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Beyond screening; emerging strategies for primary prevention of colorectal cancer

Sina Salem Ahim[1], Mandana Jahandide[2], Seyyed Mohammad Hossein Mousavi Beyuki[3], Zahed Karimi[4], Alireza Golizadeh[5], Mahsa Ebrahimi[6], Sara Teihou Jorshari[7], Anna Ghorbani Doshantapeh[8], Naeem Nikpour[9*]

[1]General Medicine, Fasa University of Medical Sciences, Fasa, Iran
[2]Department of General Surgery, Imam Ali Hospital, Iranshahr University of Medical Sciences, Chabahar, Iran
[3]Department of General Surgery, Surgical Oncology Fellowship, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[4]Department of Internal Medicine, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[5]Department of Nursing, Faculty of Nursing and Midwifery, Alborz University of Medical Sciences and Health Services, Karaj, Iran
[6]Department of Clinical Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7]Hematology-Oncology Department, Iran University of Medical Sciences, Tehran, Iran
[8]Department of Hematology-Medical Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[9]Department of Hematology and Medical Oncology, Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran

Correspondence to:
Naeem Nikpour,
Email:
Dr.nikpour1360@gmail.com

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Abstract

Emerging strategies for colorectal cancer (CRC) primary prevention are rapidly evolving, emphasizing modifiable lifestyle factors, precise risk assessment, and targeted early interventions. A substantial body of evidence highlights the critical role of maintaining a healthy weight, regular physical activity, and dietary modifications, including limiting red and processed meats, along with avoiding tobacco and moderating alcohol consumption. Innovations in microbiome research are uncovering how gut dysbiosis influences carcinogenesis, paving the way for potential probiotic and prebiotic interventions to restore gut health. Advances in genetic and molecular profiling now facilitate personalized risk stratification, enabling tailored preventive approaches for high-risk populaces, like cases with hereditary syndromes or elevated polygenic risk scores. Chemoprevention, particularly with aspirin and other nonsteroidal anti-inflammatory drugs, shows promise for at-risk individuals, though careful consideration of benefits versus potential harms, such as gastrointestinal bleeding, is essential. Public health initiatives promoting fiber-rich diets, whole grains, and adequate calcium intake are gaining momentum as safe and scalable preventative measures. The integration of digital health tools and AI-driven models is further enhancing early identification of at-risk individuals and improving adherence to preventive behaviors. By deepening our understanding of CRC pathogenesis and combining these multifaceted strategies into routine clinical care and community health programs, there is a significant opportunity to substantially reduce the global burden of CRC. Continued research, robust policy support, and equitable access to preventive resources are crucial for achieving this transformative potential.

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Introduction

Colorectal cancer (CRC) is a significant global health concern, ranking as the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide (1). Colorectal cancer incidence and mortality rates exhibit significant global variations, with distinct gradients across different human development levels (2). Historically, Western countries, particularly North America, Australasia, and northern and western Europe, have reported the highest incidence rates (3). In contrast, countries with initially low-mortality rates have seen substantial increases, while those with moderately high rates have experienced slight increases or stabilization (4). The burden of CRC is shifting towards developing areas, with regions of middle human development index (HDI) experiencing increasing burdens, while high HDI regions show decreasing trends (5). Colorectal cancer is a type of gastrointestinal malignancy that originates from either the colon or rectum. It usually arises from glandular, epithelial cells of the large intestine, developing when a series of genetic or epigenetic mutations confer a selective advantage to certain mucosal cells. These hyper-proliferative cells initially form a benign adenoma, which can then evolve into carcinoma and metastasize over decades

Key point

Colorectal cancer (CRC) is a main global health burden, but it is largely preventable. New strategies emphasize primary prevention through modifiable lifestyle, dietary, and pharmacological interventions to reduce CRC incidence. Key preventive modalities comprise a high-fiber diet, regular exercise, weight management, and limited intake of red/processed meats and alcohol. The gut microbiome is also crucial, with research focusing on probiotics, prebiotics, and dietary patterns that promote a healthy microbial environment. Pharmacological options like long-term aspirin use show promise for high-risk individuals after careful risk-benefit assessment. Personalized prevention, guided by genetic and molecular profiling, allows for targeted interventions in those with hereditary syndromes or high polygenic risk.

