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Flexible Sigmoidoscopy for Colorectal Cancer Screening

An Evidence-Based Analysis

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The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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List of Abbreviations

AUC	Area under the curve
CI	Confidence interval(s)
CRC	Colorectal cancer
CT	Computed tomographic
CTC	Computed tomographic colonography
FIT	Fecal immunochemical test
FOBT	Fecal occult blood test
FS	Flexible sigmoidoscopy
GP	General practitioner
MACS	Multicentre Australian Colorectal Neoplasia Screening
MAS	Medical Advisory Secretariat
MR	Magnetic resonance
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SROC	Summary receiver operating characteristic

Glossary

Average risk for colorectal cancer	The risk of developing colon cancer among people 5o years of age and older who do not have any other risk factor for colorectal cancer
Cecum	The proximal section of the colon
Neoplasia	Abnormal growth of cells that may be benign or malignant
Sigmoid colon	The distal section of the colon

Background

The colorectal cancer (CRC) screening project was undertaken by the Medical Advisory Secretariat (MAS) in collaboration with the Cancer Care Ontario (CCO).

In November 2007, the Ontario Health Technology Advisory Committee (OHTAC) MAS to conduct an evidence-based analysis of the available data with respect to colorectal cancer diagnosis and prevention. The general purpose of the project was to investigate the effectiveness, cost effectiveness, and safety of the various methods and techniques used for colorectal cancer screening in average risk people, 50 years of age and older.

The options currently offered for colorectal cancer screening were reviewed and five technologies were selected for review:

- Computed tomographic (CT) colonography
- Magnetic resonance (MR) colonography
- Wireless capsule endoscopy (PillCam Colon)
- Fecal occult blood test (FOBT)
- Flexible sigmoidoscopy

In this review, colonoscopy was considered as the "gold standard" technique by which the effectiveness of all other modalities could be evaluated. An economic analysis was also conducted to determine cost-effectiveness of different screening modalities.

Evidence-based analyses have been prepared for each of these technologies, as well as summary document that includes an economic analysis, all of which are presented at the MAS Web site: http://www.health.gov.on.ca/english/providers/program/mas/tech/tech_mn.html

Objective

The objective of this review was to determine the effectiveness and safety of flexible sigmoidoscopy (FS) for the identification of cancers and adenomatous polyps in the colon and rectum in average risk people, 50 years of age and older, in the context of CRC screening.

Colorectal Cancer Screening

The objective of CRC screening is to reduce the burden of CRC and thereby the morbidity and mortality rate of the disease. It is believed that this goal can be achieved by regularly screening the average-risk population, enabling the detection of cancer at early, curable stages, and polyps before they become cancerous. Several methods for CRC screening have been proposed by various organizations, each with their own advantages and disadvantages. There is no single infallible technique for detection and thus there is an ongoing need for improvement of screening methods. However, as with other screening tests, an effective screening technique for CRC should be feasible, accurate, safe, acceptable, and cost-effective.

Optical Colonoscopy

Colonoscopy is currently considered the gold standard for detection of colorectal neoplasia, yet its true sensitivity is difficult to determine. The success of the technique in identification of colorectal lesions is highly dependent on the skills of the endoscopist. The initial measures of sensitivity of colonoscopy for adenomas were made by tandem colonoscopy studies. (1;2) Rex et al. (1) determined miss rate of colonoscopy by same day back-to-back colonoscopy, which was shown to be 13% for adenomas 6-9 mm, and 6% for adenomas ≥ 10 mm. Right colon adenomas were missed more often (27%) than left colon adenomas (21%), but the difference was not statistically significant. Hixson et al. (2) studied the colonoscopic miss rate in a blinded trial. In this study, colonoscopy identified all of the 63 lesions that were ≥10 mm, while 12% of the 6-9 mm lesions were missed.

More recently, the technique of segmental unblinding in CT colonography studies has been used to demonstrate the true sensitivity of colonoscopy for detection of adenomas. This technique is, however, an unreliable method for determination of sensitivity of colonoscopy for polyps <10 mm in size. Pickhardt et al. (3) used the technique of segmental unblinding and reported that colonoscopy had a higher sensitivity for detection of patients with adenomas ≥6 mm (90%) than that for detection of patients with adenomas ≥10 mm (88%).

The interior lining of the colon from anus to cecum can be visualized through colonoscopy, allowing for a high rate of detection for potentially curable CRCs and precancerous adenomatous polyps. The advantage of colonoscopy is that it allows detection, biopsy, and removal of the lesions identified. A single session detection and treatment would thus be more convenient for patients. In addition, the longer interval between repeat screens has the potential to minimize the costs associated with two-stage screening with other tests.

The drawback of the technique is that it is invasive and is associated with clinically important complications such as bleeding and/or perforation, but the likelihood of these risks are small and they are more commonly associated with polypectomy and/or biopsy. (4) The risk of perforation is higher in the presence of conditions such as active colitis, inflammation, diverticular or ischemic disease, and prior irradiation. Although colonoscopy is not routinely indicated for patients with inflammatory bowel disease, it may be indicated for patients with ulcerative colitis of more than 10 years' duration because of an increased risk of carcinoma.

A study conducted among the United States Medicare population examined the risk of colonic perforation following colonoscopy and sigmoidoscopy. (5) Overall, 77 perforations occurred following 39,286 colonoscopies (incidence = 1.96/1,000 procedure). The risk of perforation for those who underwent screening colonoscopy (n = 20,163) was thus 1.3/1,000. In a separate Swedish study (6) involving 6,066 diagnostic and therapeutic colonoscopies, bleeding and perforation occurred in 0.2% and 0.1% respectively, with no colonoscopy related mortality. Bleeding was confined to therapeutic colonoscopy and occurred immediately (mainly after removal of large polyps with thick stalks). Perforation at diagnostic colonoscopy occurred in the left colon and was diagnosed sooner than perforations due to therapeutic colonoscopy where the cecum was the most frequent site. Bleeding was correlated to the experience of endoscopist.

