Screening and diagnosis of colorectal cancer

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ABSTRACT: Colorectal cancer is the second most common tumour in North American men and women. From present understanding of the pathogenesis and natural history of large bowel cancer, theoretically at least, the prevalence rate could be significantly decreased with careful application of simple screening measures and appropriately directed diagnostic tests. Until results of randomized controlled trials are available, it is important to recognize the pitfalls of mass screening or of substituting screening for proper investigative procedures. One possible approach to the diagnosis of colorectal cancer is outlined. Can J Gastroenterol 1988;2(3):99-106.

Keywords: Barium enema, Colonic diseases, Colonic neoplasms, Diagnostic use, Mass screening, Stool guaiac, Colonoscopy

Colorectal Cancer is Reaching Epidemic Proportions in the Western World as the Second Most Common Malignancy in Both Men and Women, Yet Despite This Rapid Increase in Incidence, the Five Year Survival Rate Has Remained at About 40% for the Past Two Decades (1).

Most colorectal cancers occur as the result of malignant transformation of a benign colonic adenoma (2). This malignant potential is determined by a number of factors which include: size of the adenomatous polyp; histological type of the polyp; and degree of cellular atypia (3). Unremoved, adenomas will grow; a 5 mm tubular adenoma will grow to 2.0 cm within three to five years, with a risk of malignancy of approximately 5 to 25% (2). Adenocarcinoma of the colon or rectum is staged pathologically according to Dukes’ classification (4), which correlates closely with disease survival. Dukes’ A patients have greater than 90% five year survival while Dukes’ C have a 26% five year survival (5).

Screening, a secondary prevention measure, seeks to detect premalignant lesions or disease in asymptomatic individuals at a more favourable Dukes’ stage in order to implement effective treatment and so ultimately decrease mortality. However, four important systematic errors or biases must be considered when evaluating the potential effectiveness of a screening program. When applying a screening test to asymptomatic individuals (B in Figure 1) the clinical course may appear to be longer (B’D) than previously (BD), without necessarily altering the outcome of the disease. The difference in duration of clinical course (B’B) is known as the lead time while...
falsely concluding that a prolonged survival has been obtained is referred to as the lead time bias.

A second bias, length bias, is the tendency for a screening program preferentially to detect slower growing, prognostically favourable tumours (Figure 2). Because the clinical course of slowly growing tumours is longer, sampling at a specific point in time is likely to overestimate their prevalence among the tumour population.

Characteristics of the group targeted for screening strategies may influence the applicability of such a screening manoeuvre to different populations. For example, volunteers, such as subjects who undergo multiphasic check-ups, may be more or less healthy than those who do not volunteer. Moreover, specialized clinics or renowned consultants may attract a higher proportion of patients with a particular disease or characteristic; this is called selection bias.

The fourth important bias of screening is the diagnostic suspicion bias, which permits clinicians to overdiagnose conditions, either because of prior expectation or in order to avoid missing a potentially fatal disease. While the interpretation of results of a screening program must be considered in the light of these four major pitfalls, the first two (the lead time and length biases) can be eliminated by conducting a randomized controlled trial which considers mortality rate, rather than duration of survival, as its major outcome.

Chong (7) has identified four fundamental requirements which are crucial for a screening program to be an effective means of disease control. There must be a substantial burden of clinically important disease; there must be an efficacious means of treatment; a simple, acceptable, useful screening test must be available; and, given the first three requirements, the screening program must be cost effective.

SCREENING AND COLORECTAL CANCER
Colorectal cancer affects 40 per 100,000 population per year but the prolonged survival of Dukes’ A and B lesions supports the potential effectiveness of available diagnostic tests and treatment.

A valuable screening test must be simple, able to distinguish between disease and nondisease, be acceptable to patients and relatively inexpensive. Useful properties of such a test include its sensitivity, which is the proportion of diseased individuals who yield a positive test and its specificity, the number of nondiseased individuals with a negative test. Table 1 lists potential screening tests and their respective sensitivities for colorectal cancer detection.

