

# Quarterly Review

## A Holistic, Evidence-Based Approach to Preventing Colorectal Cancer with a Focus on Early Detection, Risk Factor Management, Diet, and Lifestyle Modification with an Emphasis on Oral Dysbiosis, Chemoprevention, and Immunoprevention

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### ABSTRACT

**Background:** Colorectal cancer is the third most commonly diagnosed and second most deadly cancer in 2020. Although the incidence of disease has decreased among older adults, recently there has been an alarming emergence of early-onset colorectal cancer among people <50 years of age. 9.4% of cancer-related deaths globally occurred due to colorectal cancer in 2022. The critical shift in health-care focus from treatment to disease prevention necessitates the development of a well-thought-out integrative prevention strategy that is both practical and evidence-based. The study's goal is to provide a holistic, wellness-oriented disease prevention strategy to reduce the incidence of both early-onset and late-onset colorectal cancer.

**Materials and Methods:** A systematic search from databases (PubMed, Wiley, Elsevier, and Google Scholar) for articles published in the past 7 years in peer-reviewed journals was conducted, aiming at articles regarding risk factors and modification, screening and early detection with biomarkers, diet and lifestyle, traditional and modern chemo-preventive compounds, immunoprevention, and oral dysbiosis. All of the authors independently assessed the quality of the studies.

**Results:** 32 studies, including 13 systematic reviews, 3 cohorts, 3 randomized control trials, 1 case-control, 3 in vitro, 2 in vivo, and 7 reviews. Evidence synthesis is presented as an integrated preventive strategy for colorectal cancer, focusing on different aspects of prevention.

**Conclusion:** A holistic approach to CRC prevention should include improved screening, early detection, dietary and lifestyle changes, good communication to perceive risk, need-based nutrition supplementation, and stress management.

**KEYWORDS:** Colorectal cancer screening, Biomarkers for colorectal cancer, Diet and colorectal cancer, Physical activity and colorectal cancer, Risk factors, Oral dysbiosis, Chemoprevention, Immunoprevention.

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## Introduction

Colorectal cancer (CRC) is an uncontrollable growth occurring in the colon and rectum<sup>1</sup> that starts in the innermost mucosal layer, grows outward (polyp), and spreads through lymphatics. The polyps, which are sessile, serrated, traditional serrated polyps, polyps with a diameter greater than 1 cm and more than 3 in number, and polyps with a dysplastic nature have the highest risk for CRC. Adenocarcinoma, the most common type of CRC, arises from glandular epithelial cells. Other less common types are carcinoid tumors from hormone-making cells, gastro-intestinal stromal tumors from intestinal cells of Cajal, lymphomas from the immune cells of the digestive tract, and sarcomas that start in blood vessels and connective tissues of the walls of the colon and rectum<sup>2</sup>. Among CRCs, colon cancer is predominant (59.5% of new cases and 61.9% of deaths)<sup>3</sup>. Incident cases (45.94%) and deaths (49%) are more remarkable in areas with higher income levels<sup>4</sup>. Despite various methods of CRC prevention openly available in scientific literature and the availability of recommendations given by international organizations, the emerging incidence of early-onset CRC cases is posing a public health challenge, as the global incidence of CRC cases is predicted to reach 3.2 million in 2040<sup>5</sup>. This disparity results from various barriers to CRC prevention, among which the most important is a lack of awareness among the general population and a lack of perception towards the importance of prevention among health care providers. To address this gap, the present review focuses on creating awareness by providing a holistic insight into the prevention of CRC.

## Methodology

*Search Strategy:* We systematically searched PubMed, Web of Science, Elsevier, Wiley Online Library, and Google Scholar databases for articles using keywords and included studies following PRISMA guidelines (**Figure 1**).

*Study Selection:* Inclusion and exclusion criteria: Articles published in peer-reviewed journals in the past 7 years were included. Criteria for inclusion included (i) articles

that contained preventive methods for colorectal cancer; (ii) studies that were published in the past 7 years to include recent evidence; and (iii) articles that were available in full text. Criteria for exclusion included (i) studies conducted on cancers other than CRC. (ii) studies conducted on patients already diagnosed with cancer. (iii) studies available in languages other than English. Quality assessment: The quality of the studies was methodologically examined for adequate sample size, selection bias, and standardization of reporting guidelines. Bias was assessed for observational studies done using the New Castle Ottawa scale and for RCTs using the Jadard scoring system. Scores for relevant studies indicated low risk of bias (scores 6 to 8). The studies selected were reviewed by rest of the investigators for eligibility and quality assessment. The extraction of data pertaining to authors, study design, and outcomes was done and synthesized in the form of narrative synthesis, which was later clustered and presented in tabular forms. (**Table 1**). The extraction of findings from the studies was focused on (i) screening, (ii) early detection, (iii) dietary modification, (iv) lifestyle modification, (v) risk factor management, (v) chemoprevention, and (vi) immunoprevention.