It should also be noted that colonoscopy does fail to reach the cecum in 5% to 10% of average-risk people due a variety of reasons such as tortuousity or malrotation of the loops, bowel spasm, diverticulitis or diverticulosis, ischemic colitis, colonic configuration from previous surgery, obstructive tumors, external compression from masses or hernia. (7)

Though there are no published randomized trials, there is indirect evidence that the technique can reduce

the overall incidence and mortality of CRC. Colonoscopy was an integral part of the FOBT clinical trials that demonstrated reduction in mortality through CRC screening.
Existing techniques for CRC screening generally fall into the following three categories:

Endoscopic techniques:

- Optical colonoscopy
- Flexible sigmoidoscopy (FS)

Stool-based techniques:

- Fecal occult blood test (FOBT)
- Fecal Immunochemical Test (FIT)
- Fecal DNA testing

Imaging techniques:

- Virtual colonoscopy techniques using:
  a) Computed tomographic colonography (CT colonography)
  b) Magnetic resonance colonography (MR colonography)
- Wireless capsule endoscopy (PillCam Colon)
- Double-contrast barium enema (DCBE)

Flexible Sigmoidoscopy

Flexible sigmoidoscopy is similar to colonoscopy but examines only the rectum and distal part of the colon, while colonoscopy examines the entire colorectal lining. The flexible sigmoidoscope itself is a lighted flexible tube, 60 cm long, connected to a video screen. The device also has an open channel for tissue sampling and polyp removal. The advantage of the FS technique is that it can be performed as an outpatient procedure and without the need for sedation. Findings at FS may lead to referral for colonoscopy. Complications following FS are rare and include risk of perforation and/or bleeding.

Cancers and polyps in the sigmoid colon and rectum can be diagnosed by FS, although advanced significant lesions beyond the reach of the sigmoidoscope would remain undetected. There are also concerns that anatomical and gender differences may limit the use of this technique in women.

Literature Review of Effectiveness

Research Questions

1. What percentages of CRCs/polyps in individuals 50 years of age and older are detected by FS compared with the gold standard optical colonoscopy?
2. How safe is the FS procedure in the context of CRC screening?

Methods

Outcome Measure

- Yield of CRCs and advanced neoplasia in patients 50 years of age and older

Inclusion Criteria

- Prospective cohort studies comparing yield of FS with optical colonoscopy for detection of CRCs and polyps in men and women 50 years of age or older
- Studies including 20 or more patients

Exclusion Criteria

- Retrospective studies
- Studies of bodily areas other than the colon
- Studies addressing other diseases of the colon
- Studies addressing technical, educational, or other aspects of the technique

Literature Search

A search of electronic databases (OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library, and the International Agency for Health Technology Assessment [INAHTA/CRD] database was undertaken to identify evidence published from January 1, 2004 to November 20, 2007. The search was limited to English-language articles and human studies. The search strategy is detailed in the Appendix. The literature search identified 457 citations, of which three met inclusion criteria (Table 1). The search was updated in July 31, 2008. A total of 108 new citations were retrieved, but none met the inclusion criteria.

Table 1: Quality of Evidence of Included Studies

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, systematic reviews of RCT	1	1
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	1
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modelling	4d	0
Case series presented at international conference	4(g)	0

RCT refers to randomized controlled trial; g, grey literature.

Results of Literature Review

Results of Literature Review

Two RCTs and one prospective cohort study met our inclusion criteria (the characteristics of these studies are summarized in Table 2). The largest of the identified studies was the SCORE 3 Trial, a population-based RCT on CRC screening conducted across six centres in Italy. (8)

SCORE3 Trial

The SCORE 3 Trial used the same design adopted in a previous population-based multicentre RCT on CRC screening. (9) Patients enrolled in the previous study were not targeted for this trial. The objective of the study was to assess the attendance and to compare the detection rate and acceptability of different strategies for CRC screening.

A random sample of 18,447 average-risk men and women, aged 55–64 years, was drawn from the rosters of 172 general practitioner (GPs) and randomized to one of the three different screening strategies (ratio 1:1:1): 1) biennial fecal immunological test (FIT), 2) once-only FS, and 3) once-only colonoscopy. A computer-generated allocation algorithm based on randomized blocks was used to allocate the patients on an individual basis with the algorithm automatically assigning spouses to the same arm. The original plan was to enrol 18,000 subjects to allow for an 80% power to detect a 6% absolute difference within groups in each centre, assuming a 30% attendance rate in the comparison group (biennial FIT) and based on a conventional 5% (2-tailed) level of statistical significance. Since prior large colorectal screening studies showed that the overall prevalence of advanced adenomas and CRC in the target age range was 5% at FS screening and the expected prevalence at colonoscopy screening was between 6.9% and 8.7%, it was calculated that the study would have an 80% power to declare a 2.3% absolute difference (from 5.0% to 7.3%) in the prevalence of advanced proximal lesions between FS and colonoscopy groups.

Eligible people were mailed a personal invitation letter, signed by their GP or by a local coordinator if the GP refused to participate. The letter indicated that the person had been randomized in a study comparing different screening strategies. The letter included a leaflet containing information about the procedure and the operating characteristics of the test to which the person had been randomized, and its possible adverse effects. A reminder letter was mailed to non-respondents in the biennial FIT arm, and two additional invitations were mailed at 12 and 24 months to non-respondents in the FS and colonoscopy arms.

In the end, a total of 18,114 people were randomized to the three screening strategies with 5,483 attending the study. The attendance rate was 32.3% for biennial FIT, 32.3% for FS, and 26.5% for colonoscopy. After adjusting for screening centre, age, and gender, the proportion of attendees was significantly lower in the colonoscopy arm compared with the FS group [OR, 0.74, 95% confidence interval (CI), 0.68–0.80]. When invited for biennial FIT screening, men showed a lower response rate compared with women (OR, 0.87, 95% CI: 0.78–0.98); however, their response was higher than women when invited for FS screening (OR, 1.23, 95% CI: 1.10–1.38) or colonoscopy (OR, 1.14, 95% CI: 1.02–1.29).

Advanced adenoma was defined as villous component >20%, high-grade dysplasia, polyp size ≥10 mm. People with advanced adenoma, those with more than 2 adenomas at FS, and/or those with a positive FIT were referred for colonoscopy. Polyps <10 mm detected during FS were removed and sent for pathologic examination. Patients with polyps ≥10 mm or advanced adenomas were referred for colonoscopy. People with suspected CRC or with polyps too large to be removed endoscopically were referred for surgery. If the baseline colonoscopy could not be completed to the cecum, patients were referred for double contrast barium enema whenever advanced adenomas were detected.

