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MINIREVIEWS

Unraveling colorectal cancer prevention: The vitamin D - gut flora - immune system nexus

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Abstract

Colorectal cancer (CRC) is one of the most common cancers diagnosed in the world. Although environmental and genetic factors play a major role in the pathogenesis of CRC, extensive research has suggested that vitamin D may play a pivotal role in the development of CRC. Vitamin D, primarily obtained through sunlight exposure, dietary sources, and supplements, has long been recognized for its essential functions in maintaining health, including immune regulation. This article delves into the intricate relationship between vitamin D, the immune system, gut flora, and the prevention of CRC. It presents a synthesis of epidemiological data, experimental studies, and clinical trials, highlighting the mechanisms by which vitamin D influences immune cell function, cytokine production, and inflammation. By enhancing the immune system's surveillance and antitumor activity, vitamin D may offer a promising avenue for CRC prevention. Furthermore, this comprehensive review delves into the prospective clinical applications of vitamin D supplementation and delineates the forthcoming avenues of research in this dynamic domain. Additionally, the paper tentatively outlines a spectrum of prophylactic impacts of vitamin D on CRC, emphasizing its significant potential in reducing CRC risk through shedding light on its

mechanisms, encompassing antineoplastic mechanisms, influences on the immune system, and modulation of the gut microbiome.

Key Words: Colorectal cancer; Vitamin D; Immune system; Gut flora; Immunomodulation; Microbial dysbiosis; Cancer prevention

Core Tip: Our study explores the intricate connections between vitamin D, the immune system, and gut flora in the context of colorectal cancer (CRC) prevention. We uncover how vitamin D influences these interrelated factors and its potential role in reducing CRC risk. This research sheds light on novel avenues for preventive strategies and underscores the importance of a holistic approach to CRC prevention.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies in the world, showing high incidence and mortality rates in both China and the United States[1,2]. In the United States, the American Cancer Society periodically releases updates on CRC occurrence, utilizing incidence data up to 2016 from population-based cancer registries and mortality data up to 2017 from the National Center for Health Statistics[2]. In 2020, it was estimated that around 147950 individuals would receive a CRC diagnosis, with 53200 succumbing to the disease[2]. This included 17930 cases and 3640 fatalities among individuals under the age of 50[2]. Annually in China, it is estimated that there are over 376000 new cases of CRC and approximately 191000 deaths associated with the disease[3]. With its distressingly high incidence and mortality rates, it imposes an enormous burden on societies worldwide[4,5].

CRC is a disease with a multifaceted origin influenced by both genetic predisposition and environmental factors[6]. Given its prevalence and the significant impact it has on public health, preventing CRC has become a central focus in clinical practice and medical research. Importantly, screening for CRC plays a critical role in its prevention by identifying and removing colon polyps before they can develop into cancer[7,8]. Historically, preventive measures primarily involved lifestyle modifications such as quitting smoking, reducing alcohol intake, minimizing high-salt and high-fat foods, and adopting healthier diet and lifestyle habits to mitigate the risk of CRC. In recent years, relevant researchers have divided the prevention of CRC into two categories: Molecular prevention and chemoprevention. Molecular prevention focuses on early-stage intervention mainly through a comprehensive understanding of the complex mechanisms involving adenoma and CRC. On the other hand, chemoprevention involves direct interventions utilizing drugs, various anti-inflammatory substances, and nutrients. This article focuses on the role of vitamin D as a method of chemoprevention in CRC and explores related mechanisms[9].

To gain a comprehensive understanding of the potential for preventing CRC, it is essential to delve into the intricate web of associations involving vitamin D, the immune system, gut flora, and CRC itself[10]. This journey takes us on a thorough exploration of the multifaceted relationships among these elements, each contributing to the complex landscape of CRC development.