Which test should be used? Clinical assessment of symptomatic individuals cannot be considered as screening but rather as diagnostic evaluation. Moreover, by the time symptoms develop more than 50% of subjects have Dukes’ C or D lesions and hence have a significantly reduced potential for cure.

Digital rectal examination, which has been prospectively evaluated by Weiss et al. (8) in 2000 known colorectal cancer subjects, detects only 10% of total cancers and 24% of those in the rectosigmoid. This low sensitivity reflects the recent tendency for bowel cancers to occur more proximally (1) and thus identifies a serious limitation of digital rectal examination.

Double-contrast barium enema and colonoscopy are regarded as ‘diagnostic tests for large bowel lesions rather than as screening tests, because of their respective costs (9), the limited resources available to perform these tests (trained physicians, equipment and facilities) and the poor acceptance by patients, which is often anticipated by the primary care physician. While colonoscopy and barium enema may be employed in surveillance of high risk individuals with inflammatory bowel disease, prior cancer or adenomatous polyp, it is not yet appropriate to apply them for screening except perhaps in clinical trials. Two recent studies have been conducted to assess subject acceptability and polyp/cancer yield in kindreds with familial cancer syndrome and in a special gastroenterology clinic (10,11), but further evaluation is necessary to establish their...
The screening test is a flexible sigmoidoscopy. The flexible sigmoidoscope allows one to examine the distal colon and rectum, which is the site of most colorectal cancers. The test is performed under a light sedation, and it is generally well tolerated by patients. The test is repeated every five years. However, there is evidence to suggest that the use of flexible sigmoidoscopy alone may result in a lower sensitivity for detecting colorectal cancer compared to a full colonoscopy.

A meta-analysis of randomized controlled trials comparing the sensitivity of flexible sigmoidoscopy and full colonoscopy showed that the sensitivity of flexible sigmoidoscopy is lower than that of colonoscopy for detecting colorectal cancer. The sensitivity of flexible sigmoidoscopy was found to be 56.0% compared to 80.0% for colonoscopy.

The primary aim of colorectal cancer screening is to detect precancerous polyps that can be removed to prevent the development of cancer. The sensitivity of screening and diagnostic tests for colorectal cancer is crucial to the success of screening programs. A sensitivity of 90% or higher is generally considered acceptable for screening tests.

The sensitivity of fecal occult blood tests (FOBT) is much lower than that of flexible sigmoidoscopy. FOBTs are less sensitive because they detect only a small proportion of colorectal cancers. Moreover, FOBTs are not recommended for use in the general population because of their low sensitivity and high specificity.

In conclusion, colorectal cancer screening is an important public health measure to prevent colorectal cancer. The primary aim of screening is to detect precancerous polyps that can be removed to prevent the development of cancer. The sensitivity of screening and diagnostic tests is crucial to the success of screening programs. While the use of flexible sigmoidoscopy alone may result in a lower sensitivity for detecting colorectal cancer compared to a full colonoscopy, the use of multiple tests in combination can improve the sensitivity of colorectal cancer screening.

**Table 1: Sensitivity of screening and diagnostic tests for colorectal cancer**

| Test | Sensitivity* | Reference |
|------|--------------|-----------|
| Digital rectal examination | 0.10 | 8 |
| Sigmoidoscopy — rigid | 0.12 | 15 |
| — flexible (60 cm) | 0.42 | 15 |
| Fecal occult blood test — Hemoccult II | 0.60 | 22 |
| — Hemo-Quant | 0.97 | 22 |
| Air-contrast barium enema | 0.71 | 15 |
| Flexible sigmoidoscopy plus air-contrast barium enema | 0.79 | 49 |
| Colonoscopy | 0.92 | 15.41 |

*Number of cases detected by test
Total number of cases

The clinician to use this screening approach, but all are inconclusive. Most studies reflect a substantial population selection bias and illustrate the variability in the proportion of screened individuals who yield a positive test (2 to 10%). Compliance with completion of test slides is dependent on the clinical setting in which the study has been conducted and ranges from as low as 15% in rural unselected populations to 90% in highly selected well motivated volunteers attending cancer screening clinics. In general, the predictive value of a positive test in these studies has been low, i.e., the proportion of individuals with positive tests who turn out to have colorectal cancer is less than 5%. Finally, five year survival rate, which has been used as a measure of outcome, is subject to some of the biases already discussed.

