Diagnostic Yield of One-Time Colonoscopy vs One-Time Flexible Sigmoidoscopy vs Multiple Rounds of Mailed Fecal Immunohistochemical Tests in Colorectal Cancer Screening

Esmée J. Grobbee,[*,a] Manon van der Vlugt,[‡,a] Anneke J. van Vuuren,[*] An K. Stroobants,[§] Rosalie C. Mallant-Hent,[‖] Iris Lansdorp-Vogelaar,[¶] Patrick M. M. Bossuyt,[#] Ernst J. Kuipers,[*] Evelien Dekker,[‡] and Manon C. W. Spaander[*]

[*]Department of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, The Netherlands; [‡]Department of Gastroenterology and Hepatology, Academic Medical Centre Amsterdam, Amsterdam, The Netherlands; [§]Clinical Chemistry, Academic Medical Centre Amsterdam, Amsterdam, The Netherlands; [‖]Gastroenterology and Hepatology, Flevoziekenhuis, Amsterdam, The Netherlands; [¶]Department of Public Health, Erasmus University Medical Centre, Rotterdam, The Netherlands; and [#]Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam, The Netherlands

BACKGROUND & AIMS: **We compared the diagnostic yields of colonoscopy, flexible sigmoidoscopy, and fecal immunochemical tests (FITs) in colorectal cancer (CRC) screening.**

METHODS: **A total of 30,007 asymptomatic persons, 50–74 years old, were invited for CRC screening in the Netherlands. Participants were assigned to groups that received 4 rounds of FIT (mailed to 15,046 participants), once-only flexible sigmoidoscopy (n = 8407), or once-only colonoscopy (n = 6600). Patients with positive results from the FIT (≥10 μg Hb/g feces) were referred for colonoscopy. Patients who underwent flexible sigmoidoscopy were referred for colonoscopy if they had a polyp of ≥10 mm; adenoma with ≥25% villous histology or high-grade dysplasia; sessile serrated adenoma; ≥3 adenomas; ≥20 hyperplastic polyps; or invasive CRC. The primary outcome was number of advanced neoplasia detected (diagnostic yield) by each test. Secondary outcomes were number of colonoscopies needed to detect advanced neoplasia and number of interval CRCs found during each primary screening test. Patients with interval CRCs were found through linkage with Netherlands Cancer Registry. Advanced neoplasia were defined as CRC, adenomas ≥ 10 mm, adenomas with high-grade dysplasia, or adenomas with a villous component of at least 25%.**

RESULTS: **The cumulative participation rate was significantly higher for FIT screening (73%) than for flexible sigmoidoscopy (31%; $P < .001$) or colonoscopy (24%; $P < .001$). The percentage of colonoscopies among invitees was higher for colonoscopy (24%) compared to FIT (13%; $P < .001$) or flexible sigmoidoscopy (3%; $P < .001$). In the intention to screen analysis, the cumulative diagnostic yield of advanced neoplasia was higher with FIT screening (4.5%; 95% CI 4.2–4.9) than with colonoscopy (2.2%; 95% CI, 1.8–2.6) or flexible sigmoidoscopy (2.3%; 95% CI, 2.0–2.7). In the as-screened analysis, the cumulative yield of advanced neoplasia was higher for endoscopic screening with colonoscopy (9.1%; 95% CI, 7.7–10.7) or flexible sigmoidoscopy (7.4%; 95% CI, 6.5–8.5) than with the FIT (6.1%; 95% CI, 5.7–6.6). All 3 screening strategies detected a similar proportion of patients with CRC. Follow-up times differed for each test (median 8.3 years for FIT and flexible sigmoidoscopy and 5.8 years for colonoscopy). Proportions of patients that developed interval CRC were 0.13% for persons with a negative result from FIT, 0.09% for persons with a negative result from flexible sigmoidoscopy, and 0.01% for persons with a negative result from colonoscopy.**

[a]Authors contributed equally and share co-first authorship.

Abbreviations used in this paper: AN, advanced neoplasia; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; IQR, interquartile range; NCCO, Netherlands Cooperative Cancer Organisation; NNI, number needed to invite; SSP, sessile serrated polyp.

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CONCLUSIONS: **Mailed multiple-round FITs detect significantly more advanced neoplasia, on a population level, compared with once-only flexible sigmoidoscopy or colonoscopy screening. Significantly fewer colonoscopies are required by individuals screened by multiple FITs. Trialregister.nl numbers: first round, NTR1096; second round and additional invitees, NTR1512; fourth round, NTR5874; COCOS trial NTR1829.**

Keywords: Colon Cancer; Early Detection; Noninvasive; Compliance.

See editorial on page 546.

