Received: 23 August 2024 | Revised: 1 February 2025 | Accepted: 4 February 2025

DOI: 10.1002/ijc.35371

RESEARCH ARTICLE

Cancer Epidemiology

IJC INTERNATIONAL JOURNAL of CANCER | UICC

The impact of extended invitation intervals on stage distribution of screen-detected and interval cancer within the Dutch colorectal cancer screening program

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Funding information
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Abstract

This study investigates the impact of extended invitation intervals on the stage distribution of screen-detected and interval colorectal cancers (CRCs) in the Netherlands' fecal immunochemical test (FIT)-based screening program during the COVID-19 pandemic. Using data from individuals with negative FIT results in 2017–2019 and subsequent screening round in 2019–2021, we examined whether delays of up to 6 months affected CRC stage at diagnosis. We performed multivariate logistic regression to assess the association between invitation intervals and cancer stage. Our analysis found no significant difference in stage distribution for both screen-detected and interval CRCs despite the delays. Specifically, odds ratios for late-stage cancer remained close to 1 across various intervals, indicating minimal impact of extended invitation times. These results suggest that the short-term delays caused by the pandemic did not significantly affect the performance of the CRC screening program. This highlights the program's ability to adapt to temporary disruptions while maintaining effective early cancer detection. Our findings support the notion that such disruptions, when managed appropriately, do not substantially compromise the quality of screening outcomes, reinforcing the resilience and flexibility of CRC screening programs in the face of health crises.

KEYWORDS
colorectal cancer (CRC), COVID-19, delayed screening intervals, stage distribution

What's New?

As the COVID-19 pandemic unfolded, many countries suspended colorectal cancer screening programs to reduce the burden of nonemergency healthcare services, leading to delays in diagnosis. This study evaluates the impact of extended invitation intervals on colorectal cancer stage distribution within a national fecal immunochemical test-based screening program

during COVID-19. It uniquely analyzes individual-level data for screen-detected and interval cancers separately, revealing no significant changes in stage distribution despite screening delays. This finding underscores the resilience and adaptability of colorectal cancer screening programs to temporary disruptions, demonstrating that short-term delays do not substantially compromise early cancer detection.

1 | INTRODUCTION

COVID-19 started as an outbreak in China in December 2019 and quickly escalated into a global pandemic by spreading worldwide.[1–3] During that period, it was necessary to reallocate healthcare staff and resources to address the emerging demands. This affected numerous cancer screening programs across several countries that needed to suspend their screening programs to reduce the burden of non-emergency healthcare services.[4–9] Consequently, there was a delay in diagnosing CRCs, which could affect the long-term incidence and mortality reduction of CRC screening programs.[10,11]

Several studies across different countries have explored the impact of such a suspension of the screening programs on different aspects, including CRC detection, incidence patterns, and alteration in the stage distribution.[5,6,8,12–15] More specifically, during the onset of COVID-19, numerous countries witnessed a reduction in cancer detection rates, and individuals exhibiting symptoms tended to avoid or postpone seeking medical attention, compounding the impact.[10,12,16] Furthermore, CRC incidence rates were significantly impacted, with many countries indicating a decline in their CRC incidence rates.[6,8,12,13,15,17–20]

Regarding the stage distribution, a recent cohort study by Rottoli et al. investigated the impact of COVID-19 on CRC stage at diagnosis in patients that needed to undergo surgery. This Italian study showed that during the pandemic, CRCs were more often detected at an advanced stage irrespective of the mode of detection (odds ratio [OR] 1.07; 95% confidence interval [CI], 1.01–1.13).[21] Similarly, a procedural modelling study by Ricciardiello et al. using predictions rather than observational data, showed an association between the extended invitation intervals, from 4 to 6 months during the pandemic, and the increased incidence of advanced stage cancers.[22] Additionally, a large prospective cohort study by Medina-Prado et al. found a significant decrease in Stage I CRC diagnoses during the pandemic, illustrating the long-term effects of disrupted screening programs across Spanish hospitals.[23] On the other hand, other studies have suggested no significant upshifting in CRC stage distribution.[15,24,25]