UNDERSTANDING VITAMIN D

The "sunshine vitamin" and its sources

Vitamin D, often referred to as the "sunshine vitamin", is a fat-soluble vitamin that plays a pivotal role in human health [11]. One of the primary sources of vitamin D is sunlight exposure. When the skin is exposed to ultraviolet B rays from the sunlight, it can synthesize vitamin D from cholesterol derivatives[12]. This natural synthesis process in the skin is a crucial means by which individuals obtain this essential nutrient[13]. In addition to sunlight, dietary sources and vitamin D-rich supplements are significant avenues through which people acquire vitamin D[14]. It's important to note that there are two primary forms of vitamin D: Vitamin D2 and vitamin D3. Both of these forms have essential roles in maintaining human health[15].

Metabolism and forms of vitamin D

The major form of vitamin D metabolite found in the serum is 25-hydroxyvitamin D (25-OH-D)[16]. In the body, both vitamin D_2 and D_3 are converted into 25-OH-D in the liver. Subsequently, this form of vitamin D travels through the

bloodstream to the kidneys, where it undergoes further metabolism, transforming into 1,25-dihydroxyvitamin D (1,25-D) or osteotriol (25-(OH) D_3)[17]. Among these metabolites, 1,25-dihydroxyvitamin D is the active form of vitamin D in the body, while 25-(OH) D_3 serves as the stored form primarily found in the liver[18].

Throughout this metabolic process in the human body, active vitamin D binds to transporter proteins and is transported to various organs *via* the bloodstream. At the same time, the concentration of the stored form, 25-(OH) D_3, is maintained at a relatively constant level[12,19]. These intricate processes underscore the significance of vitamin D in maintaining overall health and its potential role in various physiological functions[20].

THE GUT MICROBIOTA

The complex world of gut microbiota

The human microbiota encompasses a diverse array of microorganisms, comprising bacteria, archaea, fungi, viruses, and parasites. These microorganisms inhabit and colonize various niches within human tissues and biofluids, as well as on their surfaces[21,22]. Extensive study has established the crucial relationship between a healthy gut microbiome and its impact on the host's immune response, energy metabolism, and pathogen colonization resistance[23]. The gut microbiota is a highly intricate and diverse community of microorganisms residing in the human gastrointestinal tract. In the digestive system of healthy individuals, this microbial ecosystem is composed of an astonishingly diverse array of over 100 trillion microorganisms[14,24], representing a complex interplay of various bacterial species.

This microbial community is a dynamic and ever-changing system influenced by a myriad of factors, including diet, genetics, age, and environmental exposures[25]. It plays a pivotal role in shaping the overall health and well-being of an individual. Understanding the intricate composition and dynamics of the gut microbiota is fundamental to comprehending its impact on health and diseases like CRC[26].

Gut microbiota functions: Comprehensive overview

The main functions of the gut microbiota extend beyond traditional classifications, encompassing nutritional, defensive, metabolic, and additional key roles[27]. Nutritional functions: The gut microbiota plays a vital role in nutrient metabolism. It assists in the breakdown of indigestible food components, such as dietary fiber, through a process of fermentation. This fermentation process results in the production of short-chain fatty acids (SCFAs), including butyrate [28]. Butyrate, in particular, is crucial for maintaining intestinal homeostasis, as it promotes the development of colon cells while repressing the growth of cancerous cells[29]. SCFAs also serve as an energy source for colonocytes and contribute to the secretion of mucin, which is essential for maintaining the integrity of the intestinal barrier[30].

Defensive functions: The gut microbiota has a defensive role in protecting against harmful pathogens and bolstering the immune system[31]. It helps prevent inflammation and reduce the risk of cancer by generating regulatory T cells, which are involved in maintaining immune balance. Additionally, a diverse and balanced gut microbiota can compete with pathogenic bacteria for resources and inhibit their growth, further enhancing the defensive functions of the gut[32].