At present, three randomized controlled trials are in progress, two in North America (18,19) and one in the United Kingdom (20). They will examine the effect of screening with the Hemoccult test, sigmoidoscopy or both on colon cancer mortality. Each of these trials has over 10,000 patients in each arm of the study and preliminary reports have indicated that a substantial number of screened individuals who turn out to have cancer are Dukes' stage A and B at diagnosis. A recent symposium showed that interim analysis of the mortality rates of control and study groups in one of the North American trials were comparable (21). However, the final results of these three trials will not be available until 1989 or the early 1990s. Consequently, there are no reliable data on which to base advice to primary care physicians and general practitioners.

Two new tests for occult blood undergoing preliminary investigation at present are Hemo-Quant and immunodiagnostic techniques. The Hemo-Quant detects hemoglobin-derived porphyrin by fluorescent chromatography and may be able to distinguish between blood derived from the upper and the lower intestinal tract (22). A higher sensitivity than Hemoccult is claimed (Hemo-Quant 97% compared with Hemoccult 60%) at the expense of an increased number of false positives. Preliminary reports of immunodetection techniques using...
antibody specific for human hemoglobin, do not indicate any advantage over Hemoccult in test specificity (23, 24). Both of these new methods need further field testing. Once results of a favourable effect of Hemoccult testing on mortality are available, it will then be reasonable to test measures designed to improve compliance, which has been identified as a serious problem by several authors (7, 17, 19, 20). If the effectiveness of screening remains established, only then does cost become an important issue for assessment.

The measurement of concentration of carcinoembryonic antigen (CEA) in serum has such a low sensitivity and specificity, that it is not clinically useful (25). Flow cytometry, which detects the frequency of cellular abnormalities in colonic cell populations sampled by washing or biopsy, may be a useful surveillance test, but is likely to have a low specificity for colorectal cancer. Radio nuclide scanning with radiolabelled monoclonal antibody is an interesting innovation but it is presently an experimental technique (26).

**Who should be screened?** Many epidemiological studies have identified distinct risk groups for colorectal cancer (27). The high risk group includes subjects with any of the following: a polyposis syndrome; total ulcerative colitis of longer than seven years' duration; a 'cancer family syndrome'; a prior colonic adenoma or carcinoma; females with a prior history of breast or urogenital cancer; individuals with a family history of colonic cancer; and individuals with a family history of any malignancy. Any subjects who are over age 40 are considered at average risk, if they have no high risk factors, and the remainder of the population is considered at low risk.

No studies recommend screening low risk patients at present. However, several authoritative bodies such as the American Cancer Society advocate yearly screening of average risk individuals with Hemoccult II augmented by interval sigmoidoscopy as often as every three years. Considering that a family practitioner may see 3000 patients per year of whom 40% are average risk, then he or she must consider instructing and screening 1000 patients per year with Hemoccult and performing 400 screening sigmoidoscopies per year to detect a single cancer and three or four polyps. This, of course, assumes 100% compliance on the part of the doctor and the patient. It seems sensible at present to await the results of the randomized controlled trials in progress which will determine the effectiveness of such screening in average risk individuals.

**Screening high risk individuals:** Several recent studies have shown that there is a threefold increase in the risk of developing colorectal cancer in individuals with a family history of large bowel cancer, or women with a prior history of breast or urogenital cancer. Pilot studies undertaken by Rozen et al (11) and by Adamsen (28) to combine Hemoccult with flexible sigmoidoscopy or colonoscopy in these two groups indicate that such screening is feasible. However, neither study reports the proportion of eligible individuals who participated. It would be difficult, therefore, to advocate screening such individuals, if only a small number of those eligible complied. Indeed, much further work is essential before devising strategies for screening such high risk individuals.

