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Colorectal cancer: screening

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Introduction

Colorectal cancer (CRC) is one of the biggest killers worldwide, with the highest incidence and prevalence in economically developed countries. In the United States CRC is the third most common type of tumor and the second most common cause of death [1]. In Europe CRC accounts for 8% of the total cancer prevalence in both genders [2] and is the second leading cause of death [3].

CRC is rare under the age of 45 years: the incidence and the cumulative risk of disease increase with age. The mean age of diagnosis is 68 years. The 5-year survival rate depends on stage of disease: from 80% to 90% when confined to the bowel wall, to <5% in the metastatic setting.

In 1985–1989 the population-based CRC 5-year relative survival was lower in Europe than in the USA (45% versus 59%). This difference in survival was partly explained by differences in the distribution of cancer subsites and morphology and partly attributable to differences in stage at diagnosis [4], but the main explanation was the proportion of adenocarcinoma in polyps (13% versus 2%) [5].

The great majority of CRC comes from premalignant lesions (adenomatous polyps). It is estimated that in the general population the risk of developing a colorectal adenoma is nearly 19%, and that 2–5% of sporadic polyps will develop into an invasive carcinoma. Hyperplastic polyps are not considered premalignant lesions and do not predict adenomas or cancer. Between 5% and 15% of individuals develop a CRC on the basis of a genetic predisposition (because of a germline mutation), and in this case, the onset of cancer occurs at earlier age than the sporadic form.

Screening

The aim of cancer screening is the identification of an asymptomatic and earlier stage disease, when it is potentially treatable and curable, resulting in an improvement of outcomes (reduction of morbidity and mortality), modifing the natural history of the disease.

CRC is a good candidate for a screening for several reasons: (i) high incidence, prevalence and cause of death worldwide, expecially in non-smokers; (ii) the long period between the development of earlier abnormalities of the mucosa (polyps) and of an invasive cancer (~10 years [6]); (iii) adenomatous polyps are well managed by endoscopic intervention; and (iv) survival depends on stage of the neoplastic lesion (early stage leads to better prognosis).

The risk of CRC is not the same in all subjects. There are groups that have a high incidence of cancer (high risk subjects) compared with the general population (average risk subjects). For this reason the recommendations for CRC screening depend on the individual risk.

Screening individuals at average risk

Individuals at average risk for CRC are healthy people with no known risk factors other than age.

In this setting the aim of the screening is the detection of sporadic cancer in asymptomatic individuals. The diagnosis of CRC at an earlier age than 50 years is uncommon; therefore, the practical guidelines for screening in average subjects recommend starting screening at 50 years.

Tests for CRC screening

Fecal occult blood test

Stool testing for the presence of haemoglobin either with rehydrated or non-rehydrated specimen is simple, inexpensive, non-invasive and widely available. The guaiac-based test is the most common test used in clinical trials and practice.

Randomized controlled [7–9] and population-based [10, 11] trials have shown that annual or biennual fecal occult blood testing (FOBT) in people aged 50–80 years reduces the CRC mortality by 13–33% (follow-up 10–13 years). A systematic review, including a meta-analysis, showed a reduction in CRC mortality of 16% [12]. The mortality reduction was 23% when adjusted for attendance for screening in the individuals trials.

Rehydration of guaiac specimen greatly increases sensitivity but reduces specificity (because of an increased rate of false-positive tests) and consequently, increases the number of colonoscopys performed. Since <10% of those with occult blood in their stool have cancer and ~20–30% have adenomas [13], the major determinant the costs of screening with FOBT is the number of subjects who have a positive test and than require colonoscopy.

An immunological FOBT appears more specific (low risk of false-positive result), and is theoretically representative of all

colorectal blood loss; however, it is more expensive. FOBT is recommended every 1–2 years. Testing must be conducted on two samples from three different stool specimens on consecutive days as multiple consecutive samplings, as this offers multiple potential opportunities to detect intermittent bleeding.

A positive FOBT requires follow-up with a complete evaluation of colorectal tract (colonoscopy).

Sigmoidoscopy

About half of polyps are detected with a 35 cm flexible-sigmoidocope (FS) and two-thirds to three-quarters with a 60 cm sigmoidoscope [14, 15].

The best evidence of effectiveness in reducing mortality related to CRC is indirect and derives from a case–control trial of rigid sigmoidoscopy [16], which described a mortality reduction in 60% of cases for lesions within reach of the sigmoidoscope. These findings are supported by other two case–control study: sigmoidoscopy was associated with an 80% reduction in mortality from rectal and distal colon cancer, and with a 60% reduction in incidence [17, 18].

