

Prevention of colorectal cancer and the importance of primary care

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Abstract

Colorectal cancer (CRC) is one of the most frequent and deadliest types of cancer. Its incidence seems to be increasing in age groups 20–49 years old, without a parallel increase in mortality. Improvement of nutrition with the inclusion of more fruit and vegetables and less consumption of red meat, along with more frequent exercise are the most important elements of primary CRC prevention. Screening is arguably a valuable tool for CRC prevention. Current European guidelines recommend starting screening for CRC in the general population at the age of 50, while the American Cancer Society recommend screening start at the age of 45. Colonoscopy is considered the most reliable screening test for the detection of CRC, but at the same time it is the most inconvenient to conduct both for patients and doctors. After performing any test other than colonoscopy, any abnormal findings should be followed up with colonoscopy. The role of primary care physicians in the prevention of CRC is very important, so there should be constant updates on behalf of physicians and the general population on current CRC prevention guidelines and available screening tests.

Key words: *Colorectal cancer; prevention; screening; primary care*

INTRODUCTION

Colorectal cancer (CRC) is a common and lethal disease. The risk of developing CRC is influenced by both environmental and genetic factors. CRC incidence and mortality rates vary significantly around the world. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females. Death rates from CRC have declined progressively since the mid-1980s in the United States and in many other western countries. 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 surgical and adjuvant treatments. Current efforts to

reduce CRC incidence and mortality in adults younger than 50 years old are focused on identifying those eligible for earlier age surveillance, based on family history, and promoting both clinician and patient awareness of symptoms that could potentially point to malignancy, such as persistent rectal bleeding at any age [1].

In this review, we provide an overview of the epidemiology and risk factors of CRC, the importance of preventive medicine, the screening tests and current guidelines for CRC prevention, along with factors influencing adherence to CRC screening programmes. Moreover, we focus on the important role of primary care in CRC prevention, and suggest some actions that could improve its function.

Epidemiology and pathophysiology of colorectal cancer

In the United States, both the incidence and mor-

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tality of CRC have been slowly but steadily decreasing. Annually, approximately 149,500 new cases of large bowel cancer are diagnosed, 104,270 of which are colon cancer, and the remainder are rectal cancer. Annually, approximately 52,980 Americans die of CRC, accounting for approximately 8 percent of all cancer deaths [1]. In the European Union (EU) in 2020, it was estimated that CRC accounted for 12.7% of all new cancer diagnoses and 12.4% of all deaths due to cancer. That made it the second most frequently occurring cancer (after breast cancer) and the second cause of cancer death (after lung cancer) [2]. According to GLOBOCAN 2020, 12.2% of all new cancer cases and 11.8% of all deaths due to cancer in Greece were attributed to CRC, making it the second most frequently occurring and second most lethal type of cancer in the country [3].

Age is a major risk factor for sporadic CRC. 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. More recent data from the United States Surveillance, Epidemiology, and End Results (SEER) database and other Western cancer registries suggest that CRC incidence is increasing in the under age 50 group while it is decreasing in older groups. In the United States, the incidence of CRC in males and females under the age of 50 steadily increased at a rate of 2 percent per year from 1995 through 2016 [1]. In Europe, a study by Fanny ER Vuik *et al*, published in *Gut* 2019, showed that during the period 1990-2016, the incidence of CRC increased in Europe among subjects between the ages of 20 and 49 years old, with the fastest rise in incidence occurring in the youngest age group (20-29 years old). The rise in incidence was more prominent for colon cancer than for rectal cancer, but it was not associated with a similar rise in mortality. They suggest that, while current guidelines in Europe recommend starting CRC screening from the age of 50, a continued increase in incidence in people aged under 50 will require to lower the age to start screening, similarly to the American Cancer Society (ACS) guideline of 2018 [4].