In the Netherlands, the fecal immunochemical test (FIT)-based CRC screening program was halted from March 16, 2020 to May 11, 2020. During this period, no invitation was sent to the population, and subsequent invitations were delayed for some individuals after the restart of the program due to limited colonoscopy capacity. This disruption led to delays in CRC diagnosis and a decline in the CRC incidence rate.[15]

Despite evidence from previous studies on CRC stage distribution, the impact of the temporary suspension of population-based screening programs—which resulted in extended invitation intervals—on the stage distribution of screen-detected cancers and interval cancers remains unknown. Therefore, we assessed the impact of the extended invitation intervals separately by mode of detection—namely, screen-detected and interval cancers—using individual-level data. By examining them independently, we aim to capture the unique clinical trajectories of each mode of detection, offering a more detailed understanding of the impact of invitation delays.

2 | METHODS

2.1 | The Dutch colorectal cancer screening program during COVID-19

In the Netherlands, the first COVID-19 case was confirmed on February 27, 2020, and the epidemic spread rapidly, placing an enormous burden on the healthcare system. The Institute for Public Health and Environment announced the suspension of the cancer screening programs from March 16, 2020, as a measure of redirection and prioritization of the healthcare resources for urgent situations. For the first 2 weeks after the suspension, individuals were still able to return their FIT kits and/or undergo a colonoscopy if their results were positive. After those 2 weeks, individuals were advised not to return their FIT tests and wait for further notice. This suspension lasted approximately 2 months, and then the screening invitations were resent to these individuals, prioritizing those eligible for a subsequent screening round. On June 1st, new invitations were sent to the population. However, there was still a delay in invitations for approximately 2.5 months after the restart of the program to anticipate the disruption and avoid non-emergency healthcare. This gradually returned to the regular schedule over the following months.

2.2 | Study population

In our study, we focused on intervals for repeated screening; therefore, we included all participants in the Dutch screening program in 2017, 2018, and 2019 with a negative FIT and a subsequent scheduled screening in 2019, 2020, and 2021. During this period, the participation rate for subsequent round invitees remained relatively stable throughout the study period: 93% for 2017 and 2018 and 92%

for 2019.[26–28] To ensure sufficient follow-up time for our analysis, we did not include data from people invited after December 1, 2021. Data on age, sex, invitation dates, participation status, and FIT results were requested from the national screening database (ScreenIT). Data on CRC incidence date and stage distribution were requested from the Dutch Cancer Registry.

2.3 | Invitation intervals and cancer stage definition

For the invitation intervals, we considered the following categories:

<760 days:	>24 and ≤25 months as reference group
760–790 days:	>25 and ≤26 months
791–820 days:	>26 and ≤27 months
>820 days:	>27 months.

The ">27 months" category comprises individuals who received their invitations between 27 and 34 months (see Supporting Information Figure 1 for details). The median invitation interval for the 24–25 months category was 733 days, while the median for the >27 months category was 837 days. Cancer stage distribution was considered a binary variable with Stages I and II as early stage and Stages III and IV as late stage. The TNM staging system, eighth edition, was used at the time of diagnosis. Screen-detected CRCs were cancers detected after a positive FIT by colonoscopy, during the scheduled screening intervals. Interval CRCs were cancers detected after a negative FIT and before the next FIT screening test, typically diagnosed based on the presentation of symptoms or incidental findings.

2.4 | Statistical analysis

X^2-test was used to assess the impact of each invitation interval for four groups with a significance level equal to 0.05. We applied multivariable logistic regression to assess the association between the extended invitation intervals and CRC stage distribution for screen-detected and interval cancers. Analysis was conducted independently for both screen-detected and interval cancers, as they have totally different stage distributions, with screen-detected cancers having a much more favorable stage distribution; therefore, pooling data is not desirable. We considered the comparison of early Stages I and II versus late Stages III and IV versus four different time intervals, namely 24–25, 25–26, 26–27, and >27 months. Since we are interested in the impact of the invitation interval, we considered the current screening round (Rounds 2, 3, and 4) for screen-detected cancers and the previous screening round (Rounds 1, 2, and 3) for interval cancers. Cancer stage was the dependent variable, and regression was adjusted for age, sex, screening round, invitation intervals, and levels of fecal hemoglobin (f-Hb in the previous screening round).

