Review

Cost-Effectiveness of Double-Contrast Barium Enema in Screening for Colorectal Cancer

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Evidence continues to mount that screening of older adults at average risk for colorectal cancer reduces mortality from colorectal cancer. Three recently reported randomized clinical trials of screening with fecal occult blood tests tell a consistent story: The cumulative mortality rate from colorectal cancer is lower in populations offered periodic fecal occult blood tests screening than in those not offered screening [1–3]. Studies of rigid or flexible sigmoidoscopy, although using retrospective designs, also support the notion that screening reduces colorectal cancer death rates [4–6].

Despite this evidence, considerable controversy exists about which screening technologies and schedules are most appropriate. Although it is widely agreed that screening achieves mortality reduction through early detection of colorectal cancer when it is more curable and through detection and removal of precancerous adenomas, much less agreement exists about the relative effectiveness and cost of alternative strategies for prevention and early detection. At least four different tests are available today for colorectal cancer screening: fecal occult blood tests, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy. These technologies vary in their sensitivity and specificity for early cancerous lesions and polyps, their cost, medical risks, and comfort and acceptability to patients. However, the evidence on these parameters varies in quantity and quality, and different interpretations of the evidence have fueled the controversy rather than resolved it.

Until recently, double-contrast barium enema had not fared well in the debate over the most appropriate screening technology. In 1995 the United States Preventive Services Task Force recommended screening for average-risk adults 50 years old and older, with annual fecal occult blood tests or flexible sigmoidoscopy at unspecified time intervals, but excluded both double-contrast barium enema and colonoscopy because no direct evidence was available on their effectiveness in altering colorectal cancer death rates [7]. Recently an expert panel convened by the United States Agency for Health Care Policy and Research added double-contrast barium enema every 5–10 years and colonoscopy every 10 years to the list of recommended screening strategies for average-risk adults 50 years old and older [8], although the panel noted the lack of direct evidence of mortality benefit for these screening strategies.

Identification of the most appropriate screening strategy (comprising one or more technologies applied at specified time intervals) requires information on the trade-offs between gains in longevity and the costs of achieving them. Clinical trials of all possible screening strategies are simply not feasible. Computer models of the disease process and its associated costs offer a more efficient means of comparing many alternative strategies with one another. Although such models rely on assumptions about the course of disease under different screening strategies, they invite "what if" analyses of the impact of uncertainty in assumptions on the cost-effectiveness of screening strategies.

In this paper we use the modeling approach to compare the cost-effectiveness of double-contrast barium enema with other colorectal cancer screening technologies. We address three research questions. First, what is the evidence on the test performance (sensitivity and specificity) of double-contrast barium enema as a general colorectal cancer screening technology? Second, using the best evidence on test performance of double-contrast barium enema and competing screening procedures, how cost-effective is double-contrast barium enema compared with other tests? Third, can double-contrast barium enema be made even more cost-effective for general screening? Specifically, how would cost-effectiveness change if a minimal size threshold were adopted for calling a lesion "positive," a practice not customary today?

Literature Review

We identified all studies published in the medical literature on the test performance of double-contrast barium enema through a

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search of the National Library of Medicine's MEDLINE database for the period 1970–1996. This search was augmented by a review of citations in the published papers so identified. Every study containing estimates of double-contrast barium enema sensitivity and specificity was included in our review regardless of its study design. Multiple reports of the same study population were identified to eliminate duplicate research studies.

All studies of double-contrast barium enema sensitivity were evaluated for study biases arising from case selection methods or film interpretation techniques. Studies with the strongest (i.e., least biased) research designs were identified from this evaluation.

Cost-Effectiveness Analysis

We applied a model of colorectal cancer screening to 16 different screening strategies. A screening strategy comprises one or more technologies offered at specified time intervals, beginning at the age of 50 years. The screening model, developed by the United States Congress Office of Technology Assessment [9, 10] and described in detail elsewhere [11, 12], estimates the net present value of lifetime costs and years of life gained in a cohort of 100,000 50-year-old persons from different colorectal cancer screening strategies under specified assumptions about the natural history of colorectal cancer and the adenoma or carcinoma sequence; the sensitivity and specificity of each technology for early cancer and polyps; the cost of screening, follow-up, and post-polypectomy surveillance procedures; and the incremental costs of treating early- and late-stage colorectal cancer. Costs and years of life gained are discounted to their present value at 5% per year. (The discount rate is analogous to an interest rate and must be applied in cost-effectiveness analyses because individuals prefer to get health benefits earlier rather than later and to incur costs later rather than earlier [13]. For example, with a 5% discount rate, $105 spent 1 year from today has a value today of $100, because $100 could be put aside today to meet the obligation a year hence.) The 16 strategies are annual fecal occult blood tests; flexible sigmoidoscopy every 3, 5, or 10 years; double-contrast barium enema every 3, 5, or 10 years; colonoscopy every 3, 5, or 10 years; annual fecal occult blood tests and flexible sigmoidoscopy every 3, 5, or 10 years; and annual fecal occult blood tests and double-contrast barium enema every 3, 5, or 10 years.

