Costs and Effectiveness of Colorectal Cancer Screening in the Elderly

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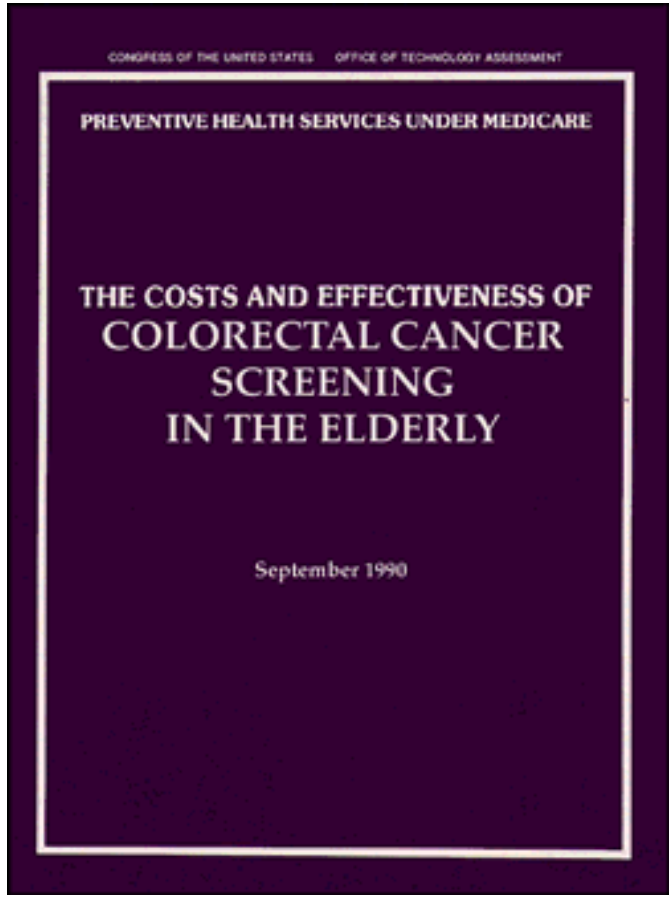

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COSTS AND EFFECTIVENESS OF COLORECTAL CANCER SCREENING IN THE ELDERLY

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FOREWORD

Interest in health promotion and disease prevention strategies for the elderly has grown in the last 10 years, at least partly as a result of the search for ways to moderate the rising costs of health care in this growing segment of the population. Reflecting this interest, the House Committee on Ways and Means requested that OTA analyze the costs and effectiveness of providing selected preventive health services to the elderly under the Medicare program. The Senate Labor and Human Resource Committee had earlier requested that OTA provide information on the value of preventive services for the American people.

OTA responded with a study of the effectiveness and costs of four specific preventive services for the elderly: glaucoma screening; cholesterol screening; cervical cancer screening; and, in this background paper, colorectal cancer screening.

In this paper OTA summarizes the evidence on the effectiveness and costs of colorectal cancer screening in the elderly and explores the implications for Medicare of offering this preventive technology as a Medicare benefit. Nowhere are the hard choices between potential medical benefits and high costs illustrated more clearly than with this cancer screening technology.

JOHN H. GIBBONS
Director

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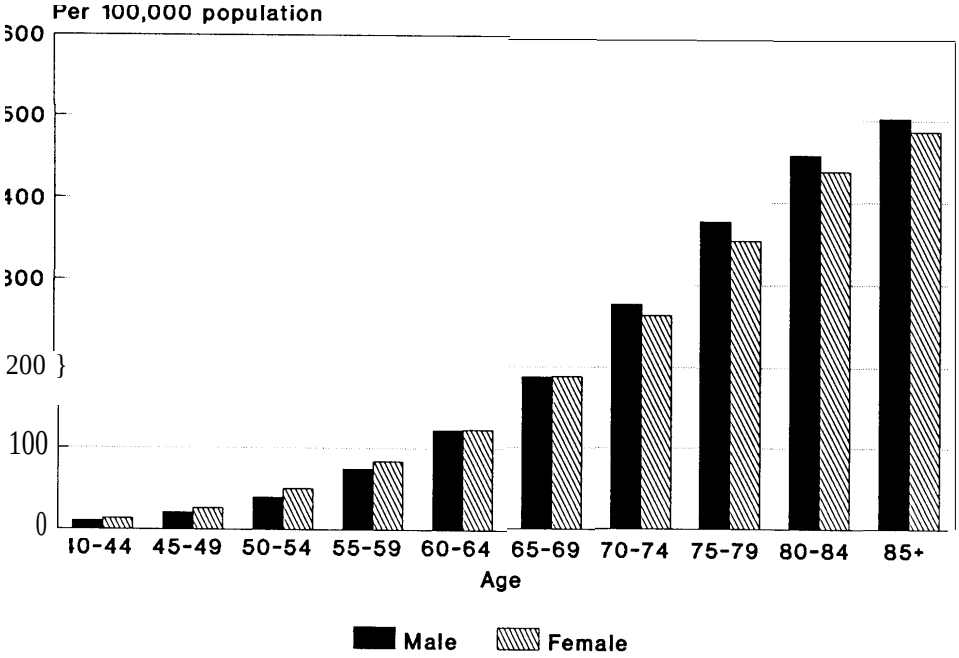
Cancer of the colon or rectum -- commonly referred to together as colorectal cancer (CRC)[1] -- is primarily a disease of the elderly. Every year, about 110,000 people 65 years of age and older are diagnosed with CRC. Almost three out of every four new cases of CRC occur in people 65 years of age and older. In 1989, about 61,500 people died from the disease. A 65-year-old man without previously diagnosed CRC has about 6 chances in 100 of ultimately developing CRC, and about 3 chances out of 100 of eventually dying from the disease (134). As a person ages, the risks of CRC increase dramatically. At 50 years of age, the incidence of CRC in men is 57 per 100,000; by 65 years of age, it has risen to 244 in 100,000; and by 75 years of age it is 411 in 100,000. Though women have a lower overall incidence rate for CRC, it still rises dramatically with age, from 46 per 100,000 at 50-54 years of age to 156 per 100,000 at 65-69 years of age (chart 1).

Although environmental factors, particularly diet, appear to play a role in the development of CRC, little is known today about how to prevent CRC through dietary or environmental interventions. Promising new approaches to cancer therapy appear to offer significantly better prognosis for people with moderately advanced colon cancer, but these improvements are likely to have only modest impacts on overall survival rates for late stage CRCs. Thus, clinicians and researchers have sought ways to reduce the burden of illness and death associated with CRC by detecting more cancers in early and still curable stages, before they progress to more advanced stages.

[1]**Colorectal cancer is also referred to as cancer of the large bowel, the portion of the alimentary canal that begins at the cecum, the juncture between the small intestine and the large intestine, and ends at the anus.**

Chart l--Annual Colorectal Cancer Incidence Rates, United States



SOURCE: U.S. Department of Health and Human Services, National Cancer Institute, *Cancer Statistics Review 1973-1986* (Bethesda, MD: May 1989)

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 -- adenomatous polyps (benign growths in the colon or rectum) -- 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 adenomatous polyps out of which most CRCs are suspected to arise.

The detection of neoplasms (cancers and adenomatous polyps) in the colon or rectum involves either direct inspection of the colon and rectum or indirect measurement of biochemical markers for the presence of cancer or polyps. Today, the most common screening technologies are the fecal occult blood test (FOBT), which analyzes samples of stool for the presence of blood, and flexible fiberoptic sigmoidoscopy (FSIG), a flexible tube with a light and mirror at the end inserted into the colon through the anus to examine the dista1[2] end of the large bowel.

The full impact of screening does not end with these tests. Over the course of his or her remaining life, an elderly person would not only undergo repeated CRC screening tests but also followup diagnostic testing when the screening tests are positive, polyp removal (polypectomy) when polyps are found as part of the screening ***or*** followup tests, and periodic surveillance with colonoscopy after polypectomy to screen for new polyps. In addition, when cancers are found, patients undergo evaluation and treatment for the cancer based on the stage at detection.

Numerous expert groups in the United States and other industrialized countries have made recommendations "about the frequency with which elderly people should receive particular colorectal screening tests. Although the American Cancer Society and the National Cancer Institute both recommend periodic screening for CRC with an annual FOBT and FSIG every 3 to 5 years for all Americans beginning at age 50, the U.S. Preventive Services Task Force, an expert group sponsored by the U.S. Department of Health and Human Services, declined to recommend either for or against periodic screening with either FOBT or sigmoidoscopy in average risk individuals.

The differences in recommendations regarding CRC screening for average-risk older people reflect two facts. First, the evidence on the effectiveness of specific CRC 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 for CRC must be shown to reduce CRC 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 to recommend embarking on a screening strategy for CRC. The critics also point out that screening and diagnostic follow-up have medical risks and costs. Advocates 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 of such cases cannot be ignored.

EVIDENCE ON EFFECTIVENESS

Although a large literature exists on the use of the FOBT as a strategy for CRC screening, only six controlled studies of FOBT screening in asymptomatic individuals have been reported, and four of these are still underway. All but one of the studies are large randomized clinical trials conducted in older average-risk individuals, beginning at ages 45 to 60-years-old. The exception is a study of volunteers

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2. Distal" refers to the parts of the large bowel closest to the anus. "Proximal" is the term for the part-of the large bowel that is closest to the cecum, the point of juncture between the small intestine and the large intestine.

over 40 years old attending a cancer prevention clinic in New York City who were assigned to the experimental or control group according to the month in which they presented at the clinic.

Despite imperfect compliance, rates of detection of CRC are consistently higher in the intervention groups than in the control groups, and a higher proportion of those found are early cancers. Only one of the trials has reported on mortality differences between intervention and control groups. A large trial of biannual FOBT screening of 45- to 70-year-olds in Denmark found a 27 percent lower CRC mortality rate in the group offered screening after about 3 years of study, but the number of deaths ***in*** the study so far is very small and the difference is not statistically significant by conventional standards.

To summarize, the six controlled studies of FOBT screening suggest that in an ongoing screening program, FOBT screening improves the stage distribution of cancers detected, which may translate into decreases in cancer mortality. However, even in very large trials, no such mortality effect has been identified to date.

Studies of the impact of sigmoidoscopic screening on cancer incidence or mortality are even fewer than for FOBT. Only three studies of outcomes of screening programs using sigmoidoscopy have been reported. Two of these were long-term observational studies of screened subjects without comparison groups. The third was a randomized clinical trial of rigid sigmoidoscopy as part of a program of periodic preventive health services offered to non-elderly enrollees in an Hospital Maintenance Organization (HMO).

These studies have universally shown dramatic shifts of detected cancers to early stages. Although two of the three studies reported declines in the incidence or mortality of cancers, critics have concluded that attribution of such changes to screening is not possible given the studies' methods.

Taken as a whole, the evidence on FOBT and sigmoidoscopy suggests a major shift in the stage at which CRCs are detected but inadequate evidence that this stage shift actually reduces death rates from cancer over time. How can these two seemingly contradictory findings be reconciled? One possible explanation is that there are biases in the detection of cancers in these studies. The stage shift may reflect earlier diagnosis, not improved outcomes. This greater "lead time" between diagnosis and death would improve the stage distribution of cancers detected without affecting mortality in randomized trials. There is also a real possibility that "length bias" -- the higher rate of detection of the slowest growing tumors which by definition are less lethal than faster growing tumors -- may account for the inconsistency. Those who believe that length bias can be a powerful influence on outcomes are likely to discount the evidence on stage shift as inadequate, whereas those who see the dramatic shifts in stage at detection as unlikely to be caused simply by lead time or length bias accept this evidence as sufficient to justify periodic CRC screening with sigmoidoscopy or FOBT.

POTENTIAL COST-EFFECTIVENESS OF CRC SCREENING IN THE ELDERLY

Cost-effectiveness analysis is a process of comparing the net health care costs brought about by a screening strategy with the health effects achieved as a result. Estimating the cost-effectiveness of CRC screening in the elderly is a difficult undertaking because of the uncertainty about whether CRC screening is effective at all in preventing CRC or reducing its lethality. If CRC screening is not effective in reducing CRC incidence or mortality in the elderly, then it is clearly not cost-effective. It is only costly. It may even be both costly and risky, because the screening and followup procedures associated with CRC screening strategy carry their own medical risks.

Whether CRC screening can extend the lives of elderly people through prevention or earlier detection of CRCs is simply unknown at present. Indirect evidence does exist, however, about the natural course of the disease, the accuracy of the various screening tests in detecting polyps and CRC, rates of medical complications associated with the various tests and cancer treatment, and the life

expectancy of people with CRC at various stages. Though this evidence is imperfect and has some important gaps, if used judiciously it is possible to explore the potential impact of CRC screening on the health of elderly people. These potential net health impacts can then be compared with the net health care costs associated with screening in elderly people.

To resolve the dilemma posed by uncertainty about net effects, the Office of Technology Assessment (OTA) estimated the net health care cost per additional year of life gained from CRC screening using data and assumptions that were in every case unfavorable toward screening. OTA examined the existing evidence on screening test accuracy, the natural course of the disease in the elderly, medical risks, and costs with the objective of deliberately underestimating the effectiveness and overestimating the costs associated with screening. If the resulting conservative estimate of cost-effectiveness of CRC screening compares favorably with other preventive interventions for the elderly, particularly those that have already been included as Medicare benefits, then confidence that CRC screening is at least as cost-effective as these other services would be high.

Some experts argue that such an analysis is inappropriate at this time (20). Because there is no direct evidence of effectiveness for either FOBT or FSIG, critics argue that an analysis that predicts any positive health effects is not truly pessimistic; a truly pessimistic analysis would posit no health effects. Moreover, evidence on FOBT may become available within the next two to five years as the five ongoing or completed clinical trials report their results. A large National Cancer Instutitue (NCI)-sponsored trial of FSIG screening in older people is also in planning and will probably provide information on that screening procedure within the next 15 years. In the absence of the direct evidence that can come only from these trials, critics argue, an assessment of the medical benefits and potential cost savings associated with screening would entail too many unproven assumptions. Given the high costs and potential medical complications of screening in the elderly, the most prudent strategy is to wait a few years for the results of such studies before deciding whether to take any action, such as providing a Medicare CRC screening benefit, that would encourage screening in the elderly.

The proponents of this view reject the value of the substantial body of indirect evidence that does exist on the accuracy of the screening tests, the natural course of the disease in the elderly, and the effectiveness and cost of treating CRC. It is also not clear that the existing FOBT trials, even when they are reported, will settle the question of FOBT screening effectiveness once and for all. If results differ across trials, for example, the reasons for such discrepancies could be debated for years. Most important, a decision to wait must be recognized as carrying its own implicit value judgment that the potential lives saved from CRC screening are not as important as the potential medical risks and costs of undertaking screening. OTA's analysis is intended to explore just how great the potential gains from screening might be using what information is available now.

OTA constructed a model of the cost-effectiveness of periodic CRC screening in a population at age 65 and continuing until they die or reach the age of 85. OTA made pessimistic assumptions (i.e., biased against finding in favor of screening) about the accuracy of the screening tests, the speed of progression of polyps to cancer and cancers from early to late stages, the proportion of cancers that arise out of polyps, the stages at which cancers would be found in an unscreened elderly population, and the impact of early detection of CRC on life expectancy.

OTA found that a CRC screening regimen consisting of an annual FOBT beginning at age 65 would prevent approximately 23,000 cases of CRC in the 2.1 million people who were 65 years of age in 1989 and would provide almost 45,000 added years of life to that population.[3] These benefits would come at a net discounted cost of roughly $1.5 billion over the remaining lives of the people in the cohort. This net lifetime expenditure amounts to about $737-$1,263

[3]Both added yearn of life and costs are discounted at 5 percent per year.

for every person who complies with screening, diagnostic protocols and surveillance guidelines. The net cost per added year of life is about $35,000. Screening strategies that combine annual FOBT with sigmoidoscopy prevent more cancers and add more years of life but are also more expensive; consequently, the net discounted health care cost per added year of life ranges from approximately $42,000 to $47,000 depending on the frequeney with which sigmoidoscopy is included in the screening program.

Studies of other preventive services legislated as covered services under Medicare in the past (pneumococcal pneumonia vaccine, cervical cancer screening, and breast cancer screening[4]) have reported lower costs for each additional year of life gained from screening. However, when both costs and years of life gained were discounted to their present value at an annual rate of 5 percent, as they were in this study, breast cancer screening in elderly women was estimated to cost about $34,000 per year of life gained. This is approximately equal to the cost per year of life gained from annual FOBT screening in the elderly under the pessimistic set of assumptions.

OTA attempted to submit CRC screening to a stringent test of cost-effectiveness by making assumptions that were uniformly unfavorable to screening. For most of the assumptions, we are reasonably confident that the true value is more favorable to screening than the value assumed in the analysis. By combining so many unfavorable assumptions together, the analysis represents a reasonable upper bound on the potential costs per year of life gained from each screening regimen. Data were sparse to support several assumptions, however. A test of how sensitive the results of the study are to changes in the assumed costs of treating cancer determined that even if such costs are as low as $5,000 per case for both early and late cancer, the discounted net cost per year of life gained from annual FOBT screening is still under $40,000. The results of the analysis were more sensitive to a change in assumptions about the speed with which colorectal polyps become cancers. If a very rapid rate of progression is assumed, the cost per additional year of life gained by an annual FOBT could be as high as $50,000. The ability of the FOBT to detect early cancers (FOBT sensitivity rate) also has a major influence on the outcome of the analysis. If FOBT is a very poor detector of early cancer, the cost per year of life gained from annual FOBT testing in the elderly could be as high as $47,000.

