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ABSTRACT

Background: Screening for colorectal cancer (CRC) is widely accepted, but there is no consensus on the preferred strategy. We conducted a randomised trial comparing participation and detection rates (DR) per screenee of guaiac-based faecal occult blood test (gFOBT), immunochemical FOBT (FIT), and flexible sigmoidoscopy (FS) for CRC screening.

Methods: A representative sample of the Dutch population (n = 15 011), aged 50–74 years, was 1:1:1 randomised prior to invitation to one of the three screening strategies. Colonoscopy was indicated for screenees with a positive gFOBT or FIT, and for those in whom FS revealed a polyp with a diameter ⩾10 mm; adenoma with ⩾25% villous component or high grade dysplasia; serrated adenoma; ⩾3 adenomas; ⩾20 hyperplastic polyps; or CRC.

Results: The participation rate was 49.5% (95% confidence interval (CI) 48.1 to 50.9%) for gFOBT, 61.5% (CI, 60.1 to 62.9%) for FIT and 32.4% (CI, 31.1 to 33.7%) for FS screening. gFOBT was positive in 2.8%, FIT in 4.8% and FS in 10.2%. The DR of advanced neoplasia was significantly higher in the FIT (2.4%; OR, 2.0; CI, 1.3 to 3.1) and the FS arm (8.0%; OR, 7.0; CI, 4.6 to 10.7) than the gFOBT arm (1.1%). FS demonstrated a higher diagnostic yield of advanced neoplasia per 100 invitees (2.4; CI, 2.0 to 2.8) than gFOBT (0.6; CI, 0.4 to 0.8) or FIT (1.5; CI, 1.2 to 1.9) screening.

Conclusion: This randomised population-based CRC-screening trial demonstrated superior participation and detection rates for FIT compared to gFOBT screening. FIT screening should therefore be strongly preferred over gFOBT screening. FS screening demonstrated a higher diagnostic yield per 100 invitees than both FOBTs.

Screening can reduce the colorectal cancer (CRC) mortality rate based both on early detection of CRC and endoscopic removal of adenomas.[1 2] CRC screening is therefore widely accepted, but there is no consensus on the preferred strategy. The European Council recommends faecal occult blood (FOBT) screening for CRC in average-risk men and women aged 50–74 years.[3] More than 50% of the target population in the European Union is, however, offered no screening at all. In those regions where screening is being offered, this usually occurs with guaiac-based FOBT (gFOBT) or more rarely with flexible sigmoidoscopy (FS).

Four large randomised controlled trials (RCT) have consistently shown that biennial gFOBT screening reduces CRC mortality.[4–7] This reduction mainly occurs due to early detection of CRC. However, gFOBT is hampered by a low sensitivity for advanced neoplasia (11–37%),[8 9] which explains the limited impact of repeated gFOBT screening on CRC mortality. Recently, immunochemical FOBT (FIT) screening has become available. FIT has a better sensitivity and similar specificity for detecting advanced neoplasia compared to the gFOBT,[8 10–15] since it specifically detects human haemoglobin. Sigmoidoscopy screening is possibly more effective than FOBT screening due to the considerable higher sensitivity for detection of early neoplastic lesions and the possibility of removing adenomas during the screening procedure.[16 17] Case–control studies reported a CRC mortality reduction of 59–79% within the reach of the endoscope following single FS.[18 19] The results of RCTs on mortality reduction of FS screening are expected in the near future.[20–23]

In addition to mortality reduction, uptake of screening is the second major determinant of effectiveness of a CRC screening programme. Until now, randomised trials directly comparing the three most relevant screening methods in an unselected asymptomatic population are lacking. We therefore conducted a randomised population-based trial to compare gFOBT, FIT and FS screening in an average-risk screening naïve population. The primary endpoint of this study was the participation rate to each of the three screening strategies. Detection rate (DR) of advanced neoplasia with each screening strategy was the secondary aim.

METHODS

Study population

Names, dates of birth, and postal addresses of all individuals aged 50–74 years in the region Rijnmond in the southwest of The Netherlands were obtained from the eight regional municipality offices. From this dataset of 338 000 individuals, a random sample of 15 011 individuals was taken by computer generated algorithm and 1:1:1 randomised using this computer generated algorithm (Tenalea, Amsterdam, The Netherlands). Randomisation was done per postal address after stratifying by age, sex and social economic status (SES) into groups A (gFOBT), B (FIT) or C (FS) (fig 1). The SES was based on the data of Statistics Netherlands (www.cbs.nl; accessed 3 September 2009) providing average SES per postal code area, each representing small neighbourhoods. Randomisation occurred prior to invitation. Informed consent was obtained after randomisation.

