Participation, yield, and interval carcinomas in three rounds of biennial FIT-based colorectal cancer screening

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Author contributions

ED, PB and PF developed the idea for the study, designed the study and protocol, were responsible for project organization and supervision, and obtained funding. MM and RM were involved in further development of the idea, data collection, and supervision. ME and EB were responsible for data collection for the study. IS and SvD were involved in further development of the idea, collection of the data, and writing the manuscript. IS was responsible for the statistical analyses of the data and was principally responsible for drafting this manuscript. All authors contributed to the final manuscript through critical revision and correction of draft versions, and they approved the final manuscript.

www.trialregister.nl number NTR2755

Abstract

Background

The effectiveness of colorectal cancer screening programs based on the fecal immunochemical test (FIT) is influenced by program adherence during consecutive screening rounds. We aimed to evaluate the participation rate, yield, and interval cancers in a third round of biennial CRC screening using FIT and to compare those with the first and the second screening round.

Methods

A total of 3566 average-risk individuals aged 50–75 years were invited to participate in a third round of biennial FIT-based CRC screening. All FIT positives were recommended to undergo colonoscopy. We merged our data with the national cancer registry in the Netherlands to identify all non-screen-detected cancers in our cohort.

Results

Of the invitees, 2142 (60%) returned the FIT in this third screening round, compared to 56% in the second round and 57% in the first round. Overall, 153 of the third-round participants (7.1%) had a positive FIT result, versus 7.9% in the second round and 8.1% in the first round ($P = 0.05$). Of all FIT positives, 123 (80%) underwent colonoscopy. Within this group, 33 persons had advanced neoplasia. The predictive value of FIT positivity for advanced neoplasia was 27% (33/123), compared to 42% in the second round and 54% in the first round – a significant decline ($P < 0.01$).

Conclusion

In an FIT-based screening program, participation rates remained stable over consecutive biennial screening rounds, while the FIT positivity rate and positive predictive value for advanced neoplasia gradually declined. Cancers in non-participants are significantly more advanced in staging than cancers in participants in the first round of screening.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death. [1] The prognosis of patients is determined largely by the clinical and pathological stage of the colorectal cancer at the time of diagnosis. Population screening by guaiac fecal occult blood testing and sigmoidoscopy has been shown to reduce the CRC-related mortality rate. [2–4] More recent studies used the fecal immunochemical test (FIT), a quantitative test for the detection of advanced neoplasia.

In FIT screening, all individuals with a positive FIT test are recommended to undergo colonoscopy. A major advantage of an FIT-based screening program is the relatively high participation rate. [5] However, the effectiveness of FIT-based CRC screening programs is influenced not only by the initial participation rate but also by program adherence over consecutive screening rounds. The downside of this screening method is the limited accuracy of the FIT. Approximately 25% of cancers are missed in a single round of FIT screening. [2,4,6] By repeating the screening – e.g. by biennial invitation – program sensitivity will be increased.

Several screening trials based on fecal occult blood testing (FOBT) have been conducted. A study in Scotland reported a reduction in colorectal cancer mortality in a third round of

biennial FOBT-based screening. [4,7] In Italy participation rates in an FIT-based biennial colorectal cancer screening program were high (60%). The positive predictive value of FIT was 40% in the first round compared to 33% in the later rounds. [6,8] In the second round of the biennial pilot screening program in the Netherlands, the predictive value of FIT positivity for advanced neoplasia was lower than in the first round, and fewer advanced neoplasias were detected. [5]

Despite the documented mortality reduction, literature about interval cancers and the inability of colonoscopy to protect against right-sided interval cancers demonstrates that FIT has a suboptimal sensitivity in screening.[7] Interval carcinomas – defined as carcinomas detected between two consecutive screening rounds – can occur. These cancers can be missed by either the primary screening test or during colonoscopy after a positive primary test, but they can also develop rapidly between consecutive screening rounds.

