Cost-Effectiveness Analyses of Colorectal Cancer Screening: A Systematic Review for the U.S. Preventive Services Task Force

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Purpose: To perform a systematic review of the cost-effectiveness of colorectal cancer screening for the U.S. Preventive Services Task Force.

Data Sources: MEDLINE and the British National Health Service Economic Evaluation Database, January 1993 through September 2001.

Study Selection: Original economic evaluations of colorectal cancer screening in average-risk patients were reviewed. The authors sought studies addressing the incremental cost-effectiveness of different screening strategies compared with no screening, of different screening strategies compared with one another, and of different ages of screening initiation and cessation. Two investigators independently reviewed each abstract, and potentially eligible articles were retrieved. A four-member working group reached consensus regarding final inclusion or exclusion of articles.

Data Extraction: One reviewer extracted data into evidence tables. The results were checked by other members and discrepancies resolved by consensus.

Data Synthesis: Among 180 potential articles identified, 7 were retained in the final analysis. Compared with no screening, cost-effectiveness ratios for screening with any of the commonly considered methods were generally between $10 000 and $25 000 per life-year saved. No one strategy was consistently found to be the most effective or to have the best incremental cost-effectiveness ratio. Currently available models provided insufficient evidence to determine optimal starting and stopping ages for screening.

Conclusions: Screening for colorectal cancer appears cost-effective compared with no screening, but a single optimal strategy cannot be determined from the currently available data. Additional data regarding adherence with screening over time, complication rates in real-world settings, and colorectal cancer biology are needed. Additional analyses are necessary to determine optimal ages of initiation and cessation.

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See related articles on pp 129-131 and pp 132-141.

Colorectal cancer is the second leading cause of cancer mortality in the United States, with more than 57 000 deaths expected in 2001 (1). Evidence from several studies suggests that screening for, detecting, and removing colorectal cancer and precancerous adenomatous polyps can reduce the incidence of colorectal cancer and colorectal cancer–related mortality (2). Questions remain, however, about which method or methods of screening should be used, how frequently screening should be performed, and at what ages screening should begin and end. In addition, health care policymakers wish to know not only whether screening is effective but also whether it is cost-effective. Existing clinical trials of colorectal cancer screening have not directly compared different screening approaches and have not tested different starting and stopping ages. In the absence of such data, cost-effectiveness analyses using simulation models may provide the best information for answering such questions (3).

To help inform the U.S. Preventive Services Task Force's deliberation on recommendations regarding screening for colorectal cancer, we examined three questions:

1. What is the cost-effectiveness of colorectal cancer screening by any method compared with no screening?

2. Can we use incremental cost-effectiveness data to determine the relative effectiveness and cost-effectiveness of different screening options and thus determine whether there is a preferred strategy for screening?

3. What is the incremental cost-effectiveness of continuing screening to 85 years of age compared with stopping screening at 70, 75, or 80 years of age? What is the incremental cost-effectiveness of starting screening at 40 or 45 years of age compared with 50 years of age?

Methods

Search Strategy

The principles and rationale for our approach to conducting systematic reviews of cost-effectiveness studies are described elsewhere (4). We searched MEDLINE and the British National Health Service Economic Evaluation Database (NHS EED) (http://agatha.york.ac.uk/nhsdhp.htm) between January 1993 and September 2001. We exploded the Medical Subject Headings "colorectal neoplasms" and "mass screening." We used different strategies in each database to identify cost-effectiveness analyses. For our MEDLINE search, we added the exploded Medical Subject Heading "costs and cost analysis." In the NHS EED, we limited the search to "economic evaluations." We chose 1993 as a starting point because it was the year in which the first trial establishing strong evidence for the effectiveness of colorectal cancer screening was published (5). To identify studies not captured by our database searches and studies that are ongoing or unpublished, we manually searched the reference lists of retrieved articles and contacted selected authors and experts in the field.

Two investigators reviewed titles and abstracts of publications identified by the literature searches. Using information in the abstracts, we excluded studies that were not cost-effectiveness or cost-utility analyses, including other types of economic evaluations that did not quantify the health outcomes achieved for a given cost; studies that reported only cost per patient screened, cost per cancer detected, or cost per death prevented; studies that did not contain original analyses; articles that did not address at least one of our three questions of interest; studies performed from perspectives other than the societal perspective or the perspective of public third-party payers; and studies that used cost or disease incidence estimates from outside the United States. When we encountered multiple publications that reported results from the same cost-effectiveness model, we included the most comprehensive analysis and used other papers for supplemental information. When the decision about whether to include a study could not be made by reading the title or abstract, we evaluated the full article. Disagreements on study inclusion were resolved by consensus of the authors.