Colorectal cancer (CRC) is the third most common malignancy in the world. The implementation of CRC screening programs has increased substantially during the past decades. A range of screening methods is available, varying in invasiveness and diagnostic accuracy. It is yet unclear which modality has the largest effect on CRC-related morbidity and mortality.[1] At present, screening programs differ markedly around the world, with colonoscopy, flexible sigmoidoscopy (FS), and fecal immunochemical tests (FITs) as the most commonly used screening strategies.[2]

Because advanced neoplasia (AN) are often located in the rectosigmoid, FS is considered a suitable method for CRC screening.[3] Several large randomized trials reported CRC-related mortality reductions ranging between 31% and 38% in average-risk screening populations.[3–6] Concerns have been raised about missing proximal AN and subsequent limited efficacy in reducing proximal CRC.

Colonoscopy is currently considered the reference standard for diagnosing CRC and its precursor lesions. Currently no literature is available on the effect on mortality rates of primary colonoscopy screening in randomized trials. For that purpose, 4 randomized controlled colonoscopy screening trials started a few years ago; the first results are expected after 2020.[7–11] A systematic review and meta-analysis of observational colonoscopy studies suggested that colonoscopy led to a significant mortality reduction with a summary estimate of 68%.[12] Although colonoscopy is highly effective in detecting CRC and its precursors, it is also an invasive procedure associated with patient discomfort, complication rates, and substantial costs. This could in part explain why previously reported participation rates in population-based screening have been low.[2]

Although FIT-based randomized controlled trials with long-term follow-up are lacking, a recent observational study demonstrated 22% reduction in CRC mortality in areas where FIT screening programs were implemented, compared with areas without screening.[13] Nevertheless, FIT still has a relatively low sensitivity for CRC detection and especially advanced adenomas, with reported cancer miss rates of 25% in a single round of FIT screening.[14] Consequently, the effectiveness of a mailed FIT screening program is highly dependent on participation and adherence to repeat screening.[15,16]

Although the impact of FIT screening is attained over multiple rounds, no literature is available on the comparison between endoscopic screening strategies and multiple rounds of FIT screening. It is of key importance for policy makers to know the impact of different screening programs over multiple rounds with long-term follow up. For this reason we aimed to compare the diagnostic yield of once-only colonoscopy, once-only FS, and 4 rounds of FIT in population-based CRC screening, including interval cancer rate.

Methods

Study Population and Design

For the purpose of this study we combined results of 3 population trials, each comprising randomly selected, screening-naive persons. At the start of these trials there had been no previous CRC screening trials in The Netherlands or any screening programs. The design of these trials has been described previously and can be found in the Supplementary Methods.[17–19]

Interventions

All invitees received an advance notification letter, followed by a kit 2 weeks later by postal mail; all of these were sent from one national organization (Bevolkingsonderzoek Zuid-West and Midden-West). This kit contained an invitation letter, information brochure, and an informed consent form. For FIT invitees the kit further contained a single FIT test and testing instructions. For FS invitees and colonoscopy invitees the invitation letter contained a telephone number of the screening unit to schedule an appointment for an intake. A reminder was sent 6 weeks after the initial invitation to invitees who had not yet responded.

Fecal Immunochemical Test

Persons allocated to FIT received 1 FIT every 2 years. The test result was considered positive when the hemoglobin concentration in the FIT sample was $\geq$10 μg Hb/g feces. Information on analyses of the FIT samples can be found in the FITTER checklist (Supplementary Methods).

Flexible Sigmoidoscopy

Invitees allocated to FS who had scheduled for an endoscopy received a phosphate enema by mail with

instructions for self-administration. Administration of the enema by a nurse in the screening unit was offered as an alternative. Experienced endoscopists (>1000 colonoscopies) performed all sigmoidoscopies. The FS was defined as complete when reaching the splenic flexure. Participants were referred for colonoscopy when one of the following criteria was met: presence of a polyp with a diameter ≥10 mm; adenoma with ≥25% villous histology or high-grade dysplasia; sessile serrated adenoma; ≥3 adenomas; ≥20 hyperplastic polyps; or invasive CRC.

Colonoscopy

All FIT-positive, FS-positive, or once-only colonoscopy participants were scheduled for colonoscopy. Experienced endoscopists performed all colonoscopies for this study. Participants received standard bowel preparation: low-fiber diet and split-dose oral intake of 2 L transparent fluid and a laxative solution (Moviprep; Norgine, or Picoprep; Ferring Pharmaceutical, Saint-Prex, Switzerland) at home. Colonoscopy was performed under conscious sedation. Surveillance after removal of adenomatous polyps, large (≥10 mm) serrated lesions, or cancer was recommended according to the Dutch surveillance guideline.[20] Screenees with a negative colonoscopy were discharged from screening for 10 years.

