THE AMERICAN JOURNAL OF GASTROENTEROLOGY
Vol. 95, No. 7, 2000

ISSN 0002-9270/00/$20.00
Published by Elsevier Science Inc.
PII S0002-9270(00)00964-3

Cost-Utility of One-Time Colonoscopic Screening for Colorectal Cancer at Various Ages

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OBJECTIVE: One-time colonoscopy has been recommended as a possible colorectal cancer (CRC) screening strategy. Because the incidence of colorectal neoplasia increases with age, the effectiveness and cost of this strategy depend on the age at which screening occurs. The purpose of this study was to investigate the age-dependent cost-utility of one-time colonoscopic screening.

METHODS: We constructed a computer simulation model of the natural history of colorectal neoplasia. This model was used to compare the cost-utility of no screening and age-based strategies employing one-time colonoscopic screening (age ranges evaluated: 45–49, 50–54, 55–59, and 60–64 yr).

RESULTS: We determined that one-time colonoscopic screening in men age <60 yr and in women age <65 yr dominates never screening and screening at older ages. For both sexes, one-time colonoscopic screening between 50 and 54 yr of age is associated with a marginal cost-utility of less than $10,000 per additional quality-adjusted life-year compared to screening between 55 and 60 yr of age. One-time colonoscopic screening between 45 and 49 yr of age is either dominated (women) or associated with a marginal cost-utility of $69,000/per quality-adjusted life-year (men) compared to screening between 50 and 54 yr of age. The marginal cost-utility of one-time colonoscopic screening is relatively insensitive to plausible changes in the cost of colonoscopy, the cost of CRC treatment, the sensitivity of colonoscopy for colorectal neoplasia, the utility values representing the morbidity associated with the CRC-related health states, and the discount rate.

CONCLUSIONS: One-time colonoscopic screening between 50 and 54 yr of age is cost-effective compared to no screening and screening at older ages in both men and women. Screening in men between 45 and 49 yr of age may be cost-effective compared to screening between 50 and 54 yr of age depending on societal willingness to pay. (Am J Gastroenterol 2000;95:1800–1811. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Colorectal cancer (CRC) remains the second leading cause of cancer death in the United States (1). However, there are reasons for optimism in the battle against CRC. Screening for CRC using fecal occult blood tests (FOBT) has been shown to decrease CRC-related mortality by 15–30% (2–4). Furthermore, removing adenomatous polyps has been shown to decrease CRC incidence by 70–90% (5).

Although previous decision analysis models have indicated that CRC screening using colonoscopy is more effective than other screening modalities at decreasing CRC-related mortality, this increased effectiveness comes at a significant additional cost (6–10). Most of this increased cost is generated by the need for repeated colonoscopic screening and postpolypectomy surveillance in patients found to have adenomas on initial screening (6). Evidence now exists that patients can be stratified as to their risk of neoplasia recurrence based on the number, size, and histology of adenomas identified at initial screening (11–19). Some have suggested that this information could be used to identify patients at a low risk for recurrence in whom no further screening is necessary, making one-time screening colonoscopy a potentially cost-effective screening alternative (7, 12, 14, 17, 19, 20).

Because the incidence of colorectal neoplasia is age-dependent (21–28), both the effectiveness and cost of one-time colonoscopic screening depend on the age at which the initial screening examination is performed. A previous decision analysis model found that, in general, screening at age 40 yr was less cost-effective than screening at age 50 yr (22). Another study that specifically looked at the cost-effectiveness of one-time colonoscopic screening found that screening at age 60 yr was more cost-effective than screening at age 50 or 70 yr (29). Unfortunately, this study did not take into account either the cost or morbidity associated with having CRC. To investigate this question adequately, we built a computer simulation of the natural history of colorectal neoplasia that accounted for both the morbidity and cost of having CRC and used it to compare the cost-utility

of one-time colonoscopic screening at different screening ages.

MATERIALS AND METHODS

We constructed a discrete-event simulation model to compare the cost-utility of one-time colonoscopic screening at different initial screening ages. The model follows a hypothetical cohort of patients over time and tracks the incidence of adenomatous polyps, the progression of adenomas to CRC, the stage progression of CRC, CRC-related morbidity, CRC-related mortality, and the costs associated with CRC diagnosis and treatment. Morbidity and mortality related to complications of diagnostic and therapeutic procedures were also incorporated into the model.

Reference Case Analysis

We initially compared the effectiveness and cost of one-time colonoscopic screening at various initial screening ages (40, 45, 50, 55, 60, 65, 70, 75, and 80 yr). Based on the results of this preliminary analysis, the decision was made to compare the cost-utility of the following screening strategies for the reference case analysis: no screening and one-time colonoscopic screening of patients 45–49, 50–54, 55–59, and 60–64 yr of age. The reference population for this analysis was 40-yr-old men or women with life-expectancies based on United States norms.

All one-time colonoscopic screening strategies modeled in this study included the performance of a full colonoscopy in every simulated patient at a specified age (patients who developed CRC before age 40 yr were not considered in this analysis). Every adenoma identified at colonoscopy was cataloged according to size and location; then the adenoma was removed. All simulated patients found to have one large or more than one adenoma at screening colonoscopy were entered into a current, standard, post-polypectomy surveillance protocol. (Colonoscopy is performed every 3 yr after the initial screen. If no adenomas or only one small adenoma are subsequently discovered, the surveillance interval is extended to 5 yr; otherwise, the surveillance interval remains at 3 yr.) (7). This same surveillance strategy was also employed after colonic resection for CRC in all investigated screening strategies.

For each run, the model was programmed to analyze either 100,000 female or 100,000 male patients from age 40 yr until death while employing colonoscopic screening at a specific age in all patients. The principal outcomes of each run were mean CRC-related costs per person and the mean number of QALYs accumulated per person. In the preliminary analysis, individual model runs representing screening at specific ages were compared (40, 45, 50, 55, 60, 65, 70, 75, and 80 yr). In the reference case analysis, each one-time colonoscopic screening strategy involved screening over a 5-yr period. To generate the principal outcomes for these strategies, five runs representing screening at each specific age within a given 5-yr range were combined and averaged. All cost-effectiveness ratios were expressed as marginal cost-utility ratios in which a given strategy is compared to the strategy ordered just below it in terms of effectiveness. In the reference case, all costs and QALYs were discounted at a 3% annual rate. The societal viewpoint was used in all analyses.

Sensitivity Analyses

We tested the stability of the reference case conclusions to changes in various underlying assumptions and probability estimates by performing one-way sensitivity analyses. One-way sensitivity analysis involves changing one underlying assumption or probability estimate and then repeating the model runs necessary to compare the different screening strategies. All tested variables were varied over a plausible range based on our literature review (Table 1).

Discrete-Event Simulation

A discrete-event simulation is a type of computer model used to imitate real-world systems: in this case, the development, diagnosis, and treatment of colorectal neoplasms. The system is modeled as it evolves over time by a representation in which the variables that define a state change instantaneously at discrete points in time, called "events." The model moves through time by advancing from one event to the next with the time interval between events being determined by the input probability estimates. The probability estimates used in modeling the system are random variables described by defined mathematical distributions. This means that the principal outcome measures from any given run of the model are also described by a distribution with a mean and standard deviation. A simple illustration of how a discrete-event simulation works is presented in Figure 1. The main benefit to using a discrete-event structure is the ability to assign attributes to each simulated patient, which are retained as the patient transitions between different health states. The modeled evolution of these attributes over time can in turn influence the timing and nature of the health state transitions. In our model, we used a programming language specifically designed for discrete-event simulation, Insight 5.4 (30).