(3). Most CRCs begin with non-cancerous proliferation of mucosal epithelial cells, known as polyps, which can take 10–20 years to become cancerous (3). Invasive cancer arising from these polyps is known as adenocarcinoma, accounting for 96% of all CRCs (3). The extent of invasion determines the staging and prognosis of a CRC diagnosis (6). Local cancers have grown into the wall of the colon or rectum but have not extended past it (7). Regional cancers involve nearby lymph nodes or tissues, while distant cancers have metastasized to remote organs such as the lungs or liver (8). Surgical removal remains the primary treatment for early-diagnosed cases but is less effective in advanced cases with metastasis, which occurs in about 25% of diagnoses (8). In addition, CRC incidence rates have been decreasing in older adults (over 50 years) since the early 1990s, likely due to increased screening and changes in risk factors (9). However, there has been a notable increase in early-onset CRC, defined as diagnosis before age 50 years (10). Sex disparities in CRC are consistently observed across epidemiological studies (11). Globally, males have a higher incidence and mortality rate than females (12). The male-to-female incidence ratio is approximately 1.3:1, with mortality rates also significantly higher in men (13). Biological factors likely contribute to this disparity; since, sex hormones may modulate CRC risk, with estrogen potentially exerting protective effects in premenopausal women (14). Additionally, differences in body fat distribution, insulin resistance, and immune responses between sexes may influence carcinogenesis (15). Behavioral factors also play a role, since men are more likely to engage in CRC risk-enhancing behaviors such as smoking, excessive alcohol consumption, and poor dietary habits, and are less likely to participate in screening programs (12). Geographic and socioeconomic factors further modulate the CRC patterns (16, 17). In high-income countries, CRC incidence has been declining in older adults, largely attributable to widespread screening (e.g., colonoscopy, fecal immunochemical testing) and improved public health modalities (18). However, these benefits are not equally distributed; racial and ethnic minorities, as well as socioeconomically disadvantaged groups, continue to experience higher CRC burden and later-stage diagnoses (16). In contrast, many low- and middle-income countries face dual challenges; limited access to screening and rising incidence due to urbanization and lifestyle changes (19). Moreover, the global burden of CRC is projected to increase by 60% to over 3 million new cases annually by 2040, driven largely by population growth and aging in regions with historically low incidence (20).

Method of the search

To identify relevant literature for this narrative review, we queried multiple databases including PubMed, Scopus, Embase, Web of Science, EBSCO, DOAJ, and Google Scholar, using related keywords such as 'colorectal neoplasms', 'preventive health services', 'dietary supplements' and 'lifestyle'.

Prevention modalities of CRC

Primary prevention strategies involve avoiding known risk factors and adopting a healthy lifestyle (20). These strategies include maintaining a healthy weight, exercising regularly, and consuming a balanced diet rich in fruits, vegetables, and whole grains while limiting red and processed meats (21). Modifiable lifestyle factors such as obesity, physical inactivity, and unhealthy diets are critically linked to the increasing incidence of CRC (22). Studies indicate that a significant number of CRC cases are preventable through regular screenings and healthy lifestyle choices (23). Half of all CRC cases may be prevented through simple lifestyle changes (24). The geographic distribution of CRC reveals higher rates in Western countries like North America, Australia, and Europe, while lower rates are observed in Africa and Asia (25, 26). However, rates are rising in countries that are adopting Western-style dietary habits, underscoring the impact of lifestyle on CRC incidence (1). Meanwhile, dietary interventions play a crucial role in primary prevention (27). A well-balanced diet that limits red and processed meats and emphasizes fruits, vegetables, and whole grains is recommended (28). High vegetable and fruit consumption has been associated with a decreased risk of CRC in numerous observational studies, and high fiber intake appears to have a similar effect (29). The concept of a high-fiber diet, particularly from fruits and vegetables, lowering CRC risk has been recognized for over four decades (30). Conversely, diets high in red meat are linked to a higher incidence of CRC (31). The World Cancer Research Fund (WCRF) suggests limited but suggestive evidence that animal fat consumption increases CRC risk (32). There is also data indicating a causal relationship between high intake of n-3 long-chain polyunsaturated fatty acids (LC-PUFA) and a reduced risk of CRC, implying that fish consumption may offer a protective effect (33). However, a systematic review of five studies did not demonstrate a clear benefit of increased dietary fiber intake in reducing the incidence or recurrence of adenomatous polyps