To summarize, the net health care costs of any CRC screening strategy are high. The present value of the lifetime health care costs of an annual FOBT screen for the 2.1 million people who were 65 years old in 1989 may be as high as $1.5 billion, but these high costs have the potential for adding 45,000 years to these people's lives, and the net costs per added year of life are within a range that has been judged reasonable for one other screening examination (mammography) that had been legislated as a Medicare benefit.

The lifetime health care costs of screening strategies that include FSIG as well as FOBT are even higher than those for FOBT alone ($2.4 billion to $2.6 billion, depending on the frequency of FSIG screening), and the added health benefits associated with FSIG over and above FOBT may be quite low. Thus, the additional cost per added year of life gained for FSIG screening over and above FOBT screening may be much higher than those of other preventive services that have been legislated as Medicare benefits.

IMPLICATIONS FOR MEDICARE

If CRC screening were a covered Medicare benefit, Medicare's share of the net cost of screening would be high. Even today, Medicare covers a large but unknown proportion of the total net costs of such a screening strategy, because all diagnostic, followup, and surveillance procedures are covered Medicare services. The costs of the screening tests themselves,

[4]Mammography was briefly legislated as a covered benefit under Medicare, but the provision was repealed when the Medicare Catastrophic Health Act of 1988 was repealed late in 1989.

particularly the FOBT, are very low compared to the costs of followup, treatment, and surveillance. Medicare's average allowed charge for the FOBT when it is ordered for diagnostic reasons is under $4 and for FSIG is about $100.

The national cost estimates above are based on the assumption that all elderly Medicare beneficiaries will follow the screening regimen outlined in the model. In reality, the use of CRC screening examinations in the elderly is quite low, and it is unknown how much it will increase by making FOBT alone or in combination with FSIG a covered Medicare benefit. In 1987, for example, only 34 percent of people 60 years of age or over reported ever having undergone a screening FOBT test and 7.4 percent reported ***ever*** being screened with proctoscopy (rigid sigmoidoscopy) Thus, the net additional health care cost of a Medicare CRC screening benefit may be much lower than the estimates given here. On the other hand, if screening is differentially used by those at low risk of CRC, then the medical benefits projected in the cost-effectiveness analysis would be reduced, and the cost per year of life added would be higher.

The total costs of CRC screening to Medicare and beneficiaries also depend on the amount that Medicare pays for screening, followup and surveillance examinations. In the estimates of screening costs, OTA used Medicare's average allowed charges in 1988 for procedures conducted in physicians' offices. To the extent that FOBT and endoscopy procedures are billed at rates above these amounts and physicians do not accept assignment of the Medicare allowed amount as reasonable, these allowed charges underestimate total health care costs. In addition, when followup and surveillance colonoscopies are performed in hospital outpatient departments, Medicare also pays the hospital for the technical costs of the procedure. If Medicare cannot limit the payment rates for surveillance colonoscopies to the average amounts allowed in physicians' offices, the actual outlays could be higher than the estimates given in this paper.

Finally, the net costs of the strategy are very sensitive to the frequency with which CRC screening results in followup or surveillance colonoscopy. If physicians recommend and patients who have had adenomatous polyps removed comply with a frequent schedule of surveillance with colonoscopy (every two years instead of every four), the costs of the strategy could be much higher than estimated in this paper. The extra costs could amount to almost $1 billion over the lifetime of the 1989 65-year-old population if all members of the population fully comply with the protocol.

This analysis highlights the substantial net costs that can be associated with a preventive service, even one that offers a high potential for major health benefits. CRC screening in the elderly will NOT reduce total health care costs. Depending on which tests are employed and how widely they are used, screening may raise the total lifetime health care cost for a 65-year-old person who undergoes screening as a result of a Medicare benefit by as much as $1,300. That expenditure, which will be borne in large part by Medicare, offers a good chance, but not a certainty, of providing elderly people with substantial gains in health.

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.

SO

[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).

ISSUES IN MEASURING EFFECTIVENESS

To be judged effective, a cancer screening protocol must either increase life spans, improve the quality of life, or both. Changes in the length and quality of life associated with a screening protocol can be both positive and negative; the net effectiveness of a strategy would depend on how such changes balance out. For example, if a positive screening test result leads to risky or uncomfortable confirmatory tests, the increased life expectancy and decreased morbidity resulting from early detection would have to be weighed against the increased mortality, morbidity, or discomfort for those who undergo the followup testing.

Accurate assessment of the full effects (both positive and negative) of a screening strategy requires controlled experiments in which observed differences in mortality and morbidity between those who undergo screening and those who do not can be validly ascribed to the screening program and not to uncontrolled differences between the screened and unscreened groups. When such studies are not available, judgments about the importance of departures from full validity must be made, and studies of more intermediate measures of effectiveness are often used.

One intermediate measure of effectiveness commonly used in evaluating colorectal cancer (CRC) screening is the ***positive predictive value*** (PPV), the percent of all positive screening tests that lead to a diagnosis of cancer or polyps. If the screening test has a high false positive rate[1], the PPV will be low. Even with a low false positive rate, however, if the disease is rare, the PPV will be low, because the vast majority of people who are screened will be disease free and the number (though not the rate) of false positive findings high. The PPV can also be expected to decline with increasing frequency of periodic screening, because the prevalence of previously undetected cases would be lower in more frequent screening programs. A low PPV implies that for every cancer (or polyp) found, a large number of people will be subjected to followup testing with its inherent medical risks and costs.

Although it is a useful indirect indicator of effectiveness, by itself the PPV is insufficient. A screening procedure with a low PPV can still be effective if the reductions in mortality or morbidity resulting from early detection are great compared to the morbidity and mortality associated with the screening and followup procedures. Consequently, the use of PPV to guide screening decisions involves implicit judgments about the relative importance of a screening strategy's benefits and risks, which must be based on other information.

Another measure of effectiveness often used in evaluations of CRC screening is the ***stage-distribution of cancers (or neoplasms) found.*** If a screening program detects a high proportion of cancers relative to the rate expected in the general population, particularly a high proportion in early stages with effective treatment available, it is sometimes reasonable to assume that this shift in the distribution of lesions found toward earlier stages (or even toward precancerous stages) will ultimately be translated into changes in mortality and morbidity, as fewer cancers progress to more serious stages. Without additional information, it is impossible to know to what degree the increase in early-stage cancers (or precancerous lesions) detected will actually translate into reductions in later cancers, because such studies are potentially biased in three ways:

- o Lead time bias - the shift in cancer stage at detection may reflect earlier diagnosis unaccompanied by equal improvements in benefit. Earlier detection of a completely incurable cancer, for example, will improve survival time but will not help the patient. Indeed, the patient may suffer unnecessary anxiety from knowing early about a cancer with effective therapy.
- o Length bias[2] - Because the length of time spent in pre-clinical stages is longer for slow-growing

[1] **The false positive rate is the percent of all people free of disease whose screening test is positive.**

[2] **This kind of bias has also been referred to as "overdetection" bias (116).**

lesions than for fast-growing lesions, slow-growing lesions have a greater chance of being detected in a periodic screening program.

These slow-growing lesions are not as invasive or lethal as fast-growing cancers. Thus, the stage shift will overestimate the number of late cancers averted or the years of life gained.[3]

- o Volunteer bias - people who agree to participate in screening (or even in a cancer screening trial) may have a different clinical course from those who do not, possibly leading to a different distribution of cancers found by screening.

In addition, reliance on the shift in the stage distribution of detected lesions as the principal indicator of effectiveness ignores the medical risks and inconvenience of the screening and followup testing required to find the early cancers.

The problem with stage-specific case finding rates as measures of effectiveness is even greater if the focus is on colorectal polyps, the suspected precursors to cancer. Since only a small minority (perhaps 5 to 10 percent) of colorectal adenomas progress to cancer (106), the potential impact of length bias is even greater, and screenees will be subjected not only to the medical risks of followup testing, but also to the risks of removal of many polyps that would not have progressed to cancer.

Because of these problems, most experts would agree that fully valid evidence on the effectiveness of any CRC screening program requires randomized clinical trials comparing mortality and morbidity rates in those offered screening with such rates in those not offered screening (39,157,158). Such studies are difficult and costly to mount, however. CRC is relatively rare and takes as long as 10 to 15 years to progress from polyps to clinically detectable stages (106), so that measurement of the effects of screening requires many participants and many years to follow the medical histories of study subjects. Despite these problems, several well-designed studies of selected CRC screening protocols are currently underway and may in time provide highly valid information on the effectiveness of certain colorectal screening protocols.

The inadequate evidence on the net effectiveness of CRC screening underlies the present disparity among experts in conclusions about the appropriate place of CRC screening in average-risk older adults. Those who require high standards of validity in studies of screening techniques generally conclude that no CRC screening protocol has been shown to be effective (48,49,50,116,133,137). Others who examine the shift in the distribution of lesions found to early or precancerous stages have concluded that the potential biases are unlikely to account for all of the benefit afforded by early detection (35,171). Eddy has observed that "There is a conceptual issue here -- how certain do you have to be before you say it is beneficial?" (81).

EVIDENCE ON EFFECTIVENESS OF FECAL OCCULT BLOOD TEST (FOBT)

Although a large literature exists on the use of the FOBT as a strategy for CRC screening, only six controlled studies of FOBT screening in asymptomatic individuals have been reported, and four of these are still underway.[4] The researchers in each of these studies have reported the PPV of the FOBT and most have studied differences between the intervention and control groups in the stage of cancers detected. Interim mortality data are available from only one study, a large ongoing study of FOBT screening in a community in Denmark begun in 1985. Table 3 summarizes the study designs and results of the trials to date.

All but one of the studies are large randomized clinical trials conducted in older average-risk individuals, beginning at ages 45- to 60-year-olds. The exception is a study of volunteers over 40 years old attending a cancer prevention clinic in New York City who were assigned to experimental and control groups according to the month in which they presented at the clinics

[3] An even stronger argument can be made with respect to screening and removal of colonic polyps. If the cancers that tend to progress rapidly are not those arising from polyps, then removing a large number of polyps may not have much effect on the incidence of cancer (101).

[4] For reviews of uncontrolled studies of FOBT screening, see Simon (137); Frank (48,49,50); and Fletcher and Dauphinee (46).

[5] In this trial, both groups received sigmoidoscopy as part of a cancer checkup. Only the experimental group received FOBT.

All six studies have reported on the PPV for cancer, adenomatous polyps, or neoplasms (cancer + adenomas). As discussed above, the PPV for a specific condition is directly related to the prevalence of the sought-after condition in the screened population and inversely related to the false positive rate. The prevalence of previously undetected disease would decrease as screening frequency increases; therefore, programs with more frequent screening intervals should have lower PPVs. Also, the first screen in a new FOBT screening program should have a higher PPV than subsequent screens. Thus, studies undertaken for longer periods of time, with periodic rescreening, should report lower PPVs overall and declining PPVs as the trial progresses. These trends are apparent in the studies. The University of Minnesota study has had the longest period of screening (at 1- and 2-year intervals) and has reported the lowest PPV for FOBT, only 2.5 percent for cancer (i.e., a positive FOBT resulted in a cancer diagnosis less than 3 percent of the time). The other controlled studies reported PPV for cancer on first and second screens in the neighborhood of 10 to 20 percent.

Because PPV depends on prevalence, it should be higher in populations with higher prevalence of CRC. Where data on PPV are available by age, the results are consistent with expectations. In the Strang Clinic study, the PPV for cancer in screenees 70 years of age or older (23 percent) was almost twice as high as the PPV in the screened population as a whole (170).

The method of preparing FOBT specimens for analysis also affects the PPV because it alters the false positive rate. Dehydration (adding a few drops of water to the test slide prior to analysis) is frequently practiced to increase the test's sensitivity to blood in the stool. But dehydration also increases the false positive rate. Consequently, the PPV of FOBT under dehydration is lower than the PPV without such a procedure. The Swedish study showed that dehydration reduced the PPV for all neoplasms by 10 percentage points. Dehydration of test slides was gradually introduced in the University of Minnesota study in order to increase test sensitivity; in all, approximately two-thirds of all slides were dehydrated. Thus, the low PPV in that study may be partly due to dehydration.

Because the prevalence of adenomatous polyps is much higher than the prevalence of cancer, particularly in elderly people, the PPV is substantially higher for neoplasms than it is for cancer alone. In the Danish study of biannual FOBT screening in 45- to 70-year-olds, 52 percent of all positive FOBTs were diagnosed either with a cancer or adenoma, compared to 7 percent for cancer alone. Among 60- to 64-year-olds in Sweden, the PPV for neoplasm (i.e., cancer plus polyps) with dehydrated slides on the second screen was 24 percent. Ransohoff and Lang have observed that the calculated PPV of the FOBT may actually reflect a random selection of elderly people for followup and detection of their polyps. To the extent that false positive FOBTs occur serendipitously in patients who happen to have polyps, the PPV will give the FOBT credit for "finding" the polyp even though it occurred by chance (123).

The success of an FOBT screening program in detecting early cancer or altering mortality rates depends in large measure on the rate of compliance with screening regimens in the population. If few people avail themselves of the opportunity to be screened, then the potential for detecting and treating cancer early is compromised. Compliance appears to vary widely across the studies, depending on the age of the screenee (older people are less compliant); the age of the program (compliance with rescreening is lower than with the first screen); the population on which randomization was based (volunteers are more compliant, at least in the beginning); and the kinds of recruitment efforts made by the program.

Despite imperfect compliance, rates of detection of CRC are consistently higher in the intervention groups than in the control groups, and a higher proportion of those found are early cancers. For example, an ongoing British trial begun in 1984 found 58 percent more cancers in the group offered screening than in the control group after 2 screening periods. These extra cancers detected were heavily concentrated in Stage A, the most curable stage of CRC. The Swedish study also found a much higher rate of cancers in the intervention group after 27 months of study, but differences in the distribution of cancer stage, which favored earlier cancers, were not

Table 3-Fecal Occult Blood Teat (FOBT) Controlled Clinical Trials

Study/site	Years	Study population	Intervention group(s)	Control group	Screening compliance rates	Dehydration status	FOBT positive predictive value	Cancer stage et detection	Mortality
Strang Clinic Colon Project, New York, NY a,b,c	1975-1079	21,008 symptomatic volunteers › 40 years old (33% › 60) attending cancer prevention clinic and followed up in 1984	Annual medical exam, rigid sigmoidoscopy and FOBT (group selected by calendar period of entry to clinic (Hemoccult and Hemobcult II)	Same as intervention except no FOBT	60-80% compliance in year 1, declining to 20-40% in year 5	Unspecified, but most No	PPV on all screens [initial + followup]: Tot PPV: 12% for cancer 36% for cancer + adenomas PPV (60-69 years old) 13% for cancer 42% for cancer + adenomas PPV › 70 years old) 23% for cancer 42% for cancer + adenomas	Percent of all cancer detected in Dukes' A and B: 65% in intervention group 33% in control group	NA
Funen, Denmark d,e	1985-ongoing	60,00045 to 70-year-olds asymptomatic for colorectal cancers, adenomas, or metastasis from all cancers	Randomized: 30,000 offered screening every 2 years with reminders	No screening offered	First screen: 65-69 70-74 men 63% 54% women 64% 50%	No	First screen: 18% cancer 58% cancer + adenomas Second screen: 7% cancer 52% cancer + adenomas	Rate of CRC detection after 34 months Test grp Control grp All CRC 0.428% 0.306% (p<0.01) Stage A CRC 0.122%0 002% (p‹0.0001) Other Stages 0.204% 0.286% (p<0.002)	First 38 months of Study: 27% reduction in CRC mortality, not statistically significant (p=0.16)
Hardcastle, Nottingham, England f	1983	20,525 patients 45 to 74-year-olds in 9 general practices in Nottingham, England without known bowel disease or cancer	Randomized: 10,253 sent instructions on Hemoccult II	No screening	35.1% men 34.8% women 27% for › 70 year	No	52% neoplasm	Rate of CRC detection Test grp Control grp All CRC 0.225% 0.097% Stage A CRC 0.092% 0.000%	NA

ABBREVIATIONS: CRC = colorectal cancer FOBT = fecal occult blood test; NA = not available; NS = not significant; PPV = positive predictive value.

a B J Flehinger, E. Herbert, S.J. Winawer et al., "Screening for Colorectal Cancer With Fecal Occult Blood Test and Sigmoidoscopy: Preliminary Report of the Colon project of Memorial Sloan-Ketting Cancer Center and PMI-Strang Clinic," J Chamberlain and A.B. Miller (eds.) *Screening for Gastrointestinal Cancer* (Lewiston, NY: Hans Huber Publishers, 198S).

b S.J Winawer, M. Baldwin, E. Herbert et al., "screening& Experience With Fecal Occult Blood Testing as a Function of Age," in *Perspectives on Prevention and Treatment of Cancer In the Elderly*, R Yancik, P.P. Cat'bone, W.B. Patterson et al. (eds.) (New York, NY: Raven Press, 1983).

c 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*.

d o Kronborg, C. Fenger, O. Sondergaard et al., "Initial Mass Screening for Colorectal Cancer With Fecal Occult Blood Test," *Scand. J. Gastroenterol.* 22:677-686, 10S7.

e OKronborg, "Mass Screening for Colorectal Cancer With Hemoccult-II at Funen in Denmark," Interim Report, June 19SS, unpublished.

f J.D Hardcastle, P.A. Farrands, T.W. Balfour et al., "Controlled Testing in the Detection of Colorectal cancer," *Lancet* 2:1-4, 1983.

g J.D. Hardcastle, "Randomized Controlled Trial of Fecal Occult Blood: Screening for Colorectal Cancer," unpublished paper. no date.

h J.S Mandel, J.H. Bond, M Bradley et al., "Sensitivity, Specificity and Positive Predictivity of the Hemoccult Test in Screening for Colorectal cancers: The Univereityof Minnesotans Colon Cancer Control Study," unpublished paper, undated.

i J S Mandel, J.H Bond, D C Snover et al., "screening for Colorectal Cancers: The University of Minnesota's Study," unpublished paper, undated.

j J.S Mandel, University of Minnesota, personal communication, July, 1990.

k K. Klaaborg, M.S. Madsen, O. Sondergaard et al., "Participating in Mass screening Colorectal Cancer With Fecal Occult Blood Test" *Scand. J. Gastroent.* 21:1 1S0-1 1S4, 19S6.

l J, Kewenter, S.Bjork, E.Haglind et al., "Screening and Rescreening for Colorectal Cancer: A Controlled Trial of Fe@ Occult Blood Testing in 27,700 Subjects," *Cancer* 62(3):645651, 1988.

