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).