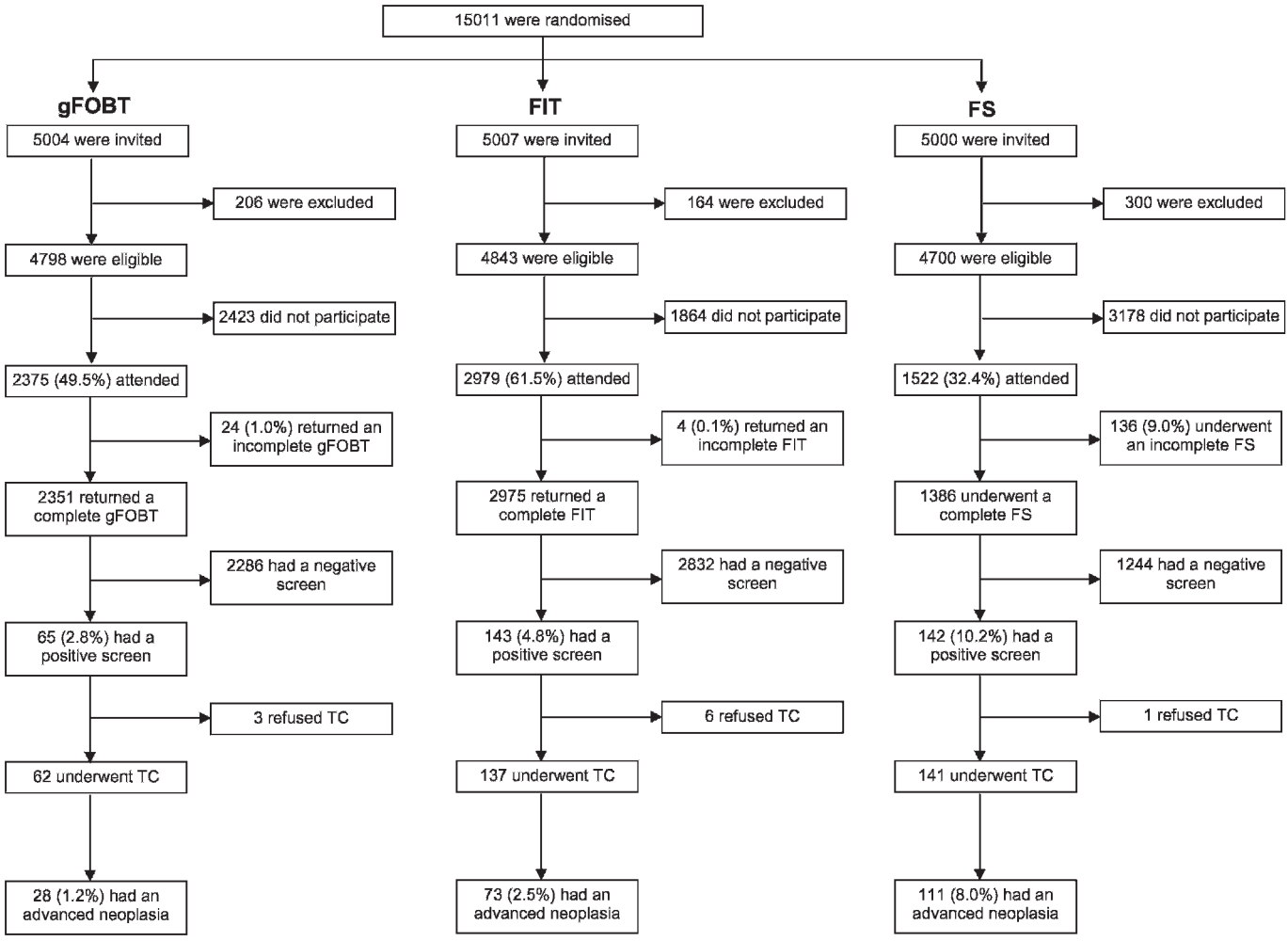

Figure 1 Trial profile. FIT, immunochemical faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based faecal occult blood test; TC, total colonoscopy.

Individuals with a history of inflammatory bowel disease or CRC, a colonoscopy, sigmoidoscopy or barium contrast enema in the last 3 years, major health problems, or those who moved away or died were excluded from analyses. Recruitment took place between November 2006 and November 2007.

