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Role of Diet and Probiotic in Prevention of Colorectal Cancer with a Review on Interplay of Pathogenesis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Colorectal cancer has always been a focus for early detection by widely available screening procedures, yet it is the third common cancer worldwide. Dietary habits have a significant impact on the colonic microenvironment. Food can modify colonic microbiota composition to prevent the development of colonic neoplasia. Nutrients play a role via immunomodulation in colonic tissue, and their metabolites influence cellular arrangement. Diet has a crucial role both as causal and preventive, which is why extensive epidemiological and experimental studies are the demands to build a diet plan to ensure gut hygiene. Red meat, processed meat, has been considered to have a role in carcinogenesis, so changing the processing procedure, using colon-friendly additives, and decreasing toxic food compounds are a few of the possible preventive approaches. In this review, we aim to discuss the influence of dietary components, metabolites, and microbiota composition on colon cancer prevention.

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1. INTRODUCTION

Colorectal cancer (CRC) remains a major worldwide health problem, accounting for increasing incidence four times higher in developed countries than developing countries. Environmental factors such as food carcinogens, physical inactivity, smoking, and gut microbiomes are implicated for CRC onset and can intervene in the disease's onset.

Gut health has always been a neglected part of self-care yet a significant field of research to prevent CRC. Diet substantially can act in the prevention of CRC, evidenced by a role in preserving mucosal health [1].CRC is primarily sporadic, and the rate of carcinogenesis is interrelated between the aggressive nature of environmental insult and the extent of genetic defect [2].We searched for articles in pub-med using keywords followed by selecting relevant article.Steps of data extraction,quality assessment and data synthesis was followed accordingly.Primary focus of this research is establishing diet and probiotic as imperative component in prevention of colon cancer.We also discuss their causal pathway in colonic neoplasm along with feasible solution to make diet more colonic-mucosa friendly.

Mechanism of CRC: There are theories suggesting that harmful dietary ingredient as well as genetic modulation in oncogenes,tumor suppressor gene initiate the gradual disturbances in the combination of the gut microbiota.Firstly,mutation in APC gene,a tumor suppressor regulating Wnt signaling via the role of controlling Beta catenin level,is a major fact in pathogenesis of CRC [3]. Additionally, promoter hypermethylation of various tumor suppressor genes, most importantly MGMT and MLH1 plays role in CRC pathogenesis in another way known as CIMP pathway often associated with microsatellite instability(MSI) and BRAF mutation too [4].15% case of sporadic CRC can be caused through DNA mismatch repair alteration following inactivation of genetic alteration in short repeated sequence known as microsatellite instability arising a hallmark condition names Lynch syndrome.

Nitric oxide with its bidirectional effect may play both a causative and therapeutic role in concentration dependent manner via affecting different signaling pathways [5].cGMP signalling,PI2 kinase-akt signaling are mostly involved pathways in NO induced sequelae of CRC.[3-6]

The Role of Diet: Adherence to diet excess in protein and fat possibly promote inflammation hence may initiate neoplastic events. In the colonic cellular environment, a diet high in plant polysaccharides [7] such as fiber and low in fat, as opposed to a diet high in fat and processed meat, is associated with a low Ki-67 index; reported by Rothschild et al. Diet, rather than genetics, appears to play an essential role in gut microbiome heterogeneity. In terms of gut health maintenance, complex carbohydrates producing short-chain fatty acids (SCFAs), low protein fraction of dietary intake, bile acids play a crucial role [8]. Protein fermentation and bile acid deconjugation are digestive events promoted by the western diet rich in meat [9]; enhance the risk of CRC via their pro-neoplastic and pro-inflammatory effects [10]. De Filippo et al. and Ou et al. had different studies, but an identical observation on Native African is having a low risk of colon cancer attributed to the diet and microbiome delivering plenty SCFAs, especially butyrate.

Additionally, some studies emphasize that colonic butyrate deficiency reinforces the neoplastic capability of secondary bile acid. Obesity is another contributory factor responsible for 5% of cases of CRC in the US [11]. Decreased ratio of Bacteroidetes: Firmicutes have been observed in overweight and obese people. Additionally, increased LPS level and excessive DNA damaging bile acids are the possible linked mechanism of microbiota-related CRC in an obese individual [12].

Carbohydrates: Carbohydrates are a significant portion of our daily dietary habits and proving their role on CRC is still a fact to evaluate. Several epidemiological studies and clinical trials were conducted to establish the interlink between carb-based diet and CRC, describing the simple carbohydrates can enhance cancer risk due to activation of insulin IGF-1 axis. Complex carbohydrates play the opposite role on this axis. Eventually, IGF-1 promotes cell growth, proliferation [1].

Resistant starch, an ingredient extensively found in carbohydrates starch, increases butyrate concentration, fecal pH. A randomized control

trial was conducted, and the protective role of resistant starch has been observed, given that consumption for a long time is required [2].