All authors reviewed each included article. Reviews focused on the assumptions of each study regarding the epidemiology and natural history of colorectal cancer; estimates of variables related to the effectiveness of screening, including test accuracy, adherence rates, and complication rates; estimates of the costs of screening, diagnosis, and treatment; the proportion of cancer cases and cancer deaths prevented by screening; and the effect of varying key variables (sensitivity analyses).

For each study, we used available data to tabulate life-years gained and costs per person for each of the major strategies under consideration: annual fecal occult blood testing, sigmoidoscopy every 5 years, combination of annual fecal occult blood testing and sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, and colonoscopy (every 10 years, at 55 and 65 years of age, or once in a lifetime). The evaluated strategies were arrayed in order of effectiveness. Costs were updated to U.S. dollars in 2000 by using the Consumer Price Index for medical care.

If one strategy was more costly and less effective than another strategy, it was considered to be strongly dominated. If a strategy was both less effective and had a higher cost-effectiveness ratio than another strategy, it was considered to be weakly dominated. Incremental cost-effectiveness ratios were then calculated for all nondominated strategies by using the following formula: (costs strategy 2 − costs strategy 1)/(life-years gained with strategy 2 − life-years gained with strategy 1).

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Context

It is unclear which colorectal cancer screening strategy is most cost-effective.

Contribution

On behalf of the U.S. Preventive Services Task Force, the authors reviewed seven published analyses that addressed the cost-effectiveness of fecal occult blood testing (single or annual), flexible sigmoidoscopy every 5 years alone or with fetal occult blood testing, barium enema every 5 years, and colonoscopy every 10 years.

The screening strategies all cost $10 000 to $25 000 per year of life saved.

Implications

Physicians should discuss the advantages and disadvantages of the various colorectal cancer screening strategies with their patients to decide which test is best for each individual.

–The Editors

Results

Identification of Cost-Effectiveness Analyses

Our initial searches identified 180 potentially relevant studies. On initial review of titles and abstracts, we excluded 159 articles that were clearly not related to our topic of interest. Of the 21 full articles retrieved and reviewed by the investigators, six met the inclusion criteria. **Appendix Table 1** (available at www.annals.org) shows the reasons for exclusion of the remaining articles.

Through supplemental searches, we identified two additional studies that met our inclusion criteria. One was identified through manual searching of the reference lists of retrieved articles (6), and the other was identified through contact with experts but was subsequently published and indexed in MEDLINE (7). Because the book chapter by Wagner and colleagues (6) was the most comprehensive description of the model developed by the Office of Technology Assessment, we used it rather than the more recent analysis by Glick (7).

Study Descriptions

Table 1 shows the basic features of the included analyses. All but one were cost-effectiveness analyses that expressed benefits in days of life or life-years gained and costs in U.S. dollars. One study presented results in cost per quality-adjusted life-year gained (13). Each study considered one or more alternative means of screening in addition to the option of no screening. The perspective of the analyses was societal or that of a third-party payer. All studies considered direct costs, including the costs of screening, diagnostic tests, and treatment; no studies considered patient time costs associated with attendance for screening, diagnostic, or surveillance procedures or for treatment of cancer.