Understanding the incidence of these interval cancers can help to improve the quality and impact of a screening program. In addition, valid estimates of the likelihood of having an interval cancer in the screening program may be relevant information for invitees.

In the Netherlands, an FIT-based nationwide screening program is being introduced. To investigate the effectiveness and efficiency of such a screening program we designed a pilot population screening program in the Amsterdam region. We aimed to evaluate the participation rate and yield of a third round of CRC screening using FIT, and to study the occurrence of interval cancers between the rounds.

Methods

Three consecutive rounds of FIT-based screening have been organized in Amsterdam, the Netherlands. In the first round 10,054 individuals were randomized to receive a guaiac FOBT or an FIT test. Since the yield and participation were more favorable in participants receiving FIT, only the FIT test was used in successive rounds. The methods and results for the first two rounds have been reported in detail elsewhere.[2] The protocol of the third-round evaluation has been published.[9]

Population and design

Randomly selected individuals between 50 and 75 years of age, living in the same postal code areas in Amsterdam region as those invited to rounds one and two, were invited to

participate in this third round of biennial FIT screening (eligible invitees). This study was designed as a dynamic cohort study. All individuals invited to the first and second rounds were re-invited, except for those who had moved out of the area, passed the upper age limit, or had tested positive in a previous screening round. Also invited to the third round were individuals between the ages of 50 and 75 who had moved into the target area, and all others in the target area who had reached the age of 50 at the time of the invitation (May 2011–January 2012). Eligible invitees were identified using the electronic database of the regional municipal administration registration. Institutionalized people were excluded from participation. The invitation letter indicated that invitees with rectal blood loss and/or a change in bowel habits should not participate in screening, but contact their general practitioner instead.

Invitation

Invitations for the third round were sent out by the Foundation of Population Screening Mid-West, using the same centralized invitation program as in previous screening rounds (ICOLON). Invitees received a pre-announcement, followed by an invitation kit 2 weeks later by postal mail, including a pre-paid envelope. This invitation kit contained an invitation letter, an information leaflet, an FIT, testing instructions, and a card with frequently asked questions. A reminder was sent 2–8 weeks after the initial invitation.

Stool tests

In all three screening rounds, the OC-Sensor FIT (Eiken Chemical Co, Tokyo, Japan) was used. The OC-Sensor FIT provides a quantitative measurement of fecal human hemoglobin. The FIT consists of a probe attached to a cap, which fits a collection tube containing hemoglobin-stabilizing buffer. Participants were instructed to collect one stool, to sweep the tip of the probe several times through the feces, and to insert the probe into the tube. No diet restrictions were specified. In the specialized laboratory of the Academic Medical Center, returned FITs were processed using the OC-Sensor automated instrument (OC-sensor; Eiken Chemical Co, Tokyo, Japan). In parallel with the definition used in previous screening rounds, a test result was considered positive if it exceeded the cut-off level of 50 ng hemoglobin/ml feces (10 µg/hemoglobin/g feces). [1,3–5,10]

Colonoscopy

All participants with a positive FIT result were invited to a consultation at one of the screening centers. During this consultation, the implications of the positive test were explained and the medical history was discussed. If no contraindications were present, a colonoscopy was advised, and the procedure itself and instructions for bowel preparation were discussed with the participant. For bowel preparation we used a polyethylene glycol (PEG) solution (Moviprep, 2 liters) combined with 10 mg bisacodyl. Colonoscopies were scheduled within 2 weeks of the consultation.

Colonoscopy quality indicators were recorded on a case record form. In cases of polyps, endoscopic removal of the lesions was attempted during the same procedure. If cancer was suspected or if endoscopic removal was not possible, biopsies were obtained and histopathological assessment provided a definitive diagnosis used for further treatment strategies.

