VOLUME - 15, ISSUE - 08, AUGUST - 2026 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Oncology

THE GUT MICROBIOME PLAYS A VITAL ROLE IN HORMONE-DRIVEN CANCERS

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ABSTRACT

Cancer has traditionally been viewed as a disease driven by genetic mutations, environmental exposures, and lifestyle factors. While these remain fundamental determinants, an exciting new frontier has emerged in oncology—the human microbiome. Once considered a passive collection of microorganisms, the microbiome is now recognized as an active participant in human health, influencing immunity, metabolism, inflammation, and even the effectiveness of cancer therapies. As our understanding deepens, the microbiome is rapidly becoming an integral component of precision medicine. The human microbiome refers to the collective genomes and functional activities of trillions of microorganisms—including bacteria, viruses, fungi, and archaea—that inhabit the human body. These microbes reside primarily in the gastrointestinal tract but also colonize the skin, oral cavity, lungs, and genitourinary system. Together, they form a complex ecosystem that interacts continuously with the host, contributing to physiological homeostasis and disease. The gut microbiome, in particular, is often described as a "forgotten organ" because of its remarkable metabolic and immunological functions. It contains more microbial cells than human cells and possesses millions of genes, far exceeding the genetic content of the human genome. These microorganisms assist in digestion, synthesize vitamins, produce bioactive metabolites, regulate immune development, and protect against pathogenic organisms. When this balanced ecosystem is disrupted—a condition known as dysbiosis—the consequences may include chronic inflammation, metabolic disorders, autoimmune diseases, and cancer.

KEYWORDS : Helicobacter pylori, Plasmodium falciparum, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, Kaposi sarcoma virus, human immunodeficiency virus-1, human papillomaviruses, and human T-cell lymphotropic virus

INTRODUCTION

The human microbiome contains a diverse set of bacteria, viruses, fungi, protozoa, and archaea that exist on and within the human body. It has been estimated that the human-associated bacteria alone outnumber human cells in the body (1)

Organisms include one species of bacteria (Helicobacter pylori), seven species of viruses (Epstein-Barr virus, hepatitis B virus, hepatitis C virus, Kaposi sarcoma virus, human immunodeficiency virus-1, human papillomaviruses, and human T-cell lymphotropic virus), and three species of parasitic worms (Opisthorchis viverrini, Clonorchis sinensis, and Schistosoma haematobium) and together, are responsible for about 2.2 million cancer cases annually worldwide (2)

The IARC has further categorized other microbes, such as protozoan parasite Plasmodium falciparum and multiple polyomaviruses, as being probably carcinogenic (Group 2A) or possibly carcinogenic (Group 2B)3, as the current data is insufficient to show that these are directly carcinogenic. (3)

The IARC is also currently evaluating additional microbes for their carcinogenicity, including bacterium Salmonella typhi and its association with gallbladder cancer, human cytomegalovirus with multiple cancer types, parasitic worm Schistosoma mansoni with multiple cancer types, hepatitis D virus with liver cancer, and parasitic worm Opisthorchis felineus with bile duct cancer (4)

While the IARC mostly focuses on categorizing agents that directly cause cancer, many more have been shown to indirectly cause cancer. It is for this reason that studying the normal microbial flora of different regions and how dysbiosis may occur is imperative to better understanding how microbes affect cancer. This is also reflected in the recent addition of polymorphic microbes as an enabling characteristic in the hallmarks of cancer (5)

One of the most heavily studied regions of the human microbiota is that of the gut. The gut microbiome was a focus of the Human Microbiome Project and in other studies that followed, and has been implicated in cancer susceptibility and carcinogenesis for over a decade, though many of the causal relationships between these gut microbes and disease are still being understood (6)

One of the most notable and researched examples of a gut

microbe implicated in cancer development is colibactin-producing Escherichia coli. Colibactin has been found to trigger DNA double-stranded breaks, cause chromosomal instability, and alkylate DNA, and for these reasons, is involved in colorectal cancer (CRC) development (7,8).