Table 1. **Study Characteristics***

Characteristic	Study, Year (Reference)		
	Wagner et al., 1996 (6)	**Frazier et al., 2000 (8)**	**Khandker et al., 2000 (9)**
Model type	Unknown	Markov	Dynamic state transition
Perspective	Societal	Societal	Unknown (appears to be societal)
Age range for screening, *y*	50–85	50–85	50–85
Time horizon	Lifetime	Lifetime	35 years
Key biological assumptions			
Cancer from adenomas, %	70	100	100
Polyp dwell time, *y*	10	NR	Variable
Time from early to late cancer, *y*	2 (2 from late disease to symptoms)	NR	5
Additional features			
Relevant interventions considered	Annual FOBT FS every 5 years Annual FOBT + FS every 5 years BE every 5 years Colonoscopy every 10 years	Annual FOBT FS every 5 years Annual FOBT + FS every 5 years BE every 5 years Colonoscopy every 10 years	Annual FOBT FS every 5 years FOBT + FS, annually + every 5 years BE every 5 years Colonoscopy every 10 years
Discount rate, %	5	3	3
Was adherence modeled?	No	Yes	Yes (2 scenarios)
How were benefits measured?	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment
Adverse effects			
Source of harms data	Systematic review	2 articles	Unclear
Perforation rate for colonoscopy (with polypectomy), %	0.07 (NR)	NR	0.85†
Bleeding rate for colonoscopy (with polypectomy), %	NR	NR	NR
Deaths for colonoscopy per 100 000 examinations (range), *n*	5 (NR)	5 (0.5–50)	23.6 (12–35)
Costs			
Types of costs included	Direct	Direct	Direct
Sources of cost information	Medicare reimbursement data	Data from large HMO	Medicare and survey of private payers
Cost of colonoscopy (cost with polypectomy), $	285 (434)	1012 (1519)	438–670 (702–981)
Cost of FOBT, $	10	38	7.50–10
Cost of sigmoidoscopy, $	80	279	94–175
Cost of care for perforation (cost of care for bleeding), $	35 000	NR	28 200
Cost of cancer care, $	Early: 35 000 Late: 45 000	Local: 22 000 Regional: 43 900 Distant: 58 300	Local: 49 587 Regional: 79 857 Distant: 60 180
Measured in U.S. dollars from what year?	1995	1998	1994
Relevant intermediate outcomes			
Sensitivity of a single test for detection of cancer (detection of large polyps), %	FOBT: 40–60 (10)	FOBT: 33 (10) FS: 95 BE: 70 (50) Colonoscopy: 95	FOBT: 60 (10) FS: NR BE: 84 (82) Colonoscopy: 97 (85)
Polyps and cancer reachable by sigmoidoscopy, %	50	Variable	70
Reduction in mortality with screening, %	FOBT: 28 FS: NR FOBT + FS: NR BE: NR Colonoscopy: NR	FOBT: 55 FS: 40 FOBT + FS: 71 BE: 47 Colonoscopy: 64	FOBT: 80 FS: 69 FOBT + FS: 88 BE: 89 Colonoscopy: 90
Proportion of colorectal cancer cases prevented during course of program, %	NR	FOBT: 39 FS: 37 FOBT + FS: 60 BE: 38 Colonoscopy: 58	FOBT: 60 FS: 66 FOBT + FS: 80 BE: 86 Colonoscopy: 86
Important variables in sensitivity analysis	Polyp dwell time	Death due to colonoscopy	Polyp dwell time, adherence, cost of colonoscopy

* BE = barium enema; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; HMO = health maintenance organization; NA = not available; NR = not reported; QALY = quality-adjusted life-year; SEER = Surveillance, Epidemiology, and End Results.
† Rate of any complication.

Table 1—**Continued**

Study, Year (Reference)			
Sonnenberg et al., 2000 (10)	**Vijan et al., 2001 (11)**	**Loeve et al., 2000 (12)**	**Ness et al., 2000 (13)**
Markov	Markov	Microsimulation model	Discrete-event stimulation and cost-utility analysis
Third-party payer	Third-party payer	Unknown	Unknown
50–death	50–85	50–75	Single screening
Lifetime	Lifetime	Lifetime	Lifetime
100	75	100	100
NR	10 years	20 years	2 groups: one with mean of 26 years, other with mean of 52 years
NR	2 in localized disease, 1 in regional disease	5.3	5.55
Annual FOBT FS every 5 years Colonoscopy every 10 years	Annual FOBT FS every 5 years Annual FOBT + FS every 5 years Colonoscopy at 50 and 60 years of age	FS every 5 years between 50 and 75 years of age	Single colonoscopy at 45–50, 50–54, 55–59, or 60–64 years of age
3	3	3	3
Yes	Yes	No	No
Costs per life-year saved; most benefit from prevention; early detection reduces mortality by 18%	Costs per life-year saved; SEER data based on stage at diagnosis used to determine effect of treatment	Net costs per person and life-years gained per 1000 persons	Cost per QALY saved
2 articles	2 articles	Nonsystematic reviews	Multiple studies
0.2 (0.38)	0.1 (NR)	0.2 (NR)	0.1 (NR)
0.15 (2.0)	NR	NR	NR (0.3)
10 (NR)	7.5 (0–30)	NR	20 (NR)
Direct	Direct	Direct	Direct
Medicare cost data from 1998	Data from Medicare and Kaiser Permanente	Estimates based on published literature	Medicare rates and previous studies
695 (1003)	550 (765)	300 (400)	303 (530)
3.50	17	NA	NA
400	225	100	NA
13 000 (4360)	20 000	30 000	NR
45 228	Local: 60 000 Regional: 82 800 Distant: 73 000	Initial 25 000 over 6 months Ongoing 2200/year Terminal: 16 000 over 6 months	Initial Local: 16 051 Regional: 18 457 Distant: 21 093 Ongoing Local: 425/year Regional: 1944/year Distant: 21 209 Terminal: 16 722
2000	1999	1993	1998
FOBT: 40 (NR)	FOBT: 30 local, 50 regional (5)	Colonoscopy: 95 (95)	Colonoscopy: 95 (85)
45	55	Unknown	NA
FOBT: 18 FS: 34 FOBT + FS: NR BE: NR Colonoscopy: 90	FOBT: 52 FS: 44 FOBT + FS: 70 BE: NR Colonoscopy: 75	55	Men: 68 Women: 65
FOBT: 16 FS: 34 FOBT + FS: NR BE: NR Colonoscopy: 75	FOBT: 60 FS: 66 FOBT + FS: 70 BE: 86 Colonoscopy: 86	47	Men: 64 Women: 61
Adherence	Adherence	Dwelling time distribution, mean dwelling time	NR