Table 3-Fecal Occult Blood Teat (FOBT) Controlled Clinical Trials (continued)

Study/site	Years	Study population	Intervention group(s)	Control group	Screening compliance rates	Dehydration status	FOBT positive predictive value	Cancer stage at detection	Mortality
Hardcastle, England [a]	1984-ongoing	107,000 50 to 74-year-olds	Randomized: 53,464 offered A) 3day Hemoccult II B) 6-day Hemoccult II with reminder; positive tests repeated; rescreen at 2-year intervals offered to those accepting first screen	No screening	Initial screen: 52.9% First rescreen: 77.0% Second rescreen: 80.0%	No	Initial screen: 10% for cancer First rescreen: 8% for cancer Second rescreen: 12% for cancer All screens: 10% for cancer	Rate of CRC detection after 2 rescreens Teat grp / Control grp All CRC: 0.33% / 0.22% (p<.0.01) Stage A CRC: o 10% / o 02% (p<.0.01) Other Stages CRC: 0.23% / 020%	NA
University of Minnesota [a,h,i]	1070-1982 (phase 1) 1 9 8 6 - (phase II - ongoing)	46,622 volunteers aged 50-80 recruited from community	Randomized: 1) annual FOBT 2) biannual FOBT	No screening	Phase I (1976-1982) 1) 75.7% 2) 76.7% declined preciplously for those ›80 years old (@ 55%)	No/Yes (gradually introduced during phase i) overall,	1st phase: 2.5% cancer 16.2% adenomatous polyps <60 = 1.690 2/3 = yes	Percent of all CRCs detected in Stage A in screen group: 35%	NA
Gothenberg, Sweden [c,j]	1982-1983; 1984-1985; and ongoing	27,503 residents of Gothenberg aged 60-64 in 1982	Randomized: First screen – mailed Hemocult II with mail return &two reminders 1) dehydrated 2) not-dehydrated Second screen – dehydrated only	No screening	First screen: 66% Second screen: 58%	First screen: random allocation of specimens to dehydration and no dehydration; on second screen dehydration only	First screen: Dehydrated – 22'% for neoplasms Not dehydrated – 32% for neoplasms Second screen: 24% for neoplasm	Rate of CRC detection after 27 months Test grp / Control grp All CRC: 0.44% / 0.15% (p<0.001) Stage A: 0.09% / 0.02% (NS) Stage B: 0.1 1% / O 04% (NS) (C& D): 0.24% / 0.09 (NS)	NA

ABBREVIATIONS: CRC = colorectal cancer; FOBT = fecal occult blood test; NA = not available; NS = not significant; PPV = positive predictive value.

[a] B.J. Flehinger, E. Herbert, S.J. Winawer et al., "Screening for Colorectal Cancer With Fecal Occult Blood Test and Sigmoidoscopy: Preliminary Report of the Colon Project of Memorial Sloan-Kettering Cancer Center and PMI-Strang Clinic," J. Chamberlain and A.B Miller (eds.) *Screening for Gastrointestinal Cancer* (Lewiston, NY: Hans Huber Publishers, 198S).

[b] S.J. Winawer, M, Baldwin, E. Herbert et al., "Screening Experience With F@ Occult Blood Testing aaa Function of Age," in *Perspectives on Prevention and Treatment of Cancer in the Elderly*, R. Yancik, P. P. Carbine, W.B. Pattereon et al. (eds.) (New York, NY: Raven Press, 19S3).

[c] S.J. Winawer, J. St. John, J Send et al., "Position Paper: Risk and Screening of Average Risk Individuals for Colorectal Cancer," forthcoming in *WHO Bulletin*.

[d] O. Kronborg, C. Fenger, O. Sondergaard et al., "Initial Mass Screening for Colorectal Cancer With Fecal Occult Blood Test," *Scand. J. Gastroentero* 1. 22:677-686, 1987.

[e] Kronborg, "Mass Screening for Colorectal Cancer wnh Hemoccult-II at Funen in Denmark," Interim Report, June 19SS, unpublished.

[f] J.D. Hardcastle, P.A. Farrands, T.W. Balfour et al., "Controlled Testing in the Detection of Colorectal Cancer," *Lancet* 2:1-4, 1983.

[g] J.D. Hardcastle, "Randomized Controlled Trial of Fecal Occult Blood: Screening for Colorectal Cancer," unpublished paper. no date.

[h] J.S. Mandel, J.H. Bond, M.Bradley et al., 'Sensitivity, Specificity and Positive Predictivity of the Hemoccult Teef in Screening for Colorectal Cancers: The University of Minnesota's Colon Cancer Control Study," unpublished paper, undated.

[i] J.S. Mandel, J.H. Bond, D.C. Snover et al., "Screening for Colorectal Cancers: The University of Minnesota's Study," unpublished paper, undated.

[j] J.S. Mandel, University of Minnesota, personal communication, July, 1990.

[k] K. Klasborg, M.S. Mad-,0, Sondergaard et al., "Participating in Mass Screening Colorectal Cancer With Fecal Occult Blood Test" *Scand. J. Gastroent.* 21:11s0-11s4, 1SS6.

[l] J. Kewenter, S. Bjork, E. Haglind et al., "Screening and Rescreening for Colorectal Cancer: A Controlled Trial of Fecal Occult Blood Testing in 27,700 Subjects," *Cancer* 62(3):645651, 1sss

statistically significant. The Swedish study is much smaller than the British trial, however, which may account for the lack so far of statistically significant differences in cancer stage distribution.

Only one of the trials has reported on mortality differences between intervention and control groups. A large trial of biannual FOBT screening of 45- to 70-year-olds in Denmark found a 27 percent lower CRC mortality rate in the group offered screening after about 3 years of study, but the number of deaths in the study so far is very small and the difference is not statistically significant by conventional standards ($p = 0.16$).

To summarize, the six controlled studies of FOBT screening suggest that in an ongoing screening program, a large number of screenees will undergo followup diagnostic tests for every CRC found, but this number decreases with the age of the screenee. It is clear that FOBT screening improves the stage distribution of cancers detected, which should translate into decreases in cancer mortality. However, even in very large trials, no such mortality effect has been identified to date. This leads to the possibility that length bias may have a strong influence on the screening programs.

EVIDENCE ON THE EFFECTIVENESS OF SIGMOIDOSCOPY

The argument for effectiveness of sigmoidoscopy as a screening tool is most forcefully made through direct comparison with the FOBT. Unlike the FOBT, which has many false negatives for cancer, sigmoidoscopy has high sensitivity and specificity for rectal or colonic lesions within its reach into the colon. Indeed, endoscopic examination is the diagnostic standard against which most other CRC detection methods are assessed (133). In studies comparing sigmoidoscopy with barium enema, sigmoidoscopy generally had a very high sensitivity -- on the order of 90 to 95 percent in detecting lesions found by either method in asymptomatic or symptomatic persons (148,167).

Because polyps and cancers are directly visualized in sigmoidoscopy, a positive finding is always a true positive. The virtual non-existence of false positives would imply a high PPV for sigmoidoscopy. If, however, one considers some of those positive findings to be clinically insignificant, then sigmoidoscopy may have a substantial false positive rate and, hence, a lower PPV. Hyperplastic polyps, for example, do not progress to cancer, but it is impossible to accurately differentiate hyperplastic polyps from neoplastic polyps without a biopsy. Consequently, when such polyps are found they are typically removed and biopsied. The clinical significance of very small polyps (i.e., those smaller than 5 mm) is also questionable (106); some researchers believe that these are highly unlikely to progress to cancer, yet they, too, are typically removed when found on an endoscopic examination.[6] Thus, for every "positive" sigmoidoscopic screening examination, a relatively small number may actually be at risk for developing into CRC.

The rapid change in endoscopic technology that occurred in the mid-1970s increased the tension between detection capability and clinical significance of lesions detected. The development of flexible fiberoptic sigmoidoscopes with lengths of up to 60 cm, compared to the 25 cm length of the rigid sigmoidoscope, increased the potential proportion of polyps and cancers that are detectable with high sensitivity and specificity with sigmoidoscopy at the same time that it increased the number of clinically insignificant lesions found and removed. A review of studies comparing flexible with rigid sigmoidoscopes found about 2.6 times as many cancers and 2.5 times as many polyps with a 60 cm flexible sigmoidoscope as with a rigid sigmoidoscope (76).

Studies of the impact of sigmoidoscopic screening on cancer incidence or mortality are even fewer than for FOBT. Only three studies of outcomes of screening programs using sigmoidoscopy have been reported and all used the rigid sigmoidoscope. Two of these were long-term observational studies of screened subjects without comparison groups. The third was a randomized clinical trial of rigid sigmoidoscopy as part of a program of periodic preventive health services offered to non-elderly

[6] This position is controversial. Tedesco found that almost 50 percent of very small polyps were adenomatous, but the study was in a symptomatic group of people (147).

enrollees in an HMO. These studies have been carefully reviewed and critiqued by several experts (101,116,133).

The two observational studies of CRC sigmoidoscopy screening programs showed dramatic shifts of detected cancers to early stages. A study of annual sigmoidoscopy examinations offered from 1946 to 1954 at the Strang Clinic in New York to 26,126 patients 45 years of age and older, most of whom (89 percent) were asymptomatic at the time of sigmoidoscopy, detected 81 percent of CRCs in Stage A or B (67). In a study of annual sigmoidoscopy offered to people 45 years of age and older in Minnesota between 1948 and 1974, all cancers detected on the second or subsequent screens were in stage A or B (54).

An analysis of cancer incidence and mortality in the Minnesota program's followup period suggested that, after eliminating cancers found on the first screen, the rate of CRC detected in subsequent years was much lower than would be expected in a like unscreened Minnesota population (54). This would imply that removal of polyps found on sigmoidoscopy prevented CRC. But the cancers found at the first screen were not prevented; rather they were found early (101,105,114,133). In a reanalysis that included pre-existing cancers, Miller concluded that the CRCs detected over the period were strikingly similar to the age-adjusted rate in an unscreened population (101). Selby and Friedman have also pointed out that the reported incidence rate in the screened group was based on the number of person-years of observations, and people may have dropped out of followup if CRC was discovered. Thus, the actual CRC incidence rate in the population offered screening was probably higher than reported in the study (133). Finally, as a program that enrolled volunteers, the cancers in the Minnesota study may have had an unrepresentative incidence and stage distribution (114), although the direction of such "volunteer bias" cannot be predicted.

The one randomized clinical trial involving annual rigid sigmoidoscopic screening for 40- to 54-year-olds as part of a multiphasic health examination for enrollees in an HMO found significantly lower death rates from CRC over an n-year period in the group offered screening than in the control group (27). On its face, this finding from a randomized trial would be strong evidence of an effect on mortality from sigmoidoscopy. But several reviewers, including one of the investigators on the original study, have called these results into question. First, the difference between the study group and control group in the use of sigmoidoscopy over the 10 year period (31 percent vs. 26 percent) was not great enough to account for the two-fold observed difference in CRC mortality (133). Second, most tumors found in both groups were detected from symptoms, not through screening (133). Third, given the design of the study, the authors probably used too lenient a test for statistical significance (101, 114,133). Thus, several reviewers have concluded that whatever real differences existed in CRC incidence and death between the study group and control group were due to factors other than the availability of sigmoidoscopy (101,114,133).

Taken as a whole, the evidence on sigmoidoscopy suggests a major shift in the stage at which CRCs are detected, but inadequate evidence that this stage shift actually reduces death rates from cancer over time. How can these two seemingly contradictory findings be reconciled? First, there has never been a good trial of the effect of screening flexible fiberoptic signodoscope (FSIG) on cancer mortality, so the lack of evidence on outcomes should not be equated with the existence of negative evidence. But, second, if future randomized studies do confirm that stage shift is unaccompanied by changes in mortality from CRC, then one must look for possible biases in screening programs. Only if therapy is no more effective in early cancers than in late cancers or if length and volunteer biases are strong can the stage shift coincide with no impact on mortality. Experts agree that therapy is much more effective in early CRC than it is once cancer has spread beyond the wall of the colon or rectum (23,145). Thus, increased lead time would not explain the lack of mortality differences between screened and unscreened groups. Many experts believe that length and volunteer biases can be powerful influences on outcome and consequently discount the evidence on stage shift as inadequate. Others see the dramatic shifts in stage at detection as unlikely to be caused simply by length

and volunteer bias; they accept this evidence as sufficient to justify periodic CRC screening with sigmoidoscopy or FOBT.

Virtually all CRCs are removed promptly after detection, so there is no direct evidence on how the length of time in each stage of cancer varies among patients. If the distribution of time spent in early stages is very wide, with some cancers progressing rapidly but many progressing slowly or hardly at all, then the **case** for length bias is strengthened. Numerous experts have commented on the high variability in the speed with which cancers grow in size or progress (29,145). Periodic screening would be likely to pick up relatively few of the rapidly progressing cancers (a high proportion of which would develop and grow in the time interval between screenings) but a large number of indolent cancers. On the other hand, if all CRCs progress at a similar speed, then the argument for length bias would be weaker, and the evidence on the proportion of early cancers detected would be compelling. Because it is unethical to leave CRCs detected but untreated, direct observation of the distribution of cancer progression rates is infeasible; only controlled cancer screening trials of sufficient size and duration will provide definitive information on the extent of length bias. The National Cancer Institute (NCI) has recently announced plans for a 5-year randomized clinical trial of sigmoidoscopy screening in men 60- to 74-year-olds (152). This trial, which will enroll enough men to detect a 20 percent decrease in mortality, will test whether a sigmoidoscopy every 3 years will affect outcomes in the elderly. The results of the trial will probably not be available for at least 10 to 15 years.

EFFECTIVENESS ISSUES SPECIFIC TO THE ELDERLY

Although all CRC screening programs have targeted older people (generally over 45 or 50 years of age), screening in the elderly (people 65 years of age and older) raises issues that may not be so important in middle-aged people.

High Incidence of CRC in the Elderly--The incidence of CRC rises dramatically with age (see Chart I); the incidence of CRC **at ages** 70-74, for example, is 5.7 times higher than at ages 50-54 (152). At the same time, it does not appear that CRC progresses at a different rate in the elderly; the distribution of stage at detection is virtually the same in the elderly as in the non-elderly (58,73,75,104). Thus, the potential burden of illness in those over 65 years of age is much higher than for other groups, and the potential effectiveness of screening in reducing morbidity and mortality is higher as well.

The distribution of cancers throughout the large intestine appears to be different in the elderly. The elderly tend to have more CRC located proximal to the splenic flexure than do the non-elderly (45,63,139). In a Swedish study of 264 patients with polyps found through colonoscopy, polyps in patients over 65 years of age were much more uniformly distributed throughout the large intestine than were polyps found in people 55 years of age and under. There, almost 70 percent of all polyps were found in the sigmoid colon and rectum, compared to only about 35 percent of polyps in the elderly (59,161). Consequently, within their limited reach, sigmoidoscopes would probably detect a smaller fraction of all CRCs in the elderly than in non-elderly screenees.

High Prevalence of Colorectal Polyps in the Elderly--The prevalence of asymptomatic benign adenomatous polyps increases dramatically in the elderly. Autopsy studies conducted in the United States and other countries over the years have consistently found an increase in the prevalence of polyps with age up to approximately 60- to 70-year-olds. Beyond that point, the prevalence of polyps shows no systematic relationship to age (table 4).

Although the frequency of adenomas increases dramatically with age, the average size of these lesions does not vary with age, which suggests that "while new adenomas develop with aging most tend to remain static in size after reaching a diameter of less than 10 mm" (128).

