

**COLORECTAL CANCER**  
**FROM GENETICS TO PREVENTION**



**EDITURA UNIVERSITARĂ**  
**București**

**CONTENTS**

<b>BACKGROUND</b> .....	7
<b>CHAPTER I. INTRODUCTION</b> .....	11
I.1. Definition .....	11
I.2. Incidence and Mortality .....	14
I.3. Etiology and Pathogenesis of Colorectal Cancer .....	19
I.4. Pathology and Immunohistochemistry of Colorectal Cancer .....	23
I.5. Colorectal Cancer = Three Colons – Three Cancers .....	28
Paradigm Shift and Clinical Implications .....	28
<b>CHAPTER II. COLORECTAL CARCINOGENESIS</b> .....	31
II.1. Introduction .....	31
II.2. Stages of Carcinogenesis .....	34
II.3. Colon: Function, Anatomy and Morphology .....	38
II.4. Cell Renewal (Turnover) .....	44
II.5. Stem Cells and Colorectal Carcinogenesis .....	46
II.6. The Pathways Associated with Colorectal Oncogenesis .....	54
II.6.1. Adenoma – Carcinoma Sequence Type .....	56
II.6.2. Serrated Polyp Pathway .....	57
II.6.3. Molecular Pathways Of Colorectal Carcinogenesis .....	59
II.7. Pre-Malignant Lesions of Colorectal Cancer .....	60
II.7.1. Aberrant Crypt Foci .....	61
II.7.2. Adenomatous and Non-Adenomatous Polyps .....	66
II.7.3. Polyps and Dysplastic Lesions in Inflammatory Bowel Disease .....	72
II.8. Colonic carcinogens .....	84
II.8.1. Definition .....	84
II.8.2. Rodent Models in Colorectal Carcinogenesis Study .....	85
II.8.3. Classification of Colonic Carcinogens .....	88
II.8.4. Mechanism of Action .....	89
II.8.5. Chemoprevention .....	96
References .....	101
<b>CHAPTER III. COLORECTAL CANCER SCREENING</b> .....	129
III.1. Introduction .....	129

III.2. Screening methods   We know	130
III.2.1. Visual Examinations	131
III.2.2. Stool Tests	133
III.3. Non-recommended Tests for Colorectal Cancer Screening	134
III.4. Strategies Implemented to Overcome Screening Barriers	135
References	136
<b>CHAPTER IV. FOLLOW-UP CARE IN COLORECTAL CANCER.</b>	<b>141</b>
IV.1. Definition	141
IV.2. Method evaluation: Objective clinical examination	142
IV.3. Method evaluation: Carcinoembryonic antigen (CEA)	143
IV.4. Method evaluation: Circulating tumor DNA	144
IV.5. Method evaluation: Computed tomography (CT)	145
IV.6. Method evaluation: Endoscopic surveillance	147
IV.7. Method evaluation: MRI detection	151
IV.8. Vitamin D supplementation	152
References	154
<b>CHAPTER V. COLORECTAL CANCER SURVIVAL AND PROGNOSTIC</b>	<b>157</b>
V.1. Introduction	157
V.2. Histopathological Prognostic Factors	158
V.2.1. Prognostic Factors Relating to the Primary Tumor	158
V.2.2. Prognostic Factors Relating to the Evolution of the Primary Tumor	161
V.3. Prognostic Factors Relating to the Surgical Procedure	173
V.4. Clinical Factors with Prognostic Importance	176
V.5. Immunological Prognosis Factors	178
V.6. Biochemical and Genetic Prognostic Factors	180
V.7. Analytical Prognosis Factors	182
V.8. Conclusions	182
References	185
<b>CHAPTER VI. COLORECTAL CANCER-MULTIDISCIPLINARY TREATMENT</b>	<b>192</b>
VI.1. The issue of colorectal cancer	192
VI.2. Etiology	193
VI.3. Prognostic factors	194
VI.4. Diagnosis and Staging	200
VI.5. Multidisciplinary treatment of colorectal cancer	204
VI.6. Follow up and Survivorship	224
References	227