Table 2. **Cost-Effectiveness Ratios of Various Tests for Colorectal Cancer Compared with No Screening***

Test	Study, Year (Reference)				
	Wagner et al., 1996 (6)	Frazier et al., 2000 (8)	Khandker et al., 2000 (9)	Sonnenberg et al., 2000 (10)	Vijan et al., 2001 (11)
Annual FOBT, $	11 725	17 805	13 656	10 463	5691
FS every 5 years, $	12 477	15 630	12 804	39 359	19 068
Annual FOBT + FS every 5 years, $	13 792	22 518	18 693		17 942
DCBE every 5 years, $	11 168	21 712	25 624		
Colonoscopy every 10 years, $	10 933	21 889	22 012	11 840	9038

* All costs are updated to U.S. dollars in 2000. DCBE = double-contrast barium enema; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy.

In general, each model used data on the incidence of colorectal neoplasms (adenomatous polyps and cancer) to simulate the natural history of disease in a cohort of adults at average risk, typically those between 50 and 85 years of age. These neoplasms were subject to detection and removal by the different screening strategies as they progressed from adenomas to early-stage cancer and then to late-stage cancer. Survival after detection was generally considered to be stage-related. The costs and complications of screening and treatment were modeled with various degrees of precision.

Benefits and costs were discounted at 3% or 5% in the base-case analyses. Sensitivity analyses were used to examine uncertainty about the variables used to build the models. Most sensitivity analyses were one-way, although some studies examined the effect of setting several variables to the most pessimistic levels. Factors that caused cost-effectiveness ratios to vary more than twofold in sensitivity analyses were polyp dwell time, the proportion of cancer arising from adenomas, adherence rates, and the cost and adverse effects of colonoscopy.

The effectiveness of screening in preventing colorectal cancer and cancer deaths also varied considerably. The analysis by Khandker and associates (9) was the most optimistic: Most strategies prevented more than 60% of cases of cancer and 80% of colorectal cancer deaths. Frazier and colleagues' analysis produced the smallest reductions (8), whereas Vijan and coworkers (11) found reductions in incidence similar to those of Khandker and associates and mortality reductions similar to Frazier and colleagues. The analyses by Loeve and associates (12) and Ness and colleagues (13) were intermediate. The model of Sonnenberg and coworkers (10) produced the lowest estimates of efficacy for fecal occult blood testing and for sigmoidoscopy, but their estimate for the efficacy of colonoscopy was among the highest.

Question 1: Cost-Effectiveness of Screening for Colorectal Cancer with Any Method Compared with No Screening

All studies found that screening for colorectal cancer by any of the included screening strategies reduced deaths from colorectal cancer in adults older than 50 years of age who were at average risk for colorectal cancer. **Table 2** shows cost-effectiveness ratios for analyses that examined two or more of the most commonly evaluated strategies: fecal occult blood testing annually, flexible sigmoidoscopy every 5 years, a combination of fecal occult blood testing and sigmoidoscopy, barium enema every 5 years, and colonoscopy every 10 years, each compared with no screening. In base-case analyses, most strategies had average cost-effectiveness ratios, ranging from $10 000 to $25 000 per year of life saved. Among the studies examining single methods of screening, the analysis by Loeve and colleagues found sigmoidoscopy to be cost saving when relatively optimistic cost values were used and the time range for the analysis was extended beyond 35 years (12). Ness and associates found that screening adults with colonoscopy between 50 and 54 years of age had a cost-effectiveness ratio of less than $10 000 per life-year saved (13).

