The Rationale for Colorectal Cancer Screening

INTRODUCTION

The argument for colorectal cancer (CRC) screening rests on evidence that patients whose cancers are detected in earlier stages do much better than patients with more advanced cancer on detection. Patients whose cancers are detected in early stages (Dukes' Stage A and B--see box A on cancer stages) have an 85 percent 5-year relative survival rate compared to 38 percent in patients with late cancer (Dukes' C and D) (152). The availability of curative surgery for localized disease is a primary reason for these differences in survival (23,145).

If people wait for symptoms before seeking care, the distribution of detected cancers by stage contains a high proportion of more advanced cancers. Table 1 shows the stage distribution of cancers reported in various studies. The high death rate from CRC in this country -- almost one-half of all CRC victims die within five years of the detection of the disease -- is a reflection of the preponderance of cancers detected at later stages.

Although environmental factors, particularly diet, appear to play a role in the development of CRC (112,162), little is known today about how to prevent

Box A--Staging Colorectal Cancers

The primary purpose of staging systems is to indicate the severity of the disease state. There are, however, several other important functions of classification systems. They are used for treatment planning, comparing results of different studies, and predicting recurrence patterns and survival rates (23). The staging of colorectal cancer is muddled by the presence of several staging systems that use the same nomenclature to represent different disease states.

The Dukes' system is one of the oldest and most commonly employed colorectal cancer staging systems. Cuthbert Dukes, a pathologist at St. Mark's Hospital, London, England, is responsible for much of what we know about the spread of colorectal cancer (23). He performed meticulous gross and microscopic studies of over 2,000 rectal cancer specimens and concluded that a patient's prognosis was significantly correlated with the depth of invasion of the tumor and with the presence or absence of lymph node spread (145). The chance of recovery diminishes as the carcinoma penetrates into the bowel wall.

In 1930, Dukes proposed a three-letter classification system for rectal cancers based on his findings; this system was revised in 1967 by Turnbull to include a fourth stage (23,145).

- Stage A indicates the least severe disease state: the cancer penetrates into but **not** through the bowel wall.
- Stage B represents penetration through the bowel wall, but no invasion of the lymph nodes.
- ***Stage C indicates involvement*** of the lymph nodes regardless of the extent of bowel wall penetration.
- Stage D, the most advanced stage, indicates the presence of a primary tumor, lymph node invasion, and the presence of distant metastasis.

Since 1930 many investigators, including Dukes, have proposed modified staging systems. These systems express finer degrees of penetration and nodal involvement. The existence of several staging systems has made it difficult to compare the results of clinical studies. In an effort to modernize and simplify staging systems, the American Joint Committee on Cancer and the International Union Against Cancer recently proposed the TNM Classification system (23). TNM may replace Dukes' system, but almost all of the current studies employ Dukes' staging.

Table 1 -Stage at Detection of Colorectal Cancers

study	Population	Stage at detection [a] A	B	C	D
Allison & Feldman, 196&	Large HMO without screening program, 1974	25% [d]	29% [d]	23% [d]	11% [d]
Holmes et al., 1961[b]	Missouri Tumor Registry, 1944-79	34.6%[e]		47.4%[e]	17.996[e]
U.S. DHHS, 1989[c]	Tumor Registry (selected sited	37%[e]		41%[e]	22%[e]

SOURCES:

[a] J.E. Allison and F. Feldman, "Cost Benefits of Hemoccult Screening for Colorectal Carcinoma," *Dig. Dis. Sci.* 30(9):860-865, 19S5.
[b] F.F. Holmes and E. Hearne, "Cancer Stage-To-Age Relationship: Implications for Cancer Screening in the Elderly," *J. Am. Geriatr. Soc.* 29(2):55-57, 1SS1.
[c] U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute, *Cancer Statistics Review* 1973-1988 (Bethesda, MD: 1989).
[d] Reported by Dukes' A, B, C, or D.
[e] Reported as local, regional, or widespread.