Model Structure

We first assumed that all CRCs originate from pre-existing colorectal adenomas. This assumption is supported in the literature by direct observation of CRCs arising within or adjacent to adenomas (15, 31–33), by direct observation of CRCs arising where adenomas had been previously identified (15, 31–33), by epidemiological evidence concerning the timing and distribution of adenomas compared to CRCs (12, 16, 31–35), by comparison of sporadic CRC to familial adenomatous polyposis (FAP) (31), by the presence of similar genetic errors in both adenomas and CRCs (36–43), and by the documented protection from CRC afforded by polypectomy (5, 13, 14, 35, 44–47). We also assumed that the underlying (genetic) risk of sporadic (nonfamilial) CRC principally affects the adenoma incidence rate. This assump-

Table 1. Parameters Used in Baseline Analysis and Ranges for Sensitivity Analyses

Variable	Reference Value (Range)*	Reference
Colonoscopy sensitivity		(92–100)
CRC	95% (90–100)	
Large polyps (≥1 cm)	85% (80–90)	
Intermediate polyps (6–9 mm)	80% (75–85)	
Small polyps (≤5 mm)	75% (70–80)	
Colonoscopy complication rates		(3, 4, 45, 101–109)
Postpolypectomy hemorrhage	0.3% (0.15–0.3)	
Perforation	0.1% (0.05–0.1)	
Mortality	0.02% (0.005–0.02)	
Procedural costs		(6, 110)
Colonoscopy	$303 ($151–606)	
Polypectomy	$159 ($80–318)	
Pathology (per polyp)	$68 ($34–136)	
CRC costs (by stage)		(61)
Initial	Local: $16,051 ($12,038–20,064)	
	Regional: $18,457 ($13,843–23,071)	
	Distant: $21,093 ($15,820–26,366)	
Continuing (≤4 yr)	Local: $425/yr ($319–531)	
	Regional: $1,944/yr ($1,458–2,430)	
	Distant: $21,209/yr ($15,907–26,511)	
Terminal	$16,722 ($12,542–20,902)	
Utilities		(63, 66)
No known adenomas	0.91	
Known adenomas	0.91	
Local colon cancer	0.74 (0.74–0.91)	
Local high rectal cancer (resection only)	0.74 (0.74–0.91)	
Local high rectal cancer†	0.59 (0.59–0.91)	
Local low rectal cancer (resection only)	0.74 (0.74–0.91)	
Local low rectal cancer‡	0.50 (0.50–0.91)	
Regional colon cancer (no chemo side effects)	0.70 (0.70–0.91)	
Regional colon cancer (chemo side effects)	0.63 (0.63–0.91)	
Regional high rectal cancer	0.59 (0.59–0.91)	
Regional low rectal cancer	0.50 (0.50–0.91)	
Distant metastatic CRC	0.25 (0.25–0.91)	

* The baseline estimate represents the best estimate for each value, whereas the ranges represent plausible variation that was investigated with sensitivity analyses.
† Treated with resection, chemotherapy, and radiation therapy.
‡ Treated with resection, ostomy formation, chemotherapy, and radiation therapy.
CRC = colorectal cancer.

tion is supported by studies that have revealed that the most common genetic mutations found in both sporadic adenomas and CRCs occur in the adenomatous polyposis coli (APC) gene (36, 39, 42, 48). These APC mutations are believed to result in the loss of normal cellular apoptosis, allowing the accumulation of other mutations leading to carcinogenesis (48, 49). This assumption is also supported by a study showing a higher adenoma prevalence in patients with a family history of CRC (50) and by studies showing a higher adenoma recurrence rate post-polypectomy in those patients with ≥3 polyps at the initial screening (11, 19).

Based on these assumptions, we specified the steps in colorectal neoplasm development (normal tissue, adenoma, asymptomatic CRC, and symptomatic CRC) and the variables that define a colorectal neoplasm at each step (location, and size [adenomas] or stage [cancers]). The presence and nature of any colorectal neoplasms discovered at colonoscopy (colonoscopy prompted by symptoms related to the neoplasm, findings on a previous diagnostic test, or a colonoscopic screening regimen) define the disease-specific health state for each simulated patient (no known colorectal neoplasia, known adenoma(s), known CRC(s), and death) (Fig. 2). Modeled transitions between these health states can occur because of either the emergence of CRC-related symptoms, the scheduling of clinical interventions (*i.e.*, colonoscopy), or death (either natural or CRC-related).

The model first assigns to each simulated patient a lifetime risk of CRC. That lifetime risk value is used to adjust the age-dependent adenoma incidence rate. The model then schedules all lifetime incident adenomas, transitions from adenomas to asymptomatic CRC, transitions from asymptomatic to symptomatic CRC, CRC-related death, and death due to other causes. The relative ordering of these events determines which events will occur or not occur and through which health states the simulated patient will pass. The scheduling of a clinical intervention alters the natural progression of all identified neoplasms at a specific point in time resulting in a reordering of neoplasm and health state transition events. A simple illustration of this process is shown in Figure 1.

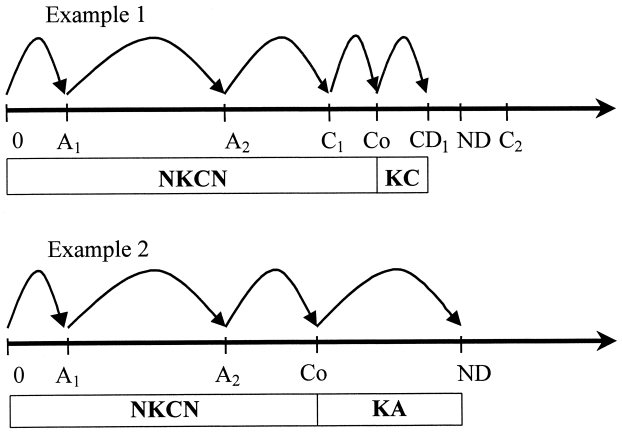

Figure 1. The above examples represent simplifications of possible timelines that the computer model could follow for a simulated patient. The markers on the timeline represent modeled "events" whereas the boxes below the timeline represent the patient's health state during the covered period of time. The arrows represent the model's movement between one event and the next on the timeline. In Example 1, the simulated patient is born at time = 0 and begins life in the "no known colorectal neoplasia" health state (KNCN). The model then moves to the ages at which the patient develops his/her first adenoma (A_1) and second adenoma (A_2). Because these adenomas are not discovered by any diagnostic test, their presence does not cause the patient's health state to change. The model then moves to the scheduled development of CRC (C_1) from A_1. The cancer eventually causes symptoms leading to the performance of a colonoscopy (Co) that results in a change to the "known CRC" health state (KC). Finally, the patient reaches the scheduled death (CD_1) from C_1 and his/her life is terminated. He/she never reaches the scheduled ages for natural death (ND) or development of CRC from A_2 (C_2). In Example 2, a colonoscopy (Co) is scheduled before the development of C_1, leading to the removal of the adenomas and their associated CRCs from the timeline but causing the patient to enter the "known adenoma" health state (KA). The patient now reaches his scheduled natural death (ND).