(34). Research on nutritional supplementation has been challenging, with some studies on folic acid and antioxidant vitamins yielding no significant evidence of benefit for CRC prevention (35). For example, pooled data from 60 epidemiological studies showed that higher consumption of milk and dairy products, and high calcium intake, reduced the risk of colon cancer, while calcium supplementation in two randomized controlled trials moderately prevented colorectal adenomas (36, 37). However, a high-quality meta-analysis found no benefit from antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, or selenium) in decreasing CRC risk (38); in fact, vitamin E was associated with an increased risk of colorectal adenomas (39). Beyond diet, physical activity and maintaining a healthy weight are essential components of primary prevention. Regular moderate to intense exercise may help reduce the development of precancerous polyps (40). Overweight and obesity are strongly linked to an increased risk of CRC and colon adenomas, with obesity approximately doubling the relative risk of adenomas (41). Abdominal obesity is considered a stronger risk factor than truncal obesity or body mass index (BMI) (42). A physically active lifestyle contributes to preventing CRC (40).

Behavioral modifications also extend to avoiding smoking and limiting alcohol consumption (43). Smoking is a significant predictor of CRC, with a history of over 20 pack-years increasing the risk for colorectal adenomas and CRC and accounting for 12% of CRC deaths (34). Limiting alcohol intake, or abstaining entirely, can reduce risk, with recommendations of no more than one drink per day for women and two for men if alcohol is consumed (44).

Focus on modulation of gut microbiome

One of the most compelling areas of emerging primary prevention lies in the modulation of the gut microbiome (45). The human gut harbors trillions of microorganisms that collectively influence host metabolism, immune function, and epithelial integrity (46). Accumulating evidence suggests that dysbiosis, as an imbalance in the composition and function of the gut microbiota, is a key driver of colorectal carcinogenesis (47). Specific bacterial species, such as *Fusobacterium nucleatum, Escherichia coli* strains have been consistently associated with CRC in both human and animal models (48). These microbes can promote tumorigenesis through multiple mechanisms; inducing DNA damage, activating pro-inflammatory signaling pathways, disrupting epithelial barrier function, and modulating host immune responses toward a tumor-permissive state (48). Consequently, strategies aimed at reshaping the gut microbiome represent a promising avenue for primary prevention (45). Probiotics, prebiotics, synbiotics, and dietary interventions that foster a beneficial microbial ecosystem are under active investigation (49). For instance, diets rich in fiber promote the production of short-chain fatty acids (SCFAs) like butyrate by commensal bacteria such as *Faecalibacterium prausnitzii* and *Roseburia* spp (50). Butyrate serves as the primary energy source for colonic epithelial cells and exerts anti-inflammatory, anti-proliferative, and pro-apoptotic effects, thereby maintaining colonic homeostasis (51). Clinical trials are exploring whether targeted prebiotic supplementation or high-fiber dietary patterns can reduce biomarkers of CRC risk, such as mucosal proliferation or inflammatory cytokines (52). Fecal microbiota transplantation, though primarily used for recurrent *Clostridioides difficile* infection, is also being evaluated for its potential to restore a protective microbiome in high-risk individuals, such as those with inflammatory bowel disease or hereditary CRC syndromes (53). While still in early stages, microbiome-based prevention holds the promise of personalized interventions tailored to an individual's microbial profile (54). Closely intertwined with microbiome modulation is the role of diet as a modifiable risk factor. While the association between diet and CRC has long been recognized, red and processed meats increase risk, whereas fruits, vegetables, and whole grains are protective; since the mechanisms are increasingly understood at the molecular level (55). Beyond fiber, dietary components such as polyphenols, omega-3 fatty acids, and cruciferous vegetables exhibit chemopreventive properties (56-58). Sulforaphane, for example, activates the Nrf2 antioxidant pathway and inhibits histone deacetylases, leading to enhanced detoxification and suppression of tumor-promoting genes (59). Similarly, curcumin, the active compound in turmeric, modulates multiple signaling pathways involved in inflammation and cell survival, including Wnt/β-catenin, which is aberrantly activated in the majority of sporadic CRC cases (60). Recent studies also emphasize on importance of dietary patterns rather than isolated nutrients (61). The Mediterranean diet, characterized by high intake of plant-based foods, olive oil, and fish, and low consumption of red meat and processed foods, has been consistently linked to reduced CRC risk in epidemiological studies (62). Ongoing randomized controlled trials are testing whether adherence to such dietary patterns can alter molecular endpoints in the colonic mucosa, such as DNA methylation profiles or expression of oncogenes and tumor suppressors (63). Importantly, dietary interventions may exert their effects not only directly on epithelial cells but also indirectly through modulation of the gut microbiome and systemic metabolism, underscoring the integrative nature of nutritional prevention (64).