Metabolic functions: Beyond nutritional support, the gut microbiota plays a significant role in metabolic processes[33]. It is involved in the synthesis of essential vitamins and amino acids necessary for human growth and development. These bacteria also contribute to sugar and protein metabolism and aid in the absorption of essential minerals. The gut microbiota's metabolic functions are critical for overall health, and imbalances in this ecosystem can give rise to various diseases[34].

Regulation of gas composition and redox potential: The microbiota regulates intestinal gas mixtures, including hydrogen, methane, and carbon dioxide production, playing a key role in physiological processes and maintaining gut redox balance[35].

Production of digestive enzymes: It produces a broad spectrum of enzymes for breaking down proteins, carbohydrates, and lipids, aiding the digestion and absorption of nutrients beyond the capacity of human enzymes[36].

Participation in water-salt metabolism: Microbial activity regulates intestinal movement, facilitating food transit and preventing disorders like constipation and irritable bowel syndrome[37].

Enhancement of intestinal motility: Furthermore, the microbiota contributes to the body's water-salt equilibrium, influencing electrolyte and water absorption and secretion in the intestines, essential for hydration and blood pressure regulation[38].

THE IMMUNE SYSTEM AND CRC

Vitamin D's role in immune regulation

Vitamin D is not just essential for bone health; it also plays a crucial role in regulating the immune system[39]. This multifaceted vitamin is known to modulate various aspects of immune function. Vitamin D does this by interacting with immune cells and signaling pathways, ultimately contributing to the body's ability to defend against infections and maintain immune homeostasis[40].

Vitamin D exerts a significant impact on the immune system by reducing the activity of T helper 1 (Th1) and Th17 CD4 T cells, while promoting the activity of regulatory T cells (Tregs)[39]. It inhibits the production of Th1 cytokines, including interleukin (IL)-2 and interferon-γ, as well as Th17 cytokines like IL-17 and IL-21, and the Th9 cytokine IL-9[39,41,42]. This shift in T cell activity has profound implications for immune balance, inflammation, and autoimmunity. Moreover, vitamin D has been shown to inhibit dendritic cell differentiation in the intestinal lamina propria, further contributing to immune regulation[39] (Figure 1).

Moreover, vitamin D enhances the production of antimicrobial peptides (AMPs) and cytokines like β-defensin[43]. These AMPs are critical components of innate host defense against infections. Vitamin D also has a direct role in reducing the production of pro-inflammatory molecules by downregulating nuclear factor κB (NF-κB) activation, an essential pathway in inflammatory responses[44]. These immune-regulatory effects of vitamin D are particularly relevant in the context of CRC prevention, as they contribute to maintaining a balanced and controlled immune response in the gut[45].

How vitamin D influences gut function

Vitamin D's influence extends beyond immune regulation to impact gut function. In the gut, vitamin D and its receptor (VDR) are involved in various processes that contribute to gut health[46]. One notable aspect is the improvement of the intestinal barrier. Vitamin D helps strengthen the intestinal barrier, which is essential for preventing the infiltration of harmful pathogens and maintaining gut integrity[47].

Additionally, vitamin D affects antigen presentation and adaptive T cells in the gut[48]. This means that it can influence how the immune system recognizes and responds to potential threats, including cancer cells. The role of vitamin D in the regulation of the gut microbiota is also of significance. It can shape the composition of the gut microbiome, promoting a balanced microbial ecosystem that contributes to overall gut health[49].

ROLE OF GUT FLORA IN CRC

Dysbiosis and CRC

The emergence of inflammatory bowel disease (IBD) frequently coincides with shifts in microbial communities, a condition known as dysbiosis, within the gut[50]. The interplay between genetic predisposition and environmental factors can set the stage for chronic inflammation in the intestinal tract[51]. In line with the "common ground hypothesis", it is proposed that microbial dysbiosis, coupled with compromised intestinal barrier function leading to increased permeability (leaky gut), forms the crux of the chronic inflammatory process that underlies IBD-CRC[52]. A body of research, encompassing investigations with patient cohorts and gnotobiotic mouse models[53,54], has lent substantial support to this hypothesis[55].