Interventions

All individuals were sent a pre-invitation letter containing information on CRC screening. Two weeks later an invitation letter was sent with information on possible advantages and risks of screening and on the specific screening test that was offered. This was accompanied by an informed consent form, which had to be signed and returned. A test set was sent along with the invitation in case of gFOBT or FIT screening. The FS group received an invitation letter with a telephone number of the screening unit to schedule an appointment. A reminder was sent six weeks afterwards to all non-respondents. Information about the study was further given to all general practitioners (GP) in the region by direct visits of research physicians prior to start of the study, providing them with background, a contact address, and an information folder. All information was made available via a dedicated website (www.dikkedarmkankerpreventie.nl; accessed 3 September 2009), mailings and information sites of the municipality offices, regional newspapers and national and regional broadcasting.

Group A: guaiac-based FOBT

All randomised individuals received three guaiac-imprinted test cards at invitation (Hemoccult II; Beckman Coulter, Fullerton,

Table 1 Participation by age, gender, social economic status and rural versus urban in all screening arms; multivariate analysis

Parameter	gFOBT, OR (CI)	FIT, OR (CI)	FS, OR (CI)
Men	1	1	1
Women	1.1 (0.9 to 1.4)†	1.3 (1.1 to 1.4)*	0.9 (0.8 to 1.0)*
50–59 years	0.8 (0.7 to 1.0)*†	0.8 (0.7 to 0.9)*	0.9 (0.7 to 1.0)*
60–64 years	1	1	1
65–74 years	1.0 (0.8 to 1.2)†	1.0 (0.8 to 1.2)	0.8 (0.6 to 0.9)*
SES low	1	1	1
SES middle	1.2 (1.1 to 1.4)*	0.9 (0.8 to 1.1)	1.0 (0.8 to 1.2)
SES high	1.1 (1.0 to 1.3)	1.3 (1.1 to 1.5)*	1.2 (1.0 to 1.4)*
Strong urban	1	1	1
Urban	1.7 (1.4 to 2.1)*	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.5)
Rural	2.6 (1.9 to 3.6)*	2.3 (1.6 to 3.3)*	1.8 (1.3 to 2.6)*

Odds ratios (ORs) adjusted for all the other variables in the table.
*$p<0.05$.
†Interaction of age and sex in the gFOBT arm. Therefore age-specific OR (participants aged 60–64 years) are presented for men and women and sex specific ORs (male) for the different age groups.
CI, confidence interval; FIT, immunochemical faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based faecal occult blood test; SES, social economic status.

California, USA) to be used on three consecutive bowel movements without dietary restrictions or medication limitations. Participants returned the test kit by mail to the Gastroenterology and Hepatology Laboratory of the Erasmus University Medical Centre. Tests were analysed without rehydration. A test was considered positive if one or more panels were positive. A digital picture of the test cards was taken and stored in a database. A subset of 241 photographs was re-evaluated by a second technician blinded for the initial test results. A third technician reviewed the tests in case of inter-observer variation.

Group B: immunochemical FOBT

Subjects received one immunochemical FOBT kit (OC-Sensor micro; Eiken Chemical, Tokyo, Japan) to collect a single faecal sample of one bowel movement. Participants returned the test kit by mail to the same laboratory as mentioned above for quantitative analysis using the automatic OC-sensor μ instrument (Eiken Chemical). The test was considered positive at a cut-off value of 100 ng haemoglobin/ml according to the manufacturer's instructions and in agreement with previous studies using the same test.[24 25]

Group C: flexible sigmoidoscopy

Individuals randomised to FS, once scheduled for an appointment, received a 120 ml phosphate enema (Clyssie, B; Braun Medical, Oss, The Netherlands) by mail with instructions for self-administration. Administration of the enema by a nurse in the screening unit was offered as an alternative. Flexible sigmoidoscopy was performed with a regular forward-looking video-colonoscope (Olympus Europe, Hamburg, Germany). All sigmoidoscopies were performed by experienced endoscopists (>200 colonoscopies) in a dedicated screening centre. The endoscope was advanced as far as could be achieved without causing undue pain or distress, aiming to reach the splenic flexure. The FS was considered complete when the endoscope was advanced beyond the colon descending–sigmoid junction into the proximal descending colon and more than 50 cm of the anal verge with endoscope in straightened position. Participants did not receive sedatives. The reach of the endoscope in the straightened position (in centimetres) and the location were recorded. The adequacy of bowel preparation was also recorded. If bowel preparation was inadequate, the participant was offered an additional enema in the screenings unit followed by repeated FS during the same appointment, or a new appointment with oral bowel preparation (Prunacolon, 75 ml) in combination with an enema. During FS, characteristics including size and location of all polyps were noted and recorded. The size of each polyp was measured using an open biopsy forceps with 7 mm span. All polyps up to a diameter of 9 mm were removed at FS and sent for histological evaluation. Polyps with a diameter of ⩾10 mm were left in situ for removal during colonoscopy. Participants were referred for colonoscopy when one of the following criteria was met: presence of a polyp with a diameter ⩾10 mm; an adenoma with serrated, villous histology (⩾25% villous) or high-grade dysplasia; ⩾3 adenomas; ⩾20 hyperplastic polyps; or invasive CRC.[22] In accordance with the international classification, CRC was defined as the invasion of malignant cells beyond the muscularis mucosa. One experienced gastrointestinal pathologist evaluated all samples. A second gastrointestinal pathologist evaluated a subset of 50 adenomas and all advanced neoplasia.