The main assumptions used in this analysis are summarized in Tables 1–4. An analysis based on our best estimate of the true value of each parameter in question is referred to as the base-case analysis; our best estimates are shown in the base-case column. The range of values reflects reasonable upper or lower bounds for each parameter suggested by the available evidence. The effect of such alterations in model parameters is explored in a series of supplementary analyses, referred to as sensitivity analysis [13]. Justification for our estimates, which were based on reviews of the published literature, can be found elsewhere [9, 11, 12]. Assumptions about double-contrast barium enema sensitivity and specificity were based on the literature review.

Model results are particularly sensitive to one uncertain parameter of the disease process: the precancerous dwelling time. This term refers to the length of time it takes a polyp to progress from its earliest point of detectability by a screening technique to its transformation into invasive cancer. Because the natural history of adenomas is virtually always interrupted at the time they are found, studies monitoring large numbers of small adenomas over time do not exist. A few studies that monitored patients who refused treatment have recorded a long precancerous dwelling time [14, 15]. In patients monitored with frequent colonoscopic surveillance after polypectomy, only five cases of cancer were found in 1418 patients after 6 years, but new adenomas were detected in 30% of all study subjects [16, 17]. Thus, a few polyps may progress rapidly, but most apparently develop into cancer over a long period of time. Because so little is known about this model parameter, we analyzed all screening strategies under two alternative dwelling time assumptions: 5 and 10 years. The relative performance of different screening strategies should be evaluated across both of these assumptions.

Results

Double-Contrast Barium Enema Test Performance

We identified 25 studies of double-contrast barium enema sensitivity. All were conducted in patients referred for examination because of symptoms or suspicion of disease. When sensitivity is measured in a population with a high expected disease prevalence, radiologists may be more vigilant than they would be in a screening context [18], and the population is likely to exhibit a high proportion of larger polyps or later-stage cancers that are presumably easier to detect. Both of these factors promote upwardly biased estimates of test sensitivity. Bias in the opposite direction is apparent in one study [19], which restricted the universe of confirmed cases to patients with negative findings on prior flexible sigmoidoscopy. This restriction may have excluded all but the most diminutive polyps from the study.

Often the sample of cases with confirmed positive findings was limited to, or overrepresented by, those referred as a result of positive findings on a double-contrast barium enema [20–29]. Individuals with negative findings on double-contrast barium enemas (presumably including some false-negatives) were not generally referred for further evaluation. This method of selecting confirmed cases, even when the confirmatory procedure is highly sensitive and independent of the double-contrast barium enema, is a serious source of upward bias. Not surprisingly, these studies uniformly found sensitivity of double-contrast barium enema in the range of 85–95% for polyps.

Other investigators identified the universe of confirmed cancer cases from tumor registries or medical record systems and estimated double-contrast barium enema sensitivity from the subset of cases in which double-contrast barium enema had been performed within a specified period before diagnosis [30–40]. If the specified period before diagnosis is short, one would expect an upward bias, because some false-negative findings on double-contrast barium enemas would presumably not present clinically for some time. Conversely, a long period implies a downward bias because any cancer arising in the interval between a true-negative finding on double-contrast barium enema and clinical

TABLE 1 Summary of Assumptions: Sensitivity and Specificity of Screening and Diagnosis

Parameter	Base-Case Value (%)	Range (%)
Sensitivity		
FOBT for polyps	10	5
FOBT for cancer	60	40
CSCPY for polyps or cancer	90	
DCBE for polyps or cancer	70	50
FSIG for polyps or cancer	90	
60-cm FSIG[a]	50	35
Specificity		
FOBT	90	98
CSCPY	100	
FSIG	98	
DCBE	90	

Note.—FOBT = fecal occult blood test, CSCPY = colonoscopy, DCBE = double-contrast barium enema, FSIG = flexible sigmoidoscopy.

[a]Percentage of polyps and cancers reachable with 60-cm FSIG.

TABLE 2 Summary of Assumptions: Natural History of Polyp–Cancer Sequence

Parameter	Base-Case Value
Prevalence of polyps at 50 years old	30%
Annual polyp incidence rate	Age specific: 50–65 years, 1.33% per year; 66–70 years, 2% per year; >70 years, 1% per year
Percentage of cancer originating as polyps	70% (range, 95%)
Annual cancer incidence with no screening	Age specific (based on SEER data)
Percentage of cancer detected in early stage with no screening	40%
Dwelling time of cancer in early stage	2 years
Percentage of total dwelling time in early stage before clinical detection	100%
Dwelling time of cancer in late stage before detection	2 years
5-year all-cause survival for early cancer	Age specific (based on SEER data)
5-year all-cause survival for late cancer	Age specific (based on SEER data)
Precancerous polyp dwelling time detectable by	
Flexible sigmoidoscopy, double-contrast barium enema, colonoscopy	10 years
Fecal occult blood test	10 years

Note.—SEER = Surveillance, Epidemiology and End Results Tumor Registry System funded by the United States National Cancer Institute, Bethesda, MD.

