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EDITORIAL

Familial colorectal cancer screening: When and what to do?

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Abstract

Colorectal cancer (CRC) is the third leading cause of death worldwide and represents a clinical challenge. Family members of patients affected by CRC have an increased risk of CRC development. In these individuals, screening is strongly recommended and should be started earlier than in the population with average risk, in order to detect neoplastic precursors, such as adenoma, advanced adenoma, and nonpolypoid adenomatous lesions of the colon. Fecal occult blood test (FOBT) is a non invasive, widespread screening method that can reduce CRC-related mortality. Sigmoidoscopy, alone or in addition to FOBT, represents another screening strategy that reduces CRC mortality. Colonoscopy is the best choice for screening high-risk populations, as it allows simultaneous detection and removal of preneoplastic lesions. The choice of test depends on local health policy and varies among countries.

Key words: Colonoscopy; Colorectal cancer screening; Fecal occult blood test; Advanced adenoma; First-degree relative; Sigmoidoscopy

Core tip: One-fifth of people who develop colorectal cancer (CRC) have a first-degree relative (FDR) affected by this malignancy. Screening is an efficient method to reduce mortality for CRC and should be started in FDRs earlier than in the population at average risk. There is a large disparity in guidelines for screening in familial CRC, therefore, here we address the principal indication and methods for screening in this population at increased risk. Recent or emerging methods to improve the participation rate in screening programs are described. Ongoing trials on CRC screening are also reported.

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INTRODUCTION

Colorectal cancer (CRC) remains a major health problem in industrialized countries, being responsible for > 550000 deaths annually, and representing the third leading cause of cancer mortality worldwide[1,2]. In Europe in 2012, it is estimated that 3.45 million new cases of cancer were diagnosed and 1.75 million patients died from malignant diseases. Concerning CRC, the annual number stands at 447000 new cases[3].

The incidence of CRC increased from 22 cases per 100000 individuals in 1960 to 34 per 100000 in 2007[2] in Northern Europe. From 1998 to 2002, the incidence in the United States and Europe was similar, being, respectively, for men 38.6 and 38.5 and for women 28.3 and 24.6 world age standardized rate (ASR-W), as calculated per 100000 inhabitants[4]. However, mortality both for men and women, over the same period, was higher in Europe than in the US, being 18.5 and 10.7 *vs* 13.5 and 9.2 ASR-W, respectively, as calculated per 100000 inhabitants[5]. The estimated Italian median annual incidence rate in 2010 was 88.8 cases per 100000 individuals among men and 70.3 cases per 100000 among women per year[6].

The lifetime risk of CRC for average-risk subjects in industrialized countries is about 5%[1,7], but it increases 2-4-fold if there is a family history of CRC[8]. Studies in kindred and twins estimated that approximately 30% of all cases of CRC occur in patients with a family history of CRC, but only 2%-5% of cases of inherited CRC are caused by a syndrome-related to a Mendelian pattern of inheritance[8-12]. These rare syndromes are associated with a known gene mutation (Table 1). Familial adenomatous polyposis (FAP) syndrome is the most common hereditary condition, with a prevalence of 1 in 10000 individuals. Young adolescents with FAP develop hundreds to thousands of colonic adenomas and CRC is inevitable before age 40 years if preventive surgery (colectomy) is not performed. Attenuated FAP is a less severe form of the disease, characterized by an average 69% lifetime risk of CRC and an average of approximately 30 colonic adenomatous polyps (range 0 to 100 s). Both FAP and attenuated FAP result from germline mutations in the APC gene[10]. In the absence of these inherited syndromes, occurrence of CRC in family members of a CRC patient is nowadays considered to be a heterogeneous condition, including a cluster of patients with undefined hereditary syndromes that have not yet been completely defined in terms of molecular pathogenesis. A study in sibling pairs and parent/child pairs reported the presence of chromosomal regions containing low penetrance susceptibility genes possibly associated with high risk of familial CRC[10]. Together with genetic conditions, a combination of different environmental factors plays a role in the development of familial CRC. As in the average-risk population, in familial CRC, several environmental and lifestyle factors may increase the risk of malignancy, such as obesity, high intake of alcohol, cholesterol-rich diet, low consumption of green vegetables, low level of physical exercise, and smoking[13,14]. In contrast to what would be expected, family members of a CRC patient often do not seem to change their lifestyle, including physical exercise, smoking and eating/drinking habits[14].