The advantage of an endoscopic procedure is the chance of detecting and removing colorectal adenomas and cancers, up to or near the splenic flexure.

The greatest limit of FS is the identification of ∼50% of premalignant or malignant lesions because it can examine only half of the colon, even though far less than half might be examined owing to a poorly trained examiner, inadequate preparation of lower colon or a patient's intolerance. Like a positive FOBT, an abnormal sigmoidoscopy also requires colonoscopy. The real question is the determination of the best interval at which perform sigmoidoscopy screening. It is common practice to reccomend FS every 5 years beginning at age 50 years [19, 20].

Combination of FOBT and FS

The Norwegian Colorectal Cancer Prevention (NORCCAP) once-only screening study randomized more than 20 000 subjects, aged 50–64 years, to FS or a combination of FS with FOBT [21]. A positive FS (the detection of any neoplasia or any polyp ≥10 mm) or positive FOBT qualified an individual for colonoscopy. CRC was detected in 0.3% of individuals screened. Any adenoma was found in 17%, and in 4.2% a high-risk adenoma was detected. There was no difference in diagnosis of CRC or high-risk adenoma between the 'FS only' group and the 'FS plus FOBT' group. An accepted CRC screening strategy is annual FOBT, FS every 5 years or the combination of both, beginning at age 50 years.

Colonoscopy

Colonoscopy has the potential to detect lesions in the entire colorectal tract, remove benign precursor adenomas and corroborate by biopsy the diagnosis of any suspected neoplastic lesion. This endoscopic procedures can detect 87–94% of polyps (6–10 mm in size) [22]. Even if colonoscopy is recommended as screening test, there are no randomized clinical trials that support its use in reducing colorectal cancer mortality. Reports of its effectiveness come from clinical practice, from a case–control study [17] and from an uncontrolled observational study [23].

Indirect evidence also derives from FOBT trials that required colonoscopy to ascertain the diagnosis and the source of occult blood [7–9] and from the previously citated sigmoidoscopy studies [16–18].

In one randomized controlled trial [24] conducted in over 3000 predominantly male US veterans, screening performed with sigmoidoscopy followed by colonoscopy identified advanced neoplasia (adenoma that was ≥10 mm in diameter, a villous adenoma, an adenoma with high-grade dysplasia or invasive cancer) in 10.5% of the individuals and detected 2.7% of advanced proximal neoplasia among patients without adenomas in the distal tract. Another finding was that the presence in the distal colon of large or small adenomas (≥10 or <10 mm, respectively) was associated with an increased risk of advanced neoplasia in the proximal tract. Another study conducted in nearly 2000 adults (aged 50 years or older) who underwent colonoscopic screening detected that 46% of those with advanced proximal neoplasms had no distal polyps [25]. If colonoscopic screening is performed only in patients with distal polyps, about half of cases of advanced proximal neoplasia will not be detected.

The optimal interval of CRC screening with colonoscopy is not known, but based on the long period between the development polyps and an invasive cancer [6], the preferred attitude is to perform colonoscopy every 10 years beginning at age 50 years.

Double-contrast barium enema

Double-contrast barium enema is insensitive for the detection of flat or small adenomas. When compared with colonoscopy the detection rate of adenomatous polyps depends on the size of the adenoma. Double-contrast barium enema is an acceptable alternative only when colonoscopy cannot be carried out. Because of its lower sensitivity it is recommended every 5 years.

Digital rectal examination

Digital rectal examination is not associated with a statistically significant reduction in mortality from CRC. It is part of routine physical examination and is not recommended as a CRC screening procedure.

Virtual colonoscopy [computed tomography (CT) colonography or CT pneumocolon]

Virtual colonoscopy is the examination of the colon using the three-dimensional images generated by a conventional CT scan. In the same time, the entire colon can be seen outside and within the lumen (as with double-contrast barium enema and with an endoscope). Up to now, traditional and virtual colonoscopy seem to have similar efficacy in detecting polyps >5 mm in size. Results coming from highly specialized centers

demonstrate that virtual colonoscopy achieves an accuracy equivalent to traditional colonoscopy [26], but this finding is not confirmed by another study conducted in an hospital with less experience, where the accuracy of CT colonography was found to be substantially lower [27].

None of the clinical practice guidelines or societies recommends this technique for CRC screening.