TABLE 3 Summary of Assumptions: Complications and Unintended Consequences

Parameter	Base-Case Value
Colon perforation rate in	
Colonoscopy	0.0007
DCBE and FSIG	0.0
Death rate from colonoscopy	0.00005
Surgical mortality rate from colonic resection	2%
Prevalence of lifetime-latent cancer at 50 years old	0.2%
Annual incidence of lifetime-latent cancer	Age specific: 50–65 yr, 0.02%; 65–85 yr, 0.05%

Note.—DCBE = double-contrast barium enema, FSIG = flexible sigmoidoscopy.

detection would be wrongly classified as a false-negative. These two contradictory biases make assessment of the accuracy of the sensitivity estimates difficult. Sensitivity for colorectal cancer ranged from 70% to greater than 96% in these studies, with all but two studies finding sensitivity greater than 85%. This method is relevant only to sensitivity for cancer because most polyps, even large ones, are likely to remain asymptomatic for long periods of time.

Although no studies were conducted in a screening population, five studies avoided the common tendency to undercount false-negative findings on double-contrast barium enemas without introducing other serious biases. Williams et al. [41] studied 530 patients undergoing surveillance for previous polyps. Colonoscopy and double-contrast barium enema were performed on the same day. Sensitivity for polyps at least 7 mm in diameter was 71%. Steine et al. [42] studied 190 randomly selected patients referred for double-contrast barium enema in family practices in Norway. All double-contrast barium enema examinations were followed by colonoscopy. A second double-contrast barium enema was performed if the colonoscopy findings were negative and the first double-contrast barium enema had positive findings. The sensitivity for polyps at least 5 mm in diameter was 70% and for polyps at least 10 mm was 81%. Saito et al. [43] examined 193 rectosigmoid polyps found by either double-contrast barium enema or flexible sigmoidoscopy in 675 patients. Double-contrast barium enema immediately followed flexible sigmoidoscopy in all cases. Double-contrast barium enema sensitivity for polyps between 6 and 10 mm in diameter was 70% and for polyps greater than 10 mm was 81%. However, in a similarly designed study, Brewster et al. [44] found double-contrast barium enema sensitivity for rectosigmoid polyps of all sizes in the range of 30–35%. Kewenter et al. [45] reported on patients receiving follow-up tests after positive findings on screening fecal occult blood tests. All double-contrast barium enemas were followed by flexible sigmoidoscopy or colonoscopy. Double-contrast barium enema found 71% of all rectosigmoid adenomas confirmed by flexible sigmoidoscopy or colonoscopy, 77% of lesions larger than 10 mm, and 80% of colonic cancerous lesions. Except for the study of Brewster et al., which included diminutive polyps in the universe of confirmed cases, these well-designed studies universally found double-contrast barium enema sensitivity for adenomas larger than 5–7 mm to be equal to or greater than 70%.

Evidence on double-contrast barium enema specificity is far less abundant than is the evidence on sensitivity. We found only three estimates of the specificity of double-contrast barium enema for polyps. Rex et al. [46] placed clips in the colons of 115 study subjects, some near or adjacent to a polyp and others in an area of normal mucosa. Film interpreters judged whether a polyp was present in the area of each clip. Reported specificity for polyps greater than 10 mm was 96%. This estimate is probably biased upward because false-positives on radiography are often

TABLE 4 Summary of Assumptions: Costs

Parameter	Base-Case Value	Range
Unit cost of		
Screening fecal occult blood test	$10	+100%
Screening flexible sigmoidoscopy	$80	+100%
Screening double-contrast barium enema	$131	+100%
Screening colonoscopy	$285	+100%
Diagnostic colonoscopy	$285	+100%
Diagnostic colonoscopy with polypectomy	$434	+100%
Surveillance colonoscopy	$285	+100%
Tissue pathology for polyps and lesions	$64	+100%
Lifetime cost of		
Treating early cancer	$35,000	$20,000
Treating late cancer	$45,000	$30,000
Treating perforated colon	$35,000	
Discount rate	5% per year	

TABLE 5 Cost-Effectiveness of Colorectal Cancer (Base-Case Assumptions)