Table 1 Hereditary syndromes associated with high risk of colorectal cancer and principal involved genes

Syndrome	Mendelian pattern	Gene
Lynch syndrome	Autosomal dominant	*hMLH1*
Familial adenomatous	Autosomal dominant	*APC*
Attenuated FAP	Autosomal dominant	*APC FAP*
MUTYH-associated polyposis	Autosomal recessive	*MUTYH*
Peutz–Jeghers syndrome	Autosomal dominant	*STK11*
Juvenile polyposis syndrome	Autosomal dominant	*SMAD4*

CRC in subjects with a family history seems to have a better prognosis, with a greater overall 5-year survival rate and an 11% reduction in the risk of death compared with those with no family history[15]. Further studies support a better prognosis in patients with a family history of CRC[16,17]. The reason for the survival advantage associated with familial CRC is not known. It could be that a family history of CRC leads to earlier detection of tumor and therefore a better prognosis. Indeed, the survival difference persisted when patients with or without a family history were matched by stage at diagnosis. An alternative explanation suggests a deficit of mismatch repair mechanisms in patients with familial CRC[15], which has been linked to a longer survival rate in CRC[18]. This hypothesis is based on the finding that patients with a family history of CRC have a high proportion of right-sided tumors, which frequently are associated with deficient mismatch repair mechanisms[18].

A first-degree relative (FDR), namely a family member who shares at least 50% of genes with a particular individual in the same family, such as parents, offspring and siblings, of a CRC patient is at higher risk of developing CRC[8]. Additional risk factors are age of tumor occurrence in the index case and the number of affected relatives[12,19], which contribute to increasing the CRC risk from moderate (1.5-2.5 times), when only one FDR is affected by CRC, to high (4-6 times), when two or more FDRs are affected or when cancer is diagnosed before age 50 years[8]. In a large population study[19] from the Utah database, including persons with a family history of CRC of ⩾ 3

generations, an increased number of affected FDRs was demonstrated to influence the risk much more than an affected second-degree relative (SDR) or third-degree relative (TDR). However, when combined with a positive FDR history, a positive SDR and TDR family history represents a further increase of risk.

An increased rate of colonic adenoma detection is also reported in individuals with a family history of CRC in comparison with average-risk subjects[20-26]. Colorectal adenoma > 10 mm, with high-grade dysplasia and/or a villous component, termed as advanced adenoma (ADA), is a precursor of CRC. Several colonoscopy-based screening studies[21-25] reported an increased prevalence of ADA in FDRs of CRC patients, ranging from 3.3% to 21.3%, in relation to average-risk subjects in whom it was defined as 1.9%-11.5%. A high prevalence of ADA has also been described among young FDRs aged 40-45 years, which increased with age[25]. Additional risk factors are male sex and the strength of family history, increasing the risk of developing CRC or ADA by 1.5-3.0-fold[27]. The number of FDRs affected also influences the risk of ADA, being higher in asymptomatic subjects with two FDRs with CRC diagnosed at any age in comparison to asymptomatic subjects with only one FDR with CRC at age < 50 years[22]. All these risk factors have to be taken into consideration in a screening program, in order to select a subpopulation of patients with highest risk, and in whom screening investigations could be indicated earlier than in subjects without these risk factors. According to these studies, United States scientific societies[28-32] suggest a different and more aggressive screening program in subjects with familial CRC in comparison to that recommended in average-risk populations.

Data on familial CRC screening from Asia confirm the increased risk in FDRs of CRC patients. A study from Taiwan[33] reported that among FDRs of patients with CRC, the risk of adenoma detected by colonoscopy was 2.5-fold and the risk of ADA was 4.5-fold higher compared with that in control subjects without a family history of CRC. Another study from Hong Kong[24] reported that the risk of detecting adenoma and advanced neoplasms in asymptomatic FDRs of patients with CRC was, respectively, 2.19-fold and 3.07-fold higher than in those with a negative family history of CRC. The increased risk is more marked if the index case were diagnosed with CRC before the age of 50 years.

