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Impact of gut microbiome dysbiosis on prostate cancer

ნაწლავის მიკრობიომის დისბიოზის გავლენა პროსტატის კიბოზე

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Abstract

Introduction: The gut microbiome is integral for regulating metabolism, immune functions, and inflammation, with growing evidence suggesting its involvement in the growth and course of prostate cancer (PCa). This review examines the effect of gut microbiome alterations in influencing PCa incidence and risk, factors leading to prostate cancer development, advancement, and resistance to treatment. **Methodology:** A comprehensive literature review was conducted, analysing peer-reviewed studies on the effects of gut microbiome dysbiosis on prostate cancer. **Results:** Distinct microbial patterns such as a rise in pro-inflammatory Bacteroides massiliensis and a decrease in anti-inflammatory Faecalibacterium prausnitzii seen in PCa patients which can be used as a biomarker for making a diagnosis of prostate cancer from other prostate-related conditions. Also, the production of bile acids and short-chain fatty acids by gut bacteria can interfere with hormone synthesis, and a diet high in fat and reduced fiber can lead to dysbiosis eventually causing PCa. **Conclusion:** The study underscores the relevance of gut microbiome dysbiosis and its relation to androgen regulation, inflammatory reactions, and metabolic pathways—all of which have a role in the development of prostate cancer. A good dietary approach and probiotics together with traditional methods like androgen restriction therapy can lead to well-balanced outcomes in patients.

Keywords: gut microbiome dysbiosis, prostate cancer, metabolic pathways, short chain fatty acids, diet, probiotics

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აბსტრაქტი

შესავალი: ნაწლავის მიკრობიომი მნიშვნელოვან როლს თამაშობს მეტაბოლიზმის, იმუნური ფუნქციების და ანთების რეგულირებისთვის. სულ უფრო მეტი კვლევა მიუთითებს მის მონაწილეობაზე პროსტატის კიბოს ზრდასა და მიმდინარეობაში. ეს მიმოხილვა განიხილავს ნაწლავის მიკრობიომის ცვლილებების ეფექტს პროსტატის კიბოს სიხშირესა, და რისკ-

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ფაქტორებზე, რომლებიც გავლენას ახდენენ პროსტატის კიბოს განვითარებასა, პროგრესირებასა და მკურნალობისადმი რეზისტენტობაზე. **მეთოდოლოგია:** ჩატარდა ლიტერატურის ყოვლისმომცველი მიმოხილვა, რომელიც აანალიზებდა ნაწლავის მიკრობიომის დისბიოზის პროსტატის კიბოზე გავლენის კვლევებს. **შედეგები:** ანთების საწინააღმდეგო Bacteroides massiliensis-ის მატება და Faecalibacterium prausnitzii-ის დაქვეითება შეიძლება გამოყენებულ იქნას, როგორც ბიომარკერი პროსტატის კიბოს დიაგნოზის დასადგენად. ასევე, ნაწლავის ბაქტერიების მიერ ნაღვლის მჟავების და მოკლე ჯაჭვის ცხიმოვანი მჟავების გამომუშავებამ შეიძლება ხელი შეუშალოს ჰორმონების სინთეზს, ხოლო ცხიმიანი და შემცირებული ბოჭკოების დიეტამ შეიძლება გამოიწვიოს დისბიოზი, რომელიც საბოლოოდ იწვევს პროსტატის კიბოს. **დასკვნა:** მიმოხილვა ხაზს უსვამს ნაწლავის მიკრობიომის დისბიოზის შესაბამისობას და მის კავშირს ანდროგენების რეგულაციასთან, ანთებით რეაქციებთან და მეტაბოლურ გზებთან - ყველა მათგანს აქვს როლი პროსტატის კიბოს განვითარებაში. ტრადიციულ მეთოდებთან ერთად, როგორიცაა ანდროგენების შეზღუდვის თერაპია, სწორმა დიეტურმა მიდგომამ და პრობიოტიკების გამოყენებამ შეიძლება მოგვცეს პროსტატის კიბოს მქონე პაციენტებში დაბალანსებული შედეგები.