Test results

In the case of a positive gFOBT, FIT or FS the general practitioner (GP) was informed by telephone and mail within 2 weeks. The GP informed the participant about the test result and referred the participant for colonoscopy. A colonoscopy was scheduled within 4 weeks after the screening test results had become available. Participants with a negative gFOBT or FIT and participants with no or low-risk polyps at FS were informed by mail within 2 weeks.

Power calculation

The primary outcome measurement was the participation rate. The sample size was chosen based on a presumed overall 50% participation rate to yield an 80% power to discern a 2.0% difference in participation rate between the three screening strategies and a 2.5% difference in participation rate between a maximum of three equal-sized subgroups per arm.

Statistical analysis

Differences in proportions between screening strategies were calculated using the χ^2 test. Differences in means between screening strategies were calculated using a Student t test. The participation rate was calculated by dividing participants by all eligible subjects (defined as all randomised subjects minus the excluded subjects). A univariate logistic regression model was fitted to the data to determine differences in participation rate between the three screening strategies. Separate uni- and multivariate models were fitted to the three screening arms with participation as function of age, sex, SES and rural versus urban domicile. Interaction of age and sex was determined using a multivariate model for each screening arm. A significant interaction was found in the gFOBT arm between age and sex on participation ($p = 0.009$). Age- and sex-specific participation rates to gFOBT screening were therefore presented in the result section. The DR was defined as the proportion of screenees with advanced neoplasia. This definition included subjects with CRC, and those with advanced adenomas. Advanced adenoma was defined as adenoma ⩾10 mm, with a villous histology (⩾25% villous) or with high-grade dysplasia. The DR was calculated using the most advanced lesion detected per screenee. A multivariate logistic regression model with advanced neoplasia or CRC as a function of age, sex and screening test was used to determine the differences in DR between screening tests. The diagnostic yield per 100 invitees was calculated as subjects with an advanced neoplasia or CRC divided by all eligible subjects. All p values were two-sided and considered significant if <0.05.

RESULTS

Participation

Of the 15 011 subjects who were randomised prior to invitation to one of the three tests 670 were excluded from analysis (4.5%; 608 subjects met one of the exclusion criteria, 43 had moved away and 19 had died). The overall participation rate was 48.0% (CI, 47.1 to 48.7%). In total, 49.5% (CI, 48.1% to 50.9%) attended gFOBT, 61.5% (CI, 60.1% to 62.9%) FIT and 32.4% (CI, 31.1% to 33.7%) FS screening (fig 1).

In univariate analysis sex, age, SES and rural versus urban domicile were associated with participation rate in all screening arms (all $p<0.05$). Multivariate analysis showed indication between sex and age on participation rate in the gFOBT arm ($p = 0.009$). The age-specific participation rate to gFOBT screening was significantly higher in women than in men aged 50–59 years (OR, 1.6; CI, 1.4 to 2.0), while no difference

Table 2 Most-advanced lesion identified by screening

	gFOBT, n (%)	FIT, n (%)	FS*, n (%)
Completed screening test	2351	2975	1386
Positive screening tests	65 (2.8)	143 (4.8)	142 (10.2)
Colonoscopy performed	62 (95)	137 (96)	141 (99)
Detection rate			
Non-neoplastic polyp	4 (0.2)	7 (0.2)	272 (19.6)
Non-advanced adenoma	12 (0.5)	23 (0.8)	183 (13.2)
Advanced adenoma†	22 (0.9)	59 (2.0)	103 (7.4)
Colorectal cancer	6 (0.3)	14 (0.5)	8 (0.6)
Positive predictive value			
Advanced adenoma	35.5	43.1	na
Colorectal cancer	9.7	10.2	na