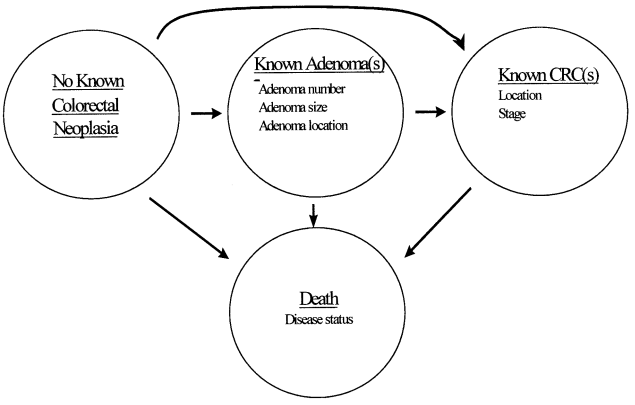

Figure 2. Health state transition schematic. This is an overview of the colorectal neoplasia-related health states used in the model and their possible transitions. All simulated patients enter the model having "no known colorectal neoplasia." Patients may advance from this state to having "known adenoma(s)" (defined by adenoma number, size, and location) and from there to "known CRCs" (defined by CRC location and stage). Patients may also transition directly from "no known colorectal neoplasia" to "known CRCs." Patients may transition to "death" (defined as secondary to either CRC or to natural causes) from any health state. The timing of transitions between these health states can be altered by clinical interventions such as diagnostic tests or surgical procedures.

Natural History Parameters

Within the basic model framework described above, we constructed our simulation of the natural history of colorectal neoplasia to fit the available data concerning CRC incidence (51) and adenoma prevalence (21–28). Separate male and female models were constructed because of gender-related differences in natural life expectancy and colorectal neoplasia incidence.

We represented the underlying lifetime risk of CRC in the population using a bounded Johnson distribution with a mean value of 5.5% for women and 6% for men (51). The mode of this distribution was set near to zero for both men and women ($<0.5\%$) because approximately half of all patients do not develop colorectal adenomas in their lifetime and thus have little or no risk of developing CRC (21–28).

Adenoma incidence is determined using a time-varying, piecewise exponential function that assigns higher incidence rates with increasing age. When generated, each adenoma is assigned a specific location in the colon (right, left, sigmoid, high-rectum, and low-rectum). Based on our review of the literature, we made two assumptions concerning the rate of adenoma transition to asymptomatic CRC: 1) Less than 2.5% of adenomas become CRC within the first 10 yr of their existence (5, 11, 13, 14, 32, 33, 44, 46, 47, 52); and 2) there are adenomas that progress to CRC relatively quickly and those that progress only very slowly to CRC (*i.e.*, the population is dichotomous) (34, 44, 53–55). For this reason, incident adenomas are assigned to either a "slow-progressing" or "fast-progressing" group in a proportion that is age-dependent. The time to transition from adenoma to asymptomatic CRC is determined by random assignment to one of two bounded Johnson distributions representing the two adenoma progression rate groups. "Fast-progressing" adenomas transition to CRC over a mean period of 26 yr, whereas "slow-progressing" adenomas transition to CRC over a mean of 52 yr. The result of this modeling is that the majority of "slow-progressing" adenomas do not transition to CRC during the natural life span of the simulated patient.

While transitioning to CRC, adenomas are simultaneously transitioned in size from small ($\leq$5 mm) to intermediate (6–9 mm) to large ($\geq$1 cm). The parameters of each bounded Johnson distribution used to model these size transitions depends on the patient's sex, the rate of progression to CRC (fast *vs* slow), and the transition being made (small to intermediate *vs* intermediate to large). This allows adenomas of all sizes to transition potentially to CRC while favoring transition from larger adenomas.

Each incident asymptomatic CRC progresses toward symptomatic CRC (CRC diagnosed because of the emergence of symptoms) using a normal distribution with a mean

value of 4.8 yr (56). An asymptomatic CRC is initially assigned a "local" (Duke's A or B) stage. The lesion is then transitioned to "regional" (Duke's C) and "distant" (Duke's D) disease at the same time using normal distributions with mean values of 5.2 and 5.55 yr after the initial appearance of the asymptomatic CRC, respectively. This method of modeling allows for "local" stage CRC to transition directly to either "regional" or "distant" disease. A transition to "distant" disease supercedes a transition to "regional disease." Thus, once a patient transitions into the "distant" disease health state, he or she continues in that health state until death. The transition time distributions were chosen to fit data on the distribution of CRC stage at diagnosis in symptomatic patients (2–4, 57). When a CRC either transitions to symptomatic disease or is discovered during a clinical intervention, its stage at "diagnosis" is used to determine both treatment, *i.e.*, appropriate segmental colonic resection and adjuvant therapy (58–60) and survival, determined using survival curves derived from data collected as part of the SEER database (51).

The model was adjusted to fit the age-dependent CRC incidence rates for a population of 100,000 to that expected based on the SEER database 1988–1993. The goal of this fitting was to minimize the χ^2 statistic for the comparison of 12 different 5-year age ranges between 30 and 95 yr of age. The model was further adjusted to approximate the CRC-related mortality rate derived from the SEER database (51) and the age-dependent adenoma prevalence rate and size distribution derived from previous autopsy studies (21–28).

Diagnostic Test Parameters

The natural history model was designed to accommodate various diagnostic testing regimens. From our review of the literature, we determined values for the sensitivity of colonoscopy for the identification of colonic neoplasms (Table 1). These values represent the low end of the reported range of sensitivity for these lesions. We adjusted for less than perfect specificity in the endoscopic identification of adenomas by assuming that 30% of colonoscopies would result in the identification of a nonadenomatous lesion (21–28). Specific complication rates derived from the literature were also determined (Table 1). These represent the upper range of reported values. Within the limitations posed by its test characteristics, colonoscopy was able to detect and remove colonic lesions at various stages and sizes.

Cost Parameters

All direct costs related to the diagnosis and treatment of colorectal neoplasia were incorporated into the model. (Table 1). Costs related to colonoscopy were derived from Medicare reimbursement rates and taken from a previously published study (6). Costs related to the treatment of cancer were assigned to initial, continuing, or terminal care based on whether or not they occurred within 6 months of diagnosis or death (61). All costs were adjusted to 1998 US dollars using the Medical Consumer Price Index. Direct non–health care costs related to the diagnosis and treatment of colorectal neoplasia (*e.g.*, patient travel costs) were not included in this model.

Quality of Life Adjustments

Our simulation was designed to calculate quality-adjusted life-years (QALYs) as the primary outcome measure. To calculate QALYs, the societal preferences (utilities) for the disease-specific health states were included (Table 1). Stage-specific health states of CRC were previously determined by our group and were found to be dependent on stage-specific therapy for nonterminal health states (62). Subsequently, our group measured utilities for these CRC health states (63). Based on previous clinical trials, we assumed that half of those patients with regional colon cancer treated with adjuvant chemotherapy without radiation therapy would have "significant" side effects from treatment (64, 65). Simulated patients with and without "significant" side effects of chemotherapy were assigned different utility weightings based on our previous assessment (63). We further assumed that half of those patients with local, rectal cancer could be treated by segmental or local resection only, whereas the other half would require segmental resection with adjuvant chemotherapy and radiation therapy (58, 60). Simulated patients treated with local or segmental resection only were assigned the utility score previously assessed for simple colonic resection (63), whereas those patients with rectal cancer treated with adjuvant chemotherapy and radiation therapy were assigned the health utility score measured for that health state (63). Because the absence of cancer does not imply perfect health, utilities for the non-CRC health states used in the model were taken from a study by Fryback *et al*. that determined age-dependent utilities for persons with various degrees of morbidity (66). The value used was that determined for middle-aged individuals with one chronic health problem (the model group in their study).

Validation

This simulation model was validated by three methods. We attempted to establish content validity by performing a thorough, reproducible literature search; construct validity through our ability to match CRC incidence (51) and adenoma prevalence (21–28) data simultaneously; and criterion validity by modeling the National Polyp Study (NPS) and correctly predicting their CRC outcomes by simulation (5).