## Results

(Figure 1)

### Identifying The Risk<sup>6,7</sup>

Some currently available risk prediction models include APCS (Asia Pacific Colorectal Cancer Screening score) questionnaires<sup>8</sup> and PRA (Polygenic Risk Assessment) genetic tests<sup>9</sup>. Risk prediction can increase screening uptake, encourage knowledge and lifestyle changes due to an increase in risk perception, and reduce the burden of screening. However, there are challenges such as population variability preventing the development of "one for all model," communication of risk output individually to large populations, and differences in location, socio-economic, cultural, and resource availability of the population. Addressing these challenges is crucial for effective cancer prevention and management.

## Early Detection by Biomarkers [Table 2-4]

Non-invasive biomarkers provide convenient screening, aid in increasing screening uptake, and reduce the probability of over screening by invasive methods like colonoscopy.

*Biomarkers for CRC*:<sup>14,15</sup>

## Oral Dysbiosis In CRC:<sup>16,17,18</sup>

Different studies identified various bacteria associated with CRC, including *Fusobacteria*, *Bacteroidetes*, *Prevotella*, *Veillonella*, and *Treponema denticola*, present in individuals with poor oral health. They may play a crucial role in the development, progression, and potential diagnosis of CRC. In PPI (Proton Pump Inhibitor) users,

patients with achlorhydria, IBD (Inflammatory Bowel Disease), and the gastric acidic barrier get weakened, leading to the survival of harmful oral-ingested bacteria. They colonize the intestinal tract and may contribute to tumorigenesis by (i) activating inflammatory and NF-κB cascade pathways and (ii) creating an immunosuppressive microenvironment. *Fusobacterium nucleatum* is most significantly associated with CRC. *Actinomyces odontolyticus* increased only at an early stage of CRC, while *Parvimonas micra*, *Peptostreptococcus stomatis*, *Solobacterium moorei*, *Gemella morbillorum*, and *Fusobacterium nucleatum* increased at both early and late stages [Table 4]. Some of the new diagnostic techniques for identifying oral dysbiosis include PCR, RT-PCR (Reverse Transcriptase-Polymerized Chain Reaction), metagenomics, gel-based electrophoresis, etc.

