

Gastrointestinal Cancers: The Impact of Gut Prebiotics

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Abstract

Gastrointestinal cancers, including those of the esophagus, stomach, and colon, represent a significant global health challenge with high morbidity and mortality rates. Recent research has highlighted the potential role of gut prebiotics in influencing cancer development and progression. This review examines the mechanisms by which prebiotics, non-digestible fibers that promote the growth of beneficial gut bacteria, may contribute to gastrointestinal health and cancer prevention. We explore the impact of prebiotics on gut microbiota composition, immune modulation, and the production of short-chain fatty acids (SCFAs), which have been associated with anti-inflammatory and anticancer properties. Additionally, we discuss emerging evidence from clinical and preclinical studies that suggest a protective effect of prebiotics against gastrointestinal cancers. By synthesizing current findings, this review aims to underscore the importance of dietary interventions utilizing prebiotics as a potential strategy for reducing the risk of gastrointestinal cancers and improving patient outcomes. Future research directions are proposed to further investigate the clinical implications and optimal application of prebiotics in cancer prevention and management.

Keywords: Gastrointestinal cancers, Prebiotics, Gut microbiota, Cancer prevention

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Introduction

Intestinal microbiota includes different types of microorganisms that live in the human digestive system and their number reaches 10^{10} to 10^{12} in the large intestine. These microorganisms exist especially in the large intestine and are mainly anaerobic and are of great importance to human health. Diet, especially non-digestible carbohydrates, is the main source of energy for the growth of this microbiota.¹ Prebiotics, which are non-digestible nutrients, are fermented by beneficial gut microbes and can selectively affect the composition of gut microbiota. Also, gut microbiota has an effect on gut functions and immunity and can suppress pathogens. Various compounds have been tested to investigate the function of prebiotics.² Fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS) and trans-galacto-oligosaccharides (TOS) are among the most common prebiotics that are fermented by gut microbiota and produce short-chain fatty acids (SCFAs). These acids,

such as lactic and butyric acid, have multiple effects on the body, including lowering the pH of the colon and affecting the immune system. The structure of prebiotics and intestinal bacterial composition determine fermentation products and their effects on human health are carried out through these products.³ The concept of prebiotic was first introduced in 1995 by Glenn Gibson and Marcel Roberfroid and defined as a non-digestible food substance that helps to improve the health of the host by selectively stimulating the growth and activity of specific bacteria in the large intestine. This definition did not change for more than 15 years, and only a few specific combinations of carbohydrates, such as beta-fructans, lactulose, and GOS, were recognized as prebiotics.⁴ In 2008, a new definition of prebiotics was proposed, emphasizing the changes in the gastrointestinal microbiota and its benefits to host health. To classify a compound as a prebiotic, it must meet certain conditions,

including resistance to the acidic pH of the stomach and the ability to be fermented by the intestinal microbiota. The two main criteria for distinguishing fiber from carbohydrate prebiotics include a degree of polymerization (DP) equal to or higher than 3 and the absence of hydrolysis by small intestinal enzymes.⁵ Also, the definition of prebiotics, which was presented in 2017, refers to the connection between their consumption and human well-being. The concept of prebiotics being "selective" to stimulate specific gut microbiota is also a key element of the definition, but this concept has recently been challenged. In 2013, a report showed that the effect of prebiotics is enhanced by cross-feeding, which has led to doubts about the use of the term "selective". The debate about the definition of prebiotics continues.