Although the results of the different studies are relatively consistent, the base-case assumptions about the effectiveness or costs of screening for colorectal cancer may have been overly optimistic. Alternative sensitivity analyses that assumed "worst-case" scenarios about the biological behavior of neoplasms and effectiveness of treatment generally produced cost-effectiveness ratios of less than $100 000 per life-year saved.

Question 2: Use of Incremental Cost-Effectiveness Data To Determine the Relative Effectiveness and Cost-Effectiveness of Different Screening Options and the Preferred Screening Strategy

Five studies we identified examined multiple screening strategies (annual fecal occult blood testing, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, colonoscopy every 10 years, and the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years) and reached heterogeneous conclusions about their effectiveness and incremental cost-effectiveness (**Table 3**; **Appendix Table 2** [available at www.annals.org]).

With regard to the most effective strategy, defined as that yielding the greatest average number of life-years gained, the analyses by Wagner (6), Frazier (8), and Vijan (11) and their colleagues found the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years to be most effective. Khandker and associates (9) and Sonnenberg and coworkers (10) found colonoscopy every 10 years to be the most effective, although the latter researchers did not consider the combination of fecal occult blood testing and sigmoidoscopy. Of note, four of five multiple-strategy analyses found fecal occult blood testing alone to be more effective than sigmoidoscopy alone for reduction of deaths from colorectal cancer (6, 8, 9, 11).

The most "cost-effective" strategy depends on the cost threshold beyond which one no longer wishes to "pay" for additional years of life saved. If it is assumed that one does not wish to pay more than $20 000 per life-year saved, the five studies reached heterogeneous conclusions about the best strategy. At least one analysis found annual fecal occult blood testing, sigmoidoscopy every 5 years, or colonoscopy every 10 years to be the optimal method of screening. As one's willingness to pay to save more life-years increases, colonoscopy every 10 years or the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years becomes favored.

Factors That Affect Cost-Effectiveness Results

Several important variables differed across the five multiple-strategy analyses and may explain some of the variability in incremental cost-effectiveness ratios (**Table 1**). However, we could not identify a single variable as being solely responsible for the heterogeneity in the outcomes we detected.

Assumptions about the biological behavior of colorectal cancer are important factors in the ability of the model to accurately simulate real life. Assumptions about the proportion of cancer arising from adenomas are particularly important because screening strategies that work mostly by preventing cancer through the removal of polyps, such as screening colonoscopy, appear to be most effective when it is assumed that all cancer arises from detectable adenomas (8, 11).

Similarly, the duration of the precancerous and early cancer detectable phases (dwell time) affects the relative rank of screening strategies. If the dwell time is long, strategies that involve a highly accurate test at a less frequent interval (for example, screening colonoscopy every 10 years) will appear to perform well compared with a more frequent but less accurate test, such as annual fecal occult blood testing.

Screening adherence is another important factor. No analysis was completely successful in simulating actual patterns of adherence. In all models, the adherence level was changed for all tests equally, an assumption that may not be correct (for example, adherence may differ for fecal occult blood testing and colonoscopy). This assumption of equal adherence among methods again favors the more accurate but more onerous screening methods, such as colonoscopy, particularly when adherence is assumed to be low.

Most of the analyses assumed that survival was based on the stage at diagnosis and estimated stage-specific survival from the National Center of Health Statistics and Surveillance Epidemiology and End Results Survey (14). Of note, Sonnenberg and coworkers made the very conservative assumption that cancer detected early by screening would produce a mortality rate only 18% lower than that detected clinically (10). This assumption makes fecal occult blood testing appear much less effective than a method that relies more on detection and removal of polyps, such as colonoscopy.

Modeling of adverse effects also influences the cost-effectiveness of different strategies. The adverse effects of colorectal cancer screening are mainly those associated with complications of colonoscopy (whether initially for screening or as part of the "diagnostic cascade" after positive results on another screening test), which include perforation; bleeding; or, rarely, death. Studies that fail to model all adverse consequences of colonoscopy will overestimate cost-effectiveness and will favor screening colonoscopy over strategies that involve fewer colonoscopic examinations.