In 2020, Yu Lei et al. concluded that inhibiting lipogenic pathways via ChREBP (Carbohydrate response element binding protein) impairs epithelial-mesenchymal transformation which results in impaired migration and invasion of colon cancer cells. ChREBP are glucose-mediated transcription factors that regulate glycolytic and lipogenic pathways and their expression is strongly associated with cell proliferation and several malignancies including colon cancer. This study showed future promise that adhering to low carbohydrate diet will regulate glucose induced ChREBP activation as well as inhibition of ChREBP as a potential therapeutic significance in preventing colon cancer metastasis. [13].

Protein: Processed meat carries a similar risk as cigarettes, alcohol in carcinogenic potential categorized in the same group 1 carcinogen and red meat as group 2A by World Health Organization's International Agency for Research on Cancer. Meat, when it is processed, smoked, or cured, delivers N-nitroso Compounds (NOCs) that eventually transformed to diazomethane through a process catalyzed by activated p450 isoenzymes resulting in the formation of DNA adducts which, if not repaired, can cause transition mutation (G:C to A: T). This type of genetic change is commonly identified in the K-ras gene involved in one of the CRC causal pathways mentioned earlier [9].

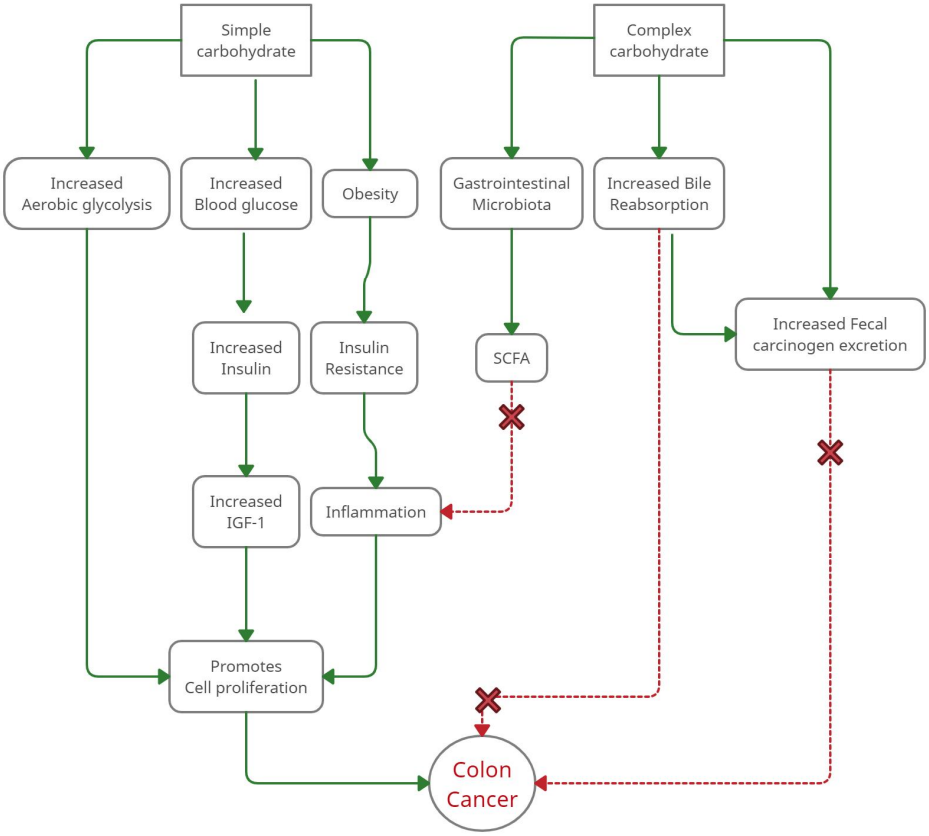

Fig. 1. Figure shows effects of carbohydrate on the development of colon cancer. Simple carbohydrates increase aerobic glycolysis, blood glucose and insulin resistance, thus promoting cell proliferation and the risk of colon cancer. On the other hand, complex carbohydrates increase fecal carcinogen excretion, bile reabsorption and decreases the risk of colon cancer. SCFA also plays a role in inhibiting inflammation

Though a healthy person has a colon with a low bacterial count producing NOCs, a diet increased in nitrates and nitrite promotes their accumulation, thus increasing CRC risk. Heterocyclic amines (HCA) generally made after cooking meat at open high flame are classified in group 2B and 2A carcinogen, but HCAs way of contribution to CRC pathogenesis is still an area of further scientific studies [3].

Via N-nitrosation (a reaction that produces NOC from amino acid decarboxylation) and lipid peroxidation, heme iron of red meat increases CRC risk. The latter is a prominent pathway that links fresh red meat and CRC promotion [4].