Colorectal lesions

For all lesions, exact data on location, size, macroscopic aspect, morphology, removal and endoscopic assessment of radical resection were recorded during colonoscopy. All lesions were evaluated by an experienced gastrointestinal pathologist according to the Vienna criteria.[14] Lesions were classified as adenocarcinoma, adenoma (tubular, tubulovillous, villous), hyperplastic, sessile serrated adenoma, traditional serrated adenoma, or miscellaneous. Dysplasia was defined as either low-grade or high-grade. Advanced adenoma was defined as any adenoma ≥ 10 mm or an adenoma with a villous component $>25\%$ or with high-grade dysplasia. Cancers were staged according to the 7th edition of the American Joint Committee on Cancer classification. [10]

Non-screen-detected carcinomas

Interval cancers were defined as suggested by the World Endoscopy Organization (WEO). [11] Interval cancers were defined as cancers detected in screening participants after a negative screening examination, but before the next invitation to screening. This includes individuals with a cancer detected after a negative FIT test (FIT interval carcinoma), as well as individuals with a cancer detected after a positive FIT but a negative colonoscopy (colonoscopy interval carcinoma). To calculate the number of interval carcinomas detected

between the three consecutive screening rounds and the number of cancers in non-participants, data from all invitees were linked to the Netherlands Cancer Registry, which is a nearly complete national database containing data on all new cancer patients, including tumor type, date of diagnosis and stage. [1–3,5,12]

Data analysis

We evaluated participation, yield, and interval carcinomas in the third round of FIT-based screening and compared it to the two previous rounds of FIT-based screening. The participation rate was defined as the number of invitees returning an FIT relative to the number of all eligible invitees. We calculated FIT positivity and its positive predictive value for advanced neoplasia (cancer and advanced adenoma). FIT positivity was defined as the proportion of participants with a positive FIT test result. Positive predictive value was defined as the number of participants with advanced neoplasia and a positive test relative to all participants with a positive test result. For all outcomes assessed in this paper we reported the outcomes for the participants invited to FIT-based screening only, excluding the participants invited to the guiac FOBT in the first round.

Screen-detected carcinomas were defined as cancers detected during screening. Non-screen-detected carcinomas could be either detected in screening participants (interval carcinoma) or in non-participants. Chi-square test statistics were used to test for differences in the distribution of cancer stage and location between screen-detected cancers, interval cancers, and cancers detected in non-participants. All authors had access to the study data and have reviewed and approved the final manuscript.

Results

Participation

In total, 2142 of 3566 invitees (60%) participated in this third round of FIT-based screening. Baseline characteristics of the participants in all three rounds are summarized in Table 1. Figure 1 shows the flow of participants. There were no significant differences between age and sex distribution for participation rates.

Yield

Of the 2142 third-round participants, 153 (7.1%) had a positive FIT; 123 of these (80%) underwent colonoscopy. Advanced neoplasia was detected in 33 participants, leading to an

FIT positive predictive value estimate of 27%. One or more advanced adenomas were found in 29 participants (88%); colorectal cancer in four (12%).

The FIT positivity rate in this third round was significantly lower than that in the first and second rounds (7.1% versus 8.1% and 7.9% respectively, $P = 0.001$). Table 2 shows the location and morphology of the advanced adenomas in the three rounds. [1,5,7] In the first round of screening, 12 carcinomas had been detected in 5038 participants (0.23%); in the second round six carcinomas were detected in 4211 participants (0.14%), and in this third round four carcinomas in 2142 participants (0.19%).

Screen-detected cancers, interval cancers, and cancers in non-participants

Eight interval carcinomas were detected after the first screening round (0.2%), seven after the second screening round (0.3%). The total number of carcinomas detected in non-participants did not significantly differ between rounds, with 28 carcinomas in 5012 (0.6%) non-participants in the first round, and 27 carcinomas in 4898 non-participants (0.6%) in the second round.

