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Breekveldt, E.C.H.; Lansdorp-Vogelaar, I.; Toes-Zoutendijk, E.; Spaander, M.C.W.; Vuuren, A.J. van; Kemenade, F.J. van; ... ; Dutch Natl Colorectal Canc Screeni

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*Emilie C H Breekveldt, Iris Lansdorp-Vogelaar, Esther Toes-Zoutendijk, Manon C W Spaander, Anneke J van Vuuren, Folkert J van Kemenade, Christian R B Ramakers, Evelien Dekker, Iris D Nagtegaal, Myrtle F Krul, Niels F M Kok, Koert F D Kuhlmann, Geraldine R Vink, Monique E van Leerdam, Marloes A G Elferink, on behalf of the Dutch National Colorectal Cancer Screening Working Group**

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*Members are listed at the end of the Article

Department of Public Health (E C H Breekveldt MD, I Lansdorp-Vogelaar PhD, E Toes-Zoutendijk PhD), Department of Gastroenterology and Hepatology (Prof M C W Spaander MD, A J van Vuuren PhD), Department of Pathology (Prof F J van Kemenade MD), and Department of Clinical Chemistry (C R B Ramakers PhD), Erasmus MC, University Medical Centre Rotterdam, Rotterdam, Netherlands; Department of Gastroenterology and Hepatology (E C H Breekveldt, Prof M E van Leerdam MD) and Department of Surgery (M F Krul MD, N F M Kok PhD, K F D Kuhlmann PhD), Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Department of Gastroenterology and Hepatology, Amsterdam University Medical Centre—Location AMC, Amsterdam, Netherlands (Prof E Dekker MD); Department of Pathology, Radboud University Medical Centre, Nijmegen, Netherlands (Prof I D Nagtegaal MD); Department of Medical Oncology, University Medical Centre Utrecht, Utrecht University, Utrecht, Netherlands (G R Vink PhD); Department of Gastroenterology and Hepatology, Leiden University

Summary

Background In 2014, a population-based colorectal cancer (CRC) screening programme was stepwise implemented in the Netherlands comprising faecal immunochemical testing once every 2 years, with a cutoff value for positivity of 47 µg haemoglobin per g faeces. We aimed to assess CRC incidence, mortality, tumour characteristics, and treatment before and after introduction of this screening programme.

Methods We did a retrospective, observational, population-based study in the Netherlands and gathered CRC incidence data from the Netherlands Cancer Registry from Jan 1, 2010, to Dec 31, 2019, in people aged 55 years or older. Patients with a CRC diagnosis between Jan 1, 2014, and Dec 31, 2018, in the Netherlands Cancer Registry were linked with the nationwide registry of histopathology and cytopathology (PALGA) to identify mode of detection (ie, screening-detected *vs* clinically detected). We calculated age-standardised CRC incidence rates and used data from Statistics Netherlands to calculate CRC-related mortality in 2010–19. We compared localisation, stage distribution, and treatment of screening-detected CRCs with clinically detected CRCs diagnosed in 2014–18 in patients aged 55–75 years.

Findings Between Jan 1, 2010, and Dec 31, 2019, 125 215 CRCs were diagnosed in individuals aged 55 years or older and were included in the analyses for CRC incidence. Before the introduction of the screening programme, the age-standardised CRC incidence rate was 214·3 per 100 000 population in 2013 in people aged 55 years or older. After the introduction of the screening programme, this rate initially increased to 259·2 per 100 000 population in 2015, and subsequently decreased to 181·5 per 100 000 population in 2019. Age-standardised incidence rates for advanced CRCs (stage III and IV) were 117·0 per 100 000 population in 2013 and increased to 122·8 per 100 000 population in 2015; this rate then decreased to 94·7 per 100 000 population in 2018. Age-standardised CRC mortality decreased from 87·5 deaths per 100 000 population in 2010 to 64·8 per 100 000 population in 2019. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be located in the left side of the colon (48·6% *vs* 35·2%) and to be detected at an early stage (I or II; 66·7% *vs* 46·2%). Screening-detected CRCs were more likely to be treated by local excision compared with clinically detected CRCs, and this finding persisted when stage I CRCs were analysed separately.

Interpretation After introduction of this national screening programme, a decrease in overall and advanced-stage CRC incidence was observed. In view of this observation, together with the observed shift to detection at earlier stages and more screening-detected CRCs being treated by local excision, we might cautiously conclude that, in the long-term, faecal immunochemical testing-based screening could ultimately lead to a decrease in CRC-related morbidity and mortality.

Funding None.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the Netherlands and the third most common type in cancer incidence for both men and women.[1] CRC incidence is affected by risk factors, such as diet and lifestyle characteristics (ie, smoking, obesity, and physical inactivity).[2,3] CRC screening programmes have been shown to be effective in reducing CRC incidence and mortality in the long-term, resulting in the implementation of various screening programmes worldwide.[4–8]

After an extensive pilot phase, a population-based CRC screening programme has been stepwise implemented in the Netherlands from 2014 onwards, using

Research in context

Evidence before this study

Faecal immunochemical testing (FIT)-based colorectal cancer (CRC) screening programmes have been adopted widely, with the main goal to reduce CRC-related mortality. As there might be a considerable period between the introduction of screening and observation of a mortality reduction, alternative indicators for the effectiveness of CRC screening can be used. One of these commonly adopted indicators is the reduction in overall CRC incidence and, ideally, stage-specific incidence reduction. We searched PubMed on Dec 20, 2020, from database inception, for studies published in English, with the terms "colorectal neoplasms", "occult blood", "early detection of cancer", "incidence", "mass screening", or "diagnostic screening programs", complemented with title and abstract terms for incidence, mortality, screening tests, and outcomes of interest. Various studies have reported on changes in CRC incidence. However, all randomised controlled trials on screening with stool-based tests that showed a CRC incidence reduction used guaiac faecal occult blood testing (gFOBT) rather than FIT. As FIT is superior to gFOBT in terms of participation rates and yield of screening, a decrease in CRC incidence might be expected after introduction of a FIT-based screening programme. Furthermore, specifics on (local) treatment of screening-detected and clinically detected CRCs during implementation of the screening programme were not included in previous studies.