Fecal DNA testing

An interesting and promising area for colorectal cancer screening is the analysis of a fecal DNA test. DNA markers (usually multiple DNA markers deriving from neoplastic or premalignant cells) are analyzed starting from a single stool. The procedure does not required bowel preparation or diet restriction. Early clinical trials have shown that multitarget DNA testing has high sensitivity and specificity for carcinoma and adenoma. This test is still under investigation and is not recommended as screening method.

In the above sections we listed the principle recommendations derived from international and national societies for screening average-risk subjects (Table 1).

The American Cancer Society (ACS) Guidelines for the Early Detection of CRC [28] recommends beginning screening at age 50 years, using one of the following options: annual FOBT; FS every 5 years; annual FOBT plus FS every 5 years; double-contrast barium enema every 5 years; or colonoscopy every 10 years. These recommendations are very similar to those issued in the US Preventive Services Task Force guidelines, which were updated in 2002 [29].

The Advisory Committee on Cancer Prevention in the European Union [30] suggests that if screening programmes for colorectal cancer are implemented they should use the FOBT, and colonoscopy should be used for the follow-up of positive cases. Screening should be offered to both gender aged 50 to ~74 years.

In Italy the Consiglio Nazionale delle Ricerche (CNR) and the Ministero dell'Istruzione, dell'Università e della ricerca (MIUR) [31] have recently updated the scientific basis for defining the clinical guidelines for colorectal tumor. This document recommends biannual FOBT starting at age 50 years, and that FS should be performed at least once between age 55 and 64 years. Indications about the optimal interval of CRC screening with sigmoidoscopy and colonoscopy are pending.

The Associazione Nazionale di Oncologia Medica (AIOM) [32] recommends CRC screening beginning from 50 years with: annual FOBT or sigmoidoscopy every 5 years, or colonoscopy every 10 years. A positive FOBT requires colonoscopy.

Screening individuals at high risk

Individuals at high risk for CRC are subjects with: a personal history of adenomatous polyps or CRC, a family history of either CRC or colorectal adenomas diagnosed in a first-degree relative before age 60 years, a history of inflammatory bowel disease of significant duration, and a family history of or genetic testing indicating the presence of one of two hereditary syndromes.

The recommendations for different groups according to various international and national societies are listed in Table 2.

The ACS recommends more intensive surveillance for these subjects, and the recommended options vary from beginning screening at an earlier age with the same procedures of average risk group, to more frequent screening with colonoscopy and sometimes with genetic counselling and genetic testing.

Inherited CRC syndromes

Inherited CRC syndromes account for ~3–6% of all colorectal tumors. The lifetime risk of cancer is high because of underlying germline mutations. Familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) are the major inherited syndromes.

Familial adenomatous polyposis. When the APC mutation is known genetic testing should be considered in the relatives of patients with FAP. Failure to find the APC mutation does not

Table 1. Colorectal cancer screening recommendations for average-risk individuals

ACS guidelines [28]	ACCP guidelines [30]	CNR-MIUR guidelines [31]	AIOM guidelines [32]
Begin screening at age 50 years with one of the following options:	Begin screening at age 50 to ~74 years with FOBT	Begin screening with biennually FOBT at age 50 years	Begin screening at age 50 years with one of the following options:
Annual FOBT	Colonoscopy should be used for the follow-up of positive cases	FS at least once from age 55–64 years	Annual FOBT
FS every 5 years			Sigmoidoscopy every 5 years
Annual FOBT+FS every 5 years		Indications for optimal interval of sigmoidoscopy and colonoscopy are pending	
DCBE every 5 years			Colonoscopy every 10 years
Colonoscopy every 10 years			A positive FOBT requires colonoscopy

ACS, American Cancer Society; ACCP, Advisory Committee on Cancer Prevention in the European Union; CNR-MIUR, Consiglio Nazionale delle Ricerche and Ministero dell'Istruzione, dell'Università e della ricerca; AIOM, Associazione Nazionale di Oncologia Medica. FOBT, fecal occult blood test; FS, flexible sigmoidoscopy; DCBE, double-contrast barium enema.

