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Original Research

Advanced-stage CRC incidence patterns following the phased implementation of the CRC screening programme in the Netherlands

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Abstract ***Background and aims:*** From 2014, the Dutch colorectal cancer (CRC) faecal immunochemical testing-based screening programme was gradually rolled out by birth cohort. We evaluated changes in advanced-stage CRC incidence by timing of invitation to further strengthen the evidence for the effectiveness of CRC screening.
Methods: Data on advanced-stage CRC incidence in the period 2010–2019 by invitation cohort were collected through the Netherlands Cancer Registry. Crude rates of advanced-stage CRC incidence and cumulative advanced-stage CRC incidence were calculated. Observed advanced-stage CRC incidence and cumulative advanced-stage CRC incidence were compared with expected advanced-stage CRC incidence and cumulative advanced-stage CRC

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incidence by invitation cohort using trend lines extrapolating data prior to the introduction of screening.

Results: For the invitation cohort that was first invited for screening in 2014, advanced-stage CRC incidence increased before the introduction of screening from 94.1 to 124.7 per 100,000 individuals in the period 2010–2013. In 2014, the observed increase was higher than in preceding years, to 184.9 per 100,000 individuals. Hereafter, a decrease in incidence was observed to levels below expected incidence based on trends before the introduction of screening. A similar pattern was observed for invitation cohorts in subsequent years, coinciding with the first invitation to the screening programme. In 2019, the observed incidence for all invitation cohorts remained below expected incidence. The cumulative advanced-stage CRC incidence in the 2014–2016 invitation cohorts was significantly lower than the expected cumulative CRC incidence in the period 2010–2019.

Conclusions: In the period 2014–2019, an increase in advanced-stage CRC incidence was observed for all invitation cohorts first invited for screening, followed by a decrease below expected incidence, following the pattern of the phased implementation. The cumulative advanced-stage CRC incidence in invitation cohorts invited for screening multiple times was lower than expected based on trends from the pre-screening era. These findings support a causal relationship between the introduction of the Dutch screening programme and a decrease in advanced-stage CRC incidence.

1. Introduction

The global burden of colorectal cancer (CRC) is high, with nearly two million new cases and one million deaths worldwide in 2020 [1]. To reduce the burden of CRC, screening programmes have been implemented in many countries around the world. In the Netherlands, a faecal immunochemical testing (FIT)-based CRC screening programme has been gradually rolled out by birth cohort from 2014. Since 2019, all screening-eligible individuals are invited every two years to CRC screening.

The aim of CRC screening is to detect and treat CRC early to ultimately reduce CRC-related morbidity and mortality. To assure that CRC screening programmes achieve this aim, European guidelines for quality assurance in CRC screening and diagnosis prescribe regular monitoring of the early performance indicators for effectiveness [2]. Previously, it has been described that CRC screening leads to a more beneficial stage distribution of screening-detected CRC than clinically detected CRC [3–7]. However, over diagnosis and lead-time bias could be introduced by screening and the, herewith, early detection of precursor lesions and CRC might not lead to a reduction in CRC-related mortality. Therefore, other surrogate indicators might be used, such as the incidence of advanced-stage CRC, which is associated with higher morbidity and mortality than early-stage CRC.

In previous publications, advanced-stage CRC incidence in the Netherlands as an early performance indicator was assessed and a significant decrease in advanced-stage CRC incidence after introduction of the screening programme was observed [6,7]. However, when interpreting these results, understanding potential caveats of trend analyses in incidence rates is of great importance. Improved diagnostic methodology, changes in population size and age structure, differences in risk patterns over time and several other factors might introduce bias in the interpretation of trend changes in CRC incidence [8]. Therefore, strengthening the causal relationship between the introduction of a screening programme and a decrease in the advanced-stage CRC incidence is deemed necessary. If the decrease in advanced-stage CRC incidence was indeed the result of the implementation of the screening programme, changes in the advanced-stage CRC incidence are to be expected at a later time point for birth cohorts that were invited at a later date. In this study, we assessed advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence by birth cohort to further strengthen the evidence for the association between the implementation of the screening programme and a decrease in advanced-stage CRC incidence.