If adenomas are precursors of the vast majority of CRCs, as many researchers have suggested (25,35,106,108), then removal of adenomas would appear to be prudent even if the great majority of them will not develop into cancer, but this would imply that a large number of elderly people entering

Table 4-Age-Specific Polyp Prevalence: Autopsy Studies

Study	Year	population	Polyp type	Age-specific prevalence rate (number) 60-69 Male	60-69 Female	70-79 Male	70-79 Female	80 and over Male	80 and over Female
United States:									
Rickert et al., 1979	NG	518 autopsies of males and females between ages 20 and 102 not previously diagnosed with carcinoma of the bowel	Adenomatous	59.8% (58)	48.8% (19)	68.996 (51)	40.0% (20)	61.1% (22)	63.0% (17)
Stemmermann and Yatani, 1973	1960-1972	Autopsies from 202 Hawaiian Japanese at the Kuakini hospital in Honolulu, HI	Adenomatous	60.0% (22)	59.0% (10)	70.0% (16)	60.0% (18)	66.0% (23)	83.0% (12)
			Hyperplastic	81.0% (30)	77.0% (13)	87.0% (20)	67.0% (21)	86.0% (30)	16.0% (16)
Arminski and McLean, 1964	NG	1,000 autopsies of men and women aged 20 and over at the Grace Hospital, Detroit, MI	Adenomatous	39.9% (79)	25.3% (28)	46.1% (53)	47.3% (35)	46.3% (19)	42.5% (17)
Chapman, 1963	NG	Autopsies of 443 adults in New York hospital	Adenomatous	43.0%[a] (NG)	37.0% (NG)	65.0% (NG)	37.0% (NG)	63.0% (NG)	50.0% (NG)
Blatt, 1961	1960	556 autopsies performed during a 9-month period in NY (446 colons used in the study)	Adenomatous	35.0% (23)	37.5% (15)	45.0% (42)	46.0% (29)	46.7% (21)	40.0% (20)
Correa et al., 1977	1970-75	301 autopsies performed in New Orleans	Hyperplastic	14.3%[b] (177)	10.4%[b] (124)				
Other countries:									
Williams et al., 1982	NG	365 autopsy specimens in a l-year period in Liverpool, England. 134/365 came from cases dying in hospital.	Adenomatous	44.0%[d] (25)	35.0% (18)	52.0% (22)	33.0% (21)		
			Hyperplastic	47.0% (27)	13.0% (7)	33.0% (14)	34.0% (22		
Restrepo et al., 1981	1971-1973	529 specimens from consecutive autopsies of persons age 10 and over in a hospital in Medellin, Colombia	Adenomatous	7.0%[b] (32)	16.7% (24)				
			Hyperplastic	31,2% (lo)	29.2% (7)				
Hughes, 1968	1964	200 colons from autopsies done in Queensland, Australia examined for polyps	Not Specified	22%[c] (10)		17% (11)		32.4% (12)	

NG = not given.
a In this study groups are divided at age 65 to 74, 75 to 84, and 85 and over.
b In this study the prevalence rate for elderly people is reportad as one group, age 60 and over.
c Male and female prevalence rates are combined.
d In this study groups are divided at age 65 to 74, and 75 and over.

SOURCE: T.C. Arminski end D.W. McLean, "Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations," *Dis. Colon Rectum* 7:249–261, 1964; LJ. Blatt, "Polyps of the Colon and Rectum: Incidence and Distribution," *Dis. Col.* Rec. 4:277-282, 1961; 1. Chapman, "Adenomatous Polypi of Large Intestine: Incidence and Distribution, "Ann. *Surg.* 157(2):223-226, 19S3; P. Correa, J.P. Strong, A. Reif, et al., "The Epidemiology of Colorectal polyps: Prevalence in New Orleans and International Comparisons," *Cancer* 39:2258-2264, 1977; LE. Hughes, "The Incidence of Benign and Malignant Neoplasms of the Colon and Rectum: A Post Mortem Study, " *N.Z. J. Surg.* 38(1):30-35, 19SS; C. Restrepo, P Correa, E. Duque, et al., "polyps in a Low-Risk Colonic Population in Columbia, South America. " *Dis. Colon Rectum*, 24:29-36, 1981; R.R. Rickert, O. Auerbackk, L Garfinkel, et al., "Adenomatous Leaions of the Large Bowel: An Autopsy Survey," *Cancer* 43:1847-1857, 1979; G.N. Stemmerman and R. Yatani, "Diverticulosis and Polyps of the Large Intestine: A Neocropsy Study of Hawaii Japanese, " *Cancer* 31(5):1260-1270, 1973; A.R. Williams, B.A. Balascoriya, D.W. Day, et al., "Polyps and Cancer of the Large Bowel: A Necropsy Study in Liverpool," Gut 23:835–842, 19S2.

a screening program for the first time would have one or more polyps removed, with consequent risks and costs. In addition, with FOBT and sigmoidoscopy as the screening tools, elderly people would not be likely to have as high a proportion of polyps found and removed as would the non-elderly, mainly because more are located beyond the reach of the sigmoidoscope and are not likely to be picked up by the FOBT. If the detection and removal of polyps are important for the success of a CRC screening program, then perhaps a screening tool with greater sensitivity and reach into the colon, such as DCBE or colonoscopy, would be more effective (but also more costly) in the elderly.

Decreased Acceptability of Screening Procedures--There is some question as to whether the elderly find the current screening methods acceptable. The discomfort of sigmoidoscopy and the preparation required for all screening, including dietary restrictions, purging, etc. may be more difficult for elderly people to undertake than younger people.

Increased Fragility in the Aged--The ability of elderly people to withstand the discomfort and risks of sigmoidoscopy and colonoscopy is highly variable, of course, but the issue of increased complications with age needs to be considered. The elderly tend to have more underlying diseases that may make it more difficult to pass these instruments (135), and rates of post-colonoscopy hemorrhage may be higher in the elderly than in the non-elderly (30). In addition, the dietary preparation needed both for adequate endoscopy and DCBE may be more difficult for frail or very old people to withstand (135). Especially in the very elderly (those 80 years of age and above), the question must be asked how much morbidity is associated with the screening tests themselves and any followup procedures, such as the DCBE, colonoscopy, or surgery (120). Studies of resection for CRC in the elderly showed increasing postoperative complication and mortality rates with advanced age (42,89).

Decreased Life Spans in the Elderly--The progression from polyp to cancer and from early cancer to late cancer is not well understood, but the process is generally thought to be gradual, and does not change with age. Studies of the growth rates of small CRCs have indicated that colorectal tumors may grow from 5 mm to 1 cm in a median time of 30 to 40 months, with a lower bound of 12 to 16 months (18). Some experts claim that it takes from 5 to 10 years for an adenomatous polyp of 1 cm in size to develop into cancer (35,135). The slow progression of polyps to cancer raises the question whether screening for polyps in patients over 70 years of age can increase longevity (135). Yet, avoiding CRC has benefits that are independent of effects on length of life. The real question is whether detecting and removing the polyps and early cancers are worth the inconvenience, medical risk, and cost that are implied for the very old.

The Cost-Effectiveness of Colorectal Cancer Screening in the Elderly

INTRODUCTION

How cost-effective is colorectal cancer (CRC) screening in the elderly? This question can be answered only by comparing the net health care costs brought about by a screening strategy with the health effects achieved as a result. The health effects of a preventive strategy such as CRC screening include impacts on quality of life as well as on its length. Measuring these two dimensions of health effects is often difficult; some cost-effectiveness analyses include only mortality effects -- life-yeas gained -- and leave quality-of-life improvements implicit; others attempt to capture both dimensions in composite measures such as "wellness years" or "quality-adjusted life years" gained from a preventive strategy.

Estimation of the cost-effectiveness of CRC screening in the elderly is especially difficult because of the uncertainty about whether CRC screening is effective at all in preventing CRC or reducing its lethality. If CRC screening is not effective in reducing CRC incidence or mortality in the elderly, then it is clearly not cost-effective. It is only costly. It may even be both costly and risky, because the screening and followup procedures brought about by a screening strategy carry their own medical risks. However, if CRC screening is effective in reducing cancer incidence and death, then the ratio of net health care costs to a measure of effectiveness can help policy makers determine whether the strategy is worth its costs and risks.

Whether CRC screening can extend the lives of elderly people through prevention or earlier detection of CRCs is not known at present. Indirect evidence does exist, however, about the natural course of the disease, the accuracy of the various screening tests in detecting polyps and CRC, rates of medical complications associated with the screening tests, followup procedures and cancer treatment, and the life expectancy of people with CRC at various stages. Though this evidence is imperfect and has some important gaps, if used judiciously it is possible to explore the potential impact of CRC screening on the health of elderly people. These potential net health impacts can then be compared with the net health care costs associated with screening in elderly people.

To resolve the dilemma posed by uncertainty about net effects, Office of Technology Assessment (OTA) estimated the net health care cost per additional year of life gained from CRC screening using data and assumptions that were in every case pessimistic toward screening. We examined the existing evidence on screening test accuracy, the natural course of the disease in the elderly, medical risks, and costs with the objective of deliberately underestimating the effectiveness and overestimating the costs associated with screening. If the resulting conservative estimate of cost-effectiveness of CRC screening compares favorably with other preventive interventions for the elderly, particularly those that have already been included as Medicare benefits, then confidence that CRC screening is at least as cost-effective as these other services would be high.

The remainder of this chapter describes OTA's analysis of the cost-effectiveness of four alternative strategies for CRC screening and compares the results of that analysis with findings about other preventive services for the elderly and with other studies of CRC cost-effectiveness.

SCREENING, FOLLOWUP, AND SURVEILLANCE STRATEGIES

The National Cancer Institute (NCI) recommends that adults without specific risk factors for CRC begin a program of periodic screening for CRC at age 50 and continue for the rest of their lives. The recommended screening program entails an annual fecal occult blood test (FOBT) and flexible fiberoptic sigmoidoscopy (FSIG) at 3- to 5-year intervals (See table 2). OTA examined four screening schedules, including the NCI schedules, for people beginning at age 65 and continuing until they die or reach the age of 85:

- Regimen 1: Annual FOBT and a sigmoidoscopic examination every 3 years;

- Regimen 2: Annual FOBT and a sigmoidoscopic examination every 5 years;
- Regimen 3: Annual FOBT and ***one*** sigmoidoscopic examination upon entry to Medicare at age 65;
- Regimen 4: Annual FOBT with ***no sig***moidoscopy.

For all regimens, screening was assumed to cease when the individual reaches age 85, although surveillance of people previously found to have polyps would continue for the rest of their lives. Because the lengths of sigmoidoscopes vary, the model was further refined to estimate separately the effectiveness and costs of screening with a 60 cm sigmoidoscope and a 35 cm sigmoidoscope. The longer scope detects a greater proportion of colonic polyps and cancers than the shorter one, but the costs and medical risks of followup and surveillance are higher.

Over the course of their remaining lives, 65-year-old people would undergo repeated screening tests, followup diagnostic testing when the screening tests are positive, polyp removal (polypectomy) when polyps are found as part of the screening or followup tests, and periodic surveillance with colonoscopy after polypectomy to screen for new polyps. In addition, when cancers are found, patients undergo evaluation and treatment for the cancer based on the stage at detection.

The effectiveness and cost of following up on a positive screening test depends on the diagnostic technologies employed. Two alternative followup protocols have been recommended (32,44,47,72,91, 122,143,155). The first is to go directly from a positive screening test to a full colonoscopy with polypectomy if necessary. The alternative is to followup with sigmoidoscopy (if the screening test was an FOBT) and a DCBE. The relative advantages of the two followup procedures are currently subjects of debate (44,53). Comparisons of relative accuracy, procedure risk, patient comfort and cost underlie different conclusions about the two procedures.

In this study OTA assumed a positive screening sigmoidoscop would result in full colonoscopy with polypectomy.[1] All positive FOBT tests were also assumed to result in a diagnostic colonoscopy and, if a polyp is found, polypectomy. Pathological tests are universally recommended for all removed polyps, and the OTA analysis assumed that they will be done.

Once a polyp has been discovered and removed, the patient is typically subject to periodic surveillance by colonoscopy, on the assumption that people previously discovered to have polyps are at higher risk of future recurrence of polyps and cancers (87,114). The American Gastroenterological Society recommends that surveillance begin one year after the polypectomy and, if the first surveillance colonoscopy is negative, that it continue at 3- to 5-year intervals (44). A large multi-center randomized trial funded by the NCI is currently underway to compare the effectiveness of surveillance at 1 year and 3 years vs. 3 years after polypectomy (113). The OTA analysis assumed a surveillance colonoscopy frequency of every 4 years beginning 4 years after the initial polypectomy, but the impact of moving to a 2-year surveillance interval was investigated in a sensitivity analysis reported later in this paper.

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[1] **The procedure costs of colonoscopy are higher than a combination of sigmoidoscopy and DCBE. The average Medicare allowed payment for a sigmoidoscopy and a DCBE together in 1986 was $213 compared to $376 for a diagnostic colonoscopy and $626 for a colonoscopy with polypectomy. The impact on total costs of assuming followup with colonoscopy rather than with FSIG and DCBE may not be to overestime costs, however. Any polyps discovered by DCBE beyond the reach of the sigmoidoscope would be removed through colonoscopy, requiring an additional procedure, and those within the reach of the followup sigmoidoscopy might also require an additional procedure for removal, thereby necessitating a further charge for the polypectomy. Because polyps are present in a high proportion of 65-year-old people (perhaps as many as one-half), basing the cost of diagnostic followup on the assumption that it will always be colonoscopy does not substantially overestimate true costs. It might even underestimate these costs in some circumstances. For example, if 50 percent of all people referred for follow-up from a positive FOBT had polyps, then the average followup cost of the FSIG and DCBE in 1986 would have been $526 [1/2($213 +$626)+ 1/2($213)] compared to $445 [1/2($213) + 1/2($676)] for colonoscopy.**

STRUCTURE AND ASSUMPTIONS OF THE COST-EFFECTIVENESS ANALYSIS

The cost-effectiveness analysis enumerates and estimates the size of the potential health effects and health care costs of CRC screening over the remaining lifetime of a cohort of 65-year-olds. The analysis assumes that these people have not been screened before reaching the age of 65 and that all people in the cohort will fully comply with the screening, followup and surveillance regimen. The 2.1 million people who were 65 years of age in 1989 served as the illustrative cohort for the analysis.

Table 5 arrays the potential effects and costs brought about by any particular CRC screening strategy. Notice that screening potentially affects both costs and outcomes in both positive and negative ways. OTA's analysis estimated the size of each potential category of cost and effect ***except*** those involving changes in quality of life. Individuals vary greatly in perceptions of pain and discomfort associated with particular procedures. Consequently, OTA did not attempt to adjust the analysis for quality of life impacts but recognized that such considerations would and should enter into individual clinical decisions about the value of CRC screening in a particular person[2].

In OTA's analysis a population of 65-year-olds embarks on a screening regimen and begins to incur costs and reap medical effects (measured by additions to or reductions in life expectancy) over the succeeding years. The estimated costs and effects incurred over time are discounted to their net present value.[3] The size of these estimated costs and effects depends on assumptions about the following:

Table 5- Effects and Coats of CRC Screening in the Elderly

Effects
Longer life:
● Removal of polyps prevents cancers that would have been fatal.
● Early detection of CRC reduces death rate from cancers.
Shorter life:
● Detection and removal of polyps carries small risk of colon perforation and death.
● Surveillance with colonoscopy of people previously detected with polyps carries small risk of colon perforation and death.
● Treatment of cancers detected in screening that would have remained latent for the duration of the patient's life carries risk of surgical, medical complications.
Higher quality of life:
● pain associated with cancer or cancer treatment is avoided for those whose cancer would have been clinically detected in the absense of screening.
Lower quality of life:
● Discomfort, pain is incurred from screening, followup, and surveillance procedures.
● Pain of cancer treatment is incurred for those whose cancer would have remained latent for the rest of their lives.
● False positive screening results cause unnecessary anxiety.
costs
Higher costs:
● Screening and followup tests cost money.
● Polyp removal procedures cost money.
● Surveillance procedures for those found with polyps cost money.
● Treatment of cancers that would have remained latent for the duration of the patient's life costs money.
Lower costs:
● Reduction in need for cancer treatment due to prevention of CRC saves costs.
● cost of cancer treatment is reduced due to detection in earlier stages where treatment is less expensive.

SOURCE: Office of Technology Assessment, 1990.

0 natural history of the disease:

the underlying prevalence of polyps and cancers by stage in 65-year-olds;
the incidence of new polyps and cancers at various stages that would be expected in succeeding years in the absence of screening;
the rate at which polyps become cancers and early cancers progress to late cancers;
the rate at which latent cancers become diagnosed clinically;
the life expectancy of people in each year from age 65 to 85 without CRC and with CRC detected in early and late stages;

[2] These quality of life effects, particularly the discomfort of the screening, followup and surveillance procedures themselves, may partly explain why colorectal screening use rates are so low today.

%0 compare outlays occurring in different time periods, they must each be discounted to their to their present value. The discounting of health effects as well as costs is necessary to insure that programs whose benefits lie well in the future will not be found more cost-effective if postponed indefinitely (77). A discount rate of 5 percent per year was used to convert both additional years of life gained (effects) and costs in future years to their value in 1989.

o test accuracy:

the sensitivity and specificity of the screening, followup and surveillance tests in detecting polyps and CRC;

o ***medical risks:***

the rates of colon perforation and death from screening, followup and surveillance;
the rate of surgery-related mortality associated with treatment of cancer;

[0] ***costs:***

the costs of screening, followup, polyp removal, surveillance, and treatment of early and late cancers;
the cost of treating colonoscopy-induced injuries;
the cost of treating surgery-related injuries in patients with cancers that would have remained latent in the absence of screening for the remainder of the patient's life ("lifetime latent" cancers).

Detailed descriptions of the sources of data and rationale for assumptions in each of these areas are presented in appendix C. Table 6 summarizes the critical assumptions underlying the results presented for the pessimistic analysis.

RESULTS

Table 7 shows the results of a cost-effectiveness analysis of the four screening regimens under assumptions that are pessimistic about the cost-effectiveness of CRC screening. Regardless of the screening regimen employed, CRC screening is potentially costly. The present value of the net lifetime health care costs of periodically screening the 1989 population of 65-year-olds could be as high as $1.5 billion to $2.6 billion if all of these people were to fully comply with the screening, followup and surveillance protocols. This net lifetime expenditure amounts to about $737-$1,263 for every person who does comply with the protocols.