Colorectal Lesions

All removed lesions were collected and evaluated by an experienced gastrointestinal pathologist according to the Vienna criteria.[21] The lesions were classified as adenoma (tubular, tubulovillous, villous), serrated polyp (hyperplastic, sessile serrated adenoma, traditional serrated adenoma), or adenocarcinoma. Dysplasia was defined as either low-grade or high-grade. Advanced adenomas were defined as adenomas ≥10 mm, adenomas with high-grade dysplasia, or adenomas with a villous component of at least 25%. Cancers were staged according to the American Joint Committee on Cancer classification.[22] AN was defined as advanced adenoma and/or colorectal cancer.[23]

Screen Detected and Interval Colorectal Cancers

Screen detected CRCs were defined as CRCs detected by screening. An interval CRC was defined as a CRC diagnosed in the interval between a negative screen and the next recommended exam.[24,25] A post-colonoscopy interval CRC was defined as a cancer diagnosed after a negative colonoscopy before the date of the next surveillance colonoscopy as recommended by the applicable guidelines. A FIT-interval CRC was defined as a cancer diagnosed after a negative FIT but before the date of the next screening test as recommended by the applicable guidelines. Data from all invitees were linked to the Netherlands Cancer Registry, managed by the Netherlands Comprehensive Cancer Organisation (NCCO) to identify interval cancers, which was up-to-date until March 2015. Then, linkage to the NCCO led to a follow up of 8.3 years for FIT and FS and 5.8 years for colonoscopy.

What You Need to Know

Background

We compared the diagnostic yields of colonoscopy, flexible sigmoidoscopy, and fecal immunochemical tests (FITs) in colorectal cancer (CRC) screening.

Findings

Mailed multiple-round FITs detect significantly more advanced neoplasias, on a population level, than once-only flexible sigmoidoscopy or colonoscopy screening. Significantly fewer colonoscopies are required by individuals screened by multiple FITs.

Implications for patient care

Our findings support the use of the FIT in colorectal cancer screening and should aide in selection of screening strategies worldwide, based on expected participation rates and available colonoscopy resources.

Outcomes and Statistical Analysis

The main outcome was diagnostic yield of AN. Secondary outcomes were participation rate, positivity rate, and colonoscopy rate per screening strategy. Diagnostic yield of AN was analyzed both in an intention-to-screen analysis, defined as number of screenees with AN relative to all invitees, and as an as-screened analysis, defined as number of screenees with AN relative to all participants. Definitions of secondary outcomes can be found in the Supplementary Methods. Differences in means were analyzed by using Student t test. Differences in proportions were analyzed by using χ^2 testing. Participation rate, positivity rate, and diagnostic yield are reported as proportions with 95% confidence intervals. All tests were conducted by using SPSS version 21.0 (SPSS Inc, Chicago, IL).

Ethical Approval

The Dutch National Health Council approved the study (decisions 2006/02 WBO, 2009/03WBO, 2013/20 WBO, The Hague, Netherlands). All screenees gave written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Screening Population, Participation, and Colonoscopy Rates

A total of 30,052 average-risk persons were invited. Median age was similar for all 3 screening groups: 59

