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Editorial

Is colonoscopy the most important screening modality for colorectal cancer?

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EPIDEMIOLOGY

Colorectal cancer (CRC) is a major cause of cancer mortality and morbidity in western countries representing over half of all gastrointestinal cancers. Especially in the United States, CRC is the third most commonly diagnosed cancer in both men and women, with nearly 150,000 new cases expected in 2003, and the second most common cause of death from cancer, with more than 55,000 deaths annually.[1] CRC is the single most common cancer site in Europe: 304,687 new cases were identified in 2000, with an incidence of new cases per year varying from 15 to 60/100,000. Czech Republic, Hungary and Slovakia are the "leaders" with an incidence of 60.3 in males and 34.5 in females. On the other hand, Lithuania, Romania and Finland have the lowest incidence among all European countries. Data concerning Greece (for the year 2000) showed a very low incidence (17.4 and 13.6 for males and females respectively), while the mortality rate does not exceed 50% of the incidence rate.[2]

THE NEED OF PREVENTION AND EARLY DIAGNOSIS

The 5-year survival for localized cancers is very satisfactory (80-90%), although for invasive carcinomas it is less than 10%.[2,3] Adenomatous polyps are considered an important premalignant situation, as over 85% of all CRC arise from a pre-existent polyp. Depending on the histological type of a polyp, the estimated time for the evolution from adenoma to an invasive carcinoma is 4 to 12 years. Epidemiologic data on the prevalence of gastrointestinal polyps in asymptomatic patients vary from 23-41%. In 502 autopsies performed on people aged 16-93, 73 adenomas (14.5%) were found.[24] The recognition of the polyps as well as the identification of CRC, at an early stage (Dukes A and B) significantly affects the overall mortality of the disease.[2,3-6] Hereditary colorectal cancer represents a small proportion of all CRC although the risk for developing CRC in these families is high. There are four genetically determined conditions that give rise to polyps in the intestine: Familial Adenomatous Polyposis (FAP) (representing 1% of all patients who will develop CRC), Peutz-Jegher's syndrome, Juvenile polyposis and Hereditary Non-polyposis syndrome (HNPPS) with a risk of CRC development of 95, 30, 30 and 70% respectively.[11] On the other hand 20% of all CRC cases are associated with strong family history of bowel cancer (lifetime risk of CRC 6% if there is one first degree relative over 45 years, 10% if there is one first degree relative under 45 years of age and 17% if two first degree relatives are affected).[11,43]

TO WHOM AND WHICH SCREENING METHOD SHOULD BE RECOMMENDED?

CRC is most common between ages of 50-80 years, but individuals with a family history of CRC develop cancer at a younger age.[2] The American Gastroenterological Association and many other professional societies have published guidelines recommending screening practices for CRC.[7-10] The aim of all screening programmes is a) to find cancers and polyps at an early stage and b) to remove the polyps endoscopically. Patients who undergo endoscopic polypectomy must then be followed regularly life in order to early identify other metachronous polyps. There is a debate as to whether all these screening procedures must be used for the whole population or for high-risk subgroups only.[12-14]

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A special subgroup of high-risk patients is that of patients suffering from Inflammatory Bowel Disease (IBD). It is well known that the risk of developing CRC is greater in patients with total ulcerative colitis (UC) and increases with time, especially after 15-20 years. After 10 years there is an annual incidence of 0.5-1.0%.[27] On the other hand, in the group of patients with UC and primary sclerosing cholangitis (PSC), the frequency of development of CRC is approximately 4-10% and the risk of colon dysplasia 22%.[28,29] The risk of CRC in Crohn's disease patients seems to be lower, although there is data showing equivalent risk in both diseases.[30-32] Colonic and ileocolonic Crohn's disease and long duration of the disease are factors predisposing to the development of CRC.[30,31] The existence of high-grade dysplasia in colon biopsies is a strong indication that CRC could be present in another site of the colon.[33]

So far, there are three main accepted methods of screening for CRC, namely fecal occult blood testing (FOBT), flexible sigmoidoscopy alone or in combination with FOBT, and colonoscopy. Computed tomography colonography (also called "virtual colonoscopy") and special DNA markers may be used as alternative methods in the future.

FECAL OCCULT BLOOD TESTING (FOBT)

There is strong evidence rising from three randomized, controlled trials that FOBT saves lives.[3-5] Three European publications have demonstrated that using FOBT could result in a 16-30% reduction in mortality from CRC.[15-17] CRC produces a positive fecal occult blood test in only 50-60% of cases with a low sensitivity (65%) and a high specificity (98%), resulting in a need for repeated tests at least every two years.[2] A positive test means that 15% will have CRC (16% of them in the Dukes' A classification) and 45% adenomatous polyps.[16] About 5% of those undergoing screening for 10 years will test positive for occult blood, but in 90% of these individuals the test will be a false-positive, leading to unnecessary and expensive diagnostic testing.[4,5] Countries in Europe with a very high incidence of CRC, like Czech Republic, develop national programmes with GP support to find early cancers or polyps. The expected reduction in mortality could be 8,5 deaths/10,000/10 years if the compliance rate is over 68%. Unfortunately, the data from the three first years of this programme in Czech Republic have shown that compliance of the population is poor.[26] Compliance is influenced by education and social deprivation.[20-22]