More recently, there has been an increasing interest in the microbiome of regions previously thought to be sterile and how changes to these regions may promote local cancer development and progression, Following recent advances in characterization methods, there has also been an emerging focus on the tumor microbiome, or organisms that are present within the tumor microenvironment or the tumor cells themselves, and how these microbes may serve to improve the fitness and immune evasion of cancer cells (9,10)

The human body harbors an estimated three trillion bacterial members that orchestrate a comprehensive interplay of physiological processes and disease susceptibilities (11)

Although there is a similar number of bacterial cells as compared with human cells in the body, the 100-fold higher genetic diversity of bacteria encodes for outstanding mechanistic and metabolic competences that influence not only their own microbial niche, but host tissue–specific and immune cell functions (12)

Beyond bacteria, the human microbiome is also composed of eukaryotic fungi and protozoa, and viruses(13)

Overall, under healthy conditions, the host and its microbiome exist in symbiosis as a metaorganism by providing a nutrient-rich microenvironment in return for aid in digestion and metabolism(14,)

The gut, skin, and oral microbiomes are known to feature a highly enriched and diverse population of microbes, whereas the vaginal microbiome is similarly well-studied but is rather characterized by lower diversity with highly specific and dominant microbial members(15)

Furthermore, organs and tissues, such as the lung, prostate, bladder, breast, liver, and pancreas, that were previously considered to be sterile, are now, with the advent of next-generation sequencing (NGS), identified as potentially harboring low-biomass microbial populations(16,17)

By sustaining proliferation, evading cell growth suppression, activating invasion and metastatic pathways, enabling replicative immunity, inducing angiogenesis, and resisting autophagy, cancer cells effectively proliferate and evade the immune system(18)

While these processes have been extensively studied for decades, potential microbiome impacts on cancer development, progression, and treatment responsiveness remained elusive until recently. In a disease scenario, each microbial niche may influence cancer promotion via community-level interactions mediated by altered microbiome configurations (also termed "dysbiosis"), direct interaction of individual members, or via secreted or modulated metabolites (19)

Niche-specific microbiome impacts on cancer can be exemplified by oral microbiome modulation of cancers in the oral cavity (oral squamous cell carcinomas [OSCC]), colon (colorectal cancer [CRC]) and pancreas (pancreatic ductal adenocarcinoma [PDAC]). Likewise, the microbiomes of both male and female pelvic organs feature important implications for urological (20)

Microbiome and Cancer: The Hidden Frontier in Precision Oncology

Cancer has traditionally been viewed as a disease driven by genetic mutations, environmental exposures, and lifestyle factors. While these remain fundamental determinants, an exciting new frontier has emerged in oncology—the human microbiome. Once considered a passive collection of microorganisms, the microbiome is now recognized as an active participant in human health, influencing immunity, metabolism, inflammation, and even the effectiveness of cancer therapies. As our understanding deepens, the microbiome is rapidly becoming an integral component of precision medicine.

The human microbiome refers to the collective genomes and functional activities of trillions of microorganisms—including bacteria, viruses, fungi, and archaea—that inhabit the human body. These microbes reside primarily in the gastrointestinal tract but also colonize the skin, oral cavity, lungs, and genitourinary system. Together, they form a complex ecosystem that interacts continuously with the host, contributing to physiological homeostasis and disease.

The gut microbiome, in particular, is often described as a "forgotten organ" because of its remarkable metabolic and immunological functions. It contains more microbial cells than human cells and possesses millions of genes, far exceeding the genetic content of the human genome. These microorganisms assist in digestion, synthesize vitamins, produce bioactive metabolites, regulate immune development, and protect against pathogenic organisms. When this balanced ecosystem is disrupted—a condition known as dysbiosis—the consequences may include chronic inflammation, metabolic disorders, autoimmune diseases, and cancer.

Gut Microbiome May Offer New Therapeutic Opportunities in Hormone-Driven Cancers

A review published in npj Biofilms and Microbiomes highlights the growing role of the endocrine-microbiome axis in hormone-driven cancers, while emphasizing that clinical evidence is still evolving.