Added value of this study

This observational study combined data from three large national registries and evaluated the overall, early stage, and advanced stage CRC incidence before and after the introduction of a FIT-based CRC screening programme in the Netherlands. Our analysis showed that after the introduction of the screening programme, the overall and advanced-stage CRC incidence decreased. Cancers that were detected through screening and not because of symptoms (ie, clinically detected) were more likely to be detected at an early stage (I or II) and to be treated by local excision.

Implications of all the available evidence

This study showed that FIT-based screening, using a non-invasive, sensitive, stool-based test, was associated with reduced overall and advanced-stage CRC incidence, and was likely to detect CRCs at an early stage. These results are encouraging and are an initial indication that FIT-based screening might lead to a CRC-related-mortality reduction in the near future. These benefits of CRC screening—ie, incidence reduction, a shift in stage distribution at detection, and the possibility for more favourable treatment strategies—could have a positive effect on health-care costs and resource utilisation for treating CRCs, which could (partially) compensate for the costs associated with CRC screening.

Medical Centre, Leiden, Netherlands (Prof M E van Leerdam); **Department of Research and Development, Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands** (G R Vink, M A G Elferink PhD)

Correspondence to:
Dr Emilie C H Breekveldt, Department of Public Health, Erasmus MC, University Medical Centre Rotterdam, Rotterdam 3015GD, Netherlands
e.breekveldt@erasmusmc.nl

faecal immunochemical testing (FIT) to detect and quantify human haemoglobin level in faeces once every 2 years. As of 2019, the complete target population is being invited, with consistently high participation rates (around 72%) and satisfactory detection rates of advanced neoplasia over each of the screening rounds.[9]

Monitoring of CRC screening programmes is important to evaluate their efficacy and optimise screening strategies. The main objective of these programmes is to reduce CRC-related mortality. This reduction can be achieved by a decrease in CRC incidence rate as well as by detecting CRCs at earlier stages. It was hypothesised that after initiation of the Dutch national CRC screening programme, CRC incidence rates would initially increase due to detection of prevalent—yet asymptomatic—cancers, and would subsequently decrease over time due to the removal of (advanced) adenomas. In the Netherlands, it has been shown that the stage distribution of screening-detected CRCs was more favourable than clinically detected CRCs (ie, a greater proportion of screening-detected CRCs were early stage).[10] However, these results should be interpreted with caution, because a shift in stage distribution does not necessarily mean that the number of advanced-stage CRCs detected on a population level decreases. The shift could simply be the result of detecting more indolent CRCs, while the number of advanced-stage CRCs diagnosed remains equal. However, if the incidence of advanced-stage CRCs at a population level would decrease after initiation of the screening programme, we could conclude that screening leads to early detection of CRCs and will probably result in reduced CRC-related mortality in the long-term.

Few data are available on the effect of implementation of FIT-based screening programmes on CRC incidence and mortality rates. We aimed to evaluate CRC incidence and mortality rates before and after introduction of the Dutch national CRC screening programme and analyse trends in incidence rates of early-stage and advanced-stage CRCs. Our secondary objective was to assess the effect of a national FIT-based CRC screening programme on tumour characteristics (localisation and stage distribution) and type of treatment of screening-detected CRCs versus clinically detected CRCs.

Methods

Study design and participants

We did a retrospective, observational, population-based study in the Netherlands and gathered CRC incidence data from Jan 1, 2010, to Dec 31, 2019, in people aged 55 years or older.

The Dutch national CRC screening programme was launched in 2014 with a stepwise introduction by age

cohorts, until all eligible age cohorts were invited in 2019. Men and women aged 55–75 years were invited once every 2 years to send in stool samples for FIT (FOB-Gold; Sentinel Diagnostics, Milan, Italy). The (invitation) coverage of the target population increased from around 40% in 2014 to 100% in 2018. Initially, in 2014, a cutoff for positivity of 15 µg haemoglobin per g faeces was used. 6 months after the start of the programme, the cutoff was adjusted to 47 µg haemoglobin per g faeces, because the initial positivity rate was higher than expected and the positive predictive value was lower than expected. Decision analysis at that time showed that an increase to 47 µg haemoglobin per g faeces would result in the desired balance between true and false positive test results.[11] Overall sensitivity of FIT for CRC was high (around 82%) and decreased slightly after the first invitation round.[12–17] An overview of screening participation rates in the target population aged 55–75 years is shown in the appendix (p 1). On average, the participation rate was around 72%. Participation rates were higher in women than in men (around 74% *vs* 71%, respectively). Individuals with a positive FIT were invited to a precolonoscopy assessment and referred for colonoscopy if considered eligible. The overall participation rate for colonoscopy was around 85% and was similar for men and women.[12–17] Relevant outcomes of screening within the Dutch CRC screening programme are advanced adenoma and CRC. Advanced adenoma is defined as any adenoma with histology of 25% or greater villous component, diameter of 10 mm or greater, or high-grade dysplasia.