2. Methods

2.1. The Dutch CRC screening programme

In 2014, the Dutch national CRC screening programme was stepwise implemented by birth cohort (Table 1). In 2014, five birth cohorts (1938, 1939, 1947, 1949 and 1951) were first invited to participate in screening, while in 2015, six other birth cohorts (1940, 1946, 1948, 1950, 1952 and 1954) were first invited to participate, and so on. By 2019, all screening-eligible birth cohorts (aged 55–75) were at least invited once, and from 2019 onwards, all individuals were biennially invited to participate in FIT for haemoglobin (FOB-Gold; Sentinel Diagnostics®, Milan, Italy) at a cut-off for FIT-positivity of 47 μg Hb/g faeces. FIT

Table 1
Overview of invitation cohorts 2014–2019.

	Birth cohorts first invited for screening
Invitation cohort 2014[a]	1938, 1939, 1947, 1949, 1951
Invitation cohort 2015[a]	1940, 1946, 1948, 1950, 1952, 1954
Invitation cohort 2016[b]	1941, 1945, 1953, 1955, 1957
Invitation cohort 2017[b]	1942, 1944, 1956, 1958, 1960
Invitation cohort 2018[c]	1943, 1959, 1961, 1963
Invitation cohort 2019[c]	1962, 1964

[a] Three times invited for screening.
[b] Two times invited for screening.
[c] One time invited for screening.

participation rates within the screening programme were consistently high, at around 72% [9].

2.2. Data

We retrieved CRC incidence data from the Netherlands Cancer Registry for individuals aged 45 and older in the period 2010–2019. Tumour stage was coded using the effective tumour, node, metastases classifications of malignancies (7th edition until to 2016, 8th edition from 2017 onwards) [10,11] and stored in the Netherlands Cancer Registry. Data from Statistics Netherlands were used to calculate population size by age cohort and calendar year. A total of 125,417 CRCs were identified in the period 2010–2019. Tumour stage was not reported in 3990 (3.2%) of cases. Only advanced-stage CRCs detected in individuals that were age 55 and older in the screening period were included.

2.3. Outcomes

In this retrospective observational study, we calculated crude rates of advanced-stage (stage III and IV) CRC incidence and the cumulative advanced-stage CRC incidence in the period 2010–2019 in individuals who were aged 55 and in the screening period. Incidence rates were grouped by *invitation cohort*. An invitation cohort consists of birth cohorts first invited for screening in the same calendar year. For example, *invitation cohort 2014* consists of all birth cohorts first invited for screening in 2014. For some birth cohorts, the invitation extended beyond one calendar year; then, the calendar year in which most individuals were invited was used. Advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence was presented for both sexes combined and for men and women separately. We included cancers in the right-sided colon (cecum to transverse colon, C18.0, 18.2 – C18.4), left-sided colon (splenic flexure to rectosigmoid, C18.5-C18.7, C19), rectum (C20) and overlapping and unspecified (C18.8-C18.9). Appendiceal cancers (C18.1) were excluded for analyses.