The vast majority of tumors of the colon and rectum are carcinomas. Other histologic types (neuroendocrine neoplasms, hamartomas, mesenchymal tumors, lymphomas) are relatively unusual. Among the carcinomas, more than 90 percent are adenocarcinomas [5]. The disease begins as a benign adenomatous polyp, which develops into an advanced adenoma with high-grade dysplasia

and then progresses to an invasive cancer over a period of 10-20 years. There are many genes and growth factor pathways that drive the progression of CRC, some of them being activated (oncogenic mediators such as KRAS, BRAF, PTEN, EGFR) and others deactivated (tumor suppressor factors such as APC, b-Catenin, TP53) during the process [6].

Types of prevention and their importance

Preventive measures have decreased morbidity and mortality from both acute and chronic conditions [7]. There are three main types of prevention. Primary prevention refers to actions before health effects occur, through actions such as vaccinations, altering risky behavior (poor eating habits, tobacco use), and banning substances known to be associated with disease. Secondary prevention (screening) aims to identify diseases in the early stages, before the onset of signs and symptoms, through measures such as mammography and regular blood pressure testing. Tertiary prevention refers to managing disease post diagnosis to slow or stop disease progression through measures such as chemotherapy, rehabilitation, and screening for complications. Most prevention suggestions are primary or secondary prevention efforts for individuals [8]. Much of medical practice is based on a disease/treatment model rather than a prevention model in that the predominant focus is on treating existing symptoms and conditions. While few would argue this approach is necessary for acute conditions, there is some question as to whether this is the most efficient and effective way of delivering preventive care. A major task, therefore, is to modify the traditional medical model to incorporate more preventive services [7].

Risk factors and primary prevention of colorectal cancer

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 for CRC in observational studies [1]. Primary prevention is based on altering modifiable risk factors. Several studies have shown that high intake of red and processed meats, highly refined grains and starches, and sugars are related to increased risk of colorectal cancer. Replacing these foods with poultry, fish, and plant sources as the primary source of protein; unsaturated fats as the primary source of fat; and unrefined grains,

legumes and fruits as the primary source of carbohydrates is likely to lower the risk of colorectal cancer. With respect to lifestyle, compelling evidence indicates that avoidance of smoking and heavy alcohol use, prevention of weight gain, and maintenance of a reasonable level of physical activity are associated with markedly lower risks of CRC [9]. Medications such as aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are associated with substantial reductions in CRC risk, probably achieved through increased apoptosis and impairment of tumor cell growth by inhibition of cyclooxygenase-2, though their utility is affected by associated side effects, most frequent of whom are gastroduodenal toxicity and, with non-aspirin NSAIDs, increased cardiovascular risk [1,9,10]. Modifications in diet and lifestyle, alongside screening, are the major factors that can substantially reduce the risk of colorectal cancer [1,9].

Although the majority of CRC cases are sporadic, there are certain hereditary forms of CRC cancer, such as Familial Adenomatous Polyposis (FAP) and Lynch syndrome, that can be diagnosed and followed up with screening. Other factors that influence screening recommendations are age greater than 45 years old, a personal or family history of sporadic CRC (and possibly large or advanced adenomas), inflammatory bowel disease, and a history of abdominal radiation. 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 [1].

Screening tests

Screening is the process of searching for cancer or pre-cancer abnormalities, such as colon adenomas, in people who have no symptoms of disease. Screening is the main form of secondary prevention of CRC. According to the ACS, there are two main types of screening tests for CRC: those based on analyzing feces samples and those based on visualization of the colon and rectum. The first category includes guaiac-based fecal occult blood test (g-FOBT), fecal immunochemical test (FIT) and stool DNA test. The second category includes flexible sigmoidoscopy, colonoscopy and computed tomography colonography (CT colonography) [11]. The methodology of performance of each test is analyzed below, and the advantages and disadvantages of each test are displayed on Table 1.