Prebiotics

Prebiotics are mainly a subset of carbohydrates, especially oligosaccharides (OSCs). The two main types of prebiotics include fructans and GOS. Fructans include inulin and fructo-oligosaccharides and have a linear chain of fructose with specific bonds. Research has shown that the chain length of these compounds can affect their fermentation by bacteria.⁷ GOS arise from the expansion of lactose and are divided into two subgroups. These compounds can specifically stimulate beneficial bacteria such as *bifidobacteria* and *lactobacilli*, especially in infants. Other bacteria are also less affected by GOS. Some GOS are derived from lactulose and are known as prebiotics. Also, there are other types of GOS called raffinose family oligosaccharides (RFO) whose effects on gut microbiota are still unknown.⁸ Resistant starch (RS) is a type of starch that is resistant to the upper intestinal digestive tract and can contribute to health by producing butyrate, which is why it is considered a prebiotic. Different groups of Firmicutes are the most combined with RS. Studies have shown that RS is degraded by bacteria such as *Ruminococcus bromii* and *Bifidobacterium adolescentis*, but in the absence of *Ruminococcus bromii*, its degradation is impossible. Also, polydextrose, an oligosaccharide derived from glucose, can stimulate *bifidobacteria*, but this has not yet been definitively confirmed.⁹ Oligosaccharides can originate from pectin polysaccharide, which is called pectic oligosaccharide (POS). These oligosaccharides are classified based on the galactronic acid or rhamnose extension, and the carboxyl groups may be replaced by methyl esterification. Their structure can be acetylated at C2 or C3, and different types of sugars or ferulic acid are attached to their side chains. The structure of POSs varies considerably depending on their source.¹⁰ Non-carbohydrate

oligosaccharides, such as cocoa-derived flavanols, are known as prebiotics, although they are not formally considered carbohydrates. Research shows that these compounds can stimulate lactic acid bacteria. Prebiotics are recognized as important nutrients for human health and occur naturally in foods such as asparagus, garlic, onions, and bananas. Due to the low concentration of these substances in foods, their industrial production is carried out on a large scale. Some prebiotics are produced from raw materials such as lactose and starch, and most of them are classified as GOS and FOS, which have been extensively researched.¹¹ FOS is present in about 36000 plants, but its concentration in these sources is insufficient for prebiotic effects and therefore requires synthesis. There are different methods for FOS production, but chemical methods using glycosidase and glycosyltransferase are not suitable on an industrial scale due to the cost and risks of the materials used, as well as the low concentration of the final product. The key enzyme in FOS production is fructosyl transferase (FTase), which can produce one to three molecules of fructose from sucrose. Several microorganisms possess FTase, including *Aspergillus niger* and *Oreobasidium pullulans*, which are most commonly used in industry.¹² To produce FOS, whole cells of microorganisms or free enzymes can be used. The initial concentration of sucrose has a great effect on the amount of FOS produced, and the maximum production reaches 55-60%. Glucose, which is a co-product of fermentation, inhibits transglycosylation, so its removal and sucrose are necessary to increase fermentation efficiency. Some researchers use glucose oxidase and β -fructofuranosidase to increase FOS production. These enzymes can convert sucrose into FOS and glucose into gluconic acid, which is easily eliminated. The use of these enzymes can increase the production efficiency of FOS up to 98%. Also, microorganisms such as *Saccharomyces* (*S. cerevisiae*) and *Zymomonas mobilis* are able to ferment small saccharides, but *S. cerevisiae* cannot ferment oligosaccharides.¹³ GOSs were first synthesized chemically, but this method is now uneconomical on an industrial scale. Key enzymes for GOS production include galactosyltransferase and galactosidase. Galactosyltransferase can produce GOS in large quantities, but it is expensive because it requires nucleotide sugars. In contrast, galactosidase is cheaper, but produces less GOS and is less stereospecific. To improve the production of GOS by galactosidase, one can increase the concentration of donors and acceptors, decrease the water activity, shift the reaction equilibrium towards the final product, and modify the synthesis conditions.¹⁴ β -Galactosidases are obtained from various sources such as *Aspergillus oryzae*, *Streptomyces alveae*,