საკვანძო სიტყვები: ნაწლავის მიკრობიომის დისბიოზი, პროსტატის კიბო, მეტაბოლური გზები, მოკლე ჯაჭვის ცხიმოვანი მჟავები, დიეტა, პრობიოტიკები.

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Introduction

Prostate cancer is a type of cancer that occurs worldwide and can cause death in males and the rates are increasing because of different reasons. Many factors are known to cause prostate cancer like hormonal imbalance, age, genetics, and obesity. But now another important factor is also believed to be a reason for cancer growth and that is the gut microbiome, a collection of bacteria inside the gastrointestinal tract by causes inflammation and metabolic changes.

It is believed that long-term inflammation and changes in metabolism can be caused by dysbiosis in the gut which can promote the growth of prostate cancer. On top of that maintenance of androgen levels can also be done by certain types of microbes and their products which again can influence cancer growth. These gaps need to be studied on exactly how the gut microbiome makes the disease and finally leads to prostate cancer for a sound understanding and therapy and prevention

The study of gut microbiome and its effect on cancer growth is very important both from academic and practical points. The relationship between gut and prostate opens up ideas and methods by which how individual microbes inside the gut can cause benefits as well as disease under different situations. This can be utilized by different fields in medicine to work together for a good understanding. Practically, understanding this relationship can be used to make better ways to improve the diagnosis and treatment of prostate cancer like changing lifestyle, changes in diet, and use of probiotics along with known methods to increase the benefits.

Existing studies highlight the systemic influence of the gut microbiota, particularly its role in the regulation of metabolism, immune system function, and inflammation. Specific microbial changes have been observed in PCa patients, including alterations in Akkermansia muciniphila and Bacteroides massiliensis. These changes are linked to metabolic pathways implicated in PCa progression. Furthermore, androgen deprivation therapy (ADT), a primary treatment for PCa, has been shown to affect gut microbial composition, indicating a bidirectional relationship between therapy and microbiota.

However, the field faces several unresolved questions. Many studies are observational, limiting their ability to establish causation. Insights into how gut microbiota influences androgen metabolism, immune responses, and inflammation in PCa remain incomplete. Additionally, the influence of diet and microbial interventions in modifying PCa risk and its development is underexplored. These gaps underscore the need for integrative research combining the diversity of bacteria in the gut microbiome, and phytochemicals in everyday diet to prevent or slow the progression of chronic diseases like prostate cancer.

The goal of this research is to better understand the gut-prostate relation by investigating how the gut microbiota affects the onset and spread of prostate cancer. In particular, it looks at how microbial dysbiosis and its byproducts affect androgen levels, inflammatory pathways, and the development of cancer. It also aims to examine the scientific material that is now available and reveal any knowledge gaps.

Methodology

A literature search was done through PubMed, Scopus, and Web of Science databases, and data were extracted according to inclusion criteria. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and relevant keywords, such as "gut microbiome dysbiosis“, „prostate cancer“, „metabolic pathways“, „short chain fatty acids“, ,,diet“, ,,probiotics“. The search was limited to peer-reviewed articles and reviews published in English between January 2000 and April 2024 to ensure the inclusion of recent and relevant studies.

Literature review

The gut microbiome holds a significant role in regulating various physiological functions, including immune responses, metabolic pathways, and inflammation. Increasing evidence indicates that dysbiosis, an imbalance in gut microbial composition influences the development, progression, and treatment resistance of prostate cancer (PCa).

Alterations in Gut Microbiome Composition in Prostate Cancer

It has been demonstrated that the gut microbiome made up of people with prostate cancer and healthy controls differ significantly, indicating that some bacterial species may hold a role in the progression of prostate cancer. Studies show that individuals with prostate cancer had higher concentrations of Streptococcus and Bacteroides species than men without the disease, suggesting a possible link between these bacteria and the risk of developing cancer. Furthermore, their functional analysis demonstrated that patients with prostate cancer had a higher prevalence of pathways linked to arginine and folate metabolism, providing insight into how alterations in gut microbial activity may aid in the development of cancer.