Strategy	5-Year Polyp Dwell Time			10-Year Polyp Dwell Time		
	Years of Life Gained ($\times 10^3$) per 100,000 Persons Screened	Added Cost per 100,000 Persons Screened ($ millions)	Cost per Added Year of Life ($)	Years of Life Gained ($\times 10^3$) per 100,000 Persons Screened	Added Cost per 100,000 Persons Screened ($ millions)	Cost per Added Year of Life ($)
Annual FOBT	5.15	70.0	13,581	5.88	58.2	9,906
FSIG every 3 years	3.91	53.0	13,554	3.99	51.9	13,001
FSIG every 5 years	3.37	40.2	11,947	3.58	37.8	10,541
FSIG every 10 years	1.90	38.3	20,122	3.13	24.9	7,966
FSIG every 3 years and annual FOBT	6.40	95.8	14,992	6.78	89.3	13,180
FSIG every 5 years and annual FOBT	6.28	85.7	13,639	6.72	78.3	11,652
FSIG every 10 years and annual FOBT	5.79	84.0	14,509	6.64	70.0	10,526
DCBE every 3 years	6.18	82.1	13,268	6.72	74.7	11,115
DCBE every 5 years	5.05	68.2	13,495	6.02	58.8	9,435
DCBE every 10 years	2.96	64.7	21,887	4.78	44.1	9,224
DCBE every 3 years and annual FOBT	7.21	116.6	16,165	7.47	112.1	14,996
DCBE every 5 years and annual FOBT	6.87	101.4	14,750	7.33	93.9	12,815
DCBE every 10 years and annual FOBT	6.13	96.0	15,665	7.06	80.7	11,444
CSCPY every 3 years	6.69	120.9	18,076	6.82	118.8	17,424
CSCPY every 5 years	8.10	87.7	14,383	6.50	82.9	12,750
CSCPY every 10 years	3.68	81.5	22,171	5.93	55.1	9,287

Note.—FOBT = fecal occult blood test, FSIG = flexible sigmoidoscopy, DCBE = double-contrast barium enema, CSCPY = colonoscopy.

caused by inadequate bowel preparation. Given the highly stylized experimental conditions of the study, bowel preparation was probably optimal, and reading technique may have been affected. Williams et al. [41] studied specificity in a more realistic clinical setting. All positive findings on double-contrast barium enemas in a sample of clinic patients were confirmed by colonoscopy or a second double-contrast barium enema. Specificity of double-contrast barium enema for cancer or polyps greater than or equal to 7 mm was 98%. In a similar study, Steine et al. [42] found double-contrast barium enema specificity of 90% for polyps and 98% for cancer when colonoscopy was the gold standard. When the existence of the lesion was reconfirmed by double-contrast barium enema (implying false-negative findings on colonoscopic examinations), specificity for polyps increased to 96%. Thus, double-contrast barium enema specificity for polyps or cancer can be conservatively estimated at 90% and may be higher.

Comparative Cost-Effectiveness of Colorectal Cancer Screening Strategies

In the absence of screening, 6025 members of a cohort of 100,000 50-year-olds would be diagnosed with colorectal cancer at some time in their remaining lives. The Office of Technology Assessment model predicts that these people lose approximately 37,000 years of life expectancy (or about 10,000 years when years of life lost are discounted to their net present value at 5% per year). The net present value of incremental health care costs attributable to colorectal cancer in the cohort is estimated to be about $97 million in the absence of screening.

Table 5 summarizes the results for various colorectal cancer screening strategies under the two alternative assumptions about precancerous dwelling time (5 or 10 years) and under the base-case assumptions for all other parameters. Regardless of the length of time that cancerous lesions spend as precancerous adenomas, each of the screening strategies meets commonly accepted standards for cost-effectiveness compared with doing nothing. Although no a priori "correct" threshold exists for a cost-effectiveness ratio above which an intervention can be deemed to be too costly for its medical benefits, commonly referenced values are in the range of $40,000–60,000 per quality-adjusted year of life added [47]. All strategies deliver an additional year of life at a cost of less than $25,000. Thus, if our base-case assumptions are reasonably accurate, colorectal cancer screening, although costly in the aggregate, delivers medical benefits that lie well within the usual bounds of acceptability.

Of greater interest is the relative performance of different colorectal cancer screening strategies. Figures 1 and 2 show the extra costs and gains in years of life lived from each colorectal cancer screening strategy under the two different assumptions about precancerous polyp dwelling time and base-case assumptions for all other parameters. Any strategy that offers both greater medical benefits and lower lifetime costs than another strategy is said to "dominate" the second strategy; it is simply better than the second strategy on both costs and effectiveness. Conversely, dominated strategies are clearly inferior and can be ignored by health care policy makers. Any strategy in Figure 1 or Figure 2 that lies above and to the left of another strategy in the figure is a dominated strategy. Only those points on the lower right-hand periphery represent real choices between greater lifesaving benefits and greater cost. Selecting among these screening options depends on society's willingness to pay for extra lifesaving benefits.