Table 2: Characteristics of the Studies Comparing the Yield of Flexible Sigmoidoscopy With the Yield of Colonoscopy for Detection of CRCs and Advanced Adenomatous Polyps

Study (Country)	Objective	Study Design	No. of Patients; Gender; Age Range (Years)	Inclusion Criteria	Exclusion Criteria
Segnan et al., 2007 (8) (Italy)	To estimate attendance and to compare detection rate and acceptability of different strategies of CRC screening	Population-based RCT comparing 3 strategies: 1) Biennial immunologic FOBT 2) Once-only FS 3) Once-only colonoscopy	18,114 M: 48% F: 53% 55–64	Average-risk population	▪ Unable to provide informed consent ▪ Terminal illness ▪ Inflammatory bowel disease ▪ Personal history of CRC/polyp ▪ Having 2 first-degree relative with CRC ▪ Prior colorectal endoscopy or FOBT (within 2 years)
The Multicentre Australian Colorectal Neoplasia Screening (MACS) Group, 2006 (10) (Australia)	To determine whether choice of test improved participation in screening and to determine the diagnostic yield of advanced colorectal neoplasia, acceptability, and safety of each procedure	Randomized comparative study offering one of 6 screening strategies: FOBT FOBT & FS CTC Colonoscopy A choice of these strategies (Two of these choices were FOBT kit with a letter of invitation – Patient can request FOBT kit by telephone if FOBT was the test chosen)	278 M: 51% F: 49% 2 age groups: 50–54 and 65–69	Asymptomatic and at average risk for colorectal neoplasia	▪ Symptomatic ▪ Strong family history of CRC ▪ Altered bowel habit ▪ Rectal bleeding ▪ Unexplained weight loss within last 12 months ▪ Prior colonoscopy, FS, or barium enema within last 5 years ▪ FOBT within last 12 months ▪ Personal history of colorectal neoplasia ▪ Serious comorbidities ▪ Could not speak English
Schoenfeld et al., 2005 (11)	To examine the yield of screening colonoscopy	Prospective cohort	1,483 F: 100% 50–79 58.9±8.1	Asymptomatic women who had been referred for CRC screening	▪ Positive FOBT within 6 months ▪ Iron deficiency anemia within 6 months ▪ Rectal bleeding or hematochezia within 12 months ▪ Unintentional weight loss >10 lb within 6 months ▪ History of adenoma, CRC, IBD, or hereditary popyposis syndromes ▪ Normal findings on colonoscopy or barium enema within 10 years ▪ Normal findings on FS within 5 years

CRC refers to colorectal cancer; CTC, computed tomographic colonography; FOBT; fecal occult blood test; FS, flexible sigmoidoscopy; IBD; irritable bowel disease; lb, pound; RCT, randomized controlled trial.

Polyps detected at FS were defined as distal even if they were located beyond the sigmoid-descending colon junction. Colonoscopy detected polyps were defined as distal if they were located in the rectum and sigmoid colon. A complete colonoscopy was reported if the cecum could be visualized. In the case of failure, a subsequent colonoscopy was performed within 6 months after the first colonoscopy. The combined results of the two examinations were included in the analysis.

In the FIT arm, 92 of 1,965 (4.7%) people had a positive result, of which 81 (88%) underwent colonoscopy. The examination was completed to the cecum in 72/81 (89%) of these cases. Two CRCs (0.1%) and 21 advanced adenomas (1.1%) were detected. The positive predictive value for advanced neoplasia was 23/81 (28.4%).

In the FS arm, 22 people had inadequate bowel preparation and refused to fix another test date. From the remaining 1,922 people, 1730 had a complete examination (89%) and 192 had a partial examination of the distal colon (9.9%). A total of 138 people (7.2%) were referred for colonoscopy, out of which 124 (89.9%) attended. In these people, colonoscopy could not be completed to the cecum in seven cases (5.7%); four had a repeat colonoscopy within 12 months, two underwent a double contrast barium enema, and one refused further assessment.

In FS arm, cancers were detected in the distal colon in 12 (0.6%) people and adenomas were detected in the distal colon in 214 (11.2%). Advanced adenoma was found in 88 (4.6%) people; the prevalence of distal advanced neoplasia was thus 5.2% (100/1922). The prevalence of adenoma in the proximal colon among people undergoing subsequent colonoscopy was 19.5% (25/124); eight (6.5%) of these were advanced proximal adenomas. Therefore, advanced colorectal neoplasia was detected in 108 (5.2%) of cases.