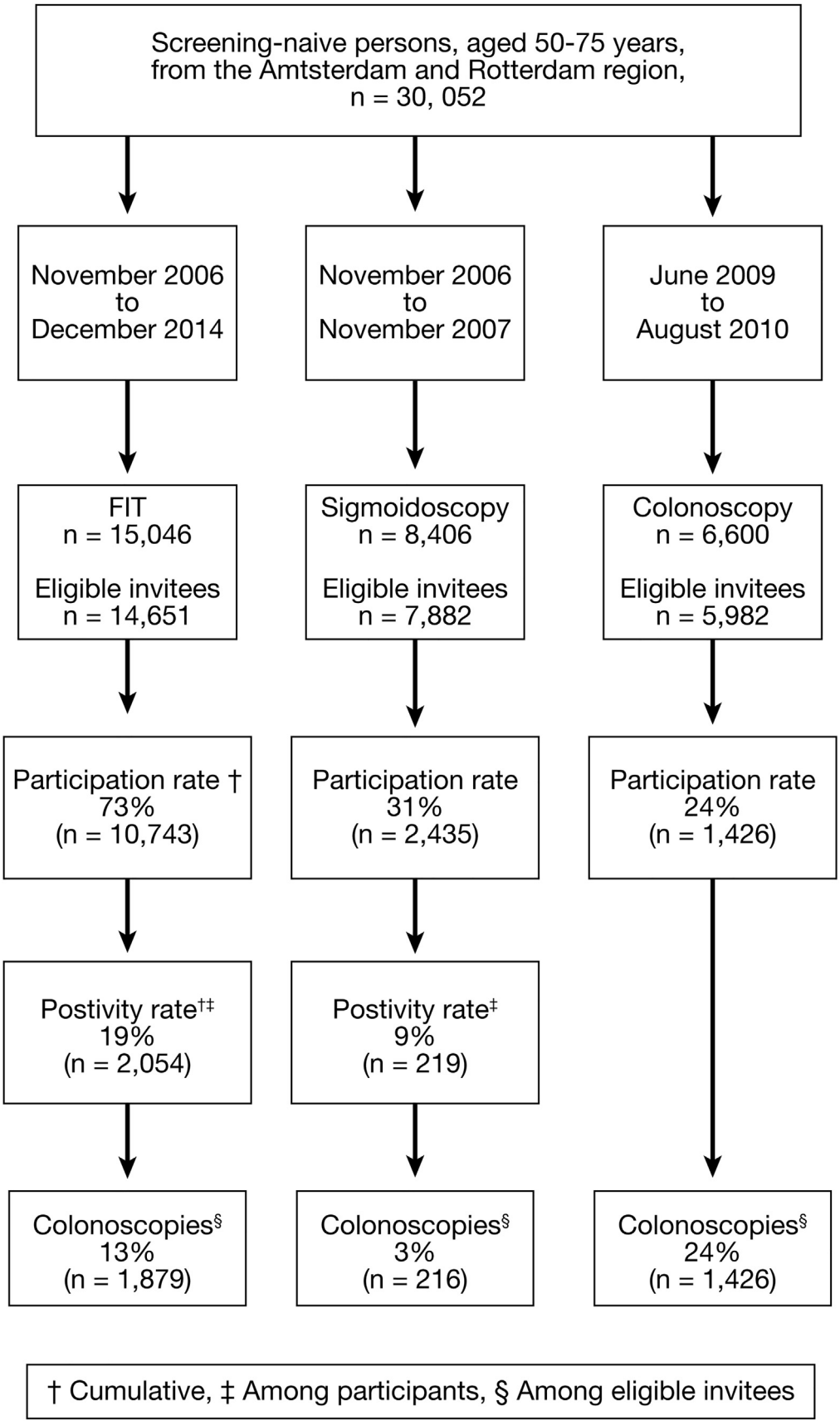

Figure 1. Study enrollment. FIT, fecal immunochemical test.

years for FIT (interquartile range [IQR], 55–65 years), 59 years for FS (IQR, 54–65), and 60 years for colonoscopy (IQR, 54–65). There were no gender differences, with 50% (n = 14,328) of the invitees being male (FIT, n = 7264 [50%]; FS, n = 3941 [50%]; and colonoscopy, n = 2982 [50%]). An overview of the study design, participation rates, and adherence to diagnostic follow-up is provided in Figure 1.

Diagnostic Yield

In the intention-to-screen analysis including all invitees, offering FIT every 2 years over 4 rounds resulted in significantly more AN compared with FS and colonoscopy (Table 1). Moreover, FIT detected 3 times more CRC per invitee than endoscopic screening: 0.6% (95% confidence interval [CI], 0.5%–0.7%) versus 0.2% (95% CI, 0.1%–0.3%; Table 1) for both FS and colonoscopy. Higher rates of non-advanced adenomas were found for colonoscopy and FS compared with FIT, whereas similar rates of sessile serrated adenomas and large hyperplastic polyps (ie, >10 mm) were found for all strategies, with 1.1% (95% CI, 0.9%–1.3%) for FIT, 5.9% (95% CI, 5.4%–6.4%) for FS, and 3.9% (95% CI, 3.5%–4.5%) for colonoscopy.

In the as-screened analysis, colonoscopy detected more AN (9.1%; 95% CI, 7.7%–10.7%) than FS (7.4%; 95% CI, 6.5%–8.5%) and FIT (6.1%; 95% CI, 5.7%–6.6%). However, CRC detection rates were similar for FIT (0.8%; 95% CI, 0.6%–0.9%), FS (0.5%; 95% CI, 0.3%–0.9%), and colonoscopy (0.6%; 95% CI, 0.3%–1.2%). Colonoscopy detected more non-advanced adenomas, with almost one-fourth of the participants having non-advanced adenomas as the most advanced finding (23.4%; 95% CI, 21.3%–25.7%; Table 1).

Figure 2 shows the cumulative increase in diagnostic yield for AN and CRC over 4 rounds of FIT screening. It shows that in the intention-to-screen analysis, FIT already detected significantly more AN and CRC after only 2 rounds of FIT screening compared with endoscopic screening. Cumulative rates of FIT screening over 4 rounds are provided in Table 2.