Bifidobacteria and *Lactobacilli* and produce different types of GOS that differ in amount, DP and glycosidic linkages. These enzymes require specific conditions to optimize GOS production; For example, fungal and bacterial sources require acidic and neutral pH, and high temperatures require thermophilic sources. Whole cell or free form β -galactosidase can be used for GOS biocatalysis. In cases where enzyme isolation is uneconomical, using the whole cell is a good option due to the presence of natural cofactors and lower cost, although β -galactosidase requires metal ions as cofactors.¹⁵ Some byproducts such as glucose and galactose do not have prebiotic effects and may reduce the efficiency of GOS synthesis. Using whole cells can remove these products through metabolic processes. For example, some microorganisms such as *Sirobasidium magnum* and *Sterigmatomyces elviae* consume glucose as a carbon source. Also, galactose can stimulate the expression of β -galactosidase enzyme. However, the production of metabolic end products such as ethanol and lactic acid can negatively affect GOS production. Temperature is also known to be an unfavorable factor in the use of whole cells, as it may be lethal to non-thermophilic cells. In some studies, non-viable and resting cells have been used, which have higher GOS production efficiency.¹⁶ Recombinant β -galactosidases have additional advantages over their native type, including high production yields and better stability. *Escherichia coli* (*E.coli*) and *Bacillus subtilis* are known as the main hosts for the production of these enzymes. *E.coli* has disadvantages such as endotoxin production and problems in expressing disulfide bonds, while *Bacillus subtilis* does not produce endotoxins but faces problems such as high production of proteases and plasmid instability. Also, some yeasts such as *S. cerevisiae* and *Pichia pastoris* are used to produce recombinant β -galactosidases, which have advantages such as higher productivity and the ability to produce disulfide bonds.¹⁷ By providing energy sources to the intestinal microbiota, prebiotics can change the composition and function of these microorganisms. Different bacterial species share their skills in consuming specific prebiotics, and using metagenomics techniques, genes related to prebiotic degradation are identified. Some species such as *Bifidobacterium*. They are able to ferment starch and fructans. The chain length of prebiotics also has an effect on their fermentation ability; for example, inulin can only be fermented by a few species, while more microorganisms can degrade FOS.¹⁸ Fermentation of prebiotics can lead to the production of by-products that act as nutritional substrates for other microorganisms. For example, *Ruminococcus bromii* is able to break down resistant starches and some species exploit the products of

this fermentation. Also, prebiotics can lower the pH of the gut, which can affect the composition and population of the gut microbiota. In particular, a decrease in pH from 6.5 to 5.5 can lead to a change in the population of acid-sensitive bacteria and an increase in butyrate production by Firmicutes, a process called the butyrogenic effect.¹⁹ The mechanisms of prebiotics help maintain health and protect against disorders. Degradation products of prebiotics mainly include SCFA, which can enter the circulation through intestinal enterocytes and affect distant organs and systems. There are limited studies on gastrointestinal disorders such as irritable bowel syndrome (IBS) and Crohn's disease. IBS is characterized by chronic abdominal pain and changes in bowel habits, while Crohn's disease is an inflammatory bowel disease that can affect any part of the digestive tract. In both diseases, a decrease in the population of *Bifidobacteria* and *Faecalibacterium prausnitzii* as well as the ratio of *Bacteroides* to *Firmicutes* has been reported.²⁰ A double-blind study showed that administration of 6g of oligofructose per day for 4 weeks had no effect on patients with IBS. Also, another trial with 20g of FOS per day was also unsuccessful in improving IBS. In contrast, two more recent trials showed that taking 5g of FOS for 6 weeks and 3.5g of GOS for 12 weeks helped improve IBS symptoms. A 2006 study found that 15g of FOS per day for 3 weeks increased *bifidobacteria* and improved Crohn's disease, but other trials found no clinical benefit for 15g of FOS in patients with active Crohn's disease and 20g of inulin in inactive patients or mild did not show.²¹ Colorectal cancer, the third most common malignancy in the world, is a multistage disease that progresses from genetic mutations to adenomatous polyp formation and can lead to invasive and metastatic cancer. Research has shown that fermentation products of prebiotics, such as butyrate, can have protective effects against this cancer and its progression through the induction of apoptosis. Also, a clinical trial has shown that symbiotic treatment with *Lactobacillus rhamnosus* and *Bifidobacterium lactis* along with inulin can reduce the risk of colorectal cancer by reducing the proliferation rate and improving the epithelial barrier function.²²