To establish construct validity, we modeled 100,000 simulated patients from birth until death and compared the age-dependent CRC incidence obtained from the model to that expected, based on the application of the age-specific CRC incidence rates reported for the SEER database to a single birth cohort of 100,000. Men and women were modeled separately (Fig. 3*A* and 3*B*). The resulting total χ^2

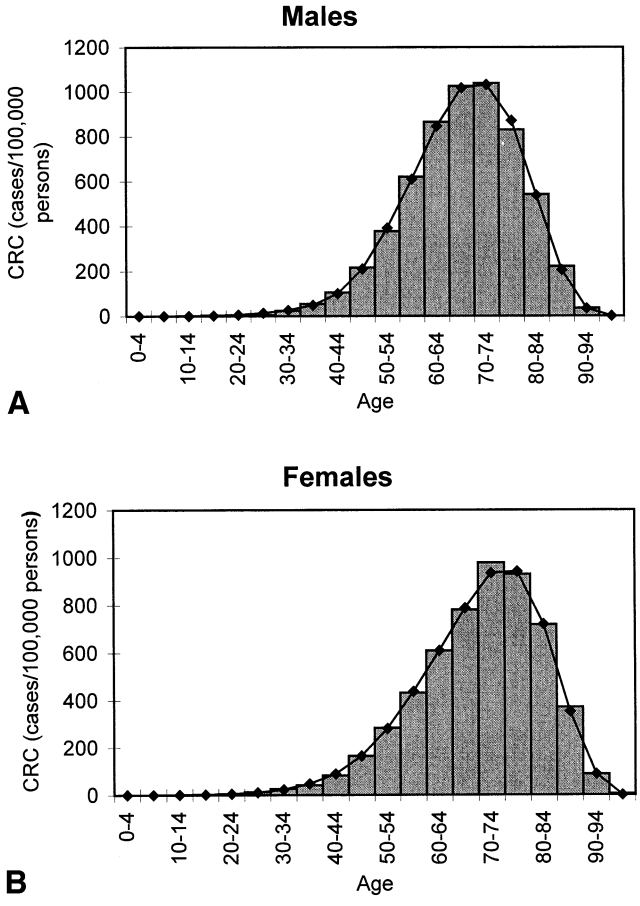

Figure 3 (A, B). Age-dependent CRC incidence for a single birth cohort of 100,000 as generated by the model (bars) and based on SEER data (◆) (51).

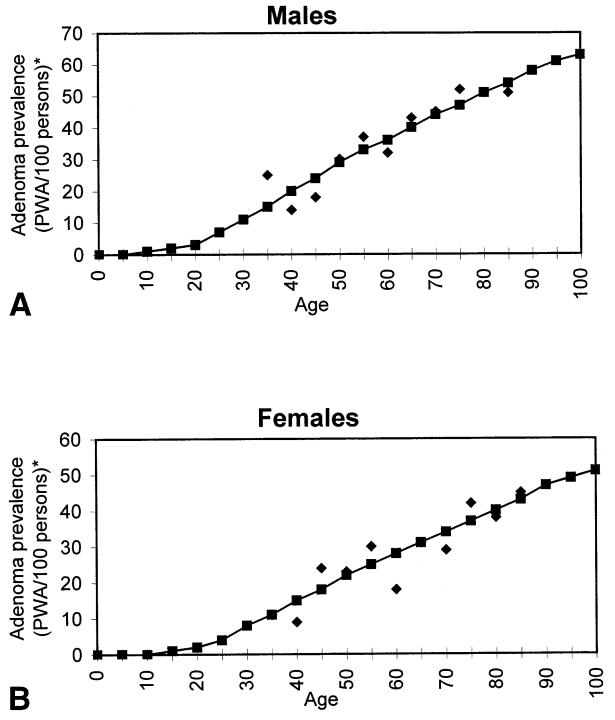

Figure 4 (A, B). Age-dependent colorectal adenoma prevalence and adenoma prevalence for a single birth cohort of 100,000 as generated by the model (■) and based on cumulative data from various autopsy studies (◆) (21–23, 25–27). *PWA = Persons with adenomas.

statistic for the fit of 12 different 5-yr age ranges between 30 and 95 yr of age was 6.04 for the male model and 4.97 for the female model. A χ^2 value of 19.68 was needed to reject the null hypothesis that the model-generated, age-dependent CRC incidence and the age-dependent CRC incidence predicted by SEER data were the same. We also graphically compared age-dependent, model-generated adenoma prevalence to the available autopsy data and achieved a reasonable visual fit (Fig. 4*A* and 4*B*).

To establish criterion validity, we modeled a population of 100,000 patients with demographic characteristics and initial endoscopic findings similar to those reported by the NPS group (5) and followed them for 6 yr after an initial clearing colonoscopy. Half of the simulated patients had repeat colonoscopy at 1, 3, and 6 yr, and half had repeat colonoscopy at 3 and 6 yr. The fraction of the cancers identified by the model that would have been expected in a sample of 1405 patients (the number who participated in the NPS) was calculated and compared to the number found during the NPS. The model produced three cancers (95% confidence interval, 0–6) compared to the five reported by the NPS.

RESULTS

Optimal Screening Age

Using the simulation model described, we computed mean accumulated QALYs and costs per person related to CRC care (screening, surveillance, and treatment) for 40-yr-old men and women screened for CRC using one-time colonoscopy at 40, 45, 50, 55, 60, 65, 70, 75, and 80 yr old. The results of this analysis indicated that the effectiveness of one-time screening peaks around age 50 yr, whereas CRC-related costs reach a minimum around age 60 yr for both men and women (Fig. 5).

To achieve more precise estimates of the effectiveness and cost of one-time colonoscopic screening at different screening ages, we repeated our analyses at 1-yr age intervals and averaged the results of these analyses over 5-yr time periods. Because screening at ages $<$45 yr and $>$65 yr were clearly dominated (*i.e.*, were less effective and more costly), we limited our analysis to the age range between 45 and 64 yr of age. These decisions defined the screening strategies that we would compare: no screening, and one-time colonoscopic screening between 45–49, 50–54, 55–59, and 60–64 yr of age.

For a cohort of 100,000 men, one-time colonoscopic screening anytime within 45–64 yr of age resulted in a dramatic decrease in both the number of persons with diagnosed CRC and the number with CRC-related deaths compared to never screening (Table 2). Screening between

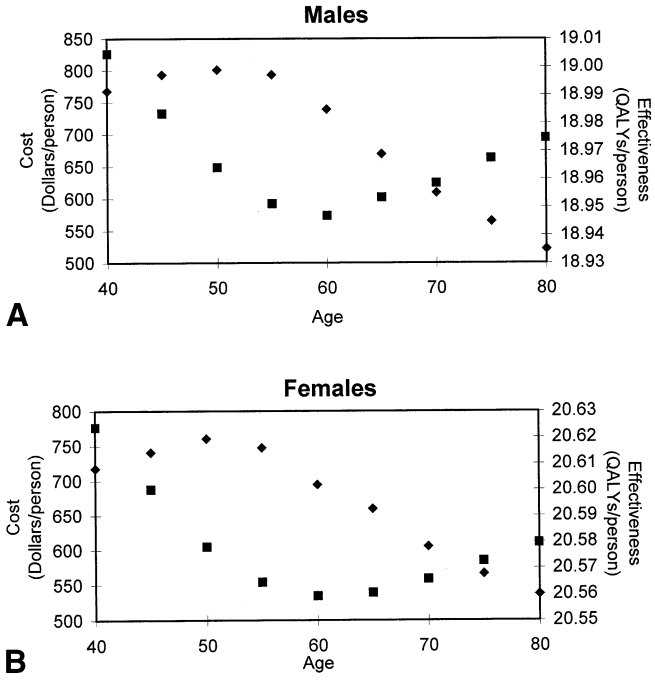

Figure 5 (A, B). Model-generated cost and effectiveness associated with various initial screening ages. The ■'s represent the cost in $/person and the ◆'s represent effectiveness in QALYs/person. QALY = quality-adjusted life-year.