Table 2. Colorectal cancer screening recommendations for high-risk individuals

	ACS	CNR-MIUR	AIOM
FAP	Annual sigmoidoscopy, starting at age 10–12 years. The frequency of sigmoidoscopy should be decreased with increasing age by decade until 40–45 years. By the age of 50 years the same clinical screening as for average-risk individuals is recommended. It is recommended endoscopic survaillence of upper gastrointestinal tract and surveillance of distal ileum every 1–3 years.	First colonoscopy at age 10–12 years. If negative repeat colonoscopy every 2–3 years until age 40–45 years.	First colonoscopy should be performed at earlier age of 20 years.
HNPCC	Colonoscopy every 1–2 years beginning at age 20–25 years or at 10 years younger than the earliest CRC diagnosis in the family. Annual screening for endometrial cancer is recommended to start at age 30–35 years. If no mismatch repair gene mutation is found in the first family member tested, all family relatives should undergo surveillance colonoscopy every 1–2 years. Genetic testing should be offered to first-degree relatives of persons with a known inherited mismatch repair gene mutation.	Colonoscopy every 1–2 years for lifetime, starting at age 20–25 or at 5 years younger than the earliest diagnosis in a relative.	First colonoscopy should be performed at earlier age of 20 years.
Common familial risk	The first-degree relatives of individuals with CRC or adenomatous polyps diagnosed at age ≤50 years or two first-degree relatives diagnosed with CRC at any age, should undergo colonoscopy starting at age 40 years, or 10 years younger than the earliest diagnosis in the family, whichever comes first, and repeated every 5 years. Second- or third-degree relatives of subjects with CRC are advised to follow the same screening recommendations as those at average risk.	First colonoscopy at age 45–50 years.	The same recommendations for average-risk subjects, beginning at age 40 years.
Personal history of CRC	Colonoscopy should be performed around the time of diagnosis to rule out synchronous neoplasms. In case of preoperative obstruction, colonoscopy can be performed ∼6 months after surgery. Subsequent colonoscopy should be offered at 3 years, and then, if normal, every 5 years.	Repeat colonoscopy after 1, 3 and 5 years.	The same guidelines as ACS.
Personal history of adenomatous polyps	After one or more adenomatous polyps is removed, patients should have their first subsequent colonoscopy in 3–5 years, depending on the pathology and the number of adenomas removed. Evidence is still being accumulated regarding the appropriate timing of subsequent colonoscopies.	If single adenoma removed, repeat colonoscopy after 3 years than every 5 years; if multiple adenomas removed repeat colonoscopy after 1 year than after 3 years and finally every 5 years; in case of malignant polyps colonoscopic surveillance should be done at 3 months, then 6 months, later at 1 and 3 years and then eventually every 5 years.	First colonoscopy after 6–12 months; if negative repeat colonoscopy after 1 and 3 years.
Inflammatory bowel diseases	Colonoscopic surveillance (with systematic biopsies to detect dysplasia) should begin annually after 8 years of pancolitis and after 15 years in those with colitis involving the left side of the colon.	The same as ACS. Random biopsy should be performed every 10–12 cm and for every suspected lesion. Colonoscopy should be repeated 3–6 months later in case of moderate-dysplasia. Total colectomy is indicated in case of persistent moderate dysplasia, suspected macroscopic lesions and high-grade dysplasia.	First colonoscopy should be performed 8 years after diagnosis; if negative the next should be repeated 12–15 years after diagnosis and than every 1–2 years.

ACS, American Cancer Society; CNR-MIUR, Consiglio Nazionale delle Ricerche and Ministero dell'Istruzione, dell'Università e della ricerca; AIOM, Associazione Nazionale di Oncologia Medica; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer; CRC, colorectal cancer.

European oncologists follow the same guidelines as the ACS (START state-of-the-art, Oncology in Europe, http://www.startoncology.net/default.jsp).

exclude the syndrome, and all family members should undergo clinical screening. People who have a genetic diagnosis of familial FAP, or are at risk of having FAP but in whom genetic testing has not been performed or is not feasible, should have annual sigmoidoscopy, beginning at age 10–12 years, to determine whether they express the genetic abnormality. The frequency of sigmoidoscopy should be decreased with increasing age by decade until 40–45 years [33]. By the age of 50 years the same clinical screening as for average-risk individuals is recommended.

FAP patients should also undergo endoscopic surveillance of upper gastrointestinal tract and surveillance of distal ileum every 1–3 years (because of the increased risk of extracolonic benign and malignant lesions).

CNR-MIUR guidelines: first colonoscopy should be performed at age 10–12 years, if negative, repeat subsequent colonoscopies every 2–3 years until age 40–45 years.

AIOM guidelines: first colonoscopy should be performed before 20 years.

Hereditary non-polyposis colorectal cancer. Diagnosis of HNPCC patients can be very difficult using clinical criteria (Amsterdam criteria), because of the absence of a clear phenotype. The Amsterdam criteria have been expanded to select those who should undergo confirmatory genetic testing. The Bethesda criteria have a great sensitivity for the identification of individuals with *MLH1* and *MSH2* mutations, but the specificity is low.