See Online for appendix

This study was approved by the privacy review board of the Netherlands Cancer Registry and did not require approval from an ethics committee in the Netherlands. Informed consent was not required due to the study design.

Procedures

We extracted data from three independent databases: the Netherlands Cancer Registry (NCR), Statistics Netherlands, and the Dutch nationwide registry of histopathology and cytopathology (PALGA). All newly diagnosed malignancies in the Netherlands are registered in the NCR. Data on CRC incidence were retrieved from the NCR and were available from Jan 1, 2010, to Dec 31, 2019. Detailed information on tumour localisation, stage distribution, and treatment was collected from the patients' medical records by trained personnel and registered in the NCR. Tumour stage was coded using the TNM classifications of malignant tumours at that time and topography was classified according to the International Classification of Disease for Oncology.[18–21] Data on stage distribution were only available for CRCs diagnosed from Jan 1, 2010, to Dec 31, 2018. To extract data on CRC-related mortality, we used cause of death information from Statistics Netherlands. Data on CRC-related mortality were available from Jan 1, 2010, to Dec 31, 2019. Within PALGA, it is recorded if the biopsy taken at colonoscopy was obtained after a positive FIT within the screening programme; we were therefore able to identify if a CRC was screening-detected or clinically detected.

For more on **Statistics Netherlands** see https://www.cbs.nl/en-gb

Outcomes

The primary outcome was CRC incidence rates in people aged 55 years or older in 2010–19. This age range was chosen to estimate the effect of CRC screening in the long-term, because the effects of screening will continue after people reach the upper age limit of the screening programme. Additionally, we evaluated trends in early-stage and advanced-stage CRC incidence rates. To determine CRC incidence rates, we obtained information on all CRCs detected in 2010–19 through the NCR. Early-stage CRCs were defined as stage I and II cancers; advanced-stage CRCs were defined as stage III and IV cancers. Guidelines of the International Association of Cancer Registries on reporting incidence data were used to calculate age-standardised rates, using the European Standard Population.[22] Hereafter, age-standardised CRC incidence rate will be referred to as CRC incidence.

Next, we used data from Statistics Netherlands to calculate CRC-related mortality in 2010–19 in people aged 55 years or older. Hereafter, age-standardised CRC-related mortality will be referred to as CRC-related mortality.

Lastly, we compared tumour localisation, stage distribution, and treatment of screening-detected CRCs with clinically detected CRCs diagnosed in 2014–18. For this analysis, we restricted cases to those diagnosed within the target population aged 55–75 years to avoid bias in the comparison because of age differences. We linked data from the NCR on CRCs diagnosed in 2014–18 to PALGA to identify mode of detection (ie, screening-detected or clinically detected). Clinically detected CRCs included all CRCs not detected through FIT-based screening. Patients that did not meet the age criteria set for these analyses were excluded.

Tumour localisation was categorised into right-sided colon (caecum to transverse colon, C18·0, C18·2–18·4), left-sided colon (splenic flexure to rectosigmoid, C18·5–18·7, C19), rectum (C20), and overlapping and unspecified (C18·8–18·9).[23] Appendiceal cancers (C18·1) were excluded from analyses. Treatment options included local excision (endoscopic resection, transanal endoscopic microsurgery, or transanal minimally invasive surgery), oncological surgical resection, (chemo)radiotherapy, systemic therapy, a combination of the aforementioned treatments, other, or none. Treatment was analysed separately for colon and rectal cancers. Because local excision only is advised for stage I colon and rectal cancers,[24] we also analysed treatments in these stage I cancers separately. When multiple synchronous primary CRCs were diagnosed, only the most advanced lesion was included in the analyses.

Statistical analysis

Joinpoint regression analyses were performed to detect changes in trends by calculating and comparing annual percentage change in overall, early-stage, and advanced-stage CRC incidence. The maximum number of joinpoints was limited to two with a minimal percentage point difference of 0·5. Data were summarised using standard descriptive statistics. To compare tumour characteristics and treatment of screening-detected CRCs with clinically detected CRCs, χ^2 testing was used. Calculated p values were two-sided and were considered significant if less than 0·05. Joinpoint regression analyses were performed using Joinpoint regression software (version 4.9.0.0) of the US National Cancer Institute. Further data management and analyses were performed using STATA (version 16.1).

Role of the funding source

There was no funding source for this study.

Results

Between Jan 1, 2010, and Dec 31, 2019, 125 215 CRCs were diagnosed in individuals aged 55 years or older and were included in the analyses for CRC incidence (figure 1).

CRC incidence in people aged 55 years or older decreased slightly in the period 2010–13 (annual percentage change –1·2% [95% CI –4·1 to 1·8]). Thereafter, CRC incidence temporarily increased from 214·3 per 100 000 population in 2013 to 259·2 per 100 000 population in 2015 after initiation of the screening programme (annual percentage change 10·1% for 2013–15; figure 2). By 2019, CRC incidence had decreased to 181·5 per 100 000 population. The decrease in CRC incidence in the period 2015–19 (annual percentage change –8·7% [95% CI –10·4 to –7·0]) was significantly larger than the decrease in the period 2010–13.