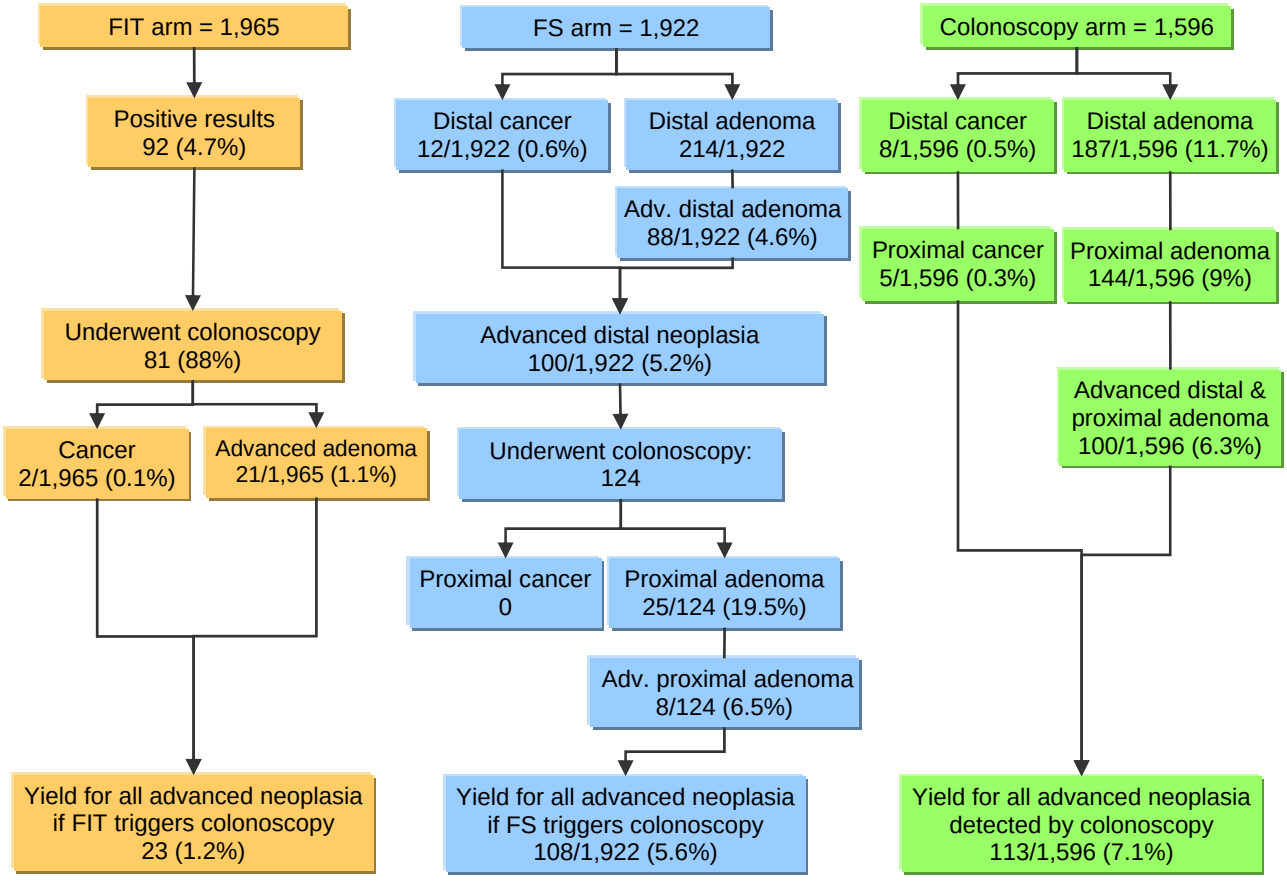
Among those in the colonoscopy arm (1,597 attendees), examination could not be performed in 33 (2.1%) because of incomplete preparation. A new appointment was offered to these people and 32 attended the second colonoscopy. Colonoscopy was complete to the cecum in 1,383/1,596 (86.7%) of these cases. Pain and bowel adhesions were reported as the reason for incomplete colonoscopy in 44% and 38% of the cases, respectively. Inadequate bowel preparation accounted for 9% of incomplete examinations.

In the colonoscopy arm, cancer was detected in 13 (0.8%) people. The prevalence of advanced distal or proximal neoplasia was 6.3%. Advanced colorectal neoplasia was detected in 113 (7.1%) cases. The overall prevalence of colonic polyps and cancers was 31.1%. Advanced proximal neoplasia was found in 4% of the cases among men and in 1.6% cases among women (OR, 2.64, 95% CI: 1.30–5.46).

In the colonoscopy arm, FS would have detected 27.3% (95% CI: 15.5%–43%) of the proximal advanced neoplasms detected by colonoscopy. This proportion would have been the same for men and women, with an insignificant trend toward an increase for people aged 60 years and over (32%) compared with those younger than 60 years (21.1%). In 62.5% of men and 58.3% of women in the colonoscopy arm who had proximal advanced neoplasia, no adenoma was found in the distal colon. The prevalence of adenomas in the proximal colon markedly increased with age, while the prevalence of adenomas in the rectum and sigmoid colon showed a plateau after age 59 years.

A 42% increase in detection rate was observed in the colonoscopy arm compared with the FS arm after adjusting for age, gender, and screening centre (OR, 1.42; 95% CI: 1.08–1.88). This gain in detection rate was mainly explained by a marked increase in detection of advanced neoplasia among those people aged 60 years and over (OR, 2.00; 95% CI: 1.30–3.09). The detection rate was not different between the FS and colonoscopy arms for those younger than 60 years of age (OR, 1.08; 95% CI: 0.74–1.57). The detection rate for advanced neoplasia in the distal colon was the same for the FS and colonoscopy arms (OR, 1.02; 95% CI: 0.75–1.37).

The detection rate was markedly lower in the biennial FIT arm compared with the FS arm (OR, 0.22; 95% CI: 0.14–0.35). Figure 1 and Table 3 show the yield of different CRC screening strategies. Based on the observed prevalence of advanced adenomas in the FS arm and the colonoscopy arm, it was estimated that screening by FS would result in identification of 72% of people with advanced neoplasia.



FIT refers to fecal immunologic test; FS, flexible sigmoidoscopy.

Figure 1: Yield of Three CRC Screening Strategies

Table 3: Comparison of Three CRC Screening Strategies

Screening Test	Detection Rate, %		
	Cancer	Advanced Adenomas	Advanced Neoplasia
FIT (n=1,965)	0.1	1.1	1.2 (OR, 0.22; 95% CI: 0.14–-0.35)*
FS (n=1,922)	0.6	4.6	5.2
Colonoscopy (n=1,596)	0.8	6.3	7.1 (OR, 1.42; 95% CI: 1.08–1.88)*

CI refers to confidence interval; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; OR, odds ratio.
*Compared with FS.

The Multicentre Australian Colorectal Neoplasia Screening Study

A randomized comparative study conducted in Australia (10) compared the participation rate, yield of advanced colorectal neoplasia, acceptability, and safety of six different screening strategies. It was hypothesized that providing a choice of screening test would itself significantly increase participation. The study was planned to have a power of 80% based on a conventional 5% level of significance. Those participants in the FS, colonoscopy, and computed tomographic colonography (CTC) arms were also given a questionnaire to evaluate five test variables: perception of pain, tolerance, satisfaction, embarrassment, and readiness for a repeat test. Recruitment consisted of a total of 1,679 people aged 50–54 or 65–69 years, randomly selected from the electoral roll. Invitation letters were sent to these people, of which 1,333 were later considered eligible. Overall, 278 were screened (participation rate: 20.9%'; 95% CI: 18.7%–23.1%) and of these, 68% responded to the first, and 32% to the second invitation letter.