## CHAPTER I

### INTRODUCTION

#### I.1. Definition

**Colorectal cancer**, also called **colon cancer** or **large bowel cancer**, includes cancerous-growths in the colon, rectum and appendix. Over 1 million new cases of colorectal cancer are diagnosed worldwide each year, and incidence seems set to rise with the progressive westernization of lifestyles in Asian and African populations. With 655,000 deaths worldwide per year, it is the third most common form of cancer and the second leading cause of cancer-related death in the Western world. [1] Although colorectal cancer mortality has been progressively declining since 1990, at a current rate of approximately 1.6 to 2.0 percent per year [2] [3], it remains the **third** most common cause of cancer death in the United States in **women and the** second leading cause of death in men. In contrast to these declines, **the** incidence of colorectal cancer in men and women under the age of 50 steadily increased at a rate of 2.1 percent per year from 1992 through 2012 and has continued to increase since then; through 2015 there was a **30** percent increase in colorectal cancer in 40-year-olds. [4] These increases are driven predominantly by left-sided cancers in general and rectal cancer (3.9 percent per year). [5] Current literature suggests that over 86 percent of those diagnosed under the age of 50 are symptomatic at diagnosis, and this is associated with more advanced stage at diagnosis and poorer outcomes. [6]

Many colorectal cancers are thought to arise from *adenomatous polyps* in the colon, defined as well demarcated masses of epithelial dysplasia, with uncontrolled crypt cell proliferation. These mushroom-like growths are usually benign, but some may develop into cancer over time. Most of the time, the diagnosis of localized colon cancer is through colonoscopy. Therapy is usually through surgery, which in many cases is followed by chemotherapy. Colorectal cancer and/or pre-neoplasms can be prevented by interfering with the various steps of oncogenesis, which begins with uncontrolled epithelial cell replication, continues with the formation of

adenomas, and eventually evolves into malignancy. The 2019 classification of **tumors** of the colon and rectum of World Health Organization (WHO) [7] was updated by 2022 World Health Organization classification of **carcinomas** of the colon and rectum. [7]

## **World Health Organization (WHO) classification of tumors of the colon and rectum**

### **1. Benign epithelial tumors and precursors**

#### **Serrated dysplasia, low grade**

#### **Serrated dysplasia, high grade**

- Hyperplastic polyp, microvesicular type
- Hyperplastic polyp, goblet cell

#### **Adenomatous polyp, low-grade dysplasia**

#### **Adenomatous polyp, high-grade dysplasia**

- Tubular adenoma, low grade
- Tubular adenoma, high grade
- Villous adenoma, low grade
- Villous adenoma, high grade
- Tubulovillous adenoma, low grade
- Tubulovillous adenoma, high grade
- Advanced adenoma

#### **Glandular intraepithelial neoplasia, low grade**

#### **Glandular intraepithelial neoplasia, high grade**

### **2. Malignant epithelial tumors**

#### **Adenocarcinoma NOS**

- Serrated adenocarcinoma
- Adenoma-like adenocarcinoma
- Micropapillary adenocarcinoma
- Mucinous adenocarcinoma
- Poorly cohesive carcinoma
- Signet ring cell carcinoma
- Medullary adenocarcinoma
- Adenosquamous carcinoma
- Carcinoma, undifferentiated, NOS
- Carcinoma with sarcomatoid component

## **Neuroendocrine tumor NOS**

- Neuroendocrine tumor, grade 1
- Neuroendocrine tumor, grade 2
- Neuroendocrine tumor, grade 3
- L cell tumor
- Glucagon-like peptide-producing tumor
- PP/PYY-producing tumor
- Enterochromaffin cell carcinoid
- Serotonin-producing tumor