In a review published in NPJ Biofilms and Microbiomes, researchers examined how the gut microbiome interacts with the endocrine system to influence hormone-driven cancers. Gut microbes can regulate estrogen metabolism, produce hormone-like metabolites, and shape immune and inflammatory responses. These interactions may contribute to the development and progression of estrogen receptor-positive breast cancer, endometrial cancer, and other hormone-sensitive malignancies (21)

Approaches such as probiotics, prebiotics, selective enzyme inhibitors, defined microbial consortia, live biotherapeutics, and fecal microbiota transplantation are being investigated to improve endocrine responses and support cancer management.

Lung Cancer

Gut-organ crosstalk has been confirmed in other cancer-related studies; however, whether there is a similar relationship in lung cancer is less known. In recent decades, immunotherapy has become the focus of lung cancer research (22)

Since the discovery of immune checkpoint proteins, there has been a special interest in developing antibodies that block programmed cell death 1 receptor (PD-1) and programmed cell death receptor ligand 1 (PD-L1) for a subset of cancer

patients. PD-1 signalling negatively regulates T cell-mediated immune responses and serves as a mechanism for tumours to evade an antigen-specific T cell immunologic response. It plays a role in promoting cancer development and progression by enhancing tumour cell survival. With this background, PD-1 signalling represents a valuable therapeutic target for novel and effective cancer immunotherapy. Clinical data show that blockade of this PD-1 signalling significantly enhances antitumor immunity, produces durable clinical responses, and prolongs survival. Currently, there are three FDA-approved PD-L1 inhibitors for various malignancies, ranging from non-small cell lung cancer to Merkel cell carcinoma. (23)

Gut dysbiosis is involved in carcinogenesis and the progression of lung cancer through genotoxicity, systemic inflammation, and defective immunosurveillance. In addition, the gut microbiome harbours the potential to be a novel biomarker for predicting sensitivity and adverse reactions to immunotherapy in patients with lung cancer. Probiotics and fecal microbiota transplantation (FMT) can enhance the efficacy and depress the toxicity of immune checkpoint inhibitors by regulating the gut microbiota. (24)

The Microbiome and Cancer Development

The microbiome—consisting of bacteria, viruses, and fungi inhabiting the body—influences cancer development primarily through chronic inflammation, genetic damage, and metabolic disruption. While specific pathogens (like H. pylori) cause distinct malignancies, broader imbalances, known as dysbiosis, alter the tumor microenvironment. Cancer development is a multistep process involving genetic mutations, epigenetic changes, immune dysregulation, and environmental influences. Increasing evidence suggests that the microbiome contributes to each of these processes.

One of the principal mechanisms is chronic inflammation. Certain microorganisms stimulate persistent inflammatory responses that create a microenvironment favorable for tumor initiation and progression. Inflammatory mediators generate oxidative stress, promote DNA damage, and stimulate uncontrolled cellular proliferation.

The microbiome also influences carcinogenesis through the production of microbial metabolites. Beneficial bacteria produce short-chain fatty acids such as butyrate, which possess anti-inflammatory properties, maintain intestinal barrier integrity, and regulate cellular differentiation. Conversely, harmful bacterial metabolites may promote DNA damage and facilitate malignant transformation.

Equally important is the microbiome's role in regulating host immunity. The gut-associated lymphoid tissue contains a substantial proportion of the body's immune cells, and microbial signals continuously educate and modulate both innate and adaptive immune responses. An imbalanced microbiome may impair immune surveillance, allowing malignant cells to escape detection and grow unchecked.

Microbes have been implicated in indirectly affecting many types of cancer. For example, gut microbes have been shown to impact cancer stem cells, or cancer cells that become quiescent and are thought to be responsible for disease relapse (26)

Metabolites from archaea, specifically the phyla Euryarchaeota and the TACK superphylum (Thaumarchaeota, Aigarchaeota, Crenarchaeota, and Korarchaeota), are associated with many types of cancer, despite these microbes often being disregarded due to their low prevalence (27)

By and large, the majority of research linking microbes and cancer has been focused on bacteria and their roles in a variety of cancers, though some have also covered the possible associations of fungi and viruses.