2.4. Statistical analysis

Crude rates of advanced-stage CRC incidence were calculated by dividing the number of advanced-stage CRC per invitation cohort by the total population size of that cohort in each respective calendar year. Annual advanced-stage CRC incidence was displayed per 100,000 individuals. Next, we generated trend lines for each invitation cohort based on advanced-stage CRC incidence in the years before first invitation. Trend lines were generated by fitting a linear regression line using the natural logarithm of the incidence rates with the calendar year as regression variable. For invitation cohort 2014, trend lines were based on advanced-stage CRC incidence in the period 2010–2013; for invitation cohort 2015, trend lines were based on incidence in the period 2010–2014, and so on. Next, we calculated cumulative advanced-stage CRC incidence in the period 2010–2019 in all invitation cohorts by dividing the number of advanced-stage CRCs per invitation cohort by the number of individuals at risk per invitation cohort in 2010. We compared the cumulative advanced-stage CRC incidence to the expected cumulative advanced-stage CRC incidence in the period 2010–2019 for all invitation cohorts. The expected cumulative advanced-stage CRC incidence was calculated by dividing the number of expected advanced-stage CRCs per invitation cohort by the number of individuals at risk per invitation cohort in 2010. The number of expected CRCs was based on the trend lines from the pre-screening era. Data were summarised using standard descriptive statistics. Calculated p values were two-sided and were considered statistically significant when <0.05.

2.5. Sensitivity analysis

We performed a sensitivity analysis to assess the robustness of results for the choice of trend line. For invitation cohort 2014 (birth cohort 1938; 76-year olds, 1939; 75-year olds, 1947; 67-year olds, 1949; 65-year olds), we constructed an alternative trend line using the observed advanced-stage CRC incidence for birth cohorts that had the same age in 2010 (1934, 1935, 1943, 1945) as the 2014 invitation cohort in 2014. We projected observed advanced-stage CRC incidence of these 2010 cohorts in the graph at time point 2014, to compare observed and expected advanced-stage CRC incidence at a particular age. Birth cohort 1951 (part of invitation cohort 2014) was not included in the sensitivity analysis since the respective comparison cohort in 2010 (1947) was invited in 2014.

3. Results

A total of 45,990 advanced-stage CRCs were diagnosed in the period 2010–2019 in individuals who were 55 and

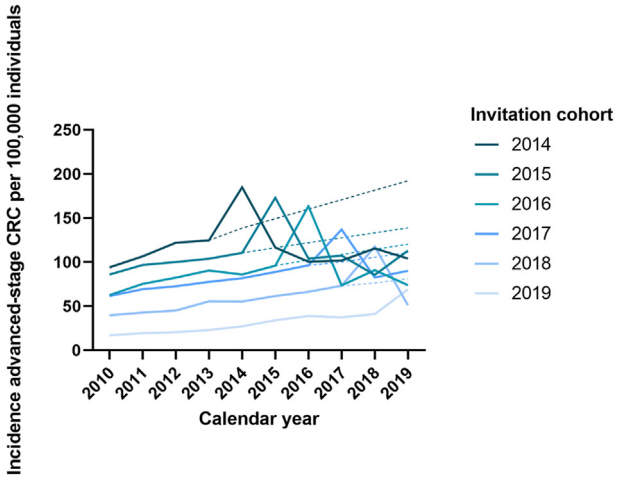

Fig. 1. Advanced-stage CRC incidence patterns in different invitation cohorts. CRC, colorectal cancer.

older in the screening period. For invitation cohort 2014, advanced-stage CRC incidence increased prior to the introduction of screening, from 94.1 to 124.7 per 100,000 individuals in the period 2010–2013 (Fig. 1). In 2014, the observed increase was larger than in preceding years, with an incidence of 184.9 per 100,000 individuals (+33.4% relative to trend). Hereafter, in 2015, a decrease in advanced-stage CRC incidence was observed (−21.9% relative to trend). When these birth cohorts were invited for the second time in 2016, no increase was observed, probably because a large part of the invitation cohort was not again invited to screening due to reaching the upper age limit. A slight increase was again observed in 2018 when this cohort was invited to screening for the third time, but this was lower than expected (−36.3% relative to trend). In 2019, at the end of our study period, the observed advanced-stage CRC incidence was lower than the expected incidence, with an observed incidence of 104.0 per 100,000 individuals versus an expected incidence of 192.2 per 100,000 individuals (−45.9% relative to trend).

