused dysbiosis of gut microbiome [225,245] could subsequently affect the local inflammatory environment in the intestinal tract, systemic inflammatory effects, and/or the administered cancer therapies efficacy [246]. Steroid biosynthesis takes place in prokaryotes [247] and some bacterial species are able to metabolize estrogen and androgen precursors and to catabolize them, so affect systemic levels of these hormones [214]. On the other hand, hormone levels can affect the microbiome [244]. The species capable of steroid/hormone biosynthesis were significantly more abundant in the gut flora of men taking oral ATT [246]. This finding may show an alternative mechanism for the production of steroid metabolites that could affect treatment response to oral ATT [246]. Moreover, overrepresentation of certain types of bacteria including Ruminococcaceae and particularly *Akkermansia muciniphila* was seen in the fecal microbiome of men taking oral ATT [246]. A series of human studies in melanoma patients have indicated the association between the presence of these same species (Ruminococcaceae, Bifidobacteriaceae, and *Akkermansia muciniphila*) and positive response to anti-PD-1 immunotherapy [229,248]. These studies may show that the gut microbiome has an important role both for therapeutic efficacy and as a target that could be modulated to improve treatment response. This influence may contribute to the variation in the effectiveness of immunotherapies [246].

Collectively, regarding the importance of gut microbiome content for the effectiveness of treatment as well as increasing the treatment response, therefore it is possible to reduce the toxicity and increase efficacy of chemotherapy by using symbiotics (combination of prebiotics and probiotics). The introduction of various useful bacteria as probiotics with anticancer properties forms the subject of many current studies [249].

Both probiotics and prebiotics have important roles in maintaining microbiota composition. Probiotics are microbial food supplements that may improve the gut microbiome balance and can increase the host's immune response through numerous mechanisms [250]. They can stimulate the immunity by increasing the mucosal barrier function, enhancing the mucosal antibody production, and increasing the epithelial integrity and direct antagonism of pathogenic microorganisms [251]. One study has shown a relationship between the efficacy of CTLA-4 blockade and microbiota composition (*B. fragilis* and/or *B. thetaiotaomicron* and Burkholderiales) [252]. A previous *in vivo* study demonstrated the role of commensal *Bifidobacterium* in increasing antitumor immunity. They reported alteration of innate immune function and improved antitumor activity through an antigen-independent fashion. Oral administration of the Bifidobacteria alone or in combination with anti-PD-L1 immunotherapy in melanoma murine models led to a decrease in tumor growth [226]. Additionally, the antitumor activity of cisplatin could be restored by *Lactobacillus acidophilus*. Also this bacterium reduces the side effect of platins including nephrotoxicity [249].

Probiotics such as lactobacilli are found in dairy products [253]. A previous study showed that the production of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was induced by lactobacilli in human immune cells [254]. Treatment with lactobacilli also have facilitated NK activity through TRAIL production against prostate cancer cells. TRAIL is an endogenous cytokine that induces apoptosis in tumor cells [254]. *L. acidophilus* and *L. salivarius* are commonly used for probiotic supplementation. *L. acidophilus* may help digesting lactose and *L. salivarius* can help kill *Listeria* [255,256].

Prebiotics are a type of fibers that are nonviable and indigestible compounds inducing the quantity and activity of specific gut microbiota including Bifidobacteria and Lactobacilli [257]. They are considered as a potential treatment option and have also been proposed as a supplement to repair chemotherapy-induced gut dysbiosis [258]. Prebiotics have a positive effect in rebalancing the gut microbiota and can stimulate the host to respond appropriately to immunotherapies [259]. Some of the prebiotics such as phytoestrogens downregulate the COX-2 mediated inflammation and have been shown to have preventive roles in cancer [199].

Fiber presents in many fruits and vegetables and is fermented by gut bacteria into short-chain fatty acids such as butyrate which has tumor suppressive properties [258]. A fiber-poor diet and rich of fat alters the microbiome-associated metabolites, such as vitamins B7 and B12 correlating with enhanced inflammatory state. Prolonged calorie restriction diets leads to an increase in *Lactobacillus* species [199]. In addition, the role of short-chain fatty acids produced by bacterial fermentation of fibers has been shown in protection against cancer development [187]. Therefore, using fiber-rich foods and prebiotics may help to decrease global cancer burden in the long run [187].

Conclusions and future perspectives

Recently, the role of the human microbiome in health and disease is highly regarded. There are several studies exploring the potential role of the microbiome that inhabit the human body (including gut, urinary, and skin) and prostate cancer. However, it is still blurred whether the human microbiome is causative or contributory to prostate cancer. It is noteworthy that the data at this time suggest the probable role of microbiome on this disease. The exact mechanisms of microbial involvement in prostate cancer development described in this review remain to be fully understood. The studies published so far utilizing molecular approaches to characterizing microbial diversity have radically changed our view of the human microbiome, consequently raising many questions about the human microbiota relationship and its relevance to cancer. Metagenomic analysis of whole microbiota composition and function could provide insight into these questions.

Advanced molecular analysis suggests significant differences in the gut microbiome of men with prostate cancer in comparison to benign controls, which may associate in the pathobiology of prostate cancer.

Overall, microbiome is linked to prostate health and disease and future investigations are needed to discover whether the human microbiota and/or their metabolites can be considered as novel biomarkers and therapeutic targets for prostate cancer. The mechanisms by which the human microbiome modulates carcinogenesis, including systemic inflammatory state, ability to affect systemic hormone levels, metabolism and genotoxicity, can provide opportunities to target the microbiome for diagnostic, preventive, and therapeutic strategies. Moreover, microbiology-MPE evaluating microbiome profile can provide new insights into the tumor-immune-microbiome interaction from human tissue and population-based data, so suggesting targeted microbiome-modulating strategies for prevention and treatment of prostate cancer.

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Compliance with ethics guidelines

Solmaz Ohadian Moghadam and Seyed Ali Momeni declare that they have no conflict of interest. This manuscript is a review article and does not require approval by the institutional ethics committee.

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