Heme iron of red meat oxidizes polyunsaturated fatty acid, producing aldehyde as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE).BY binding with DNA, MDA forms mutagenic adducts.4-HNE kills normal cells, but preneoplastic cells carrying mutated APC genes hold out against this apoptosis induction. In essence,pro-neoplastic factors derived from red meat can be categorized as excessive iron, protein, fat, or heat-induced mutagen. Genetic polymorphism, another factor considered to tie up with CRC risk, needs more studies to get a convincing picture for establishing the relationship.[10]

It should be a great topic of discussion on how we can make meat safer to eat. Avoiding red meat and processed meat should be the first option. As heme iron is a significant role player in toxic pathways so quelling, its toxicity could be another option. Studies on rats speculated that calcium carbonate and calcium phosphate could block the CRC promotion by beef meat since they trap heme iron in the colon (Sesink et al. 2001. van der Veere et al. 1995, Pierre et al. 2003,2008). However, Calcium decreases iron absorption resulting in iron deficiency, especially in menstruating and pregnant women [14]. Adding dairy products to the diet plan has also been suggested. Despite using calcium compounds, blocking fat peroxidation or the N-nitroso pathway with antioxidants might be an option. Santarelli et al. performed a study on rats supporting the fact that removing oxygen and nitrites from the meat can inhibit carcinogenesis. These two processes will prevent peroxidation and nitrosation from occurring, respectively. According to mice studies, additives like alpha-tocopherol (Vit E) can reverse the neoplastic changes in the colon, evidenced by decreased lipid peroxidation products [15].

Indeed, the event of DNA adducts formation accelerates the malignant transformation in the colon.

Fiber: Nonetheless, based on the inconsistency of dietary fiber effect on CRC prevention, the prediction has been made about the beneficial role of dietary fiber against colorectal cancer. Supposedly variation of gut microbiota is the cause of this inconsistent result. Fiber intake significantly alters the colonic environment and microbiota composition in a varied way by producing fermentation products including butyrate, acetate, and propionate. These short-chain fatty acids (SCFAs) play a role in CRC prevention via 1. inhibition of histone deacetylase,2. modulation of regulatory T cells, and 3.Interaction with G protein-coupled receptors. More concretely, all these processes are resulting in decreased inflammation, increased immune homeostasis [16]. Another meta-analysis and systematic review found strong evidence that both proximal and distal colon cancers can be significantly reduced by the increased intake of dietary fibers [17]. Furthermore, changes in the composition of the gut microbiota via fiber supplementation and curbing fat intake has proven to be an effective strategy to reduce the colorectal carcinoma risk [18-20].

Fat: Animal studies have concluded that a high-fat diet (HFD) causing high bile acid disposal to the colon may potentiate inflammation attributing to low risk of CRC in native African who subsisted on a low-fat diet instead of African Americans eating a high-fat diet. Conversely, short-term exposure could have a beneficial effect of inducing apoptosis via ROS production. Decreased TP53 expression of PI3K/Akt signaling results from prolonged exposure to a high-fat diet. Obesity resulting from fatty food intake can also be a contributor by increasing circulation IGF-1 that enhances the rate of cellular proliferation [21].

However, human studies failed to establish fat as one of the leading promoters of CRC (16). Few other pathways involved in CRC promoted by HFD can be categorized as (1) JNK pathway (2) STRA6 pathway (3) MAPK/ERK signaling pathway. Increased STRA6 activation transduces the JAK2-STAT3 cascade, which is ultimately responsible for maintaining CRC stem cells. Standard ATR interacting protein relationship is deranged by lysine homocysteinylation, influenced by HFD. Thus, ATR loses its p53

activity due to the impairment of DNA damage and accelerated cell growth.HFD renders an additional role in CRC via decreasing bile acid reabsorption (Bile acid has toxic effects on colonic epithelium).DNA damage can be promoted by bile acid components like Tauro-Beta-muricholic acid, Deoxycholic acid, which has antagonistic property against the FXR receptor, eventually encouraging lgr5+ tumor stem cell proliferation. Park et al. found that HFD intake and the resultant obesity raise IL-2, MCP-1, IL-6, TNF-alpha in a microcellular environment which is how inflammation-related CRC in obesity occurs driven by PI3K/Akt pathway.

There is evidence of a higher risk of CRC in Western society, where people eat more red and processed meat, compared to those living around the Mediterranean coast, who have a lower overall cancer mortality rate that is linked to their eating habits, such as the Mediterranean diet (MedD). A MedD lifestyle contains specific foods and beverages that, when consumed together, provide nutritional synergy. Traditional MedD emphasizes the eating of fruits, vegetables, and fish, as well as a reduction in red meat consumption. Olive oil is the primary source of fat in theMedD and has a preventive effect in lowering CRC risk. Many preclinical and clinical research has looked into how the MedD dietary pattern may influence cancer development and progression. Plants produce secondary antioxidants such as polyphenols in olive oil, resveratrol in red wine, and lycopene in tomatoes. They showed many potentials to disrupt molecular cancer pathways in vitro. Although the mechanisms are unknown, several chemopreventive benefits have been linked to the components of olive oil in preclinical studies, primarily because they interfere with the initiation, development, and progression of cancerogenesis pathways.