## **Neuroendocrine carcinoma NOS**

- Large cell neuroendocrine carcinoma
- Small cell neuroendocrine carcinoma

## **Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)**

*NOS: not otherwise specified; PP: pancreatic polypeptide; PYY: peptide YY.*

## **2022 World Health Organization classification of carcinomas of the colon and rectum**

### **Adenocarcinoma**

- Cribriform comedo-type adenocarcinoma
- Medullary carcinoma
- Micropapillary carcinoma
- Mucinous (colloid) adenocarcinoma (>50% mucinous)
- Serrated adenocarcinoma
- Signet-ring cell carcinoma (>50% signet-ring cells)

### **Adenosquamous carcinoma**

### **Spindle cell carcinoma**

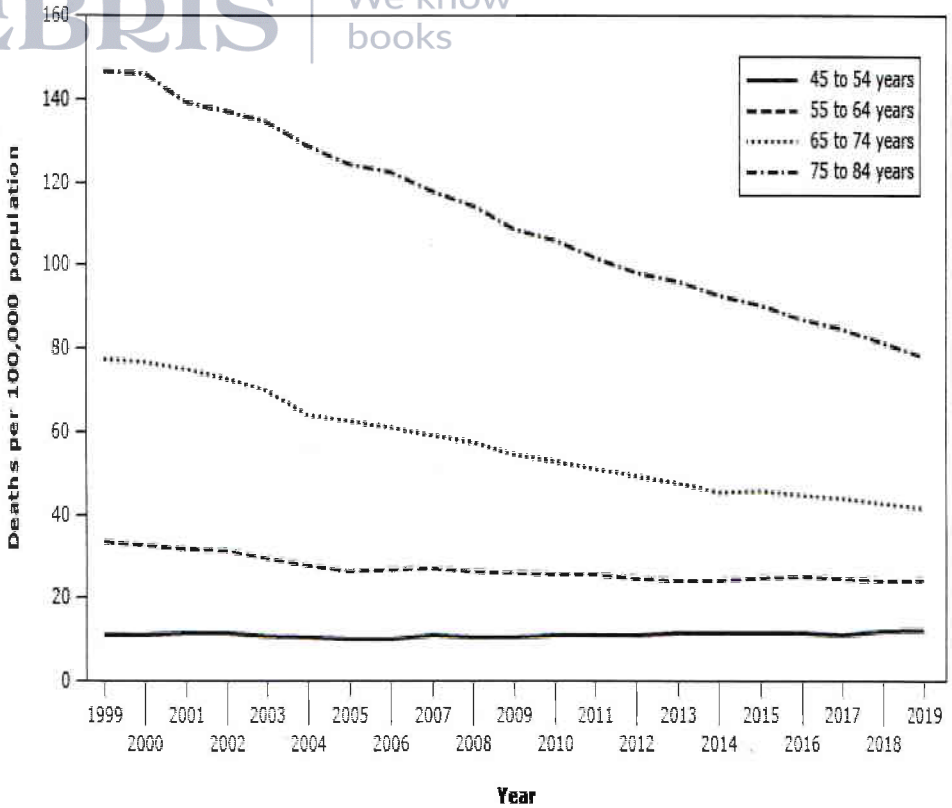
### **Squamous cell (epidermoid) carcinoma**

### **Undifferentiated carcinoma**

## 1.2. Incidence and Mortality

Carcinoma of the colon or rectum is a common and lethal disease. Every year, more than 940,000 cases of colon cancer occur worldwide and nearly 500,000 people die from it. Colorectal cancer is the third most common malignant neoplasm worldwide [2] and the second leading cause of cancer deaths (irrespective of gender) in the United States: every year 151,030 cases of colorectal cancer are diagnosed, of which 106,180 are colon cancers and the remainder are rectal cancers. Annually 52,980 patients die of the disease [2]. Global, country-specific data on incidence and mortality are available from the World Health Organization (WHO) **GLOBOCAN database**. Although colorectal cancer mortality has been progressively declining since 1990, at a current rate of approximately 1.6 to 2.0 percent per year [3], it remains the third most common cause of cancer death in the United States in women and the second leading cause of death in men. In contrast to these declines, the incidence of colorectal cancer in men and women under the age of 50 steadily increased at a rate of 2.1 percent per year from 1992 through 2012 and has continued to increase since then; through 2015 there was a 30 percent increase in colorectal cancer in 40 year old [4]. These increases are driven predominantly by left-sided cancers in general and rectal cancer (3.9 percent per year) [5]. Current literature suggests that over 86 percent of those diagnosed under the age of 50 are symptomatic at diagnosis, and this is associated with more advanced stage at diagnosis and poorer outcomes [6].