People with a genetic or clinical diagnosis of HNPCC or who are at increased risk for HNPCC should have colonoscopy every 1–2 years beginning at age 20–25 years, or at 10 years younger than the earliest CRC diagnosis in the family. Annual screening for endometrial cancer is recommended starting at age 30–35 years [33, 34], but no consensus exists as the methods of choice (gynecological exam, transvaginal ultrasound, testing CA125). If no mismatch repair gene mutation is found in the first family member tested, all family relatives should undergo surveillance colonoscopy every 1–2 years. Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited mismatch repair gene mutation.

CNR-MIUR guidelines: colonoscopy every 1–2 years for lifetime, beginning at age 20–25 years or at 5 years younger than the earliest CRC diagnosis in a relative.

AIOM guidelines: first colonoscopy should be performed before 20 years.

Common familial risk

These are subjects with a family history of CRC or adenomatous polyps (10–30% of cases). The risk is related to the number of first-degree relatives with cancer or adenoma and the age of diagnosis.

People with a first-degree relative (parent, sibling, children) with CRC have a risk of developing a tumor two to three times greater than that of the general population.

In case of two or more first-degree relatives or if the immediate relative received a diagnosis of CRC before the age of 50 years, the risk increases to three to four times that of the general population.

First degree-relative with adenomas have also a two-fold increased risk for CRC if adenoma was found at age 60 years or older.

The ACS recommends that first-degree relatives of individuals with CRC or adenomatous polyps diagnosed at age ≤50 years or two first-degree relatives diagnosed with CRC at any age, should be advised to be screened by colonoscopy starting at age 40 years, or 10 years younger than the earliest diagnosis in the family, whichever comes first, and this should be repeated every 5 years.

Second- or third-degree relatives of subjects with CRC are advised to follow the same screening recommendations as those at average risk.

CNR-MIUR guidelines: first colonoscopy at age 45–50 years.

AIOM guidelines: same recommendations as for average-risk subjects, beginning at age 40 years.

Personal history of CRC or adenomatous polyps

People with a personal history of CRC should have a colonoscopy around the time of diagnosis to rule out synchronous neoplasms. In case of preoperative obstruction, colonoscopy can be performed ∼6 months after surgery. If this or a complete preoperative examination is normal, subsequent colonoscopy should be offered at 3 years, and then, if normal, every 5 years.

Patients who have had one or more adenomatous polyps removed at colonoscopy should be managed according to the findings on that colonoscopy. They should have their first subsequent colonoscopy in 3–5 years, depending on the pathology and the number of adenomas removed. Evidence is still being accumulated regarding the appropriate timing of subsequent colonoscopies.

CNR-MIUR guidelines in case of cancer: subsequent colonoscopies should be offered after 1 and 3 years, and finally every 5 years.

CNR-MIUR guidelines: in the case of a single adenoma being removed: subsequent colonoscopy after 3 years than every 5 years; if multiple adenomas removed: subsequent colonoscopy after 1 years than after 3 years and finally every 5 years; in case of malignant polyps: colonoscopic surveillance beginning at 3 months, than 6 months, later at 1 and 3 years and then eventually every 5 years.

AIOM guidelines in case of cancer: the same recommendations as the ACS.

AIOM guidelines in case of adenoma removed: first subsequent colonoscopy in 6–12 months; if negative repeat colonoscopy after 1 and 3 years.

Inflammatory bowel diseases

In individuals with ulcerative colitis and Crohn's colitis, the cancer risk is high. Patients with long-standing, extensive inflammatory bowel disease should received surveillance colonoscopy with systematic biopsies. Colonoscopic surveillance should begin annually after 8 years of pancolitis and after

15 years in those with colitis involving the left side of colon. Random biopsy should be performed to detect dysplasia. There is no direct evidence that this practice is more effective than total colectomy.

CNR-MIUR guidelines: Colonoscopy should begin annually after 8 years of pancolitis and after 12–15 years in subjects with colitis involving the left side of colon. Random biopsy should be performed every 10–12 cm and for every suspected lesions. In case of moderate dysplasia, colonoscopy should be repeated 3–6 months later. Total colectomy should be performed in case of persistent moderate dysplasia, suspected macroscopic lesions and high-grade dysplasia.

AIOM guidelines: first colonoscopy should be performed 8 years after diagnosis; if negative the next colonoscopy should be repeated 12–15 years after diagnosis and than every 1–2 years.

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