50 and 54 yr was associated with the highest total number of colonoscopies related to either screening or surveillance (142,310) and the lowest total number of persons with diagnosed CRC (2,051). Screening at 55–59 yr of age resulted in the fewest CRC-related deaths (654). Compared to never screening, this represented a decrease in CRC-related deaths of 1,523 (70.0%).

For men, one-time colonoscopic screening anytime between 45 and 64 yr of age was more effective (increased remaining QALY/person) than never screening (Table 2). Screening specifically between 45 and 49 yr of age was more effective than the other possible age-range options for one-time colonoscopic screening (19.000 QALYs/person). Screening between 55 and 59 yr of age was the least costly strategy ($633/person).

Screening male patients between 55 and 59 yr of age dominated never screening and screening at 60–64 yr of age (Table 2). Compared to screening at 55–59 yr, screening between 50 and 54 yr of age had a marginal cost-utility (additional cost per QALY comparing one clinical strategy to another) of $3,625/QALY. Likewise, screening at 45–49 yr of age had a marginal cost-utility of $69,000/QALY compared to screening between 50 and 54 yr of age.

For a cohort of 100,000 women, one-time colonoscopic screening anytime within the range from 45 to 64 yr of age also resulted in a dramatic decrease in both the number of persons with diagnosed CRC and the number with CRC-related deaths, compared to never screening (Table 2). Screening at 55–59 yr of age was associated with the highest total number of colonoscopies related to either screening or surveillance (138,816), the lowest total number of persons diagnosed with CRC (1,953), and the fewest CRC deaths (676). Compared to never screening, this represented a decrease in CRC-related deaths of 1,522 (69.2%).

For women, one-time colonoscopic screening anytime between 45 and 64 yr of age was more effective than never screening (Table 2). Screening specifically between 45 and 54 yr of age was more effective than the other possible age-range options for one-time colonoscopic screening (20.616 QALYs/person). Screening was least costly at 60–64 yr of age ($574/person).

Screening female patients 60–64 yr of age dominated never screening (Table 2). Compared to screening at 60–64 yr of age, screening between 55 and 59 yr had a marginal

Table 2. Clinical Outcomes, Cost, and Effectiveness of Colonoscopic Screening for Colorectal Cancer (CRC) at Various Initial Screening Ages for a Cohort of 100,000 40-Yr-Old Patients*

Sex Screen Age (yr)	Colonoscopies (n)	CRC (n)	CRC Deaths (n)	QALYs/person	Cost/Person ($)	Marginal† Cost/QALY ($)
Male						
Never	13,452	5672	2177	18.933	749	Dominated‡
60–64	131,023	2389	731	18.978	640	Dominated
55–59	139,254	2060	654	18.991	633	–
50–54	142,310	2051	690	18.999	662	3625
45–49	140,649	2365	848	19.000	731	69,000
Female						
Never	12,850	5348	2198	20.551	676	Dominated
60–64	135,326	2066	710	20.600	574	–
55–59	138,816	1953	676	20.611	581	636
50–54	138,286	2089	780	20.616	625	8800
45–49	135,742	2424	935	20.616	690	Dominated

* For each outcome above, 100,000 simulated patients were scheduled to be screened at each integer age within a given age range. Five runs were averaged to obtain each age range result.

† Each marginal value compares the value for that strategy to the one listed immediately above it in the table. Screening strategies are listed from least to most effective moving from top to bottom for both men and women.

‡ The term "dominated" means that the indicated screening strategy was of equal or lesser effectiveness than a less costly strategy.

QALY = quality-adjusted life-year.

Table 3. Marginal Cost-Utility for Sensitivity Analyses ($/QALY)*

Sex Screen Age (yr)	Colonoscopy Sensitivity −5%	Colonoscopy Sensitivity +5%	Colonoscopy Cost +50%	Colonoscopy Cost +100%	CRC Treatment Cost −25%	CRC Treatment Cost +25%	Discounting Rate 0%	Discounting Rate 5%	CRC Morbidity None
Male									
Never	Dominated†	Dominated	Dominated	–	Dominated	Dominated	Dominated	Dominated	Dominated
60–64	Dominated	Dominated	Dominated	3,000	–	Dominated	Dominated	–	Dominated
55–59	–	–	–	3,692	692	–	–	1,571	–
50–54	3,375	4,429	375	9,875	4,250	2,750	1,467	7,400	5,800
45–49	Dominated	21,667	47,000	114,000	64,000	75,000	Dominated	35,500	Dominated
Female									
Never	Dominated	Dominated	Dominated	–	Dominated	Dominated	Dominated	Dominated	Dominated
60–64	–	–	Dominated	3,120	–	Dominated	Dominated	–	–
55–59	167	417	–	4,545	1,455	–	–	3,000	1,000
50–54	9,200	6,333	4,600	17,200	8,800	8,800	7,714	14,667	14,667
45–49	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	34,500	Dominated

* For each outcome above, 100,000 simulated patients were scheduled to be screened at each integer age within a given age range. Five runs were averaged to obtain each age range result. Each marginal value compares the value for that strategy to the one listed immediately above it in the table. Screening strategies are listed from least to most effective moving from top to bottom for both men and women.

†The term "dominated" means that the indicated screening strategy was of equal or lesser effectiveness than a less costly strategy.

CRC = colorectal cancer; QALY = quality-adjusted life-year.

cost-utility of $636/QALY. Likewise, compared to screening at 55–59 yr, screening between 50 and 54 yr of age had a marginal cost-utility of $8800/QALY. Screening at 45–49 yr of age was dominated by screening between 50 and 54 yr of age.

Sensitivity Analyses

The effects of changing the values of selected input variables on the relative cost-effectiveness of the different screening strategies were examined using one-way sensitivity analyses. We varied each input value over what we considered its plausible clinical range based on our review of the literature (Table 1). The discount rate was varied from 0% to 5% according to convention (67). We found that the marginal cost-utility of one-time colonoscopic screening was relatively insensitive to plausible changes in the sensitivity of colonoscopy for colorectal neoplasia, the cost of colonoscopy, cost of CRC treatment, utility values representing the morbidity associated with CRC-related health states, and discount rate. (Table 3).

DISCUSSION

We constructed a computer simulation of the natural history of colorectal neoplasia and used it to examine the effect of changing the initial screening age on the cost-utility of one-time colonoscopic screening with limited surveillance. We compared the cost-utility of no screening and age-based strategies employing one-time colonoscopic screening (age ranges evaluated were 45–49, 50–54, 55–59, and 60–64 yr). We determined that one-time colonoscopic screening in men <60 yr and in women <65 yr dominates never screening and screening at older ages. For both sexes, one-time colonoscopic screening at 50–54 yr of age is associated with a marginal cost-utility of less than $10,000 per additional quality-adjusted life-year (QALY) compared to screening at 55–60 yr. One-time colonoscopic screening at 45–49 yr of age is either dominated (in women) or associated with a marginal cost-utility of $69,000/QALY (in men) compared to screening at 50–54 yr. The marginal cost-utility of one-time colonoscopic screening is relatively insensitive to plausible changes in the cost of colonoscopy, cost of CRC treatment, sensitivity of colonoscopy for colorectal neoplasia, utility values representing the morbidity associated with the CRC-related health states, and discount rate.