Additional studies have identified specific bacterial species associated with prostate cancer. For example, a bacteria called Bacteroides massiliensis was more in number and another bacteria like Faecalibacterium prausnitzii was low in number in people with prostate cancer when compared with people having benign prostatic hyperplasia (BPH).

A study by Golombos et al. showed that a common bacteria in the gut microbiota of patients with prostate cancer was Bacteroides massiliensis when compared to those with benign prostatic hyperplasia (BPH). On the other hand, Faecalibacterium prausnitzii, an anti-inflammatory bacterium, appeared to be less common in PCa patients. The loss or decrease in F. prausnitzii is important because the metabolic products produced by them is believed to show anti-inflammatory activities which can prevent prostate cancer. Liss et al. in a study by analysing rectal swabs, found that Bacteroides and Streptococcus were more seen in patients with prostate cancer. These results show that prostate cancer and other prostate-related diseases have an individual microbial presence in high or low numbers thus making it useful to find the difference between prostate cancer and BPH (Munteanu et al. 2023)

Ways by which gut dysbiosis affects prostate cancer

1) *Metabolic Pathways*

Bacteroides can change the metabolism of arginine and folic acid in the gut and this can lead to a problem in the normal synthesis of DNA and its repair function. This is one of the ways by which a change in the normal metabolism of the gut microflora could cause abnormalities in genetic material thereby increasing the number of cell divisions and finally making prostate cancer. (Fujita et al. 2023)

2) *Short Chain Fatty Acids (SCFAs)*

Patients with high Gleason score prostate cancer had higher levels of the SCFA-producing bacteria Rikenellaceae, Alistipes, and Lachnospira than did healthy people. These bacteria, which produce metabolites like butyrate, have anti-inflammatory properties normally but inflammatory properties on the prostate and may be able to influence the course of prostate cancer. The study also showed that microbial profiles may be able to detect high-risk prostate cancer with a higher degree of diagnostic accuracy than conventional PSA tests. (Matsushita et al. 2021)

3) *Inflammation and Immune System Modulation*

Dysbiosis can also influence prostate cancer through its impact on systemic inflammation. A high-fat diet (HFD) promotes gut permeability, which allows bacterial components to enter the bloodstream, triggering inflammation. This inflammation can support prostate cancer growth by promoting cell proliferation. The microbiome's involvement in regulating this systemic inflammation is important for understanding its contribution to prostate cancer development.

1. *Antibiotic Studies and Microbial Manipulation*

Important signaling pathways like PI3K and MAPK, are found to have a role in the growth of cancer, and changing these pathways and changing the composition of gut microflora can be done with the help of antibiotics. This can decrease the progression of prostate cancer. Still, the type of bacteria and the activity by it decides whether cancer develops or not so different antibiotics can have different effects on cancer cells. (Fujita et al. 2022)

Changes in Akkermansia muciniphila levels and its impact on prostate cancer

Akkermansia muciniphila is a good bacteria that is important for maintaining the intestinal barrier has also been linked to prostate cancer. In a study (Sfanos et al. 2018), the authors found patients undergoing androgen receptor axis targeted therapy for prostate cancer showed increased levels of A. muciniphila when compared to healthy individuals. These findings show a possibility that A. muciniphila may be involved in prostate cancer development or progression, but further study is needed to know its exact role.

Gut Microbiome and Hormone Regulation

Metabolic products are formed by gut bacteria which can act on the systemic and endocrine system of an individual. Androgens, in general testosterone and dihydrotestosterone can act on cells of the prostate gland and can lead to cell division causing prostate cancer. So, this relation between the gut bacteria and the production of androgens is important in the way how prostate cancer develops.