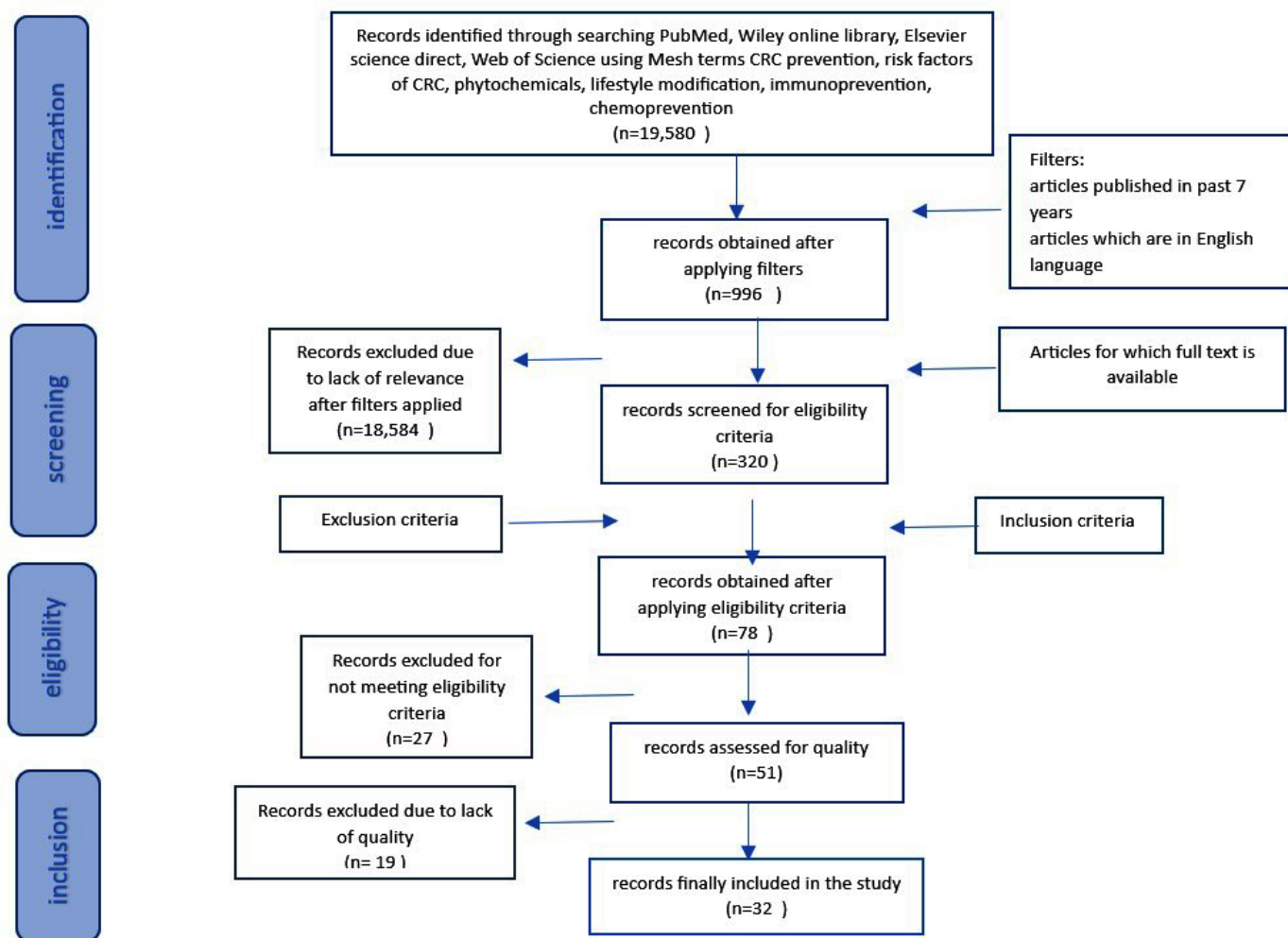


Figure 1: PRISMA flow chart for inclusion of articles in the review.

**Table 1: Studies included to synthesize evidence.**

Author, Year	Study Design	Outcome	Bias Assessment Status	Remarks
Juliet A et al. 2016	Systematic review of risk prediction models	Feasibility and impact of risk prediction models should be assessed by further studies	Publication bias exists	TRIPOD guidelines
Gene K. Ma et al. 2014	Systematic review of risk prediction models	Risk prediction models present have weak discriminatory power	-	PRISMA guidelines
Chenchen Zhang et al. 2023	Retrospective cohort: APCS scoring system prediction potential	Simple and useful in population of China	6	Selection bias present
Jungyoon Choi et al. 2021	Prospective cohort to study polygenic risk score	Individuals with high PGR scores benefit more from lifestyle modification	8	Recall bias eliminated
Hongda Chen et al. 2020	Multicentre RCT to evaluate different screening methods	Risk adapted screening showed high participation rate, superior diagnostic yield and low resource load.	6	
Donna Fitzpatrick-Lewis et al. 2016	Systematic review and meta-analysis of screening methods	FOBT and FS is effective for reducing CRC mortality and incidence of late-stage disease. Colonoscopy is more feasible for >60-year-old patients.	Cochrane risk of bias tool used	
Florine H. Zwezerijnen-Jiwa et al. 2023	Systematic review of microbiome derived biomarkers	Faecal and oral gut microbiome has the potential to complement existing screening tools but not yet ready for clinical use.	QUADAS-2 was used	
Jacqueline I. Keenan et al. 2022	Biomarkers to detect early-stage CRC	FIT in combination of biomarkers can help identify symptomatic patients to be directed for clinical investigation.	-	
Olivia Marx et al.	Molecular genetics of early-onset CRC	Inflammatory, molecular, DNA methylation biomarkers can have a role in early detection	-	
Haim Shirin et al. 2019	RCT to compare G-EYE colonoscopy with standard colonoscopy	Highly effective when compared to standard colonoscopy	7	Optics related bias eliminated
Lorne J. Hofseth et al. 2020	Current views on early-onset CRC	Risk factor management, gut microbial analysis are very important to control incidence of early-onset CRC.	-	
Ahmad Jayedi et al. 2018	Systematic review: DII and site-specific cancer	1-unit increment in the DII was associated with a 6% higher risk of CRC	Publication bias for some indications found	
Keneswary Ravichanthiran et al. 2018	Brown rice: phytochemical, antioxidant, nutrigenomic implications	Cancer preventive effects are seen with germinated brown rice	-	
Shiza Arshad et al 2022	Review of potential benefits of natural sweeteners like honey, jaggery, dates, sugar beet, sugarcane, sorghum, grape sugar.	Maintainning overall gut health, contain vitamins, minerals, phytochemicals, antioxidants.	-	
Laura Barrubés et al 2019	Systematic review & meta-analysis of association between dairy and CRC risk	Low fat milk: reduce risk of colon cancer; pure cheese help in prevention of proximal colon cancer	Confounding bias may be present	Validation of questionnaire done to reduce bias
Zhi Liang, Xiaobiao Song et al 2022	Systematic review & meta-analysis of fermented dairy & CRC	Fermented dairy(yogurt, buttermilk) is effective for early prevention of CRC; calcium from fermented dairy reduce incidence of colorectal adenomas	No publication bias	Funnel plot, Begg's rank correlation method used
Shiori Mori et al 2021	In vivo(mice model) study: anti tumoral activity of $\beta$ -Casomorphin-7 in CRC	Has anti-tumor effect and it can suppress the development and progression of colorectal cancer.	-	