A similar pattern was observed for invitation cohort 2015. In this cohort, advanced-stage CRC incidence increased from 85.9 to 110.6 per 100,000 individuals in the period 2010–2014. In 2015, advanced-stage CRC incidence substantially increased to 173.0 per 100,000 individuals (+48.7% relative to trend). This was followed by a decrease in 2016, after which an increase was observed when this invitation cohort was invited for screening for the second time (2017) and the third time (2019). However, observed advanced-stage CRC incidence in 2019 was lower than expected. Expected incidence was 138.8 per 100,000 individuals, whereas observed incidence was 113.0 per 100,000 individuals in 2019 (−18.6% relative to trend). For all other invitation cohorts (2016–2019), the same pattern was observed; advanced-stage CRC incidence increased in the year these birth cohorts were first invited to screening (between +36.7 and + 59.1% relative to trend), followed by a decrease, and an increase in the years, these birth cohorts were invited for the second time. In 2019, observed advanced-stage CRC incidence was far below the expected advanced-stage CRC incidence for all invitation cohorts. The cumulative advanced-stage CRC incidence in invitation cohort 2014 was 1.10% in the period 2010–2019 and was lower than the expected cumulative advanced-stage CRC incidence based on the trends from the pre-screening era (1.34%, $p < 0.0001$; Table 2). The cumulative advanced-stage CRC incidence in invitation cohorts 2015 and 2016 was also significantly lower than the expected cumulative advanced-stage CRC incidence. No significant differences were observed between the observed and expected cumulative advanced-stage CRC incidence in invitation cohorts 2017 and 2018. The cumulative advanced-stage CRC incidence in invitation cohort 2019 was slightly higher than the expected cumulative advanced-stage CRC incidence (0.32% versus 0.30%, $p = 0.034$; Table 2).

Similar patterns in advanced-stage CRC incidence were observed for men and women separately, although the incidence was higher in men than in women (Fig. 2a–b). However, the increase in the first year was greater in men than in women. Differences between

Table 2
Cumulative observed and expected advanced-stage CRC incidence in the period 2010–2019.

	Number of individuals at risk (2010), n	Total advanced-stage CRCs from 2010 to 2019, n	Total expected advanced-stage CRCs from 2010 to 2019, n	Cumulative advanced-stage CRC incidence, %	Expected cumulative advanced-stage CRC incidence, %	*p* value
Invitation cohort 2014	919,000	10,108	12,294	1.10	1.34	<0.0001
Invitation cohort 2015	1,180,000	12,119	12,687	1.03	1.08	0.00029
Invitation cohort 2016	981,000	8466	8854	0.86	0.90	0.0031
Invitation cohort 2017	1,015,000	8338	8401	0.82	0.83	0.62
Invitation cohort 2018	896,000	5294	5196	0.59	0.58	0.34
Invitation cohort 2019	516,000	1665	1545	0.32	0.30	0.034