Chemoprevention strategies

Chemoprevention represents another promising area in primary prevention, utilizing medications to reduce the risk of cancer (65). Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have shown promise in reducing the incidence of colorectal adenomas and CRC (66). Aspirin can decrease the development of polyps,

particularly in individuals with a history of polyps or CRC; though aspirin can reduce CRC incidence, these medications can be associated with risk gastrointestinal bleeding, necessitating a careful evaluation of risks and benefits (67). Likewise, NSAIDs, including selective cyclooxygenase-2 inhibitors, have a chemopreventive effect on CRC by reducing prostaglandin production through COX-2 activity inhibition (68). Besides, COXIBs have been shown to cause polyp regression in patients with familial adenomatous polyposis (69). However, long-term efficacy data for NSAIDs are currently lacking, and potential severe adverse events must be considered (70). The use of NSAIDs in familial adenomatous polyposis patients does not replace prophylactic colorectal surgery (66). Other chemopreventive agents include aminosalicylic acid (ASA) and ursodeoxycholic acid (71). Observational studies have linked ASA to significant reductions in colorectal adenoma recurrence, CRC incidence, and mortality (34). Pooled results from observational studies support a protective association between 5-aminosalicylate (5-ASA) and CRC or a combined endpoint of CRC/dysplasia in patients with ulcerative colitis (72). Recently, ursodeoxycholic acid has been investigated for CRC prevention, significantly lowering the odds of advanced lesions in men with colorectal adenomas and reducing the risk of colorectal dysplasia or CRC in patients with primary sclerosing cholangitis and ulcerative colitis (34). Statins have also been explored, with a population-based case-control study finding that CRC was 30% less likely to occur in patients who took statins for at least five years, although randomized controlled trial data are needed (73). Hormone therapy has shown a 20-30% reduction in colon cancer incidence in women who used it, but those who developed cancer were diagnosed at a more advanced stage (34). Metformin has also been suggested as beneficial in the primary prevention of CRC, particularly in patients with diabetes, though more research in diverse populations is needed (74). Likewise, detecting genetic predisposition and family history is crucial for personalized primary prevention strategies. Inherited susceptibility plays a significant role in CRC pathogenesis, making it essential to obtain a careful family history (75). For individuals with a family history of CRC, specific screening recommendations exist, such as colonoscopy every 5 years starting at age 40, or 10 years younger than the youngest affected relative, if certain criteria are met (76). Genetic counseling and molecular genetic testing are advised for individuals whose phenotype or inheritance pattern indicates an inherited CRC syndrome (77). Screening strategies based on family history are estimated to prevent up to 15-20% of all CRC cases (34). Inflammatory bowel disease, particularly longstanding extensive ulcerative colitis, is also associated with an increased risk of CRC (78). Regular surveillance colonoscopy is proposed for these patients, and pharmacological intervention with 5-ASA has been shown to reduce the risk of CRC and dysplasia by up to 50% (79). Developing strategies are also exploring new modalities for primary prevention and early detection. Probiotics may become an indispensable part of CRC prevention and treatment in the future due to their anti-inflammatory, immune-enhancing, and tumor-suppressing effects (80). They may offer safe and effective prevention strategies, reduce complications from surgery and chemotherapy, and improve chemotherapy effectiveness (80). Blood-based tests, or liquid biopsies, are emerging as promising tools for early CRC detection, leveraging advancements beyond traditional screening modalities (81). These innovations aim to improve screening efficiency and reduce mortality rates by identifying those at high risk and optimizing the selection of individuals who would benefit most from preventive strategies (81). The future of CRC prevention is moving towards personalized management based on individual risk estimates that integrate environmental factors, lifestyle, family history, and various biomarkers, including genetic factors (82).