Dysbiosis has emerged as a significant factor in the development and progression of CRC[56]. In individuals with CRC, there is often a notable shift in the gut bacterial composition compared to healthy individuals[34]. This shift, characterized by reduced levels of beneficial bacteria and an increase in opportunistic pathogens, is indicative of intestinal dysbiosis [57].

One critical aspect of dysbiosis in CRC is the reduction in butyrate-producing bacteria. Butyrate promotes the growth and differentiation of colon cells while inhibiting the proliferation of cancerous cells[58]. Lower levels of butyrate are associated with increased intestinal inflammation and a higher risk of CRC development[59].

Additionally, dysbiosis can lead to the overgrowth of pro-inflammatory bacteria in the gut of CRC patients[60]. This shift in bacterial composition contributes to a pro-inflammatory environment, which is a known factor in the development of cancer[60]. Furthermore, invasive pathogens, such as *Escherichia coli* (*E. coli*), can inhibit the host's epithelial colonocytes' antimicrobial responses, potentially exacerbating the inflammatory milieu in the gut[61].

Specific bacterial species in CRC

Research has identified specific bacterial species that are associated with CRC. Comparative analysis of stool samples from CRC patients and healthy individuals reveals notable differences in gut bacterial composition. CRC patients often exhibit an enrichment of pro-inflammatory species, including *Micrococcus microti*, *Clostridium nucleatum*, and *Bacteroides fragilis*, compared to control samples[58]. Conversely, control samples tend to have a higher abundance of beneficial bacteria such as *Bacteroides* and *Bifidobacterium* species[62]. This distinction in bacterial profiles underscores the potential role of these specific bacterial species in either promoting or inhibiting CRC development[63]. Notably, patients with IBD face an increased risk of CRC, and this risk is correlated with the duration and severity of colitis. The connection between IBD, gut inflammation, and CRC highlights the critical link between chronic intestinal inflammation and cancer development[64].

VITAMIN D'S ANTI-TUMOR EFFECT

Vitamin D as a protective factor in CRC

Mounting evidence suggests that vitamin D plays a vital role as a protective factor against CRC. Studies have provided compelling evidence supporting the notion that increased levels of vitamin D, defined quantitatively as higher serum concentrations of 25(OH)D, are associated with a reduced risk of CRC development[65]. These elevated serum 25(OH)D levels, which are indicative of sufficient vitamin D intake and effective bodily absorption, are crucial for the activation of