Table 3 shows the numbers for the several types of cancer detected. There were no significant differences in age and sex between the respective groups. Table 3 also displays the stage and location of interval cancers. Carcinomas detected in first-round participants were significantly lower in staging than carcinomas detected in non-participants ($P = 0.05$). Carcinomas detected during the second round of screening were not significantly lower in staging than those found in non-participants. We compared all cancers in participants (interval and screen-detected) and all cancers in non-participants, and observed no significant differences in staging.

Of the eight interval cancers found between the first and second rounds, five participants had tested negative on the FIT test, and three tested positive. One participant with a positive FIT result had undergone a colonoscopy, in which no lesions were detected. This colonoscopy was completed to the cecum and visualization was assessed as adequate with adequate bowel preparation. The interval carcinoma was located in the cecum near the appendix base. Additional molecular evaluation demonstrated a microsatellite stable tumor. The two other FIT-positive participants with interval cancers did not have a colonoscopy, both because they did not show up for colonoscopy.

Seven participants had an interval cancer between the second and third rounds of screening. Five were FIT-negative, two FIT-positive. One of the FIT-positive patients underwent a complete and adequate colonoscopy in which no advanced adenomas were found. She was later diagnosed with a stage IV tumor in the ascending colon. The other patient did not show up for colonoscopy and was later diagnosed with a stage III sigmoid carcinoma.

Discussion

In the third round of an FIT-based screening study in the Netherlands we observed a stable participation rate, at around 60%, and a significant decrease in FIT positivity and FIT positive predictive value compared to the first and second rounds. Cancers in non-participants are of a significantly higher stage than cancers detected during the screening process.

An important strength of our study is the possibility of merging our data with the cancer registry in the Netherlands, which enabled us to generate reliable information about interval cancers and cancers in non-participants. Some limitations to this study also need to be mentioned. We were not able to obtain and compare FIT sensitivity estimates because colonoscopies were not done in individuals with a negative FIT result. Although the positive predictive value for advanced neoplasia was high, it is known that sensitivity in FIT-based screening is limited. [4,7] Absolute numbers of screen-detected and non-screen-detected cancer cases were small, which limits the power of statistical tests for comparisons of cancers in the different groups.

Participation rates in three consecutive rounds of FIT screening did not significantly change. Participation rates were lower than the 61% and 63% participation rates of a first- and second-round pilot program in another Dutch region [6,8], but were comparable to that of the third round of the Scottish guaic FOBT screening cohort. [5,13] In the first round of this screening project screening guaic FOBT was compared with FIT. The participation rate in that round was significantly lower in the guiac group (47% for guiac and 60% for FIT) while the detection rate for advanced neoplasia was higher in the FIT group. [2,9]

In this third round of screening, advanced neoplasia was detected in one third of FIT-positive participants undergoing colonoscopy, which is a significant decrease from earlier rounds. It seems that the yield of biennial FIT-based screening declines over consecutive rounds, in line with the results of earlier studies. The Scottish guaic FOBT-based screening cohort showed a decline in yield for the first two rounds, but no significant decrease in the third round. [13] In

a Danish study, a decrease in positive predictive value in guaic-based screening was observed until the fifth round of screening. [14] In our study, FIT positivity was also significantly lower in the third round compared to earlier rounds. Based on the experience in FOBT screening,[14] we expect that in our cohort the positivity and positive predictive value of FIT will reach a plateau after several screening rounds, but we have not yet observed this plateau after three rounds.

In FIT-based colorectal cancer screening, cancers and advanced adenomas can be missed either by the FIT or during colonoscopy after a positive FIT. Both may leave patients with false reassurance. Steele et al investigated interval cancers in a screening program using guiac FOBT.[14] They concluded that there is a substantial number of interval cancers with this type of screening, and that those cancers are associated with a better prognosis than cancers in non-screened individuals. The number of non-screen-detected cancers is used as an indicator for the effectiveness of a screening program. Gill et al compared screen-detected and interval cancers in the British Bowel Cancer Screening Program. In their study no significant differences in staging were found between interval cancers and cancers in non-invitees. [15] Morris et al showed that screen-detected cancers have a better prognosis than cancers detected outside screening. [16] In our study the tumor stages of screen-detected cancers and interval cancers were not significantly different, but statistical power was low. We do not yet have data on survival for these patients.

