# Colorectal Cancer Stage Distribution at First and Repeat Fecal Immunochemical Test Screening

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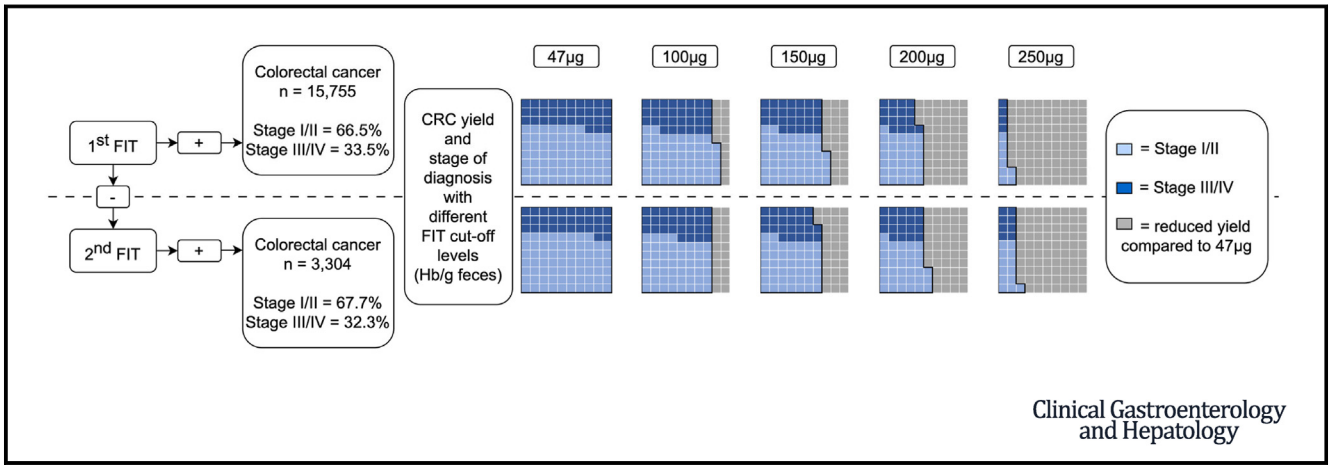


**BACKGROUND & AIMS:** **For colorectal cancer (CRC) screening to be effective, it is important that screen-detected cancers are found at an early stage. Studies on stage distribution of screen-detected CRC at repeat screening of large population-based fecal immunochemical test (FIT)-based screening programs and the impact of FIT cut-off values on staging currently are lacking.**

**METHODS:** **We obtained data for FIT-positive participants (FIT cut-off, 47 $\mu$g hemoglobin/g feces) at their first or second (ie, repeat) screening from the Dutch National Screening Database from 2014 to 2018. Tumor characteristics were acquired through linkage with The Netherlands Cancer Registry. We compared stage at diagnosis (I–II vs III–IV) of CRCs detected at a first or second screening. In addition, we analyzed the hypothetical yield and stage distribution of CRC for different FIT cut-off values up to 250 $\mu$g hemoglobin/g feces.**

**RESULTS:** **At the first and second screenings, respectively, 15,755 and 3304 CRCs were detected. CRCs detected at the first or second screening were equally likely to be stages I to II (66.5% vs 67.7%; relative risk, 1.02; 95% CI, 1.00–1.05). A hypothetical increase of the FIT cut-off value from 47**

*Abbreviations used in this paper:* CRC, colorectal cancer; FIT, fecal immunochemical test; Hb, hemoglobin; RR, relative risk.



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**μg to 250 μg resulted in a reduction of detected CRCs by 88.3% and 79.0% at the first or second screening, respectively. Even then, the majority of detected CRCs (63%–64%) still would be diagnosed at stages I to II.**

**CONCLUSIONS:** **FIT-based screening is effective in downstaging CRC, and also at repeat screening. Increasingly, the FIT cut-off level has a limited impact on the stage distribution of detected CRCs, although it greatly affects CRC detection and thus is important to keep low.**

*Keywords:* Colorectal; Cancer; Screening; FIT; Stage; Cut-Off.

Cancer screening aims to reduce disease-related mortality through prevention and early detection of cancer. When cancer is detected at a late stage, more invasive treatment is needed and survival rates decrease. This also holds for colorectal cancer (CRC), for which 5-year survival rates are considerably lower when the cancer is detected at late stages compared with early stage CRC.[1,2] CRC screening programs using a fecal immunochemical test (FIT) for occult blood showed that screen-detected CRCs are diagnosed more often at stages I to II (66%–71%) than clinically detected CRCs (40%–57%).[1,3–7] Because these results were based predominantly on CRCs detected at first screening, it remains unclear whether the stage distribution of CRCs detected at repeat screenings will remain as favorable. If the stage distribution moves toward the distribution of clinically detected CRCs, this would suggest that the downstaging effect of FIT-based screening decreases at repeat screening.

The quantitative nature of most FITs provides the opportunity to choose a cut-off level for a positive test result in accordance with the preferred balance between true- and false-positive results as well as with local colonoscopy resources. Recent publications have shown that increasing the FIT cut-off level decreases the yield of CRC and consequently slightly increases the risk of interval CRC after a negative FIT.[8–10] The impact of the FIT cut-off level on the stage distribution of screen-detected CRCs, however, has not yet been evaluated. Assuming that advanced-stage cancers bleed more, our hypothesis was that a higher FIT cut-off level particularly misses stages I and II CRCs. Detection of CRCs in early stages and preventing them from advancing to stages III or IV improves CRC survival rates. A less-favorable stage distribution when using a higher FIT cut-off level not only will reduce CRC yield, but also may affect the intended mortality and morbidity reduction negatively.