Fruits, whole grains, vegetables, tea, coffee, wine, tea are rich in polyphenol, a compound not absorbed in the small intestine resulting in a high concentration of this in the colon [22]. Polyphenol equilibrates the gut microbiome, specifically lowers the growth of Clostridium and Bacteroides. Phytochemicals like polyphenol disinhibit apoptosis of cancer cells similarly to quercetin, a flavonol found in onions, apples.Several clinical studies exhibited that cocoplum(anthocyanin),blueberries ,red grapes,cocoa(tannins) advantageous role in CRC.Pathogenic species like F.nucleatum and P.gingivalis are inhibited when exposed to red wine polyphenol.

Brazil nuts, shellfish, turkey, chicken are rich in selenium. Large-scale studies have been done to determine the role of dietary selenium in CRC, strongly suggesting their protective role in chronic inflammatory colon cancer via upregulation of neoplastic cell apoptosis [22]. Selenium also increases mucin secretion by encouraging differentiation of epithelial cells to goblet cells. Mucin gives protection against Chronic inflammation-related colorectal carcinoma [23].Taking everything into account, it's a reality that a western diet high in processed meat, red meat, high fat, and low in fiber, whole grain, and vegetables have a detrimental impact on CRC; thus, following a diet high in fiber and low in processed protein sources is recommended to prevent CRC.

2. ROLE OF GUT MICROBIOTA IN PATHOGENESIS

Gut microbiota can influence the development of colorectal cancer in several ways. Gut microbiota, host genetic makeup, chronic inflammation, and many other environmental factors lead to the development of colorectal cancer [24].

Microorganisms can cause chronic inflammation in various ways, including adhesion to the epithelium, activation of an immune response via Toll-like receptor binding and activation of regulatory T (Treg)cells, synthesis, and secretion of cytotoxic biomolecules or metabolites, and translocation into the body [1][25]. Microorganisms can cause chronic inflammation by producing TNF alpha, IL6, and IL1b, which activates NF-kappa B and contributes to colon cancer. For example, the expression of IL-8, C5a, TGF beta, Leukotriene 4(LTB4), and growth-related oncogene-alpha is facilitated by enterotoxins from bacterial cells [26]. Toxins from B.fragilis induce E-cadherin expression -catenin, NF-B, and STAT3, leading to cell proliferation in the large intestine. For example, fragilysin, a B.fragilis enterotoxin, increases the production of IL-8, TGF, C5a, leukotriene 4 (LTB4), and growth-related oncogene-α (GRO-α), resulting in an inflammatory environment. The proliferation of colonic epithelial cells and expression of the oncogene c-myc are both induced by fragilysin. It has been demonstrated that patients with CRC who also have IBD have a worse prognosis than those that don't have IBD. The presence of

active IBD correlates with the presence of enterotoxigenic Bacteroides fragilis (ETBF) [27]

Fusobacterium also plays a role in abnormal cell growth via E-cadherin/Beta-catenin pathway. Fusobacterium adhesin A (FadA) is a cell surface virulence factor that increases Fusobacterium adherence to an invasion of E-cadherin-expressing cells. As a result, the proliferation and development of epithelial cells are directly affected. [28][29].

Enterococcus faecalis, Proteus mirabilis, Candida parasitosis are few collagenase releasing microorganisms interlinked with CRC; when colonized, alteration of permeability and transmigration of cancer cells occurs [30]. The earlier fact was described by Gaines et al. along with the variety of HFD playing a contributory role in collagenase releasing microorganism colonization. Through imbalance in microbial composition in the colon, HFD accelerates the MCP-1/CCR2 axis (CCR2 is a receptor for cell factor MCP-1), causing more monocyte recruitment in the neoplastic area with local immune system alteration. *Lactobacillus acidophilus* has been studied after deleting its lipoteichoic acid showing anti-inflammatory properties favoring downregulation of CRC polyposis [31]. As a result, it can be concluded that organisms' cell surface properties can be utilized to prevent CRC. For example, bacterias favoring colon cancer prevalence are *Bacteroides fragilis*, *Fusobacterium nucleatum*, *Enterococcaceae*or *Campylobacter, Peptostreptococus, Enterococcus faecalis, Escherichia coli, Shigella*, and *Streptococcus gallolyticus* [32]. Food additives such as monosodium glutamate and titanium dioxide impact the composition of gut microbiomes; animal models exposed to additives have shown susceptibility to CRC. Several animal model studies have concluded that food emulsifiers (carboxymethylcellulose, polysorbate-80) can also be linked with the risk of developing CRC in humans [33].