All studies included only the direct costs of screening. No study examined the cost of patient time missed from work for screening and treatment. The effect of considering such costs on the relative cost-effectiveness of each method is unclear: Colonoscopy would have higher patient

Table 3. **Preferred Strategy at Different Levels of "Acceptable" Costs per Life-Year Saved***

Study, Year (Reference)	Most Effective Strategy†	Preferred Strategy if Willing to Pay‡			
		<$20 000 per Life-Year Saved	$20 000–$30 000 per Life-Year Saved	$30 000–$50 000 per Life-Year Saved	$50 000–$100 000 per Life-Year Saved
Wagner et al., 1996 (6) (alternative)§	FOBT + FS	Colonoscopy every 10 years	Colonoscopy every 10 years	FOBT + FS	FOBT + FS
Frazier et al., 2000 (8)	FOBT + FS	Annual FOBT	Annual FOBT	FOBT + FS	FOBT + FS
Khandker et al., 2000 (9)	Colonoscopy every 10 years	FS every 5 years	FS every 5 years	Annual FOBT	Colonoscopy every 10 years
Sonnenberg et al., 2000 (10)	Colonoscopy every 10 years	Colonoscopy every 10 years	Colonoscopy every 10 years	Colonoscopy every 10 years	Colonoscopy every 10 years
Vijan et al., 2001 (11)	FOBT + FS	Annual FOBT	Annual FOBT	Colonoscopy at 55 and 65 years of age only	Colonoscopy at 55 and 65 years of age only

* FOBT = fecal occult blood test; FS = flexible sigmoidoscopy.
† Most effective strategy = largest number of life-years saved among 5 main strategies.
‡ All costs are updated to U.S. dollars in 2000.
§ Using sensitivity of 50% for double-contrast barium enema, rather than 70% used in base case.

costs per test but would be required less frequently than other methods. Overall, the cost per life-year saved would probably increase for all methods.

Another important factor is the way in which each analysis models postpolypectomy surveillance for new adenomas and cancer. Studies differed with respect to the interval for repeating colonoscopy after detection and removal of a clinically significant adenomatous polyp. Wagner and colleagues assumed that all patients with adenomatous polyps would undergo surveillance colonoscopy every 4 years and that none of these patients would develop additional polyps or cancer and would die of other causes (6). Frazier and associates assumed that all patients with a "high-risk polyp" (>1 cm in size or having villous histology) would undergo surveillance colonoscopy every 3 years until 85 years of age or death (8). Khandker and coworkers used a more complicated model in which after an initial polyp larger than 1 cm in size was detected, an initial surveillance colonoscopy was performed at 3 years and subsequent follow-up studies were performed every 5 years if polyps were detected on the previous examination (9). In that study, it appears that regular screening was reinitiated if colonoscopy results were negative, but the documentation was unclear on this point. Sonnenberg and colleagues modeled surveillance colonoscopy 3 years after polyp detection but allowed screening to be suspended for 10 years after negative results on colonoscopy (10). Vijan and associates (11) also modeled initial surveillance colonoscopy 3 years after detection of a large adenoma (>1 cm) and lengthened the interval for future surveillance examinations to every 5 years after negative results on examination. More aggressive programs with more frequent examination can increase effectiveness in preventing future cancer but will increase complications and costs.

Question 3: Incremental Cost-Effectiveness of Continuing Screening to 85 Years of Age Compared with Stopping Screening at 70, 75, or 80 Years of Age, or of Starting Screening at 40 or 45 Years of Age Compared with 50 Years of Age

Ness and colleagues (13) examined different ages at which to perform one-time screening colonoscopy and found that for women, screening between 45 and 49 years of age was dominated by one-time screening between 50 and 54 years of age. For men, screening at 45 to 49 years of age compared with screening from 50 to 54 years of age was associated with a cost of $69 000 per quality-adjusted life-year gained. An older study by Eddy (15) found that starting annual fecal occult blood testing at 40 years of age added less than 1 day of average life expectancy and increased costs per person screened almost twofold compared with starting at 50 years of age.

We found no studies that examined the incremental cost-effectiveness of different stopping ages, although Rich and Black (16) used life-table analyses to suggest that by 75 years of age, 68% of the potential mortality reduction from initiating fecal occult blood testing at 50 years of age had been achieved. If screening were continued to 80 years of age, 83% of the potential reduction in mortality would be achieved.

DISCUSSION

Our systematic review identified seven high-quality cost-effectiveness analyses; five examined multiple colorectal cancer screening strategies, and two examined single strategies. Compared with no screening, all seven analyses found that any of the common screening strategies for adults 50 years of age or older will reduce mortality from colorectal cancer. The cost per life-year saved for colorectal cancer screening ($10 000 to $25 000 for most strategies compared with no screening) compares favorably with other commonly endorsed preventive health care interventions, such as screening mammography for women older than 50 years of age or treatment of moderate hypertension.