In this study, we evaluated stage distribution of CRCs detected at first and second (ie, repeat) screenings in a FIT-based screening program. The secondary aim was to estimate the impact of an increased FIT cut-off level on the yield and stage distribution of screen-detected CRCs.

## Methods

Data for this study were obtained from the population-based Dutch CRC screening program, which started in 2014. The design of the program and its real-time monitoring system have been described previously.[8,11] In summary, the target population consists of asymptomatic average-risk individuals aged 55 to 75 years old, who are invited every 2 years to perform a FIT (FOB-Gold; Sentinel). The target population was invited gradually by birth cohort, with a rollout period of 5 years. Invitees already under colonoscopy surveillance were advised not to participate. Participants with a FIT result higher than the cut-off value of 47 μg hemoglobin (Hb)/g feces were referred for colonoscopy. In case of detection of an adenoma or CRC upon colonoscopy, the participant was referred for further treatment and/or colonoscopy surveillance. If colonoscopy revealed no relevant findings, participants were allocated to receive a new invitation for CRC screening by FIT in 10 years. Per the program design, all participants undergoing a second screening by definition had a negative FIT result at first screening.

### Study Population

We selected all participants who tested positive (FIT cut-off, 47 μg) at their first or second (ie, repeat) screening between January 2014 and December 2018. Because of the gradual rollout of the program by birth cohort, the study population included birth cohorts from 1938 to 1961 and 1963 for first screening and birth cohorts from 1945 to 1955 and 1957 for the first and second screenings. Figure 1 shows a flowchart that illustrates the study population.

### Data Collection

Participants with a positive FIT were obtained from the national screening database (ScreenIT). ScreenIT includes all information about the screening process, from invitation to colonoscopy and pathology results, providing us with baseline characteristics and quantitative FIT results (Hb per gram of feces) of all included participants. Through linkage with The Netherlands Cancer Registry, tumor characteristics were obtained such as staging and primary tumor location. CRC was considered screen-detected when detected within 180 days (6 months) after colonoscopy, to include CRC with a short delay in histology

diagnoses resulting from waiting time for polypectomy or surgery. If the colonoscopy was not registered in ScreenIT, for example, when the colonoscopy was performed in a center that did not participate in the screening program, CRCs were considered screen-detected if diagnosed within 216 days (6 months plus the median waiting time of 36 days for colonoscopy in the Dutch screening program) of a positive FIT. In case individuals were diagnosed with multiple CRCs, the CRC with the most advanced stage was included in the analyses. All authors had access to the study data and reviewed and approved the final manuscript.

### *Definitions*

The Netherlands Cancer Registry classified the stage of CRC at the time of diagnosis according to the 7th edition (until 2016) or the 8th edition (2017 and later) of the Union for International Cancer Control TNM Classification.[12,13] Cancer stages were defined as TNM stage I (T1–T2, N0, M0), II (T3–T4, N0, M0), III (T1–T4, N1–N2, M0), or IV (T1–T4, N0–2, M1). A CRC was classified as right-sided when the tumor was located in the cecum, ascending colon, hepatic flexure, transverse colon, or splenic flexure; classified as left-sided when located in the descending colon, sigmoid, or rectosigmoid; and classified as rectal when located in the rectum. Based on age at invitation, participants were divided in age categories, as follows: 55 to 59 years, 60 to 64 years, 65 to 69 years, and 70 to 76 years.

## What You Need to Know

### Background

A first fecal immunochemical test (FIT)-screening detects colorectal cancer (CRC) in a favorable stage distribution. We examined whether this persists at repeat FIT screening and how CRC stage distribution is affected by the FIT cut-off level.

### Findings

Approximately two thirds of screening-detected CRCs are diagnosed at stage I or II at first, but also at a second FIT screening. Increasing the FIT cut-off level leads to missing almost as many early as late-stage CRCs.

### Implications for patient care

The downstaging effect of FIT-based screening on CRC remains evident at repeat screening. The impact on CRC yield is much more important when deciding on the FIT cut-off level than the impact on stage distribution of the detected CRCs.

### *Statistical Analyses*

We tested for statistically significant ($P < .05$) differences in sex, age, tumor location, and stage distribution between participants who tested positive at the first or second screening using the chi-square or $t$ test. We used binomial logistic regression to compare the probability (odds ratio) of detecting CRC at stages I to II