The net costs of screening regimens that involve FSIG are much higher than the net cost of an annual FOBT, largely because FSIG is such a sensitive

Table 6-Summary of Assumptions for Coat-Effectiveness Analysis

Accuracy	
FOBT sensitivity for polyps	10%
FOBT sensitivity for CRC	40%
FOBT specificty	96%
FSIG sensitivity for polyps	
– for polyps destined to become clinically detected cancer.	92%
– for polyps destined not to progress	96%
FSIG sensitivity for CRC	92%
Reach of 60 cm FSIG	
– for polyps destined to become clinically detected cancer.	35%
– for polyps destined not to progress	70%
– for CRC	35%
FSIG Specificity	95%
Natural history of the disease	
Percent of all clinically detected cancers that begin as polyps	57%
Number of years for a 5 mm adenoma to progress to CRC	6
Number of years required for a new invasive CRC to progress to late CRC (for CRCs destined to be clinically detected)	1
Number of years required for a late CRC destined to be clinically detected to be detected	1
Percent of CRCs clinically detected in early stage	40%
Prevalence of lifetime latent cancers at age 65	5/1000
Annual incidence of lifetime latent cancers	5/10,000
Medical risks	
Rate of colonoscopy-induced perforation of the large bowel	0.1%
Colonoscopy-induced motility rate	0.02%
Surgery related mortality in patients with primary colorectal cancer surgery	7%
coats	
Cost of FOBT	$3.56
Cost of Screening FSIG	$96
Cost of diagnostic colonoscopy	$411
Cost of colonoscopy with polpectomy	$653
cost of pathology	$51.37
Cost of treating early cancer	$20,000
Cost of treating late cancer	$30,000
Cost of treating colonoscopy-induced perforations	$20,000
Cost of treating colonoscopy-induced deaths	$30,000
Cost of treating fatal complications in early cancer patients	$30,000

SOURCE: Office of Technology Assessment, 1990.

Table 7-Cost-Effectiveness of Colorectal Cancer Screening in the 1989 U.S. 65-Year-Old Population Under Assumptions Unfavorable to Screening[a,b]

	Costs				Effects					Cost Effectiveness
screening Regimen	Costs of screening, followup and surveillance[c,d]	Extra costs of treating lifetime latent cancers[c,f]	Savings in treatment costs[c,d]	Net additional costs of screening	Number of cancers prevented	Years of life gained from reduction in cancer mortality[c]	Years of life lost from operative mortality	Years of life lost from complications of colonosoopy[c]	Net gain in years of life[c]	Cost per year of life gained[c,e]
Regimen 4: Annual FOBT	$1.597 billion	$0.387 billion	$0.450 billion	$1.534 billion	22,756	61,821	12,723	5,340	43,758	$35,054
Regimen 3: Annual FOBT 60cm FSIG on entry to Medicare	$2.526 billion	$0.397 billion	$0.524 billion	$2.399 billion	26,484	72,455	13,316	8,425	50,714	$47,308
Regimen 2: Annual FOBT 60cm FSIG every 5 yrs	$2.705 billion	$0.404 billion	$0.604 billion	$2.504 billion	32,579	81,016	13,567	8,528	58,92'	$42,509
Regimen 1: Annual FOBT 60cm FSIG every 3 Yrs	$2.849 billion	$0.404 billion	$0.623 billion	$2.630 billion	33,549	83,593	13,660	8,610	61,323	$42,892

FOOTNOTES:
[a]For assumptions, see table 6.
[b]Costs shown in table are rounded to the nearest million dollars Underlying calculations carried OUt on exact numbers
[c]Years of life and costs are discounted to present value at a rate of 5 percent per year.
[d]This category includes costs of treating complications of colonoscopy
[e]Compared to no screening.
[f]This category includes costs of treating complications of surgery.

SOURCE: Office of Technology Assessment, 1990.

detector of polyps. Once an adenomatous polyp is detected and removed, a person enters a costly schedule of surveillance by colonoscopy.[4]

The screening procedures alone (FOBT and FSIG) represent a relatively small proportion of the overall cost of the program. For example, screening costs constitute 4 percent of the total costs of screening, followup and surveillance under Regimen 4 (which has no sigmoidoscopy) and 18 percent of the total screening, followup and surveillance costs of Regimen 1, the most intensive screening schedule. Followup and surveillance costs are each a large part of lifetime costs, because 45 percent of the population sooner or later will be subjected to followup and then surveillance under Regimen 4 (FOBT only) and 55 percent would ultimately be placed in surveillance under any screening regimen involving FSIG.

The importance of surveillance as a component of program costs suggests that costs to Medicare are likely to be high even if screening begins well before the person becomes eligible for Medicare. For example, if all people begin CRC screening in keeping with the NCI guidelines at 50 years of age, then many of those with colorectal polyps would already be in a surveillance pool at the time they reach age 65. Though they would not be incurring additional screening and followup costs, they would be in surveillance from the time of entry into Medicare through the rest of their lives.

The net costs of the program could be even higher than those presented here if the schedule of surveillance by colonoscopy were reduced from four years to two. In that case, the total cost associated with screening increases to between $2.3 billion and $3.9 billion, depending on the screening regimen employed (table 8).

[4]**The screening, followup, and surveillance costs shown in Table 7 assume that FSIG screening will be performed with a long (60 cm) FSIG. Use of the shorter (35 cm) FSIG would lower the screening, followup and surveillance costs but would also reduce the effectiveness of screening.**

Table 8-impact of Surveillance Schedule on the Cost-Effectiveness of CRC Screening in the 1989 U.S. 65-year-old Population[a]

	Surveillance schedule			
	Total program costs		Cost per year of life gained [b]	
	4 year	2 year	4 year	2 year
Regimen 4[c]	$1.534 billion	$2.320 billion	$35,054	$58,879
Regimen 3[d]	$2.399 billion	$3.656 billion	$47,308	$80,381
Regimen 2[e]	$2.504 billion	$3.785 billion	$42,509	$70,140
Regimen 1[f]	$2.830 billion	**$3.893 billion**	$42,892	$69,445

ABBREVIATION: FOBT = fecal occult blood test.

[a] Screening with a 60 cm sigmoidoscope.
[b] Cost and years of life gained in the future are discounted to their present value@ a rate of 5 percent per year.
[c] Regimen 4: Annual FOBT; sigmoidoscopy every 5 years.
[d] Regimen 3: Annual FOBT; sigmoidoscopy every 5 years.
[e] Regimen 2: Annual FOBT; sigmoidoscopy once upon entry to Medicare.
[f] Regimen 1: Annual FOBT; no sigmoidoscopy.

SOURCE: Office of Technology Assessment, 1990.

The analysis suggests that in preventing some cancers (between 22,000 and 33,000 depending on the screening regimen) and detecting others in an earlier stage than they would otherwise be detected, substantial savings in health care costs are obtained, but these savings are markedly reduced by the extra costs of treating the many lifetime latent cancers detected through screening. With Regimen 4 (FOBT only) the net saving in cancer treatment cost is only $63 million, a small sum compared to the $1.6 billion spent in screening, followup and surveillance (table 7).

The potential health benefits achieved by this high cost are substantial. Under the assumptions of the OTA analysis, annual FOBT screening would prevent almost 23,000 cases of CRC that are otherwise destined to become clinically manifest sometime during the remainder of the population's life. This represents approximately 17 percent of all cancer incidence expected in the 65-year-old population. In addition to this gain, some cancers that would have manifested themselves in late stages will, under screening, be detected in early stage, with con-

sequent improvements in survival. Taken together, the benefits of prevention and early detection of CRC result in a total gain of between 43,000 and 61,000 additional years of life[5] in the cohort under study (table 7).

The critical measure of cost-effectiveness is the cost per added year of life from a specific CRC screening regimen. As table 7 shows, adopting a CRC screening program for the elderly costs between $35,000 and $47,000 per added year of life gained, depending on the particular screening regimen adopted. Strategy 4 (FOBT only) is the most cost-effective strategy compared to no screening.

The cost-effectiveness of CRC screening depends strongly on the surveillance protocol adopted. The high procedure cost of colonoscopy relative to the screening procedures makes colonoscopy a critical resource whose overuse could render CRC screening much more expensive per year of life gained. As table 8 shows, a 2-year surveillance schedule increases the total costs of the program by almost 50 percent and raises the cost per year of life saved by over 60 percent, to about $57,000 in the case of Regimen 4. In keeping with the pessimistic structure of the analysis, OTA assumed that surveillance colonoscopy adds no health care benefits beyond those achieved by the discovery and removal of the initial polyp in screening. Consequently, the extra costs and risks of more frequent surveillance add only costs and reduce effectiveness without providing any compensating benefits. The National Polyp Study currently underway is intended to determine whether more frequent surveillance does improve outcomes; in the meantime, it is worth noting that the total costs of any CRC screening program are very sensitive to the surveillance schedule.

The cost per year of life saved for each of the screening regimens is based on a comparison with no screening. Ideally, decisions about the frequency of screening with FSIG should be made by comparing the incremental, or additional, costs with the additional health benefits of moving from no FSIG screening or from a less frequent screening interval to the next most frequent screening interval. After all, more frequent screening costs more money. That extra cost should be compared with the extra benefits it provides. Unfortunately, the model is not a reliable estimator of these incremental costs and effects. OTA assumed that cancers destined to be diagnosed clinically (in the absence of screening) progress very rapidly. While this assumption underestimates the effectiveness of any screening regimen compared to no screening, it also overestimates the effectiveness of more intensive or frequent screening compared to less intensive screening regimens. If CRCs destined to be diagnosed clinically progress slowly, then infrequent screening with FSIG should be almost as effective as, and much less costly than, more frequent screening with FSIG.[6] The pessimistic assumptions regarding the speed of polyp and cancer progression (i.e., very fast progression from early to late cancer for those cancers that would become clinically manifest without screening) makes more frequent screening with sigmoidoscopy appear incrementally more effective than it would be if cancers actually progress more slowly.

Because the model is deliberately biased upward in cost and downward in effectiveness when comparing each regimen with no screening, OTA is reasonably confident that, compared to no screening at all, screening according to one of the four schedules provides an added year of life at a cost no greater than, and probably less than, those shown in Table 7. Studies of other preventive services legislated as covered services under Medicare in the past (pneumococcal pneumonia vaccine, cervical cancer screening, and breast cancer screening) have reported lower costs for each additional year of life gained from screening. (36,149,150) However, when both costs and years of life gained were discounted to their present value at an annual rate of 5 percent, as they are in this study, breast cancer screening with mammography was estimated to cost about $34,000 per year of life gained. This is approximately equal to the cost per year of life gained from annual FOBT screening in the elderly under the pessimistic set of assumptions.

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[5] Years of life gained in future years are discounted to their present value at a rate of 5 percent per year.

%0 test this assumption, OTA lengthened the assumed CRC progression rate from one year to three years. As expected, the cost per year of life gained compared to no screening declined, but the additional cost per additional year of life gained from offering more frequent FSIG screening compared to less frequent FSIG screening increased greatly.

To summarize the results of this analysis, under pessimistic assumptions about the potential effectiveness and costs of screening, the discounted cost per year of life gained for FOBT is within the range of cost-effectiveness values calculated for mammography screening in elderly women (36), provided that the post-polypectomy surveillance schedule is no more frequent than every 4 years. Thus, if the assumptions outlined above are as conservative as we believe them to be, CRC screening is as cost-effective as one other preventive intervention that had been covered under Medicare.[7] At the same time, it is impossible to say whether the extra costs of periodic sigmoidoscopy compared to annual FOBT alone are high or low in relation to the extra medical benefits they provide, because the magnitude of those incremental costs varies so greatly with changes in assumptions about the rates of polyp and cancer progression. Indeed, if the great majority of polyps and cancers progress much more slowly than assumed in the model, the incremental cost of regimens 1 to 3 (i.e., those involving FSIG) relative to regimen 4 (FOBT only) would be very high. Yet, the cost per year of life saved ***compared to no screening*** for any of the screening regimens would be even lower than they are in table 7.

Distribution of Effects Across Time and Individuals

The estimated cost per year of life gained represents an average of medical gains and losses incurred by different people at different times in their lives. CRC screening subjects some people to risks of illness and death that they would not have suffered had they not been screened. Those risks are borne relatively early in their remaining lives, whereas the substantial gains from reductions in the incidence and lethality of cancer occur later on. For example, under the pessimistic assumptions, an annual FOBT would detect about 4,200 lifetime latent cancers in year 1, when the 2.1 million 65-year-olds have just enrolled in Medicare; an estimated 300 of these people would die in that year from complications of surgery for CRC. These 300 excess deaths in the first year of screening must be weighed against the 23,000 eases of cancer prevented and the lives saved from early detection of the cancers that are not prevented, both of which occur later in life. To some extent, discounting lives saved in future years to their "present value" takes account of these differences in the time distribution of effects. Yet, the selection of a uniform discount rate for all people, necessary for a public policy analysis, masks wide variation in individuals' preferences for early losses versus late gains in life expectancy. Differing valuations of the tradeoff between risks now and risks later on could make an individual's assessment of the cost-effectiveness of CRC screening very different from the estimates given in this paper.

Sensitivity Analysis

OTA attempted to submit CRC screening to a stringent test of cost-effectiveness by making assumptions that were uniformly unfavorable to screening. For most of the assumptions, we are reasonably confident that the true value is more favorable to screening than the value assumed in the analysis. By combining so many unfavorable assumptions together, the analysis represents a reasonable upper bound on the potential costs per year of life gained from each screening regimen.

Data were very sparse to support several assumptions (Appendix C). The most uncertain and potentially important are the costs of treating early and late cancer; the speed of progression of polyps to cancer; and the sensitivity of FOBT for early cancer. Although OTA attempted to be conservative about each of these assumptions, it is important to know how the results of the cost-effectiveness analysis would change if the true values were at levels even more unfavorable to screening than those assumed in the original analysis.

Costs of Cancer Treatment

The cost-effectiveness model assumed that the additional net costs of treating early and late cancer are $20,000 and $30,000 respectively. The basis for these estimates is tenuous. Higher costs lead to greater savings in the cost of treating cancers that are prevented or detected earlier than they would be

[7] **Mammography was briefly legislated as a covered benefit under Medicare, but because it was legislated as part of the Medicare Catastrophic Health Act of 1988, the provision was repealed when the Catastrophic law was repealed late in 1989.**

without screening but they also increase the costs of treating lifetime latent cancers detected through screening. Consequently, the impact of any change in cancer treatment costs cannot be predicted beforehand. OTA examined how reductions in the cost of early and late cancer treatment would affect the outcome of the analysis.

Table 9 shows the results of changing these values on the estimated cost-effectiveness of regimens 4 and 2. As the table shows, the costs of cancer treatment have little effect on the cost per year of life gained from screening. Even under the extreme assumption that the discounted cost of treating both early and late cancers is only $5,000, the net discounted cost per year of life gained from screening rises from about $35,000 to $37,000 for FOBT.

Speed of Polyp/Cancer Progression

Although most experts believe that the polyp/cancer sequence occurs over a long period of time, it is possible that the most lethal cancers -- those destined to be discovered late and to be least responsive to therapy --progress more quickly, even when they are still polyps. Changing the assumptions about the speed with which polyps that are destined to become clinically detected cancers actually progress from their beginning to early stage cancer has a greater impact on estimated cost-effectiveness than do changes in the cost of cancer treatment. If the polyp/cancer progression time is assumed to be 3 years in length rather than 6 years, the cost per year of life gained from an annual FOBT screen increases to almost $51,000 (table 10). Other screening regimens also become substantially more expensive for the medical benefits they produce.

Table 9-Cost-Effectiveness of CRC Screening Under Differing Assumptions About the Cost of Treating Early and Late CRC[a]

cost of treating early CRC	cost of treating late CRC	Cost per added year of life Regimen 4[b]	Cost per added year of life Regimen 2[c]
$5,000	*$5,000*	$37,150	$45,950
$5,000	$10,000	$35,120	$44,171
$10,000	$15,000	$35,774	$44,210
$10,000	$20,000	$33,745	$42,430
$20,000	*$30,000*	$35,054	$42,509

a Costs and years of life discounted at annual rate of 5 percent.
b Regimen 4 = annual FOBT.
C Regimen 2. annual FOBT + FSIG every 5 years.

SOURCE: office of Technology Assessment, 1990.

Table 10- Sensitivity of Coat-Effectiveness Results to Faster Polyp/Cancer Progression Time[a]

Screening regimen	Cost per year of life gained with 6 year progression time	Cost per year of life gained with 3 year progression time
4	$35,054	$50,992
3	$47,306	$71,547
2	$42,509	$59,751
1	$42,692	$51,666

a Polyp/cancer progression time refers to the number of years for a polyp that is destined to be detected without screening to progress from it's earliest detectable state to invasive cancer.

SOURCE: Office of Technology Assessment, 1990.

FOBT Sensitivity for Early Cancer

OTA assumed that FOBT can detect a cancer (early or late) with a 40 percent probability. (See app. C for the evidence on which this assumption is based.) This is substantially lower than the values used in recent cost-effectiveness studies of FOBT screening (8,39). Although this assumption is on the low end of the existing studies of FOBT sensitivity, most studies of FOBT sensitivity include symptomatic patients, who would be more likely to present with blood in the stool. One study comparing FOBT with sigmoidoscopy in asymptomatic non-elderly people found a sensitivity for cancer of 25 percent (6). OTA examined the impact on costs and effectiveness of using this lower value. As table 11 shows, changing this assumption raises the cost per additional year of life gained by about 23 percent, to $43,000 for screening regimen 4 (FOBT only) but has less proportional impact on regimens that include FSIG.

Table 11- Effect of Lower FOBT Sensitivity on Cost-Effectiveness of CRC Screening

Screening regimen	Cost per year of life gained from screening	
	FOBT sensitivity 40%	FOBT sensitivity 25%
4	$35,054	$43,167
3	$47,306	$55,525
2	$42,509	$48,338
1	$42,692	$46,194

SOURCE: Office of Technology Assessment, 1990.