The g-FOBT identifies hemoglobin by turning guaiac reagent-impregnated paper blue as the result of

a peroxidase reaction. Guaiac testing of stool samples can identify hemoglobin that may be present due to bleeding from a colon lesion or for other reasons [11,12]. The FIT also checks for non-visible blood in the stool from the intestine. The idea behind this type of test is that blood vessels in larger colorectal polyps or cancers are often fragile and easily damaged by the passage of stool. The damaged vessels usually bleed into the colon or rectum, but only rarely is there enough bleeding for blood to be seen by the naked eye in stool [11,12]. Multitarget stool DNA testing (MT-sDNA, also known as FIT-DNA, called Cologuard in the United States), is a composite of tests that include molecular assays to test for DNA (KRAS) mutations, a gene amplification technique to test for methylation biomarkers associated with colorectal neoplasia, and an immunochemical assay (FIT) to test for hemoglobin from blood that may be shed into the stool by colorectal lesions. DNA shed into stool by colorectal neoplasms may reveal genetic mutations and epigenetic changes occurring during carcinogenesis [11,12].

A flexible sigmoidoscopy is similar to a colonoscopy except it does not examine the entire colon. The 60 cm flexible fiberoptic sigmoidoscope reaches from the rectum up to the splenic flexure, allowing visualization of lesions, biopsies, and removal of polyps in the left-side of the colon only [11,12]. Colonoscopy is performed by a trained clinician using a flexible fiberoptic endoscope to directly visualize the interior of the rectum, colon, and a portion of the terminal ileum. It allows the visualization of lesions, biopsy and removal of polyps in the whole colon [11,12]. Finally, CT colonography involves obtaining multiple, thin-slice CT data and using computers to construct images of the bowel mucosa in two and three dimensions, with other enhancements to assist in interpretation [11].

Current guidelines for colorectal cancer screening

In May 2018 the ACS revised its colorectal screening guidelines, advising that regular screening for people at average risk start at age 45 years. ACS recommendations include the following: for people in good health and with a life expectancy of more than 10 years, regular colorectal cancer screening should continue through to the age of 75. People aged 76 to 85 should make a decision with their medical provider about whether to continue screening, based on their own personal preferences, life expectancy, overall health, and prior screening history. People over 85 should discontinue

Table 1. Screening tests for colorectal cancer (gFOBT=guaiac-fecal occult blood test, FIT= Fecal Immunochemical Test).

TEST	ADVANTAGES	DISADVANTAGES
gFOBT	No danger for the colon No bowel preparation needed Cheap Easy to perform at home	May not detect present polyps or tumors May be false positive Performed once a year (if normal) Diet and/or medication adjustments required prior to the test Any abnormal finding should be followed up with a colonoscopy
FIT	No danger for the colon No bowel preparation needed Cheap Easy to perform at home No diet and/or medication adjustments required prior to the test	May not detect present polyps or tumors May be false positive Performed once a year (if normal) Any abnormal finding should be followed up with a colonoscopy
Stool DNA Test	No danger for the colon No bowel preparation needed Easy to perform at home No diet and/or medication adjustments required prior to the test	May not detect present polyps or tumors May be false positive More expensive than other fecal tests Performed every three years (if normal) Any abnormal finding should be followed up with a colonoscopy
Flexible sigmoidoscopy	Safe and fast Sedation usually not required No bowel preparation required Performed every 5 years (if normal)	Does not visualize the whole colon May not detect polyps Uncomfortable for the patient Small risk of hemorrhage, infection or colon rupture Any abnormal finding should be followed up with a colonoscopy
Colonoscopy	Allows visualization of the whole colon Allows Biopsies and polyp removal Detects other possible abnormalities Performed every 10 years (if normal) The most reliable of all the CRC screening tests	Bowel preparation required Sedation may be required May miss small polyps More expensive than other tests Patient might miss a work day Small risk of hemorrhage, infection or colon rupture Uncomfortable for both doctor and patient
CT colonography	Safe and fast Usually visualizes the whole colon No sedation required Performed every 5 years (if normal)	Not widely available May miss small polyps Bowel preparation required Some false positive results Exposure to radiation Does not allow biopsies or polyp removal Any abnormal finding should be followed up with a colonoscopy

colorectal cancer screening. In addition, individuals with family history of colorectal cancer or polyps, family history of a hereditary colorectal cancer syndrome such

as Familial Adenomatous Polyposis (FAP) or Hereditary Non-Polyposis Colon Cancer (HNPCC), personal history of colorectal cancer and personal history of chronic in-

inflammatory bowel disease (ulcerative colitis or Crohn's disease) should undergo colonoscopy at an earlier age and more frequently than average risk individuals [13].