CRC through dietary or environmental interventions (136). Although new approaches to cancer therapy for Stage B and C colon cancers appear to be promising (97,102), they are likely to have only modest overall effects on survival rates from late CRCs. Thus, the most promising opportunity at present for reducing the burden of illness and death associated with CRC is to detect more cancers in early and still curable stages, before they progress to more advanced stages.

If early detection of CRC can interrupt or delay the natural course of the disease, then detection and removal of the suspected precursors to cancer -- colorectal adenomatous polyps -- might actually prevent the onset of cancer itself and lower its incidence. Thus, the notion of CRC screening has come to encompass a search not only for early cancers, but also for the benign growths, referred to as adenomas or adenomatous polyps, out of which most CRCs are suspected to arise (44,115). Not all colorectal polyps are adenomas (a large number are "hyperplastic", a type of polyp that is thought not to progress to cancer (88,118,167). It is believed that only a small proportion of these adenomas -- as few as 5 to 10 percent -- will progress to cancer, (35,71, 106), but clinicians and researchers generally agree that the vast majority of CRCs begin as benign adenomas (12,108,118)(See box B for a description of polyps and their relationship to CRC.).[1] Thus, detection and removal of adenomas is a second objective of CRC screening.

TECHNOLOGIES FOR COLORECTAL CANCER SCREENING

The detection of neoplasms (cancers and adenomas) in the colon or rectum involves either direct inspection of the large bowel or indirect measurement of biochemical markers for the presence of cancer or polyps. Direct inspection of part or all of the 145 cm-long (57 inch) large bowel can be accomplished with a digital rectal examination, with endoscopes of various lengths, or with the barium enema, an x-ray examination of the colon and rectum. At present, indirect tests are limited largely to measurement of the presence and quantity of hemoglobin in the stool, although other tests, such as one measuring occult albumin in the stool (110) and another using a sample of mucin from the rectum, are currently under development (99).

In the ***digital rectal examination,*** the clinician inspects the interior of the rectum with a finger in search of a rectal mass. The reach of this examination is limited to 7 to 10 cm (3 or 4 inches), so it is unable to identify the vast majority of colorectal neoplasms, which arise beyond the area of inspection.

Endoscopy refers to the insertion of a tube with a light and mirror at the end into the gastrointestinal tract for direct visualization of its interior. Before the late 1970s, endoscopes were made of rigid materials and could be inserted through the anus only about 20 cm (8 inches) to the distal end of the sigmoid colon. These ***rigid sigmoidoscopes,*** or proctoscopes, are still used to screen for colon cancer, but

[1] **Definitive proof that CRC begins with polyps is not available, however. See Castleman (19) for reasons not to accept the polyp-cancer sequence.**

Box B--Polyps and Cancer

There are two major types of colorectal polyps: neoplastic and non-neoplastic. Neoplastic polyps are called adenomatous polyps, or adenomas. They constitute between 50 and 75 percent of all polyps (118,167) and have a malignant potential.

The proportion of adenomas that progress to cancer appears to be very small. Several authors have estimated that 5 to 10 percent of adenomas will progress to cancer (35,71). The rationale for this estimate is based on studies determining the invasive malignancy rate of polyps. Morson estimated that 11 percent of all adenomas contain cancers. Assuming that at least some carcinomas originate in adenomas, one can conclude that many polyps do not progress to cancer, since adenomas have a much higher prevalence than carcinomas. In addition, observations of patients with familial polyposis (an inherited condition in which many polyps arise beginning in early adulthood) show that over time only a few out of hundreds of polyps progress to cancer (106).