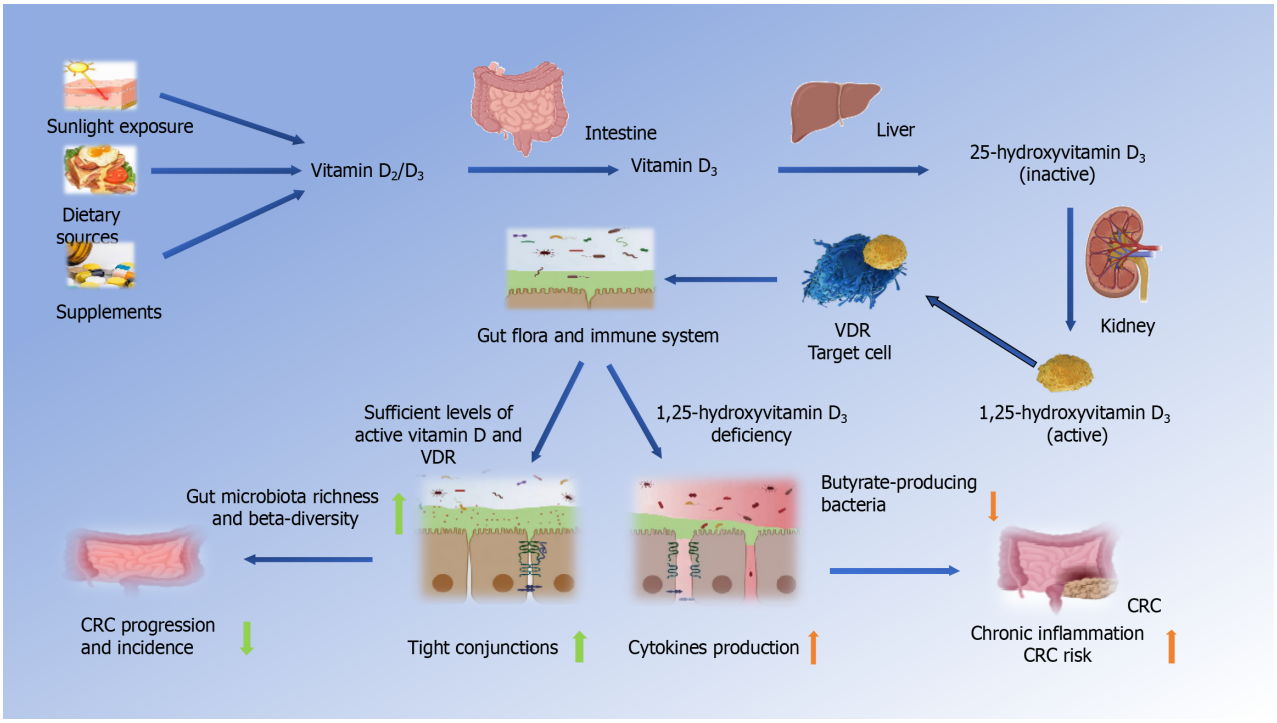

Figure 1 Vitamin D's impact on immune system and gut microbiota in colorectal cancer progression. VDR: Vitamin D receptor; CRC: Colorectal cancer.

various protective mechanisms within the body. Such mechanisms include modulation of cell growth, reduction of inflammation, and enhancement of immune function, which collectively contribute to a significant reduction in CRC risk[66].

One such study, conducted by Tsounis *et al*[67], revealed a robust protective effect of vitamin D against CRC. This effect extended not only to the development of CRC but also to colon polyps, which are often precursors to cancer[67]. The findings of this study, and others like it, highlight the potential of vitamin D as a crucial factor in preventing CRC[68, 69]. The protective effect of vitamin D in CRC is not merely coincidental. Instead, it arises from a complex interplay of molecular mechanisms that influence various aspects of cancer biology and immune regulation[70].

Molecular mechanisms of vitamin D's action

Vitamin D's anti-tumor effect is underpinned by a multitude of molecular mechanisms that impact cell growth, differentiation, and apoptosis[71]. When vitamin D binds to its receptor VDR, it initiates a cascade of intracellular and nuclear pathways that collectively act as a formidable barrier against the onset and progression of CRC[72].

VDRs, which belong to the nuclear receptor superfamily, are expressed in a wide range of tissues, including the intestine, activated B and T lymphocytes, monocytes, and more[39]. This broad representation of VDRs throughout the body underscores the multifunctional role of vitamin D, particularly in the colonic mucosa[47]. One critical function of VDR in the intestine is the stabilization of cell tight junctions between intestinal epithelial cells[73]. Vitamin D induces the expression of proteins such as Zo-1, E-cadherin, and occludin, all of which are essential for maintaining the integrity of the intestinal barrier[47]. This barrier is crucial for preventing the invasion of harmful pathogens and toxins into the bloodstream.

Furthermore, VDR is directly involved in the regulation of NF-κB activation in activated B cells, an essential pathway in inflammatory responses[74]. VDR deficiency leads to reduced levels of an endogenous inhibitor of NF-κB, contributing to heightened inflammation[75]. Vitamin D's ability to inhibit NF-κB activation serves as a mechanism to mitigate inflammation in the gut[76].