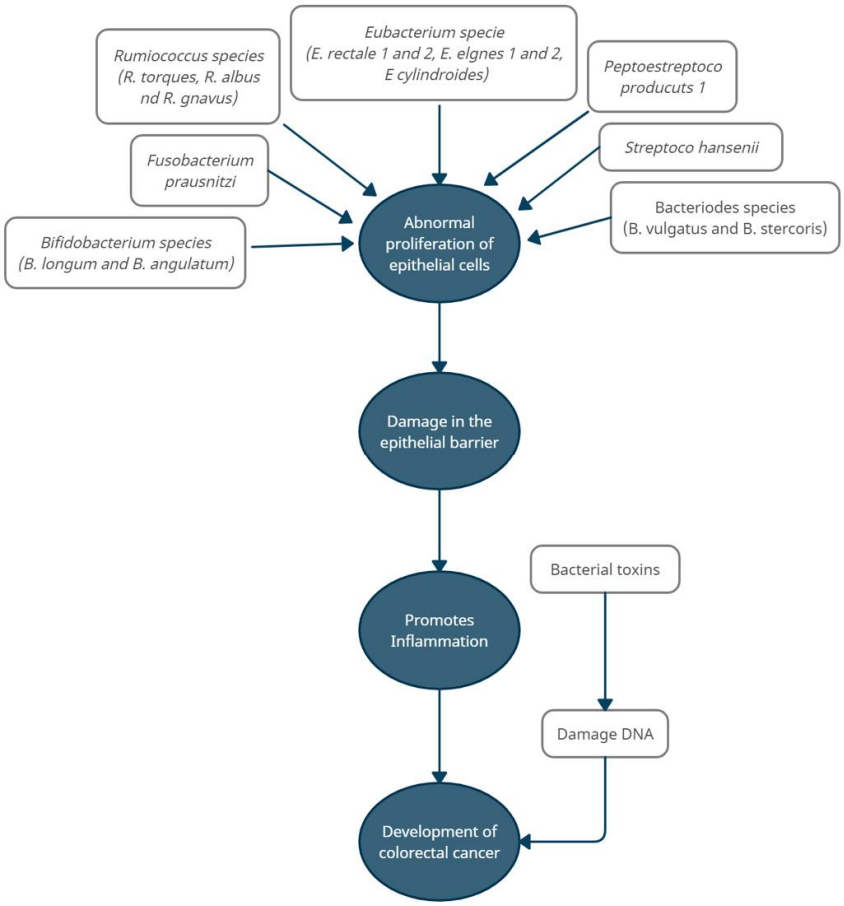

Fig. 2. Shows roles of gut microbiota in the development of colon cancer

Probiotic role in prevention: Probiotics are live microorganisms that can be introduced to the human colon for beneficial effects in CRC prevention. The role of probiotics has been widely studied for a long time. Tight junction maintains the integrity of the gut wall. Probiotic strains like *Lactobacillus rhamnosus*, *Lactobacillus Plantarum* and *Escherichia coli Nissle* control protein (claudin, ZO) expression in tight junction, attenuate inflammation, repair epithelial disruption; indeed a beneficial role in the prevention of CRC [32-34]. Cheese, yogurt, and dairy food are rich in lactobacillus [30]. Lactic acid bacteria neutralize the effect of mutagenic amines, destroy nitrosamines, and alleviates the function of Beta glucuronidases, nitroreductases, azo reductases [35,36]. Probiotics may also enhance the impact of immunotherapy against colon cancer, yet a matter to establish with enough evidence after performing more studies. Probiotics increase tight junction protein to improve the barrier function in the colon.

Few studies on mice concluded that American Ginseng decreases CRC, favoring Gram neg phyla as Bacteroides, in contrast, increases antitumorigenic Gram-positive species.Furthermore, mice models expressed the effect of cytokine level reduction resulting in attenuation of colon carcinogenesis. American ginseng metabolized into the compound as CK, Reg3 with the help of gut microbiota, finally inhibiting colon carcinogenesis [37].

Lactobacillus rhamnosus GG and Lactobacillus acidophilus, two common probiotic bacteria, may inhibit STAT3 and NF-kappaB signaling resulting in downregulation of Th17 cells expression, interleukin (IL23, IL17) secretion. In addition, these probiotics can cause macrophage phenotypic change from pro-inflammatory M1 to immunosuppressive M2 [38]

Bifidobacterium infantis and *Bifidobacterium breve* can induce immune sequelae as toll-like receptor interaction, retinoic acid metabolism, activation of intestinal dendritic cell, expression of Foxp3+ regulatory T cell(Treg) and type 1 regulatory T cells, IL10 release. In addition, their positive role on phagocytic and natural killer cell activity is associated with infectious microorganism eradication [39].

Alternate fasting can change the microbiota in the gut, causing a rise in acetate and lactate levels. In addition, as tumors use ketone bodies that cannot be used for generating energy, a Ketogenic diet may cease tumor expansion [40,41].