The type of adenomatous polyp and its size are indicators of its malignancy potential. Villous polyps and intermediate type polyps have higher malignancy rates than tubular adenomatous polyps (106,113). Many investigators have determined that the diameter of the adenoma is positively correlated with the incidence of invasive malignancy. Muto and colleagues estimated that adenomatous polyps less than 1 cm had an incidence of invasive malignancy of 1 percent; polyps between 1 and 2 cm, an incidence of 10.2 percent; and polyps greater than 2 cm an incidence of 34.7 percent (109). More recent data from the National Polyp Study indicate a similar positive correlation between adenoma size and presence of invasive cancer, but the incidence of invasive cancer in the adenomas studied was much lower than that found by Muto (113).

they now must compete with newer flexible fiberoptic endoscopes, which, depending on their length, can examine greater proportions of the colon. Flexible fiberoptic sigmoidoscopes (FSIG) are now available in various lengths, 35 cm or 60 cm being the most common; these generally can reach an average of 30 and 55 cm (12 to 20 inches), respectively, into the colon. Full visualization of the entire colon is possible with a 180 cm ***colonoscope.*** The longer the endoscope, the more technically difficult is the procedure, the greater is the risk of bowel perforation, and the more intensive is the patient's required bowel cleansing preparation (116). Full colonoscopy also requires patient sedation (164).

Prior to the development of flexible fiberoptic colonoscopy, the ***ban-urn enema*** x-ray was the only procedure available to inspect the entire colon for tumors or polyps. Barium enema is a generic term referring to radiological studies of the colon and rectum using contrast materials injected into the colon through the anus. The procedure has evolved over time, and today the double contrast barium enema (DCBE), which uses both contrast solution and air to help visualize the colon, is the procedure of choice (47,83,143,144). The barium enema is a somewhat uncomfortable procedure whose accuracy depends in part on the thoroughness of the patient's bowel cleansing preparation in the day or two prior to the procedure (160). Its accuracy also varies with the technical competence of the radiologist performing the study (47).

The ***fecal occult blood test (FOBT)*** indirectly tests for the presence of CRCs or polyps by detecting blood in samples of stool collected over three successive days. Many CRCs and some polyps become ulcerated and bleed. If enough blood is present in

the stool, paper impregnated with the chemical guiaic will turn blue when smeared with the stool sample. The guiaic-based FOBT test will also turn blue in the presence of other substances (90), particularly peroxidases present in some foods (93), and intestinal bleeding may occur due to conditions other than neoplasia, so that the test involves some false positive results for neoplasia (56). Also, some CRCs and most polyps bleed only intermittently or not at all, so the test has a relatively high inherent false negative rate. Several variations of the FOBT are available, some of which give quantitative results and others which give only a positive or negative reading. The most widely used test is the Hemoccult II (t.m.). Newer tests for occult blood based on immunochemical techniques and heme-porphoroxal assays have also been developed, but they are not in widespread use as screening techniques (7,51,129,130, 131,140).

RECOMMENDATIONS FOR COLORECTAL CANCER SCREENING IN THE ELDERLY

Numerous expert groups in the United States and other industrialized countries have made recommendations about the periodicity with which the elderly should receive particular colorectal screening tests. The recommendations vary widely due to fundamental differences in interpreting the evidence on the medical benefits, risks and costs of CRC screening.

Recommending groups include professional societies, voluntary health associations, government-sponsored consensus panels, and third-party payers. The discussion below first summarizes the positions of major groups in the United States and then describes the positions taken by government and expert groups in selected industrialized countries. Table 2 summarizes the recommendations for each specific screening test.

All recommending bodies differentiate people at low or average risk from those at increased risk of CRC because of predisposing conditions or family history. For high-risk people (e.g., those with one or more first-degree relatives with CRC or people with a history of CRC or adenamatous polyps) there is general agreement that periodic surveillance beginning some time before the age of 50 is prudent. Low-risk individuals, defined mainly as young people (under 40 years of age) without any high-risk conditions, should not be screened for CRC, according to all groups. As people age, the risk of CRC increases even for those without high-risk conditions; for these "average-risk" individuals (over 40 or 50 years of age) the recommendations of various groups differ widely.