The participation rate was calculated as the number of participants divided by the total number of eligible people. Participation in screening by FOBT/FS was defined as completion of the screening strategy. As summarized in Table 4, participation was highest in screening by FOBT at 64/234 (27.4%), while in the other screening strategies it was: FOBT/FS 31/224 (13.7%; $P < .001$ compared with FOBT), CTC 35/215 (16.3%; $P = .005$), colonoscopy 38/214 (17.8%; $P = .02$), choice of test with FOBT kit 42/226 (18.6%; $P = .03$), choice of test without FOBT kit 50/220 (22.7%; $P = .3$). In the choice of screening arm, most preferred FOBT [61/92 (66%)] or colonoscopy [25/92 (27%)]; however, this difference was less marked in the arm for choice without FOBT kit: FOBT [29/50 (58%)] and colonoscopy [18/50 (36%)].

The yield of advanced colorectal neoplasia was calculated as the number of participants with one or more lesions per 100 people screened. Advanced neoplasia was defined as any adenoma >10 mm in diameter, presence of villous histology, high-grade dysplasia, or cancer.

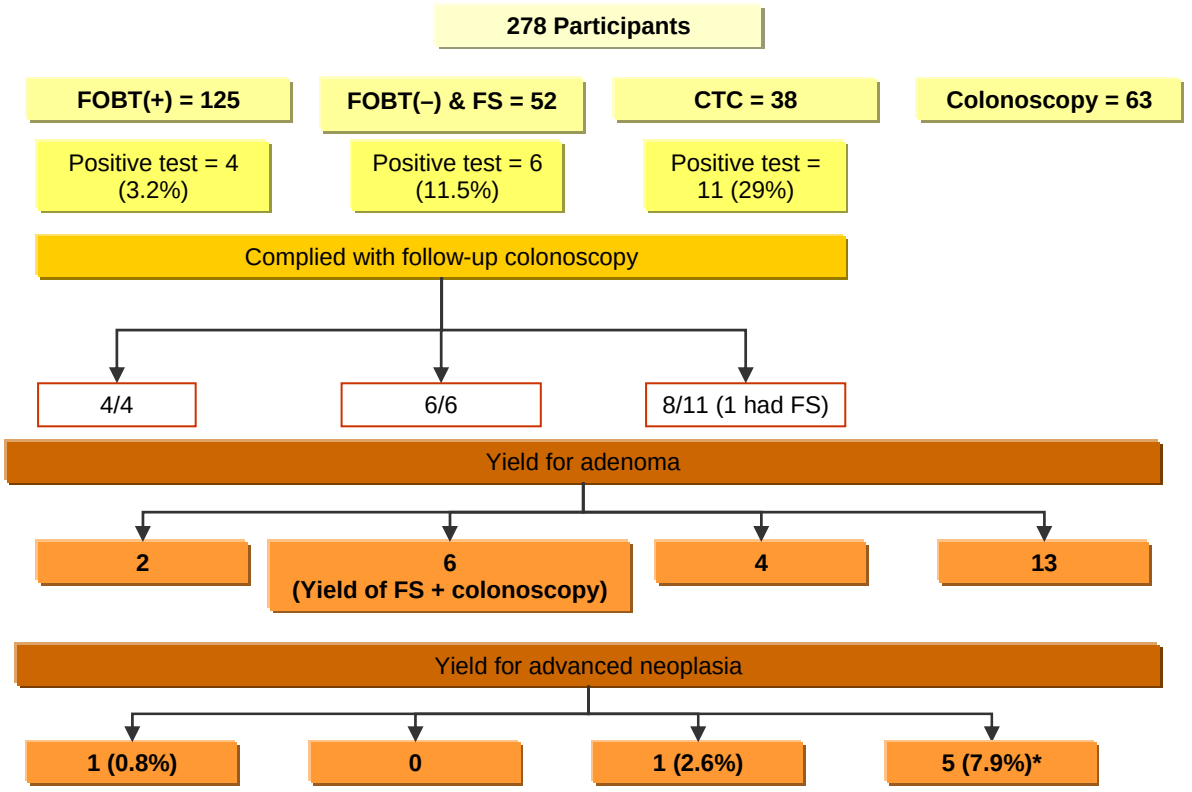
All participants with a positive screening test underwent colonoscopy with the exception of three of 11 people with a positive CTC test. Of 112 people undergoing colonoscopy, either as primary screening or follow-up procedure, complete colonoscopy was achieved in 110 (98%). The results showed that the highest yield for advanced neoplasia was in participants having colonoscopy (7.9%). Yield of advanced neoplasias was 2.6% in CTC and 0.8% in the FOBT group (see Figure 2). Visual analogue scores for pain, tolerance, satisfaction, embarrassment, and readiness to repeat the test showed that all tests were well accepted. There were no episodes of bleeding, perforation, or other serious complications arising from screening.

Table 4: Participation Rate for CRC Screening in Randomized Trials

	SCORE3 Trial	MACS Trial	
	Participation Rate, %	Participation Rate, %	*P**
FIT	32.3	27.4	
FS	32.3	FOBT(–) & FS: 13.7	<.001
CTC	N/A	16.3	.005
Colonoscopy	26.5, OR, 0.74 (95% CI: 0.68–0.80) †	17.8	.02
Choice of screening	N/A	With FOBT kit: 18.6 Without FOBT kit: 22.7	.03 .3

CI refers to confidence interval; CTC, computed tomographic colonography; FIT, fecal immunochemical test; FOBT, fecal occult blood test; FS, flexible sigmoidoscopy; MACS, Multicentre Australian Colorectal Neoplasia Screening, OR, odds ratio.

*Compared with FOBT. †Compared with FS arm.



**P* = 0.02 compared with FOBT

CTC refers to computed tomographic colonography; FOBT, fecal occult blood test; FS, flexible sigmoidoscopy.

Figure 2: The Multicentre Australian Colorectal Neoplasia Screening (MACS) Study

Women's Study

Schoenfeld et al. (11) examined the diagnostic yield of FS and colonoscopy in the detection of colorectal cancers and polyps in women. Existing data from Veterans Affairs Cooperative Study 380 showed that the diagnostic yield of FS for advanced colorectal neoplasia is 70%, however, 97% of the patients in this study were men. This study was conducted to determine whether FS would be a reasonable alternative to colonoscopy in screening asymptomatic women. The secondary objective of the study was to calculate the diagnostic yield of FS, assuming that the finding of small adenomas in the distal colon would trigger the performance of colonoscopy, which would then detect the advanced neoplasia in the proximal colon.