Between 1998 and 2004, colorectal cancer incidence rates in the United States declined by 2.3% per year. Over the past 20 years, the mortality rate has been declining. This improvement in outcome can be attributed, at least in part, to detection and removal of colonic polyps, detection of CRCs at an earlier stage, and more effective primary and adjuvant treatments. There was a 1.8% decline in mortality rate per year between 1985 and 2002. Between 2002 and 2004, the mortality rate declined by 4.7% per year. During 1999 to 2019, deaths per 100,000 persons from colorectal cancer decreased among persons aged 55 to 64 years (from 33.5 to 24.4), persons aged 65 to 74 years (from 77.4 to 41.5), and persons aged 75 to 84 years (from 146.7 to 77.9). The death rate from colorectal cancer among persons aged 45 to 54 years generally increased from 1999 (11.1) to 2019 (12.0). In each year during 1999 to 2019, the death rate was highest among persons aged 75 to 84 years and lowest among persons aged 45 to 54 years. (**Figure I.1**)



**Figure I.1. Death rates from colorectal cancer, by age group 1999 to 2019**  
 Adapted from Death Rates from Colorectal Cancer, by Age Group, 1999–2019. MMWR Morb Mortal Wkly Rep 2021; 70:1233. [8].

The overall 5-year survival rate is 65.6%. About 6% of Americans are expected to develop the disease within their lifetimes [9]. In 2006, in Europe, there were an estimated 31916000 cancer cases diagnosed and 1703000 deaths from cancer. The most common form of cancers was breast cancer (429900 cases, 13,50% of all cancer cases), followed by colorectal cancer (412900, 12,90%) and lung cancer (386300,12,1%). Lung cancer, with an estimated 334800 deaths (19,7% of total), was the most common cause of death from cancer, followed by colorectal (207400 deaths), breast (131900) and stomach (118200) cancers [10]. Over the past 20 years, colorectal cancer rates have risen in 27 of 51 countries including Eastern Europe, most of Asia, and some South American countries. The highest incidence rates are in Australia and New Zealand, Europe, and North America, and the lowest rates are found in Africa and South-Central Asia [11]. These geographic differences appear to be attributable to differences in dietary and environmental exposures, low socioeconomic status, and lower rates of CRC screening that are imposed upon a background of genetically

determined susceptibility [12-14]. The burden of cancer doubled between 1975 and 2000, and it is predicted to double again by 2020 and triple by 2030. According to the 2008 World Health Organization, the total number of cases of cancer in the developing world between 2000 and 2020 is expected to increase by 73 per cent. Rates for men are rising faster than those for women, so colorectal cancer rates increasing worldwide is a real fact.

In the United States, CRC incidence rates had been declining by approximately 2 percent per year, but this rate of decline has slowed to approximately 1 percent per year in the period 2013 to 2017. [3] Incidence rates in most other western countries have been stable or increased slightly during this period. By contrast, CRC incidence rates have rapidly increased in several areas historically at low risk, including Spain, and several countries within Eastern Asia and Eastern Europe. [15] [16]

Incidence rates closely parallel economic development, reflecting a westernized lifestyle and attendant risk factor exposure. Including obesity, physical inactivity, smoking, heavy use of alcohol, and diets with lots of red or processed meats and fewer fruits and vegetables. Among dramatic increases were a 70 percent male and 28 percent female rise in colorectal cancer in Slovenia. In Mijagi, Japan male rates nearly doubled, while female rates increased 47 percent. In some countries, like Israel, there are significant differences in incidence among different ethnic groups. Rates for men in Japan, Slovakia, and the Czech Republic have now surpassed peak US rates and are still rising. Colorectal cancer incidence rates continue to increase in economically transitioning countries, with incidence rates among men in the Czech Republic and Slovakia exceeding the peak incidence observed in the United States and other long-standing developed nations. Targeted prevention and early detection programs could help reverse the trend in these countries [17].