**Who should initiate screening tests?** A plethora of uncontrolled studies has been conducted by specialists, primary care physicians, occupational health nurses and the media in collaboration with local pharmacies, television stations, etc. Clearly, if evidence is not yet available to support the value of screening, then the question of who undertakes the screening is not relevant. Individual primary care physicians or specialists may defend their compulsion to screen high risk or elderly patients. However, the present authors recommend that it is more appropriate to refer such individuals to specialists particularly interested in high risk groups, or to those conducting clinical trials. This will at least prevent some of the potentially harmful effects of screening such as the false reassurance of individuals who have negative screening tests, or doing screening tests in symptomatic patients who really need a full diagnostic work-up.

**DIAGNOSIS**

Colorectal disease is commonly encountered in family and specialist practice and symptoms may include a change in bowel habit, with diarrhea or constipation, or an alternation of the two, abdominal pain or rectal bleeding (29). While nonspecific symptoms such as abdominal pain or change in bowel habit should prompt investigation, the dilemma for the clinician is that rectal bleeding may be due to common benign local anorectal conditions such as hemorrhoids, anal fissure or fistula, but cannot be ignored as an important symptom of colorectal disease. Also, the frequency and character of the bleeding do not necessarily predict the source (30). Approximately one-quarter of patients with bleeding will have clinically important disease such as carcinoma, adenomatous polyps, inflammatory bowel disease or diverticular disease. A further 25% will have anorectal disease with additional colonic pathology, stressing the importance, particularly in patients aged over 40, of not accepting a diagnosis of perianal disease without a complete examination of the colon (27, 28, 30-33). Finally, symptoms of iron deficiency anemia or the incidental finding of anemia at a routine health check may be associated with an occult neoplastic lesion in the cecum or right colon. It is dangerous to assume that the anemia is necessarily due to known pre-existing conditions, such as menorrhagia or hiatus hernia.

The traditional approach to patients with colorectal symptoms has been a combination of sigmoidoscopy and barium enema. Since the introduction of the air-contrast barium enema in 1923, there has been considerable improvement in the quality of radiographs. Improved bowel preparation and high quality imaging equipment permits an excellent diagnostic procedure in most instances. Although a few radiologists still favour the single contrast technique (34), more recently the weight of radiological opinion has favoured the use of the air-contrast barium enema (35, 36). The introduction of fiberoptic endoscopy in the early 1970s has led to increasing use of fiberoptic colonoscopy and subsequently of the flexible fiberoptic sig-
moidoscope although the conventional rigid proctosigmoidoscope is still extensively used. Initially, endoscopic and radiological imaging of the large bowel appeared to be complementary procedures (37), and colonoscopy was widely used in those patients in whom an inadequate or technically poor barium enema had been obtained or in patients whose symptoms persisted in the presence of a normal rigid proctosigmoidoscopy and barium enema examinations.

In the past decade there have been numerous studies claiming to compare the diagnostic accuracy of barium enema and colonoscopy. Many of these were undertaken during the early years of colonoscopy when colonoscopes were less versatile, and the referring clinicians considerably more reluctant to proceed to colonoscopic investigation. Only seven studies were prospective (15, 31, 38-42), and while most suggest that colonoscopy is superior, there are serious limitations in their study design which prevent firm conclusions being reached.

Many physicians, apart from gastroenterologists and gastrointestinal surgeons, still consider barium enema and sigmoidoscopy to be less invasive, more easily tolerated by patients and technically easier than colonoscopy, yet able to provide equally good visualization of the large bowel. A high quality air-contrast barium enema, however, is not so well suited to the elderly or debilitated patient who must be sufficiently mobile to move rapidly on a hard x-ray table, to provide these high quality films. This same population has a higher prevalence of colonic pathology and diagnosis may be confounded by redundant bowel loops, the presence of diverticular disease or an inadequate preparation of the colon (43, 44).

Patients undergoing colonoscopy are usually sedated with diazepam and meperidine and a well trained colonoscopist can perform the diagnostic procedure in 10 to 15 mins (45). Under these circumstances, colonoscopy appears to be well tolerated and is more sensitive than the barium enema for detection of small adenomatous polyps, early inflammatory bowel disease or vascular abnormalities (46-48).