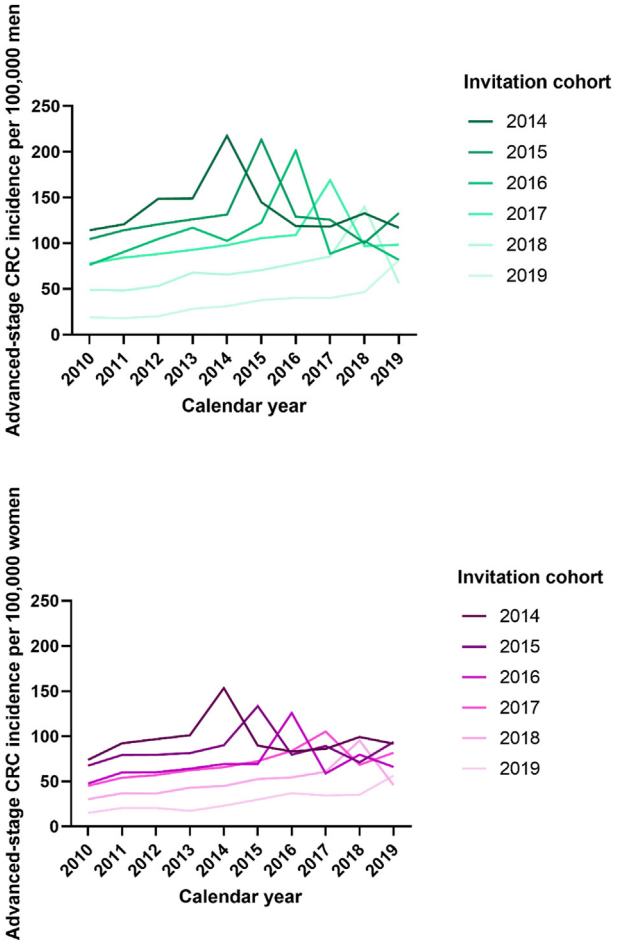

Fig. 2. (**a**), (**b**) Advanced-stage CRC incidence patterns for men and women in different invitation cohorts. CRC, colorectal cancer.

expected and observed advanced-stage CRC incidence in 2019 were slightly greater in men (between −19.6% and −49.6% relative to trend) than in women (between −16.2% and −40.9% relative to trend). The observed and expected cumulative advanced-stage CRC incidence were higher in men than in women, but patterns by sex were similar as for the population as a whole (Table 3). No significant differences were observed between the observed and expected cumulative advanced-stage CRC incidence in the male 2017–2019 invitation cohorts and the female 2016–2019 invitation cohorts.

The sensitivity analysis showed that the advanced-stage CRC incidence of birth cohorts invited to participate in screening in 2014 (1938, 1939, 1947, 1949) is different than that of birth cohorts of the same age 4 years earlier (1934, 1935, 1943, 1945; Fig. 3a–d). Advanced-stage CRC incidence of 65-year olds in 2014 (birth cohort 1949) increased in 2014 and decreased in 2015, after which a slight increase was observed in 2016 (Fig. 3a–d). A higher incidence was observed for birth cohort 1945 (65-year olds in 2010), implying that the difference between the observed and expected incidence based on the generated trend lines cannot only be attributed to by choice of trend lines. This was underlined by similar observed trends for other birth cohorts invited to screening in 2014 (1938, 1939 and 1947).

4. Discussion

This study evaluated patterns in advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence resulting from the phased rollout by birth cohort in the Dutch CRC screening programme, to estimate the effect of screening on CRC stage at diagnosis. We observed a temporary increase in advanced-stage CRC incidence in the first year individuals were invited. This increase was followed by a decrease below expected incidence levels. This pattern followed the phased implementation of the screening programme and was observed for all invitation cohorts. The cumulative advanced-stage CRC incidence in the 2014–2016 invitation cohorts was significantly lower than the expected cumulative advanced-stage CRC incidence in the period 2010–2019. Similar patterns in

Table 3
Cumulative observed and expected advanced-stage CRC incidence in men and women in the period 2010–2019.

	Number of individuals at risk (2010), n	Total advanced-stage CRCs from 2010 to 2019, n	Total expected advanced-stage CRCs from 2010 to 2019, n	Cumulative advanced-stage CRC incidence, %	Expected cumulative advanced-stage CRC incidence, %	*p* value
Men						
Invitation cohort 2014	456,000	5830	7186	1.28	1.58	<0.0001
Invitation cohort 2015	589,000	7203	7501	1.22	1.27	0.013
Invitation cohort 2016	495,000	5107	5521	1.03	1.12	<0.0001
Invitation cohort 2017	507,000	4915	4886	0.97	0.96	0.77
Invitation cohort 2018	450,000	3101	3045	0.69	0.68	0.47
Invitation cohort 2019	260,000	927	848	0.36	0.33	0.060
Women						
Invitation cohort 2014	464,000	4278	5123	0.92	1.10	<0.0001
Invitation cohort 2015	591,000	4916	5178	0.83	0.88	0.0068
Invitation cohort 2016	496,000	3359	3341	0.68	0.67	0.83
Invitation cohort 2017	508,000	3423	3515	0.67	0.69	0.27
Invitation cohort 2018	446,000	2193	2151	0.49	0.48	0.52
Invitation cohort 2019	256,000	738	697	0.29	0.27	0.28