To provide further insights into the robustness of our findings, we conducted sensitivity analysis for both screen-detected and interval cancers, considering an alternative dichotomization for early versus late stages, considering only Stage I as an early stage and Stages II, III, and IV as late stage. This approach reflects the significant clinical progression between Stage I and later stages, capturing the potential impact of screening delays more distinctly.

3 | RESULTS

Our dataset consisted of 3,444,482 individuals who were initially screened with a negative FIT result during the 2017–2019 period and were subsequently eligible for repeat screening in the 2019–2021 FIT-based CRC screening program in the Netherlands. For the screen-detected cancer analysis, 282,439 (8.2%) were first-time invitees and were excluded from the analysis, leaving 3,162,043 individuals for the analysis. The screen-detected cancer dataset included 1,501,774 (47.5%) males and 1,660,269 (52.5%) females, with a mean age of 65.8 (SD 5.8) years.

On the other hand, for the interval cancer analysis, we included all 3,444,482 individuals, without excluding first-time invitees. The interval cancer dataset comprised 1,645,269 (47.8%) males and 1,799,213 (52.2%) females, with a mean age of 66.2 (SD 6.1) years.

Mean time invitation interval in both datasets was 773.3 (SD 52.0) days, with a minimum of 723 up to maximum of 1043 days (Supporting Information Table 1). In the screen-detected dataset, the majority of individuals (87.7%) received their invitations within 27 months, with only 12.2% invited after an interval of more than 27 months (Supporting Information Figure 2a). For the interval cancer dataset, 84.8% of individuals were invited within 27 months, while 11.8% had an invitation interval exceeding 27 months (Supporting Information Figure 2b).

A total of 6456 screen-detected and 3885 interval cancers were detected from January 2019 to December 2021. Four thousand eight hundred nineteen (74.6%) screen-detected cancers were diagnosed in individuals that had received their invitations in time, while 1637 (25.4%) individuals received their invitations beyond 25 months (Table 1) Similarly, for the interval cancers, 2886 (74.3%) individuals were diagnosed within 24–25 months, while 999 (25.7%) interval cancers were found in individuals invited after 25 months (Table 2).

3.1 | Impact of the extended invitation intervals on screen-detected cancers

Overall, the extended invitation interval had no significant impact on the stage distribution of screen-detected CRC, despite the slight differences observed when comparing the late Stages III and IV in 24–25 and >27. Results from the regression analysis showed that the stage distribution was not significantly different for the various lengths of

TABLE 1 Descriptive statistics of the study population having a screen-detected cancer.

Screen-detected cancers	Total *n*	Early stage *n* (%)	Late stage *n* (%)
Total	6456	4214 (65.3)	2242 (34.7)
Men	3549	2321 (65.4)	1243 (34.6)
Women	2907	1893 (65.1)	1014 (34.9)
Screening round			
1	–	–	–
2	1760	1095 (62.2)	665 (37.8)
3	2852	1884 (66.1)	968 (33.9)
4	1844	1235 (67.0)	609 (33.0)
Time intervals			
24–25	4819	3145 (65.3)	1674 (34.7)
25–26	644	436 (67.7)	208 (32.3)
26–27	494	319 (64.6)	175 (35.4)
>27	499	314 (62.9)	185 (37.1)
Hb in previous round			
0 μg Hb/g feces	4069	2634 (64.7)	1435 (35.3)
>0 μg Hb/g feces	2387	1580 (66.2)	807 (33.8)

TABLE 2 Descriptive statistics of the study population having an interval cancer.