The positive predictive value was 32% for FIT and 83% for FS. The number needed to invite (NNI) to detect 1 participant with AN was 22 for FIT, 43 for FS, and 46 for colonoscopy. The NNI to detect 1 CRC was 178, 606, and 664, respectively. The number needed to scope to detect 1 AN was 2 for FIT, 3 for FS, and 11 for colonoscopy. The number needed to scope to detect 1 CRC was 23, 17, and 159, respectively.

Interval Cancers

Linkage to the NCCO provided data on interval cancers (Table 1). Among invitees, 19 FIT-negative screenees (0.13%) developed CRC within the screening interval compared with 6 FS-negative screenees (0.09%) and 1 colonoscopy screenee (0.01%), despite the absence of AN at colonoscopy. Furthermore, 7 colonoscopy interval cancers (0.05%) were diagnosed in screenees with a positive FIT and 1 (0.03%) in a participant with a positive FS. Taking into account these program-related interval cancers, endoscopic screening had a significantly lower interval cancer rate compared with FIT screening (Table 1).

Location and stages are described in Table 3. No significant differences were seen between the 3 screening

Table 1. Diagnostic Yield of 3 Colorectal Cancer Screening Strategies

	FIT	Sigmoidoscopy	Colonoscopy
	% (95% CI)	% (95% CI)	% (95% CI)
Intention-to-screen	(n = 14,651)	(n = 7882)	(n = 5982)
Advanced neoplasia	4.5 (4.2–4.9)	2.3 (2.0–2.7)	2.2 (1.8–2.6)
Colorectal cancer	0.6 (0.5–0.7)	0.2 (0.1–0.3)	0.2 (0.1–0.3)
Advanced adenomas	3.9 (3.6–4.3)	2.1 (1.8–2.4)	2.0 (1.7–2.4)
Non-advanced adenomas	3.2 (2.9–3.5)	3.7 (3.3–4.1)	5.6 (5.0–6.2)
Serrated polyps	1.1 (0.9–1.3)	5.9 (5.4–6.4)	3.9 (3.5–4.5)
As-screened	(n = 10,743)	(n = 2435)	(n = 1426)
Advanced neoplasia[a]	6.1 (5.7–6.6)	7.4 (6.5–8.5)	9.1 (7.7–10.7)
Colorectal cancer	0.8 (0.6–0.9)	0.5 (0.3–0.9)	0.6 (0.3–1.2)
Advanced adenomas	5.4 (5.0–5.8)	6.7 (5.8–7.8)	8.5 (7.1–10.0)
Non-advanced adenomas	4.3 (3.9–4.7)	12.0 (10.7–13.3)	23.4 (21.3–25.7)
Serrated polyps[b]	1.5 (1.3–1.7)	19.1 (17.5–20.7)	16.5 (14.6–18.5)
Non-screen detected[c]	(n = 14,651)	(n = 7882)	(n = 5982)
Interval cancer	0.2 (0.1–0.3)[d]	0.2 (0.1–0.3)[e]	0.01 (0–0.1)

CI, confidence interval; FIT, fecal immunohistochemical test; FS, flexible sigmoidoscopy.
[a]Definition of advanced neoplasia: advanced adenoma and/or colorectal cancer.
[b]Including large hyperplastic polyps (>10 mm).
[c]Follow-up: FIT and FS = 8.3 years, colonoscopy = 5.8 years.
[d]0.13% FIT interval cancer; 0.05% colonoscopy interval cancer within FIT screening program.
[e]0.09% FS interval cancer; 0.03% colonoscopy interval cancer within FS screening program.

