COLORECTAL CANCER: PREVENTION AND EARLY DETECTION

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Abstract
Colorectal cancer (CRC) is the third most common malignancy and second leading cause of cancer death irrespective of gender.

A number of genetic, environmental and life style risk factors are involved in the pathogenesis of CRC. In addition, several studies have established a number of factors with a protective role against development of colorectal cancer. Identification of these factors and subsequent modification can help us in preventing this potentially lethal disease.

Screening for CRC can help us in two ways. First, it can detect sub-clinical abnormalities which may have a potential for malignant transformation and prompt us for early action and thus can prevent CRC. Secondly, it helps in the detection of CRC at an early stage when clinical symptoms may not be that evident for an affected individual to seek medical advice. However, treatment at this early stage is most effective and curative in most cases.

The following manuscript describes the summary of protective and risk factors of CRC and screening modalities which can help us in prevention and early detection of colorectal cancer.

Introduction
Colorectal cancer (CRC) is the third most common malignancy and potentially a lethal disease if not treated.[1] It is the second leading cause of cancer death in the US.[2] The importance of prevention and early detection of certain cancers cannot be over-emphasized due to the fact that many malignancies are potentially preventable. 3, 4

Epidemiology
The number of diagnosed cases of CRC annually in the U.S. is close to 150,000 and approximately one third of them die from the diseas.2

CRC is seen mostly after the age of 40, with the risk increasing with each decade. 5,6 90 percent of cases are seen in age more than 50 years. It is seen most common in North America, Australia and Europe as compared to Africa and Asia.7

The overall 5-year survival rate for colorectal cancer is approximately 66 percent. Although there have been advances in the surgical and adjuvant treatment of CRC, the prognosis remains poor for patients who present at an advanced stage. 8, 9

Pathogenesis of Colorectal Cancer
Adenomatous polyps are thought to be a precursor of CRC. 10 It takes about 10 years in the progression of a polyp from a small size to a large one, then dysplasia and ultimately neoplastic appearance. 11, 12

This has led to the development of screening tools for early detection and removal of adenomatous polyps with evidence of lower incidence of CRC in such patients.13

Risk Factors for Colorectal Cancer

The various risk factors increasing the likelihood of development of colorectal cancer are listed in Table 1.

Table 1: Risk Factors for Colorectal Cancer

Risk Factors	Ralative Risk	Age	Comments
Familial adenomatous polyposis (FAP)	- 90% absolute risk of development of colorectal cancer by age 45 in mutation carriers	- Appearing during childhood - Symptoms at 16 years - Colorectal cancer by age 45 (in 90% of untreated individuals)	- Account for less than 1% of colorectal cancers
Hereditary nonpolyposis colorectal cancer (HNPCC)	- 80% absolute risk of development of colorectal cancer by age 75 in mutation carriers	- Early age of onset (mean age 48 years, some present in 20s)	- Autosomal dominant - 1-5% of colorectal cancers - Predominant right colon involvement
Personal history of colorectal cancer or adenomatous polyps	3.5 to 6.5 with adenomatous polyps >1cm		-Metachronous primary cancer in 1.5-3% patients (5 years post single CRC resection)
Family history of colorectal cancer or adenomatous polyps	1.7 fold increased risk with single affected first degree relative with CRC	- Increased risk of index case diagnosed at age <55	- Family history of adenoma >1cm has same significance as positive family history of CRC
Inflammatory bowel disease	5 to 15-fold increased risk with pancolitis. Three-fold relative risk with left-sided disease	- Increased risk begin 8-10 years after pancolitis diagnosis	- Increased risk of ulcerative colitis and primary sclerosing cholangistis are together
Diabetes mellitus	CRC 30% higher in diabetics. Relative Risk 1.30		
Cholecystectomy	Standardized incidence ratio 1.16		- Data shows slightly increased risk of right-sided colon cancer - Conflicting data also reported
Alcohol Consumption	Adjusted relative risk 1.41		- Seen with alcohol consumption > 45 g/day
Obesity	1.5-fold increased risk		- Increased likelihood of death from CRC
Cigarette Smoking	Relative risk of 1.18 for CRC development. Relative risk of 1.25 for death from CRC		- Stronger association with rectal cancer - Stronger risk for development of polyps
Coronary heart disease			- Increased risk of advanced adenomas
Acromegaly			- Increase prevalence of polyps in males only
Red meat and caffeine			- Increased risk of CRC with long-term red meat/ processed meat consumption - Data inconsistent and controversial

A. Familial Adenomatous Polyposis (FAP)
FAP is caused by a mutation in adenomatous polyposis coli (APC) gene and accounts for less than 1% of cases of CRC.14, 15 It is characterized by appearance of numerous colonic polyps appearing in childhood and may transform into malignancy by age 45 in 90% untreated cases.