Comparison With Other CRC Cost-Effectiveness Analyses

Several researchers have analyzed the cost-effectiveness of CRC screening, but none has examined the effectiveness and cost of repeated screens beginning at 65 years of age. Barry, Mulley and Richter (8) examined the cost-effectiveness of a one-time FOBT screen for an asymptomatic 65-year-old who had not been previously screened. The gain in years of life from screening was based on assumed changes in the stage distribution of cancers detected as a result of the screening examination. They found that the net discounted cost[8] per added year of life ranges from about $9,000 to $14,000, depending on the followup procedures used. Their analysis assumed that the prevalence of polyps in this population would be about 18 percent, a substantially lower estimate than OTA used. The low estimate of polyp prevalence reduces the estimated costs of following up positive FOBT examinations. Barry and Mulley also did not include the costs of surveillance following polypectomy, which represent a major component of net health care costs in the OTA study.

England and colleagues (40) studied the effect of a one-time colorectal screening examination in a population of asymptomatic people 40 years and over. The impact of screening on life expectancy was based on assumptions about the shift in the stage distribution of cancers that can be expected from screening. The analysis did not include the costs of surveillance resulting from detection and removal of polyps, and it did not estimate the savings in health care costs that can be expected from improvements in the stage at detection. The authors found that the cost per year of life gained[9] from an FOBT and sigmoidoscopic examination ranged from $19,000 to $21,000.

Allison and Feldman examined a one-time FOBT screen in people 45 years of age and older who were enrolled in an Health Maintenance Organization (HMO) in 1979-1980 (l). The gains in survival from screening were estimated by comparing the stage distribution of CRCs detected in the HMO in 1974 (before screening was available) with that observed in the screened patients in 1979-1980. Savings in medical care costs were netted out of the total cost estimate, but surveillance costs were not included in the analysis. The FOBT was found to cost $765 per person-year of extended life.[10]

In several studies based on a mathematical model of CRC, Eddy and colleagues (33,35,39) estimated the cost-effectiveness of alternative screening and followup strategies for various populations. The impact of screening at various frequencies with different combinations of potential screening tests was calculated based on assumptions about the natural history of polyps and cancer that are similar but not identical to those used by OTA. Costs include screening and followup but not surveillance. Nor did the analyses account for the cost or risk of treating screening-detected cancers that would otherwise remain latent through the remaining life of the screened individual. The net savings in the costs of treating CRC were subtracted from total costs.[11] In the most recent version of the model, Eddy assumed a lower sensitivity of FOBT for polyps than did OTA. Eddy assumed an effective sensitivity for polyps of 19 percent for just the last 2 years before the polyp progresses to invasive cancer. While most of Eddy's other assumptions are more favorable to screening than are OTA's assumptions, this assumption significantly reduces the potential effectiveness of FOBT to prevent cancer compared to OTA.[12] In average risk 50-year-old men, the net discounted cost per additional year of life gained from a screening regimen that would continue to age 75 was estimated at about $19,200 for an annual FOBT and sigmoidoscopy every 5 years, and $25,300 for an annual FOBT and a sigmoidoscopy every 3 years (39).

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[8] The discount rate was 6 percent in that study.

[9] Neither costs nor years of life were discounted in this analysis.

[10] Costs and years of life gained were not discounted in this analysis.

[11] Both costs and increases in life expectancy were discounted at 5 percent.

[12] For example, in OTA's analysis, a cancer that would become clinically manifest in its late stage at age 75 has six chances to be detected (between the ages of 67 and 72), with a 10 percent probability of detection in each year. This corresponds to an overall probability of detection as a polyp of 47 percent, compared to an overall detection probability in Eddy's study of 36 percent.

Discussion

Virtually all cost-effectiveness analyses of CRC screening, including our own, have concluded that this kind of cancer screening delivers substantial benefits with a sizable investment. All of the models, including our own, assume that it is possible to prevent cancer or alter the pattern of mortality from the disease through early detection. Definitive evidence that screening can indeed deliver such effects simply does not exist. Yet, in building from what is known about the polyp and cancer detection capability of the screening tests and the natural course of the disease, we concluded that CRC screening is likely to deliver health benefits at a cost that is roughly in line with those offered by at least one other preventive health service that was covered under Medicare.

The uncertainty about the relative merits of alternative CRC screening strategies is great, however, and the potential costs of screening, followup and surveillance are high. In particular, the incremental cost of each year of life added by sigmoidoscopic screening (on top of an annual FOBT) is unclear and could well be very high. The sigmoidoscopy screening clinical trial currently under development at the National Cancer Institute promises to provide information on the medical effects and net health care costs of sigmoidoscopic screening in older Americans within 10 to 15 years (152).

IMPLICATIONS FOR MEDICARE

OTA's cost-effectiveness analysis followed a cohort of 65-year-olds through the remainder of their lives. The net program costs represent the discounted value of the stream of outlays over the next 30 or more years for people who were 65 years old in 1989. If Medicare were to offer a CRC screening benefit, all elderly people, not just those newly eligible for Medicare in years after coverage begins, would be offered screening. What is the magnitude of the health care costs that would be incurred in any year?

OTA calculated the annual national costs associated with screening, followup and surveillance of three CRC screening regimens beginning in 1989 assuming that all elderly people fully comply with the screening, followup and surveillance protocols. (The savings in health care costs from reductions in cancer treatment and the added costs of treating lifetime latent cancers were not included, but as table 7 showed, these other components of cost are minuscule compared to the costs of screening, followup and surveillance.) For this estimate of the annual national health care bill associated with CRC screening in the elderly, OTA made more realistic (i.e., less pessimistic) about the accuracy of the screening tests and the prevalence and incidence of polyps in the population (table 12).

Costs vary from year to year as the program gears up and the size and age-distribution of the population over 65 years of age changes. In the ninth year of program operation, the annual cost of Regimen 1 with 60 cm FSIG (in 1988 dollars) would be $2.5 billion, and the cost of Regimen 2 would be $2.2 billion. Regimen 4 (FOBT only) would be substantially less expensive to implement ($1.2 billion per year) because it excludes the costs of FSIG and all the followup and surveillance that would have been induced by detection of polyps at sigmoidoscopy. Chart 2 shows the estimated annual cost for each of the three screening regimens during the first nine years of operation of such a program.

If CRC screening were a covered Medicare benefit, Medicare's share of the net cost would be high. Even today, Medicare covers a large but unknown proportion of such costs because all diagnostic, followup, and surveillance procedures are

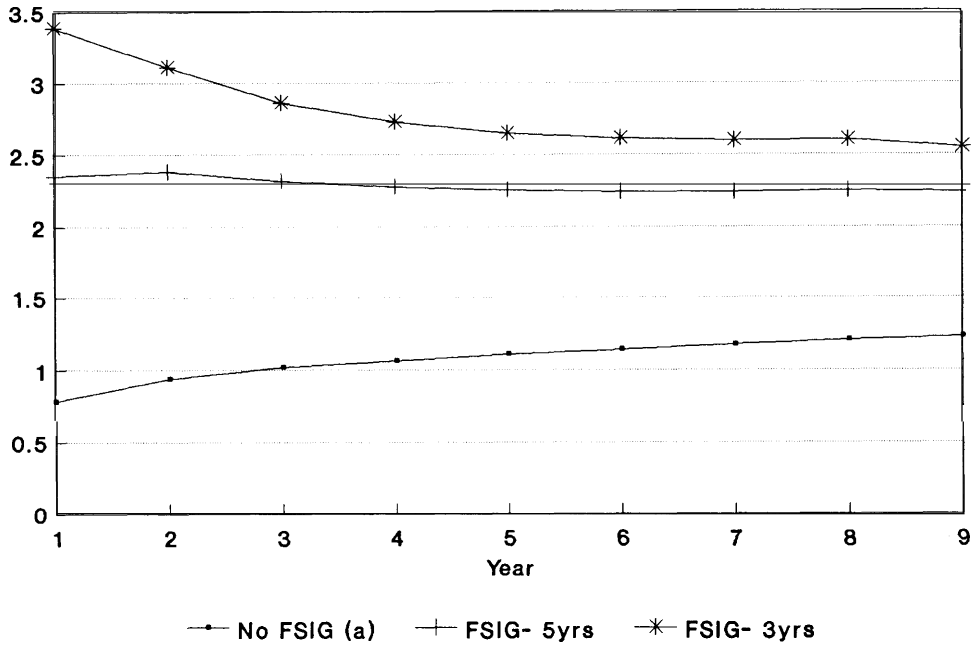
Table 12-Assumptions Underlying Estimates of the Annual National Costs of CRC Screening, Followup, and Surveillance In the Elderly

FOBT sensitivity for polyps	5%
FOBT specificity	98%
FSIG sensitivity for polyps	95%
FSIG specificity	10096
Reach of 60cm FSIG[a]	50%
Reach of 35cm FSIG[a]	30%
Prevalence of polyps[b]	5096

[a] Percent of polyps located within the reach of a FSIG of designated length.
[b] Percent of 65-year-olds with colonic polyps.

SOURCE: Office of Technology Assessment, 19S0.

Chart 2--Annual Cost of CRC Screening, Followup, and Surveillance ($ billions)



(a) all regimens include FOBT annually
SOURCE: Office of Technology Assessment, 1990.

covered Medicare services. The cost of screening alone is just the tip of the iceberg. Medicare allowed under $4 for an FOBT and about $100 for FSIG in 1988 (if performed for diagnostic, not screening purposes).

The annual cost profile outlined in chart 2 represents the net additional cost of screening, followup and surveillance compared to no such procedures in the population. However, a small but growing number of elderly people already receives CRC screening, and Medicare is already paying for the diagnostic followup and surveillance procedures engendered by the screening examinations.[2]

The national cost estimates assume that all elderly Medicare beneficiaries will fully comply with the screening regimen and all followup and surveillance procedures resulting from screening. In reality, the use of CRC screening examinations in the elderly is quite low, and it is unknown how much it will increase by making a combination of FOBT and FSIG a covered Medicare benefit. In 1987, for example, only 34 percent of people 60 years of age or over reported ***ever*** having undergone a screening FOBT test and 7.4 percent reported ***ever*** being screened with proctoscopy (rigid sigmoidoscopy) (152). Whether paying $4 for a FOBT will bring forth substantial additional use is unknown. The actual impact of an FOBT benefit on annual health care costs will depend on the degree to which covering the service will encourage use. Also, if a screening benefit brings about greater increases in use of those at lowest risk of CRC, then the medical benefits projected in the cost-effectiveness analysis would be reduced, and the cost per added year of life would be higher.

[2]**Medicare may be paying inadvertently for some screening procedures if they are billed as diagnostic procedures. Evidence has accumulated that full colonoscopy used as a screening procedure may be paid for by Medicare** in a substantial number of cases (98,151).

Advisory Panel--Project on Preventive Health Services Under Medicare

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NOTE: Advisory Panel members provide valuable guidance during the preparation of OTA reports. However, the presence of an individual on the Advisory Panel does not mean that individual agrees with or endorses the conclusions of this particular report.

Appendix B
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Basis for Cost-Effectiveness Analysis of Colorectal Cancer Screening

MEASUREMENT OF EFFECTS

Natural History of Colorectal Cancer (CRC)

The Office of Technology Assessment (OTA) cost-effectiveness analysis traces the experience of a population of 65-year-old people through the remainder of their lives, recording from year to year the incidence of newly detected cancers by stage in an environment first without any CRC screening and then under each of the four CRC screening regimens. The difference between the screening and no-screening scenarios in incidence by stage of detected cancers is then combined with stage-specific CRC mortality data to estimate the net gains in expected years of life for the population from prevention and early detection.

The incidence of clinically detected CRC in the absence of screening can be estimated from The National Cancer Institute's (NCI) Surveillance, Epidemiology and End Result (SEER) tumor registry data for the period 1979-1984 (152). Although the observed incidence in these years reflects a certain number of cases detected through screening and therefore may be skewed toward detection of cancers earlier in the lives of elderly people than would occur without any screening, the actual use of CRC screening by the elderly in the early 1980s was quite low, so the bias toward early detection in this group is likely to be small. The distribution of stages of clinically detected cancers (i.e., in the absence of screening) was also estimated from SEER data. National data on the stage at detection are unavailable for specific age groups, but numerous studies have shown that the stage distribution of clinically detected CRCsS does not vary appreciably with age except for very young people (58,73,75,104). Between 35 and 40 percent of all CRCs are detected in early (localized) stages (152). A higher estimate will be less favorable to screening, so OTA assumed that in the absence of a screening program the percentage of clinically detected cancers that would be found in early stages was 40 percent.

To estimate how the incidence of clinically detected CRC will change under a given CRC screening regimen, one must know the prevalence of polyps and silent cancers (both early and late) in the population at age 65, the incidence of new polyps and silent cancers in each succeeding year, and the rate and time profile of conversion of polyps into cancers and silent cancers into detected cancers.

Estimates of the prevalence of polyps in 65-year-olds and the incidence of new polyps in succeeding years come from two kinds of evidence: autopsy studies and randomized screening in populations. Estimates of the prevalence of adenomatous polyps in autopsy studies of the elderly range from 40 to 62 percent. (See table 4 in the main report). Estimates taken from autopsy studies may be biased upward, because the presence of adenomas may be correlated with the presence of other diseases (such as atherosclerosis) (71), although this bias may be more serious in younger age groups. A Norwegian study of colonoscopy given to over 400 randomly selected people between 50 and 59 years of age showed the presence of polyps in 35 percent (69). It is well documented that polyp prevalence increases with age (145). A higher estimate of polyp prevalence will increase the estimated cost of CRC screening, which is unfavorable to screening, so OTA chose an estimate of 60 percent.

The incidence of new polyps in the elderly is unknown. New polyps do develop, at least in people with previously detected polyps. Data from the National Polyp Study indicate that 30 percent of patients followed with colonoscopy after polyp removal had additional polyps (either new or previously missed) within 1 year of a polypectomy (172). Polyps also are subject to spontaneous regression, however, particularly in the rectum (70). Autopsy studies show no consistent increase in the prevalence of polyps across age groups over 65 (table 4 in main

[1] **For example, in 1980, only 28 percent of all people 60 years of age or older had ever had an FOBT for any reason** (screening or symptoms) and only 31 had had a rigid sigmoidoseopic examination (52).

report), which suggests that the incidence of new polyps is low, but these cross-sectional studies may reflect inherent differences in polyp incidence among age-specific cohorts. OTA assumed that the incidence of new polyps in people who reach the age of 65 polyp free is so small in relation to the underlying prevalence at age 65 that it can be effectively considered to be zero. This assumption will very slightly underestimate the costs of screening, followup and surveillance.

If 60 percent of all 65-year-olds have colorectal polyps, but only 6 percent of these people will ever be diagnosed with CRC (134), then only a small percent of polyps, fewer than 10 percent, will ultimately progress to cancer. An estimate of the proportion of polyps that eventually becomes clinically manifest cancer (as measured by the SEER incidence rates for 1979-1984) can be derived from the proportion of CRCs that arise from polyps.

Although most experts agree with Morson's claim that the "great majority of cancers of the colon and rectum have evolved through the polyp-cancer sequence," (106), there is no direct evidence on the proportion of cancers arising out of polyps. The arguments in favor of a high proportion are strong but indirect (145).[2] In a study of almost 2,000 malignant colorectal tumors, Morson and colleagues found that 57 percent of very early cancers were unequivocally located in a benign adenoma (106). The rest were cancers with no contiguous benign adenoma. The proportion of cancers found together with benign tumors declined with the degree of spread of the cancer, which suggests that cancer cells rapidly overcome the surrounding benign tissue. Therefore, 57 percent represents a lower bound on the proportion of CRCs arising from polyps, because many of the early cancers unassociated with adenoma may have already overcome the surrounding benign tumor.[3] Because a lower estimate is less favorable to CRC screening (since it reduces the opportunity to prevent cancers by removing polyps), OTA used 57 percent as an estimate of the percent of cancers arising from polyps. (In contrast, a recent cost-effectiveness analysis of CRC screening assumed that 93 percent of all cancers arise from polyps (39).

If only 57 percent of all newly diagnosed cancers come from polyps, then at most only about 5 or 6 percent of the polyps present at age 65 are destined to become clinically manifest CRCs. Of these polyps that will progress to cancers, it is necessary to estimate the number of years for the progression to occur. There is undoubtedly a range of progression times from polyp to cancer (84), but OTA assumed that all polyps destined to become cancer would proceed at a uniform rate. The faster the speed of progression assumed, the less favorable will the results of the analysis be toward screening, because there will be fewer opportunities to detect the polyp with a screening test before it becomes cancer. The speed with which adenomas destined to become cancers actually progress from any specific size to early cancer is unknown, because adenomas are generally removed when found. Isolated reports of adenomas followed when a patient refused treatment suggest that the elapsed time from first diagnosis of the polyp to the development of a cancer is in the range of 5 to 12 years. (106). Since these polyps existed for some unknown period of time before they were clinically diagnosed, the true range of time from the emergence of a polyp to cancer is probably longer than the observed period. OTA assumed that polyps destined to become invasive cancers uniformly take 6 years to reach that point.[4]

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[2] **Fenoglio and Lane have observed that in autopsy studies, small areas of isolated cancer cells are frequently found associated with polyps but virtually** never found growing alone on the wall of the colon or rectum (41). Since CRC is such a common disease, if a substantial proportion of cancers arose de novo from previously normal tissue, a greater number of isolated focal points of cancer would have been seen in autopsies. This suggests that most, if not all, cancers start as polyps.

[3] Some pathologists question whether the "evidence" of benign adenomatous tumor found in the histological studies of cancers is actually residual polyp or abnormal cellular structures and secretions that develop in normal tissues as a reaction to the presence of the cancer. For a discussion of the arguments against the polyp-cancer sequence, see Castleman (19).

[4] The impact of changing the progression rate to three years was also examined and is reported in the text.

