# Colorectal cancer screening for average- and high-risk individuals: beyond one-size-fits-all

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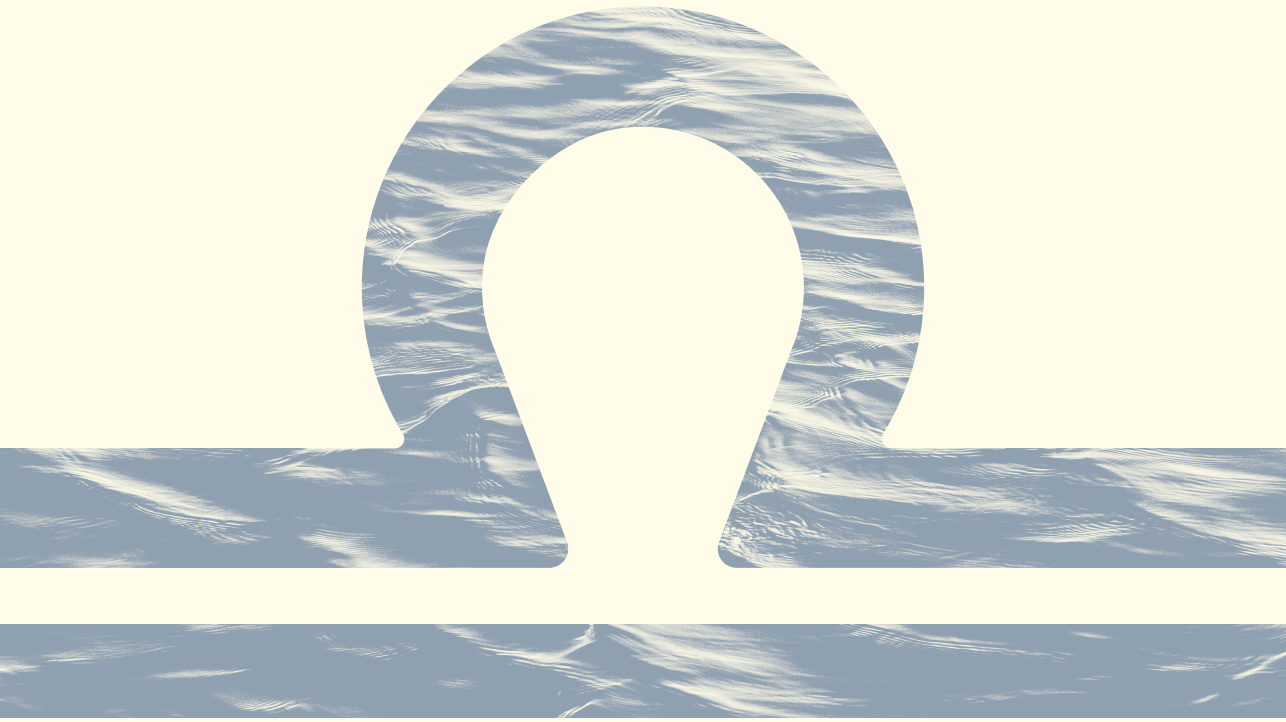
# Part I

## Evaluation of the Dutch colorectal cancer screening program



# Chapter 2

## Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study

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**ABSTRACT**

*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 (i.e., 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.

*Results*

Between Jan 1, 2010, and Dec 31, 2019, 125215 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.

*Conclusions*

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.

## 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 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 (Table 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. 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.

*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 (i.e., 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 join-points 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, $\chi^2$ 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).