The study population was made up of consecutive asymptomatic women aged 50–79 years, who had been referred for colonoscopy for CRC screening at four military medical centres. Asymptomatic women 40–79 years of age and who had a history of CRC in a first-degree relative were also offered enrolment. It was estimated that a sample size of 1,450 women would provide a statistical power of 80% to detect an absolute difference of 3% in the prevalence of advanced neoplasia in the proximal colon between women with distal colon neoplasia and women without distal colon neoplasia. Lesions were considered detectable by FS if they were located in the distal colon or if they were in the proximal colon with concurrent small adenoma in the distal colon. Colonoscopy was complete to the cecum in 1,463 of 1,483 eligible women (98.7%), and no clinically significant complications occurred.

The diagnostic yield of FS was calculated by estimating the proportion of women with advanced neoplasia whose lesions would have been identified if they had undergone FS alone. Since the finding of small adenomas in the distal colon would trigger the performance of colonoscopy, which would then detect the advanced neoplasia in the proximal colon, FS can be considered to be capable of detecting some advanced lesions in the proximal colon. The diagnostic yield of FS was also compared in men and women using data from Veterans Affairs Cooperative Study 380 by matching men from the Veterans Affairs study with women from this study by age, negative FOBT, and absence of family history of CRC.

A total of 446 neoplastic lesions were detected from among 299 (20.4%) of the 1,463 women. Advanced neoplasia (defined as adenoma ≥10 mm in diameter, villous adenoma, adenoma with high-grade dysplasia, or invasive CRC) was present in 72 women (4.9%. Small or non-advanced adenomas were detected in 227 (15.5%) women. Among women with a family history of CRC, 16 (7%) had advanced neoplasia. The proportion of women with advanced neoplasia was found to vary significantly with age (see Table 5). Those who were 70–79 years of age were more likely to have advanced neoplasia compared with those 50–59 years of age (RR, 3.56; 95% CI: 1.70–7.58; $P = .002$).

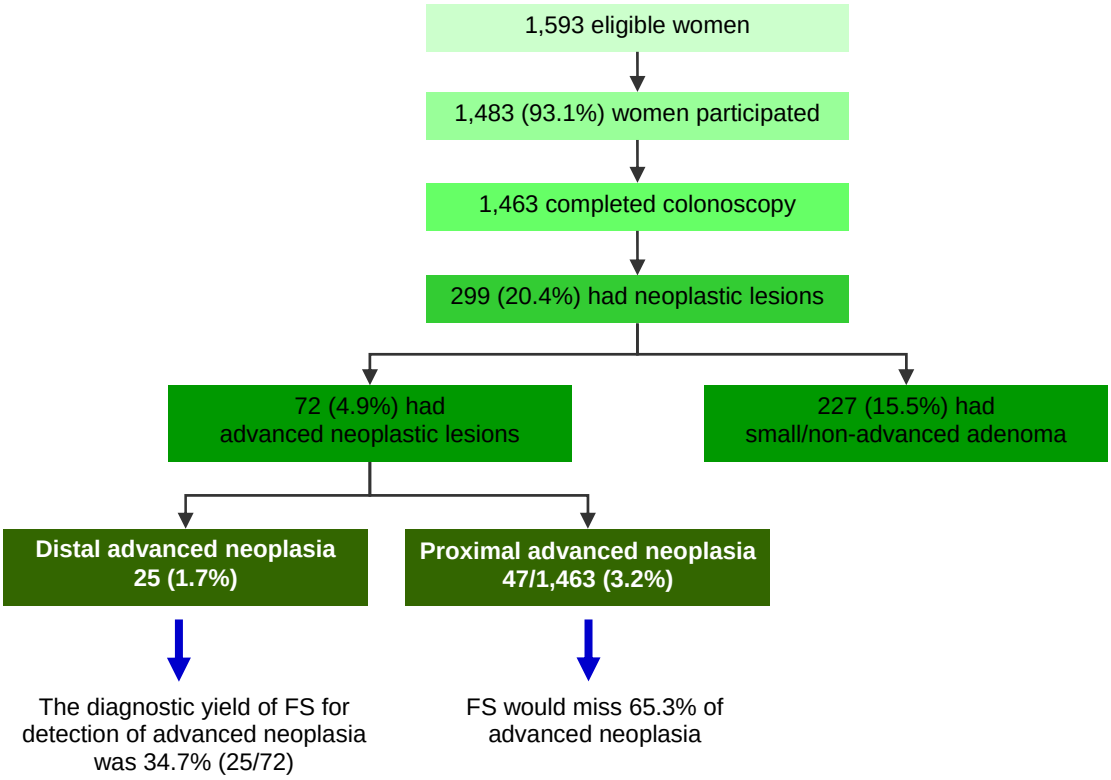
The diagnostic yield of FS for advanced neoplasia was 34.7% (25/72) if only FS had been performed. Advanced colorectal neoplasia would have been detected in 1.7% of the women and missed in 3.2% (Figure 3). Stratification according to age and family history of CRC did not show any difference in diagnostic yield of FS.

When the distal colon was defined as the rectum and sigmoid colon (Definition 1), 1,367 of 1,462 women (93.5%) did not have any distal neoplasia, whereas 95 of 1,462 (6.5%) had advanced colorectal neoplasia or small adenoma in the distal colon that would trigger colonoscopy. One woman was not included in this analysis because information about the location of her adenoma was unavailable.
The prevalence of advanced colorectal neoplasia in the proximal colon among those women who had no distal colon neoplasia was 3.4%; therefore, if only FS had been performed, advanced colorectal neoplasia would have been missed in 3.4% of women. Figure 4 shows the prevalence of advanced adenomas according to this definition.