Vitamin D also enhances immune homeostasis by modulating various immune cell activities. It decreases the activity of Th1 and Th17 CD4 T cells while increasing the activity of Tregs[77]. Additionally, it downregulates T cell-driven immunoglobulin G production and inhibits dendritic cell differentiation in the intestinal lamina propria[78]. These effects collectively contribute to the maintenance of a balanced and controlled immune response in the gut.

In summary, the anti-tumor effect of vitamin D in CRC is rooted in its ability to modulate molecular pathways involved in cell growth, differentiation, apoptosis, and immune regulation. The intricate interplay between vitamin D, the immune system, and the colonic mucosa underscores its potential role as a key player in preventing CRC.

VITAMIN D'S INFLUENCE ON GUT FLORA

The interplay: Vitamin D, immune cells, and gut microbiota

Vitamin D's influence on gut flora is a multifaceted interplay that extends beyond its role in immune regulation[79]. This

intricate relationship involves vitamin D, immune cells, and the gut microbiota, collectively contributing to gut health and, potentially, CRC prevention[80]. One of the key aspects of this interplay is the role of immune cells in the gut. VDRs are expressed in various immune cell lineages, including CD4 T cells, CD8 T cells, B cells, neutrophils, macrophages, and dendritic cells[48]. When these immune cells are exposed to vitamin D, it triggers a series of responses that have a profound impact on gut health[81].

Studies have shown that vitamin D supplementation significantly alters the composition of the gut microbiota. It leads to a reduction in opportunistic pathogens and an increase in bacterial richness[46]. Notably, there is a decrease in gamma-proteobacteria, including bacteria like *Pseudomonas* and *E. coli/Shigella*, among individuals who adhere to vitamin D supplementation. This shift in microbial composition is mediated through mucosal CD8 and T cells, which exhibit high VDR expression[21]. CD8 and T cells, influenced by vitamin D supplementation, reduce the inflammatory environment in the gut[79]. This change in the immune response allows beneficial bacteria, such as bacilli, to outcompete opportunistic pathogens. These alterations in the gut microbiota can contribute to slowing the development and progression of CRC [82].

Dysbiosis resulting from vitamin D deficiency

On the contrary, vitamin D deficiency can lead to dysbiosis in the gut microbiota, resulting in an imbalance in microbial composition[33]. This disruption in the gut ecosystem can have far-reaching consequences. This dysbiosis is characterized by reduced bacterial production of butyrate, a critical SCFA involved in maintaining intestinal homeostasis. SCFAs, including butyrate, propionate, and acetate, are the end-products of microbial fermentation and play crucial roles in numerous physiological functions[83]. These multifunctional compounds are integral in preserving the integrity of the intestinal mucosa[84], enhancing glucose and lipid metabolism[85], regulating energy expenditure[86], and orchestrating immune system responses and controlling inflammatory processes[87]. SCFAs exert their effects through a variety of mechanisms, including interaction with specific G protein-coupled receptor families[88] and *via* epigenetic modifications. Lower levels of butyrate can lead to immunosuppression, which can contribute to chronic intestinal inflammation - a known risk factor for CRC[89].

In individuals with vitamin D deficiency, the gut microbial profile may shift towards an enrichment of pro-inflammatory species and a decrease in beneficial bacteria[90]. This microbial imbalance can create a pro-inflammatory environment in the gut, which is conducive to the development and progression of CRC[91]. Notably, epidemiological investigations indicate that vitamin D deficiency is associated with a heightened risk of colon cancer incidence and has adverse implications for the survival rates of colon cancer patients[92].

In conclusion, vitamin D's influence on gut flora involves a complex interplay with immune cells and the gut microbiota. Vitamin D supplementation can promote a balanced and diverse gut microbiota, which is associated with reduced inflammation and a lower risk of CRC. Conversely, vitamin D deficiency can lead to dysbiosis, creating an inflammatory milieu that may contribute to CRC development. Understanding these interactions sheds light on the potential preventive role of vitamin D in the context of CRC.