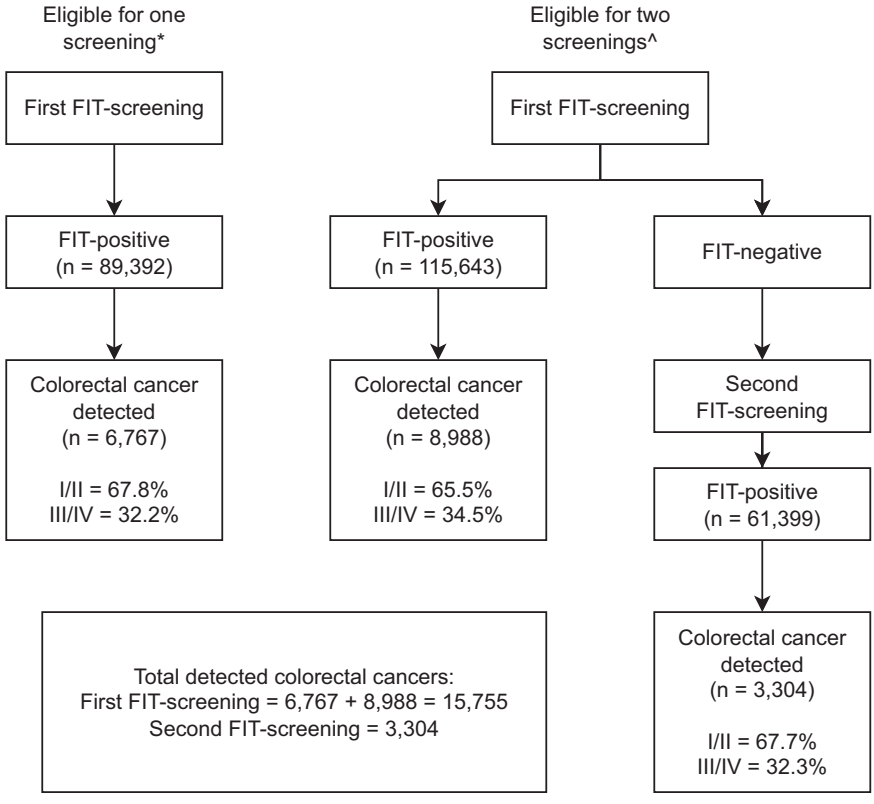


**Figure 1.** Flowchart of study population and detected colorectal cancers. FIT, fecal immunochemical test; I/II, stage I or II; III/IV, stage III or IV. *Including birth cohorts 1938–1961 and 1963; ^Including birth cohorts 1945–1955 and 1957.

between their first and second screening, between patient characteristics (ie, sex or age category), and between tumor locations (ie, left-sided, right-sided, or rectal). To prevent inflated estimates[14] of risk differences, we presented relative risks rather than odds ratios for outcomes for which incidence was common (ie, >10%). Relative risk (RR) was calculated according to the following formula[14]: $relative\ risk = \frac{odds\ ratio}{(1-P0)+(P0 * odds\ ratio)}$. In this formula, *P0* indicates the incidence of the outcome of interest in the nonexposed group. In the current study, the outcome of interest was considered CRC stages I to II and the nonexposed group were the first screening participants. Furthermore, we estimated to what extent a hypothetical increase in FIT cut-off level from 47 $\mu$g to 100 $\mu$g, 150 $\mu$g, 200 $\mu$g, or 250 $\mu$g Hb/g feces would affect the stage distribution of detected CRCs and CRC yield, stratified for first and second screening and tumor location. The CRC yield was presented per analyzed FIT cut-off level as the proportion of the original CRC yield with a FIT cut-off level of 47 $\mu$g and in addition to the overall CRC yield also estimated per cancer stage (I–IV).

When comparing the probability of detecting CRC at stages I to II between the first and second screening, a shift from stage I to stage II could be overlooked. To examine whether this occurred we performed a sensitivity analysis by changing the outcome of interest into stage I instead of stages I to II (Supplementary Table 1). In addition, we performed a sensitivity analysis (Supplementary Tables 2 and 3) to evaluate whether our findings would differ when including only birth cohorts that were eligible for 2 rounds of FIT screening.

## Results

A total of 266,434 participants had a positive FIT at the first (n = 205,035) or second (n = 61,399) screening. Follow-up colonoscopies resulted in the diagnosis of 15,755 CRCs at the first screening and 3304 CRCs at the second screening (Table 1). The majority of CRCs were detected in males; 62.1% at the first screening and 55.7% at the second screening. The mean age at the time of CRC diagnosis was 67.2 years (SD, 6.0 y) at the first screening and 67.4 years (SD, 3.2 y) at the second screening ($P = .01$). Almost half of the CRCs detected at the first screening were located in the left colon (46.5%), while CRCs detected at the second screening were distributed more equally across the right colon, left colon, and rectum.

### Colorectal Cancer Stage Distribution

CRCs detected at the first screening were as likely to be diagnosed at stages I to II as CRCs detected at the second screening (66.5% vs 67.7%), with a RR of 1.02 (95% CI, 0.996–1.05) (Table 2). The probability that CRC was diagnosed at stages I to II was similar in men and

**Table 1.** Baseline Characteristics of CRC Detected at First or Second Screening

| | Total | | First screening | | Second screening | | |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | P value |
| Screen-detected CRCs | 19,059 | – | 15,755 | – | 3304 | – | |
| Sex | | | | | | | <.001 |
| Male | 11,628 | 61.0 | 9787 | 62.1 | 1841 | 55.7 | |
| Female | 7431 | 39.0 | 5968 | 37.9 | 1463 | 44.3 | |
| Age, y | | | | | | | .01 |
| Median (IQR) | 67 (63–73) | | 67 (63–73) | | 67 (65–69) | | |
| 55–59 | 2081 | 10.9 | 2081 | 13.2 | – | – | |
| 60–64 | 4233 | 22.2 | 3650 | 23.2 | 583 | 17.6 | |
| 65–69 | 6201 | 32.5 | 4297 | 27.3 | 1904 | 57.6 | |
| 70–76 | 6544 | 34.3 | 5727 | 36.4 | 817 | 24.7 | |
| Location | | | | | | | <.001 |
| Right-sided | 5452 | 28.9 | 4251 | 27.3 | 1201 | 36.8 | |
| Left-sided | 8378 | 44.4 | 7247 | 46.5 | 1131 | 34.6 | |
| Rectal | 5019 | 26.6 | 4084 | 26.2 | 935 | 28.6 | |
| Stage | | | | | | | .02 |
| I | 8740 | 46.6 | 7170 | 46.3 | 1570 | 48.2 | |
| II | 3768 | 20.1 | 3132 | 20.2 | 636 | 19.5 | |
| III | 4919 | 26.2 | 4061 | 26.2 | 858 | 26.3 | |
| IV | 1331 | 7.1% | 1136 | 7.3 | 195 | 6.0 | |