*Findings during sigmoidoscopy and colonoscopy.
†Advanced adenoma: adenoma ⩾10 mm, villous component (⩾25% villous) or high-grade dysplasia.
FIT, immunochemical faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based faecal occult blood test; na, not applicable.

between both sexes was seen in the age groups 60–64 years (OR, 1.1; CI, 0.9 to 1.4) and 65–74 years (OR, 1.0; CI, 0.8 to 1.2). The participation rate of men aged 50–59 years was significantly lower than men aged 60–64 years (OR, 0.8; CI, 0.7 to 1.0; p<0.05). Participation rates were similar for the different age groups in female invitees to gFOBT screening (fig 2). Independent predictors for higher participation to FIT screening were female sex, and age 60–64 years (fig 2). Male sex and age 60–64 years were independent predictors for a higher participation to FS screening. Living in a rural area and a high SES were associated with a higher participation rate in all three screening arms (table 1).

Screening strategies

gFOBT was analysable in 2351 cases (99%), and was positive in 65 cases (2.8%). Sixty-two (95%) subjects underwent a colonoscopy, which was complete in all cases. Advanced adenomas were found in 22 (0.9%), and a CRC in six screenees (0.3%) (table 2). Of the six CRCs, three (50%) were classified as early stage (stage I, one; and stage II, two) and three (50%) as advanced CRCs (stage III, two; and stage IV, one). The positive predictive value (PPV) of gFOBT was 45.2% for an advanced neoplasia and 9.7% for a CRC.

FIT was complete in 2975 subjects (99.9%). A cut-off value of 100 ng/ml resulted in 143 (4.8%) positive tests. In total, 137 (96%) of the positive screenees underwent colonoscopy. This procedure was complete in 134 (98%) subjects. The colonoscopy was incomplete in two cases due to obstructing tumour. A double-contrast barium enema was performed in one subject with an incomplete colonoscopy. Advanced adenoma were detected in 59 (2.0%) and CRC in 14 (0.5%) screenees (table 2). Of all detected CRCs (n = 14) due to FIT screening, 12 (86%) were early stage (stage I, five; and stage II, seven) and two were advanced (stage III). The PPV of a FIT for finding an advanced neoplasia (53.3%) or a CRC (10.2%) was similar to the PPV of the gFOBT (respectively, p = 0.42; p = 0.93).

FS evaluation was complete in 1386 screenees (91%). Incomplete examination was due to insufficient bowel preparation in 88 (5.8%) subjects and failure to obtain full introduction (>50 cm with straightened scope) in 51 (3.4%) subjects. In total, 142 (10.2%) screenees were referred for colonoscopy. In total, 1243 screenees without polyps (n = 817; 59%) or with non-advanced polyps (424; 31%) were discharged. All but one of the positive screenees underwent a complete colonoscopy (99%). One colonoscopy was incomplete due to an obstructing tumour. In total, 103 screenees (7.4%) had an advanced adenoma and eight (0.6%) a CRC (table 2), including six early stage CRCs (75%; stage I, six) and two advanced CRCs (stage III, two). One complication occurred within 30 days after FS. A 67-year-old screenee presented 1 week after FS with symptoms of a colovaginal fistula due to a previous diverticulitis. It was considered that air insufflation might have led to symptoms, since no signs of diverticulitis were seen or biopsies had been taken during FS. An uncomplicated sigmoid resection was performed. In total, four patients (1.1%) experienced minimal rectal bleeding following polypectomy during colonoscopy without hospitalisation.

Table 3 Odds ratios (ORs) for the probability of detection of colorectal neoplasia in screened individuals which FIT and FS in comparison with gFOBT

	Advanced neoplasia OR, (CI)	Colorectal cancer OR, (CI)
gFOBT	1	1
FIT	2.0 (1.3 to 3.2)	1.8 (0.7 to 4.7)
FS	7.0 (4.6 to 10.7)	2.2 (0.8 to 6.3)

Advanced neoplasia: adenoma ⩾10 mm, villous component (⩾25% villous) or high-grade dysplasia; colorectal cancer.
CI, confidence interval; FIT, immunochemical faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac-based faecal occult blood test.