Colorectal cancer

Since the discovery of colibactin, there has been additional interest in how other gut microbes, including those thought to be commensals like E. coli, may affect CRC development and progression.(28)

Bacterial pathogen Helicobacter hepaticus has also been shown to significantly increase the incidence of colon tumors in an inflammatory-based mouse model of colorectal cancer, either due to increased inflammation or the production of virulence factors by this species (29)

Species belonging to the genera Bacteroides and Prevotella have also been noted as being significantly more abundant in CRC patients (30)

Commensal bacteria Fusobacterium nucleatum was also found to increase intestinal tumorigenesis without aggravating colitis or inflammatory pathways (31)

Instead, producing pro-tumorigenic formate and binds to proteins to mediate tumor growth.(32)

Others have recently found that increased Lactobacillus reuteri in the gut and its metabolite indole-3-lactic acid is associated with reduced CRC tumor burden.(33)

The presence of bacterial biofilms, particularly those containing bacterial phyla Bacteroidetes and Firmicutes, with significant populations of Fusobacterium spp. and the Enterobacteriaceae family, were also significantly associated with colorectal tumors.A follow-up study found that patients with familial adenomatous polyposis, an inherited condition that leads to polyps along the colon with a high incidence of CRC, had biofilms containing E. coli and Bacteroides fragilis that were capable of producing the endotoxins colibactin and B. fragilis toxin, respectively (34)

On the other hand, B. fragilis has also been shown to be protective against CRC in in vitro models, as its capsular carbohydrate Polysaccharide A can inhibit proliferation of CRC cells and impair migration (35)

Another group attempted to separate the bacterial signatures of CRC patients into clusters, finding that while some members of phyla Bacteroidetes and Firmicutes decreased, other members of these phyla increased; Prevotella and other bacterial genera thought to be oral commensals, such as Fusobacterium, Porphyromonas, Anaerococcus, Parvimonas, and Granulicatella, were also increased in CRC patients (36)

Another group similarly attempted to separate CRC microbial signatures into metacommunities, with a metacommunity mainly containing Bacteroides spp. showing decreased prevalence and a metacommunity mainly containing oral bacteria, such as Fusobacterium spp., showing increased prevalence in CRC patients (37)

Microbiome Associations Across Different Cancers

The strongest evidence linking the microbiome to cancer comes from colorectal cancer. Numerous studies have demonstrated enrichment of Fusobacterium nucleatum within colorectal tumors. This organism promotes inflammation, suppresses anti-tumor immune responses, enhances tumor cell proliferation, and has even been associated with resistance to chemotherapy. Similarly, enterotoxigenic Bacteroides fragilis and certain strains of Escherichia coli produce toxins that induce DNA damage and promote

tumorigenesis.

Gastric cancer provides another classic example of microbial carcinogenesis. Helicobacter pylori infection remains one of the few clearly established microbial causes of human cancer. Chronic infection leads to gastritis, intestinal metaplasia, dysplasia, and ultimately gastric adenocarcinoma. Importantly, eradication of H. pylori significantly reduces future gastric cancer risk, illustrating that microbial intervention can directly influence cancer prevention.

Emerging evidence also implicates the microbiome in hepatocellular carcinoma, pancreatic cancer, breast cancer, and lung cancer. In liver disease, alterations in the gut microbiota increase intestinal permeability, allowing bacterial products to reach the liver through the portal circulation, where they promote chronic inflammation and carcinogenesis. In breast cancer, microbial regulation of estrogen metabolism and systemic inflammation may influence disease risk. Researchers are also investigating the gut–lung axis, recognizing that gut microbes can shape immune responses affecting lung cancer progression and treatment outcomes.

Recent evidence has shown that the human microbiome is associated with various diseases, including cancer. The salivary microbiome, fecal microbiome, and circulating microbial DNA in blood plasma have all been used experimentally as diagnostic biomarkers for many types of cancer. The microbiomes present within local tissue, other regions, and tumors themselves have been shown to promote and restrict the development and progression of cancer, most often by affecting cancer cells or the host immune system. These microbes have also been shown to impact the efficacy of various cancer therapies, including radiation, chemotherapy, and immunotherapy. (38)

The Microbiome and Cancer Therapy

Perhaps the most exciting discovery in recent years is the microbiome's influence on cancer treatment.