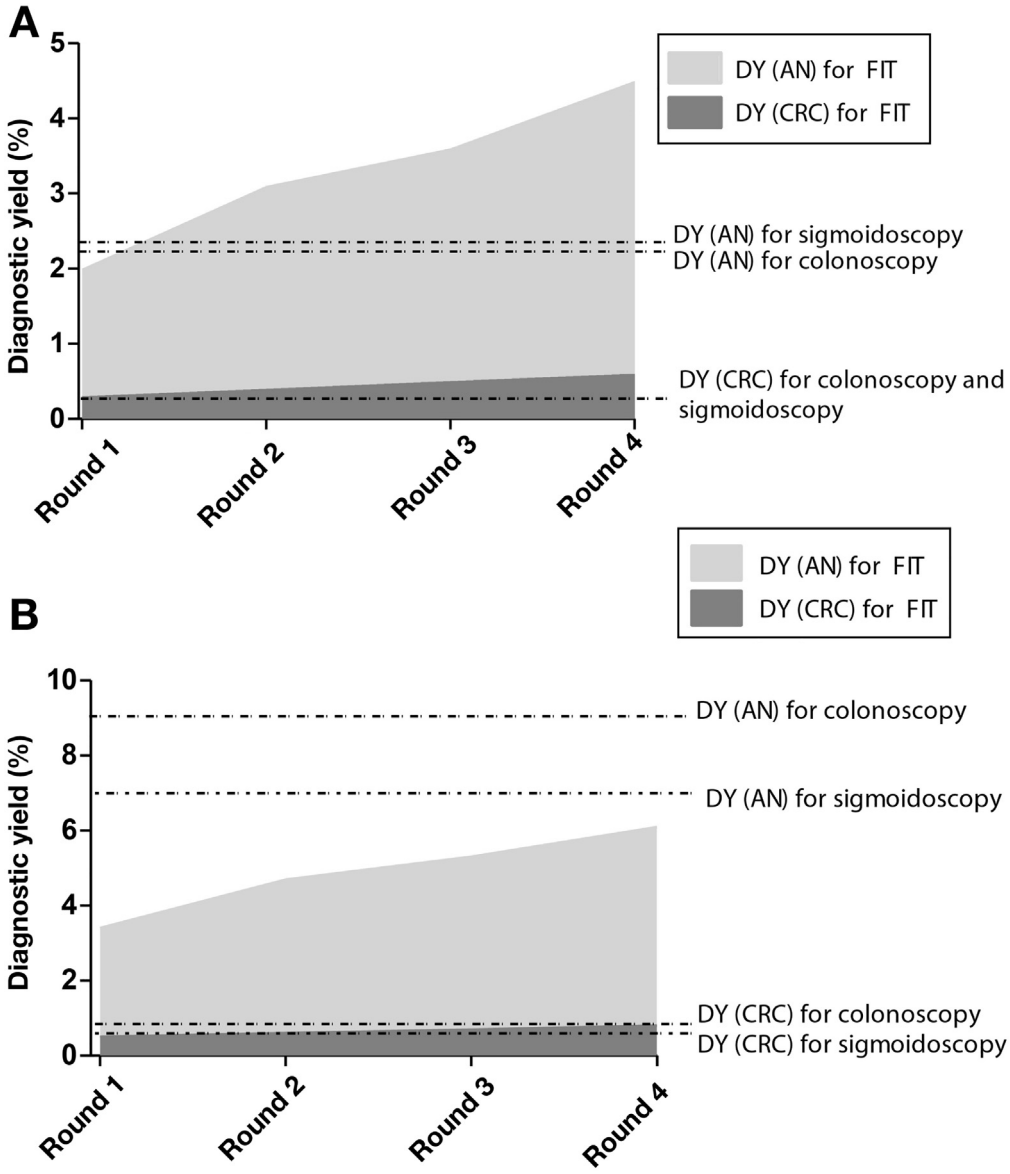

Figure 2. Cumulative diagnostic yield (DY) over 4 rounds of FIT screening for advanced neoplasia (AN) and colorectal cancer (CRC) in the intention-to-screen analysis (*A*) and as-screened analysis (*B*). FIT, fecal immunochemical test.

strategies regarding stages of screen-detected CRC ($P = .54$) or locations (ie, distal vs proximal; $P = .19$).

Interval CRC after a negative FIT or FS had a comparable distribution of cancer stage. In both strategies approximately 20% were stage IV cancers. Notably, most interval cancers in the FS group were located in the proximal colon. In the colonoscopy group 1 interval cancer was detected, which was a stage II tumor located in the proximal colon.

Discussion

This analysis comparing one-time colonoscopy with one-time sigmoidoscopy with 4 rounds of mailed FITs indicates a higher diagnostic yield of AN among invitees in FIT screening compared with endoscopic screening. This yield was reached with significantly fewer colonoscopies for FIT screening and FS screening than colonoscopy screening. No differences were found regarding the detection of CRC between all 3 strategies. Between participants, colonoscopy had the highest diagnostic yield for AN, while also detecting greater numbers of non-advanced adenomas, which are of uncertain clinical importance.