Table 1. Annual incidence rate and death due to colon cancer in the last decade in the United States

Year	Annual number of new cases	Annual number of deaths
2009	143814	51848
2010	140159	52045
2011	139947	51783
2012	139042	51516
2013	140067	51813
2014	142905	51651
2015	143903	52396
2016	144590	52286
2017	143530	52547
2018	141074	52163

Source: Center for Disease Control (CDC)

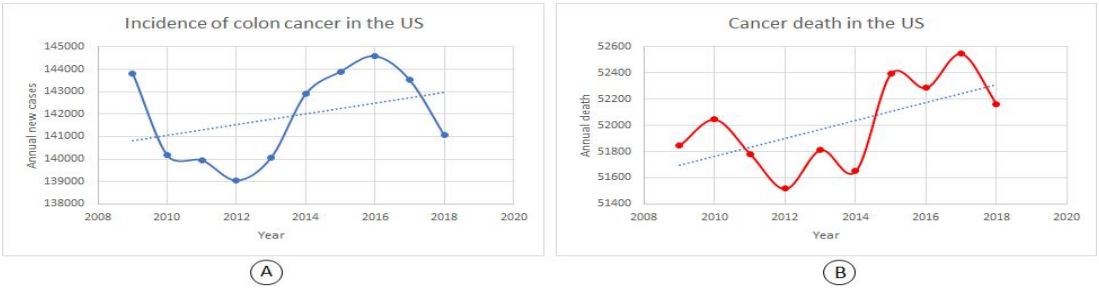

Fig. 3. Shows (A) incidence and (B) cancer death of colorectal cancer in the US, during the past decade

3. CONCLUSION

Gut health has long been an overlooked aspect of self-care, given its significance in CRC prevention studies. The gut microenvironment is influenced significantly by dietary habits. Food can affect a variety of the colonic microbiota, preventing colonic neoplasia from developing. Because red meat, mainly processed meat, has been linked to carcinogenesis, modifying the processing method, utilizing colon-friendly additives, and lowering hazardous dietary ingredients are just a few of the available preventive measures. Food carcinogens, physical inactivity, smoking, and gut microbiomes have all been linked to CRC onset. According to some theories, harmful dietary components and genetic regulation in oncogenes and tumor suppressor genes cause progressive disruptions in the gut microbiota.[20][42]

Adherence to a high-protein, high-fat diet may induce inflammation and so trigger neoplastic events. A diet high in nitrates and nitrites promotes their buildup, increasing the risk of CRC.

How we can make meat safer to eat should be a significant topic of discussion. The first step should be to decrease the consumption of red and processed meat. Colorectal cancer development can be influenced by gut bacteria in various ways, as discussed in the review. Probiotics have been widely studied for a long time and showed great benefit in preventing CRC. Although there have been many studies on CRC prevention, this review aims to raise awareness and bring more focus to modifying dietary habits and taking simple measures to prevent CRC.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. O'Keefe S. Diet, microorganisms and their metabolites, and colon cancer. Nature Reviews Gastroenterology & Hepatology. 2016;13(12):691-706.
DOI: 10.1038/nrgastro.2016.165
2. Loke Y, Chew M, Ngeow Y, Lim W, Peh S. Colon Carcinogenesis: The Interplay Between Diet and Gut Microbiota. Frontiers in Cellular and Infection Microbiology. 2020;10.
Available:https://doi.org/10.3389/fcimb.2020.603086
3. Wang H, Wang L, Xie Z, Zhou S, Li Y, Zhou Y, Sun M. Nitric Oxide (NO) and NO Synthases (NOS)-Based Targeted Therapy for Colon Cancer. Cancers. 2020;12(7):1881.
Available:https://doi.org/10.3390/cancers12071881
4. Vahora H, Khan M, Alalami U, Hussain A. The Potential Role of Nitric Oxide in Halting Cancer Progression Through Chemoprevention. Journal of Cancer Prevention. 2016;21(1):1-12. Available: https://doi.org/10.15430/jcp.2016.21.1.1
5. Saxena A, Fayad R, Kaur K, Truman S, Greer J, Carson J, Chanda A. Dietary selenium protects adiponectin knockout mice against chronic inflammation induced colon cancer. Cancer Biology & Therapy. 2017;18(4):257-267.
Available:https://doi.org/10.1080/15384047.2016.1276130
6. Thomas D, Ridnour L, Espey M, Donzelli S, Ambs S, Hussain S, et al. Superoxide Fluxes Limit Nitric Oxide-induced Signaling. Journal of Biological Chemistry. 2006;281(36):25984-25993.
Available:https://doi.org/10.1074/jbc.m602242200
7. Wang Q, Wang P, Xiao Z. Resistant starch prevents tumorigenesis of dimethylhydrazine-induced colon tumors via regulation of an ER stress-mediated mitochondrial apoptosis pathway. International Journal of Molecular Medicine; 2018.
Available:https://doi.org/10.3892/ijmm.2018.3423
8. Zeng H, Umar S, Rust B, Lazarova D, Bordonaro M. Secondary Bile Acids and Short Chain Fatty Acids in the Colon: A Focus on Colonic Microbiome, Cell Proliferation, Inflammation, and Cancer. International Journal of Molecular Sciences. 2019;20(5);1214.
Available:https://doi.org/10.3390/ijms20051214