Overall, CRC incidence was consistently higher in men than in women (figure 2). In men, CRC incidence decreased in the period 2010–13 (annual percentage change –1·3% [95% CI –5·7 to 3·4]). CRC incidence in men then increased from 267·3 per 100 000 population in 2013 to 321·1 per 100 000 population in 2015 (annual percentage change 10·7% for 2013–15), and decreased to 209·8 per 100 000 population in 2019. The decrease in CRC incidence in men in the period 2015–19 (annual percentage change –10·2% [95% CI –12·8 to –7·5]) was significantly larger than the decrease in the period 2010–13. In women, CRC incidence also decreased in the period 2010–13 (annual percentage change –1·5% [95% CI –3·6 to 0·6]). CRC incidence in women increased from 169·3 per 100 000 population in 2013 to 204·4 per 100 000 population in 2015 (annual percentage change 8·9% for 2013–15), and decreased to 156·8 per 100 000 population in 2019. The decrease in CRC incidence in women in the period 2015–19 (annual percentage change –6·7% [95% CI –8·0 to –5·5]) was significantly larger than the decrease in the period 2010–13. The difference in decrease in annual percentage change between both periods was greater in men than in women.

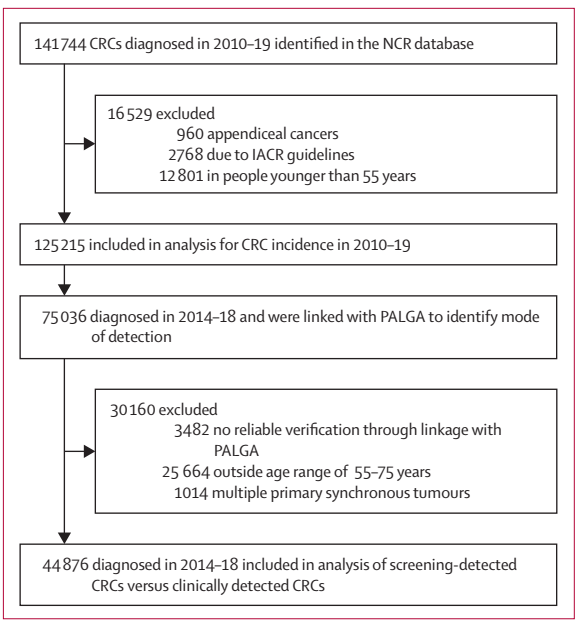

Figure 1: **Study profile**
CRC=colorectal cancer. NCR=Netherlands Cancer Registry. IACR=International Association of Cancer Registries. PALGA=Dutch nationwide registry of histopathology and cytopathology.

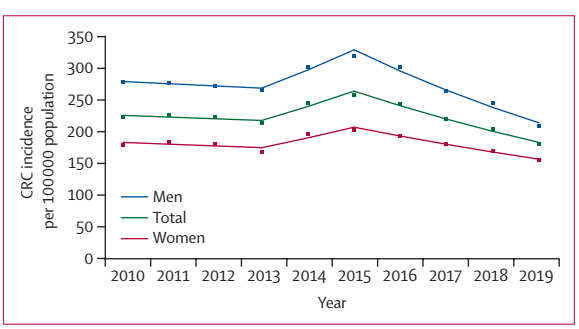

Figure 2: **Age-standardised CRC incidence rates in 2010–19 in people aged 55 years or older**
Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

Early-stage CRC incidence decreased slightly in the period 2010–13 before initiation of the screening programme, from 101·6 per 100 000 population to 92·2 per 100 000 population (annual percentage change –2·4% [95% CI –5·5 to 0·9]). There was a substantial increase in early-stage CRC incidence after introduction of the screening programme, with a maximum of 130·7 per 100 000 population in 2015 (annual percentage change 18·5% for 2013–15; figure 3). After 2015, a decrease was observed until 2018, to 106·1 per 100 000 population (annual percentage change –7·7% [95% CI –10·6 to –4·6] for 2015–18). In advanced-stage CRC incidence, a different trend was observed to overall and early-stage CRC

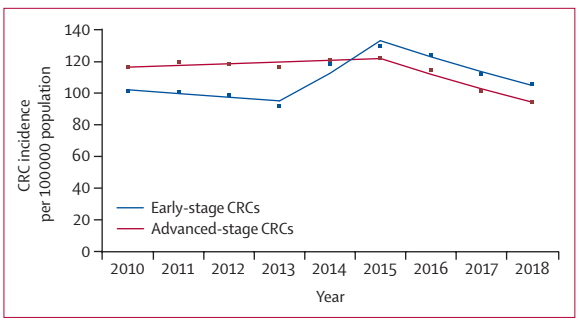

Figure 3: **Age-standardised incidence rates of early-stage CRCs and advanced-stage CRCs in 2010–18 in people aged 55 years or older**
Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

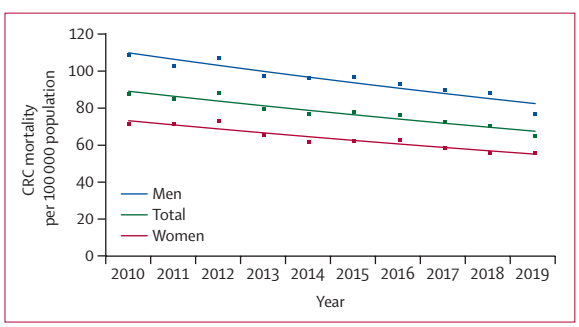

Figure 4: **Age-standardised CRC-related mortality rates in 2010–19 in people aged 55 years or older**
Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

incidence. Advanced-stage CRC incidence was 117·0 per 100 000 population in 2013; it increased only slightly until 2015, when it was 122·8 per 100 000 population (annual percentage change 0·9% [95% CI –0·7 to 2·5] for 2010–15). After 2015, a significant decrease was observed to an incidence of 94·7 per 100 000 population in 2018 (annual percentage change –8·3% [95% CI –11·5 to –4·9] for 2015–18; figure 3).