Whether one method of colorectal cancer screening is superior to other methods is not clear from these analyses. Many observers have interpreted recent studies (17–19) documenting the relative greater single-test accuracy of colonoscopy compared with sigmoidoscopy, fecal occult blood testing, or double-contrast barium enema for detection of colorectal cancer or adenomas as proof that colonoscopy should be the screening method of choice for colorectal cancer (20). The five multiple-strategy analyses that we identified, however, did not uniformly find that colonoscopic screening was the most effective or cost-effective strategy. The most effective strategy tended to be colonoscopy every 10 years or the combination of annual fecal occult blood testing and sigmoidoscopy every 5 years. The most "cost-effective" strategy identified depended on the level of incremental cost-effectiveness considered to be worthwhile and was not conclusive.

The differences in effectiveness, and hence cost-effectiveness, among the models are related to different assumptions each model makes about the biological behavior of colon cancer, the effectiveness and adverse effects associated with each strategy, and the likelihood that patients will actually complete the tests required for any given strategy. Because the limited available empirical data cannot tell us which set of assumptions is most accurate, we cannot definitively state the most effective or cost-effective strategy for screening. We can say with confidence, however, that any of the methods are effective compared with no screening for adults 50 years of age or older.

Other reviewers have recently examined the literature on the cost-effectiveness of screening for colorectal cancer. Brown and Knopf (21) reviewed cost-effectiveness analyses completed by 1998 and identified four studies for inclusion (6, 12, 15, 22). As with our analysis, they concluded that screening by any of several methods was cost-effective compared with no screening but that the available evidence could not determine the most effective strategy. McMahon and colleagues recently published a reanalysis of four previous cost-effectiveness analyses (23). They included the studies by Eddy (15) and Wagner and coworkers (6) that were examined by Brown and Knopf, as well as Glick's reanalysis (7) of Wagner and coworkers' model. They recalculated incremental cost-effectiveness ratios for the methods considered and concluded that double-contrast barium enema every 3 years or the combination of double-contrast barium enema every 5 years plus fecal occult blood testing annually were the most effective strategies. However, these conclusions were limited by the overly optimistic estimates (compared with data from the best subsequent empirical study [19] of double-contrast barium enema sensitivity and specificity) used in the four analyses that McMahon and colleagues included.

We did not find sufficient evidence about starting and stopping ages for screening to provide useful information for making recommendations. The analyses by Ness and associates (13) and Eddy (15) suggest that the benefits of starting screening at 40 or 45 years of age were small and costly compared with starting at 50 years of age, but further analyses with a range of tests are required. The cost-effectiveness of different stopping ages for screening also was not well examined and may differ substantially depending on the health of the patient being considered for screening (24).

Some potential limitations should be considered in interpreting our results. All but one of our analyses examined cost per life-year gained and did not account for differences in quality of life associated with undergoing screening, surveillance, or treatment for cancer. Differences in model structure, data inputs for key variables, and regimens evaluated limited our ability to draw definitive conclusions about the most effective and cost-effective tests. It is difficult to determine from the data presented in each report whether differences in the results obtained relate mainly to differences in the variables used or in the model structures. We considered only strategies that involved one kind of test (or a pair of tests) and repeated those tests at some regular interval. More complex strategies, including ones that screen younger persons with one test and then switch to a different test at older ages, have not been evaluated. Uncertainty about estimates for different variables was addressed in each study by one-way sensitivity analyses or by testing a set of "optimistic" or "pessimistic" assumptions, but only one of the studies provided probabilistic ranges for its results. Finally, our findings apply only to screening patients at average risk for colorectal cancer; screening higher-risk patients may be even more cost-effective.

Some modelers attempted to validate their models by comparing their results with results of empirical screening trials (6, 8, 11). It would be valuable to have the creators of the different models participate in a validation exercise to compare intermediate and long-term model outcomes by using one common set of variables for a common set of strategies. In this manner, we could confirm that the relative ranking of strategies is similar and not dependent on model structure and assumptions. Nonetheless, the consistent finding that any form of screening is superior to no screening supports the general conclusion that any of the commonly considered strategies are reasonable alternatives.

Our review has important implications for future research and policymaking. It supports the consensus view among major policymaking bodies that screening for colorectal cancer in some form is warranted for adults at average risk who are older than 50 years of age. It also shows that current evidence is insufficient to determine the most effective or cost-effective strategy for screening or to determine the optimal starting and stopping ages for screening. Because no single method of screening is clearly superior to another, patient preferences can play an important role in deciding how screening should be performed (25). Finally, our findings suggest that further research about the natural history of colorectal cancer; the effect of screening, surveillance, and treatment on quality of life; the real-world incidence of complications of screening; and longitudinal data about adherence with different screening strategies in unselected populations could help clarify some of the uncertainty about relative test performance.