Neetu kalra et al 2022	Gluten free diet in cancer, current updates	Strict GFD reduces the risk of developing colon cancer, oropharyngeal cancer and intestine adenocarcinoma in patients with celiac disease	-	
ZargarTasneef et al 2021	Hospital based case-control study: home-made ghee in CRC	Home-made ghee confers 85% protection against CRC	Confounding bias present	
Christos Markellos et al 2021	Systematic review & meta-analysis: olive oil in cancer	Risk of GI cancers is 23% lower for those who consumed the highest amounts of olive oil	Publication bias may be present	New-castle Ottawa scale was used
Alireza Emadi et al 2022	Systematic review: aflatoxin reduction in nuts	Can be reduced by roasting, irradiation & fumigation	Publication bias may exist	Funnel plot and egger's test
Marina Sartini et al 2019	Systematic review & meta-analysis: coffee consumption & CRC risk	Protective for US men & women, European men & Asian women only. Decaffeinated coffee-overall protective against CRC	No publication bias	Funnel plot was used
Ming zhi Zhu et al 2020	Systematic review & meta-analysis: tea consumption & CRC risk	Tea consumption has no significant effect. Green tea has marginal protective effect only.	Recall bias present	Funnel plot, Begg's rank correlation were used
Samhita De et al 2023	Critical evaluation of in-vivo studies about phytochemicals in prevention of CRC	Found to have protective effects through anti-oxidant, anti-inflammatory, neuroprotective and anticancer actions.	-	
Yi Yu, Xiaoli Jing et al 2016	Systematic review & meta-analysis: soy isoflavones in CRC	Significant protective effect on Asian population	Selection bias and recall bias present	Egger's & Begger's regression models were used.
Asif Khurshid Qazi et al 2018	Therapeutic potential of sour sop: in-vitro study	Anti-cancer effect on colon cancer cell lines in vitro by leaf extracts of sour soup.	-	
Smita Parekh et al 2020	Parijaata/Nyctanthes arbor-tristis effect on cancer cell lines: in vitro study	Anti-cancer effect on colon cancer cell lines	-	
Manoj Kumar et al 2021	Guava (Psidium guajava L.) Leaves, health promoting activities: in-vitro study	Anti-cancer effect on colon cancer cell lines	-	
Lin Shen et al 2020	Abnormal bowel movement in CRC risk: large cohort study	Only increased risk in rectal cancer	Publication bias present only for rectal cancer; selection bias may be present	Begg's, Egger's tests done
Adrijana D'Silva et al 2023	Randomized controlled trial: yoga & meditation on IBS	Significant reduction of IBS related inflammation, improved bowel movement	7	
Nicolas Chapelle et al 2020	Recent advances in clinical practice: review of 80 meta-analyses	Aspirin, NSAIDS, Magnesium supplementation(not combines) showed protective effect with moderate certainty of evidence	Publication bias present	PRISMA, AMSTAR guidelines followed
Katy Jackson et al 2023	Clinical review: vaccines based immunoprevention	In response to successful in-vivo trials, human immune trials in preventive setting planned based on cost-benefit effect to patient are the new promising door to cancer prevention.	-	

**Table 2: Various screening modalities for Colorectal Cancer.**

Non-invasive tests		% reduction of incidence/ mortality due to CRC
Fecal immunochemical test FIT[10]	Home based self testing, most effective	59%
Fecal occult blood test FOBT[11] annual	For polyposis & CRC	18%
Gut microbiota dysbiosis[12]	Stool examination	
<b>Invasive tests</b>		
Flexible sigmoidoscopy (FS)[11]		26%
FOBT & FS[11]		38%
Colonoscopy[10]	Gold standard	61%
Balloon-assisted colonoscopy using G-Eye device[13]	Novel highly effective	
High standard definition colonoscopy[13]	Highly effective	

**Table 3: Non-invasive biomarkers for CRC**

<b>Stool</b>	VOC patterns	Detected by electronic nose
	Hydrogen sulphide, dimethyl sulphide, dimethyl disulphide	Detected by SIFT-MS
	Methyl mercaptan, hydrogen	Detected by GC
	Propan-2-ol, hexan-2-one	Detected by GC-MS
<b>Urine</b>	VOC* fingerprint	Detected by FAIMS*
<b>Breath</b>	Acetone, ethyl acetate, ethanol, 4-methyl-octane	Detected by GC-MS*
	VOC patterns	Detected by electronic nose
<b>Inflammatory</b>	Fecal calprotectin	NPV: 93 to 97% for CRC & adenoma
	Serum chitinase-3-like protein 1 (CHI3L1)	96% sensitive, 91.7% specificity
<b>Molecular</b>	Micro RNA	
	Cologuard test	
<b>DNA methylation markers</b>	Epi proColon test: serum	gene SEPT9*in cell-free DNA
	miRNA	miR-193a-5p, miR-210, miR-513a-5p, miR-628-3pin both early and late onset. miR-31-5p over expressed in sporadic EOCRC

\*Selected-ion flow-tube mass spectrometry (SIFT-MS), Gas chromatography–mass spectrometry (GC-MS), Field-Asymmetric Ion Mobility Spectrometry (FAIMS), Septin 9 (SEPT9), volatile organic compounds (VOC).