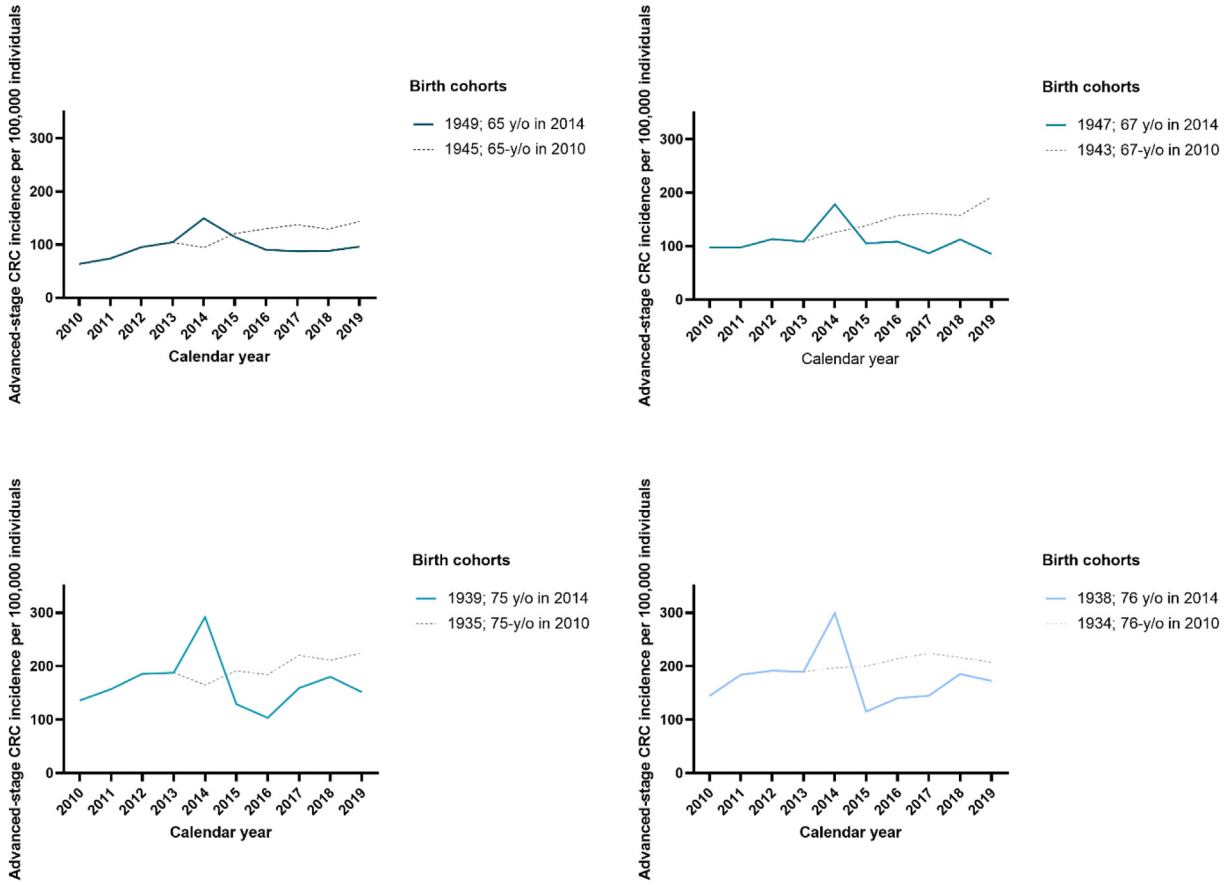

Fig. 3. (a), (b), (c), (d) Sensitivity analysis: advanced-stage CRC incidence in birth cohorts from invitation cohort 2014 (1949, 1947, 1939, 1938) compared to cohort 2010 (1945, 1943, 1935, 1934). CRC, colorectal cancer.

advanced-stage CRC incidence and the cumulative advanced-stage CRC incidence were observed for men and women separately, although the incidence was higher in men than in women.