Participation rates are of crucial importance in a screening program because they directly affect diagnostic yield. Although participation rates vary widely geographically, endoscopic screening consistently shows lower participation rates compared with FIT-based screening.[2,7,26,27] This could be explained by the invasiveness and discomfort associated with endoscopic screening, as well as the difference in infrastructure required for endoscopic screening, which is much more complex than for FIT screening. A previously published randomized controlled study in Italy showed participation rates after 1 round of screening of 14.8% for colonoscopy and 50.4% for FIT screening.[27] A Spanish

Table 2. Cumulative Participation Rate, Positivity Rate, Colonoscopy Rate, and Diagnostic Yield Among Invitees of FIT Screening Over 4 Rounds (n = 14,651)

	1 round	2 rounds	3 rounds	4 rounds
	n, % (95% CI)	n, % (95% CI)	n, % (95% CI)	n, % (95% CI)
Participation rate	**8847**	**9799**	**10,384**	**10,743**
	60 (60–61)	67 (66–68)	71 (70–72)	73 (73–74)
Positivity rate	**726**	**1194**	**1614**	**2054**
	8 (8–9)	12 (12–13)	16 (15–16)	19 (18–20)
Colonoscopy rate	**666**	**1112**	**1489**	**1879**
Among invitees	5 (4–5)	8 (7–8)	10 (10–11)	13 (12–13)
Among screenees	8 (7–8)	11 (11–12)	14 (14–15)	18 (17–18)
Advanced neoplasia[a]	**295**	**456**	**546**	**660**
	2.0 (1.8–2.3)	3.1 (2.8–3.4)	3.7 (3.4–4.0)	4.5 (4.2–4.9)
Colorectal cancer	**41**	**58**	**70**	**82**
	0.3 (0.2–0.4)	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.6 (0.5–0.7)
Non-advanced adenomas	**136**	**246**	**351**	**463**
	0.9 (0.8–1.1)	1.7 (1.5–1.9)	2.4 (2.2–2.7)	3.2 (2.9–3.5)
Serrated polyps	**43**	**83**	**122**	**158**
	0.3 (0.2–0.4)	0.6 (0.5–0.7)	0.8 (0.7–1.0)	1.1 (0.9–1.3)

NOTE. Boldface indicates n value.
CI, confidence interval; FIT, fecal immunohistochemical test.
[a]Definition of advanced neoplasia: advanced adenoma and/or colorectal cancer.

randomized controlled study comparing colonoscopy and FIT screening showed participation rates after 1 round of screening of 24.6% and 34.2%, respectively.[7] Notably, in both studies FIT participation rates were substantially lower than in our study, and study recruitment strategies differed from our study; for example, invitations in Italy were sent by general practitioners. In Spain invitees received 2 reminders at 3 months and 6 months, whereas our invitees received only 1 reminder. Other studies have reported participation rates varying from 46% to 63% over multiple rounds of FIT screening, with up to 78% of FIT screenees attending screening at least once over 4 rounds of screening.[28–30] These latter findings are in line with our results, with around 73% of FIT screenees participating at least once. Our findings also confirm the stable attendance rates over multiple rounds of FIT, as described in other large screening cohorts.[28,29]

In the intention-to-screen analysis, FIT already detected significantly more AN and CRC after only 2 rounds of FIT, and this difference increased over rounds. After 4 rounds of FIT screening, the diagnostic yield of CRC was even slightly higher with FIT than after once-only colonoscopy. Comparing CRC detection rates of FIT and endoscopic screening is complex, and results should be interpreted with caution, because CRCs

Table 3. Location and Stages of Screen-Detected Colorectal Cancer and Interval Cancers

	FIT		FS		Colonoscopy	
	% (n = 10,743)		% (n = 2435)		% (n = 1426)	
	Screen-detected cancer	Interval cancer	Screen-detected cancer	Interval cancer	Screen-detected cancer	Interval cancer
Overall	0.8 (83)	0.2 (19)	0.5 (13)	0.4 (10)	0.6 (9)	0.1 (1)
Stage	% (n = 83)	% (n = 19[a])	% (n=13)	% (n = 10[b])	% (n = 9)	% (n=1)
I	54 (45)	26 (5)	77 (10)	20 (2)	78 (7)	—
II	13 (11)	16 (3)	0 (0)	20 (2)	11 (1)	100 (1)
III	32 (26)	37 (7)	23 (3)	40 (4)	11 (1)	—
IV	1 (1)	21 (4)	0 (0)	20 (2)	0 (0)	—
Location						
Distal	68 (56)	58 (11)	85 (11)	30 (3)	44 (4)	—
Proximal	32 (27)	42 (8)	15 (2)	70 (7)	56 (5)	100 (1)

FIT, fecal immunohistochemical test; FS, flexible sigmoidoscopy.
[a]Colonoscopy interval cancers (within an FIT screening program) not included.
[b]Colonoscopy interval cancer (within an FS screening program) not included.

detected in FIT screening could in theory have been prevented in a once-only colonoscopy by the removal of adenomas.