For example, if the precancerous dwelling time is 5 years, the strategy with the most favorable cost-effectiveness ratio (flexible sigmoidoscopy every 5 years) costs less in the aggregate but saves far fewer lives per 100,000 persons than does the strategy with the most unfavorable cost-effectiveness ratio (double-contrast barium enema every 3 years combined with annual fecal occult blood tests). On the other hand, the relatively modest medical benefits of switching from single-technique strategies to those combining two different tests come at a higher incremental cost. For example, under the assumption of a 5-year precancerous adenoma dwelling time, adding annual fecal occult blood tests to a double-contrast barium enema every 3 years costs $37 million and gains only 750 additional years of life, for an incremental cost-effectiveness ratio of about $50,000 per extra year of life gained.

Certain screening strategies remain undominated regardless of assumptions about dwelling time. Double-contrast barium enema every 5 years, annual fecal occult blood tests alone, or flexible sigmoidoscopy every 5 years are highly cost-effective compared with other strategies (and are essentially competitive with one another) regardless of the precancerous dwelling time. On the other hand, the relative performance of colonoscopy is sensitive to the dwelling time assumption. Whereas colonoscopy every 10 years is competitive with double-contrast barium enema every 5 years if the dwelling time is 10 years, colonoscopy is highly cost-ineffective compared with other strategies if the dwelling time is much shorter for cancerous lesions that originate as adenomas.

The sensitivity of these results to the range of assumptions about uncertain parameters (see Tables 1–4) is reported elsewhere [12]. Briefly, in a series of analyses of the effect of changing one parameter at a time, the cost-effectiveness ratio never rose above $40,000 for any strategy, and certain changes (e.g., assuming that the proportion of cancers arising from polyps is 0.7 instead of 0.95) substantially improved the cost-effectiveness ratio.

Although double-contrast barium enema every 5 years is a competitive screening strategy under the base-case assumptions, its cost-effectiveness ratio is sensitive to changes in assumptions about its test performance characteristics. For example, if the sensitivity of double-contrast barium enema is only 50% instead of 70% as assumed in the base-case analysis, the aggregate cost per 100,000 persons screened under the 5-year dwelling time scenario rises to $73 million, the years of life saved decrease to 3690, and the cost per year of life gained is $19,800. Double-contrast barium enema every 5 years is dominated by other strategies, such as flexible sigmoidoscopy every 5 years or annual fecal occult blood tests. If the precancerous dwelling time is 10 years, double-contrast barium enema is dominated by either annual fecal occult blood tests or colonoscopy every 10 years.

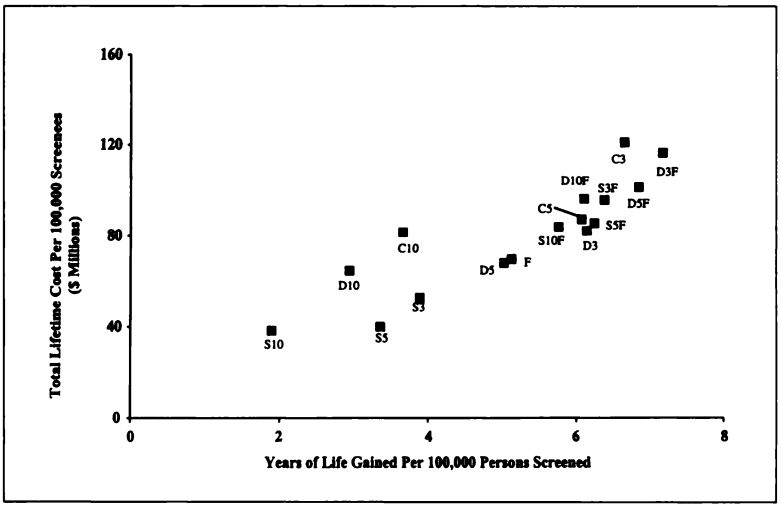

Fig. 1.—Scatterplot shows cost-effectiveness of colorectal cancer screening when 5-year precancerous dwelling time base-case assumptions are used. Note that several screening strategies are approximately equally cost-effective. S = sigmoidoscopy every *n* years, C = colonoscopy every *n* years, D = double-contrast barium enema every *n* years, F = annual fecal occult blood test, SF = S plus F, DF = D plus F.

Strategies to Improve the Performance of Double-Contrast Barium Enema

As with most diagnostic imaging procedures, an inverse relationship exists between test sensitivity and specificity. The receiver operating characteristic (ROC) curve shows this trade-off [48]. Figure 3 shows a stylized ROC curve for the detection of adenomas by double-contrast barium enema. Point A represents the consensus of the best-designed studies of sensitivity and specificity. Other points on the ROC curve can be achieved if the radiologist is willing to trade more false-positives for fewer false-negatives (and vice versa). For example, point B in Figure 3, which pairs double-contrast barium enema sensitivity of 50% with specificity of 93%, implies a cost-effectiveness ratio for double-contrast barium enema every 5 years of $19,200 per year of life gained, a slight improvement over the results when only sensitivity changed.