New cancers arise either from polyps or from the mucosal tissue of the colon or rectum. The speed of progression from early to late stage cancer and the rate at which cancers in given stages become clinically manifest must be estimated from very sparse evidence. We assume that there are two kinds of early cancers: those that progress so slowly that they will never become clinically detected for the remainder of a person's life in the absence of screening; and those that are destined to become apparent even without screening. The former are "lifetime latent" cancers; the latter are well estimated by the SEER cancer incidence rates.

Detection of lifetime latent cancers in a screening program is an unwanted occurrence. Since clinicians have no way of differentiating between those cancers that would have progressed and those that would not, lifetime latent cancers detected in a screening program are treated like any other cancer in the same stage. This treatment has both costs and medical risks, which must be accounted for.

Estimates of the initial prevalence (at age 65) and subsequent incidence of lifetime latent CRC that exists in a general U.S. population are available from only one study, a review of over 16,000 autopsies conducted at a hospital in California in the 1950s (11). In that population CRCs unrelated to the cause of death or to symptoms leading to the hospitalization were discovered at autopsy at rates of: 5 per 1,000 for people 60 to 69 years old; 10 per 1,000 for people 70 to 79-year-olds; and 15 per 1,000 for people 80- to 89-year-olds. These rates represent the cumulative life-time incidence of unsuspected cancers in people dying in the three age categories.[5] They imply that at most 10,400 cases of lifetime latent cancers would be present in the 1989 population of 65-year-olds, and in each subsequent year, an additional 0.05 percent of the remaining population would have new incidence of lifetime latent CRC that would not be included in the SEER incidence data but would be subject to detection on screening. In keeping with the pessimism of the model, OTA assumed that all of these lifetime latent cancers arise directly from the colon wall and would therefore not be preventable by removal of polyps. They are also assumed to remain early stage cancers for the duration of a person's life.

Cancers destined to become clinically detected in the absence of screening spend a certain amount of time in early or late stages before being diagnosed. The speed with which cancers destined to be detected in late stage progress through the early stage will determine the ability of a screening program to detect the cancer early. Although there is no direct evidence on cancer progression rates, mathematical models developed by Eddy (33,34,35,39) have assumed that cancers progress from Dukes' A to Dukes' C in an average of three years. Unlike Eddy's model, however, OTA's analysis does not allow for any variation in the progression rate among cases, but to be unfavorable toward screening, OTA assumed a very rapid progression rate -- one year -- from early to late cancer for all CRCs destined to be clinically detected as late cancers.

In addition to assuming that a cancer remains in the early stage (Duke's A and B) for one year, OTA also assumed that a cancer clinically detected in late stage would have entered that stage one year earlier, with no variation among cases. Thus, a late-stage cancer that is destined to become clinically detected in a person at, say, age 75 would have a one year window for detection by screening in its early stage during the age 73. Were the duration in early stage assumed to be three years, the cancer would be detectable by screening in its early stage during the ages of 71 to 73.

Accuracy of Screening

How does CRC screening alter the detection of polyps and cancer? Fecal occult blood test (FOBT) and fiberoptic signoidosocpy (FSIG), the two screening technologies, each have given levels of accuracy as measured by sensitivity (the percent of all people with a disease who test positive) and specificity (the percent of all people without a disease who test negative). These test characteristics can be used to estimate the potential of a given screening regimen to detect polyps and cancers in each stage. For example, if FOBT has a sensitivity

[5] Experts frequently observe that people who die are not representative of those who remain alive. Undiscovered cancers are likely to be overrepresented in hospital deaths (126).

for polyps of 5 percent, then every time a person with a polyp has an FOBT, he or she has a 5 percent chance of being identified as positive by the test. The more frequent the testing, the greater the chance for detection of the polyp. The sensitivity and specificity of the screening tests must be estimated for each group in the population.

Sensitivity and Specificity of FOBT

The sensitivity of FOBT for adenomatous polyps and cancer has been reported in a number of studies. Reported FOBT sensitivity can be expected to vary systematically with the population under study. In particular, test sensitivity would be higher in symptomatic patients than in asymptomatic populations, because larger polyps or cancers would be more likely both to bleed and to cause symptoms. Since FOBT is being considered as a screening test for asymptomatic populations, its sensitivity in these groups is the relevant measure.

Table C-1 summarizes the evidence on the sensitivity of FOBT for both adenomas and cancers. As the table demonstrates, studies performed on asymptomatic patients report substantially lower sensitivity for polyps than do studies on symptomatic groups. Demers (28) and Bang (6) determined the sensitivity of the FOBT in asymptomatic populations of male pattern workers (a group with high colon cancer rates). They compared polyps found by FOBT with those found by FSIG. Demers reported an FOBT sensitivity for polyps of 3 percent and Bang computed a sensitivity of 5 percent. An English study calculated the sensitivity of the FOBT for adenomas by submitting patients returning for followup after polypectomy to colonoscopy and occult blood testing (168). Williams reported a sensitivity of 5 percent.

Several investigators have estimated the sensitivity of the FOBT for polyps in symptomatic populations. In these studies, patients diagnosed with polyps are given the FOBT, and sensitivity is determined by counting the number of positive results. Estimates of FOBT sensitivity for polyps in symptomatic studies range from less than 10 percent to as much as 39 percent.

Since most polyps less than 1 cm do not bleed in considerable amounts, the test will be relatively insensitive to these smaller lesions (92). As table C-1 displays, FOBT sensitivity for carcinomas and large adenomas is considerably higher than its sensitivity for small polyps. For example, in a prospective study of asymptomatic patients, the FOBT sensitivity for large polyps (larger than 1 cm) was 11 percent (28). Smaller polyps are less likely to progress to malignancy, so FOBT's low sensitivity for small polyps and higher sensitivity for large adenomas may be desirable and appropriate for the detection of potential cancers (145). Since polyps that become cancer are more likely to grow larger and bleed more frequently than are other polyps (61,106), they would be detected more easily by FOBT than would the vast majority of colonic polyps that would never progress to cancer.

These considerations suggest that FOBT has a low sensitivity for polyps that do not progress to cancer and a higher sensitivity for polyps that do progress. However, for the results to be unfavorable to screening, FOBT sensitivity for polyps that ***will not*** progress should be high (because detecting a large number of polyps will increase costs but not improve outcomes), while FOBT sensitivity for polyps that ***will*** progress should be low in order to minimize the potential for preventing cancers. OTA concluded that an FOBT sensitivity of 10 percent for polyps that will not progress to cancer is a high estimate, and the same sensitivity (10 percent) for polyps that will progress is a low estimate. Therefore, in the pessimistic analysis, an FOBT sensitivity for polyps was assumed to be 10 percent.

FOBT's sensitivity for cancer should be higher than for polyps, and as table C-1 shows, studies generally confirm this hypothesis. In asymptomatic patients, FOBT sensitivity for cancer ranged from 25 percent to almost 90 percent, but the high estimate was based on dehydration of FOBT specimens, a practice not usually undertaken in routine screening. Reports of FOBT sensitivity for cancer in symptomatic patients are in the range of 50 to 70 percent. OTA assumed that FOBT sensitivity for cancer in asymptomatic patients undergoing screening is 40 percent. This value was applied to cancer at all

stages and both lifetime latent cancers and those destined to become clinically detected. (In contrast, a recent cost-effectiveness analysis of FOBT screening assumed a sensitivity of 70 percent for CRC (8).)

There is little disagreement about the high specificity of the FOBT. Most investigators have found a specificity of 98 percent (table C-l). This value has been computed in studies of both symptomatic and asymptomatic populations. Several models of cost-effectiveness of CRC screening have also adopted this value (8,35). Because lower specificity raises the costs of followup and induces some medical risk from followup procedures, OTA used a lower estimate of 90 percent, following the few studies that report lower specificity (table C-l).

Sensitivity and Specificity of FSIG

The sensitivity of the FSIG depends not only on its ability to detect disease but also on the length of its reach into the colon. The FSIG allows for visual examination of the more distal end of the large intestine. Selby and Friedman (133) claim that there is no more accurate standard with which sigmoidoscopy can be compared. They also add that sigmoidoscopy has complete sensitivity for both polyps and cancer. Other authorities believe that FSIG sensitivity is a little lower (35,167). Williams compared colonoscopy with double contrast barium emema (DCBE) for the detection of large adenomas and discovered that the endoscope will miss a few adenomas. Since the colonoscope and FSIG are the same tool with different lengths, OTA assumed that the FSIG would also miss a few polyps. To assure that the results would be unfavorable to screening, OTA assumed that the sensitivity of FSIG for polyps that ***will not*** progress to cancer is 98 percent within its reach and the sensitivity of FSIG for polyps that will ***progress*** to cancer and for cancer itself is 92 percent. The lower sensitivity follows Williams' estimate of the sensitivity of colonoscopy.

FSIGs are available in different lengths, the most frequent being 60 cm and 35 cm. It is important to know how far the FSIG will extend into the large intestine, because polyps are distributed throughout the large bowel. The depth of insertion will be the cut-off point for the detection of polyps. The average depth of insertion for the 60 cm FSIG is 54 cm and 34 cm for the 35 cm FSIG (14,26,31,133).

The depth of insertion must be related to the percent of colorectal polyps and cancers within the reach of the FSIG. OTA assumed that the 60 cm FSIG can reach the splenic flexure over half the times inserted and that the 35 cm FSIG can reach between 50 and 75 percent of the sigmoid colon (133,167). The distribution of polyps in the large bowel has been investigated by two methods: autopsy studies and colonoscopic studies of symptomatic patients.

In autopsy studies, the distribution of polyps is computed by noting the location of polyps in individuals who have died from unrelated causes. These studies focus on the distribution of adenomatous polyps. Hyperplastic polyps, which many experts believe are more prevalent than adenomas and are primarily concentrated in the rectal region (25,133), are not included. As table C-2 shows, autopsy studies report that approximately 30 to 50 percent of all adenomatous polyps lie between the anus and the splenic flexure. The range for adenomatous polyps between the mid-upper portion (MUP) of the sigmoid colon to the anus is from 13 percent to 25 percent. Chapman performed an autopsy analysis on individuals over 60. He found that roughly 35 percent of adenomatous polyps were below the splenic flexure and 13 percent were below the MUP sigmoid colon (21). In an autopsy study of both hyperplastic polyps and adenomas, 42 percent of all polyps were below the splenic flexure and 32 percent were in the lower fifth of the colon (25).

An alternative method for estimating the distribution of polyps is colonoscopy studies of symptomatic patients. This method may fail to give an accurate representation of polyp distribution in an asymptomatic population. It is probable that symptomatic patients suffer from rectal bleeding, indicating that larger adenomas are present. These studies are therefore likely to overestimate the presence of polyps in the lower half of the colon. Estimates of the percent of polyps below the splenic flexure range from 56 percent to 77 percent and estimates for polyps below the MUP sigmoid colon range from 30

Table C-1 – FOBT Sensitivity and Specificity

	Test	Subjects	Diagnostic standard	Sensitivity	Specificity
Demers et al., 1985	Hemoccult II	998 male workers with high CRC incidence; mean age = 42	colorectal polyps discovered with 60 cm flex. sigmoidoscope	3% – polyps 11% for polyps ≥ 1 cm	98%
Bang et al., 1986	Hemoccult II	1,473 asymptomatic male pattern workers; volunteers, mostly white	flex sig. 65 cm – cancer – polyps	25% #.1	98%[a] 98%[a]
MacRae & St. John, 1982	Hemoccult II – no rehydration – hydration	74 symptomatic patients	CRCs adenomas CRCs adenomas	69%[b] 28%[b] 91%[b] 39%[b]	
Gnauck, 1984	2 annual Hemoccult II	48 cases with CRC 152 cases with adenoma	CRC adenoma	92% 42%–74%	
Griffiths, 1981	Hemoccult	28 preoperative pats w/proven CRC	CRC	82%[b]	
Hardcastle, 1983	Hemoccult II	14 pats w/CRC detected w/in 1 yr of hemoccult	CRC	93%[a]	
Mandel et al., n.d.	Hemoccult II (mixed rehydrated/not rehydrated)	46,000 screenees with repeat screening	CRC discovered w/in 12 months of test	89.3%	92.7%
Windeler and Kobberling, 1987	Hemoccult	Meta-analysis of 12 studies in symptomatic patients (total of 153 patients)	CRC adenomas adenomas >1 cm	65%[b] <10% 20%	
Ribet, 1980	Hemoccult	230 pats at French outpat. preventive clinic; symptom free or irritable bowl syndrome	CRC + adenomas found on DCBE + rigid sigmoid	14%	89%
Williams, 1982[a]	FOBT	Patients with history of adenomas	adenomas	5%	
Simon, 1985	Hemoccult	Summary of studies	CRCs adenomas proven by endoscopy	50–60%[b] less than 25%	
Herzog et al., 1982	Hemoccult	44 consecutive patients referred for endoscopic polypectomy; 11 controls	polyps	46%[b]	100%
Winawer, Andrews, et al. 1980	Hemoccult I & II	39,000 exams of pts enrolled in screening clinic, mostly asymptomatic	adenomas GT 5 mm found in rectosigmoid by proctosigmoidoscopy	24%	0.5%–2.1%

[a] Specificity of FOBT is calculated only for portion of the colon within the reach of the sigmoidoscope.
[b] Sensitivity is likely to be overestimated in this study because sample comprises symptomatic individuals.

SOURCES: R.Y. Demers, L.E. Stawick, and P. Demers, "Relative Sensitivity of the Fecal Occult Blood Test and Flexible Sigmoidoscopy in Detecting Polyps," *Prev. Med.* 14:55-62, 1985. K.M. Bang, S. Tillett, S.K. Hoar et al., "Sensitivity of Fecal Hemoccult Testing and Flexible Sigmoidoscopy for Colorectal Cancer Screening," *J. Occupational Med.* 28(8):709-713, 1986. F.A Macrae, and D.J.B. St. John, "Relationship Between Patterns of Bleeding and Hemoccult Sensitivity in Patients With Colorectal Cancers and Adenomas," *Gastroenterology* 82(5):891-898, 1982. R. Gnauck, F.A. Macrae, and M. Fleisher, "How To Perform the Fecal Occult Blood Test," *Cancer* 34(3):134-147, 1984. C.D.M. Griffith, D.J. Turner, and J.H. Saunders, "False Negative Results Hemoccult Test in Colorectal Cancer," *Br. Med. J.* 283:472, 1981. J.D. Hardcastle, P.A. Farrands, T.W. Balfour et al., "Controlled Testing in the Detection of Colorectal Cancer," *Lancet* 2:1-4, 1983. J.S. Mandel, J.H. Bond, M. Bradley et al., "Sensitivity, Specificity and Positive Predictivity of the Hemoccult Test in Screening for Colorectal Cancers: The University of Minnesota's Colon Cancer Control Study," unpublished paper, undated. J. Windeler, and J. Kobberling, "Colorectal Carcinoma and Hemoccult: A Study of its Value in Mass Screening Using Meta-Analysis," *Int. J. Colorectal Dis.* 2:223-228, 1987. A. Ribet, J. Fexinos, J. Escourrou et al., "Occult Blood Tests and Colorectal Tumours," *Lancet* 1(8165):417, 1980. C.B. Williams, F.A. Macrae, and C.I. Bartram, "A Prospective Study of Diagnostic Methods in Adenoma Follow-up," *Endoscopy* 14(3):74-78, 1982. J.B. Simon, "Occult Blood Screening for Colorectal Carcinoma: A Critical Review," *Gastroenterology* 88:820-837, 1985. P. Herzog, K.H. Holtermuller, J. Preiss et al., "Fecal Blood Loss in Patients With Colonic Polyps: A Comparison of Measurements With 51 Chromium-Labeled Erythrocytes and With the Hemoccult Test," *Gastroenterology* 83:957-962, 1982. S.J. Winawer, M. Andrews, B. Flehinger et al., "Progress Report on Controlled Trial of Fecal Occult Blood Testing for the Detection of Colorectal Neoplasia," *Cancer* 45:2959-2964, 1980.

Table C-2-Distribution of Polyps by Location From Autopsy Studies of U.S. and Foreign Populations

					Right colon			Transverse		Left colon			
Study	Kind of polyp	Year	Population studied	Country	Cecum	Ascending colon	Hepatic flexure	Transverse colon	Splenic flexure	Descending colon	Sigmoid colon	Rectal/ sigmoid colon	Rectum
Helwig, 1943	Adenomatous	1943	1,460 consecutive autopsies	USA	11.8	15.4		21.0		8 . 1	28.0		16.0
Blatt, 1961	Adenomatous	1959-1960	446 consecutive autopsies on adults =30 years old	USA	18.0	19.0		25.0		11.0		20.0	7.0
Arminski and McLean, 1964	Adenomatous	1964	1,000 colons of adults >20 years old undergoing autopsy at Detroit, MI hospital	USA	10.0	19.0	11.0	16.0	10.0	6.0	27.0		not included
Chapman, 1963	Adenomatous	not given	443 consecutive autopsies in New York state hospital; polyps found in adults ›30	USA	All: 6.9 > 60: 7.1	35.1 35.6	10.0 10.3	11.2 11.7	8.9 9.1	6.0 6.7	19.2 16.6		2.7 2.8
Stemmermann and Yatani, 1973	Adenomatous	1969-1972	202 necropsies in Kuakini hospital on Hawaii Japanese adults	USA	10	34		22	11	15	1	6	
Rickert et al., 1979	Adenomatous	Not given	518 colon-rectum specimens recovered at autopsy in adults ›20 years old, in New Jersey hospital; excluding CRC cancer cases	USA	13.0	26.0		27.0		9.0	17.2		7.4
Restrepo et al., 1979	Adenomatous	1971-1973	506 colon rectum specimens recovered at autopsy in adults ›10 years old in Medellin, Colombia	Colombia	16.9	23.7		20.3		8.4	20.3		10.4
Correa et al.	Polyps	1970-1975	463 autopsy cases from 4 New Orleans hospitals serving poor communities	USA					42%*	32%[b]			

[a] Percent of polyps from splenic flexure to anus.
[b] Percent of polyps in last fifth of colon.