In conclusion, after three rounds of biannual screening, no plateau for FIT positivity and positive predictive value has been reached. FIT-based biennial pilot screening studies should be continued in order to assess the course of FIT-based screening over the years.

Acknowledgements

The authors acknowledge Karin de Groot, research nurse, for her professional work. The authors thank the Foundation of Population Screening Mid-West (Bevolkingsonderzoek Midden West) and the Comprehensive Cancer Centre, the Netherlands (IKNL), for their important contributions to the study.

Funding

The study was supported by a grant from the Netherlands Organization for Health Research and Development of the Dutch Ministry of Health (ZonMW 12010095420). FITs as well as the

reagents needed for laboratory assessment were provided by Eiken Chemical Co., Ltd., Japan. The sponsor was not involved in the study.

None of the authors received private funding for this study.

References

- [1] Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2006;18:581–92.
- [2] Van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, et al. Random Comparison of Guaiac and Immunochemical Fecal Occult Blood Tests for Colorectal Cancer in a Screening Population. *Gastroenterology* 2008;135:82–90. doi:10.1053/j.gastro.2008.03.040.
- [3] Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993;329:1977–81.
- [4] Libby G, Brewster DH, McClements PL, Carey FA, Black RJ, Birrell J, et al. The impact of population-based faecal occult blood test screening on colorectal cancer mortality: a matched cohort study 2012;107:255–9.
- [5] Denters MJ, Deutekom M, Bossuyt PM, Stroobants AK, Fockens P, dekker E. Lower Risk of Advanced Neoplasia Among Patients with a Previous Negative Result from a Fecal Test for Colorectal Cancer. *YGAST* 2011:1–28.
- [6] Van Roon AHC, Goede SL, van Ballegooijen M, van Vuuren AJ, Looman CWN, Biermann K, et al. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. *Gut* 2012. doi:10.1136/gutjnl-2011-301583.

- [7] De wijkerslooth TR, stoop EM, Bossuyt PM, Meijer GA, van Ballegooijen M, van Roon AHC, et al. Immunochemical Fecal Occult Blood Testing Is Equally Sensitive for Proximal and Distal Advanced Neoplasia. *Am J Gastroenterol* 2012.
- [8] Crotta S, Segnan N, Paganin S, Dagnes B, Rosset R, Senore C. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. *Clin Gastroenterol Hepatol* 2012;10:633–8.
- [9] Stegeman I, de Wijkerslooth TR, Mallant-Hent RC, de Groot K, Stroobants AK, Fockens P, et al. Implementation of population screening for colorectal cancer by repeated Fecal Immunochemical Test (FIT): third round. *BMC Gastroenterol* 2012;12:73.
- [10] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;17:1471–4.
- [11] Sanduleanu S, le Clercq CMC, Dekker E, Meijer G a., Rabeneck L, Rutter MD, et al. Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. *Gut* 2014;1–11. doi:10.1136/gutjnl-2014-307992.
- [12] Dashwood RH. Early detection and prevention of colorectal cancer (review). *Oncol Rep* 1999;6:277–81.
- [13] Steele RJC, McClements PL, Libby G, Black R, Morton C, Birrell J, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. *Gut* 2009;58:530–5.
- [14] Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467–71.
- [15] Gill MD, Bramble MG, Rees CJ, Lee TJW, Bradburn DM, Mills SJ. Comparison of screen-detected and interval colorectal cancers in the Bowel Cancer Screening Programme. *Br J Cancer* 2012;107:417–21.
- [16] Morris EJA, Whitehouse LE, Farrell T, Nickerson C, Thomas JD, Quirke P, et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. *Br J Cancer* 2012;107:757–64.