Appendix Table 1. **Excluded Articles**

Study, Year (Reference)	Primary Reason for Exclusion
Daniels and McKee, 1995 (26)	Noncomparable outcome (cost per case detected)
Delcò and Sonnenberg, 1999 (27)	Noncomparable outcome (cost per case prevented)
Faivre et al., 1998 (28)	No cost-effectiveness analysis (review article)
Glick et al., 1998 (7)	Same model used in another included study
Gyrd-Hansen et al., 1998 (29)	Costs, incidence, and prevalence estimates not comparable to U.S. data
Kronborg and Wahrendorf, 1994 (30)	No cost-effectiveness analysis (review article)
Lieberman, 1995 (31)	Noncomparable outcome (cost per death prevented)
Neilson and Whynes, 1995 (32)	No cost-effectiveness analysis (description of model only)
Norum, 1998 (33)	Costs, incidence, and prevalence estimates not comparable to U.S. data
Salkeld et al., 1996 (34)	Costs, incidence, and prevalence estimates not comparable to U.S. data
Shimbo et al., 1994 (35)	Costs, incidence and prevalence estimates not comparable to U.S. data
Sonnenberg et al., 1999 (36)	Did not evaluate commonly used test
Sorrentino et al., 1999 (37)	Noncomparable outcome (cost per death prevented)
Whynes et al., 1998 (38) and 1999 (39)	Costs, incidence, and prevalence estimates not comparable to U.S. data

Appendix Table 2. **Calculated Incremental Cost-Effectiveness Ratios from Five Major Cost-Effectiveness Analyses***

Strategy	Effectiveness	Cost per Person	Incremental Cost-Effectiveness Ratio	Calculated Relative to What Strategy?
	days of life gained	*$*		
Wagner et al., 1996 (6): base case				
No screening	–	–	–	–
FS every 5 years	13.07	447	Weakly dominated	–
Annual FOBT	21.46	689	Strongly dominated	–
Colonoscopy every 10 years	21.64	652	10 997	No screening
DCBE every 5 years	21.97	672	22 121	Colonoscopy every 10 years
FOBT + FS every 5 years	24.53	927	36 357	DCBE every 5 years
Wagner et al., 1996 (6): sensitivity of 50% for DCBE				
No screening	–	–	–	–
FS every 5 years	13.07	447	Weakly dominated	–
DCBE every 5 years	17.81	703	Strongly dominated	–
Annual FOBT	21.46	689	Strongly dominated	–
Colonoscopy every 10 years	21.64	652	10 997	No screening
FOBT + FS every 5 years	24.53	927	34 732	Colonoscopy every 10 years
Frazier et al., 2000 (8)				
No screening	17.3481	1134	–	–
FS every 5 years	17.3806	1550	12 804	–
DCBE every 5 years	17.3826	2018	Strongly dominated	–
Annual FOBT	17.3901	1708	16 568	FS every 10 years
Colonoscopy every 10 years	17.3959	2186	Strongly dominated	–
FOBT + FS every 5 years	17.4041	2181	33 786	Annual FOBT
Khandker et al., 2000 (9)				
No screening	18.1392	794	–	–
FS every 5 years	18.2250	2119	15 442	No screening
Annual FOBT	18.2375	2546	34 160	FS every 5 years
DCBE every 5 years	18.2494	3188	53 950	Annual FOBT
FOBT + FS	18.2499	3264	Strongly dominated	–
Colonoscopy every 10 years	18.2499	3219	62 000	DCBE every 5 years
Sonnenberg et al., 2000 (10)				
No screening	0	1471	–	–
Annual FOBT	6.92	1670	10 496	No screening
FS every 5 years	13.27	2902	Strongly dominated	–
Colonoscopy every 10 years	29.02	2413	12 271	Annual FOBT
Vijan et al., 2001 (11): incremental cost-effectiveness ratios				
No screening	17.1230	1357	–	–
FS every 5 years	17.1572	2010	Strongly dominated	–
Annual FOBT	17.1682	1614	5686	No screening
Colonoscopy at 55 and 65 years of age	17.1745	1822	33 016	Annual FOBT
FOBT + FS every 5 years	17.1797	2374	106 153	Colonoscopy at 55 and 65 years of age

* All costs were updated to U.S. dollars in 2000 by using the Consumer Price Index for medical care. DCBE = double-contrast barium enema; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy.

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