The concept of immunoprevention

Immunoprevention regarded, as the use of immune-based strategies to prevent cancer is another frontier in CRC primary prevention (83). Unlike therapeutic cancer vaccines, which aim to treat established disease, preventive vaccines target antigens expressed in premalignant lesions or by oncogenic pathogens (84). As mentioned, frameshift peptide vaccines are in development for Lynch syndrome (85). Additionally, given the association between certain gut bacteria and CRC, vaccines against oncogenic strains are being explored in animal models (86). Passive immunization with monoclonal antibodies against pro-tumorigenic cytokines is another possibility, though cost, since its safety considerations are significant (87, 88). More broadly, enhancing immune surveillance through lifestyle interventions such as exercise, which increases natural killer cell activity and reduces systemic inflammation may contribute to primary prevention (40). Regular physical activity is consistently associated with a 20–25% lower risk of CRC, independent of body weight, and is recommended by all major cancer prevention guidelines (89).

Conclusion

Emerging strategies for the primary prevention of CRC are increasingly focused on modifiable lifestyle factors, precision risk assessment, and early pharmacological or dietary interventions. Growing evidence underscores the importance of maintaining a healthy weight, engaging in regular physical activity, limiting red and processed meat consumption, avoiding tobacco, and moderating alcohol intake. Innovations in microbiome research are revealing how gut dysbiosis may contribute to carcinogenesis, opening avenues for probiotic or prebiotic interventions. Additionally, advances in genetic and molecular profiling now allow for more personalized risk stratification,

enabling targeted prevention in high-risk populations—such as those with hereditary syndromes or polygenic risk scores. Chemoprevention using aspirin and other nonsteroidal anti-inflammatory drugs shows promise, particularly in individuals with elevated risk, though benefits must be weighed against potential harms like gastrointestinal bleeding. Public health initiatives promoting fiber-rich diets, whole grains, and calcium intake are also gaining traction as safe, scalable approaches. Furthermore, digital health tools and AI-driven models are enhancing early identification of at-risk individuals and improving adherence to preventive behaviors. As our understanding of CRC pathogenesis deepens, integrating these multifaceted strategies into routine clinical care and community health programs offers a powerful opportunity to reduce the global burden of CRC before it begins. Continued research, policy support, and equitable access to preventive resources will be essential to realizing this potential.

Authors' contribution

Conceptualization: Seyyed Mohammad Hossein Mousavi Beyuki and Zahed Karimi.
Data curation: Sina Salem Ahim and Sara Teihou Jorshari.
Funding acquisition: Naeem Nikpour and Mahsa Ebrahimi.
Investigation: Naeem Nikpour and Mandana Jahandide.
Supervision: All authors.
Validation: Alireza Golizadeh and Mahsa Ebrahimi.
Visualization: Anna Ghorbani Doshantapeh and Sina Salem Ahim.
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Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

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