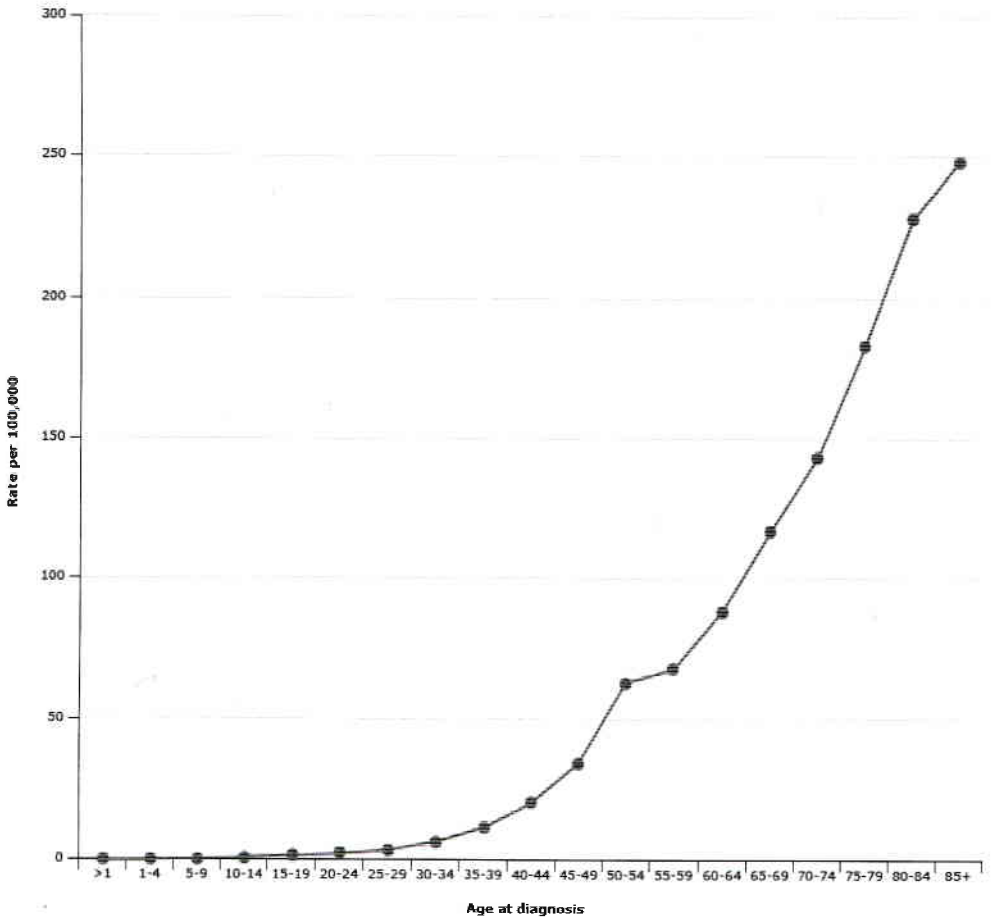
The risk of colorectal cancer begins to increase after the age of 40 years and rises sharply at the ages of 50 to 55 years; the risk doubles with each succeeding decade and continues to rise exponentially. Despite advances in surgical techniques and adjuvant therapy, there has been only a modest improvement in survival for patients who present with advanced neoplasms. [18] [19] Although the numbers of new colon and rectal cancers have been steadily declining in people over 50, the rate of newly diagnosed cancer is increasing in young adults from 20 to 49 in the United States. The increase is primarily driven by rectal cancer in non-Hispanic whites where there was an average annual increase of 3.5 percent in men and 2.9 percent in women from 1992 through 2005. Overall, incidence of colorectal cancer in young adults rose during that time 1.5 percent in men and 1.6 percent in women each year, almost all the new cancers diagnosed in the left colon