A total of 47 104 CRC-related deaths were registered between Jan 1, 2010, and Dec 31, 2019, which were used to determine CRC-related mortality. CRC-related mortality decreased from 87·5 deaths per 100 000 people in 2010 to 64·8 deaths per 100 000 population in 2019 (–3·0% [95% CI –3·8 to –2·3]; figure 4). Men were more likely than women to die of CRC. CRC-related mortality in men decreased from 109·0 per 100 000 people in 2010 to 76·6 per 100 000 population in 2019 (annual percentage change –3·1% [95% CI –4·1 to –2·2]) and in women decreased from 71·2 per 100 000 population to 55·5 per 100 000 population, respectively (–3·1% [–3·9 to –2·3]). Trends in CRC-related mortality were similar over the whole study period and did not change after initiation of the screening programme (ie, no joinpoints were detected).

Between Jan 1, 2014, and Dec 31, 2018, 75 036 CRCs were identified in the NCR. Of these CRCs, 71 554 (95·4%) could be reliably verified through linkage with PALGA and were included for further analyses (figure 1). After excluding patients that did not meet the age criteria for this analysis or who had multiple primary synchronous tumours, we included 44 876 CRCs (screening-detected and clinically detected) observed in people aged 55–75 years. Of these, 13 565 (30·2%) CRCs were screening-detected and 31 311 (69·8%) were clinically detected (table). Median age was 67 years (IQR 63–72) in people with screening-detected CRCs and 67 years (62–72) in those with clinically detected CRCs (p<0·0001). Both screening-detected and clinically detected CRCs were more frequent in men than in women.

Tumour localisation differed significantly between screening-detected and clinically detected CRCs. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be left-sided (6593 [48·6%] of 13 565 *vs* 11 005 [35·2%] of 31 311; p<0·0001; table), and less likely to be right-sided (3300 [24·3%] *vs* 10 152 [32·4%]; p<0·0001). Left-sided CRCs were more frequently diagnosed in men than in women (appendix p 1). The proportion of left-sided cancers diagnosed in men was higher for cancers diagnosed through screening (4251 [64·5%] of 6593) than for cancers diagnosed through clinical detection (6683 [60·7%] of 11 005, p<0·0001; appendix p 1).

Stage distribution differed significantly between screening-detected CRCs and clinically detected CRCs. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be stage I (6406 [47·2%] of 13 565 *vs* 7182 [22·9%] of 31 311; p<0·0001), and less likely to be stage III or IV (4291 [31·6%] *vs* 16 483 [52·6%]; p<0·0001; table).

Screening-detected CRCs were more likely to be treated with local excision than were clinically detected CRCs, both in colon and in rectal cancers (p<0·0001 for both; table). 1749 (17·4%) of 10 028 screening-detected colon cancers and 1065 (4·9%) of 21 670 clinically detected colon cancers were treated with local excision only. For rectal cancers, 781 (22·1%) of 3537 and 875 (9·1%) of 9641, respectively, were treated with local excision only.

In the analyses of stage I colon and rectal cancers only, significant differences were observed in treatments between screening-detected and clinically detected cancers (p<0·0001 for both; table). 1661 (34·4%) of 4825 screening-detected stage I colon cancers were treated with local excision, compared with 986 (20·0%) of 4935 clinically detected cancers. 760 (48·1%) of 1581 screening-detected stage I rectal cancers were treated with local excision, compared with 866 (38·5%) of 2247 clinically detected cancers.

Discussion

This study evaluated CRC incidence, mortality, tumour characteristics, and treatment before and after the introduction of the Dutch national FIT-based CRC screening programme. We observed a decrease in overall CRC incidence, which was significantly larger than the small decrease in CRC incidence before the initiation of

the programme. Advanced-stage CRC incidence also decreased significantly after the screening programme was initiated. CRC-related mortality decreased over time during the study period, but the trend did not change after introduction of the screening programme. Compared with clinically detected CRCs, screening-detected CRCs were more likely to be diagnosed in men, to have a more favourable stage, and to be located in the left side of the colon. Screening-detected CRCs were more likely to be treated by local excision than were clinically detected CRCs, and this finding persisted when stage I CRCs were analysed separately.

Our results are similar to those showing overall CRC incidence reduction in several European countries that adopted organised FIT-based CRC screening programmes.[25] In our study, after the start of the screening programme, an initial increase in CRC incidence was observed as expected, especially in early-stage CRC incidence, due to detection of prevalent (asymptomatic) CRCs.[26] Similarly, in Slovenia and Denmark, where two FIT-based organised screening programmes have been implemented, a temporary increase and subsequent large decrease in overall CRC incidence were observed after initiation of the screening programmes. CRC incidence remained stable or decreased slowly in most countries that adopted opportunistic screening programmes or used screening modalities other than FIT (ie, colonoscopy or guaiac faecal occult blood testing [gFOBT]).[25] This difference in trends might be due to lower participation rates or lower sensitivity of these screening modalities compared with FIT.