In previous publications, advanced-stage CRC incidence in the Netherlands was assessed as an early indicator for the effectiveness of the screening programme and a significant decrease in advanced-stage CRC incidence was observed after introduction of the programme [6,7]. In this study, we further strengthened the causal relationship between the introduction of the programme and a decrease in advanced-stage CRC incidence. After introduction of the screening programme in 2014, an increase in advanced-stage CRC incidence was observed for all invitation cohorts in the years they were first invited to screening. This trend was mainly observed in the years these cohorts received their first screening invitation. At the end of the study period (2019), the observed advanced-stage CRC incidence was lower than the expected incidence based on trend lines in all invitation cohorts. This indicates the causal relationship between the introduction of the screening programme and a decrease in advanced-stage CRC incidence over time. To our knowledge, this is the first study assessing advanced-stage CRC incidence related to timing of invitation. Few previous studies reported on advanced-stage CRC incidence after introduction of FIT-screening. Levin *et al.* demonstrated a decreasing trend in advanced-stage CRC incidence after introduction of FIT besides primary colonoscopy screening in 2007 [12]. At that time, sigmoidoscopy and guaiac faecal occult blood testing were discontinued. Chiu *et al.* demonstrated that advanced-stage CRC incidence and CRC-related mortality was lower for screened versus non-screened individuals (adjusted relative rate 0.66 and 0.60, respectively) [13]. This indicated an association between the decrease in advanced-stage CRC incidence and CRC-related mortality in the long-term. However, in the study of Chiu, advanced-stage CRC was defined as $\geq$ stage II, and no data over time were shown. In an observational study by Zorzi *et al.* on CRC-related mortality related to FIT-screening, an earlier decrease in age-standardised CRC-related mortality was observed for areas in Italy in which FIT-based screening was implemented early (2002–2004) compared to areas where screening was implemented at a later time point (2008–2009) [14]. The abovementioned results should be cautiously interpreted with regard to ours because multiple screening modalities were used side-by-side, different

FIT cut-offs and screening intervals were applied, and CRC background risk differed. Still, when looking at trends in CRC screening performance indicators, similar patterns were observed in our study. Last, advanced-stage CRC incidence was higher in men than in women as was observed in multiple previous studies, but trends were similar [15]. The larger differences between observed and expected advanced-stage CRC incidence in 2019 for men than women could be explained by the higher FIT-sensitivity in men than women [16,17].

We observed significant differences between cumulative advanced-stage CRC incidence and expected cumulative advanced-stage CRC incidence in the period 2010–2019 in the 2014–2016 invitation cohorts. This difference was not observed yet for the 2017 and 2018 invitation cohorts. In the 2019 invitation cohort, we actually observed a slightly higher cumulative advanced-stage CRC incidence than the expected cumulative advanced-stage CRC incidence. This pattern across all birth cohorts supports the hypothesis that screening is the main cause of changes in the cumulative advanced-stage CRC incidence. Indeed, first screening promotes the diagnosis of CRC, resulting in an initial peak in (advanced-stage) CRC incidence. This is exactly what we observe in the 2019 cohort, which was invited only once. After that first screening, time and repeated screening is needed to compensate for the peak in (advanced-stage) CRC incidence. Therefore, we do not see a statistically significant difference in the 2017 and 2018 invitation cohorts, but we do see a statistically significant difference in the earlier cohorts, which were invited for screening more often and longer ago. Interestingly, in men, the cumulative advanced-stage CRC incidence was significantly lower than the expected advanced-stage CRC incidence in the 2014–2016 invitation cohorts, whereas in women, only in the 2014 and 2015 invitation cohorts a significant difference was observed between the observed and expected cumulative advanced-stage CRC incidence. This could indicate that screening has a greater protective effect on the advanced-stage CRC incidence in men than in women. A major strength of this study is the availability of detailed data from a large national cancer registry, which allowed us to conduct analyses by birth cohort. Second, when assessing changes in trends of surrogate quality indicators, the fact that CRC survival has significantly improved in recent years due to advances in surgical oncological treatment, should also be taken into account. Modification of (treatment) guidelines usually is quite time-consuming, hence using this surrogate quality indicator (i.e. advanced-stage CRC incidence patterns over time) is more reliable, as time effects are less influential. The main limitation of this study is the introduction of bias due to the ecological design. It is inevitable that randomised controlled trials (RCTs) are considered higher level evidence than (retrospective) cohort studies. Since RCTs on the efficacy of FIT-based screening are lacking and unlikely to be initiated in the future, we must rely on the results of previous guaiac faecal occult blood testing-based RCTs and FIT-based observational studies, such as our study. Despite the design of our study, we demonstrated a stronger association between the introduction of the screening programme and a decrease in advanced-stage CRC incidence than other cohort studies due to the analyses by birth cohort.