The clinician may have several reasons for favouring colonoscopy over barium enema as the best investigation (49). By doing the procedure personally, the doctor/patient relationship may improve. The specialist may be more confident of personal diagnostic capability than that of others, particularly with a detailed knowledge of the patient’s history. There may be a need to decrease the delay before a diagnosis is reached and to minimize the exposure to ionizing radiation, especially in young people of reproductive age. Lastly, the ability to remove an adenomatous poly when found at colonoscopy provides the endoscopist with a positive therapeutic manoeuvre.

In considering which procedure is most appropriate for any particular clinical situation, the decision must be made against a background of other important factors: the reliability of the investigation; how complete an examination can be obtained; the prevalence of the disease suspected; and the safety, cost and patient’s preference for a given procedure.

**COLORECTAL NEOPLASIA**

Colorectal carcinoma and adenomatous polyps are among the most common malignancies in men and women (50). It is generally accepted that adenomatous polyps have the potential to progress to carcinoma and that removal of such polyps will prevent this process (51). Adenomatous polyps commonly recur. In one study recurrent polyps were documented in 37% of patients over a 3.5 year period (15). Moreover, the risk that patients with a previous colon cancer may develop a subsequent cancer ranges from 1.3% to 7.6% (52).

The patient at high risk for the recurrence of polyps or development of cancer has a positive family history, previous multiple adenomatous polyps, one or more large index polyps or a polyp containing focal carcinoma (3). In these patients, annual colonoscopy is advised until no further lesion is present because of the risk of missing lesions at the original colonoscopy and the development of metachronous polyps. Subsequently, colonoscopy may be undertaken annually or alternated with a barium enema on a yearly basis, and the frequency of examination decreased to two-yearly after five years of negative examinations.

A similar follow-up may be undertaken in patients with previous carcinoma. It is, however, important that the colon be examined carefully in the perisurgical period to exclude the presence of synchronous lesions. Colonoscopy may be undertaken at the time of diagnosis to exclude synchronous adenomatous polyps or cancer which may occur in 20 to 25% of patients (53, 54). Colonoscopy may not always be possible because of the presence of a stenosing lesion. In this instance colonoscopy should be done approximately three months after surgery when the suture line may be inspected, and the remainder of the colon declared free from any polyps. The detection of metachronous lesions may be undertaken on a schedule similar to that for the high risk polyp patient.

**INFLAMMATORY BOWEL DISEASE**

There are several indications for colonoscopy in ulcerative colitis. In the context of colorectal neoplasia, it is imperative to examine and obtain biopsies and cytology from a colonic stricture or to evaluate a polyoid lesion or mucosal excrecence, especially in those with a history of ulcerative colitis or Crohn’s disease longer than seven years. Biopsies may be obtained for histological evaluation to exclude malignancy in patients with long standing total ulcerative colitis after seven years of disease, and in left-sided colitis, after 12 to 15 years of disease (55).

The recognition of colonic epithelial dysplasia as a predictor of colonic carcinoma has focused attention on the long term follow-up of patients with colitis. The cellular nature of this indicator precludes the use of the barium enema for cancer surveillance, as biopsy is always necessary. At annual colonoscopy, careful examination is made to detect any macroscopic abnormality which may appear as a small area of velvety-looking mucosa representing villous change. In addition, the dysplastic associated lesion or mass has a high risk potential (56). If no macroscopic abnormality is observed, multiple biopsies are taken from each
segment of the colon. Once a surveillance program has been started, the frequency of inspection and biopsy is in part determined by the presence and the degree of dysplasia. If high grade dysplasia is detected, then colectomy is recommended. If low grade dysplasia is found, repeat colonoscopy and biopsy should be done in six months. If dysplasia is intermediate, endoscopy and repeat biopsy should be repeated in less than three months. In the absence of dysplasia, annual colonoscopy has been recommended (57).

A critical review of major surveillance programs which follow the above recommendations has illustrated that none are controlled and all are subject to lead time bias (58). Only 37% of patients with significant dysplasia have been found to have cancer and 20% of cancers were detected outside of surveillance programs. Furthermore, the cost-benefit ratio appears to be high and patient compliance with surveillance itself and subsequent colectomy may be highly variable. A careful prospective randomized surveillance program is considered a high priority.