Comparison of advanced neoplasia detection rate and yield

Older age (65–75 years; OR, 2.3; CI, 1.7 to 3.2) and male sex (OR, 2.7; CI, 2.0 to 3.6) were independent predictors for detecting advanced neoplasia. After adjusting for age and sex (table 3 and fig 2), FIT detected significantly more advanced neoplasia than gFOBT (OR, 2.0; CI, 1.3 to 3.2). The DR of advanced neoplasia was considerable higher in the FS arm than in the gFOBT (OR, 7.0 CI, 4.6 to 10.7) and FIT (OR, 3.4; CI, 2.5 to 4.7) arms. The DR of CRCs did not differ significantly among the three screening arms (table 3).

The diagnostic yield of advanced neoplasia per 100 invited subjects was significantly higher with FIT (1.5; CI, 1.2 to 1.9) than with gFOBT (0.6; CI, 0.4 to 0.8; p<0.001). FS demonstrated the highest diagnostic yield of advanced neoplasia of 2.4 (CI, 2.0 to 2.8) per 1000 invited subjects compared to gFOBT (p<0.001) and FIT (p<0.001).

DISCUSSION

Our data demonstrated a 12% higher participation rate to FIT than gFOBT screening, which is in agreement with the study by van Rossum *et al*, who used a similar study design.[24] It has been postulated that dietary restrictions required for gFOBT screening are responsible for a lower uptake.[26] However, our study shows that gFOBT screening performed without dietary restrictions remains associated with a lower uptake than FIT screening. A more demanding sampling procedure and the number of consecutive bowel movements that had to be collected[27] (three for gFOBT vs one for FIT) seem likely explanations for this difference in participation rate.

Participation to FS screening was significantly lower than to both FOBTs. The participation rate to FS screening in our population is in agreement with most previous population-based FS screening studies,[16 17 21] but significantly lower than seen in the Norwegian FS screening trial (67%).[24] Our data on participation rate cannot be directly compared to studies where only eligible and interested respondents to a questionnaire were included in the study.[20 22] However, multiplying inclusion with