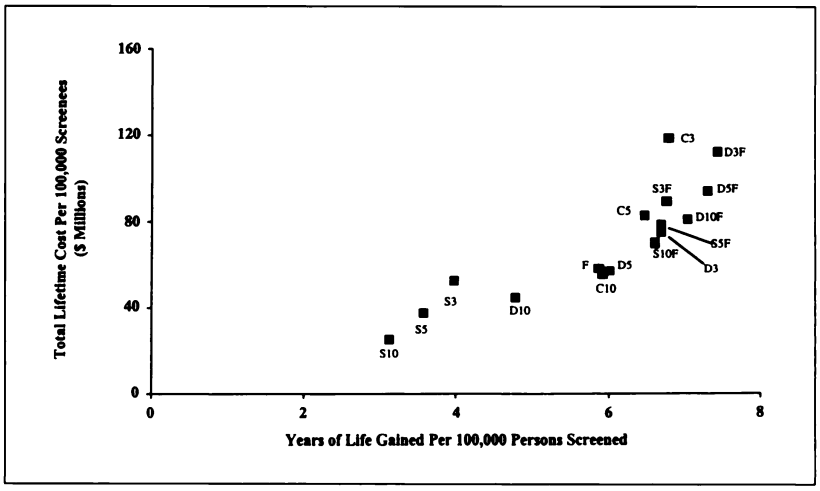

Fig. 2.—Scatterplot shows cost-effectiveness of colorectal cancer screening when 10-year precancerous dwelling time base-case assumptions are used. Note that several screening strategies are approximately equally cost-effective. S = sigmoidoscopy every *n* years, C = colonoscopy every *n* years, D = double-contrast barium enema every *n* years, F = annual fecal occult blood test, SF = S plus F, DF = D plus F.

Radiologists are inclined to identify all suspect lesions, but ample evidence has been presented that most small adenomas never progress to cancer [49–52]. The high aggregate cost of colorectal cancer screening is due in part to the costs of polypectomy and lifetime postpolypectomy surveillance with colonoscopy. When these procedures are performed on patients who are destined never to have colorectal cancer, health care resources are wasted. A screening strategy that can differentiate between small and large polyps may be much more cost-effective than a strategy that identifies all polyps for removal regardless of size. The evidence is strong that double-contrast barium enema sensitivity and specificity for large polyps (≥10 mm in diameter) are higher than for all polyps. For example, Steine et al. [42] estimated sensitivity for polyps 10 mm or more in diameter at 80% and specificity at 96%. Point C in Figure 3 represents this combination and suggests a second ROC curve, offering higher overall test performance.

Suppose the goal of double-contrast barium enema screening was redefined as the detection of cancerous lesions or of adenomas 10 mm or greater in diameter. This goal could be met either by radiologists choosing to operate on the ROC curve through point C, calling as positive findings only those polyps perceived by the radiologist as 10 mm or greater, or by a diagnostic follow-up protocol that dictates no follow-up of a positive finding on double-contrast barium enema unless the lesion is perceived by the radiologist as 10 mm or greater. What would this strategy mean for the cost-effectiveness of double-contrast barium enema compared with other procedures?

The answer to this question depends on three model assumptions: the proportion of cancerous lesions arising from polyps 10 mm or greater, the length of time for a 10-mm polyp to progress to invasive cancer, and the prevalence of polyps 10 mm or greater at each age. Although some polyps likely will become invasive cancer before they reach 10 mm in size, the assumption on which this analysis rests—that 70% of all cancerous lesions arise from polyps—is extremely conservative in light of evidence of the adenoma or carcinoma sequence [14, 53]. Consequently, we did not alter this assumption. On the other hand, the precancerous dwelling time is likely to be much shorter for polyps already 10 mm in diameter than for smaller polyps destined to progress to invasive cancer. For example, if the dwelling time for all polyps is assumed to be 10 years, an appropriate dwelling time for polyps greater than 10 mm might be 5 years or less. We assume a range of short precancerous dwelling times and examine the robustness of our findings to variations in this parameter.

