

Early Diagnosis And Screening In Colorectal Cancer Patients

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ABSTRACT The utility of a population screening program for colorectal cancer was demonstrated, but there are unresolved issues: to whom the program addresses, which are the methods to be used, when are they to be used and what are the costs. For an efficient screening we must identify the patient's level of risk by asking simple questions about personal and family medical history. The current screening methods are: the hemocult test, rectosigmoidoscopy, colonoscopy, irigography, virtual colonoscopy and fecal DNA tests. Although there are many new methods of screening for colorectal cancer, they are still under evaluation.

KEY WORDS colorectal cancer, screening, prevention, endoscopy

Introduction

Prevention is an important issue in current medical world. A screening program, with impact on morbidity and mortality, concerning a certain disease, must have the following characteristics:

- to target an important health problem for the population;
- to be based on an effective screening method;
- to have a good compliance in patients.

Colorectal cancer is an important public health problem; it stands at the top of oncologic pathology, in Romania and in the world; colon cancer is the third most frequent cancer diagnosed in men and women (data from 2003) and it is the second most frequent cancer death cause in the United States (with 55000 deaths per year) (1). The 5-year survival rate in colorectal cancer depends on the stage of diagnosis; it is about 80-90% when the tumor is strictly localized in the colon wall, 40-60% when it has regional extension, and only 5% when there are metastases (2).

The sequence adenomatous polyp - colorectal cancer is well known at the present moment, and screening can lower mortality rates by early diagnosis and removal of adenomatous polyps (3).

Based on these facts, the utility of a population screening program for colorectal cancer was demonstrated, but there are unresolved issues: to whom the program addresses, which are the methods to be used, when are they to be used and what are the costs. First of all there is a major difference between screening and diagnosis tests (4).

Screening tests address to an apparently healthy population with the purpose to improve

the long term health status by early detection of a lesion, which in the absence of testing will be diagnosed later in advanced stages.

The characteristics of an ideal screening test are:

- it is cheap, easy to be done, and accepted by the patients;
- it has high sensitivity and specificity;
- it has a good cost-effectiveness ratio;
- it is effective in lowering colorectal cancer morbidity and mortality;
- it is safe, without side-effects;
- it has a high compliance rate.

If compliance is low, only few individuals will benefit, the reduction in mortality will not be significant, and the money will be spent for nothing (5).

The risk for colorectal cancer varies widely with personal and familial history of each individual; it was decided to stratify the population in risk groups for a better balance between early diagnosis and cost-effectiveness.

The risk group will determine which screening method is the most effective, at what interval will be used, and starting from what age. There are currently defined two risk groups (6):

- moderate risk group,
- high risk group.

Screening in moderate risk population

For patients without significant personal or familial history screening will start at age 50, and there are different methods, each with advantages and disadvantages.

Hemoccult tests:

Guaiac-based - are based on the pseudoperoxidase activity of hematin, a hemoglobin degradation product. For this test the subjects must adopt a specific diet, to avoid false-positive results. It uses three consecutive stool prelevations (knowing that colon tumors bleed intermittently), from each probe two tests are done. The result is positive if at least one testing is positive.

Immunochemical hemoccult tests use monoclonal antibodies (anti- human globulin) and are more sensitive (97.2%) and with higher specificity (97.8%) (7). The down side is that they are expensive and have a relatively high false-negative rate, but they do not require dietary restrictions. The ease of use implies higher compliance and participation to a screening program using this test (8).

Endoscopic methods – diagnostic and therapeutic

Flexible rectosigmoidoscopy. Its use in colorectal tumors screening is based on the fact that 50-60% of these are located in the last 60 centimeters of the large bowel and that two thirds of proximal cancers (those of the right colon) associate with distal adenomas, which could be seen in rectosigmoidoscopy (9). There are studies that show a reduction as high as 80% of proximal colon cancer mortality through use of total colonoscopy in patients with prior identified distal polyps by sigmoidoscopy (10). Rectosigmoidoscopy is recommended to be done once every five years, it is cheap, it does not need sedation, and it requires a minimal colon preparation. It has the important disadvantage that it only examines the distal colon, and it is less sensitive than colonoscopy.