Our model was designed with several features that make it unique among decision models examining the cost-effectiveness of CRC screening or surveillance. Because we employed a discrete-event simulation, we were able to accurately model the age-dependent incidence and growth of individual adenomas in specific segments of the colon. This allowed us to fit the available adenoma prevalence and CRC incidence data more precisely than in past models. Both the model described in the guidelines paper by Winawer *et al*. (7) and that reported by Whynes *et al*. (68, 69) simulated individual adenomas but either did not distribute them to different colonic segments (7, 68, 69) or did not allow them to grow in size (68, 69). Unlike previous models, we designed our simulation to assign risk for CRC incidence based on an asymmetric distribution. This allowed us to replicate more accurately the true risk distribution in the community.

Our model simulated each adenoma as progressing to CRC with either a slow or a fast rate of progression. When all modeled adenomas progress to CRC at the same rate, it becomes impossible to match the adenoma prevalence and CRC incidence data simultaneously. Creating two rates of progression among the adenomas allowed the simultaneous fitting of both the adenoma and CRC data. The model of Whynes *et al*. made similar assumptions concerning adenoma progression (69).

We programmed our model to simulate the stage progression of CRC in specific colonic segments, allowing us to

assign stage and location to CRC at diagnosis. This is important because both CRC survival and CRC-related health state utility are dependent on CRC stage at diagnosis (51, 63). Other decision models have assigned CRC stage (usually as early *vs* advanced) either initially or in a progressive pattern, but none has assigned location and stage simultaneously (6–9).

We designed our model to accommodate quality-of-life weightings so that QALYs could be used as the principal outcome measure. The utilities were assessed as previously described using the standard-gamble technique (63). Only the model by Whynes *et al*. (69) had previously employed an adjustment for quality of life. Their group mapped health status data collected from patients with CRC using the Nottingham Health Questionnaire to the Rosser-Kind index (70). Unfortunately, their utility assessment methodology failed to elicit demonstrated differences in preferences for different stage-dependent, CRC-related health states because of a lack of disease-specific sensitivity in the Rosser-Kind instrument.

Our simulation was limited by the generalizability of the base model assumptions. Although all of the assumptions employed in our model were based on the prevailing literature opinion, they are not all without controversy. Given the preponderance of data from studies in the US of sporadic and familial CRC (5, 12–16, 31–47), we assumed that all CRCs originated from pre-existing adenomatous polyps. Certain other data, however, support the assumption that a significant percentage of CRC cases do not originate from pre-existing adenomatous polyps (71–76). If a significant fraction of CRCs do not, in fact, originate from pre-existing adenomatous polyps, then the effectiveness of one-time colonoscopic screening as reported in this study would be overstated and our findings would be biased toward screening at too early an age. We also assumed that the underlying (genetic) risk of sporadic (nonfamilial) CRC principally affects the adenoma incidence rate. This was based on a preponderance of data (36, 39, 42, 48). The alternative conceptualization would be that the underlying risk primarily affects the rate of progression of adenomas to CRC. This hypothesis has some molecular biological (77) and clinical (78, 79) support in the literature. If the underlying genetic risk of CRC primarily affects the rate of progression of adenomas to CRC, then the variance in the transition time from adenoma to CRC would have been greater. If this were the case, our results would be biased towards screening at too late an age.

Interpretation of our results should be placed in the context of societal willingness to pay. Cost-effectiveness threshold values are one method by which societal willingness to pay can be defined. Many studies have used a cost-effectiveness threshold for marginal cost-utility of $50,000 per additional QALY (80–86). Others have suggested threshold values ranging from $20,000 to 100,000/QALY (87, 88). The Panel on Cost-Effectiveness in Health and Medicine of the US Public Health Service actually recommended against the use of such thresholds for generalized use (67). Another method for defining societal willingness to pay is to compare the decision under consideration to decisions already made in similar clinical settings. For example, annual mamographic screening for breast cancer in women 50–69 yr of age costs $46,500/QALY (1995 dollars) gained compared to no screening, whereas annual mamographic screening in women 40–69 yr costs $168,400/QALY gained compared to screening limited to those 50–69 yr of age (80). Despite the fact that the marginal cost-utility for expanding annual mamographic screening to include women 40–50 yr of age is well over $100,000/QALY, the American Cancer Society currently endorses annual mamographic screening beginning at age 40 yr (89). Thus, one-time colonoscopic screening as early as 45–49 yr of age in men (marginal cost-utility of $69,000/QALY compared to screening between 50–54 yr of age) may be cost-effective, depending on how societal willingness to pay for additional QALYs is defined.

The question as to the cost-effectiveness of one-time colonoscopic screening had previously been addressed only in a study by Ransohoff and Lang (29). They used a Markov model to examine the cost-effectiveness of one-time colonoscopic screening and determined that screening at age 60 yr was less expensive in terms of cost per year of life saved than was screening at age 50 or 70 yr. However, this model failed to take into account either the cost or morbidity associated with CRC treatment. When we accounted for such costs and effects, we found that one-time colonoscopic screening is cost-effective between 50 and 54 yr of age.

The results of this study are relevant to the ongoing debate about CRC screening and which strategy is most cost-effective. Several researchers have suggested that one-time screening colonoscopy with a surveillance strategy guided by endoscopic findings is a cost-effective screening option (8, 90, 91). Others have argued that even one-time screening colonoscopy is unrealistic because of the high cost of colonoscopy. Because the incidence of colorectal neoplasia is an age-dependent phenomenon (21–28), the answer to this debate may hinge on the age at which one-time colonoscopic screening is employed.

In conclusion, we determined that one-time colonoscopic screening between 50 and 54 yr of age is cost-effective compared to no screening and screening at older ages. Screening in men between 45 and 49 yr of age may be cost-effective compared to screening between 50 and 54 yr of age, depending on societal willingness to pay.

ACKNOWLEDGMENT

This work was supported by an Outcomes Research Grant from the American College of Gastroenterology.

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Received June 16, 1999; accepted Mar. 24, 2000.