FAMILIAL CRC SCREENING: WHEN TO DO

Screening programs are based on the assumption that the vast majority of CRCs develop from a benign precursor lesion, such as adenoma, through a series of genetic changes over a long-time period (adenoma-carcinoma sequence)[7,34]. It has been estimated that a small adenoma needs at least 10 years to become a cancer[7]. Thus, screening programs are aimed to identify these preneoplastic lesions using different tools, such as fecal occult blood test (FOBT), sigmoidoscopy, and colonoscopy. Screening recommendations take into consideration the so-called anticipation phenomenon, suggesting that CRC arises 10 years earlier in FDRs of CRC patients than in subjects without a family history[7,35]. Therefore, according to United States recommendations[29-32], screening interventions should be offered to individuals with a family history of CRC earlier than for the average-risk population. Subjects with a single FDR with CRC diagnosed at age > 60 years should receive a standard CRC screening, namely every 10 years, but starting at age 40 years. Individuals having one FDR with CRC before 60 years or two FDRs with CRC should be screened every 5 years, preferably by colonoscopy, starting at age 40 years, or at 10 years younger than the earliest case in the family[36]. In individuals with SDRs or TDRs with CRC, colonoscopy every 10 years is recommended, as in subjects at average risk. In contrast to United States recommendations, European guidelines[37] suggest performing an immunochemical FOBT every 1 or 2 years in subjects at average risk, and high-risk individuals should be referred for high-risk protocols. Although CRC screening is generally considered to be an effective way to reduce the incidence and mortality of CRC, the optimal screening strategy in high-risk populations is still debated, especially regarding the appropriate age at which to start screening colonoscopy, the time interval for repeat colonoscopy, and which diagnostic tool is preferred, according to different health policy organizations in different countries[29-32,37].

Asia-Pacific guidelines also recommend earlier screening in FDRs of CRC patients, that is, before 50 years of age[38]. A scoring system, based on several risk factors, such as age, sex, family history and smoking habit, has been developed by the Asia-Pacific Working Group for stratifying risk and prioritizing high-risk individuals for earlier screening[39]. According to this scoring system, validated in a 15-country multicenter Asian study on asymptomatic subjects, moderate-to-high-risk individuals should undergo colonoscopy, while those classified as average risk should undergo a fecal immunochemical test (FIT) followed by colonoscopy in case of a positive result[38].

FAMILIAL CRC SCREENING: WHAT TO DO

An ideal biochemical test for population screening should be specific and sensitive for both cancer and preneoplastic lesions, on easily collected samples, safely and cheaply transported to a centralized laboratory for accurate, reproducible, and cheap automated analysis. Unfortunately, no investigation

fulfills those criteria. Screening tests can be grouped into those detecting cancer, such as FOBT, and those revealing cancer and adenomatous polyps or nonpolypoid lesions, such as sigmoidoscopy and colonoscopy, which allow simultaneous removal of neoplastic precursors, providing greater potential for secondary prevention. Colonoscopy has been proposed as the preferred screening method, especially in high-risk populations[40-42], while both colonoscopy and FOBT have been recommended in CRC screening program in expert panel recommendations from various countries[30,37,43].

FOBT

Screening by FOBT has been tested in large, prospective, case-controlled studies in average-risk subjects, showing a significant reduction in CRC mortality[44-46]. In an Italian screening population study based on FOBT, an increased risk of ADA (OR = 1.53) was reported in subjects with familial CRC compared to those without a family history[26]. The rationale for the use of FOBT as a screening tool in the clinical diagnosis of CRC is based on the observation that small, macroscopically invisible traces of blood (occult blood) are released into the bowel lumen by colonic neoplastic tissue. However, FOBT cannot detect nonbleeding colonic preneoplastic lesions. The main limit of FOBT is the high number of false-positive results due to gastrointestinal bleeding associated with several causes other than colonic neoplasia, such as erosions, ulcers, inflammatory bowel diseases, or therapy with antiplatelet agents, anticoagulants or nonsteroidal anti-inflammatory drugs.