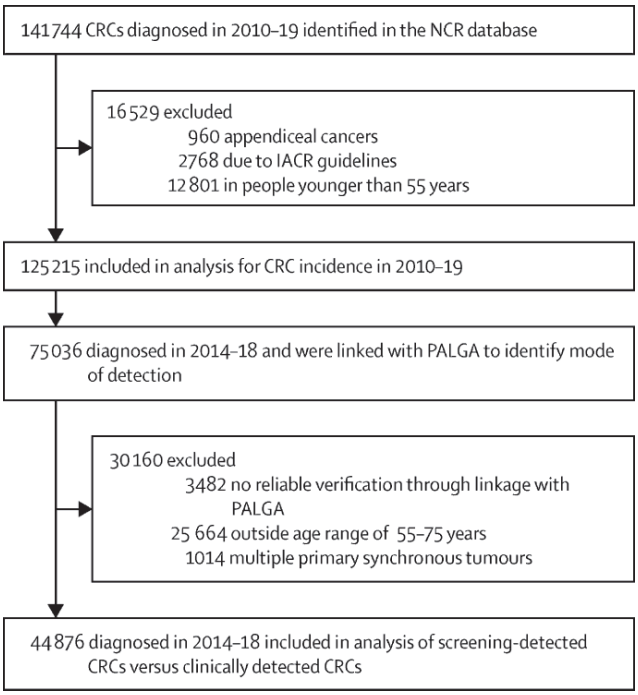


**Figure 1 - Study profile**

CRC=colorectal cancer. NCR=Netherlands Cancer Registry. IACR=International Association of Cancer Registries. PALGA=Dutch nationwide registry of histopathology and cytopathology.

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.

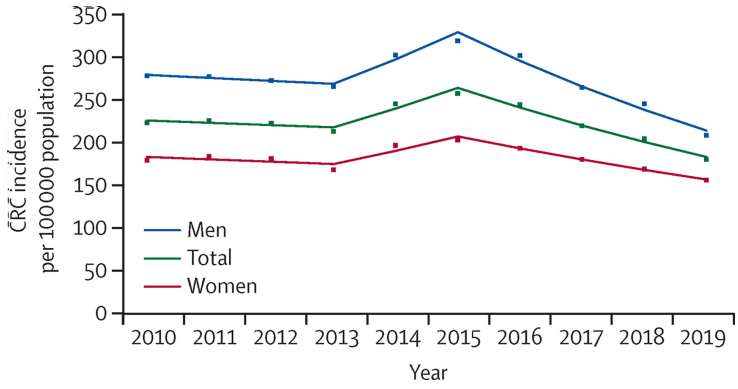


**Figure 2 - Age-standardised CRC incidence rates in 2010–19 in people aged 55 years or older**

Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

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.

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 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).

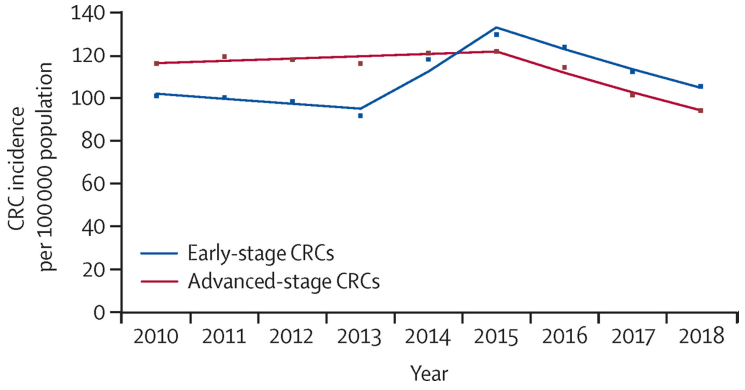


**Figure 3 - Age-standardised incidence rates of early-stage CRCs and advanced-stage CRCs in 2010–18 in people aged 55 years or older**

Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

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).