B. Hereditary nonpolyposis colorectal cancer (HNPCC)
Also know as Lynch syndrome.16 It accounts for 1-5% of CRC. It is an autosomal dominant syndrome; caused by mutations in mismatch repair genes; with early age of onset and involvement of proximal colon. It may also involved extra colonic sites including endometrial carcinoma, stomach, small bowel, Hepatobiliary system.

C. Personal history of sporadic cancers or adenomatous polyps
1.5 to 3% patients with a history of resected colorectal cancer can develop CRC in first 5 years. Presence of adenomas also poses a threat for CRC especially if multiple polyps are present.17

D. Family history of sporadic cancers or adenomatous polyps
A first degree relative with CRC increases the risk by 1.7 fold with further increase if two first degree relatives are involved. The risk is also present if there is a family history of a polyp larger than 1 cm in size.18

E. Inflammatory bowel disease
Inflammatory bowel disease (ulcerative colitis and Crohn's disease) also increase the risk of CRC by 5 to 15-fold. The risk is increased at 8 to 10 years after the onset of symptoms. 19-21

F. Other risk factors
Various other risk factors have been identified as risk factors for development of colorectal cancer. These include:

- Diabetes mellitus and insulin resistance22-27
- Cholecystectomy28-32
- Alcohol33-39
- Obesity40-43
- Coronary heart disease44
- Cigarette smoking45, 46
- Acromegaly47, 48
- Red meat and caffeine49-55
- History of radiation therapy for prostate cancer56
- HIV57, 58
- Prior treatment for Hodgkin's Lymphoma59

Protective Factors for Colorectal Cancer
A number of protective factors have been identified and have been summarized in Table 2.

Table 2: Protective Factors for Colorectal Cancer

Protective Factors	Relative Risk/Protective Effect	Comments
Dietary Factors Diet high in fruits and vegetables	0.5	- Protective effect seen in may studies - Discordant data also published
Diet low in red meat/cholesterol	Relative risk of 3.26 with high cholesterol	
Fiber	Up to 40% reduction in CRC risk as claimed in one study (on doubling fiber intake in population with low fiber intake)	- Many conflicting studies - Protective role remains controversial

Folic Acid	0.25	- Protective effect seen after 15 years use - Studies suggest protective effect seen with dietary folic acid
Vitamin B6 (Pyridoxine)	0.42	- Total vitamin B6 intake inversely related with colon cancer risk
Calcium	0.65 (Distal Colon Cancers)	- Higher calcium intake > 1250mg/d protective
Magnesium	0.59	- Up to 40% risk reduction observed
Omega 3 fatty acids (mainly fish oil)	0.88	- Protective effect with high consumption of fish
Garlic		- Reduced risk of colonic adenomas
PHYSICAL ACTIVITY		0.60 (light occupational activity) 0.45 (moderate/heavy activity) 0.33 (most active men)
ASPIRIN and NSAIDS		- No adequate studies available - Observational and intervention trial evidence supports protective effect
CHEMOPREVENTION (Combination of D,L alpha – diflouromethylornithine DFMO and sulindac (NSAID)	70% reduction in recurrent adenomas 90% reduction in advanced adenomas 95% reduction in multiple adenomas	- Protective effect in patients with history of colonic adenoma
HORMONE REPLACEMENT THERAPY	Risk reduction by 40% with combined estrogen plus progestin.	- Controversial data about protective effect. - Not routinely recommended due to associated risks
STATINS		- Conflicting data about protective effect - Use of statins for 5 years proved protective

The dietary factors with a protective role against colorectal cancer include:

- High Fiber diet, diet high in fruits and vegetables60-63
- Folic acid97, 98
- VitaminB6 64
- Calcium65-72
- Magnesium73

B. Non Steroidal Anti Inflammatory Drugs (NSAIDs)

There is evidence on bases of observational studies that aspirin and NSAIDs (Celecoxib) may have a protective role against development of colorectal cancer, however, there is also documented harm of use of aspirin and NSAIDs due to their side effects.

C. Physical Activity

Regular physical activity has been identified as a protective factor. Several studies support this finding.76-78

D. Chemoprevention

D, L, alpha-difluoromethylornithine (DFMO) and sulindac (a NSAID) used in a group of

patients with history of colonic adenoma showed reduction in development of recurrent adenomas in a clinical trial.79 However, further investigation is required to confirm the benefits of this in the colon cancer prevention.