Two types of FOBT are available, guaiac-based tests (gFOBTs) and immunochemical tests (FITs). gFOBT is unable to distinguish human from non-human blood, contained in raw meat, and requires a restricted diet before stool collection. gFOBT is available in rehydrated and non-rehydrated form, according to the mechanism of the hydration of stool samples. The mechanism of rehydration increases the sensitivity, but decreases specificity, leading to more false-positive results. FIT is based on the use of monoclonal or polyclonal antibodies against the protein component of human globin, therefore, it does not require a specific diet. Several recent studies[36,47-50] on average- and high-risk population screening programs demonstrated a higher sensitivity but lower specificity of FIT in comparison to gFOBT (61%-69% and 91%-98% *vs* 25%-38% and 98%-99%, respectively) in detecting CRC.

Different cut-off values for fecal hemoglobin detection have been proposed to increase further the diagnostic capability of FIT in identifying early neoplastic lesions and ADA. Good sensitivity of FIT was demonstrated when the cut-off level for fecal hemoglobin detection was reduced from 250 to 50 ng/mL buffer[48]. FIT with a low cut-off level repeated annually for 3 years seems to have sensitivity in detecting both ADA and CRC in FDRs of CRC patients similar to that of a single colonoscopy[51]. Thus, FIT could increase screening acceptability in high-risk subjects and reduce the number of negative screening colonoscopy results[51]. The disadvantage of FIT is the cost, even if it is now approaching that of gFOBT, particularly for qualitative tests[52].

Few data regarding diagnostic accuracy of FOBT in familial screening programs are available. In a cohort study of asymptomatic high-risk patients with a personal history of adenomas/CRC or family history of CRC, sensitivity, specificity, positive predictive value and negative predictive value of single FIT sampling were 80%, 89%, 3% and 99.9% for CRC and 28%, 91%, 24% and 92% for ADA, respectively[53]. High accuracy of FIT was confirmed in a multicenter study among FDRs of CRC patients, in which AUC was 0.96 (95%CI: 0.95-0.98) for CRC and 0.74 (95%CI: 0.66-0.82) for ADA[54].

European guidelines[37] recommend the use of FIT as test of choice for population screening, although gFOBT could be more practicable and affordable than FIT, considering the local labor costs and the mechanism of kit distribution and collection.

Advantages and disadvantages: gFOBT and FIT are both simple noninvasive screening methods, cheaper with respect to other screening tests such as colonoscopy, and easy to perform in the general screening population. The only disadvantage of gFOBT or FIT is the low sensitivity for detecting cancerous and preneoplastic lesions.

Fecal DNA test

Fecal DNA test is a new screening method based on finding several specific tumor-related DNA changes in cells shed from colonic neoplastic lesions into the bowel[55]. Most studies published to date have focused on the feasibility and characteristics of the test rather than on the real impact on reduction of CRC incidence and mortality. Fecal DNA test has higher sensitivity but lower specificity than gFOBT for CRC detection. A stool-based test for methylation analysis of the vimentin (VIM) gene has been developed recently in the United States, showing a specificity and sensitivity of almost 80%. Several additional hypermethylated genes, including APC, p16, hMLH1, MGMT, SFRP1, SFRP2 and VIM, have been isolated from stool samples and utilized as biomarkers for detecting CRC or colorectal adenomas with a sensitivity of 62%-75%[56]. In another study[57] hypermethylation of fibrillin-1 (FBN1), detected in stool samples, showed a sensitivity of 72% and a specificity of 93% for detecting CRC.

Whether ADA can be reliably detected by fecal DNA test remains to be fully clarified. Despite a recommendation for its use by the United States Multi-Society Task Force on Colorectal Cancer[28], fecal DNA test has not yet achieved wide application, probably

due to its considerable cost.

Advantages and disadvantages: Fecal DNA test offers the same advantages but is more expensive than FOBT. How frequently fecal DNA test should be done to screen adequately for CRC remains to be determined.