CRC screening puts a large demand on colonoscopy capacity, and high use of this expensive modality strains budgets.[31,32] Moreover, it is also an invasive procedure associated with patient discomfort and complication rates. FIT and FS identify participants at higher-than-average risk for AN to selectively refer those for colonoscopy. As a result, FIT and FS screening requires substantially fewer colonoscopies to yield a similar diagnostic yield. On the other hand, the lower use of colonoscopy also implies that lesions remain undetected and may progress to cancer. This is particularly applicable for large sessile serrated polyps (SSPs). However, SSPs are associated with the existence of synchronous AN.[33] This would suggest that FIT would possibly also detect these SSPs through the detection of occult blood from the also present AN. In concordance with this theory, our data show that for all 3 screening strategies, similar rates of SSP are detected and that these are found in only a small number of participants.

We are reporting interval carcinoma rates between FIT and endoscopic screening from similar populations during long-term follow-up. Our results indicate that stage distribution between the screening strategies is similar, which would imply comparable CRC-related survival benefits. However, these results also revealed substantial miss rates for all 3 screening strategies, demonstrating that there is still much to improve. Notably, 1 in 5 interval cancers among screenees were stage IV. It should be noted that numbers in this study were small, and only 1 colonoscopy interval cancer was found in the colonoscopy screening strategy. Comparing results, and especially interval cancer rates, between screening programs in different countries is challenging because of differences in organizational structures, populations, and quality parameters. Future studies and articles should strive to add uniformity and consistency to the reporting of results so that population-based screening studies can be compared more easily.

Our study has several strengths. First, all invitees were randomly selected average-risk persons living in the West of the Netherlands, comprising all age ranges commonly invited for CRC screening programs worldwide. All invitees were selected from comparable regions with the same socioeconomic status distribution including both rural and urban areas, using equal criteria for selection. All invitees were invited by the same screening organization using analogous letters for correspondence. All data were prospectively collected, and screenees were linked to the NCCO, which registers all patients diagnosed with cancer in the Netherlands and provides a fully covered database. To fully appreciate our results, some limitations also need to be addressed. Those invited for primary endoscopic screening were only invited once, as compared with FIT screenees who were approached biennially. Cumulative uptake among those invited for endoscopic screening would most likely be higher with repeated invitations over the years. Next, the colonoscopy screening trial started 3 years later than the FIT screening and FS screening trials, leading to different follow-up times. This makes comparing interval cancer rate between the 3 modalities challenging. In addition, ideally 1 more round of FIT and subsequent 2-year follow-up should be completed to encompass the same time frame (ie, 10 years) for each screening modality and thus to be able to fully compare the results with colonoscopy screening. It should be noted that our adherence rates, especially adherence to colonoscopy after a positive FIT, are relatively high compared with screening programs in other countries, making these results less generalizable for other screening programs.

In conclusion, different screening strategies are associated with marked differences in uptake and diagnostic yield. Over 4 rounds, FIT was the most effective strategy in population-based CRC screening, leading to detection of high rates of CRC and AN, while requiring the lowest endoscopy demand. Because many countries are considering implementing screening programs, the findings of this study aid in deciding on choice of screening strategies worldwide, which is based on expected participation rates and available colonoscopy resources.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.08.015.

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Reprint requests
Address requests for reprints to: Manon C. W. Spaander, MD, PhD, Department of Gastroenterology and Hepatology (Room Hs-312), Erasmus University Medical Centre, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. e-mail: v.spaander@erasmusmc.nl; fax: +31-(0)-10-7035172.

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Conflicts of interests
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Supplementary Methods

Study Population and Design

In total, 30,052 asymptomatic persons aged 50–75 years living in the Netherlands were randomly selected from municipal registers, sorted according to household, and were selected before invitation. Those allocated to FIT screening were invited between November 2006 and December 2014 for 4 rounds of biennial FIT screening. Individuals who had passed the upper-age limit were not reinvited. Those allocated to FS were invited between November 2006 and November 2007 for once-only FS. Those allocated to colonoscopy were invited between June 2009 and August 2010 for once-only colonoscopy. Persons with a history of inflammatory bowel disease, proctocolectomy, or CRC were asked not to participate in CRC screening but report this back to our screening organization via the informed consent form. Those with symptoms of CRC were advised to contact their general practitioner. Participants reporting a colonoscopy or computed tomography colonography in the past 3 years or those with an estimated life expectancy of less than 5 years were excluded.

Outcomes and Statistical Analysis

For FIT screening cumulative rates over 4 rounds were used in all analyses. Participation rate was calculated as the number of invitees returning a FIT relative to the number of all eligible invitees. Positivity rate was defined as the proportion of participants having a positive test result relative to the number of tests returned. NNI was the number that needed to be invited to detect 1 person with AN. Number needed to scope was defined as the number that needed to undergo a colonoscopy to detect 1 person with AN.