1. Short Chain Fatty Acids (SCFAs) and Androgen Modulation

SCFAs are metabolic products made by gut bacteria by acting on fibers in the food. This has a wide range of good effects on people like maintaining immunity, metabolism, and regulation of hormone activity such as androgen formation.

In a study (Matsushita et al. 2023), authors found that SCFAs produced from the gut microbiome could maintain a level of androgen and growth of prostate cancer. The study has shown that insulin-like growth factor (IGF-1) is a factor in cell division and this can be controlled by SCFAs in some tissues mainly in the prostate. Also, this has been shown to cause resistance to androgen deprivation therapy. All these point out the effect of short-chain fatty acids on prostate cancer.

2. *Influence of Gut-Derived Bile Acids on Androgen Pathways*

Another group of metabolic products produced by the gut bacteria is bile acids. These bacteria can change the makeup of bile acid by enzyme activity. Some of these include deoxycholic and lithocholic acid which can enter the circulation and cause changes in metabolism like hormone activity.

Bile acids can also regulate and maintain steroid enzymes which are needed for production of androgens. A nuclear receptor called the Farsenoid X receptor (FXR) is said to have an effect on steroid metabolism for producing sex hormones like testosterone. Bile acids normally produced in the liver act on these receptors to control the process. But when this receptor is acted upon by a changed form of bile acids, it can form a different product which can cause prostate cancer. (Baptissart et al. 2013)

3. *Gut Microbiota Modulation of the Immune Microenvironment in the Prostate*

The gut microbiota influences not only systemic inflammation but also the local immune microenvironment in the prostate. Studies have shown that SCFAs, for example butyrate help in the conversion of regulatory T cells (Tregs) to maintain the immune system from overacting and to decrease inflammation. This gives a view on these fatty acids having a role in maintaining anti-inflammatory function compared to a pro-inflammatory activity on metabolic products. (Yang & Kim, 2023)

Therefore, SCFAs can be used to control the activity of these cells from causing any effect on the prostate gland mainly cancer. Moreover, metabolites produced by the gut bacteria can help in maintaining cytokine release which is useful in cancer therapies.

Maintenance of a balanced gut microbiome is needed for a healthy body and this can be achieved by consuming a good diet. Foods rich in fiber and antioxidants with good fats can develop a gut with necessary bacteria but a diet opposite to this can cause dysbiosis, and increase the chances of diseases like prostate cancer.

1. *High-Fiber Diet and Microbiome Composition*

Fruits, vegetables, and whole grains are foods that have a good amount of fiber which can improve the gut microbiome by increasing the survival of useful bacteria and its diversity by inhibiting unwanted microflora. This can help in the formation of products like butyrate with anti-inflammatory activities which can prevent many conditions like prostate cancer.

2. *Impact of Western Diet on Prostate Cancer Risk*

Western diet contains food with increased amounts of saturated fat, red meat, and less fiber which can lead to an imbalance in the gut microflora if taken for a long time. High-fat diets (HFDs) not only create an imbalance in the gut but also help in the growth of bacteria which can cause inflammation and affect hormone activity like androgen leading to an increased chance of prostate cancer. (Kustrimovic et al. 2023)

3. *Improving Cancer Therapies with Probiotics*

Probiotics may also improve the activity of normal PCa therapies, like androgen deprivation therapy. ADT decreases the levels of androgens to inhibit the growth of cancer cells but its activity can be controlled by the state of gut microflora. Probiotics may help restore microbial balance and enhance immune function, potentially improving the response to ADT. Research has shown that probiotics can help modulate immune cells, improving the overall response to cancer therapies. (Kim et al. 2024)

Studies have shown that probiotics can decrease the growth of prostate cancer by balancing gut bacteria which in turn reduces inflammation. Common probiotic strains, such as Lactobacillus and Bifidobacterium, produce SCFAs that can inhibit pro-inflammatory cytokines such as IL-6 and TNF-α, both of which are involved in the inflammatory processes that support cancer cell growth.