NOTE. The first screening had 173 (1.1%) missing locations and 256 (1.6%) missing stages, and the second screening had 37 (1.1%) missing locations and 45 (1.4%) missing stages.
CRC, colorectal cancer; IQR, interquartile range.

**Table 2.** CRC Stage Distribution and Relative Risk for Stage I–II Diagnosis per Participant Characteristic and Primary Tumor Location

| | Stage | | | | | | | | Relative risk stages I–II diagnosis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I (n = 8740) | | II (n = 3768) | | III (n = 4919) | | IV (n = 1331) | | I–II | | | |
| | n | % | n | % | n | % | n | % | n | % | RR | 95% CI |
| Screening round | | | | | | | | | | | | |
| First | 7170 | 46.3 | 3132 | 20.2 | 4061 | 26.2 | 1136 | 7.3 | 10,302 | 66.5 | Ref | |
| Second | 1570 | 48.2 | 636 | 19.5 | 858 | 26.3 | 195 | 6.0 | 2206 | 67.7 | 1.02 | 0.996–1.05 |
| Sex | | | | | | | | | | | | |
| Male | 5484 | 47.9 | 2176 | 19.0 | 2961 | 25.9 | 827 | 7.2 | 7660 | 66.9 | Ref | |
| Female | 3256 | 44.5 | 1592 | 21.8 | 1958 | 26.8 | 504 | 6.9 | 4848 | 66.3 | 0.99 | 0.96–1.01 |
| Age category, y | | | | | | | | | | | | |
| 55–59 | 951 | 46.4 | 356 | 17.4 | 587 | 28.6 | 155 | 7.6 | 1307 | 63.8 | Ref | |
| 60–64 | 1916 | 45.9 | 761 | 18.2 | 1189 | 28.5 | 304 | 7.3 | 2677 | 64.2 | 1.01 | 0.96–1.04 |
| 65–69 | 2820 | 46.2 | 1261 | 20.6 | 1606 | 26.3 | 420 | 6.9 | 4081 | 66.8 | 1.04 | 1.00–1.07 |
| 70–76 | 3053 | 47.5 | 1390 | 21.6 | 1537 | 23.9 | 452 | 7.0 | 4443 | 69.1 | 1.07 | 1.03–1.09 |
| Location | | | | | | | | | | | | |
| Right-sided | 2052 | 38.1 | 1577 | 29.3 | 1340 | 24.9 | 415 | 7.7 | 3629 | 67.4 | Ref | |
| Left-sided | 4340 | 52.8 | 1368 | 16.6 | 1966 | 23.9 | 549 | 6.7 | 5708 | 69.4 | 1.03 | 1.01–1.05 |
| Rectal | 2248 | 45.3 | 780 | 15.7 | 1581 | 31.9 | 349 | 7.0 | 3028 | 61.1 | 0.90 | 0.86–0.93 |

NOTE. There was a total of 193 (1.0%) missing locations.
CRC, colorectal cancer; RR, relative risk; Ref, reference group.

women (RR, 0.99; 95% CI, 0.96–1.01), but higher for older age categories (70–76 vs 55–59; RR, 1.07; 95% CI, 1.03–1.09). Compared with right-sided colon cancers, diagnosis at stages I to II was slightly more likely for left-sided colon cancers (RR, 1.03; 95% CI, 1.01–1.05), but less likely when cancer was located in the rectum (RR, 0.90; 95% CI, 0.86–0.93).

Stratified for tumor location, the probability that colon cancers were diagnosed at stages I to II was similar between the first and second screening (Table 3). Rectal cancers, however, were more likely to be diagnosed at stages I to II at the second screening compared with the first screening (66.0% vs 59.9%; RR, 1.11; 95% CI, 1.05–1.16).

**Table 3.** Stage Distribution per Tumor Location of CRCs With Available Stage Detected During First or Second Screening Round

| | CRC | Stages I–II | % | RR | 95% CI |
|---|---|---|---|---|---|
| Right-sided | | | | | |
| First screening | 4199 | 2842 | 67.7 | Ref | |
| Second screening | 1185 | 787 | 66.4 | 0.98 | 0.94–1.03 |
| Left-sided | | | | | |
| First screening | 7104 | 4919 | 69.2 | Ref | |
| Second screening | 1119 | 789 | 70.5 | 1.01 | 0.96–1.05 |
| Rectal | | | | | |
| First screening | 4037 | 2420 | 59.9 | Ref | |
| Second screening | 921 | 608 | 66.0 | 1.11 | 1.05–1.16 |

CRC, colorectal cancer; RR, relative risk.