The United States

The American Cancer Society (ACS) recommended in 1980 an annual digital rectal examination beginning at 40 years of age and an annual FOBT beginning at age 50. At age 50, two initial sigmoidoscopies each one year apart should be followed, if negative, by subsequent sigmoidoscopies every 3 to 5 years. No age was suggested at which such screening might be discontinued (2). In a 1988 update, ACS left these guidelines unchanged (3), but ACS recently revised the guidelines to require sigmoidoscopy every 3 to 5 years after age 50.

The National Cancer Institute (NCI) has sponsored several panels and committees over the past 10 years (155) to develop recommendations for CRC screening (as well as for other kinds of cancer). In 1985, in the course of developing public health objectives for the year 2000, an NCI-sponsored committee could not agree on appropriate guidelines for CRC screening and left this area without objectives (37,96). More recently, NCI brought together experts and interested organizations to develop working guidelines for early detection of cancer; that effort led in 1987 to the publication of working guidelines for CRC detection. These are similar to the ACS position. Specifically, the NCI guidelines call for an annual FOBT and sigmoidoscopy every 3 to 5 years for average-risk people beginning at age 50 and continuing indefinitely. These guidelines were approved by NCI's Board of Scientific Counselors and the National Cancer Advisory Board (NCAB), (96) and have been incorporated into the NCAB's recent report (111). They are also being incorporated into NCI materials for public distribution (159).

The American Society for Gastrointestinal Endoscopy and the American Gastroenterological Association have recently published recommenda-

Table 2-Recommendations for Screening for Colorectal Cancer In the Elderly

Country/ organization (date of recommendation)	Screening recommendation by procedure		
	Digital rectal examination	Fecal occult blood testing	Sigmoidoscopy
United States:			
NCI[a] (1987)	Considered part of routine physical examination	Annually	Every 3 to 5 years
ACS[b] (1989)	Annually	Annually	Every 3 to 5 yearn
ASGE & AGA[c] (1988)	Frequency unspecified		Flexible sigmoidoscopy stating at 50, frequency unspecified
USPSTF[d] (1989)	Digital rectal examination is not an effective screening maneuver, Task Force found insufficient evidence to recommend for or against screening with fecal occult blood test or sigmoidoscopy in asymptomatic persons, but notes it may be advisable to offer screening to persons 50 and older with risk factors; Task Force does not specify what screening frequency is optimal		
Canada:			
CTF[e] (1988)		Not recommended unless *specified* risk factors are present	Not recommended unless *specified* risk factors are present
Germany:			
Government[f] (1977)		Screening is suggested in those over 45, frequency not specified	
World Health Organization:	Annually	Annually	Every 3 to 5 years

ABBREVIATIONS: ACS = American Cancer Society, AGA = American Gestroenterological Association, ASGE = American Society for Gastrointestinel Endoscopy, CTF = Canadien Task Force, NCI = National Cancer Institute, USPSTF = United States Preventive services Task Force.

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[a] U.S. Department of Health end Human Services, National Cancer Institute, Division of Cancer Prevention and Control, Early Detection Branch, "Working Guidelines for Earty Cancer Detection: Rationale and Supporting Evidence to Decrease Mortality," Bethesda, MD, December 19S7.
b American Cancer Society, "Summary of Current Guidelines for the Cancer-Related Checkup: Recommendations" (New York, NY: ACS Professional Education Publication), 19s9.
C D. Fleischer, S. Goldberg, T. Browning, et al., "Detection and Surveillance of Colorectal Cancer," *J.A.M.A.* 261 (4):580-585, 19S9.
d U.S. Preventive Services Task Force, *Guide to Clinical Preventive Services* (Baltimore, MD: Williams & Wilkins, 19S9).
e Canadian Periodic Health Examination Task Force, "Early Detection of Colorectal Cancer," *Can. Med. Assoc. J.* 141:209-216, 1989,
f F.W. Schwartz, H, Holstein, J.G. Brecht, "Preliminary Report of Fecal Occult Blood Testing in Germany," in *Colorectal Cancer: Prevention, Epidemiology, end Screening,* S. Winawer, D. Schottenfeld, end P. Shertock (eds.) (New York, NY: Raven Press, 1980).
9 S.J. Winawer, J. St. John, J. Bond, et al., "Position Paper: Risk and Screening of Average Risk Individuals for Colorectal Cancer," forthcoming in WHO Bulletin.

tions for the detection of CRC that are consistent with, though less precise than, the ACS/NCI position. These two societies endorse FOBT and sigmoidoscopy for average-risk people beginning at 50 years of age but do not specify the frequency with which such screening should occur.