In studies involving animal models, the prescription of probiotics has been shown to shift the gut microbiome towards a healthier composition, with reduced inflammation and slower tumor growth. Also, intake of probiotics by individuals can decrease inflammatory markers such as CRP which is associated with any inflammatory conditions and with prostate cancer too. So, the use of probiotics can make good bacteria which helps maintain good health.

Discussion

The review of all these studies has shown how gut bacteria and its components play a part in the growth, and development of prostate cancer and to some level its treatment. It also adds to the importance of keeping a good diet as the gut microbiome has an active role in disease formation.

Implications of the Findings

Results show that the gut microbiome is unique and is very different from a healthy person and an individual who has a disease like prostate cancer. The levels of bacteria like Faecalibacterium prausnitzii and Bacteroides massiliensis were different, the former being less in number and the latter pointing out that the gut microbiome can play a double role in either increasing or decreasing inflammation. As inflammation is a factor causing prostate cancer, the gut bacteria of a person with cancer and other prostate conditions like BPH can also vary and may help differentiate them.

The changes in gut microbiome and its contribution to prostate cancer, particularly the role of decreased levels of F. prausnitzii and its relation to inflammation have provided a strong basis for exploring anti-inflammatory mechanisms and the protective role of this bacteria in preventing cancer. The identification of microbial signatures that distinguish prostate cancer from BPH, can be used as gut microbiota profiling, a diagnostic tool. It offers practical clinical applications by suggesting a non-invasive method to differentiate PCa from BPH.

The studies offer clinical use as it is a practical method to distinguish between prostate cancer and BPH using microbial markers. Understanding a deeper understanding of the potential mechanisms involved in dysbiosis makes it a more valuable method for developing targeted therapies. The gut microbiota appears to impact PCa via altered metabolic pathways, changes in SCFA production, and modulation of immune responses. For instance, imbalances in metabolic pathways, such as folate and arginine metabolism, linked to microbial activity, could drive cancer cell proliferation. Similarly, while SCFAs are generally anti-inflammatory, their role in PCa progression, particularly in aggressive cases, suggests a nuanced relationship that warrants further exploration.

When gut integrity is damaged due to HFD-induced imbalance, bacterial components, such as lipopolysaccharides, transit into circulation. This triggers systemic inflammation, which in turn fuels cancer growth by using evolutionarily ancient mechanisms that promote both cell survival and proliferation. The results suggest that dietary changes focusing on gut health could be crucial to reducing the inflammatory conditions that fuel prostate cancer.

There is evidence that antibiotics can alter important carcinogenic pathways (such as PI3K and MAPK) and alter the gut microbiome. These reveal mechanisms that affect the survival and proliferation of tumor cells. The complexity of the effects of microbes on cancer is further emphasized by the fact that antibiotics can have varying effects depending on the specific bacterial species that are affected. This underlines the importance of adequate ways of manipulating microorganisms because treatment enhances good bacteria while inhibiting the ones that cause cancer. For example, prebiotics and probiotics developed to regain specific bacterial colonies can be used together with cancer therapies. Akkermansia muciniphilas engagement in regulating inflammation and growth of cancer is raised by the finding of increased levels of bacteria in patients with PCa receiving androgen depletion therapy.

Practical Applications

1. *Microbiome-Based Diagnostics*

Microbiome analysis by various studies has shown that certain microbes are present higher in number in patients with prostate cancer than in other diseases. This can be used as a noninvasive diagnostic approach in finding prostate cancer along with prostate-specific antigen tests or even alone.

2. *Therapeutic Interventions*

From the above discussions, treatment of prostate cancer can also be done by keeping a good balance in the gut microbiome with the help of diet changes, increasing fiber content in foods, the addition of probiotics, etc. This can ensure a good environment for good bacteria to grow and decrease inflammation and any unwanted immune responses. Also, other methods like androgen deprivation therapy can be used along with these.