### *Colorectal Cancer Yield and Stage Distribution With Increased Fecal Immunochemical Test Cut-Off Levels*

Increasing the FIT cut-off level would vastly reduce the overall yield of CRC (Table 4 and Figure 2). Ultimately, only 11.7% and 21.0% of the CRCs detected with the FIT cut-off level of 47 $\mu$g still would be detected when the FIT cut-off level was increased to 250 $\mu$g at the first or second screening, respectively. A steep decline in yield with higher FIT cut-off levels was observed for all cancer stages, yet seemed slightly sharper for stage I CRC. Increasing the FIT cut-off level showed a similar decline in yield regarding right-sided, left-sided, or rectal cancers (Supplementary Table 4).

Unlike the large impact on CRC yield, the proportion of CRCs diagnosed at stages I to II barely was reduced when increasing the FIT cut-off level from 47 $\mu$g to 250 $\mu$g at the first (66.5% to 63.8%) or second (67.7% to 62.7%) screening (Table 4 and Figure 2). When considering right-sided and left-sided colon cancers, there were minimal differences in the proportion of stage I to II CRCs at increased FIT cut-off values (Supplementary Table 4). Regarding rectal cancer, however, the proportion of stages I to II cancer would decline from 61.6% with a FIT cut-off level of 47 $\mu$g to 53.4% with a FIT cut-off level of 250 $\mu$g.

### *Sensitivity Analyses*

CRCs detected at the second screening were slightly more likely to be diagnosed at stage I than CRCs detected

**Table 4.** Stage Distribution and Yield of CRCs per Screening and FIT Cut-Off Level

| FIT cut-off level | CRC | Yield | | | | | Stages I–II | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | | Total | I | II | III | IV | | |
| First screening | | | | | | | | |
| 47 μg | 15,499 | 100% | 100% | 100% | 100% | 100% | 66.5% | 65.7%–67.2% |
| 100 μg | 13,209 | 85% | 81% | 89% | 88% | 91% | 65.0% | 64.2%–65.8% |
| 150 μg | 11,413 | 74% | 68% | 79% | 77% | 80% | 64.5% | 63.6%–65.4% |
| 200 μg | 7312 | 47% | 45% | 49% | 50% | 47% | 65.2% | 64.1%–66.2% |
| 250 μg | 1811 | 12% | 11% | 12% | 13% | 11% | 63.8% | 61.6%–66.0% |
| Second screening | | | | | | | | |
| 47 μg | 3259 | 100% | 100% | 100% | 100% | 100% | 67.7% | 66.1%–69.3% |
| 100 μg | 2602 | 80% | 74% | 84% | 85% | 87% | 65.4% | 63.5%–67.2% |
| 150 μg | 2223 | 68% | 60% | 76% | 75% | 76% | 64.4% | 62.4%–66.4% |
| 200 μg | 1718 | 53% | 46% | 60% | 59% | 58% | 63.8% | 61.5%–66.0% |
| 250 μg | 686 | 21% | 18% | 24% | 24% | 27% | 62.7% | 59.0%–66.2% |

NOTE. Yield indicates the percentage of detected CRCs compared with a FIT cut-off level of 47 μg.
CRC, colorectal cancer; FIT, fecal immunochemical test.

at the first screening (48.2% vs 46.3%), with a relative risk of 1.08 (95% CI, 1.04–1.12) (Supplementary Table 1). Restricting the analysis to only the birth cohorts that were eligible for FIT screening twice, the relative risk of stages I to II diagnosis was slightly higher at the second (67.7%) compared with the first (65.5%) screening, with a RR of 1.03 (95% CI, 1.00–1.06) (Supplementary Table 3).

## Discussion

In this study, using data from a national FIT-based CRC screening program, the majority of screen-detected CRCs were diagnosed at an early stage, with similar proportions of stages I to II CRCs at the first and second screening. Higher FIT cut-off levels at the first or second screening would reduce the yield of CRC drastically, although the proportion of stages I to II CRCs would remain high.

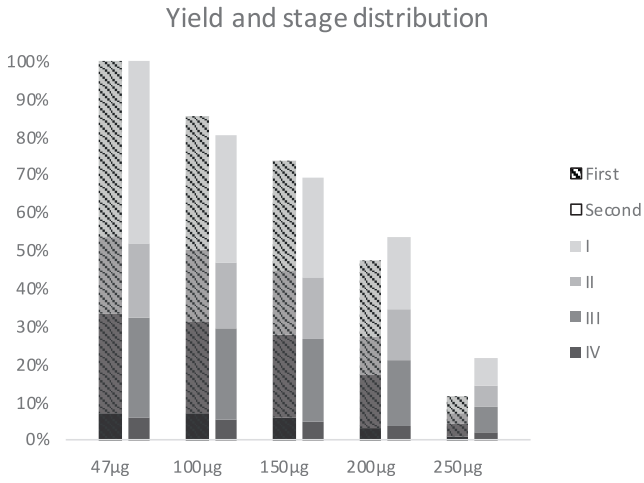


**Figure 2.** Stage distribution and yield of CRCs per screening and FIT cut-off level. Yield represents the percentage of detected CRCs compared with a FIT cut-off level of 47 μg. CRC, colorectal cancer; FIT, fecal immunochemical test.

The current study confirmed the favorable stage distribution of CRC detected by FIT-based screening (67% stages I to II) compared with clinically detected CRC (40% stages I to II),[3] illustrating one of the most important short-term effects of screening for CRC. Trials using guaiac fecal occult blood testing for primary screening observed a less-favorable stage distribution of CRCs detected at repeat screening.[15–17] As such, the clinical benefit of early stage diagnosis of CRC by guaiac fecal occult blood test screening decreased at repeated screening rounds. Our findings indicate that this was not the case for FIT-based screening because the high percentage of CRCs in early stages (I or II) was consistent for CRCs detected at repeat screening (68%).