An important addition of this study compared with previous work is that stage-specific CRC incidence was also assessed. Early-stage CRC incidence followed a similar, albeit more pronounced, pattern compared with overall CRC incidence. By contrast, advanced-stage CRC incidence followed a different pattern; from 2010 to 2015, advanced-stage CRC incidence increased slightly, followed by a decrease after 2015. Only one joinpoint was determined, in 2015, which suggests that the introduction of screening does not lead to an increase in diagnoses of advanced-stage CRC, as was observed for early-stage CRC. However, from 2015 onwards, a significant reduction in advanced-stage CRC incidence was observed compared with in 2010–15. The significant decrease in overall and advanced stage CRC incidence from 2015 onwards indicates that the Dutch CRC screening programme might have contributed to early detection of CRCs and precancerous lesions. Therefore, we cautiously expect that CRC-related mortality might also decrease in the long-term due to the screening programme. It was not unexpected that we would not see a significant effect on CRC-related mortality yet. Given that screening brings diagnosis forward, and the average overall survival of patients with CRC exceeds 5 years, we did not expect to observe an effect of screening on CRC-related mortality for at least 7 years after the introduction of the programme.[1,27,28]

	Total (n=44 876)	Screening-detected CRCs (n=13 565)	Clinically detected CRCs (n=31 311)	p value*
Age, years	..	67 (63–72)	67 (62–72)	<0·0001
Sex				
Female	18 230	5289 (39·0%)	12 941 (41·3%)	..
Male	26 646	8276 (61·0%)	18 370 (58·7%)	<0·0001
Tumour localisation				
Right-sided	13 452	3300 (24·3%)	10 152 (32·4%)	..
Left-sided	17 598	6593 (48·6%)	11 005 (35·2%)	..
Rectum	13 178	3537 (26·1%)	9641 (30·8%)	..
Overlapping or not otherwise specified	648	135 (1·0%)	513 (1·6%)	<0·0001
CRC stage				
Stage I	13 588	6406 (47·2%)	7182 (22·9%)	..
Stage II	9941	2645 (19·5%)	7296 (23·3%)	..
Stage III	13 188	3572 (26·3%)	9616 (30·7%)	..
Stage IV	7586	719 (5·3%)	6867 (21·9%)	..
Unknown	573	223 (1·6%)	350 (1·1%)	<0·0001
Treatment—colon cancers				
Number of cancers	31 698	10 028	21 670	..
Local excision	2814	1749 (17·4%)	1065 (4·9%)	..
Surgical oncological resection	16 915	5749 (57·3%)	11 166 (51·5%)	..
Surgical oncological resection with (neo)adjuvant treatment	8704	2272 (22·7%)	6432 (29·7%)	..
Systemic treatment	2052	173 (1·7%)	1879 (8·7%)	..
Other treatment	100	8 (0·1%)	92 (0·4%)	..
None	1113	77 (0·8%)	1036 (4·8%)	<0·0001
Treatment—rectal cancers				
Number of cancers	13 178	3537	9641	..
Local excision	1656	781 (22·1%)	875 (9·1%)	..
Surgical oncological resection	3356	1212 (34·3%)	2144 (22·2%)	..
Surgical oncological resection with (neo)adjuvant treatment	5666	1148 (32·5%)	4518 (46·9%)	..
Systemic treatment	977	90 (2·5%)	887 (9·2%)	..
Other treatment	1137	287 (8·1%)	850 (8·8%)	..
None	386	19 (0·5%)	367 (3·8%)	<0·0001
Treatment—stage I colon cancers				
Number of cancers	9760	4825	4935	..
Local excision	2647	1661 (34·4%)	986 (20·0%)	..
Surgical oncological resection	7073	3152 (65·3%)	3921 (79·5%)	..
None	40	12 (0·3%)	28 (0·6%)	<0·0001
Treatment—stage I rectal cancers				
Number of cancers	3828	1581	2247	..
Local excision	1626	760 (48·1%)	866 (38·5%)	..
Surgical oncological resection	2114	794 (50·2%)	1320 (58·7%)	..
None	88	27 (1·7%)	61 (2·7%)	<0·0001

Data are n, n (%), median (IQR), or p values. CRC=colorectal cancer. *p values for χ^2 testing comparing proportions of screening-detected CRCs versus clinically detected CRCs.

Table: **Characteristics of the study population aged 55–75 years with screening-detected or clinically detected CRC diagnosed in 2014–18**

Moreover, we compared screening-detected CRCs with clinically detected CRCs. Given the high participation in the Dutch screening programme and the high estimated sensitivity of FIT, the proportion of CRCs detected by

screening (approximately one-third of all CRCs diagnosed in 2014–18 were screening-detected) might seem low. However, this is due to the gradual implementation of the programme, which was not completed until 2019. To illustrate, in 2014, only around 40% of the target population aged 55–75 years were invited for screening, which consisted mainly of individuals aged 65 years or older. This age distribution of people invited also explains the relatively high median age of individuals with screening-detected CRCs. Screening-detected CRCs were more frequently diagnosed at early stages than clinically detected CRCs, resulting in more favourable treatment strategies (ie, local excision). Local excision was more likely to be performed in stage I screening-detected CRCs than in stage I clinically detected cancers. This difference in treatment might be due to a higher proportion of pT1 stage I CRCs and more rectal and left-sided cancers within screening-detected CRCs, as well as differences in high-risk features, such as differentiation grade and lymphovascular invasion. However, research on this is not yet available.

Minimal evidence is available on the effectiveness of FIT in lowering CRC incidence rates, mainly due to the observational nature of these studies.[7] Furthermore, there is conflicting evidence on the effect of gFOBT screening on CRC incidence.[29] However, sensitivity of FIT is much higher than gFOBT for detection of advanced adenoma, therefore a decrease in CRC incidence was anticipated, which is in line with our findings.[6,30–33] Studies on screening with flexible sigmoidoscopy have previously shown a significant reduction of CRC incidence of approximately 20% after 11–12 years.[34,35] Although we observed a smaller reduction in CRC incidence 5 years after the start of the programme compared with these studies, it remains to be seen how the programme affects CRC incidence in the long-term, given that FIT is repeated frequently in the population.