Interval cancers	Total *n*	Early stage *n* (%)	Late stage *n* (%)
Total	3885	1640 (42.2)	2245 (57.8)
Men	1986	849 (42.7)	1137 (57.3)
Women	1899	791 (41.7)	1108 (58.3)
Screening round			
1	1535	639 (41.6)	896 (58.4)
2	1402	564 (40.2)	838 (59.8)
3	948	437 (46.1)	511 (53.9)
4	–	–	–
Time intervals			
24–25	2886	1227 (42.5)	1659 (57.5)
25–26	379	156 (41.2)	223 (58.8)
26–27	298	132 (44,3)	166 (55.7)
>27	322	125 (38.8)	197 (61.2)
Hb in previous round			
0 μg Hb/g feces	2462	1028 (41.8)	1434 (58.5)
>0 μg Hb/g feces	1423	612 (43.0)	811 (57.0)

the invitation intervals, for example, 24–25 versus >27 months (OR 1.08, 95% CI 0.89–1.31) (Table 3). Specifically, 7% of patients in the >27 months group were diagnosed with Stage IV cancer

TABLE 3 Multivariate logistic regression for the impact of extended time intervals on the stage distribution of screen-detected cancers.

		OR	95% CI
Age	Per 10 years	0.98	0.97–1.00*
Sex	Women	1	
	Men	0.99	0.89–1.10
Screening round	2	1	
	3	0.92	0.80–1.05
	4	0.93	0.79–1.11
Invitation interval	24–25 months	1	
	25–26 months	0.88	0.74–1.05
	26–27 months	1.01	0.83–1.23
	>27 months	1.08	0.89–1.31
Hb previous round	0 μg Hb/g feces	1	
	>0 μg Hb/g feces	0.93	0.84–1.04

Note: *Statistical significance was determined at the 95% confidence level ($p < 0.05$).

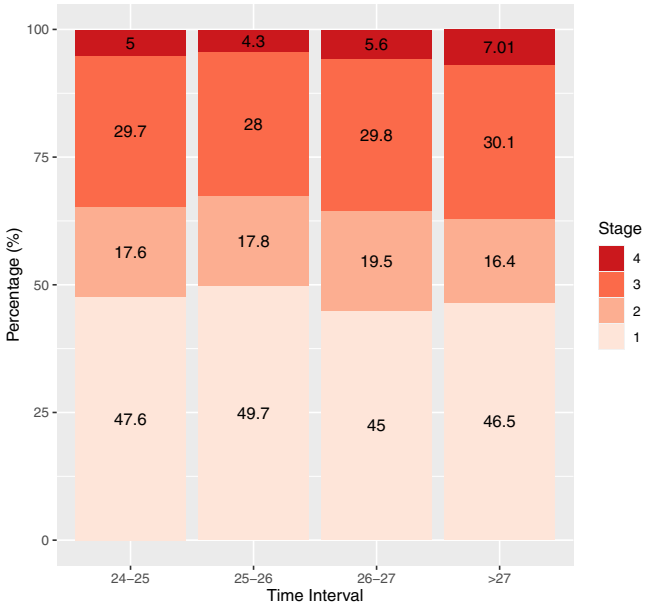

FIGURE 1 Stage distribution across the different time intervals for screen-detected cancers.

compared to 5% in the 24–25 months group, and 30.1% were diagnosed with Stage III cancer compared to 29.7% in the 24–25 months group (Figure 1).

Age was the only confounding factor that showed a small but significant effect on stage distribution, with the elderly being less likely to be diagnosed with an advanced stage CRC with an OR of 0.98 (95% CI 0.97–1.00). Sensitivity analysis, namely Stage I versus Stages II, III, and IV, for screen-detected cancers was largely in accordance with the outcomes of the main analysis, indicating no significant impact of the delayed invitation on the stage distribution. Age was

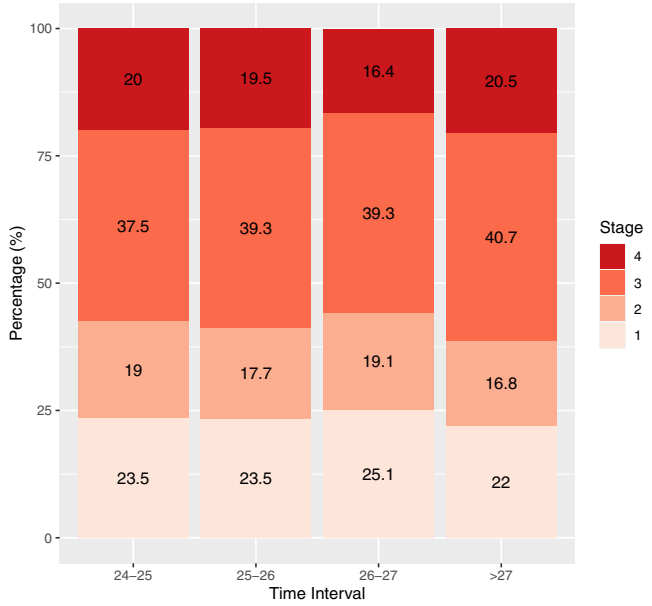

FIGURE 2 Stage distribution across the different time intervals for interval cancers.