**Table 4: CRC associated oral bacteria.**

Bacteria	CRC	Oral Conditions
<i>Fusobacterium nucleatum</i>	Most significant association in CRC	Poor oral health: periodontal disease, plaque formation
<i>Parvimonas micra</i>	Both types of CRC	Periodontitis, dental abscess
<i>Peptostreptococcus stomatis</i>	Both types of CRC	Oral ulceration
<i>Solobacterium moorei</i>	Both types of CRC	Halitosis
<i>Gemella morbillorum</i>	Both types of CRC	Necrotizing oral disease, plaque formation
<i>Actinomyces odontolyticus</i>	Only in early-onset CRC	Infections of roots and root canals
<i>Bacterioides</i>	Both types of CRC	Anerobic infections
<i>Veillonella</i>	Both types of CRC	Dental infections
<i>Prevotella</i>	Both types of CRC	Gingival sulcular inflammation
<i>Treponema denticola</i>	Both types of CRC	Periodontal disease

**Table 5: Risk factor modification for prevention of CRC.**

Risk Factor	Risk Status	Risk Group	Test	Biomarkers	Prevention
Inflammatory bowel disease	Very high	Individuals with IBD	Endoscopy	Faecal haemoglobin Calprotectin	Regular screening
Diabetes mellitus type 2	Medium	Long term individuals	H1A1c	IGF	Have glucose levels under control
Family history (germline mutations)	High	First degree relative	Genetic testing APC gene	Genetic and/or epigenetic markers MicroRNA	Regular screening
Obesity (BMI and waist circumference)	High	High BMI individuals	BMI	IGF 2, Adipokines, IL 1b, IL-6, TNF alpha	Diet modification and increase physical activity
Physical inactivity	High	Sedentary	Clinical history	IL 1b, IL-6, TNF alpha, CRP	Increase frequency and intensity of physical activity
Red meat, processed meat	high	Increase amount and frequency	Diet charts, iron levels		Reduce amount and frequency
Alcohol	High	Regular consumption	Clinical history	2 hydroxy 3 methyl butyric acid	Avoid intake
Soft drinks	Medium	High intake			Avoid intake
Vegetarian diet	Low	Pure vegetarians	Diet charts	Vit B12 deficiency	Include variety and plant-based protein
Copper to zinc ratio	High	High ratio	Biochemical		Increase antioxidant food intake and reduce red meat
Dietary inflammatory index	Medium	High DII		Chitinase 3-like 1 E-cadherin M2-pyruvate kinase	Reduce pro inflammatory food and include anti-inflammatory food.
Margarine	High	High intake			Avoid intake
Low fruits and vegetables	High	Low intake	Questionnaire Micronutrient panel	Micronutrient panel, DELPHI technique, inflammatory biomarkers	Increase intake of fruits and vegetables
Gut microbiota	Medium	Reduced individuals		<i>Fusobacterium nucleatum</i>	Include natural probiotic food

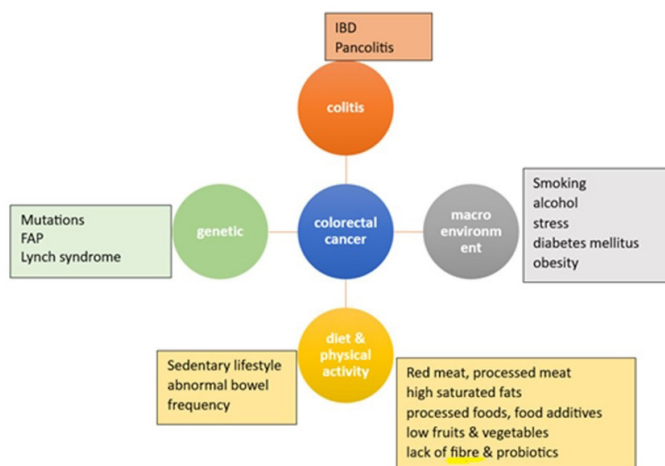
## Early-Onset CRC:<sup>19,20</sup>

Early-onset CRC differs from late-onset CRC in age of incidence (<50 years old), location of common occurrence (left distal colon and rectum in 55-80% of people), and frequency of oncogenic mutations. It is poorly differentiated histologically, with a distinct DNA methylation profile. Its polygenic risk score is higher and has worse survival.