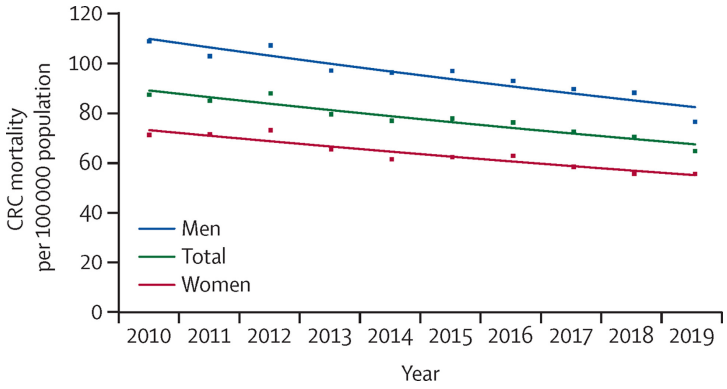


**Figure 4 - Age-standardised CRC-related mortality rates in 2010–19 in people aged 55 years or older**

Points on the graph are observed values. Lines are joinpoint regression lines. CRC=colorectal cancer.

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.

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

| | Total (n = 44,876) | Screen-detected CRCs (n = 13,565) | Clinically detected CRCs (n = 31,311) | *p* value* |
|---|---|---|---|---|
| Age | | 67 (IQR 63-72) | 67 (IQR 62-72) | <0.0001 |
| Sex | | | | |
| Men | 26,646 | 8,276 (61.0) | 18,370 (58.7) | |
| Women | 18,230 | 5,289 (39.0) | 12,941 (41.3) | <0.0001 |
| Localisation | | | | |
| Right-sided | 13,452 | 3,300 (24.3) | 10,152 (32.4) | |
| Left-sided | 17,598 | 6,593 (48.6) | 11,005 (35.2) | |
| Rectum | 13,178 | 3,537 (26.1) | 9,641 (30.8) | |
| Overlapping or NOS | 648 | 135 (1.0) | 513 (1.6) | <0.0001 |

| | | | | |
|---|---|---|---|---|
| Stage distribution | | | | |
| Stage I | 13,588 | 6,406 (47.2) | 7,182 (22.9) | |
| Stage II | 9,941 | 2,645 (19.5) | 7,296 (23.3) | |
| Stage III | 13,188 | 3,572 (26.3) | 9,616 (30.7) | |
| Stage IV | 7,586 | 719 (5.3) | 6,867 (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 | 2,814 | 1,749 (17.4) | 1,065 (4.9) | |
| Surgical oncological resection | 16,915 | 5,749 (57.3) | 11,166 (51.5) | |
| Surgical oncological resection with (neo)adjuvant treatment | 8,704 | 2,272 (22.7) | 6,432 (29.7) | |
| Systemic treatment | 2,052 | 173 (1.7) | 1,879 (8.7) | |
| Other treatment | 100 | 8 (0.1) | 92 (0.4) | |
| None | 1,113 | 77 (0.8) | 1,036 (4.8) | <0.0001 |
| Treatment rectal cancers | | | | |
| Number of cancers | 13,178 | 3,537 | 9,641 | |
| Local excision | 1,656 | 781 (22.1) | 875 (9.1) | |
| Surgical oncological resection | 3,356 | 1,212 (34.3) | 2,144 (22.2) | |
| Surgical oncological resection with (neo)adjuvant treatment | 5,666 | 1,148 (32.5) | 4,518 (46.9) | |
| Systemic treatment | 977 | 90 (2.5) | 887 (9.2) | |
| Other treatment | 1,137 | 287 (8.1) | 850 (8.8) | <0.0001 |
| None | 386 | 19 (0.5) | 367 (3.8) | |
| Treatment stage I colon cancers | | | | |
| Number of cancers | 9,760 | 4,825 | 4,935 | |
| Local excision | 2,647 | 1,661 (34.4) | 986 (20.0) | |
| Surgical oncological resection | 7,073 | 3,152 (65.3) | 3,921 (79.5) | |
| None | 40 | 12 (0.3) | 28 (0.6) | <0.0001 |
| Treatment stage I rectal cancers | | | | |
| Number of cancers | 3,828 | 1,581 | 2,247 | |
| Local excision | 1,626 | 760 (48.1) | 866 (38.5) | |
| Surgical oncological resection | 2,114 | 794 (50.2) | 1,320 (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 $\chi^2$ testing comparing proportions of screening-detected CRCs versus clinically detected CRCs.