TABLE 4 Multivariate logistic regression for the impact of extended time intervals on the stage distribution of interval cancers.

		OR	95% CI
Age	Per 10 years	0.97	0.95–0.98*
Sex	Women	1	
	Men	0.96	0.85–1,10
Screening round	1	1	
	2	1.15	0.99–1.35
	3	1.01	0.84–1.21
Invitation interval	24–25 months	1	
	25–26 months	1.01	0.81–1.26
	26–27 months	0.87	0.68–1.11
	>27 months	1.09	0.85–1.38
Hb previous round	0 μg Hb/g feces	1	
	>0 μg Hb/g feces	0.94	0.83–1.08

Note: *Statistical significance was determined at the 95% confidence level ($p < 0.05$).

also no longer significantly associated with the stage distribution (Supporting Information Tables 2 and 3).

3.2 | Impact of the extended invitation intervals on interval cancers

Similar to the screen-detected cancers, results indicated that the length of the invitation interval had no impact on the stage distribution of the interval cancers, despite the slightly higher percentage of patients diagnosed with higher stages for the >27 months time interval compared to the 24–25 months (Figure 2). Outcomes from the logistic regression showed that there was no significant association with the stage distribution for all the time intervals (Table 4). In particular, 20.5% of patients invited beyond the 27 months were diagnosed with Stage IV cancer compared to 20% who were invited within the 24–25 months, and 40.7% were diagnosed with Stage III cancer compared to 37.5% in 24–25 months.

Age was indicated as the only confounding factor associated with stage distribution; older people appear to be less likely to develop late-stage interval cancer (OR: 0.97 95% CI: 0.95–0.98), although this effect is minimal. Sensitivity analysis of interval cancers yielded similar results as the screen-detected analysis, with age being the only factor that is significantly associated with the stage distribution (OR: 1.02 95%CI: 1.00–1.03), although the effect was very limited (Supporting Information Tables 4 and 5).

4 | DISCUSSION

In this study, we evaluated the impact of the extended FIT invitation intervals on the stage distribution of screen-detected and interval CRCs. Since we were interested in intervals for repeated screening, individuals who were first-time invitees were excluded from the analysis for the screen-detected cancers, since the delays in their invitation could not be defined as the initial scheduled date for their first invitation was unknown.

Our results indicated that an extension of the invitation interval has no significant impact on the stage distribution for both screen-detected and interval cancers, although there was a slight trend towards a higher percentage of late-stage cancers in groups with extended intervals. While this trend was not statistically significant, our findings suggest that temporarily extending the screening interval during health crises, such as the COVID-19 pandemic, may be a reasonable measure to manage healthcare resources without significantly compromising early cancer detection. However, it remains important to minimize such delays where possible to avoid the potential risks associated with extended intervals.

The lack of impact of the extended interval on stage distribution is likely explained by the relatively limited extension (max. 6 months) of the invitation intervals and the slow-growing nature of CRC in its early stages. CRC gradually develops from benign polyps, a process that typically takes at least 10–15 years, and not all polyps will eventually become cancerous.[29,30] Once a polyp has transformed into cancer, it may progress more rapidly compared to its earlier, benign stage—a fact that justifies the shorter time intervals within the FIT screening program. However, this progression is still relatively slow, meaning that a delay of a few months is unlikely to result in a significant shift in the stage at diagnosis. These insights align with previous modeling studies suggesting that temporary extensions beyond 30 months could potentially lead to adverse outcomes, as observed in Italian studies.[21,22]

Age was the only demographic factor that showed an association with the stage distribution, with older individuals appearing less likely to develop late-stage CRC. This is probably because CRCs grow more slowly in old age due to delayed cell division.[31] It is important to mention that this effect was minimal and therefore possibly clinically irrelevant.