(distal colon) or rectum. A gradual shift toward right-sided or proximal colon cancers has been observed both in the United States [20] [21] and internationally [22] [23] with the greatest relative increase in incidence in cecal primaries. This change in the anatomic distribution of CRCs may be, in part, related to improvements in diagnosis and treatment, and increased screening with removal of adenomatous polyps in the distal colon. Colonoscopy is more effective in preventing left-sided than right-sided CRCs, which could also contribute to a shift in distribution of cancers in the colon. It is likely that part of the difference is due to aspects of quality relating to the colonoscopy (poor right-sided preps, incomplete colonoscopy, anatomic configurations compromising visibility) but the biology may also differ between CRCs of the right and left colon. For example, serrated adenomas, which are flatter and more difficult to visualize endoscopically, and which characteristically carry *BRAF* V600E mutations and give rise to microsatellite unstable CRCs, are more common in the right colon. Although all of these issues may contribute to a shift toward right- rather than left-sided cancers, there also appears to be a true increase in the incidence of ascending colon and cecal cancers. [23] [24].

Eating red meat increases colorectal cancer risk in the left colon and rectum, while consumption of calcium-rich foods decreases risk. Young adults' consumption of fast food increased three-fold between the late 1970's and the mid 1990's. During that time calories from hamburgers and cheeseburgers increased by 30 percent while milk consumption went down by 42 percent. Young adults are eating more red meat, more calories, and less calcium-rich foods. Two other risk factors, alcohol use and smoking, have been declining in young adults. Clinical practice guidelines suggest that patients with inflammatory bowel disease, polyposis syndromes, a known genetic predisposition, or a personal or family history of adenomatous polyps or colorectal cancer begin screening before age 50 years. Early recognition of colorectal cancer in patients under age 50 without these risk factors requires clinical awareness and aggressive pursuit of symptoms. Almost 9 out of 10 young adults had symptoms of colon or rectal cancer at the time of diagnosis. Half had rectal bleeding and a third had abdominal pain. Among those without symptoms, 14 percent had anemia. The recent increase in colorectal cancer among those under age 50 years suggests the importance of timely evaluation of the distal colorectum, at a minimum, in young adults who present with symptoms consistent with possible underlying cancer.

The increasing incidence of colorectal cancer in young adults is in contrast with the rapidly declining incidence among older individuals. **(Figure I.2)** Large bowel cancer is uncommon before the age of 40; the incidence begins to increase significantly between the ages of 40 and 50,

and age-specific incidence rates increase in each succeeding decade thereafter. Over 86 percent of those diagnosed with CRC under the age of 50 are symptomatic, and the disease is being diagnosed at later stages, suggesting that the increased incidence is real and not representative of a shift in age at diagnosis attributable to earlier detection. [25] [26] The reasons underlying this trend may be multifactorial, with contributions from genetic influences and changes in environmental and lifestyle exposures. The disparate increase in left-sided colorectal cancer suggests that particular attention be given to studies to elucidate the behavioral and environmental risk factors responsible for this trend and potential prevention and early detection strategies.



**Figure I.2. Increasing incidence of colorectal cancer with age, SEER 2014 to 2018**  
Adapted from Data from: Surveillance, Epidemiology, and End Results (SEER) Program, 2014-2018. [2] [3]

Globally, the United States has one of the highest survival rates from CRC. Data collected by the SEER Program of the United States National Cancer Institute suggest that nearly 65 percent of all patients treated for CRC (all stages and sites combined) between 2011 and 2017 survive five years [27].

In contrast to these data, mortality rates continue to increase in many countries with more limited resources and health infrastructure, particularly in Central and South America and Eastern Europe, as reflected in data from the international WHO GLOBOCAN database.