Necrotizing enterocolitis (NEC) is a gastrointestinal emergency in premature infants that can lead to intestinal necrosis and serious complications. Prebiotics such as FOS and GOS may prevent NEC by stimulating the growth of gut microbiota and reducing pathogenic bacteria. Also, SCFAs can improve feeding tolerance. However, a meta-analysis showed that the use of FOS and GOS did not have a significant effect on reducing the risk of NEC, and more research is needed in this area.²³ Prebiotics can improve the function of the

immune system by increasing the population of beneficial microorganisms. Research has shown that these substances can reduce harmful bacteria and, for example, mannose can reduce the colonization of pathogens by increasing the adhesion to *Salmonella*. Also, prebiotics can stimulate the expression of immune molecules such as cytokines. Maternal prebiotic metabolites can also affect fetal immune system development. In one study, administering FOS to pregnant mice improved the offspring's microbiota and reduced skin inflammation. However, another study found that the effects of prebiotics in humans could not be passed on to the next generation.²⁴ Prebiotics communicate with the central nervous system through the "gut-brain axis". Research has shown that administration of prebiotics to piglets can lead to reduced gray matter and improved neural pruning. However, the effects of prebiotics on the human brain are not yet fully understood. Gut microbiota affects the brain through neural, endocrine and immune pathways.²⁵ Prebiotics, especially GOS, can help reduce the risk and severity of allergic skin diseases such as atopic dermatitis. In studies on hairless mice, consuming GOS for 12 weeks increased water retention and prevented erythema. Also, GOS can improve the skin barrier by increasing the expression of cell adhesion and matrix formation markers. Metabolism of aromatic amino acids by gut microbes may produce compounds such as phenols that can be transferred to the skin and toxic to kidney patients. In women, consumption of GOS with or without probiotics can reduce the negative effects of phenols on water and creatine.²⁶ In 2013, 30% of all deaths in the United States were attributable to cardiovascular disease (CVD), largely due to changes in lifestyle and dietary habits. Researchers have investigated the effect of fibers and prebiotics on CVD, but their direct effects are not yet fully understood. Prebiotics can reduce the risk of CVD by reducing inflammatory factors. Studies have shown that the consumption of prebiotics can improve the lipid profile. In a clinical trial, taking 10g of inulin per day for three weeks reduced blood triacylglycerol, but had no significant effect on cholesterol levels.²⁷ In a randomized, double-blind crossover trial, Rousseau et al showed that consumption of inulin-enriched pasta (86% semolina, 11% inulin, and 3% gluten) reduced Triacylglycerol (TAG) and lipogenesis in healthy subjects, while Beylot Frochen reported that consumption of 10g of inulin-type fructan per day for six months had no significant effect on lipogenesis. Also, in a semi-randomized study, Vogt et al observed a significant reduction in TAG synthesis and levels, but no effect on cholesterol, by administering 25 g of L-rhamnose and lactulose per day for four weeks. In contrast, another