The amount of intestinal blood loss may increase in more advanced stages of CRC. If more advanced cancers would indeed result in a higher fecal Hb concentration, one could argue that FIT-based screening has a stage-specific CRC sensitivity.[6] Screening with higher FIT cut-off levels then could predominantly miss early stage CRCs. Our findings show that increasing the FIT cut-off level caused a decline in the detection of all cancer stages, which seemed only slightly steeper for stage I CRC compared with higher stages. The suggestion that higher FIT cut-off values miss both early (I–II) and late-stage (III–IV) CRCs is illustrated by the minimal shift in stage distribution between the FIT cut-offs used, with a 1% to 5% decrease in the proportion of CRCs diagnosed at an early stage. CRC seems to bleed independent of cancer stage. It is possible that the local tumor stage (T-stage) itself is associated with intraluminal blood loss, but cancer stage (including TNM) itself does not. This is logical because regional or distant metastases would not be expected to affect intestinal blood loss from the local tumor. Unfortunately, detailed data about the T-stage were not available. Nonetheless, increasing the FIT cut-

off value from 47 to 250 μg Hb/g feces would vastly reduce CRC yield at both the first (-88%) and second (-79%) screenings. The impact on CRC yield is therefore much more important when deciding on the FIT cut-off level in a screening program than the impact on stage distribution of the detected CRCs. It should be noted that the Dutch program applies a relatively high (47 μg Hb/g feces) FIT cut-off level, whereas many other countries use lower FIT cut-off levels (10–15 μg Hb/g feces). The correlation between fecal Hb concentration and CRC stage might be more evident at less than 47 μg Hb/g feces.

CRC detected among participants in older age categories were slightly more likely to be diagnosed at an early stage. Perhaps cases of CRC at an older age more often include indolent and slow-growing tumors. After all, cell division is known to decrease with age, therefore cancer often develops more aggressively in younger individuals. Furthermore, FIT sensitivity for colorectal cancer is higher in older people, and there also may be other factors including an increased use of anticoagulants, which may influence the detection of more early stage colorectal cancers in the elderly.

We observed differences for colon and rectal cancers. Colon cancers were as likely to be detected in stages I to II at first or repeat screening, whereas the stage distribution of rectal cancers was more favorable when detected at repeat screening. This could mean that a first screening detects a relatively larger part of the prevalent late-stage cancers in the rectum compared with the prevalent late stage cancers in the colon. Therefore, fewer late-stage rectal cancers remain to be detected at repeat screening, causing a shift toward a more favorable stage distribution. Furthermore, increasing the FIT cut-off level would barely change the proportion of stages I to II colon cancers, while the proportion of stages I to II rectal cancers would be reduced from 61% to 53% when increasing the FIT cut-off value from 47 μg to 250 μg Hb/g feces. Rectal cancers thus might be more prone to stage-specific sensitivity of the FIT compared with colon cancers. Nevertheless, the proportion of screen-detected rectal cancers diagnosed in stages I or II when using high FIT cut-off levels is still higher compared with symptomatically detected rectal cancers (53%–61% vs 30%).[3]

Studies on the stage distribution of CRCs in FIT-based screening with a large sample size are sparse. The national Irish FIT-based (cut-off, 45 μg Hb/g feces) screening program reported that 67% of 51 CRCs detected at a second screening (with a negative FIT result at the first screening) were stages I to II.[18] Although this study had a smaller sample size, the results are in line with our findings. Two other studies reported on stage distribution over 2 screening rounds. A Norwegian trial showed that 72% of 260 CRCs detected over 2 rounds of FIT screening (15 μg Hb/g feces) were diagnosed at stages I to II.[19] Two rounds of FIT-based screening (17 μg Hb/g feces) in northern Italy detected 165 CRCs, of which the proportion of stages I to II was similar in the first (74%) and second (70%) rounds.[20] An important difference between these studies and ours is that in these studies the population was not divided into first and second (ie, repeated) screenings, but instead into first- and second-round participants. Second-round participants also included individuals who rejected the invitation for screening during the first round and participated for the first time during the second round. Consequently, these studies did not evaluate CRCs that explicitly were detected by repeated screening. Nevertheless, they show that subsequent screening rounds maintain a downstaging effect. One study analyzed diagnosing CRC at stages I to II using different FIT cut-off levels and, concordant to our findings, concluded that higher FIT cut-off levels had a limited impact on the sensitivity for stages I to II CRC. However, this study estimated outcomes for FIT cut-off values up to only 34 μg and included a relatively small number (n = 79) of CRCs detected in a referral population.[21]