The updated guidelines on colorectal cancer screening by the American College of Gastroenterology (ACG) published in March 2021 in the American Journal of Gastroenterology recommend CRC screening in average-risk individuals between the ages of 50 and 75 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC. They also suggest CRC screening in average-risk individuals between the ages of 45 and 49 years to reduce incidence of advanced adenoma, CRC, and mortality from CRC. Finally, they suggest that a decision to continue screening beyond age 75 years be individualized, with colonoscopy and FIT as the primary screening modalities [14].

Current guidelines of the European Society of Medical Oncology (ESMO), with which a Pan-Asian panel of experts agreed and 'accepted' completely (100% consensus), recommend a complete colonoscopy for CRC screening in average-risk men and women based on higher sensitivity and specificity when compared to other tests. The optimal age range for testing is 50-74 with an optimal repetition interval for a negative test of 10 years. Flexible sigmoidoscopy (FS) carried out every 5-10 years may be an alternative for those who refuse colonoscopy. The combination of this method with a yearly FOBT is recommended to reduce the risk of a right colon tumor. Other invasive tests including capsule colonoscopy are not recommended for screening. Non-colonoscopy tests are recommended in average risk men and women from the age of 50 not already taking part in colonoscopic screening programmes. The optimal frequency of testing is every year and no later than every three years. A colonoscopy must be carried out at the earliest convenience when the test results are positive. Among the available tests, FIT appears to be superior to high-resolution gFOBT with respect to the detection rate and positive predictive value for adenomas and cancer. Individuals with a medical history of adenoma, colon cancer, inflammatory bowel disease (Crohn's disease and ulcerative colitis), significant family history of CRC or adenoma, or an inherited cancer syndrome (2%-5% of all CRC), such as familial adenomatous polyposis coli and its variants (1%), Lynch-associated syndromes (hereditary non polyposis colon cancer) (2%-4%), Turcot, Peutz-Jeghers and MUTYH-associated polyposis syndrome, are considered to be at high risk for developing colon cancer and must be actively screened

and in case of inherited syndromes, also referred for genetic counseling [15].

Barriers to colorectal cancer screening

Despite current guidelines and strong evidence that screening for CRC reduces incidence and mortality, the international screening for CRC uptake remains low in comparison with other screening methods such as mammography for breast cancer screening, a smear test for cervical cancer screening and PSA screening for prostate cancer [16]. CRC screening prevalence is below the national target in the USA. In 2018, 68.8% of adults were up to date with CRC screening. The percentage up to date was 79.2% among respondents aged 65-75 years and 63.3% among those aged 50-64 years. CRC screening prevalence was lowest among persons aged 50-54 years (50.0%) and increased with age [17]. An analysis of different programs in several European countries showed differences in screening participation rates, which in some countries (Croatia and Czech Republic) was lower than 30%. The same analysis showed that general participation rates in different programs globally currently exceed the acceptable minimum of 45%, but they have not reached the desired target (> 65%) [18].

Several studies have tried to identify the reasons behind low participation in CRC screening programs. By understanding the factors associated with CRC screening compliance, we may influence them and alter them. A systematic review by Wools et al, showed that frequently reported barriers for CRC adherence include female gender, age less than 65 years, low education level, low income, lack of health insurance, lack of awareness or the fear that the test might be painful or unpleasant, and ethnic minorities. On the other hand, prior experience of screening, dealing with a chronic disease, a family history of CRC, regular doctor visits and recommendation to start screening for CRC by their personal physician appear to be facilitators of CRC screening adherence [19]. Another recent systematic review by Dressler et al, found a range of barriers and facilitators of CRC screening, which could be divided into the following themes: psychology (e.g. forgetfulness, disgust for certain tests), religion, logistics (e.g. lack of time, other priorities, worries for test costs), health-related issues (e.g. mental issues), knowledge and awareness (e.g. absence of bowel related symptoms), general practitioner (support by a primary care physician) and environmental (e.g. social encouragement for participation) factors [20]. Several suggestions for increasing participation rates in CRC

screening programs have been made in the literature, including bigger involvement of general practitioners, implementation of media campaigns, an active call-recall system and systematic reminders to both patients and physicians [20,21,22].