Screening colonoscopy

The increased prevalence of CRC or ADA in FDRs of CRC patients, as mentioned above, represents the rationale for why screening colonoscopy is strongly recommended by several scientific societies[28-31] in members of families with an increased risk for CRC. The high rate of adenoma and ADA in the right colon of FDRs of CRC patients[22,58,59] and the occurrence of CRC in the right colon in 30%-40% of FDRs[60,61] indicate that an endoscopic assessment of the entire colon for screening purposes should be preferred to the limited exploration of the left colon. The usefulness of such a recommendation is confirmed by the growing evidence that colonoscopy-based screening programs are able to reduce CRC incidence and mortality. Two studies[62,63] reported that an increased use of lower gastrointestinal endoscopy led to a reduction in the incidence and mortality due to CRC in an average-risk population in the US. An Italian large population-based cohort study[64] showed that a 5-year colonoscopy-based screening for CRC in asymptomatic subjects achieved a decrease of 48% in CRC incidence and 81% in mortality. The reduction in CRC incidence was more evident in subjects who underwent complete colonoscopy[64].

However, several factors limit the use of colonoscopy as screening procedure, such as a high cost, possible occurrence of complications, and low acceptability. In a cost-effectiveness analysis[65] of different screening methods, such as FOBT, sigmoidoscopy, and colonoscopy, considering the number of prevented cases of CRC and the costs spent per life-year saved from cancer-related mortality, annual screening with FOBT was less expensive but saved fewer life-years than colonoscopy. A screening strategy based on sigmoidoscopy every 5 or 10 years is less cost-effective than FOBT and colonoscopy[66]. In prospective cohort studies[40,67-69] on asymptomatic adults undergoing colonoscopy, for screening or surveillance due to a history of CRC or adenoma, reported complication rates ranged from 0.79 to 8.4 per 1000 colonoscopies. Thus, the absolute risk of serious complications is low, even if it is higher than for FOBT or sigmoidoscopy. Finally, low acceptance of colonoscopy is still the main barrier to widespread dissemination for screening. Adherence to colonoscopy screening programs is low even in members of high-risk families, and varies from 18% to 78% in different countries. This low acceptability of colonoscopy in FDRs may have several reasons, such as invasiveness of the method, fear of feeling pain, and lack of information about the possibility to prevent CRC by simultaneous detection and removal of preneoplastic lesions. Therefore, more detailed information should be provided to subjects with a family history of CRC regarding the safety of colonoscopy and the possibility of performing the procedure under sedation. In this regard, general practitioners play a decisive role, especially in less-educated people who are less likely to obtain information in other ways[22,58,70,71].

High-quality colonoscopy is crucial to achieve good CRC screening, therefore several technical factors have to be taken into account[37]. Colonoscopy should be completed to the cecum, and withdrawal of the endoscope should be slow. The number of adenomas and ADA found during colonoscopy with a withdrawal time of $\geqslant$ 6 min is about twofold, or more, than that found with a shorter withdrawal time[72]. A 6-min withdrawal time is currently considered a standard of care. Screening colonoscopy has to be performed under conditions of good bowel cleansing, which means that, in the absence of completely removable residual tumor, the examination has to be repeated following a more intensive cleaning procedure. Of course, screening colonoscopy has to be performed by an expert, high-volume operator (> 300 colonoscopies per year), and photographic documentation of the ileocecal valve and cecum should be auditable[36,73].

Advantages and disadvantages: The main advantage of colonoscopy is the possibility to examine the entire colon and immediately remove a preneoplastic lesion. Disadvantages include the need for colonic lavage, which requires a low-residue diet on the days before the examination and oral intake of laxatives with a large amount of water. It is an invasive screening method and, therefore, is not easily accepted by asymptomatic subjects if not proposed under sedation.

Sigmoidoscopy

Flexible sigmoidoscopy (FS) is an endoscopic examination with maximum reach to the splenic flexure. When compared with no screening in average-risk populations, CRC mortality was lower with FS in comparison to FOBT[74]. In a systematic review and meta-analysis[75] of five randomized controlled trials, FS screening achieved a 18% relative risk (RR) reduction in the incidence of CRC (RR = 0.82, 95%CI: 0.73-0.91; $P < 0.001$), a 33% reduction in the incidence of left-sided CRC (RR = 0.67, 95%CI: 0.59-0.76; $P < 0.001$), and a 28% RR reduction in the mortality of CRC (RR = 0.72, 95%CI: 0.65-0.80; $P < 0.001$).

However, FS has no effect on the incidence of proximal colonic malignancy[76]. The combination of FS every 5 years with annual FOBT is better than either test used alone[29-31].