Furthermore, another noteworthy finding was that the presence of f-Hb in previous negative FIT was not associated with the stage distribution of CRC. This observation was consistent with previous findings by Kooyker et al., which indicated that while different f-Hb cut-offs can alter the detection of CRCs, the stage distribution of detected CRCs remains unaffected.[32] This is likely explained by the fact that screening protocols are designed to detect CRC regardless of the stage, and later on, further diagnostic evaluations (like colonoscopy) are used to determine the stage. Thus, while varying f-Hb cut-offs can affect detection sensitivity, they do not alter the overall stage distribution of detected cancers.

Another possible explanation of the lack of impact of the temporary suspension of the screening program on the stage distribution is the proactive measures taken by the Netherlands to promptly resume the screening program and manage delays effectively.[11] The temporary suspension during the COVID-19 pandemic was mitigated by quickly sending out postponed invitations, thereby keeping the delays short, as discussed earlier. These proactive measures ensured that the delays remained within a timeframe that was unlikely to affect the stage at diagnosis significantly. This is consistent with findings from an earlier Dutch study, which examined the stage distribution of CRCs during the COVID-19 pandemic. The study observed a catch-up effect after the nationwide CRC screening program resumed, largely due to the prioritization of individuals with missed appointments.[15] By quickly addressing the backlog, the program likely minimized the impact of the delay on cancer detection and avoided cases where a later diagnosis could potentially lead to the detection of cancers at a more advanced stage, subsequently affecting the overall stage distribution.

Additionally, another possible explanation would be the heightened awareness among the population in the Netherlands regarding the importance of screening that may have prompted individuals to schedule appointments with their GPs, most likely due to CRC-related symptoms.

It is important to mention that despite the robustness of our findings, some limitations should be acknowledged. Our study focused on the specific healthcare context of the Netherlands, which may limit the generalizability of the results to other healthcare systems with different screening protocols and population demographics. Another limitation is that the findings in our analysis are most applicable to relatively small delays in invitation intervals, as observed in the maximum extension of 6 months. Larger delays may have different impacts on CRC stage distribution, and thus our results should be interpreted within the context of these limited delays.

Our study showed that such a temporary suspension and extension of FIT invitation intervals for CRC screening during the COVID-19 pandemic did not result in a significant increase in late-stage CRCs. However, these findings should be interpreted cautiously, given that they apply to relatively short extensions of invitation intervals. These findings support the prudent management of screening programs during health crises, emphasizing the importance of timely resumption and catch-up strategies for postponed screenings to maintain program effectiveness. In conclusion, the temporary suspension of screening programs can be an appropriate response to urgent healthcare demands, now that COVID-19 is not currently a major concern, provided proactive measures are in place to minimize delays in care.

AUTHOR CONTRIBUTIONS

Maria-Alexandra Katsara: Investigation; writing – original draft; writing – review and editing; visualization; validation; methodology; formal analysis; data curation; resources. **Danica van den Berg:** Data curation; validation; writing – review and editing. **Manon C. W. Spaander:** Writing – review and editing. **Adriana J. van Vuuren:** Writing – review and editing. **Evelien Dekker:** Writing – review and editing. **Folkert J. van Kemenade:** Writing – review and editing. **Iris D. Nagtegaal:** Writing – review and editing. **Monique E. van Leerdam:** Writing – review and editing. **Iris Lansdorp-Vogelaar:** Supervision; writing – review and editing. **Esther Toes-Zoutendijk:** Supervision; resources; conceptualization; funding acquisition; project administration; writing – review and editing; methodology.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data are owned by Bevolkingsonderzoek Nederland (BVO-NL) and stored in the national screening database (ScreenIT). Researchers interested in accessing and analyzing the data may contact the data officer of BVO-NL (wetenschappelijkonderzoek@bevolkingsonderzoeknederland.nl) for access. Further information is available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Katsara M-A, van den Berg D, Spaander MCW, et al. The impact of extended invitation intervals on stage distribution of screen-detected and interval cancer within the Dutch colorectal cancer screening program. *Int J Cancer*. 2025;157(2):298-304. doi:10.1002/ijc.35371