E. Other Protective Factors/Agents

Other protective factors have been reported which includes:

1. Hormone replacement therapy8085 (Not routinely recommended for prevention of colorectal cancer in women due to long-term, risks)86
2. Statins87-89
3. Antioxidants90
4. Omega 3 Fatty Acids (Fish Oil)91
5. Garlic92, 93

F. Screening for Colorectal Cancer

Screening for colorectal cancer is summarized in Table 3. (95-101)

Screening is divided into 3 population groups:

1. Population at Average Risk
    - Age more than or equal to 50 years
    - No history of adenoma
    - No history of inflammatory bowel disease
    - Negative family history
2. Population at Increased Risk
    - Personal history of adenoma
    - Personal history of colorectal cancer
    - Personal history of inflammatory bowel disease
    - Positive family history of first degree relative with colorectal cancer or adenoma.
3. Population with Hereditary Risk
    - Hereditary non-polyposis colorectal cancer syndrome (HNPCC)
    - Familial Adenomatous Polyposis (FAP)

G. Tests Used for Screening for Colorectal Cancer

Screening with Stool-Based Tests

- Guaiac-based fecal occult blood test. (Gfobt)
- Immunochemical tests for fecal blood
- Fecal DNA tests
- Colon Imaging and Direct Visualization
- Double contrast barium enema. (DCBE)
- Sigmoidoscopy
- Colonoscopy
- Computed tomographic colonography. (CTC)

H. Recommendations for Screening for Average Risk Population

- Offer screening beginning at age 50 years for average risk patients. Colonoscopic detection of colorectal cancer is uncommon in asymptomatic people under the age of 50 [94].
- Discontinue screening when the individual's estimated life expectancy is less than 10 years.
- No single test is of unequivocal superiority. Incorporating patient personal preferences may increase the likelihood that screening will occur.
- Screening should be supported by a program that assures proper follow-up of abnormal findings, and ongoing testing at identified intervals.

I. Recommendations for Screening for High Risk Population

- People with a first-degree relative (parent, sibling, or child) with colon cancer or adenomatous polyp diagnosed at age less than 60 years, or two first-degree relatives diagnosed at any age should be advised to have screening colonoscopy starting at age 40 years, or 10 years younger than the earliest diagnosis in their family, whichever comes

first, and repeated every 5 years.

- People with a first-degree relative with colorectal cancer or adenoma diagnosed at age more than 60 years should be advised to have screening as average-risk persons but beginning at age 40 years.
- People with two or more second-degree relatives (grandparent, aunt, uncle) with colorectal cancer should similarly be advised to begin screening at age 40 years.
- People with one second-degree relative or third-degree relative (great-grandparent or cousin) with colorectal cancer should be advised to be screened as average risk persons.
- Individual at high risk with familial syndromes (NHPCC, FAP) should be screened for CRC with colonoscopy at frequent specified intervals

Table 3: Screening for Colorectal Cancer

Population at Risk	Intervention	Procedure	Frequency	Start Age (Yrs)	Stop Age (Yrs)	Further Action
AVERAGE RISK Age more than or equal to 50 yrs No history of adenoma No history of Inflammatory bowel disease Negative family history	Screening and Prevention	Colonoscopy	Every 10 yrs	50	70	Polypectomy if polyp found
		Computed Tomographic Colonography	Every 5 yrs	50	70	Colonoscopy if any positive findings
		Flexible Sigmoidoscopy	Every 5 yrs	50	70	
		Double Contrast Barium Enema	Every 5 yrs	50	70	
	Screening Only	Guaiac Based Fecal Occult Blood Testing	Annually	50	70	Flexible sigmoidoscopy or CT Colonography if positive
		Fecal Immunohisto-chemical based Testing for Blood	Annually	50	70	
		Stool DNA Testing	Uncertain Frequency	50	70	
INCREASED RISK Personal history of adenoma, colorectal or inflammatory bowel disease IBD (Crohn's disease or Ulcerative colitis)	Screening	Colonoscopy	Within 5 years of detection of polyp		70	Polypectomy
			Within 1 yr of personal history of CRC	When detected postoperative	70	Repeat every 3 yrs if normal
			Every 1-2 years (for symptomatic IBD)	8-10 yrs after IBD symptoms		Biopsies
Positive family history of first degree relative with colorectal cancer of adenoma	Screening	Colonoscopy	Every 5 yrs	At age 40 yrs or 10 yrs prior to earliest cancer in family	70	Manage per findings
HEREDITARY RISK Non-Polyposis Colorectal Cancer (HNPCC)/Lynch Syndrome	Screening	Colonoscopy	Every 1-12 years	20-25 or 10 yrs prior	70	Manage as per special scenarios Genetic counseling

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