Table 5: Proportion of Women With Advanced Colorectal Neoplasia According to Age

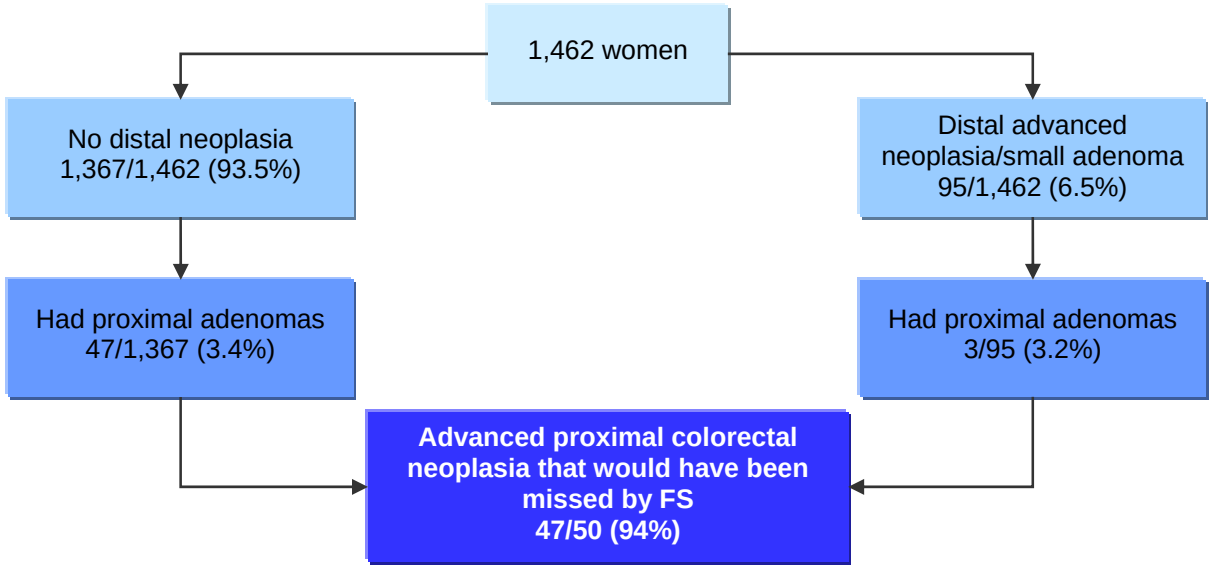
Age Group, Years	Proportion With Advanced Neoplasia	Percentage
50–59	26/786	3.3
60–69	23/420	5.5
70–79	19/162	11.7 RR, 3.56; 95% CI: 1.70–7.58; $P = .002$*

CI indicates confidence interval; RR, relative risk.
*Compared with women aged 50–59 years.



FS refers to flexible sigmoidoscopy.

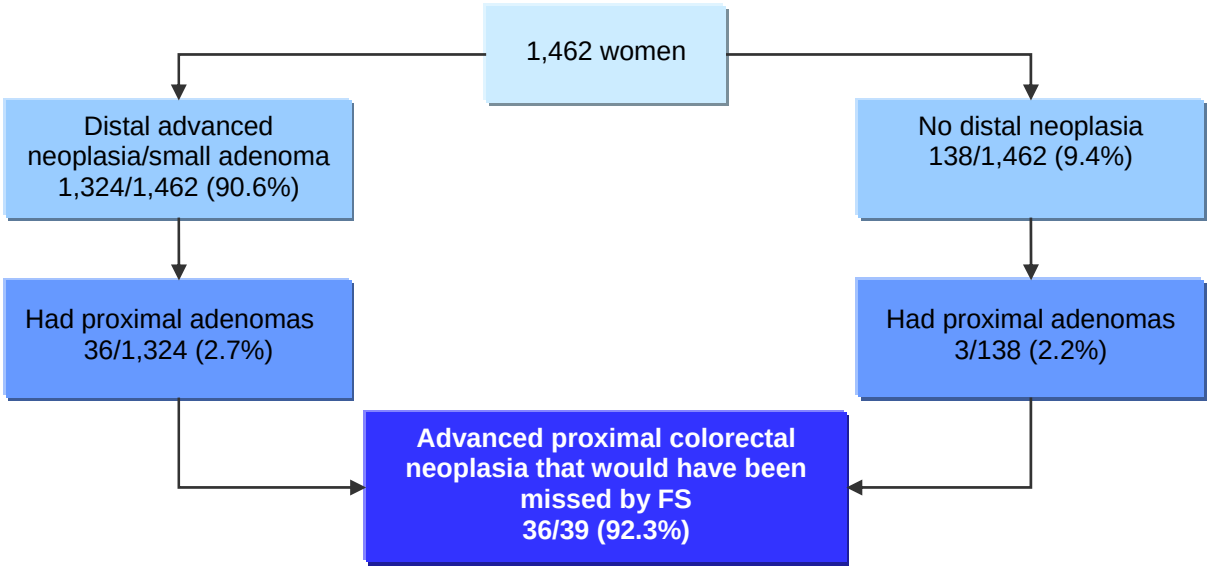
Figure 3: Diagnostic Yield of Flexible Sigmoidoscopy for Detection of Advanced Neoplasia in Women



FS refers to flexible sigmoidoscopy.
Note: Definition 1 defines the colon as the rectum and sigmoid colon.

Figure 4: Advanced Colorectal Neoplasia Missed by Flexible Sigmoidoscopy According to Definition 1

When the distal colon was defined as the rectum, sigmoid colon, and descending colon (Definition 2), 1,324 of 1,462 women (90.6%) did not have any neoplasia in the distal colon whereas 138 of 1,462 (9.4%) had advanced distal neoplasia or small adenoma in the distal colon. Figure 5 shows the prevalence of advanced adenomas according to this definition.



FS refers to flexible sigmoidoscopy.
Note: Definition 2 defines the colon as the rectum, sigmoid colon, and descending colon.

Figure 5: Advanced Colorectal Neoplasia Missed by Flexible Sigmoidoscopy According to Definition 2

The prevalence of advanced colorectal neoplasia in the proximal colon among women who had no distal colon neoplasia was 2.2%. Therefore, if only FS had been performed, advanced colorectal neoplasia would have been missed in 2.2% of women.

The Veterans Affairs study (12) has shown that the prevalence of advanced neoplasia among men with a negative FOBT varies significantly according to age ($P < .001$; Table 6).