Our data are also relevant to other FIT-based screening programmes. We have shown that CRC incidence decreases in the long-term when using FIT every 2 years with a cutoff value for positivity of 47 µg haemoglobin per g faeces. Changes in CRC incidence might be affected by the screening invitation interval (eg, annual or every 2 years testing), the age range invited, and lower or higher haemoglobin cutoffs for FIT positivity. A previous modelling study found that adopting lower positivity cutoffs, extending the age range, and offering more intensive screening (ie, annual intervals) would lead to greater reductions in CRC incidence and mortality.[36] Thus, for these more intensive programmes, our findings could be considered a conservative estimate of the potential effect.

We observed a greater difference in CRC incidence in men than in women after introduction of the programme; the difference in decrease in CRC incidence between 2010–13 and 2015–19 was greater in men than in women. Despite higher participation rates in women than in men (about 5% higher), CRC incidence reduction was lower in women than in men.[12–17] The difference in CRC incidence reduction might be explained by a difference in FIT sensitivity, as higher detection rates for advanced neoplasia and higher sensitivity of FIT in men than in women have been previously reported.[37,38] The lower sensitivity in women than in men could have two explanations: women have more proximal colon cancers than men, and a possible predominance of the serrated pathway.[39] Together with the lower sensitivity of FIT for right-sided lesions, this might explain part of the observed differences in the effect of the screening programme between sexes. To account for these differences in sensitivity, especially in right-sided lesions, optimisation of faecal testing and different positivity cutoffs for men and women could be considered in the future. Further research on why the difference in participation rate does not outweigh the CRC detection rate, resulting in a difference in CRC incidence reduction, is needed.

A strength of this study is that it used data from three large national registries, combining essential information on all cancers detected. These unique registries each provide invaluable information for evaluation and thus quality assurance of the programme. The study includes data from before and after introduction of a national, organised, screening programme. The nature of the data enabled us to gather relevant information on all CRCs diagnosed during the study period and to evaluate long-term effects of screening for the first time after the start of the programme. The main limitation of this study is the ecological design, introducing confounders that might influence the observed associations between screening and CRC incidence and CRC-related mortality. We corrected for age by using age-standardised rates, but other confounders, such as diet, incidence of obesity, alcohol consumption, smoking, and physical activity levels could not be accounted for.[40] However, such changes are unlikely to be the main driver of the observed reduction in CRC incidence, because this study included data from a relatively short time period and major changes in lifestyle factors are not likely to have an effect in such a short term. Moreover, it is implausible that lifestyle would affect trends in advanced-stage CRC incidence differently than in early-stage CRC incidence. Therefore, despite the observational nature of our study, our findings suggest a positive effect of screening on CRC incidence in the long-term.

To further strengthen the evidence for the association between the implementation of the FIT-based screening programme and the decrease in (advanced-stage) CRC incidence, a case-control study could be conducted, for which a linkage through the NCR, the national information technology screening database, and Statistics Netherlands would be necessary. This would enable us to compare screening history of individuals with advanced-stage CRC (cases) with matched individuals without advanced-stage CRC (controls).

However, such a study would require information on non-screened individuals, which for privacy law enforcement should be handled carefully, and is therefore beyond the scope of this research.

In conclusion, our data show that after introduction of the Dutch CRC screening programme, overall and advanced-stage CRC incidence decreased, which indicates that FIT-based CRC screening is effective. The decrease in advanced-stage CRC incidence coupled with the improved treatment options of screening-detected CRCs might decrease CRC-related mortality in the long-term.

Contributors

ECHB, IL-V, ET-Z, MEvL, and MAGE conceptualised the study and contributed to the study design. ECHB and MAGE performed the analyses and accessed and verified the data. ECHB and MAGE wrote the first draft of the manuscript, with supervision from IL-V, ET-Z, and MEvL. All authors contributed to reviewing drafts of the manuscript and approved the final manuscript draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Dutch National Colorectal Cancer Screening Working Group

Jeroen D van Bergeijk (Department of Gastroenterology and Hepatology, Ziekenhuis Gelderse Vallei, Ede, Netherlands), Tjerk Wiersma (Dutch College of General Practitioners, Utrecht, Netherlands), Wilhelmina M U van Grevenstein (Department of Surgery, University Medical Centre Utrecht, Utrecht, Netherlands), Marieke A M Frasa (Department of Clinical Chemistry, Reinier Haga Medical Diagnostic Centre, Delft, Netherlands), Linda J van Gestel (Department of Gastroenterology and Hepatology, Elkerliek Hospital, Helmond, Netherlands), Gerrit A Meijer (Department of Pathology, Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands).

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Data sharing

The data that support the findings of this study are available on request from MAGE (m.elferink@iknl.nl).

References

1 Netherlands Cancer Registry. National data. 2021. https://iknl.nl/nkr-cijfers (accessed March 15, 2021).

2 Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg* 2009; **22:** 191–97.

3 Carr PR, Weigl K, Jansen L, et al. Healthy lifestyle factors associated with lower risk of colorectal cancer irrespective of genetic risk. *Gastroenterology* 2018; **155:** 1805–1815.

4 Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015; **64:** 1637–49.