Colonoscopy is indicated every 10 years; it has great sensitivity (99%) and good specificity. As rectosigmoidoscopy it has the advantage that when we see a lesion, we can remove it (endoscopic polypectomy) or at least take biopsies from it. On the other side, it is expensive, it has lower patient compliance, it necessitates specific training for the physician, and it has possible serious complications: perforation, bleeding, respiratory depression caused by sedation, arrhythmias, abdominal pain, ileus, nosocomial infections (11).

Double contrast irigography

Double contrast irigography has a sensitivity of 95%, lower than rectosigmoidoscopy, but it has the advantage of examining the whole colon. The specificity is about 75% (9).

It is indicated every 5 years, and any suspicious lesion needs colonoscopic confirmation. It has moderate price, it does not need sedation.

It is with no doubt inferior to colonoscopy, especially in identifying small adenomas (less than 1 cm) and early stage tumors; it has false positives dependent on an ineffective colon preparation; it does not allow biopsies. To increase sensitivity, some authors suggest associating a hemoccult test (12).

Virtual colonoscopy

It is a new diagnosis method, with tridimensional reconstruction of the colon based on two-dimensional images obtained in spiral computer tomography. Reconstructed images allow visualization of the colon from outside, similar to irigography, but also of the lumen, similar to colonoscopy. It requires a preparation similar to endoscopy. Immediately before CT examination the colon is insufflated with carbon dioxide, because it is absorber more rapidly than air, with less patient discomfort. It does not need sedation (13). Virtual colonoscopy can be as effective as endoscopy in diagnosing polyps larger than 5 mm. A recent study (14) compared the two methods in 100 patients with high risk of colon cancer. Virtual colonoscopy detected 91% of the polyps larger than 10 mm detected by endoscopy, and 82% of those between 6 and 9 mm. The false-positive rate for virtual colonoscopy was 10% in polyps larger than 10 mm and 24% in polyps of 6-9 mm. Although it is minimally invasive it requires high-end technology and it is relatively expensive.

Fecal DNA tests

Fecal DNA tests are a great promise for screening programs. They are based on testing in the stool for DNA markers of cancerous or pre-cancerous cells. Tumor DNA is relatively stable in the stool, comparing with that of normal epithelium cells. PCR technique is used to amplify fecal DNA. There are multiple gene mutations involved in colon cancer, and APC or p53 genes are only two examples of target genes in DNA fecal testing (13). Initial clinical studies showed that multi-target DNA testing has a sensitivity of 71-91% in colon cancer detection (15, 16, 17) and a sensitivity of 55-82% in larger than 1 cm adenomas (15, 17). Estimated specificity was 93-100% (15). These tests are non-invasive, do not require preparation, dietary or drugs restrictions. They can bring information for other segments of the digestive tract.

Improved endoscopic techniques

Chromoendoscopy with magnification, narrow-band imaging colonoscopy, confocal laser endobiomicroscopy or colonoscopy with spectroscopy have substantially improved the possibility of early diagnosis in potentially malignant lesion, and are equivalent to an endoscopy with in vivo histopathology exam. The high cost of these methods, incomparable to that of classical colonoscopy, makes them accessible only to research purposes (18).

SCREENING IN HIGH RISK POPULATION

High risk individuals are (6):

- Individuals with hereditary risk for colorectal cancer:
- familial adenomatous polyposis (FAP).
- in families with hereditary non-polyposis colorectal cancer (Lynch syndrome or HNPCC).
- persons with family risk of colorectal cancer or adenomatous polyps.
- Individuals with personal history of colorectal cancer.
- Individuals with personal history of adenomatous polyps.
- Individuals with personal history of idiopathic inflammatory bowel diseases.

1.1. Subjects with clinical or genetic FAP diagnosis, or first degree relatives of patient with FAP must undergo yearly total colonoscopy starting at age 10-12, subjects with negative results through age 40 will be included in the moderate risk population screening program.