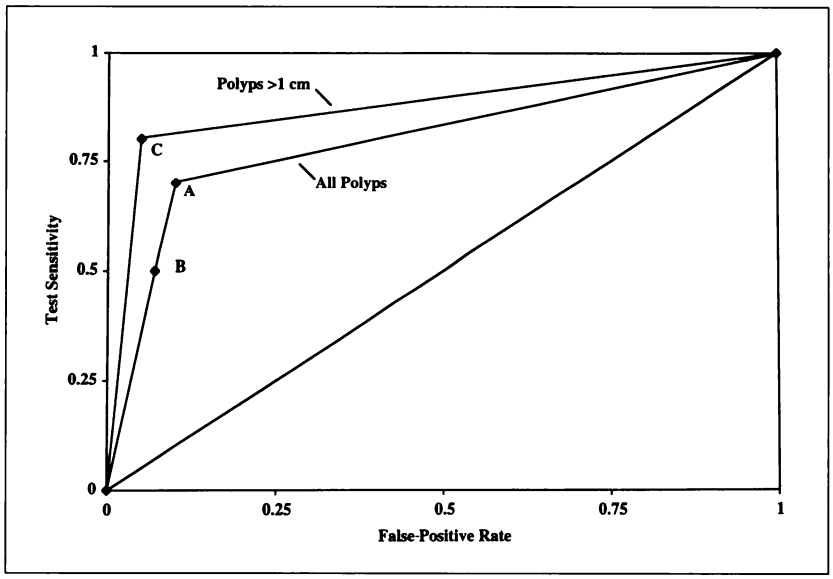

Fig. 3.—Double-contrast barium enema receiver operating characteristic (ROC) curve for polyps. A = location on ROC curve for sensitivity and specificity of double-contrast barium enema for all polyps as estimated from literature review, B = arbitrary location on same curve as A to show negative trade-off for procedure sensitivity to improve specificity, C = sensitivity and specificity estimate comparable with A when only polyps greater than 1 cm are being considered as target lesions.

Finally, at any age the prevalence of large polyps will be much lower than the prevalence of all polyps [54, 55]. In the base-case analysis, we assumed that the prevalence of at least one detectable polyp of any size is 30% at age 50 years and rises to 50% at age 65 years. When only large polyps will be pursued, we assume a prevalence of 5% at age 50 years, rising to 10% at age 65 years with no additional incidence after age 65 years.

Table 6 shows the cost-effectiveness of double-contrast barium enema every 5 years assuming that sensitivity for large polyps is 80%, specificity is 96%, and the precancerous dwelling time for double-contrast barium enema ranges from 1 to 5 years. A 5-year double-contrast barium enema strategy is highly cost-effective and actually dominates most other strategies (as reported in Table 5), provided the precancerous dwelling time for large polyps is 3 years or longer. Only if most large adenomas destined to progress to cancer do so in 2 years or less is the double-contrast barium enema large-polyp strategy dominated by other screening approaches. (Recall that the analysis assumes that only 70% of colorectal cancer arises from precancerous adenomas.)

Discussion

Although the evidence on double-contrast barium enema test performance is not well suited to screening settings, the best studies in nonscreening populations suggest a sensitivity for polyps greater than 5–7 mm of about 70% and a specificity of at least 90%. When these test performance parameters were applied in a cost-effectiveness model, screening strategies involving double-contrast barium enema were competitive with all other strategies. Although certain other strategies—notably periodic sig-

TABLE 6 Cost-Effectiveness of Double-Contrast Barium Enema Every 5 Years Using a 10-mm Cutoff for Polyp Size Under Different Assumptions About the Precancerous Dwelling Time of 10-mm Polyps

Assumed Dwelling Time (years)	Years of Life Gained ($\times 10^3$) per 100,000 Persons Screened	Added Cost per 100,000 Persons Screened ($ millions)	Cost per Added Year of Life ($)
1	2.32	64.9	27,949
2	3.51	53.7	15,282
3	4.55	43.5	9,555
4	5.21	33.8	6,492
5	5.78	24.8	4,283

moidoscopy—entailed lower aggregate lifetime costs, they also saved far fewer lives than did periodic double-contrast barium enema. The cost-effectiveness of double-contrast barium enema every 5 years was also stable across a range of reasonable assumptions about the precancerous polyp dwelling time. Such stability, which is not shared by colonoscopy, for example, is a particular advantage in public health decisions that must be made under conditions of uncertainty. Conversely, comparative cost-effectiveness or double-contrast barium enema is sensitive to its test performance parameters. If the true test sensitivity for polyps 5 mm and larger is substantially lower than 70%, double-contrast barium enema is no longer comparatively cost-effective. The unfortunate lack of well-designed studies of double-contrast barium enema performance in screening populations permits continued skepticism in some quarters about the competiveness of double-contrast barium enema as a colorectal cancer screening procedure.