study in 1991 showed that lactulose can increase blood cholesterol by 10%.²⁸ In a double-blind, placebo-controlled study in overweight subjects with metabolic syndrome risk factors, Bimuno® Galacto-oligosaccharides (B-GOS) for 12 weeks resulted in a reduction in cholesterol, TAG, and total: High-density lipoprotein (HDL) cholesterol ratio, but it did not have a significant effect on the ratio of cholesterol in the elderly. Also, a meta-analysis showed that β -glucan consumption can reduce total and Low-density lipoprotein (LDL) cholesterol levels. Finally, another meta-analysis showed that FOS can reduce TAG levels by an average of 7.5%.²⁹ Prebiotics can have negative effects on lipid profile by producing SCFA such as acetate. Acetate can be converted to acetyl-CoA and increase blood cholesterol and triglycerides. Instead, other SCFAs such as propionate and butyrate may improve the lipid profile. Propionate can inhibit the synthesis of lipids from acetate. Therefore, prebiotics can have lipogenic effects by producing these SCFAs. Determining the final products of prebiotics is essential to choose the most appropriate product. While some studies suggest that prebiotics are beneficial for obesity-related diseases, there is also conflicting evidence that refutes this claim.³⁰ Prebiotics have contradictory effects on calcium absorption. In the United States, more than 28 million people have osteoporosis, and in the European Union, one in eight citizens over the age of 50 suffer a spinal fracture each year. Some studies have shown that consumption of prebiotic fibers such as lactulose, TOS and inulin + oligofructose in certain doses can increase calcium absorption, while no such effect was observed for GOS and FOS.³¹ Prebiotics generally do not have severe side effects and intestinal enzymes are unable to break them down, so they are transported to the large intestine and fermented by the microbiota. Side effects are mainly caused by their osmotic action and include osmotic diarrhea, bloating and cramping. The length of the chain of prebiotics has an effect on side effects; Shorter-chain prebiotics may cause more complications because they ferment faster. Also, the dosage of prebiotics has an effect on their safety; Low and high doses can cause bloating and diarrhea. A daily dose of 2.5-10g is required for beneficial effects, and most products on the market have doses of 1.5-5g per serving. Prebiotics as potential alternatives or adjunctive therapies to probiotics may have similar safety concerns. Safety risks of probiotics include bacteremia, sepsis, and endocarditis, especially in immunocompromised patients, severe malnutrition, or intestinal problems. But these side effects are not specifically considered or underreported in clinical studies related to prebiotics.³² Prebiotics have a great impact on

human health and can improve the quality of life against diseases such as cancer, vascular diseases, obesity and mental disorders. Despite numerous studies in this field, there is a need to design long-term clinical trials and genomic research to confirm these claims. Identifying the mechanisms of action of prebiotics will help scientists to develop effective food supplements to improve human health. Also, the ability of prebiotics to normalize the composition of intestinal microbiota is an effective way to control and improve various disorders.³³ In general, proper nutrition of the gut microbiota with prebiotics can help promote overall health. Considering the diversity of intestinal microbiota in different populations and individuals, it seems difficult to produce effective probiotics. On the other hand, prebiotics are a more suitable option due to the ease of production, no need for cold chain and minimal side effects. Designing specific prebiotics for each population can help reduce intestinal disorders, and this concept can be addressed in future FAO and World Health Organization (WHO) guidelines.³⁴

Conclusion

This review highlights the significant impact of gut prebiotics on gastrointestinal cancers, emphasizing their potential role in prevention and management. The evidence suggests that prebiotics can positively influence gut microbiota composition, enhance immune response, and promote the production of beneficial metabolites such as short-chain fatty acids, all of which may contribute to reduced cancer risk and improved health outcomes. As research continues to evolve, it is crucial to further investigate the specific mechanisms by which prebiotics exert their effects and to identify optimal dietary strategies for cancer prevention. Incorporating prebiotics into dietary recommendations could serve as a valuable adjunct to conventional cancer therapies, fostering a holistic approach to gastrointestinal health. Ultimately, increasing awareness and understanding of the role of prebiotics may pave the way for innovative dietary interventions aimed at mitigating the burden of gastrointestinal cancers.

Highlights

What Is Already Known?

The effects of each prebiotic have been reviewed separately in original articles.

What Does This Study Add?

This study comprehensively collected the effects of various prebiotics on colorectal cancer.

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Conflicts of Interest Disclosures

The authors disclosed no competing interests.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions

Mohammad Mehdi pour: Literature search, study screening, data extraction, data analysis and interpretation, and writing of the original draft.

Sepideh Mokabberi: Conceptualization, study design, development of the systematic review methodology, supervision of the literature search and study selection process, interpretation of findings, critical review and editing of the manuscript, project supervision, and corresponding author.

All authors: Contributed to the interpretation of the findings, critically reviewed and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Consent For Publication

Not applicable.

Ethics approval

Not applicable. This study is a systematic review and did not involve the collection or analysis of primary data from human participants or animals. Therefore, ethical approval was not required.

The extent of AI use

No artificial intelligence (AI) tools were used in the preparation, analysis, interpretation, or writing of this manuscript.

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