An important strength of this study was related to the design of the Dutch program and its well-organized registries. The data collection on a national scale enabled us to include a large number of participants. The linkage to an accurate cancer registry provided us with detailed information of all screen-detected CRCs.[22] However, some limitations should be mentioned. First, we lack data on CRCs in participants with a fecal Hb concentration less than 47 μg Hb/g feces because only participants with a positive FIT were referred for colonoscopy. Therefore, the stage distribution of CRCs detected in participants with no, or a small amount (<47 μg) of, blood in their feces remains unknown. Another limitation was the rather arbitrary division of screen-detected CRCs into stages I to II and stages III to IV to compare the stage of diagnosis between screening round, sex, age categories, and primary tumor location. Although this is common in international literature,[19,21,23] stages I and II have significantly different survival rates. A shift from stage I to stage II CRCs between first and repeat screening still could indicate that the downstaging effect of FIT-based screening is reduced after the first screening. The results of our sensitivity analysis with regard to stage I vs stage II CRC (Supplementary Table 1) show that this is not the case. In fact, CRCs detected at repeat screening were slightly more likely to be diagnosed at stage I compared with CRCs detected at the first screening. Third, not all included individuals were invited twice for FIT screening during the study period as a result of the phased roll-out of the screening program, as illustrated in Figure 1. However, a second sensitivity analysis in which we selected only birth cohorts eligible for 2 FIT screenings (Supplementary Table 2) showed no substantially different results. Finally, the data only included participants in 2 screening rounds. As the screening program continues and more data are accumulated, these analyses should be repeated on a regular basis.

Our findings are important knowledge for FIT-based screening programs. After 2 screening rounds, FIT still detects CRC at an early stage and this stresses the importance of repeated participation. Moreover, the results of this study are informative for screening programs currently struggling with the optimal FIT cut-off level owing to a limited colonoscopy capacity or a (temporarily) overburdened health system. Increasing the FIT cut-off level vastly reduces the effectiveness of screening owing to a substantial reduction in yield, not because higher FIT cut-off levels miss predominantly early stage CRCs. The decline in yield becomes even steeper at higher FIT cut-off levels ($>150$ $\mu$g). When considering increasing the FIT cut-off level, there might be better alternatives to reduce the number of colonoscopies in FIT screening, for example, extending the screening interval.

In conclusion, the majority of CRCs detected by FIT-based screening are diagnosed at stage I or II, and also at repeat screening. Screening becomes much less effective when increasing the FIT cut-off level owing to a vast decrease in CRC detection. Stage distribution, however, is minimally affected by FIT cut-off level because the missed CRCs owing to higher FIT cut-off levels consider nearly as much stage I-II CRCs as stage III-IV CRCs.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.07.028.

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**Conflicts of interest**

These authors disclose the following: Evelien Dekker has received endoscopic equipment on loan from Olympus and FujiFilm, has received a research grant from FujiFilm, has received honorarium for consultancy from FujiFilm, Tillots, Olympus, GI Supply, Cancer Prevention Pharmaceuticals, PAION, and Ambu, and speakers' fees from Olympus, Roche, GI Supply, PAION, and IPSEN; Iris Lansdorp-Vogelaar is an associate editor at Gastroenterology, serves as an expert at the Health Council, serves as a panel member of the European Commission Initiative on Colorectal Cancer, and is a visiting scientist at the International Agency for Research on Cancer; and Manon Spaander has received research support from Sentinel, Sysmex, Boston Scientific, Norgine, and Medtronic. The remaining authors disclose no conflicts.

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**Data Availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Supplementary Table 1.** CRC Stage Distribution and Relative Risk for Stage I Diagnosis per Screening, Corrected for Sex, Age, and Tumor Location

| | Stages | | | | Relative risk stage I diagnosis | |
|---|---|---|---|---|---|---|
| | I | | II–IV | | | |
| | n | % | n | % | RR | 95% CI |
| FIT screening | | | | | | |
| First | 7170 | 46.3 | 8329 | 53.7 | Ref | |
| Second | 1570 | 48.2 | 1689 | 51.8 | 1.08 | 1.04–1.12 |

CRC, colorectal cancer; FIT, fecal immunochemical test; Ref, reference group; RR, relative risk.

**Supplementary Table 2.** Baseline Characteristics of Screen-Detected CRCs in Population Invited Twice for FIT Screening

| | Total | | First screening | | Second screening | | |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | P value |
| Screen-detected CRCs | 12,292 | – | 8988 | – | 3304 | – | |
| Sex | | | | | | | <.001 |
| Male | 7486 | 60.9 | 5645 | 62.8 | 1841 | 55.7 | |
| Female | 4806 | 39.1 | 3343 | 37.2 | 1463 | 44.3 | |
| Age, y | | | | | | | |
| Mean (SD) | 66.2 (3.4) | | 65.7 (3.4) | | 67.4 (3.2) | | .01 |
| Median (IQR) | 66 (63–69) | | 66 (63–69) | | 67 (65–69) | | |
| 55–59 | 348 | 2.8 | 348 | 3.9 | – | – | |
| 60–64 | 3649 | 29.7 | 3066 | 34.1 | 583 | 17.6 | |
| 65–69 | 6201 | 50.4 | 4297 | 47.8 | 1904 | 57.6 | |
| 70–76 | 2094 | 17.0 | 1277 | 14.2 | 817 | 24.7 | |
| Location | | | | | | | <.001 |
| Right-sided | 3598 | 29.6 | 2397 | 26.9 | 1201 | 36.8 | |
| Left-sided | 5202 | 42.7 | 4071 | 45.7 | 1131 | 34.6 | |
| Rectal | 3370 | 27.7 | 2435 | 27.4 | 935 | 28.6 | |
| Stage | | | | | | | .02 |
| I | 5611 | 46.3 | 4041 | 45.7 | 1570 | 48.2 | |
| II | 2391 | 19.7 | 1755 | 19.8 | 636 | 19.5 | |
| III | 3248 | 26.8 | 2390 | 27.0 | 858 | 26.3 | |
| IV | 861 | 7.1 | 666 | 7.5 | 195 | 6.0 | |

NOTE. The first screening had 85 (0.9%) missing locations and 136 (1.5%) missing stages, and the second screening had 37 (1.1%) missing locations and 45 (1.4%) missing stages.
CRC, colorectal cancer; IQR, interquartile range.