REFERENCES

1. Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1999. Ca Cancer J Clin 1999;49:8–31.
2. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993; 328:1365–71.
3. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–7.
4. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467–71.
5. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–81.
6. Wagner JL, Tunis S, Brown M, et al. Cost-effectiveness of colorectal cancer screening in average-risk adults. In: Young GP, Rozen P, Levin B, eds. Prevention and early detection of colorectal cancer. Somerset, UK: Bath Press, 1996:321–67.
7. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: Clinical guidelines and rationale. Gastroenterology 1997;112:594–642.
8. Lieberman DA. Cost-effectiveness model for colon cancer screening. Gastroenterology 1995;109:1781–90.
9. Eddy DM, Nugent FW, Eddy JF, et al. Screening for colorectal cancer in a high-risk population. Results of a mathematical model. Gastroenterology 1987;92:682–92.
10. Eddy DM. Screening for colorectal cancer. Ann Intern Med 1990;113:373–84.
11. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N Engl J Med 1993;328: 901–6.
12. Rex DK, Cummings OW, Helper DJ, et al. 5-Year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons. Gastroenterology 1996;111:1178–81.
13. Morson BC, Bussey HJ. Magnitude of risk for cancer in patients with colorectal adenomas. Br J Surg 1985;72(suppl): S23–5.
14. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658–62.
15. Shinya H, Wolff WI. Morphology, anatomic distribution and cancer potential of colonic polyps. Ann Surg 1979;190:679–83.
16. Konishi F, Morson BC. Pathology of colorectal adenomas: A colonoscopic survey. J Clin Pathol 1982;35:830–41.
17. Grossman S, Milos ML, Tekawa IS, et al. Colonoscopic screening of persons with suspected risk factors for colon cancer: II. Past history of colorectal neoplasms. Gastroenterology 1989;96:299–306.
18. Lofti AM, Spencer RJ, Ilsrup DM, et al. Colorectal polyps and the risk of subsequent carcinoma. Mayo Clin Proc 1986; 61:337–43.
19. van Stolk RU. Adenoma characteristics at first colonoscopy as predictors of adenoma recurrence and characteristics at follow-up. Gastroenterology 1998;115:13–8.
20. Byers T, Levin B, Rothenberger D, et al. American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: Update 1997. American Cancer Society Detection and Treatment Advisory Group on Colorectal Cancer. Ca Cancer J Clin 1997;47:154–60.
21. Rickert RR, Auerbach O, Garfinkel L, et al. Adenomatous lesions of the large bowel an autopsy survey. Cancer 1979; 43:1847–57.
22. Blatt LJ. Polyps of the colon and rectum: Incidence and distribution. Dis Colon Rectum 1961;4:277–82.
23. Arminski TC, McLean DW. Incidence and distribution of adenomatous polyps of the colon and rectum based on 1,000 autopsy examinations. Dis Colon Rectum 1964;7:249–61.
24. Eide TJ. The age-, sex-, and site-specific occurrence of adenomas and carcinomas of the large intestine within a defined population. Scand J Gastroenterol 1986;21:1083–8.
25. Eide TJ, Stalsberg H. Polyps of the large intestine in Northern Norway. Cancer 1978;42:2839–48.
26. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: An autopsy study. Cancer 1982;49:819–25.
27. Williams AR, Balasooriya BAW, Day DW. Polyps and cancer of the large bowel: A necropsy study in Liverpool. Gut 1982;23:835–42.
28. Correa P, Strong JP, Reif A, et al. The epidemiology of colorectal polyps: Prevalence in New Orleans and international comparisons. Cancer 1977;39:2258–64.
29. Ransohoff DF, Lang CA. Cost-effectiveness of one-time colonoscopy screening to reduce colorectal cancer mortality. Gastroenterology 1994;106:A24.
30. Roberts SD. Simulation modeling and analysis with INSIGHT. Indianapolis, IN: Regenstrief Institute for Health Care, 1983.
31. Morson BC. The evolution of colorectal carcinoma. Clin Radiol 1984;35:425–31.
32. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. Cancer 1975;36:2251–70.
33. Stryker SJ, Wolff BG, Culp CE, et al. Natural history of untreated colonic polyps. Gastroenterology 1987;93:1009–13.
34. Kozuka S, Nogaki M, Ozeki T, et al. Premalignancy of the mucosal polyp in the large intestine: II. Estimation of the periods required for malignant transformation of mucosal polyps. Dis Colon Rectum 1975;18:494–500.
35. Murakami R, Tsukuma H, Kanamori S, et al. Natural history of colorectal polyps and the effect of polypectomy on occurrence of subsequent cancer. Int J Cancer 1990;46:159–64.
36. Jen J, Powell SM, Papadopoulos N, et al. Molecular determinants of dysplasia in colorectal lesions. Cancer Res 1994; 54:5523–6.
37. Fearon ER. Molecular genetic studies of the adenoma-carcinoma sequence. Adv Intern Med 1994;39:123–47.
38. Liu B, Nicolaides NC, Markowitz S, et al. Mismatch repair gene defects in sporadic colorectal cancers with microsatellite instability. Nat Genet 1995;9:48–55.
39. Powell SM, Zilz N, Beazer-Barclay Y, et al. APC mutations occur early during colorectal tumorigenesis. Nature 1992; 359:235–7.
40. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525–32.
41. Levy DB, Smith KJ, Beazer-Barclay Y, et al. Inactivation of both APC alleles in human and mouse tumors. Cancer Res 1994;54:5953–8.
42. Miyoshi Y, Nagase H, Ando H, et al. Somatic mutations of the APC gene in colorectal tumors: Mutation cluster region in the APC gene. Hum Mol Genet 1992;1:229–33.
43. Young J, Leggett B, Gustafsen C, et al. Genomic instability occurs in colorectal carcinomas but not in adenomas. Hum Mutat 1993;2:351–4.
44. Hoff G, Sauar J, Vatn MH, et al. Polypectomy of adenomas in the prevention of colorectal cancer: 10 Years' follow-up of the Telemark Polyp Study I. A prospective, controlled population study. Scand J Gastroenterol 1996;31:1006–10.