**Risk factors for early-onset CRC:<sup>19</sup> (Figure 2)** Family history and hereditary occurrence are 30% common with familial adenomatous polyposis (FAP), Lynch syndrome (5%), and other mutations (12-16%). Diabetes can increase the risk of cancer in the colon (38%) and rectum (20%). Chronic inflammatory conditions like IBD (pancolitis) in the 4th decade (30%), and celiac disease are common risk factors. Diet, alcohol, smoking, lack of physical activity, obesity in childhood, and calorie restriction in children are other risk factors. Dietary aspects like high intake of processed and red meat (22%), cooking methods like deep frying which releases glycation end products that are pro-carcinogenic, and usage of food additives like nitrates in processed meat, over-use of synthetic dyes, monosodium glutamate, titanium dioxide (E171) (a food whitening agent) (>1% of food weight), and high fructose corn syrup increase the risk of EOCRC. Maternal stress during pregnancy and childhood perceived stress are also important risk factors. Gut dysbiosis due to increased numbers of *Fusobacterium nucleatum*, *Escherichia coli*, *Bacteroides fragilis*, and *Salmonella enterica* causes intestinal dysbiosis, inflammation, evasion of the tumoral immune response, and activation of pro-tumoral signalling. Repeated short-term or long-term exposure to antibiotics also alters the gut microbiota, which increases the risk of EOCRC.

## Management of Modifiable Risk Factors:<sup>20,21,22</sup>

**Diet Modification Recommendations to Prevent CRC:<sup>6,7,9,28,29,30,31</sup>** **Table 6** highlights the dietary recommendations for prevention of CRC.



**Figure 2: Common risk factors for colorectal cancer.**

## Natural Compounds:<sup>43,44</sup>

Natural compounds that are found to have protective effects through anti-oxidant, anti-inflammatory, neuroprotective and anticancer actions include:

1. Curcumin (polyphenol) (turmeric)
2. Resveratrol (stilbenes) (red grapes)
3. EGCG (epigallocatechin) (green tea)
4. Fisetin (hydroxy flavone) (strawberries, apples, onions, and cucumbers)
5. Genistein (isoflavone) in combination with chemotherapeutic agents (ginseng root)
6. Apple polysaccharides (apples)
7. Mushroom glucans (edible mushrooms)
8. Paris saponin 7 (ginseng plant)
9. Soy saponins (soy beans)
10. Soy isoflavones were shown to have significant protective effect in Asian population.<sup>45</sup>
11. Leaf decoctions:  
*A.muricata* / *Graviola* / *Soursop*: The leaf extracts of *Graviola* contains phytochemicals Annomuricin A, B, C, E & Muricapentocin which is found to have anticancer effects on colon cancer cell-lines in vitro.<sup>46</sup> *Parijaata/Nyctanthes arbor-tristis* for antioxidant & antibacterial properties<sup>47</sup>, *guava/Psidium guajava L* for antioxidant, antimicrobial actions<sup>48</sup> showed anticancer effects on cancer cell lines.
12. *Terminalia chebula Retz/Hartaki/Kadukkai/Manahei* is mild laxative, anti-inflammatory, remedy for hemorrhoids. Hydroalcoholic extracts from this was



**Table 6: Diet modifications recommended for prevention of CRC.**

TO EXCLUDE	TO INCLUDE
<p>Simple carbohydrates            Avoid white rice, wheat (negative millets)            Avoid neutral millets(proso, finger(rye), sorghum, barley, pearl millets)            Avoid wheat and wheat products in individuals with gluten sensitivity, IBD, celiac disease, wheat allergy, skin diseases, auto immune diseases [25]            Refined wheat flour, refined flour            Instant oats, breakfast cereal, pasta, noodles</p>	<p>Complex carbohydrates (soak before cooking)            black rice, red rice, brown rice [23]            Include positive millets(kodo, little, foxtail, barnyard, brown top)[24]            Rolled or steel cut oats with fresh fruit [26]</p>
<p>Refined added sugar            White sugar, brown sugar, artificial sweeteners</p>	<p>Natural sugars            Stevia, dates, pure honey, palm jaggery [24]</p>
<p>Dairy high fat            Full cream raw milk            Full fat yogurt, sweetened yogurt            Butter, margarine            Hydrogenated vegetable oils            To mix with milk shakes, desserts            Processed/package cheese</p>	<p>Low fat dairy [27]            Low fat pasteurized milk (A2 which does not contain <math>\beta</math> casein) [28]            Low fat yogurt, butter milk[30]            Pure, natural clarified butter (ghee)(moderate)[31][32]            Olive oil[33], sesame oil[34]            Plant milks: Coconut milk, almond milk, oats milk fortified with calcium in lactose intolerant people            Natural dairy cheese including paneer/cottage cheese [27]</p>
<p>Simple plant-based proteins            Split lentils            Dried nuts</p>	<p>Complex plant-based proteins(soak before cooking)            Unsplit lentils with outer skin intact, variety of beans and legumes            Soaked, sprouted(improve nutrient availability) legumes/ nuts</p>
<p>Unhealthy animal protein intake            Processed meat-bacon, hot dog, sausage[35]            Red meat-beef, pork, lamb, liver, meatballs[35]            Completely avoid Barbecued, smoked, grilled, deep fried            More frequent intake of meat            Nuts and nut butters(high aflatoxin)[37]</p>	<p>Healthy animal protein intake for healthy individuals;            Fresh meat            White meat(chicken, turkey, duck, rabbit, fish), eggs            Boiled, steamed, pressure cooked, stir fried, poached[36]            Less frequent meat intake not more than once a week            Seeds- pumpkin seeds, chia seeds, hemp, sesame, sunflower seeds(roasted/soaked)            At least 1 serving of mixed seeds(1 handful)</p>
<p>Frozen fruits and vegetables            Starchy vegetables like potatoes</p>	<p>Fruits and vegetables, vegetable juices[38]            Fresh fruit(apples, papaya, citrus fruits, pomegranates, amla, berries), watermelon, kiwi[39]            Increase intake of non starchy vegetables, native vegetables &amp; water rich vegetables, cruciferous vegetables [40]            Increase intake of fresh salads            At least 3 servings each of vegetables and fruits per day            Daily intake of green leafy vegetables</p>
<p>Store bought probiotics</p>	<p>Natural probiotics- fermented foods like yogurt, fermented rice, fermented vegetables like sauerkraut</p>
<p>Avoid intake of fast foods like pizza, burgers, instant noodles, breakfast cereals, ready to cook foods</p>	
<p>Beverages</p>	<p>Coffee:protective for US men &amp; women, European men &amp; Asian women only. No effect on rectal cancer [41]            Green tea[42] marginal protection against colon cancer</p>