CRC, INFLAMMATION, AND VITAMIND

Inflammation and CRC development

Inflammation has long been recognized as a significant driver in the development and progression of CRC[93]. Chronic inflammation in the gastrointestinal tract is associated with an increased risk of CRC, and conditions such as IBD, including Crohn's disease and ulcerative colitis, are well-established risk factors for CRC[94]. During chronic inflammation, immune cells are continually activated, releasing pro-inflammatory cytokines and reactive oxygen species. This sustained inflammatory environment can lead to several detrimental effects, including DNA damage, oxidative stress, and the promotion of cell proliferation-factors that contribute to the initiation and growth of cancerous cells[95]. Moreover, the gut microbiota plays a crucial role in modulating inflammation in the intestinal tract. Dysbiosis, or an imbalance in the gut microbial composition, can contribute to heightened inflammation in the gut, further increasing the risk of CRC.

IMPLICATIONS AND FUTURE RESEARCH

Potential strategies for CRC prevention

The insights gained from the intricate interplay between vitamin D, the immune system, gut flora, inflammation, and CRC hold significant implications for potential strategies in CRC prevention. One promising avenue is the utilization of vitamin D supplementation as a preventive measure. The evidence pointing to the protective effect of vitamin D against CRC is compelling. Clinical studies have demonstrated that increased levels of vitamin D are associated with a reduced risk of CRC development. Therefore, optimizing vitamin D levels through dietary sources, sunlight exposure, and supplements may be a viable strategy for reducing CRC risk, particularly in individuals with vitamin D deficiency.

Additionally, strategies aimed at maintaining a healthy and diverse gut microbiota are of paramount importance. Dysbiosis, characterized by an imbalance in gut microbial composition, is closely linked to CRC development. Encouraging dietary habits that promote the growth of beneficial bacteria, such as those that ferment dietary fiber to produce SCFAs like butyrate, could play a pivotal role in CRC prevention. Moreover, interventions like probiotics and

microbiological agents may help rectify dysbiosis and promote gut health.

The control of chronic inflammation in the gut is another critical aspect of CRC prevention. Given the well-established association between inflammation and CRC, strategies that target inflammation, such as the use of anti-inflammatory agents or lifestyle modifications, could hold promise. Maintaining an anti-inflammatory diet, rich in antioxidants and anti-inflammatory foods, may contribute to reducing the risk of CRC.

The need for rigorous clinical studies

While the existing body of research provides valuable insights into the potential preventive role of vitamin D, the immune system, and gut flora in CRC, further investigations are imperative. Rigorous clinical studies are needed to solidify the complex associations observed in experimental and epidemiological research. To establish vitamin D as a credible preventive agent against CRC, large-scale clinical trials with diverse populations are essential. These trials should focus on optimizing vitamin D levels and assessing its impact on CRC incidence. Randomized controlled trials can provide robust evidence regarding the effectiveness of vitamin D supplementation in reducing CRC risk.

Moreover, comprehensive studies that delve into the intricate interplay between vitamin D, the immune system, gut microbiota, and inflammation are warranted. These studies should encompass larger sample sizes and employ randomized designs to ensure the reliability of their findings. In conclusion, the potential strategies for CRC prevention lie in optimizing vitamin D levels, promoting gut health, and controlling inflammation. However, to translate these possibilities into practical recommendations, rigorous clinical studies are required. These studies will not only enhance our understanding of CRC prevention but also pave the way for innovative approaches to enhance public health and well-being in the fight against this devastating disease.

CONCLUSION

The intricate web of interactions among vitamin D, the immune system, gut flora, inflammation, and CRC reveals a promising avenue for CRC prevention. With CRC ranking among the most common and deadly malignancies worldwide, understanding these connections holds immense potential for improving public health.

FOOTNOTES

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