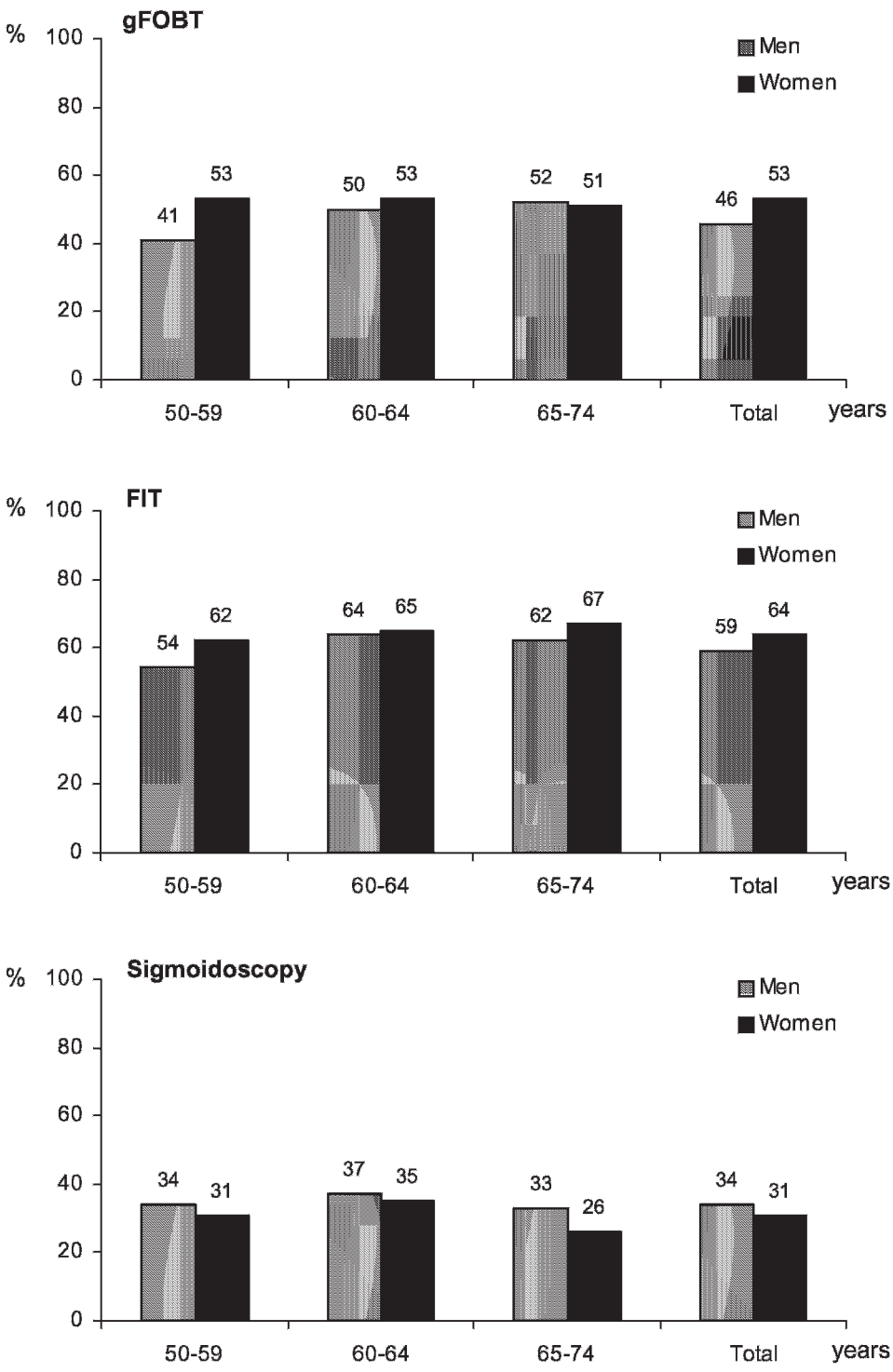

Figure 2 Age-specific participation rates to guaiac-based faecal occult blood test (gFOBT), immunochemical faecal occult blood test (FIT) and flexible sigmoidoscopy (FS) screening of men and women.

participation rates among those included results in overall participation rates in the range of 10–39%.[20 22]

Furthermore, invitees in our study were asked to schedule their own FS appointment, which may have negatively influenced the participation rate. In other studies the appointment for FS was prefixed to be confirmed or modified.[20 22]

Sex and age were independent predictors for participation in all screening arms. In both FOBT arms, men were less likely to attend. A low participation rate was especially found among men aged 50–55 years (gFOBT, 37%; FIT, 51%). In contrast, uptake of FS screening was lower among women. This is in accordance with previous studies.[16 17 20 22] Attitude and beliefs about FS screening might form a barrier to FS screening. Women more often experience fear and embarrassment when undergoing FS.[28] A special approach to women in a future nationwide FS screening programme should therefore be considered.

FS screening detected a substantially higher proportion of advanced neoplasia than both FOBTs, mainly due to a high DR of advanced adenoma (7.4%). This higher proportion of advanced neoplasia detected at FS suggests a more significant CRC incidence and mortality reduction with FS than with FOBT screening. The comparison of the DR between both FOBTs and FS screening in this study is limited, since only one screening round was taken into account. Data of successive

FOBT screening rounds should be considered in order to obtain a more accurate comparison of the DR of both FOBTs and FS screening. Our results did demonstrate a, respectively, three and seven times higher DR of advanced neoplasia of FS compared to FIT and gFOBT screening, suggesting a more favourable cumulative DR of advanced neoplasia for a 5-yearly FS compared to a biennial gFOBT or FIT screening programme but a lower DR in the case of a 10-yearly screening interval. A 10-yearly interval for FS screening might be justified if an experienced endoscopist performed an examination of at least the distal 50 cm of the colon on well-prepared subjects. These criteria are not routinely achieved in many screening settings. Current guidelines therefore recommend a 5 year screening interval.[29] Further information on the optimal screening interval is awaited from the ongoing prospective FS studies.[20–23]

The DR of advanced neoplasia (8.0%) in the FS arm was high compared to other studies (3.6–5.2%).[16 17 20–22] A possible explanation for the higher DR may lie in inclusion of subjects between 65 and 74 years of age whereas others included subjects between 55 and 64 years of age,[20 22] since more advanced neoplasia were detected in screenees aged 65–74 years than screenees aged 50–64 years. This is in agreement with studies reporting an increased prevalence of advanced neoplasia at older age.[23 30 31] The high DR can also be explained by a more extended endoscopic examination during FS. In this study, FS was performed until the splenic flexure (81% of completed FS) or at least proximal descending colon, while other studies reached for the transition from sigmoid to descending colon as anatomic extent of FS.[20 22 23]

A high compliance of positive screenees to a follow-up colonoscopy positively influences the DR. In this study, nearly all positive screenees underwent a colonoscopy (97%). This is significantly higher than observed in other screening studies in which participation rates for colonoscopy after FOBT or FS screening generally ranged between 80% and 93%.[11 16 17 20] This difference in compliance rate may be population dependent. However, our compliance rates to colonoscopy after a positive gFOBT or FIT were considerably higher than observed in the study by van Rossum *et al* (83%),[24] which had a similar design and was conducted in the same country. We think that this difference was primarily due to the fact that we, compared to van Rossum *et al*, put the GP in charge of informing the screenee on the positive test result and further handling the referral of the screenee to one of the affiliated hospitals. The GP thus acted as a central stakeholder in the follow-up process.