**Table 7: Physical activity recommendations for prevention of colorectal cancer.**

<b>Exercise for at least 30 minutes</b>	Start with low intensity like walking and gradually increase to medium intensity like jogging, aerobics, cycling etc. Frequency should be at least three times per week Consult doctor before starting any new form of exercise.
<b>Yoga[52]</b>	Few poses like Parighasana , Ardha matsyendrasana, Salamba setu bandhasana, Ananda balasana can be helpful for IBS. Uttanasana, Utthita Parsvakonasana, Ushtrasana, Dhanurasana, Eka Pada Rajakapotasana, Apanasana, Savasana can help with better digestion and colon health. Consult doctor before starting.
<b>Pranayam[53]</b>	Nadi suddhi and kapal bhati can be beneficial for proper digestion, decrease inflammatory reaction.
<b>Detoxification[54]</b>	Cleansing the colon with enemas, laxatives like castor oil, or colon hydrotherapy Fasting, detox diet Only under recommendation and supervision of health care professionals

found to have significant cytotoxicity against HCT-116 colon cancer cells indicating promising anti-cancer activity.<sup>49</sup>

### **Bowel Movement**

Abnormal frequency of bowel movements is not associated with colon cancer, but it suggests an increased risk for rectal cancer.<sup>50</sup>

### **Physical Activity<sup>51</sup>**

At least 30 minutes of physical activity is necessary to maintain health of gastrointestinal tract.

### **Chemoprevention<sup>55</sup>**

A low certainty of evidence supports a significant effect against CRC incidence with long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs) in low dose. Moderate certainty of evidence supports that aspirin in low doses has protective action as a chemo preventive agent. Magnesium had a significant protective effect when at least 225 mg/day was consumed, supported by low certainty of evidence. Very low certainty of evidence exists to prove the protective effect of vitamin D alone or in combination with calcium. The evidence for Folic Acid, Vitamins E, C, Multivitamins, Beta Carotene, and Selenium as protective agents is very weak. An analysis

of micronutrient levels is essential before prescribing the micronutrient supplement.

### **Immunoprevention<sup>56</sup>**

Immunoprevention is the concept of preventing cancer development using agents that enhance the immune system to survey and destroy tumor cells. The development of tumors is fostered by evading immune cells and creating an immune-suppressive environment for the immune response. Vaccines may help overcome this immunosuppressive environment conducive to cancer growth. The development of such vaccines will be based on tumor-associated antigens and tumor-specific antigens. Multivalent vaccines, complemented with immune adjuvants, help eliminate a larger number of tumor cells. So far, human trials of CRC vaccines have failed due to the administration of vaccines during advanced stages of carcinogenesis because of patients' inability to mount an effective immune response. But in vivo clinical trials in mouse models well before tumor incidence (presence of genetic risk, polyps) reduced the cancer risk by 100%. Also, the vaccinated mice with genetic susceptibility gave birth to offspring who were free of polyps (antibody transferred through breast feeding). Human trials in a preventive setting need to be conducted to accurately assess the efficacy of CRC vaccines. Recently, the first randomized controlled trial tested the MUC1 vaccine against CRC in a prevention setting, and results are awaited.