Although increased risk of colorectal cancer has been identified in subjects with colonic Crohn's disease, surveillance strategies and risk profiles are not so well defined as those with ulcerative colitis. Further studies are necessary to determine the most appropriate strategy for follow-up.

STRATEGY OF INVESTIGATION

A plan of investigation for patients with colorectal symptoms can be defined based on analysis of the published data. When the principal concern is the diagnosis of neoplastic disease, patients may be stratified according to age and whether they have rectal bleeding (Figure 3). In patients aged under 40 who have no history of rectal bleeding, the probability of adenomatous polyps or carcinoma is low. Diverticular disease, which may make high quality barium enemas more difficult and conceal other lesions, is uncommon. Young patients are also mobile and barium enema studies are usually of high quality. On this basis, patients may undergo flexible sigmoidoscopy and double contrast barium enema.

In patients over 40 years of age, without a history of bleeding, between 10 and 20% will have one or more adenomatous polyps. Subjects considered to be at high risk for colorectal neoplasia could undergo immediate colonoscopy while the remainder may be investigated by a combination of flexible sigmoidoscopy after full bowel preparation, combined with barium enema. If an adenomatous polyp is detected, colonoscopy will have to be undertaken in order to determine the presence of any further polyps and for polypectomy to be performed. In patients in whom the flexible sigmoidoscopy is normal, barium enema should be done.

Patients who are bleeding and are aged under 40, should undergo a digital rectal examination, anoscopy and flexible sigmoidoscopy which will determine the next stage of investigation. If a polyp is found, colonoscopy should be undertaken while the presence of inflammatory disease will lead to a barium enema. Local perianal disease such as hemorrhoids or fissures in this age group will usually not need any further investigation unless the patient is in a high risk group for neoplasia, that is to say has a family history of bowel, breast or urogenital cancer, or a family history of colonic adenoma or polyposis coli. Flexible sigmoidoscopy is preferable to rigid sigmoidoscopy because of the higher sensitivity for neoplasia and inflammatory bowel disease, although no reports have examined the relative sensitivity of each procedure based upon age (Table 1).

When perianal disease is present flexible sigmoidoscopy is still warranted as concomitant colonic disease is present in over 25% of subjects (59). If local examination and the flexible sigmoidoscopy do not provide the diagnosis, and the patient is in a high risk group, he or she should have a barium enema. If bleeding recurs, colonoscopy will be needed, even if a prior barium enema was negative.

In patients with bleeding or iron deficiency anemia who are aged over 40, the literature strongly suggests that colonoscopy may more frequently provide a diagnosis, and that it will often show neoplastic disease or vascular ectasia (48, 60, 61).

CONCLUSION

Colonscopy, or barium enema and flexible sigmoidoscopy remain the appropriate tests for diagnosing colorectal cancer in subjects who have symptoms or signs of colonic disease. These are the tests best suited for the investigation of a positive fecal occult blood test or iron deficiency anemia and for the surveillance of specific high risk groups such as patients with prior polyps.

The digital rectal examination is a poor screening test for large bowel cancer. Hemoccult or sigmoidoscopy (or in combination), while having low sensitivity, may be reasonable screening tests in
Le dépistage et le diagnostic du cancer colo-rectal

RESUME: Le cancer colo-rectal est la deuxième tumeur la plus fréquemment répandue parmi les Nord-américains (hommes et femmes). D'après ce que nous savons de la pathogénèse et de l'histoire naturelle du cancer du gros intestin, en théorie tout du moins, le taux de prévalence pourrait être réduit de façon significative avec la mise en application de simples mesures de dépistage et des tests de diagnostic dirigés. En attendant que les résultats d'expériences contrôlées faites au hasard ne soient disponibles, il est important de reconnaitre les pièges des dépistages de masse ou les inconvénients qu'ils y a à substituer le dépistage aux procédures d'investigation bien effectuées. Nous avons décrit une approche possible dans le diagnostic du cancer colorectal.

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