Advantages and disadvantages: FS is a less-invasive procedure than colonoscopy and requires easier preparation. The main disadvantage is that FS evaluates only the distal segments of the colon and, in case of a positive result, complete colonoscopy is necessary to examine the proximal colonic tracts.

Potential screening methodologies

Computed tomography colonography: Computed tomography colonography (CTC), also known as virtual or CT colonoscopy, is a low-invasive radiological method to study the colon with a low risk of complications. Thus, CTC could be an alternative to colonoscopy in CRC screening. Indeed, CTC is already used for screening purposes in patients with a positive FOBT result when colonoscopy is contraindicated or fails to reach the cecum for anatomical reasons[77]. CTC has a high sensitivity (approximately 95%) in detecting CRC[78] and colonic polyps > 10 mm[79], but sensitivity drops to 75%-80% for nonpolypoid adenomas ⩾ 5 mm[80]. Patients undergoing CTC are exposed to ionizing radiation, raising concerns about a possible increased risk for malignancy, and the need to perform colonoscopy if polyps or other possible neoplastic lesions are detected, with increased screening costs. To reduce the discomfort associated with bowel preparation, noncathartic CTC has been proposed as a screening method for CRC in FDRs, with good sensitivity and specificity for small adenoma (77% and 99%) and ADA (89% and 96%)[81]. Bearing in mind all these considerations, CTC is not yet considered for population screening programs.

Electronic nose: It is a new technology based on an array of nanosensors reacting to volatile organic compounds by a sensor-specific change in resistance. Volatile organic compounds are gaseous carbon-based chemicals derived from biochemical metabolism in the body, and in the bowel they are mainly produced by the intestinal microbiota and excreted by the feces[82]. Electronic nose has already been proposed as a potential noninvasive diagnostic biomarker test for lung cancer, breast cancer and malignant melanoma[83,84], and recently[85], it was shown to discriminate healthy subjects from patients with CRC (sensitivity and specificity: 85% and 87%, respectively) and patients with ADA (sensitivity and specificity: 62% and 86%, respectively). If diagnostic accuracy is confirmed, electronic nose could represent a new noninvasive method of screening for CRC and its adenomatous precursors.

DNA methylation blood analysis: It could be a valuable noninvasive diagnostic tool for CRC screening. Aberrant patterns of DNA methylation from CRC cells can be detected in blood and reflect DNA methylation profiles present in CRC tissue. The presence of aberrantly methylated septin 9 in plasma is a valuable and minimally invasive blood-based PCR test, showing a sensitivity and a specificity of almost 90% in detecting CRC[86].

Soluble CD26: Soluble CD26 (sCD26) is a transmembrane glycoprotein expressed in a variety of cell types and associated with neoplastic transformation. Being present in plasma, serum and other biological fluids, sCD26 has been proposed as a blood screening tool, showing a sensitivity of 39.6% for ADA and 42.1% for advanced neoplasms, achieving specificity of 90%. The combination of sCD26 and FIT increases the sensitivity for ADA and advanced neoplasms up to 52.8% and 56.1%, respectively, corresponding to 93.5% specificity[87].

ONGOING TRIALS ON COLORECTAL CANCER SCREENING

Two Italian trials are ongoing to compare colonoscopy or sigmoidoscopy *vs* CTC for CRC screening[88,89]. Data regarding acceptability, diagnostic yield, and costs of the methods emerging from these two studies will be helpful to understand better whether CTC may play a role in screening for CRC. An interesting trial[90] is ongoing to evaluate the importance of an enhanced family communication about genetic testing and hereditary risk information. The trial will evaluate the effectiveness of additional support using a randomized controlled design based on motivational interviewing; will apply an intervention for mutation carriers and counselees with relatives with an increased risk of developing cancer; and will involve relatives in the study.

CONCLUSION

CRC screening can reduce mortality and is cost-effective. Therefore, it is mandatory that clinicians and health organizations implement strategies to improve adherence to screening programs in subjects at average risk, but first of all in those having an increased CRC risk. To date, colonoscopy represents the best choice for a screening program. General practitioners and physicians should make efforts in counseling individuals at high risk of CRC to undergo this procedure, starting at 40-45 years of age. If not accepted, FOBT, preferably associated with sigmoidoscopy, has to be prescribed.

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