Most, if not all, cases of colorectal cancer develop from benign adenomatous polyps. Indirect evidence suggests that, on average, at least 10 years are necessary for the progression from normal mucosa to invasive malignancy. However, adenomatous polyps are prevalent in the average-risk population, and this prevalence increases with age. Most of these neoplasms are small (<10 mm) and the risk of an adenoma of this size harboring cancer is minimal, on the order of 1% [14]. For adenomas, the overall potential for malignancy is negligible because most never progress beyond the diminutive stage [50–52]. An estimate has been made that only 3–5% of adenoma-bearing individuals will develop a carcinoma [56]. Thus, adenomas represent a dilute marker for identifying individuals at risk. On the other hand, adenomas greater than 10 mm are much less prevalent but carry different prognostic implications. A polyp with a dimension greater than 10 mm has a 10% likelihood of containing invasive cancer [14]. Such neoplasms, even when benign, are more likely to undergo malignant degeneration. Furthermore, individuals who have had benign adenomas that are greater than 10 mm removed are at high risk for eventually developing cancer at other colonic sites [57, 58]. Thus, an ideal screening test and protocol would incorporate a high sensitivity (and specificity) for larger adenomas and would be performed at an interval that would allow timely detection of previously ignored or overlooked small polyps that had enlarged to greater than or equal to 10 mm. In addition, the examination frequency would theoretically allow the identification of a significant number of the small group of previously missed larger adenomas before they progressed to incurable neoplasms. Interestingly, even these higher risk lesions still maintain a fairly infrequent and slow rate of malignant transformation. In an observational study of polyps greater than 10 mm, the cumulative risk of cancer at the polyp site was 3% at 5 years, 8% at 10 years, and 24% at 20 years [15]. An analysis based on autopsy findings concluded that the anticipated annual conversion rate for large adenomas was 3% [55].

Double-contrast barium enema satisfies the desired qualifications for screening when considering its performance characteristics for adenomas greater than or equal to 10 mm as well as the natural history and epidemiology of the disease. Although this procedure also detects smaller adenomas, its sensitivity drops significantly. Furthermore, restricting attention to large polyps reduces the frequency of false-positive findings. Most false-positives are related to adherent particulate stool. Focusing on adenomas greater than or equal to 10 mm is likely to preserve most of the effectiveness of secondary cancer prevention while reducing the aggregate cost and risk of more invasive therapeutic procedures such as polypectomy.

The model applied in the present study estimated the effects of a conservative approach to polyp diagnosis on double-contrast barium enema and compared the results with a previously analyzed model that incorporated traditional follow-up and therapeutic strategies. As Table 6 shows, a double-contrast barium enema every 5 years, assuming at least 5 years is necessary for an overlooked 10-mm benign adenoma to become malignant, is comparable in effectiveness but is more than 50% less costly than other regimens regardless of the polyp dwelling time assumed for the other regimens. In practice, the magnitude of this cost differential may be far greater than presented here because the assumed cost of colonoscopy ($285) reflected the ideal of a highly efficient outpatient setting. Today most such procedures are performed in hospitals where the total professional and facility charges or payments range from $600 to more than $1000. The cost of colonoscopy reduces the cost-effectiveness of each strategy in proportion to the number of follow-up colonoscopies generated by that approach.

For radiologists to fail to report what they believe could be small polyps is not a simple matter. Referring physicians might also be reluctant to ignore such small lesions if reported. Both the values of traditional medical practice and medical–legal concerns represent significant obstacles to adopting a more conservative approach to follow-up of colonic neoplasms. Consequently, selective application of a conservative strategy might be appropriate. Polyps are more prevalent with increasing age [59, 60]; yet, the likelihood that an adenoma will progress to fatal cancer (even if biologically destined to do so) diminishes with aging because of the disease's long natural history and the individual's lower life expectancy. Thus, the conservative strategy might best be applied in patients who are more than 70 years old.

Discussions of polyp size usually overlook the fact that methodologic standardization for polyp measurement (even on pathologic examination) is consistently absent in the literature. Minor variations could have significant implications, particularly when the number of lesions is small. Radiologic measurements are subject to the same concerns; magnification consistently results in an overestimate of polyp size on barium enema [61]. The impact of magnification on a strategy that proposes selective therapy of lesions above a specific threshold would be the inclusion of polyps below this cutoff. Thus, although such small polyps represent adenomas, under the selective strategy they should be considered false-positives, thus technically lowering procedure specificity for 1-cm adenomas. On the other hand, magnification should have no bearing on our assumptions about sensitivity because those assumptions are based on colonoscopy with pathologic confirmation of polyp size.

The cost-effectiveness analyses presented here suggest that even under traditional practice, the double-contrast barium enema is comparatively cost-effective as a screening procedure in average-risk individuals and has some inherent advantages over other procedures, including complete penetration of the colon and good relative performance regardless of the uncertainty about the length of the precancerous polyp dwelling time. However, double-contrast barium enema can be made even more efficient with selective follow-up of lesions in screening examinations. Although selective follow-up of lesions identified on radiographs represents a new and uncomfortable paradigm for both radiologists and referring physicians, this example is not inherently different from accepting a screening technology with low sensitivity for polyps, as is true of fecal occult blood tests today. One might ask the question: If a new noninvasive technique were developed that could show only adenomatous polyps greater than 10 mm, but did so with high sensitivity, would this be acceptable for screening? Given the current state of knowledge about the polyp–cancer sequence, we suspect most experts would answer in the affirmative.

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