SOURCE: T. C. Arminski, and D.W. McLean, "Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations," *Dis. Colon Rectum* 7:249–261, 1964; L.J. Blatt, "Polyps of the Colon and Rectum: Incidence and Distribution," D/s. *Colon Rec.* 4:277-282, 1SS1; 1. Chapman, "Adenomatous Polypi of Large Intestine: Incidence and Distribution," *Ann. Surg.* 157(2):223-226, 1903; P. Correa, J.P. Strong, A Reif et al., "The Epidemiology of Colorectal Polyps: Prevalence in New Orleans and International Comparisons," Cancer 39:2258-2264, 1977; E.B. Helwig, "Benign Tumors of the Large Intestine-Incidence and Distribution," *Surg. Gynecol. Obstet.* 76:419, 1943. 1S43; C. Restrepo, P. Correa, E. Duque et al., "Polyps in a Low-Risk Colonic Population in Columbia, South America" *Dis. Colon Rectum,* 24:29-36, 19S1; R.R. Rickert, O. Auerbackk, L. Garfinkel et al., "Adenomatous Lesions of the Large Bowel: An Autopsy Survey," Cancer 43:1847-1857, 1979; G.N. Stemmerman and R. Yatani, "Diverticulosis and Polyps of the Large intestine: ANeocropsy Study of Hawaii Japanese," *Cancer* 31(5) :1260-1270, 1973.

percent to 53 percent (table C-3). In an age-specific analysis, Grandquist found that approximately 56 percent of polyps in patients 65 years of age and older were below the splenic flexure and 30 percent were below the MUP sigmoid colon (59).

As the data presented indicate, there is no consensus on the distribution of polyps in the large bowel. To be pessimistic toward screening, OTA assumed that roughly 70 percent of polyps ***that will not progress to cancer are*** within the reach of the 60 cm FSIG and that 30 percent are within the reach of the 35 cm FSIG. For polyps that ***will progress,*** the reach is assumed to be 35 percent for the 60 cm FSIG and 20 percent for the 35 cm FSIG.[6]

Authorities agree that the specificity of the FSIG is 100 percent (35,133). Since FSIG is based upon visual examination, the trained examiner will not mistakenly identify normal colonic mucosa for a polyp or tumor. To be pessimistic, however, OTA assumed an FSIG specificity of 95 percent.

Medical Risk of Screening

Detection of a polyp or carcinoma by screening brings forth the use of medical procedures that have small but non-negligible risks of complications and death. These medical risks, particularly the risk of death associated with colonoscopy in followup or surveillance and with resection of otherwise lifetime latent cancer must be accounted for as an adjustment to screening effects.

Colonoscopy carries with it a small chance of bowel perforation and, rarely, death. Nevertheless, when a large number of elderly people is expected to undergo followup or surveillance colonoscopy, these risks cannot be ignored. Reported rates of colon perforation with colonoscopy are in the range of 0.1 percent to 0.2 percent and reported mortality is between 0.02 percent and 0.05 percent (38,119,142). OTA used the low end (0.02 percent) of this mortality range to estimate the death rate from colonoscopy, because the mortality rates are taken from studies of symptomatic patients, whereas followup and surveillance would be performed on asymptomatic people.

Because the standard of care for early cancer is surgery to remove the cancer, an estimate of the surgery-induced mortality was also necessary. Operative mortality rates associated with CRC surgery increase with age (42,145), but improvements in operative technique in the 1980s have reduced the operative mortality for all ages (42). A study of surgery for CRC in elderly patients in England during the 1970s showed that in-hospital mortality rates for those over 70 years of age was about 13 percent, but for those between 70 and 79 years of age whose operations were elective, the in-hospital

[6] In contrast, in a cost-effectiveness analysis of CRC screening for colorectal cancer in a high risk population, Eddy assumed that 55 percent of the polyps could be detected by the 60 cm FSIG and 40 percent by the 35 cm FSIG (35).

Table C-3- Distribution of Polyps in Studies of Symptomatic Patients

Study	Kind of polyp	Year	Population studied	Estimated percent of patients' polyps: Below splenic flexure[a]	Below MUP[a] of sigmoid colon[b]
Tedesco et al., 1980	Polyps	1980	Symptomatic	88%	30%
Gillespie et al., 1978	Adenomas	1979	Patients with previous colonic surgery or colorectal symptoms	77%	53%
Webb et al., 1985	Adenomas	1985	Symptomatic	74%	38%
Granqvist, 1981	Polyps	1981	Patients >65 years with intestinal disorders	56%	30%

[a] MUP = mid-upper portion.
[b] The OTA estimates are calculated from data provided in cited study.

SOURCE: P.E. Gillespie, T.J. Chambers, KW. Chan et al., "Colonic Adenomas – A Colonoscopy Survey, *Gut* 20:240-245, 1978; S. Granqvist, "Distribution of Polyps in the Large Bowel in Relation to Age," *Scand. J. Gastroent.* 16:1025-1031, 1SS1; F.J. Tedesco, J.D. Wayne, J.R. Avella et al. "Diagnostic Implications of the Spatial Distribution of Colonic Mass Lesions (Polyps and Cancers). A Prospective Colonoscopic Study," *Gastrointest. Endosc.* 26(3) :95-97, 1980; W.A. Webb, L McDaniel, and L Jones, "Experience With 1,000 Colonoscopic Polypectomies," Arm. *Surg.* 201 :626-630, 19S5.

mortality rate was about 8 percent (42). Another British study found a 6 percent overall surgical mortality in patients over 70 years of age and a 4 percent mortality after elective operations (75). Because surgeries for lifetime latent cancers would be entirely elective, OTA pessimistically assumed an in-hospital mortality rate of 7 percent.

Years *of Life Gained From Screening*

The years of life gained from screening the population over time were estimated as the difference between the years of life lost from CRC in the absence of screening and the years of life lost under a screening regimen from: 1) CRC; 2) operative mortality associated with treatment of lifetime latent cancers found in screening; and 3) deaths due to complications of colonoscopy performed in both followup and surveillance. These values change with age, for the older the person is, the more likely he or she is to die of other causes, and the fewer the added years of life that can be expected from screening.

Calculation of the years of life lost due to CRC was based on assumptions about ***survival probabilities.*** Five-year survival probabilities for CRC are based on observed 5-year survival rates by age and stage for the elderly provided to OTA by NCI from the SEER database (124).

Transforming these survival rates into expected years of life requires additional assumptions about the shape of the survival curve over time. One method of approximating life expectancy from 5-year survival rates (referred to as the "DEALE" method) assumes that survival probability follows a simple declining exponential function over time (9,10). Using this assumption, the five-year survival rate would be transformed into an annual "mortality force" which is then used to adjust the life expectancy of a particular age-group. For example, if the 5-year survival rate for late CRC were 50 percent in people 65 years of age, the life expectancy of a 65-year-old newly diagnosed with late stage cancer would decline from 16.7 years to exactly 5 years. The magnitude of this calculated decline in life-expectancy due to cancer seems unduly large.

An alternative method, used by OTA, assumes that virtually all CRC patients who survive for 5 years can be considered cured.[7] Under this assumption, patients who do survive 5 years can be expected to live out the remainder of their expected years of life. Those who do not survive are assumed to die in 3 years. Using these assumptions, the expected life of a 65-year-old newly diagnosed late-stage cancer patient with a 50 percent 5-year survival rate would be 9.7 years. Then, for every late-stage cancer prevented, 7 years would be gained, compared with a gain of 11.5 years under the assumptions of the DEALE model.[8] Because OTA's method shows less gain in years of life from the prevention or early detection of CRC than does the DEALE method, it is more pessimistic about the effectiveness of screening than the other method would be.

Treatment of lifetime latent cancers detected through screening was assumed to offer no benefit in increased years of life, but surgery-related deaths were assumed to cost the remaining years of life expected for people of the age at which the surgery takes place. Similarly, colonoscopy performed for surveillance purposes was assumed to have no benefit, but colonoscopy-related deaths were assumed to cost the remaining expected years of life.

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[7] Survival probabilities **are correlated with patterns of recurrence of CRC after treatment. In a recent review of the literature, DeVesa and colleagues reported recurrence rates of CRC by stage as follows (29): Dukes' A: 0-13 percent; Dukes' B: 11-61 percent; Dukes' C: 32-88 percent. Moreover, 90 percent of all recurrences become apparent within four years of the initial operation (29). Of those with recurrent CRC, the median** survival is about 8.5 months and over 95 percent of patients are dead within three years (166). Taken together, these patterns of survival suggest that the vast majority of patients who are alive 5 years after diagnosis of CRC will not experience a recurrence of the disease.

[8] It would also be possible to calculate the number of "healthy years of life' gained from cancer screening by assuming that the quality of life of a person destined to die of CRC within three years is so low as to not be worth calculating. Using "healthy years of life" as an effectiveness criterion would increase the calculated effectiveness of screening counteracting the deliberate bias against finding screening effective.

The years of life gained and lost from screening in each year were totaled and discounted to their present value at the same discount rate--5 percent[9] used to calculate the net costs of screening.

MEASUREMENT OF COSTS

The unit costs of screening, followup and surveillance procedures were based on average Medicare Part B allowed charges for such services performed in the physician's office in 1988. Table C-4 shows how these allowed charges varied by specialty in 1986. Gastroenterologists were allowed higher charges on average than were internists. These allowed charges do not reflect the full expenditure for such services, because physicians are not required to accept Medicare's allowed rate as full payment but may bill the patient for the balance between the physician's fee and the allowed charge. Over 77 percent of all claims submitted to Medicare in 1988, however, did involve acceptance of the allowed rate (121) and almost 40 percent of all physicians agreed to accept Medicare's allowed charge as full payment for all of their Medicare claims (121). Thus, although some patients may pay more than the allowed amounts for screening, followup and surveillance procedures, it is reasonable to assume that such services are widely available in most communities at the allowed rates.

[9]The discounting of health effects as well as costs is necessary to insure that programs whose benefits lie well in the future will not be found more cost-effective if postponed indefinitely (77).

Table C4-Selected Screening, Followup, and Surveillance Charges[a] for Colorectal Cancer

CPT code	Procedure	Charges		
		Average of all MDs	Gastroenterologist	Internist
Screening:				
82270	FOBT (office lab)	$ 3.60	- - [c]	- -
	FOBT (independent lab)	4.08	--	- -
	FOBT (all settings)	3.63		
45330	Sigmoidoscopy (flexible fiberoptic)	87.53	$ 94.43	$ 85.41
45300	Proctosigmoidoscopy	39.76	- -	- -
Diagnostic followup:				
45378	Colonoscopy	$375.72	$421.60	$350.19
45380	Colonoscopy for biopsy	437.07	461.45	421.38
45383	Colonosoopy for tumor ablation	449.16	447.89	438.91
45385	Colonoscopy for polyp removal	626.48	665.83	586.20
45330	Sigmoidoscopy (flexible fiberoptic) for biopsy	115.53	127.01	107.94
45336	Sigmoidoscopy (flexible fiberoptic) for tumor ablation	162.49	195.04	118.12
45333	Sigmoidoscopy (flexible fiberoptic) for polyp removal	143.59	167.51	143.19
74280	Barium enema, air contrast	97.71	- -	- -
88302-88309	Surgical pathology	51,37[d]		
Surveillance:				
45378	Colonoscopy	$375.72	$421.60	$350.19

ABBREVIATIONS: CPT = current procedural terminology FOBT = fecal occult blood teat.

[a]Charges used in this table are Medicare average allowed charges for1SS6(117).
[b]Unless noted otherwise, the place of service for all of these procedures is the physician's office.
[c]The double dash indicates that OTA did not request this information.
[d]1988 allowed charge in all places of service for a weighted average of surgical pathology procedure in CPT codes 88302, 88304, 88305, and 88307, 88309

SOURCE: Health Care Financing Administration, 198S

Accurate estimates of the lifetime cost of treating CRC in elderly people simply do not exist. Estimates have to be pieced together from incomplete data sources, most of which are based on cases occurring in the 1970s.

Analysts at NCI have used the Medicare Continuous History Sample File, (a record of Medicare charges incurred by a sample of 1.6 million beneficiaries over an 8-year period from 1974 to 1981) to estimate the costs of cancer treatment (5). For beneficiaries with diagnoses of CRC, these researchers estimated charges made to Medicare in three periods: during the first 3 months following diagnosis; in the last 6 months of the beneficiary's life; and during the period between these two phases. Table C-5 summarizes the average charges made for the beneficiaries with CRC in the sample.

The Medicare Continuous History Sample (CHS) file does not tell the stage at diagnosis, so these estimates are based on a mix of cancer cases. Also, though the estimates are updated to 1984 dollars, they are based on a pattern of care that existed in the 1970s and that reflects neither the movement of cancer care out of hospital settings in the 1980s nor the development and diffusion of therapeutic colonoscopy for treatment of very early cancers. Finally, the estimates include all medical care costs incurred once a patient has received a recorded diagnosis of CRC, not just those specifically related to cancer care.

Three cost-effectiveness analyses of CRC screening have estimated the stage-specific costs of treating cancers. Allison and Feldman reported on stage-specific 5-year costs of treating CRC for patients first diagnosed in 1974 at the Kaiser Permanence Medical Plan, a Health Maintenance Organization in California (l). The Kaiser data are also based on patterns of care for CRC that were current almost 15 years ago, and, in any case costs in this setting of care might not adequately represent costs in fee-for-service medicine.

Studies of the cost-effectiveness of CRC screening have made "reasonable" assumptions about the costs of treating cancer detected in various stages. In a 1987 analysis, Barry and colleagues assumed that early cancer treatment would cost $10,000, while terminal care would cost $20,000. The cost of treating a perforated colon (a rare complication of colonoscopy) was assumed to be $10,000 (8). In an analysis published in the same year, Eddy assumed that initial therapy would cost $10,000 for cancer detected in local stages (Dukes A or B), $12,000 for cancer detected with regional spread (Dukes' C), and $14,000 for cancer detected with distant metastasis (Dukes' D) (35). A more recent analysis by Eddy used higher costs (39).

Table C-6 compares the estimates of the costs of treating cancers first detected in early and late stages from four analyses, updated to 1988 prices. Two of the studies (1,100) are explicitly based on empirical cost data from very different sources, but the similarity between the estimates in the four studies is striking. Only the Barr and Mulley estimates represent discounted costs[10] and should therefore be lower than the other two estimates. However, since most treatment costs occur soon after detection, discounted costs should not be much lower than undiscounted costs.

Based on the information presented above, OTA assumed that the discounted cost of treating early cancers is approximately $20,000 and of treating late cancers is $30,000. The results of a sensitivity analysis of the impact of changes in these two cost estimates on the net health care costs per year of life gained are presented in the main body of this paper.

Tablet **C-5-Average Charges Made to Medicare for Treatment During the Initial, Continuing, and Terminal Phases of CRC (1984 dollars)**

Initial phase (3 months)	**$14,190**
Continuing (monthly charges)	**$572**
Terminal phase (last 6 months)	**$15,776**

SOURCE: M.S. Belter, LG. Kessler, and R.C. Smucker, *"Site-Specific Treatment Costs for Cancer: An Analysis of the Medicare Continuous History Sample File"* unpublished, 19SS.

[10] Since the treatment costs will occur over time they should be discounted to their present value at the time of detection.

Table C-6-Estimates of the Cost of Treating Early and Late Cancers in 1988 Dollars

Study	Early cancers (Dukes' A &B)	Late cancers (Dukes' C & D)	Difference in cost between early and late cancers
Eddy, 1966*	$17,723-$21,069	$33,176	$12,067-$15,453
Allison and Feldman, 1974[b]	$22,696	$34,516	$11,817
Barry et al., 1967[c]	$10,000	$20,000	$10,000
Mellow, N. D., 1966[d]		$19,767	

[a] Calculated from Eddy 1966, using estimated costs of initial care by stage plus costs of terminal care multiplied by the assumed percent dying within 5 years by stage. Costs are undiscounted.
[b] Calculated from Allison and Feldman using observed 5-year costs of treating Cancers by stage in their study population, Coats -updated to 1988 using medical care component of CPI-U. Costs are undiscounted.
[c] These are discounted costs (6 percent rate of discount).
[d] Physician and hospital charges for *in-hospital* care at a large Midwestern hospital.

SOURCE: J.E. Allison, and F. Feldman, "Coat Benefita of Hemoccult Screening for Colorectal Carcinoma," *Dig. Dis.* &So/. 30(9):860-865, 1965; M.J. Barry, A.G. Mulley, and J.M. Richter, "The Effect of Workup Strategy on the Cost-Effectiveness of Fecal Occult Blood Screening for Colorectal Cancer," *Gastroenterology* 93:301-310, 1967; D.M. Eddy, "Screening for Colorectal Cancer," forthcoming in *Annals of Internal Medicine*; M.H. Mellow, "Endoscopic Laser Treatment of Colon Cancer," *Therapeutic Gastrointestinal Endoscopy* An *Information Resource Manual* (Manchester, MA: Amercian Society for Gastrointestinal Endoecopy, 1966).

The risk of nonfatal bowel perforations was assumed to be 0.1 percent, and the medical cost of treating these complications was assumed to be the same as the cost of treating early stage cancer ($20,000). Fatal bowel perforations were assumed to cost as much as treating a late stage cancer ($30,000).

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