Table 1. Characteristics of screening participants.

	First round	Second round	Third round	<i>P</i> -value
Invitees	5038	4211	3566	
Participants (%)	2871 (57%)	2359 (56%)	2142 (60%)	<0.05
Mean age (SD)	59 (6.8)	60 (6.8)	61 (6.5)	NS
Males (%)	1,463 (51%)	1,054 (45%)	965 (45%)	NS

Table 2. Yield in three consecutive rounds of fecal immunochemical test (FIT) based screening participants.

	First round (n = 2871)	Second round (n = 2359)	Third round (n = 2142)
FIT positives	233 (8.1%)	186 (7.9%)	153 (7.1%)
Colonoscopies	186 (80%)	156 (84%)	123 (80%)
Advanced neoplasia ^a	100 (54%)	65 (42%)	33 (27%)
Location of advanced neoplasia ^b			
Proximal	24 (27%)	21 (33%)	14 (47%)
Distal	64 (73%)	43 (67%)	16 (53%)
Type of advanced neoplasia			
Cancer	12 (12%)	6 (9.2%)	4 (12%)
Advanced adenoma	88 (88%)	59 (91%)	29 (88%)
Size of advanced adenoma ^c			
> 10 mm	66 (75%)	51 (78%)	18 (55%)
6–9 mm	12 (14%)	5 (7.7%)	7 (21%)
1–5 mm	10 (11%)	9 (14%)	8 (24%)

^a At least one advanced neoplasia detected during colonoscopy.

^b For three adenomas in the second round and 11 adenomas in the third round location was unknown.

^c For one adenoma in the second round and one adenoma in the third round size was unknown.

Table 3. Stage and location of cancers detected during screening, interval cancers, and cancers in non-participants.

	Participants				Interval cancers				Non-participants	
	First Round	Second Round	Third round	First round	Second round	First round	Second round			
	(n = 12)	(n = 6)	(n = 4)	(n = 8)	(n = 7)	(n = 28)	(n = 27)			
Stage at diagnosis										
I	6	3	1	3	1	4	3			
II	2	0	1	1	1	7	8			
III	4	3	1	2	2	13	7			
IV	0	0	1	2	3	4	7			
missing							2			
Location ^a										
Distal ^b	6	3	3	5	6	21	17			
Proximal ^c	6	2	1	3	1	7	10			

Chi-square test $P = 0.05$

Number of interval cancers shown refers to the group that underwent FIT-based screening.

^a For one adenoma in the second round and one adenoma in the third round stage was unknown.

^b Descending colon, sigmoid colon or rectum.

^c Cecum, ascending colon, hepatic flexure, transverse colon or splenic flexure.

16. DISCUSSION- Regarding the study by Gill &co, it should be mentioned their British origin, to mention "Bowel Cancer Screening Program" does not identify where this programme takes place. Also regarding the same article (ref 16) it is not true that the authors of this study did not find differences between interval cancers and screen-detected; they did find statistically significant differences between these groups, it is between the intervals and the non-invitees that they did not find differences.

Thank you. We have now included the word 'British' in the text, and adjusted the text.

17. DISCUSSION- similarly, regarding ref 17, the difference was found between screen-detected cancers and all other groups (not only non-participants).

We have now changed this sentence in 'Morris et al showed that screen-detected cancers have a better prognosis than cancers detected outside screening'

18. DISCUSSION- when the authors state that they did not find significant differences between stages of cancers in the interval vs screen-detected, it could be suggested that a possible reason for this is small sample size.

We want to thank the reviewer for this suggestion, with which we agree. We have now included this is a limitation, and call explicitly for caution in the interpretation.

19. NUMBERS - all numbers with decimals should be consistently written with one or two decimals, unless the journal rules differently.

We now report all numbers with two significant digits.

Figure 1. Flowchart