This study has some limitations. First, the trial has been performed in a screening-naive population. A previous European study reported a low awareness of CRC and CRC screening in Europe and especially in The Netherlands.[32] Awareness of CRC and the effectiveness of screening does increase participation.[33] Therefore various media were used to promote this study. However, maximising awareness requires time and effort. We hypothesise that this may further increase the uptake of screening.

Second, in this study a pre-randomisation design was used to reflect a nationwide screening programme as closely as possible. Subjects meeting the exclusion criteria were therefore excluded after randomisation. Exclusion numbers were higher in the FS arm than in the other arms partly due to the extra opportunity of recognising exclusion criteria for FS subjects during the telephone call they had to make. Not excluding those subjects would not have changed the participation rates considerably (gFOBT, 47.5%; FIT, 59.5%; FS, 30.4%) and did therefore not influence the results of this study.

Third, this study describes the first screening rounds in our population. Data on participation and detection rates of successive screening rounds are needed to provide insight in long-term effectiveness of a population-based screening programme.

Fourth, colonoscopy was not incorporated as a primary screening tool in this study. We acknowledge that colonoscopy is considered the "gold standard" for CRC screening. However, colonoscopy as primary screening tool is hampered by a low uptake and prospective data on the efficacy are lacking.

Finally, we only referred screenees for colonoscopy if one of the predefined high risk criteria was met at FS. Screenees with two or fewer tubular adenomas <10 mm were therefore not referred for colonoscopy. Our approach is in agreement with two large ongoing RCTs studying the impact of first round FS screening on CRC mortality,[20 22] but in is contrast with another European RCT on FS.[21] In the latter study, all subjects with a distal adenoma of any size were referred for colonoscopy. Our approach has the disadvantage of missing cases with proximal advanced neoplasia in the presence of no more than two small distal tubular adenomas. However, a previous study reported that 1.9% of these screenees with one or two small distal adenomas (5–9 mm) have proximal advanced lesions compared to 9.9% of screenees with distal adenomas ⩾10 mm.[20] Our referral criteria therefore limit the required colonoscopy capacity while referring screenees with a higher risk on a proximal advanced neoplasia.

In conclusion, this randomised population-based CRC-screening trial demonstrates that FIT outperforms gFOBT screening in participation and detection rate. FIT screening should therefore be strongly preferred over gFOBT screening. Apart from this, it is important to recognise that FS screening in a first screening round provides a considerably higher diagnostic yield of advanced adenomas and CRC per 100 invitees than both FOBTs, despite a lower participation rate. This supports the consideration of a dual-mode screening programme, offering FS as first screening method and FIT as an alternative. Long-term prospective RCTs have to be awaited to determine the CRC incidence and mortality reduction due to FS and FIT screening.

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Competing interests: None.

Ethics approval: The study was approved by the Dutch Ministry of Health (2006/02WBO). The approval included the pre-randomisation design. The study letters and information brochures were approved by the Institutional Review Board of the Erasmus MC (MEC-2005-264).

Study organisation

EJ Kuipers, JDH Habbema and M van Ballegooijen conceived the idea for the study; EJ Kuipers, JDH Habbema, M van Ballegooijen and ME van Leerdam designed the protocol; EJ Kuipers and JDH Habbema supervised the execution of the study; L Hol performed the retrieval of the population sample and the randomisation in collaboration with Tenalea, Amsterdam; JCIY Reijerink was responsible for the retrieval of the target population from the municipal registries and all mailings; AJ van Vuuren was responsible for the analyses of the FOBTs; ME van Leerdam was responsible for the endoscopy programme; H van Dekken evaluated all pathology samples of the sigmoidoscopies. JCIY Reijerink, ME van Leerdam and L Hol were responsible for the database design; L Hol was responsible for data entry; ACM van der Togt coordinated

the daily process. L Hol drafted the report; L Hol and C Looman performed the statistical analyses; all the collaborators listed above were given an opportunity to comment on the paper.

Trial steering committee

L Hol, ME van Leerdam, M van Ballegooijen, AJ van Vuuren, JCIY Reijerink, ACM van der Togt, JDF Habbema and EJ Kuipers.

Trial advisory board

JW Coebergh, A Cats and IMA Joung.

Provenance and peer review: Not commissioned; externally peer reviewed.

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