3. ***Dietary Strategies***

Studies are showing the importance of a good diet in maintaining a balanced gut microflora which can prevent many diseases and here prostate cancer. Foods high in fiber can act as a prebiotic and can harbor good bacteria and SCFA thereby decreasing the level of inflammation.

The information received from this study shows us that a proper diet with a combination of probiotics can change the state of gut bacteria and this can prevent the growth of prostate cancer in the first place or if developed, to treat it. Also, the metabolic products made by gut flora such as bile acids can take part in the regulation of the activity of hormones like androgen, and focusing on this can be used to slow down cancer related to hormonal imbalance. This can be utilized to increase the activity of known treatment methods like androgen deprivation therapy in a better way and by using everything in combination, more benefits can be obtained.

All these results are promising in diagnosing and managing the condition of prostate cancer in a better way but more studies and research may be useful to have a better understanding of different mechanisms if present. Being in a healthy state or disease state can be controlled by the complex activity of gut bacteria and the type of microbiome a person has. So, all these views on the relationship between gut bacteria and prostate cancer development can help to find more details on the biology of cancer and for better outcomes for patients with cancer.

Conclusion and recommendations

The study underscores the relevance of the gut microbiome in affecting the occurrence, growth, and reaction to therapy for cancer of the prostate gland. Alterations in the balance of microbial environment are described as gut dysbiosis, and it has been connected to androgen regulation, inflammatory reactions, and metabolic pathways—all of which have a major influence on the biology of prostate cancer.

It has been indicated that there is a distinct microbial signature among patients with prostate cancer, including reduced amounts of helpful bacteria such as Faecalibacterium prausnitzii and increased amounts of Bacteroides massiliensis. Such changes would therefore mean that microbial profiling may be of use in distinguishing PCa from BPH and other prostate conditions. Metabolites produced within the prostate, such as bile acids and SCFAs, can influence inflammation pathways, immune modulation, and even levels of androgen. The typical anti-inflammatory SCFA-producing bacteria through their complex interaction with the host tissue and their concentration either accelerates or slows down the course of the cancer. The balance between pro- and anti-inflammatory reactions depends on the gut microbiota; further, this balance influences the immunological microenvironment of the prostate. This might modulate tumor growth and the response to cancer treatments. There are promising chances for adjuvant therapies to classic treatments, such as ADT, through the administration of probiotics, diet regimens, and targeted microbial interventions. For example, increasing the consumption of fiber would help promote the production of SCFA and could reduce prostatic and systemic inflammation.

A long-term, comprehensive study is needed to validate the distinct microbial profiles associated with PCa. Metabolic and metagenomic studies can be coupled to ascertain the functional implications of these microbial changes. Clinical research can evaluate the effects of probiotics, prebiotics, and dietary modifications on the progression of prostate cancer and treatment outcomes. Certain bacterial strains with immunomodulatory and anti-inflammatory properties, such as Faecalibacterium prausnitzii, require further study. Understanding how metabolites like bile acids and SCFAs interact with the prostate's

immune environment and androgen signaling pathways can be the focus of future research. This will give potential therapy targets for metabolism. The microbial profiles associated with PCa could be used to develop non-invasive diagnostic and prognostic biomarkers.

The precision and risk assessment of traditional PSA testing may be enhanced by microbiome-based diagnostics. Future research can explore the value of the microbiome in systemic processes such as immune cell trafficking and endocrine signaling which may eventually lead to cancer of the prostate gland. The gut prostate pathway may be a source for diagnostic as well as therapeutic approaches according to the study, which also highlights the critical part of the gut bacteria in PCa. It might be possible to lower the incidence of prostate cancer, improve therapeutic outcomes, and thereby improve the quality of life of patients by treating gut dysbiosis using probiotics, diet, or microbial therapies. Future research may concentrate on refining these techniques and enhancing our comprehension of the intricate associations between gut flora and prostate cancer.

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