The role of primary care

During the last few years, the role of primary care physicians (PCPs) in the prevention, diagnosis, and management of a number of benign and malignant gastrointestinal disorders has been recognized as very important. The role of PCPs becomes even more significant in the case of CRC as, with suitable screening programs, the rate of this neoplasm could be diminished markedly. Improvement in CRC screening rates largely depends on the efforts of PCPs to implement effective systems and procedures for screening delivery [21]. One of the key roles of PCPs currently recognized in CRC screening is to provide information to patients for their choices and decision making on screening, and it seems that PCPs' personal involvement results in better rates of participation in CRC screening programs [19,21]. The unique patient-physician relationship in primary health care, in terms of trust and continuity of care, can effectively contribute to patient compliance [23].

Although the contribution of PCPs to colorectal cancer prevention is undoubtedly important, it remains inadequate in many cases. Both PCPs and average-risk adults have identified lack of patient awareness and physician recommendation as key barriers to obtaining CRC screening. It is very important to identify the causes of this phenomenon. Probably a major reason for that is that many PCPs do not adequately follow CRC screening guidelines [21]. Several studies have demonstrated a lack of adequate knowledge regarding CRC screening among health care providers in both developed and developing countries, and suggest it could be one of the major barriers that need urgent attention [24,25]. A study by Mauri *et al*, found that CRC screening is recommended by 65–95% of PCPs in Europe, but the majority of them implemented it only among high-risk individuals, with FOBT advised by 42–83% and prescription of screening endoscopic modalities being inconsistent [26]. In Greece, a study by Kamposioras *et al*, found a wide variety of screening recommendation habits among primary care physicians, with non-recommended tests being frequently advised [27]. Available data indicate that a large effort is required to persuade PCPs to consider

CRC screening programs as a very important part of their clinical practice [21]. Additional factors that are often reported as obstacles in CRC screening by PCPs include lack of training, not having adequate time for a stool test during a consultation, not finding screening to be effective, and a difficulty in persuading patients who had no signs of colorectal disease to participate in screening programs [22,23].

It is evident, then, that a number of actions should take place, so that primary care can have a bigger, more positive impact on increasing CRC screening adherence. Better training of PCPs on CRC screening, prevention and counseling techniques should be a priority [23]. Strategies that could be considered include integrating targeted efforts to address the deficiencies in curricula used to train nurses and PCPs, increasing access to continuing professional education programs focusing on cancer prevention and screening, and access to evidence-based protocols and guidelines about CRC screening in clinical practice settings [24]. Also, since communication skills and the doctor–patient relationship are very important in this process, the vocabulary that a doctor uses while delivering the test and the choice of when to suggest the screening should be explored [22]. A more comprehensive discussion of CRC screening can increase the rates of CRC screening and PCPs must always answer the patient's personal questions with clarity to avoid any misunderstanding. They should also be flexible in their suggestions by changing to or adding another screening modality when required [21,22]. There have also been suggestions for better health care system organization in several countries with low CRC screening participation. Countries like the UK have chosen a national organization of CRC screening, operating through a call and recall system, sending out test kits, analyzing samples and dispatching results. Such a centralized system puts less pressure on the individual organizational capacities of PCPs and can help overcome many of the difficulties mentioned for both PCPs and patients [22,23,28].

CONCLUSIONS

Despite current guidelines and screening success in the prevention of CRC, public awareness and participation in CRC screening programs remains below the desired targets. PCPs can play a major part in modifying patient adherence, and thus should be constantly up to date with recent CRC screening recommendations,

while also improve their communication skills and be ready to address any patient questions and problems. Continuing training of PCPs and improvement of primary health care systems are measures that can have a positive impact on public participation in CRC screening programs.

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