Immune checkpoint inhibitors have transformed oncology, yet only a subset of patients achieve durable responses. Landmark studies have demonstrated that patients with greater gut microbial diversity and the presence of specific bacterial species, including Akkermansia muciniphila, Bifidobacterium, and Faecalibacterium, are more likely to respond favorably to immunotherapy. These organisms appear to enhance T-cell activation and strengthen anti-tumor immune responses.

Conversely, disruption of the microbiome may reduce therapeutic efficacy. Several studies have shown that exposure to broad-spectrum antibiotics immediately before or during immunotherapy is associated with poorer clinical outcomes, likely because antibiotics reduce microbial diversity and impair immune activation. While antibiotics remain indispensable when clinically indicated, these findings highlight the importance of avoiding unnecessary antimicrobial use in oncology patients.

The microbiome also influences chemotherapy. Certain microorganisms metabolize chemotherapeutic agents, altering both efficacy and toxicity. Understanding these microbial-drug interactions may eventually enable clinicians to optimize treatment selection and minimize adverse effects.
Therapeutic Modulation of the Microbiome

The growing appreciation of the microbiome's role in cancer has prompted interest in therapeutic strategies aimed at restoring microbial balance.

Diet remains the most accessible intervention. Diets rich in fruits, vegetables, legumes, whole grains, and dietary fiber promote microbial diversity and encourage the production of beneficial short-chain fatty acids. In contrast, diets high in processed foods and saturated fats may contribute to dysbiosis.

Probiotics and prebiotics have attracted considerable attention, although current evidence remains mixed. While selected patients may benefit, routine probiotic supplementation during cancer therapy cannot yet be universally recommended, particularly in severely immunocompromised individuals.

One of the most promising investigational approaches is fecal microbiota transplantation (FMT), in which stool from healthy donors is transferred to patients to restore microbial diversity. Early clinical studies have demonstrated that FMT may overcome resistance to immune checkpoint inhibitors in selected patients with advanced melanoma, opening an entirely new therapeutic avenue. Larger randomized trials are now underway.

Future strategies may also include engineered bacteria capable of delivering anti-cancer drugs directly to tumors, personalized microbiome editing, bacteriophage therapy, and microbiome-based biomarkers that predict treatment response.

The Future of Precision Oncology

Precision oncology has evolved from targeting genetic mutations alone to integrating genomic, transcriptomic, proteomic, and immunologic information. The microbiome represents the next important layer of this multidimensional approach.

Artificial intelligence will likely play a crucial role in interpreting complex microbiome datasets alongside genomic sequencing, digital pathology, radiomics, and clinical variables. Such integrated models could help identify patients at increased cancer risk, predict treatment response, personalize immunotherapy, and monitor disease progression more accurately than ever before.

Despite these exciting advances, significant challenges remain. Human microbiomes vary widely according to geography, diet, genetics, medication exposure, and lifestyle. No universal definition of a "healthy microbiome" currently exists, and many associations remain observational rather than causal. Standardized sequencing methods, validated biomarkers, and large prospective clinical trials are essential before microbiome-guided interventions become part of routine oncology practice.

CONCLUSION

The human microbiome has fundamentally changed our understanding of cancer biology. It is no longer viewed as a passive bystander but as an active regulator of carcinogenesis, immune function, therapeutic response, and survivorship. Although microbiome-based diagnostics and therapies remain in their early stages, their potential is immense. As precision medicine continues to evolve, clinicians may soon consider not only the tumor's molecular profile but also the patient's microbial ecosystem. The future of oncology may therefore depend not only on understanding the genes within cancer cells but also on understanding the trillions of microorganisms that coexist with us. The microbiome reminds us that cancer is not solely a disease of malignant cells. It is a disease shaped by the dynamic interaction between the tumor, the immune system, the environment, and the microscopic communities that inhabit the human body. Unlocking this hidden frontier has the potential to redefine cancer prevention, diagnosis, and

treatment for generations to come.

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