Some forms of DNA markers, including mutations in k-ras, APC, p53 and BAT26, represent exciting options for the future but they are still under investigation and data indicate that, with the exception of k-ras, these markers are highly specific and therefore represent a significant improvement over FOBT. Whether these tests will replace or supplement existing methods of screening has yet to be determined. It has been suggested that BAT26, which is a marker of microsatellite instability, a feature of proximal sporadic CRC, might be a useful adjunct to sigmoidoscopy screening. Others have suggested that a test for occult blood should be included with the DNA markers, to further increase sensitivity. It is not yet known how sensitive these markers are for detecting adenomas and if CRC incidence rates can be reduced.[25]

Flexible sigmoidoscopy

There is strong evidence that screening sigmoidoscopy is effective in saving lives.[23] This endoscopic procedure picks up no more than 50% of all cancers and 18% of them require total colonoscopy. The bowel preparation differs in different centres. The method may be performed by nurse-experienced staff, educated by a specialist gastroenterologist, as there is a danger of complication development.[2] Data from UK showed a low compliance rate and a high (not expected) number of perforations.[18]

Colonoscopy

The Air Contrast Barium Enema (ACBE) was believed from many physicians to be a good screening method of early diagnosis of CRC, but in most studies was found less sensitive than colonoscopy. ACBE misses 25% of lesions found in colonoscopy and is very insensitive for the diagnosis of polyps.[34] Colonoscopy has clear advantages of all other screening methods, as it can detect small polyps, flat adenomas and dysplastic areas, having the ability to examine the whole bowel, from rectum to cecum, in more than 90% of patients undergoing this procedure.[35] It also permits invasive techniques as biopsies and polypectomy.

There are three major issues for the acceptance of the colonoscopy as the gold screening test for CRC: the cost, the safety and the emergence of new strategies for screening. Examining the safety, the risk of death from colonoscopy, usually from cardio respiratory events, is very low (1-3/10,000 examinations). The perforation risk is 0.1-0.4% and the bleeding average at about 1.2%.[36-39]

A recent study reported a miss rate of 10% for large (>5mm) precancerous polyps during conventional opti-

cal colonoscopy. CT colonography (VC) was used in this study to identify whether lesions were missed in OC. 14 of 15 (93.3%) missed neoplasms were located on a fold and 10 (71.4%) of these were located on the backside of a fold. Five of six missed rectal lesions were located within 10 cm of the anal merge.[40] This 10% miss rate seems to be identical to the largest previous study using OC as a reference standard.[35] On the other hand, in VC there is considerable radiation exposure, so an ethical problem rises if many people undergo CT scan for screening purposes.

New enhancing techniques are used now in optical colonoscopy, such as chromoendoscopy and magnification endoscopy in combination with developed equipment, to identify flat lesions of the colon mucosa and the difference between neoplastic from non-neoplastic polyps.[42]

GROUPING THE POPULATION FOR SCREENING

Low and average-risk colon cancer group:

The recommendation of the ACG is that the preferred strategy for this group is colonoscopy every 10 years, over 50 years of age. An alternative strategy (where colonoscopy is not available), is flexible sigmoidoscopy every 5 years plus FOBT every year.[10,41]

High risk colon cancer groups:

In this group there is an increasing risk depending of the relatives found with CRC (Table 1). The American Cancer Society recommends full colon examination at the age of 40 or, alternatively, 10 years before the youngest age of CRC appearance. Colonoscopy should be repeated every 5 years.[44]

Grouping the patients for surveillance:

FAP, HNPCC, Postpolypectomy, after CRC resection and IBD patients, must be followed up with repeated colonoscopies.

Table 1. Familial risk of colorectal cancer.[43]

General population risk	2%
One 1st degree relative with CRC	1-3 fold increased
Two 1st degree relatives with CRC	3-4 fold increased
1st degree relative with CRC <50 years	3-4 fold increased
One 2nd or 3rd degree relative with CRC	1.5 fold increased
Two 2nd degree relatives with CRC	2-3 fold increased
One 1st degree relative with adenomatous polyp	2 fold increased

CONCLUSIONS

Many screening tests and methods are proposed for early detection of premalignant adenomatous polyps, flat adenomas and early stage CRC, aiming to reduce the overall CRC mortality in the general population. All non-invasive techniques drive people that found "positive" to a total optical colonoscopy with or without use of special methods (chromoendoscopy, magnification endoscopy etc), in order to find and remove polyps or define definitely CRC by taking biopsy specimens.

The advantage of Optical Colonoscopy is that it can be the "unique" screening method that can prevent more than 80% of CRC from developing by removing precancerous polyps.[45] Chromoendoscopy is a complementary technique used during optical colonoscopy that permits the endoscopist to distinguish abnormal from normal patterns of the mucosa and pick-up the appropriate specimens for examination. The message for doctors and patients still remains unchanged: everyone over 50 should have a colonoscopy every 10 years by an experienced qualified endocopist.[10]

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