Table 6: Prevalence of Advanced Colorectal Neoplasia in Men

Age Group, Years	Proportion With Advanced Neoplasia	Percentage	Relative Risk
50–59	40/863	4.6	1.00
60–60	132/1217	10.8	2.34 (95% CI: 1.66–3.30)
70–79	55/481	11.4	2.47 (95% CI: 1.67–3.65)

CI refers to confidence interval.
Source: Veterans Affairs Cooperative Study 380.

After matching men and women with negative FOBT and the absence of family history of CRC, it was shown that men were more likely to have advanced neoplasia than women (8.6% vs. 4.5%; RR, 1.91; 95% CI, 1.42–2.56, $P = .002$).

The diagnostic yield of FS was significantly higher in men compared with women ($P < .001$). A total of 126 of 190 (66.3%) of men would have had their advanced neoplasia detected if FS alone had been performed. The corresponding number for women would be 19 of 54 (35.2%). Table 7 shows yield of FS for advanced colorectal neoplasia in women and men by age.

Table 7: Yield of Flexible Sigmoidoscopy for Advanced Colorectal Neoplasia in Men and Women According to Age

Age Group, Years	Yield of Flexible Sigmoidoscopy, %		*P*-value
	Women	Men	
50–59	30.0	71.4	.002
60–60	42.4	69.6	.03
70–79	33.3	53.5	.18
Overall	35.2	66.3	.001

Women are from Schoenfeld et al. 2005, (11) and men are from the Veterans Affairs study (12).

On the basis of the data presented, this study suggests that FS is an inadequate method of predicting advanced colonic neoplasia in the proximal colon in women and that colonoscopy is the preferred method of colorectal evaluation in average-risk asymptomatic women.

Although this study used colonoscopy findings as a surrogate for the findings with FS, the data on FS are estimates. It should be considered that patients undergoing colonoscopy were sedated and underwent more vigorous colonic lavage; therefore, the performance of FS might have been overestimated.

Appendix: Literature Search Strategy

Search date: November 20, 2007
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library, and INAHTA/CRD

Database: Ovid MEDLINE(R) <1996 to November Week 1 2007>

Search Strategy:

1 exp Colorectal Neoplasms/ (50696)
2 exp Colonic Polyps/ (2162)
3 ((colon$ or colorectal) adj5 (precancer$ or pre-cancer$ or polyp$ or neoplasm$ or adenoma$ or cancer$ or dysplasia$ or neoplasia$ or tumo?r$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (54496)
4 exp Precancerous Conditions/ (10380)
5 or/1-4 (71506)
6 exp Colonoscopy/ (7545)
7 colonoscop$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (9541)
8 6 or 7 (10229)
9 5 and 8 (5566)
10 exp Sigmoidoscopy/ (1289)
11 (proctosigmoidoscop$ or sigmoidoscop$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2005)
12 10 or 11 (2005)
13 9 and 12 (1172)
14 limit 13 to (humans and english language and yr="2000 - 2007") (824)
15 (meta analy$ or metaanaly$ or pooled analysis or random$ or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (368180)
16 14 and 15 (172)
17 14 (824)
18 limit 17 to (case reports or comment or editorial or letter or "review") (232)
19 17 not 18 (592)
20 16 or 19 (627)

Database: EMBASE <1980 to 2007 Week 46>

Search Strategy:

1 exp Colorectal Tumor/ (1870)
2 exp Colorectal Cancer/ (31056)
3 exp Colon Polyp/ (6647)
4 exp COLORECTAL ADENOMA/ (771)
5 exp "PRECANCER AND CANCER-IN-SITU"/ (20765)
6 ((colon$ or colorectal) adj5 (precancer$ or pre-cancer$ or polyp$ or neoplasm$ or adenoma$ or cancer$ or dysplasia$ or neoplasia$ or tumo?r$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (92024)
7 or/1-6 (111777)
8 exp COLONOSCOPY/ (15210)
9 colonoscop$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (17394)
10 8 or 9 (17394)
11 7 and 10 (8716)
12 exp SIGMOIDOSCOPY/ (3692)
13 (proctosigmoidoscop$ or sigmoidoscop$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4491)
14 12 or 13 (4491)
15 11 and 14 (1491)
16 limit 15 to (human and english language and yr="2000 - 2007") (881)
17 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. or random$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (429892)
18 16 and 17 (134)
19 16 (881)
20 limit 19 to (editorial or letter or note or "review") (393)
21 Case Report/ (966004)
22 19 not (20 or 21) (462)
23 18 or 22 (516)

References

(1) Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997; 112(1):24-28.

(2) Hixson LJ, Fennerty MB, Sampliner RE, Garewal HS. Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps. Gastrointest Endosc 1991; 37(2):125-127.

(3) Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003; 349(23):2191-2200.

(4) Anderson ML, Pasha TM, Leighton JA. Endoscopic perforation of the colon: lessons from a 10-year study. Am J Gastroenterol 2000; 95(12):3418-3422.

(5) Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 2003; 95(3):230-236.

(6) Dafnis G, Ekbom A, Pahlman L, Blomqvist P. Complications of diagnostic and therapeutic colonoscopy within a defined population in Sweden. Gastrointest Endosc 2001; 54(3):302-309.

(7) Copel L, Sosna J, Kruskal JB, Raptopoulos V, Farrell RJ, Morrin MM. CT colonography in 546 patients with incomplete colonoscopy. Radiology 2007; 244(2):471-478.

(8) Segnan N, Senore C, Andreoni B, Azzoni A, Bisanti L, Cardelli A et al. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. Gastroenterology 2007; 132(7):2304-2312.

(9) Segnan N, Senore C, Andreoni B, Arrigoni A, Bisanti L, Cardelli A et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates.[see comment]. J Natl Cancer Inst 2005; 97(5):347-357.

(10) Forbes GM, Mendelson RM, Edwards JT, Foster NM, Pawlik JZ, Brampton PA et al. A comparison of colorectal neoplasia screening tests: A multicentre community-based study of the impact of consumer choice. Med J Aust 2006; 184(11):546-550.

(11) Schoenfeld P, Cash B, Flood A, Dobhan R. Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005; 352(20):2061-2068.

(12) Lieberman DA, Weiss DG, Veterans Affairs Cooperative Study Group. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 2001; 345(8):555-560.