Regarding gene testing, it will be done prior to age 10 and always starting with patients showing FAP phenotype (more than 100 colorectal adenomas). After identifying the mutation in a subject with FAP phenotype, the other members of the family will be tested for the same mutation. When other members are negative for gene testing they will be included in moderate risk population; if the genetic test is positive, they will be examined by colonoscopy annually until polyps appear; total procto-colectomy will be considered then.

For other hereditary colonic polyposis syndromes apply the following recommendations:

- Peutz-Jeghers syndrome - colonoscopy at every 3 years starting from puberty or on symptoms onset.
- juvenile familial polyposis - colonoscopy at every 3 years starting from puberty or on symptoms onset.
- Gardner syndrome, Turcot syndrome, Cowden syndrome - there are no recommendations (19).

1.2. Individuals in families with hereditary non-polyposis colon cancer (Lynch syndrome or HNPCC).

There have been many sets of clinical criteria for defining Lynch syndrome:

- Amsterdam criteria (1991) (20) identify approximately 60% of cases.
- Amsterdam II criteria (1999) (21) identify about 80% of cases.
- Bethesda criteria (2001) (22, 23) identify about 94% of cases.

Individuals from families with Lynch syndrome diagnosed clinically or genetically must be examined by colonoscopy each one or two years starting from age 20-25 or ten years earlier than the youngest member of the family diagnosed with colorectal cancer. Genetic testing is recommended to first degree relatives of subjects with mutations in anti-mutation genes. In Lynch syndrome genetic testing has limited value because of the numerous genes possibly implicated (many of them still unknown), thus, subjects with positive Amsterdam criteria, but negative on genetic tests, will still be considered as having the syndrome but determined by an unknown mutation.

1.3. Individuals with family history of colorectal cancer or adenomatous polyps

These individuals do not fulfill the criteria of Lynch syndrome or colonic adenomatous polyposis. They will be supervised as follows:

- in subjects with a first degree relative with colorectal cancer or adenomatous polyps before age 60, or with two first degree relatives with these conditions, indifferent of age will undergo colonoscopy each 5 years starting at age 40, or 10 years earlier than the age of the youngest relative diagnosed with cancer.

- in subjects with a first degree relative with colorectal cancer or adenomatous polyps after age 60, or two second degree relatives with colorectal cancer indifferent of age, will be screened as the moderate risk population, but starting by age 40.

- in subjects with a second or third degree relative with colorectal cancer by be screened as the moderate risk group.

2. Individuals with a history of colorectal cancer

These subjects will undergo total colonoscopy before surgery to identify synchronous tumors, and then will be examined after 3 years and then each five years.

3. Individuals with a history of adenomatous polyps

In patient with multiple, sessile adenomatous polyps, larger than 1 cm or with a villous component, colonoscopy will be done each 3 years. Otherwise it will be done each 5 years.

4. Individuals with a history of idiopathic inflammatory bowel disease

Crohn disease and ulcerative colitis will undergo colonoscopy each 1 or 2 years as follows:

- after 8 years of evolution in pancolitis.
- after 15 years of evolution in left colitis.

For early diagnosis of potentially malignant lesions it is recommended to take 4 biopsies (from each cardinal points), from 10 to 10 cm, all along the colon length, and from each suspicious lesion or stenosis areas. Identifying severe dysplasia is an indication for prophylactic colectomy (22).

CONCLUSIONS

Screening for colon cancer addresses asymptomatic population, and targets colonic polyps or early colorectal cancers. The screening methods are: the hemoccult test, sigmoidoscopy, colonoscopy, irigography, virtual colonoscopy and fecal DNA tests. For an efficient algorithm the population must be divided in risk groups, using simple clinical criteria.

Colonoscopy is the most effective screening method for colon cancer, but new methods are tested regarding cost-benefit ratio (genetic tests from blood or stool, virtual colonoscopy, magnification chromoendoscopy, narrow-band imaging, confocal laser endobiomicroscopy or spectroscopic colonoscopy).

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