Effective primary and secondary preventive approaches must be developed to reduce the morbidity and mortality from colorectal cancer [17].

### **I.3. Etiology and Pathogenesis of Colorectal Cancer**

Genetics, [28] experimental, [29] [30] and epidemiologic [31-33] studies suggest that colorectal cancer results from complex interactions between inherited susceptibility and environmental factors. It has been suggested that dietary factors may be responsible for a significant but poorly number of cancer cases [34]. Efforts to identify causes and develop effective preventive measures have led to the hypothesis that adenomatous polyps (adenomas) are precursors for most colorectal cancers [35]. While most of these adenomas are polypoid, flat and depressed lesions that may be more prevalent than previously recognized. Large flat and depressed lesions are more likely to be severely dysplastic. Specialized techniques may be needed to identify, biopsy, and remove such lesions [36]. In effect, measures that reduce the incidence and prevalence of adenomas may result in a subsequent decrease in the risk of colorectal cancer.[37] The finding of an adenoma on flexible sigmoidoscopy may warrant colonoscopy to evaluate the more proximal colon for synchronous neoplasms. [38] Many of the intervention trials employ adenoma recurrence or disappearance as a surrogate endpoint. [39] The evolution of a carcinoma from a small adenoma, however, takes many years. [31].

The major factors that increase the risk of colorectal cancer (CRC) and influence screening recommendations are certain hereditary forms of CRC, age, a personal or family history of sporadic CRC (and possibly large or advanced adenomas), inflammatory bowel disease, and a history of abdominal irradiation. Several potentially modifiable factors, including obesity, diabetes, tobacco use, excess consumption of alcohol, excess consumption of processed meat, and lack of physical activity, have been consistently identified as risk factors in observational studies, but at present,

they do not alter screening recommendations. Other risk factors have been identified, including African American race, sex, acromegaly, and a history of renal transplantation, but their influence on screening recommendations has been variable.

A substantial body of evidence supports a protective effect of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) on the development of colonic adenomas and cancer. The potential role of aspirin and other NSAIDs in CRC prevention is discussed in important field of cercetation. Other protective factors have also been identified, mainly in observational studies, but the strength of some of these associations is uncertain. Specific types of diets may reduce the risk of CRC. Despite the uncertainty, a protective diet can be defined for clinical purposes to include avoidance of processed and charred red meat, inclusion of vegetables (especially cruciferous) and unprocessed forms of wheat bran (controversial), an adequate amount of folate intake from food, limited caloric intake, and avoidance of excessive alcohol.

Colorectal cancer is a complex trait influenced by genetic and environmental factors and their interactions. The lifetime risk of developing colon cancer in the United States is about 7%. Factors that increase a person's risk of developing the colorectal cancer include:

- **Age.** The risk of developing colorectal cancer increases with age. Most cases occur in the 60s and 70s, while cases before age 50 are uncommon unless a family history of early colon cancer is present.

- **Polyps** of the colon, particularly adenomatous polyps, are a risk factor for colon cancer. The removal of colon polyps at the time of colonoscopy reduces the subsequent risk of colon cancer.

- **History of cancer.** Individuals who have previously been diagnosed and treated for colon cancer are at risk for developing colon cancer in the future. Women who have had cancer of the ovary, uterus, or breast are at higher risk of developing colorectal cancer.

- **Heredity.** Family history of colon cancer, especially in a close relative before the age of 55 or multiple relatives is a very important risk factor. Evidence from twin studies indicates that inherited susceptibility is responsible from 30% of colorectal cancer. **Familial adenomatous polyposis (FAP)** carries a near 100% risk of developing colorectal cancer by the age of 40 if untreated. **Hereditary nonpolyposis colorectal cancer (HNPCC)** or Lynch syndrome is associated with a high rate of colorectal cancer.

- **Smoking.** Smokers are more likely to die of colorectal cancer than non-smokers. An American Cancer Society study found that "Women who smoked were more than 40% more likely to die from colorectal cancer than