**Supplementary Table 3.** Early Detection of CRC Using a FIT Cut-Off Level of 47 μg in Population Invited Twice for FIT Screening

| | Stage | | | | | | | | Relative risk stages I–II diagnosis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I (n = 5611) | | II (n = 2391) | | III (n = 3248) | | IV (n = 861) | | I–II | | | |
| | n | % | n | % | n | % | n | % | n | % | RR | 95% CI |
| Screening round | | | | | | | | | | | | |
| First | 4041 | 45.7 | 1755 | 19.8 | 2390 | 27.0 | 666 | 7.5 | 5796 | 65.5 | Ref | |
| Second | 1570 | 48.2 | 636 | 19.5 | 858 | 26.3 | 195 | 6.0 | 2206 | 67.7 | 1.03 | 1.00–1.06 |
| Sex | | | | | | | | | | | | |
| Male | 3524 | 47.7 | 1383 | 18.7 | 1956 | 26.5 | 521 | 7.1 | 4907 | 66.5 | Ref | |
| Female | 2087 | 44.2 | 1008 | 21.3 | 1292 | 27.3 | 340 | 7.2 | 3095 | 65.5 | 0.98 | 0.95–1.00 |
| Age category, y | | | | | | | | | | | | |
| 55–59 | 164 | 47.5 | 51 | 14.8 | 99 | 28.7 | 31 | 9.0 | 215 | 62.3 | Ref | |
| 60–64 | 1642 | 45.7 | 664 | 18.5 | 1029 | 28.6 | 261 | 7.3 | 2306 | 64.1 | 1.03 | 0.94–1.10 |
| 65–69 | 2820 | 46.2 | 1261 | 20.6 | 1606 | 26.3 | 420 | 6.9 | 4081 | 66.8 | 1.06 | 0.98–1.12 |
| 70–76 | 985 | 47.7 | 415 | 20.1 | 514 | 24.9 | 149 | 7.2 | 1400 | 67.9 | 1.06 | 0.99–1.13 |
| Location | | | | | | | | | | | | |
| Right-sided | 1352 | 38.1 | 1006 | 28.3 | 914 | 25.7 | 280 | 7.9 | 2358 | 66.4 | Ref | |
| Left-sided | 2693 | 52.7 | 839 | 16.4 | 1241 | 24.3 | 340 | 6.6 | 3532 | 69.1 | 1.04 | 1.01–1.07 |
| Rectal | 1509 | 45.3 | 519 | 15.6 | 1072 | 32.2 | 233 | 7.0 | 2028 | 60.8 | 0.90 | 0.86–0.95 |

NOTE. There were 113 (0.9%) missing locations.
CRC, colorectal cancer; FIT, fecal immunochemical test; RR, relative risk; Ref, reference group.

**Supplementary Table 4.** Stage Distribution and CRC Yield at First and Second Screening per Tumor Location and FIT Cut-Off Level

| | | Yield | | | | | | |
|---|---|---|---|---|---|---|---|---|
| FIT cut-off level | CRC | Total | I | II | III | IV | Stages I–II | 95% CI |
| Right-sided | | | | | | | | |
| 47 μg | 5384 | 100% | 100% | 100% | 100% | 100% | 67.4% | 66.1%–68.6% |
| 100 μg | 4409 | 82% | 76% | 86% | 85% | 85% | 66.1% | 64.7%–67.5% |
| 150 μg | 3737 | 69% | 63% | 74% | 72% | 72% | 66.0% | 64.5%–67.5% |
| 200 μg | 2431 | 45% | 42% | 49% | 47% | 42% | 66.7% | 64.8%–68.5% |
| 250 μg | 660 | 12% | 11% | 13% | 13% | 11% | 66.2% | 62.5%–69.7% |
| Left-sided | | | | | | | | |
| 47 μg | 8223 | 100% | 100% | 100% | 100% | 100% | 69.4% | 68.4%–70.4% |
| 100 μg | 7085 | 86% | 82% | 92% | 89% | 93% | 68.1% | 67.0%–69.2% |
| 150 μg | 6188 | 75% | 70% | 84% | 78% | 82% | 67.8% | 66.7%–69.0% |
| 200 μg | 4122 | 50% | 49% | 51% | 52% | 52% | 68.1% | 66.7%–69.6% |
| 250 μg | 1098 | 13% | 13% | 13% | 14% | 14% | 68.5% | 65.7%–71.2% |
| Rectal | | | | | | | | |
| 47 μg | 4958 | 100% | 100% | 100% | 100% | 100% | 61.1% | 59.7%–62.4% |
| 100 μg | 4156 | 84% | 78% | 88% | 89% | 93% | 58.5% | 57.0%–60.0% |
| 150 μg | 3577 | 72% | 63% | 79% | 79% | 84% | 56.8% | 55.2%–58.5% |
| 200 μg | 2425 | 49% | 42% | 54% | 54% | 58% | 56.6% | 54.6%–58.6% |
| 250 μg | 721 | 15% | 12% | 16% | 18% | 15% | 53.4% | 49.7%–57.0% |

NOTE. Yield is the percentage of detected CRCs compared with the FIT cut-off level of 47 μg.
CRC, colorectal cancer; FIT, fecal immunochemical test.