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 (6,593 [48.6%] of 13,565 vs. 11,005 [35.2%] of 31,311; p<0.0001; table), and less likely to be right-sided (3,300 [24.3%] vs. 10,152 [32.4%]; p<0.0001). Left-sided CRCs were more frequently diagnosed in men than in women (Appendix Table 2). The proportion of left-sided cancers diagnosed in men was higher for cancers diagnosed through screening (4,251 [64.5%] of 6,593) than for cancers diagnosed through clinical detection (6,683 [60.7%] of 11,005, p<0.0001; Appendix Table 2).

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 (6,406 [47.2%] of 13,565 vs. 7,182 [22.9%] of 31,311; p<0.0001), and less likely to be stage III or IV (4,291 [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). 1,749 (17.4%) of 10,028 screening-detected colon cancers and 1,065 (4.9%) of 21,670 clinically detected colon cancers were treated with local excision only. For rectal cancers, 781 (22.1%) of 3,537 and 875 (9.1%) of 9,641, 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). 1,661 (34.4%) of 4,825 screening-detected stage I colon cancers were treated with local excision, compared with 986 (20.0%) of 4,935 clinically detected cancers. 760 (48.1%) of 1,581 screening-detected stage I rectal cancers were treated with local excision, compared with 866 (38.5%) of 2,247 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).

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 (i.e., 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 (e.g., 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 (i.e., 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.

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## APPENDIX

**Table 1: Screening process from 2014-2019**

| Year | Total target population aged 55-75 | Number of individuals invited (%*) | Number of individuals participated (%**) |
|---|---|---|---|
| 2014 | 1,925,110 | 741,914 (38.5) | 529,056 (71.3) |
| 2015 | 1,963,873 | 1,171,550 (59.7) | 848,761 (72.4) |
| 2016 | 2,000,291 | 1,457,976 (72.9) | 1,063,651 (73.0) |
| 2017 | 2,041,724 | 1,941,121 (95.1) | 1,411,998 (72.7) |
| 2018 | 2,081,355 | 2,186,186 (105.0) | 1,589,322 (72.7) |
| 2019 | 2,117,415 | 2,193,058 (103.6) | 1,567,274 (71.5) |

*of the total target population

**of the number of individuals invited

**Table 2: Side distribution of localisation (2014-2018), screening-detected CRCs compared to clinically detected CRCs in individuals aged 55-75.**

| | Total (n = 44,876) | Screen-detected CRCs (n = 13,565) | Clinically detected CRCs (n = 31,311) | p value* |
|---|---|---|---|---|
| Localisation | | | | |
| Right-sided | | | | |
| Men | 6,627 | 1,575 (47.7) | 5,052 (49.8) | |
| Women | 6,825 | 1,725 (52.3) | 5,100 (50.2) | 0.042 |
| Left-sided | | | | |
| Men | 10,934 | 4,251 (64.5) | 6,683 (60.7) | |
| Women | 6,664 | 2,342 (35.5) | 4,322 (39.3) | <0.0001 |
| Rectum | | | | |
| Men | 8,728 | 2,375 (67.1) | 6,353 (65.9) | |
| Women | 4,450 | 1,162 (32.9) | 3,288 (34.1) | 0.18 |
| Overlapping or NOS | | | | |
| Men | 357 | 75 (55.6) | 282 (55.0) | |
| Women | 291 | 60 (44.4) | 231 (45.0) | 0.90 |

Values are n (%). CRC, colorectal cancer; NOS, not otherwise specified. *: p values for chi-square testing comparing proportions of screening-detected versus clinically detected CRCs.