We used advanced-stage CRC reduction as outcome, rather than CRC mortality reduction, the ultimate outcome of screening. A reduction in CRC-related mortality is not to be expected until the mid-to-long-term after the introduction of a screening programme due to lead-time bias and the average survival of CRC. Therefore, adequate surrogate quality indicators for the eventual decrease in CRC-related mortality are important to identify. Cuzick *et al.* nicely discussed surrogate end-points for cancer screening trials and demonstrated these using data from the UK Flexible Sigmoidoscopy Screening Trial [18]. Projected mortality based on stage-adjusted cancer incidence yielded most promising results and allowed the analysis of mortality to be advanced by more than three years. Though promising, a key requirement for this stage-based predicted mortality is the identification of cases and controls, which significantly complicates data retrieval. As demonstrated by Cuzick *et al.*, the results presented in our study imply that we can conservatively assume that CRC-related mortality will also decrease in the mid-to-long-term. Our results are applicable to several other countries that introduced organised FIT-screening programmes, such as Slovenia and Denmark, but especially to countries that initiated FIT-screening at a later time point, such as Finland and England [15].

To conclude, we observed a short increase in advanced-stage CRC for all invitation cohorts first invited for screening in 2014–2019, followed by a decrease below expected incidence levels, coinciding with the pattern of the phased implementation. The cumulative advanced-stage CRC incidence in the 2014–2016 invitation cohorts was lower than the expected cumulative advanced-stage CRC incidence in the period 2010–2019. These findings support a causal relationship between the introduction of the Dutch CRC screening programme and a decrease in advanced-stage CRC incidence.

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Author contributions

ECHB, ETZ, MEvL and ILV conceptualised the study and contributed to the study design. ECHB performed

the analyses and accessed and verified the data. ECHB wrote the draft version of the manuscript, with supervision from ETZ, MEvL and ILV. All authors contributed to reviewing drafts of the manuscript and approved the final manuscript draft.

Ethics approval

This study was conducted in accordance with the Dutch population screening act (WBO). Returning the FIT is considered as consent for using pseudonymised data of all screening colonoscopy reports, following the WBO. All individuals had the right to object to the use of their data.

Data availability

The data that support the findings of this study are available on request from the last author.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Manon C.W. Spaander received research support from Sentinel, Sysmex, Boston Scientific, Norgine and Medtronic. Evelien Dekker received endoscopic equipment on loan of Olympus and FujiFilm and research grant from FujiFilm; received honorarium for consultancy from FujiFilm, Tillots, Olympus, GI Supply, Cancer Prevention Pharmaceuticals, PAION and Ambu; and a speakers' fee from Olympus, Roche, GI Supply, PAION and IPSEN. All other authors have nothing to disclose.

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