5 Chiu HM, Chen SL, Yen AM, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. *Cancer* 2015; **121:** 3221–29.

6 Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2010; **59:** 62–68.

7 Lauby-Secretan B, Vilahur N, Bianchini F, Guha N, Straif K. The IARC perspective on colorectal cancer screening. *N Engl J Med* 2018; **378:** 1734–40.

8 Ventura L, Mantellini P, Grazzini G, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. *Dig Liver Dis* 2014; **46:** 82–86.

9 Kooyker AI, Toes-Zoutendijk E, Opstal-van Winden AWJ, et al. The second round of the Dutch colorectal cancer screening program: impact of an increased fecal immunochemical test cut-off level on yield of screening. *Int J Cancer* 2020; **147:** 1098–106.

10 Toes-Zoutendijk E, Kooyker AI, Elferink MAG, et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. *Gut* 2018; **67:** 1745–46.

11 Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-time monitoring of results during first year of Dutch colorectal cancer screening program and optimization by altering fecal immunochemical test cut-off levels. *Gastroenterology* 2017; **152:** 767–75.

12 National Institute for Public Health and the Environment. Monitoring and evaluation of the colorectal cancer screening programme 2014. https://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme (accessed July 15, 2021).

13 National Institute for Public Health and the Environment. Monitoring and evaluation of the colorectal cancer screening programme 2015. https://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme (accessed July 15, 2021).

14 National Institute for Public Health and the Environment. Monitoring and evaluation of the colorectal cancer screening programme 2016. https://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme (accessed July 15, 2021).

15 National Institute for Public Health and the Environment. Monitoring and evaluation of the colorectal cancer screening programme 2017. https://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme (accessed July 15, 2021).

16 National Institute for Public Health and the Environment. Monitoring and evaluation of the colorectal cancer screening programme 2018. https://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme (accessed July 15, 2021).

17 National Institute for Public Health and the Environment. Monitoring and evaluation of the colorectal cancer screening programme 2019. https://www.rivm.nl/en/national-monitoring-of-colorectal-cancer-screening-programme (accessed July 15, 2021).

18 Union for International Cancer Control. Sobin LH, Wittekind C, eds. UICC TNM classification of malignant tumours. 6th ed. New York, NY: Wiley-Liss, 2002.

19 Union for International Cancer Control. Sobin LH, Gospodarowicz MK, Wittekind C, eds. UICC TNM classification of malignant tumours. 7th ed. New York, NY: Wiley-Liss, 2009.

20 Union for International Cancer Control. Brierley JD, Gospodarowicz MK, Wittekind C, eds. UICC TNM classification of malignant tumours. 8th ed. Oxford: Wiley Blackwell, 2016.

21 WHO. International classification of diseases for oncology (ICD-O), 1st revision. 3rd ed. Geneva: World Health Organization, 2013.

22 International Agency for Research on Cancer. International rules for multiple primary cancers (ICD-O third edition). International Agency for Research on Cancer: Lyon, 2004.

23 D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, et al. Definition of the rectum: an international, expert-based Delphi consensus. *Ann Surg* 2019; **270:** 955–59.

24 National Institute for Health and Care Excellence. Colorectal cancer: management of local disease. Jan 29, 2020. https://www.nice.org.uk/guidance/ng151/chapter/Recommendations#management-of-local-disease (accessed March 31, 2021).

25 Cardoso R, Guo F, Heisser T, et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. *Lancet Oncol* 2021; **22:** 1002–13.

26 Moss S, Ancelle-Park R, Brenner H. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition—Evaluation and interpretation of screening outcomes. *Endoscopy* 2012; **44** (suppl 3)**:** SE49–64.

27 Morrison AS. The effects of early treatment, lead time and length bias on the mortality experienced by cases detected by screening. *Int J Epidemiol* 1982; **11:** 261–67.

28 Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* 2017; **389:** 1299–311.

29 Jodal HC, Helsingen LM, Anderson JC, Lytvyn L, Vandvik PO, Emilsson L. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. *BMJ Open* 2019; **9:** e032773.

30 Gunter MJ, Alhomoud S, Arnold M, et al. Meeting report from the joint IARC-NCI international cancer seminar series: a focus on colorectal cancer. *Ann Oncol* 2019; **30:** 510–19.

31 Tinmouth J, Lansdorp-Vogelaar I, Allison JE. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. *Gut* 2015; **64:** 1327–37.

32 Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut* 2012; **61:** 1036–40.

33 Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. *Eur J Cancer* 2013; **49:** 3049–54.

34 Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med* 2012; **366:** 2345–57.

35 Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010; **375:** 1624–33.

36 Wilschut JA, Hol L, Dekker E, et al. Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. *Gastroenterology* 2011; **141:** 1648–55.

37 Grobbee EJ, Wieten E, Hansen BE, et al. Fecal immunochemical test-based colorectal cancer screening: the gender dilemma. *United European Gastroenterol J* 2017; **5:** 448–54.

38 van Turenhout ST, Oort FA, van der Hulst RW, et al. Prospective cross-sectional study on faecal immunochemical tests: sex specific cut-off values to obtain equal sensitivity for colorectal cancer? *BMC Gastroenterol* 2014; **14:** 217.

39 Murphy G, Devesa SS, Cross AJ, Inskip PD, McGlynn KA, Cook MB. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. *Int J Cancer* 2011; **128:** 1668–75.

40 Chapelle N, Martel M, Toes-Zoutendijk E, Barkun AN, Bardou M. Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population. *Gut* 2020; **69:** 2244–55.