9. Baena R, Salinas P. Diet and colorectal cancer. Maturitas. 2015;80(3):258-264. Available:https://doi.org/10.1016/j.maturitas.2014.12.017
10. Turner N, Lloyd S. Association between red meat consumption and colon cancer: A systematic review of experimental results. Experimental Biology and Medicine. 2017;242(8):813-839. Available:https://doi.org/10.1177/1535370217693117
11. Roslan N, Makpol S, Mohd Yusof Y. A Review on Dietary Intervention in Obesity Associated Colon Cancer. Asian Pacific Journal of Cancer Prevention. 2019;20(5):1309-1319. Available:https://doi.org/10.31557/apjcp.2019.20.5.1309
12. Tong Y, Gao H, Qi Q, Liu X, Li J, Gao J. et al. High fat diet, gut microbiome and gastrointestinal cancer. Theranostics. 2021;11(12):5889-5910. Available:https://doi.org/10.7150/thno.56157
13. Lei Y, Zhou S, Hu Q, Chen X, Gu J. Carbohydrate response element binding protein (ChREBP) correlates with colon cancer progression and contributes to cell proliferation. Scientific reports. 2020;10(1):4233. Available:https://doi.org/10.1038/s41598-020-60903-9
14. Ekine-Afolabi B, Njan A, Rotimi SRIA, Elbehi A, Cash E, Adeyeye A. The Impact of Diet on the Involvement of Non-Coding RNAs, Extracellular Vesicles, and Gut Microbiome-Virome in Colorectal Cancer Initiation and Progression. Frontiers in Oncology. 2020;10. Available:https://doi.org/10.3389/fonc.2020.583372
15. Kim S, Abernathy B, Trudo S, Gallaher D. Colon Cancer Risk of a Westernized Diet Is Reduced in Mice by Feeding Cruciferous or Apiaceous Vegetables at a Lower Dose of Carcinogen but Not a Higher Dose. Journal of Cancer Prevention. 2020;25(4):223-233. Available:https://doi.org/10.15430/jcp.2020.25.4.223
16. Farinetti A, Zurlo V, Manenti A, Coppi F, Mattioli A. Mediterranean diet and colorectal cancer: A systematic review. Nutrition. 2017;43-44:83-88. Available:https://doi.org/10.1016/j.nut.2017.06.008
17. Yu Ma, Mingyue Hu, Lingna Zhou, Sunkai Ling, Yuan Li, Bo Kong, Peilin Huang. Dietary fiber intake and risks of proximal and distal colon cancers: A meta-analysis Medicine (Baltimore). 2018;97(36):e11678. Published online 2018 Sep 7. DOI: 10.1097/MD.0000000000011678
18. Soeren Ocvirk, Annette S. Wilson, Corynn N, Appolonia, Timothy K, Thomas & Stephen JD. O'Keefe. Fiber, Fat, and Colorectal Cancer: New Insight into Modifiable Dietary Risk Factors; Springer Current Gastroenterology Reports. 2019;21(11):62 Available: https://doi.org/10.1007/s11894-019-0725-2
19. Gaines S, Van Praagh J, Williamson A, Jacobson R, Hyoju S, Zaborin A. et al. Western Diet Promotes Intestinal Colonization by Collagenolytic Microbes and Promotes Tumor Formation After Colorectal Surgery. Gastroenterology. 2020;158(4):958-970.e2. Available:https://doi.org/10.1053/j.gastro.2019.10.020
20. Corpet D. Red meat and colon cancer: Should we become vegetarians, or can we make meat safer?. Meat Science. 2011;89(3):310-316. Available:https://doi.org/10.1016/j.meatsci.2011.04.009
21. Garcia-Villatoro E, DeLuca J, Callaway E, Allred K, Davidson L, Hensel M. et al. Effects of high-fat diet and intestinal aryl hydrocarbon receptor deletion on colon carcinogenesis. *American* Journal of Physiology-Gastrointestinal and Liver Physiology. 2020;318(3):G451-G463. Available:https://doi.org/10.1152/ajpgi.00268.2019
22. Benninghoff A, Hintze K, Monsanto S, Rodriguez D, Hunter A, Phatak S. et al. Consumption of the Total Western Diet Promotes Colitis and Inflammation-Associated Colorectal Cancer in Mice. Nutrients. 2020;12(2):544. Available:https://doi.org/10.3390/nu12020544
23. Seidel D, Azcárate-Peril M, Chapkin R, Turner N. Shaping functional gut microbiota using dietary bioactives to reduce colon cancer risk. Seminars in Cancer Biology. 2017;46:191-204. Available:https://doi.org/10.1016/j.semcancer.2017.06.009