In contrast to the recommendations of these groups, the U.S. Preventive Services Task Force (USPSTF), an expert group brought together under the sponsorship of the U.S. Department of Health and Human Services to investigate the appropriate role of preventive services in health care, has recently issued findings regarding both the FOBT and sigmoidoscopy. The USPSTF declined to recommend either for or against periodic screening with either FOBT or sigmoidoscopy in average risk individuals 45 years of age or older (80,133,157,158).

The Blue Cross/Blue Shield Association has commissioned papers on the effectiveness and costs of 10 selected preventive health services, including CRC and has collaborated with the American College of Physicians (ACP) to develop a monograph scheduled for publication in 1990. Each of the papers, one of which covers CRC screening,

will undergo peer review for publication in the ACP's journal, the ***Annals of Internal Medicine.*** ACP's Technology Assessment Committee is independently reviewing each of the papers and will endorse the papers' recommendations as it deems appropriate. For CRC, ACP has recommended annual FOBT and sigmoidosocopy every 3 to 5 years for average-risk individuals over the age of 50 (3a).

Other Countries

The USPSTF was modelled after a Canadian Periodic Health Examination Task Force (CTF), which issued its first report on preventive services in 1979, with several revisions since that time. In its original report, the CTF recommended the use of FOBT by asymptomatic people over 45 years of age ***no more frequently than once a year (16).*** A recent review of these guidelines led to a revision of CTF findings. The Task force found that there is inadequate evidence to recommend either for or against screening for CRC, either by FOBT or sigmoidoscopy in a periodic examination of people over 40 with no known risk factors (17). Thus, the CTF guidelines now match those of the USPSTF. This result is not surprising, since the USPSTF had adopted the CTFs criteria for assessing the evidence on the effectiveness of preventive services.

The Federal Republic of Germany has provided free annual FOBT screening for all people over the age of 45 since 1977 (57,132). In contrast, the United Kingdom's National Health Service holds that at present there is insufficient evidence of the effectiveness of any screening test in reducing deaths from large bowel cancer and will not provide screening as a service unless research currently underway shows such an effect (24).

The World Health Organization (WHO) Collaborating Center for the Prevention of CRC at Memorial Sloan-Kettering Cancer Center, which WHO recognizes as its authority on CRC (82), recommends annual digital rectal examinations beginning at age 40, a stool occult blood test annually beginning at age 50, and sigmoidoscopy every 3 to 5 years beginning at age 50 (174). These guidelines are suggested for asymptomatic individuals in the context of medical visits, not for general population screening, although the difference between the two is not clearly defined.

Understanding the Differences in Recommendation

The differences among groups, and even within groups over time, in recommendations regarding CRC screening for average-risk people reflect two facts. First, the evidence on the effectiveness of specific CRC screening technologies is inadequate; and second, the criteria (either implicit or explicit) for judging the evidence that does exist differ among the expert groups. At issue is whether a screening test must be shown to reduce cancer incidence or mortality in order to be considered effective, or whether demonstrating a shift in the distribution of detected cancers to earlier stages is sufficient for considering a screening regimen effective. Those who require direct evidence that CRC screening will reduce the incidence of or mortality from CRC have found the existing evidence inadequate. The critics also point out that screening and diagnostic followup have medical risks and high costs (22). Others focus on the heavy burden of illness and death brought about by CRC and conclude that even indirect evidence that screening may alter the course of a substantial proportion cannot be ignored (46,81).