45. Jorgensen OD, Kronborg O, Fenger C. The Funen adenoma follow-up study. Incidence and death from colorectal carcinoma in an adenoma surveillance program. Scand J Gastroenterol 1993;28:869–74.
46. Meagher AP, Stuart M. Does colonoscopic polypectomy reduce the incidence of colorectal carcinoma? Aust New Zealand J Surg 1994;64:400–4.
47. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995;123:904–10.
48. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996;87:159–70.
49. Morin PJ, Vogelstein B, Kinzler KW. Apoptosis and APC in colorectal tumorigenesis. Proc Natl Acad Sci USA 1996;93: 7950–4.
50. Sauar J, Hausken T, Bjorkheim A, et al. Colonoscopic screening examination of relatives of patients with colorectal cancer: I. A comparison with an endoscopically normal population. Scand J Gastroenterol 1992;27:661–6.
51. SEER cancer incidence public-use database, 1973–93. Bethesda, MD: US Department of Health and Human Services, 1996.
52. Wegener M, Borsch G, Schmidt G. Colorectal adenomas. Distribution, incidence of malignant transformation, and rate of recurrence. Dis Colon Rectum 1986;29:383–7.
53. Hofstad B, Vatn MH, Andersen SN, et al. Growth of colorectal polyps: Redetection and evaluation of unresected polyps for a period of three years. Gut 1996;39:449–56.
54. Hoff G, Foerster A, Vatn MH, et al. Epidemiology of polyps in the rectum and colon. Recovery and evaluation of unresected polyps 2 years after detection. Scand J Gastroenterol 1986;21:853–62.
55. Bersentes K, Fennerty MB, Sampliner RE, et al. Lack of spontaneous regression of tubular adenomas in two years of follow-up. Am J Gastroenterol 1997;92:1117–20.
56. Koretz RL. Malignant polyps: Are they sheep in wolves' clothing? Ann Intern Med 1993;118:63–8.
57. Kewenter J, Brevinge H, Engaras B, et al. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. Scand J Gastroenterol 1994;29:468–73.
58. Winawer SJ, Enker WE, Levin B. Colorectal cancer. In: Winawer SJ, ed. Management of gastrointestinal diseases. New York: Gower Medical, 1992:27.1–27.40.
59. Cohen AM, Minsky BD, Schilsky RL. Cancer of the colon. In: DeVita VT Jr, Hellman S, Rosenburg SA, eds. Cancer: Principles and practice of oncology, 4th ed. Philadelphia: Lippincott-Raven, 1997:1144–97.
60. Cohen AM, Minsky BD, Schilsky RL. Cancer of the rectum. In: DeVita VT Jr, Hellman S, Rosenburg SA, eds. Cancer: Principles and practice of oncology, 4th ed. Philadelphia: Lippincott-Raven, 1997:1197–234.
61. Taplin SH, Barlow W, Urban N, et al. Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. J Natl Cancer Inst 1995;87:417–26.
62. Ness RM, Holmes AM, Klein R, et al. Outcome states of colorectal cancer: Identification and description using patient focus groups. Am J Gastroenterol 1998;93:1491–7.
63. Ness RM, Holmes AM, Klein R, et al. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol 1999;94:1650–7.
64. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322:352–8.
65. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. Lancet 1995;345:939–44.
66. Fryback DG, Lawrence WF. Dollars may not buy as many QALYs as we think: A problem with defining quality-of-life adjustments. Med Decis Making 1997;17:276–84.
67. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253–8.
68. Whynes DK, Neilson AR, Walker AR, et al. Faecal occult blood screening for colorectal cancer: Is it cost-effective? Health Econ 1998;7:21–9.
69. Whynes DK. Cost-effectiveness of screening for colorectal cancer: A simulation model. IMA J Math Appl Med Biol 1995;12:355–67.
70. Whynes DK, Neilson AR, Robinson MH, et al. Colorectal cancer screening and quality of life. Qual Life Res 1994;3: 191–8.
71. Bedenne L, Faivre J, Boutron MC, et al. Adenoma–carcinoma sequence or "de novo" carcinogenesis? A study of adenomatous remnants in a population-based series of large bowel cancers. Cancer 1992;69:883–8.
72. Iishi H, Tatsuta M, Tsutsui S, et al. Early depressed adenocarcinomas of the large intestine. Cancer 1992;69:2406–10.
73. Jaramillo E, Watanabe M, Slezak P, et al. Flat neoplastic lesions of the colon and rectum detected by high-resolution video endoscopy and chromoscopy. Gastrointest Endosc 1995;42:114–22.
74. Muto T, Kamaiya, Zawada T. Small "flat adenoma" of the large bowel with special reference to its clinicopathologic features. Dis Colon Rectum 1985;28:847–51.
75. Wolber RA, Owen DA. Flat adenomas of the colon. Hum Pathol 1991;22:70–4.
76. Tada S, Iida M, Matsumoto T. Small flat cancer of the rectum: Clinicopathologic and endoscopic features. Gastrointest Endosc 1995;42:109–13.
77. Jass JR. Colorectal adenoma progression and genetic change: Is there a link? Ann Med 1995;27:301–6.
78. Boutron MC, Faivre J, Quipourt V, et al. Family history of colorectal tumours and implications for the adenoma-carcinoma sequence: A case control study. Gut 1995;37:830–4.
79. Pariente A, Milan C, Lafon J, et al. Colonoscopic screening in first-degree relatives of patients with "sporadic" colorectal cancer: A case-control study. Gastroenterology 1998;115:7–12.
80. Salzman P, Kerlikowske K, Phillips K. Cost-effectiveness of extending screening mammography guidelines to include women 40–48 years of age. Ann Intern Med 1997;127:955–65.
81. Hamel MB, Phillips RS, Davis RB, et al. Outcomes and cost-effectiveness of initiating dialysis and continuing aggressive care in seriously ill hospitalized adults. Ann Intern Med 1997;127:195–202.
82. Lee TL, Soloman NA, Heidenreich PA, et al. Cost-effectiveness of screening for carotid stenosis in asymptomatic persons. Ann Intern Med 1997;126:337–46.
83. Kallmes DF, Kallmes MH, Cloft HJ, et al. Guglielmi detachable coil embolization for unruptured aneurysms in neurosurgical candidates: A cost-effectiveness exploration. Am J Neuroradiol 1998;19:167–76.
84. Pinkerton SD, Holtgrave DR, Pinkerton HJ. Cost-effectiveness of chemoprophylaxis after occupational exposure to HIV. Arch Intern Med 1997;157:1972–80.
85. Langfitt JT. Cost-effectiveness of anterotemporal lobectomy in medically intractable complex partial epilepsy. Epilepsia 1997;38:154–63.
86. Kuntz KM, Kent KC. Is carotid endarterectomy cost-effec-

tive? An analysis of symptomatic and asymptomatic patients. Circulation 1996;94:II194–8.
87. Laupacis A, Feeny D, Detsky AS, et al. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Can Med Assoc J 1992;146:473–81.
88. McNamara RL, Lima JAC, Whelton PK, et al. Echocardiographic identification of cardiovascular sources of emboli to guide clinical management of stroke: A cost-effectiveness analysis. Ann Intern Med 1997;127:775–87.
89. Leitch AM, Dodd GD, Costanza M, et al. American Cancer Society guidelines for the early detection of breast cancer: Update 1997. Ca Cancer J Clin 1997;47:150–3.
90. Bhattacharya I, Sach EM. Screening colonoscopy: The cost of common sense. Lancet 1996;347:1744–5.
91. Rex DK. Endoscopic screening for colorectal cancer: Recent studies from Indiana University. Indiana Med 1994;68–73.
92. Rex DK, Rahmani EY, Haseman JH, et al. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterology 1997; 112:17–23.
93. Thoeni RF, Menuck L. Comparison of barium enema and colonoscopy in the detection of small colonic polyps. Radiology 1977;124:631–5.
94. Beggs I, Thomas BM. Diagnosis of carcinoma of the colon by barium enema. Clin Radiol 1983;34:423–5.
95. Durdey P, Weston PM, Williams NS. Colonoscopy or barium enema as initial investigation of colonic disease. Lancet 1987;2:549–51.
96. Fork FT. Double contrast enema and colonoscopy in polyp detection. Gut 1981;22:971–7.
97. Hoff G, Vatn M. Epidemiology of polyps in the rectum and sigmoid colon. Endoscopic evaluation of size and localization of polyps. Scand J Gastroenterol 1985;20:356–60.
98. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24–8.
99. Warneke J, Petrelli N, Herrera L, et al. Accuracy of colonoscopy for the detection of colorectal polyps. Dis Colon Rectum 1992;35:981–5.
100. Byrd RL, Boggs HW Jr, Slagle GW, et al. Reliability of colonoscopy. Dis Colon Rectum 1989;32:1023–5.
101. Lo AY, Beaton HL. Selective management of colonoscopic perforations. J Am Coll Surg 1994;179:333–7.
102. Jentschura D, Raute M, Winter J. Complications in endoscopy of the lower gastrointestinal tract. Surg Endosc 1919; 8:672–6.
103. Waye J, Lewis BS, Yessayan S. Colonoscopy: A prospective report of complication. J Clin Gastroenterol 1992;15:347–51.
104. Fruhmorgen P, Demling L. Complications of diagnostic and therapeutic colonoscopy in the Federal Republic of Germany; results of an inquiry. Endoscopy 1979;2:146–50.
105. Smith LE. Fiberoptic colonoscopy: Complications of colonoscopy and polypectomy. Dis Colon Rectum 1976;19: 407–12.
106. Silvis SE, Nebel O, Rogers G. Endoscopic complications. Results of the 1974 American Society for Gastrointestinal Endoscopy survey. JAMA 1976;235:928–30.
107. Rex DK, Lehman GA, Hawes RH, et al. Screening colonoscopy in asymptomatic average-risk persons with negative fecal occult blood tests. Gastroenterology 1991;100:64–7.
108. McAfee JH, Katon RM. Tiny snares prove safe and effective for removal of diminutive colorectal polyps. Gastrointest Endosc 1994;40:301–3.
109. Williams CB, Macrae FA, Bartram CI. A prospective study of diagnostic methods in adenoma follow-up. Endoscopy 1982;14:74–8.
110. Bhattacharya I, Sach EM. True cost of colonoscopy in a managed care organization. Gastroenterology 1996;112: A174.