24. Fong W, Li Q, Yu J. Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. Oncogene. 2020;39(26):4925-4943. Available: https://doi.org/10.1038/s41388-020-1341-1
25. Zhu W, Miyata N, Winter M, Arenales A, Hughes E, Spiga L. et al. Editing of the gut microbiota reduces carcinogenesis in mouse models of colitis-associated colorectal cancer. *Journal Of* Experimental Medicine. 2019;216(10):2378-2393. Available:https://doi.org/10.1084/jem.20181939
26. Thomas D, Espey M, Ridnour L, Hofseth L, Mancardi D, Harris C, Wink D. Hypoxic inducible factor 1α, extracellular signal-regulated kinase, and p53 are regulated by distinct threshold concentrations of nitric oxide. Proceedings of the National Academy of Sciences. 2004;101(24):8894-8899. Available:https://doi.org/10.1073/pnas.0400453101
27. Fidelle M, Yonekura S, Picard M, Cogdill A, Hollebecque A, Roberti M, Zitvogel L. Resolving the Paradox of Colon Cancer Through the Integration of Genetics, Immunology, and the Microbiota. Frontiers in Immunology. 2020;11. Available:https://doi.org/10.3389/fimmu.2020.600886
28. Karunanithi S, Levi L, DeVecchio J, Karagkounis G, Reizes O, Lathia J. et al. RBP4-STRA6 Pathway Drives Cancer Stem Cell Maintenance and Mediates High-Fat Diet-Induced Colon Carcinogenesis. Stem Cell Reports. 2017;9(2):438-450. Available:https://doi.org/10.1016/j.stemcr.2017.06.002
29. Park J, Lee W, Seo H, Oh J, Lee D, Kim S, Hahm K. Fecal microbiota changes with fermented kimchi intake regulated either formation or advancement of colon adenoma. Journal of Clinical Biochemistry and Nutrition. 2021;68(2):139-148. Available: https://doi.org/10.3164/jcbn.20-121
30. Zhong M, Xiong Y, Ye Z, Zhao J, Zhong L, Liu Y, et al. (2020). Microbial Community Profiling Distinguishes Left-Sided and Right-Sided Colon Cancer. Frontiers in Cellular and Infection Microbiology. 2020;10. Available:https://doi.org/10.3389/fcimb.2020.498502
31. Song M, Chan A, Sun J. Influence of the Gut Microbiome, Diet, and Environment on Risk of Colorectal Cancer. Gastroenterology. 2020;158(2):322-340. Available:https://doi.org/10.1053/j.gastro.2019.06.048
32. Sánchez-Alcoholado L, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina J, et al. The Role of the Gut Microbiome in Colorectal Cancer Development and Therapy Response. Cancers. 2020;12(6):1406. Available:https://doi.org/10.3390/cancers12061406
33. Perillo F, Amoroso C, Strati F, Giuffrè M, Díaz-Basabe A, Lattanzi G, Facciotti F. Gut Microbiota Manipulation as a Tool for Colorectal Cancer Management: Recent Advances in Its Use for Therapeutic Purposes. International Journal of Molecular Sciences. 2020;21(15):5389. Available:https://doi.org/10.3390/ijms21155389.
34. Pop O, Vodnar D, Diaconeasa Z, Istrati M, Bințințan A, Bințințan V, et al. An Overview of Gut Microbiota and Colon Diseases with a Focus on Adenomatous Colon Polyps. International Journal of Molecular Sciences. 2020;21(19):7359. Available:https://doi.org/10.3390/ijms21197359
35. Sánchez-Alcoholado L, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina J, et al. The Role of the Gut Microbiome in Colorectal Cancer Development and Therapy Response. Cancers. 2020;12(6):1406. Available:https://doi.org/10.3390/cancers12061406
36. Mendes M, Paulino D, Brambilla S, Camargo J, Persinoti G, Carvalheira J. Microbiota modification by probiotic supplementation reduces colitis associated colon cancer in mice. World Journal of Gastroenterology. 2018;24(18):1995-2008. Available:https://doi.org/10.3748/wjg.v24.i18.1995
37. Meng C, Bai C, Brown T, Hood L, Tian Q. Human Gut Microbiota and Gastrointestinal Cancer. Genomics, Proteomics & Bioinformatics. 2018; 16(1):33-49. Available:https://doi.org/10.1016/j.gpb.2017.06.002
38. Rea D, Coppola G, Palma G, Barbieri A, Luciano A, Del Prete P. et al. Microbiota

effects on cancer: From risks to therapies. Oncotarget. 2018;9(25):17915-17927.
Available:https://doi.org/10.18632/oncotarget.24681

39. Song M, Chan A. Environmental Factors, Gut Microbiota, and Colorectal Cancer Prevention. Clinical Gastroenterology and Hepatology. 2019;17(2):275-289.
Available:https://doi.org/10.1016/j.cgh.2018.07.012

40. Ganesan K, Jayachandran M, Xu B. Diet-Derived Phytochemicals Targeting Colon Cancer Stem Cells and Microbiota in Colorectal Cancer. International Journal of Molecular Sciences. 2020;21(11):3976.
Available:https://doi.org/10.3390/ijms21113976

41. Grosso G, Bella F, Godos J, Sciacca S. Del Rio D, Ray S. et al. Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. Nutrition Reviews. 2017;75(6):405-419.
Available:https://doi.org/10.1093/nutrit/nux012

42. Huang J, Pan G, Jiang H, Li W, Dong J, Zhang H. et al. A meta-analysis between dietary carbohydrate intake and colorectal cancer risk: evidence from 17 observational studies. Bioscience Reports. 2017;37(2).
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