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## Discussion

The present review, including 32 studies, provides insights on holistic preventive strategies for colorectal cancer. Risk identification among the general population involves developing prediction models relevant to a specific population, followed by risk stratification into high, medium, and low-risk populations<sup>6,7</sup> based on which specific screening strategy [10] would be employed, as in the low-risk population, FIT, non-invasive biomarkers, in the high-risk population, invasive biomarkers, FOBT, FS<sup>11</sup>, and then colonoscopy<sup>10</sup> for diagnostic conformation. Among early detection biomarkers, stool-based ones<sup>14</sup> are non-invasive and effective. In cases of early-onset CRC, fecal calprotectin, the Cologuard test, the EpiProColon test, and miRNA biomarkers were found to be effective. The recommendation of a healthy diet replacing unhealthy diet components is given elaborately in the present review. Including complex carbohydrates<sup>23</sup> like red, black, and brown rice, positive millets<sup>24</sup>, plant-based unpolished whole proteins, and sprouted grains can increase fiber intake and provide good glycemic control. For meat intake, avoiding red (beef, pork, lamb, liver, meatballs) and processed (bacon, hot dog, sausage, etc.) meats<sup>35</sup>, including white meats like chicken, turkey, duck, rabbit, and fish prepared by boiling, steaming, pressure-cooking, and stir-frying methods<sup>36</sup> once a week, while deep-frying, barbecued, smoked, and pickled meats should be avoided. For cooking, hydrogenated vegetable oils can be replaced by natural, unfiltered sesame oil and olive oils. Low-fat dairy products like A2 pasteurized milk<sup>27</sup>, yogurt, natural dairy cheese, and buttermilk<sup>30</sup> are found to be protective. Intake of fresh fruits like apples, papaya, citrus fruits, pomegranates, amla, berries, watermelon, and kiwi<sup>39</sup> should be regular and frequent. Increased intake of non-starchy, native, and water-rich vegetables, including cruciferous vegetables<sup>40</sup>, has been found to be protective. Regular intake of vegetable juices<sup>38</sup> is recommended for people with healthy GIT. Other dietary factors found to be protective include good-quality seeds like pumpkin, sunflower, hemp, chia, sesame, and flax seeds (avoid in cases of allergy), natural probiotic foods like yogurt, fermented rice, and sauerkraut, a cup per day of decaffeinated coffee<sup>41</sup>, and rolled or steel-cut oats with fresh fruits<sup>26</sup>. The review recommends avoiding

intake of alcohol, tobacco, soft drinks, canned food, processed and packaged food items, food additives and preservatives, fast foods, nuts like peanuts, which are highly prone to aflatoxin<sup>37</sup> presence, and wheat and wheat products in cases of gluten sensitivity. At least 30 minutes of physical activity at least three times per week<sup>51</sup>, yoga poses like Parighasana, Ardha matsyendrasana, Salamba setu bandhasana, Ananda balasana (help with IBS), Uttanasana, Utthita Parsvakonasana, Ushtrasana, Dhanurasana, Eka Pada Rajakapotasana, Apanasana, Savasana (help with digestion and colon health), and methods of prasnayam<sup>53</sup> like nadisuddhi and kapalbhati have also been found to be helpful for GI health. For chemoprevention<sup>55</sup>, moderate evidence supports low-dose aspirin, and low evidence supports magnesium 225 mg/day as chemopreventive agents for patients with high-risk serrated or adenomatous polyps. New evidence also suggests precise supplementation to address the deficiency of micronutrients. The protective role of natural compounds<sup>43</sup>, like curcumin, resveratrol, genistein, soursop, etc., is yet to be established in large-scale trials before being recommended as preventive agents. The most recent research on developing immunopreventive agents<sup>56</sup> is going on in a promising manner. Recently, a randomized controlled trial on the MUC1 vaccine against CRC in a prevention setting was conducted, and the results are yet to be unfolded. Similar evidence was presented in an umbrella review by Sajesh K. Veettil<sup>57</sup>, where an association was found between lower CRC risk and higher intakes of dietary fiber, dietary calcium, and yogurt and lower intakes of alcohol and red meat. In another umbrella review by Jakub 'Switalski et al., FIT was found to be effective and economical to be used in large-scale population screening of CRC<sup>58</sup>. Quercetin available in onions, elagic acid in green tea, and apples were found to be effective in preventing the recurrence of polyps<sup>59</sup>. The strength of the study lies in exploring prevention strategies in a holistic manner relevant to present-day scenarios applicable to the general population and providing education regarding this at a level understandable to the general population from all streams. The limitation of the study is the smaller number of studies included in multiple aspects of prevention. Elaborate studies, considering a greater number of studies in each aspect of prevention, are needed to be conducted

to develop policy recommendations for CRC prevention. Future research may focus on developing risk prediction models relevant to respective populations, developing diet and lifestyle modification methods with measurable outcomes, and testing the performance of cost-effective bio-markers for risk identification in resource limited settings. In conclusion, the study suggested an integrated holistic approach for risk identification and stratification, improving screening uptake with non-invasive biomarkers, to motivate people to take steps towards prevention. Effective interventions for diet and lifestyle modification, supplementation on a deficiency basis, proper use of phytochemicals for risk factor modification, along with correction of oral dysbiosis<sup>60</sup>, and chemoprevention in high-risk populations, constitute a holistic approach for risk reduction and early intervention to prevent the progression to colorectal carcinoma.

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