Gastroenterology 2024;167:788–797

PREVENTION AND EARLY DETECTION

Risk of Cancers Proximal to the Colon in Fecal Immunochemical Test Positive Screenees in a Colorectal Cancer Screening Program

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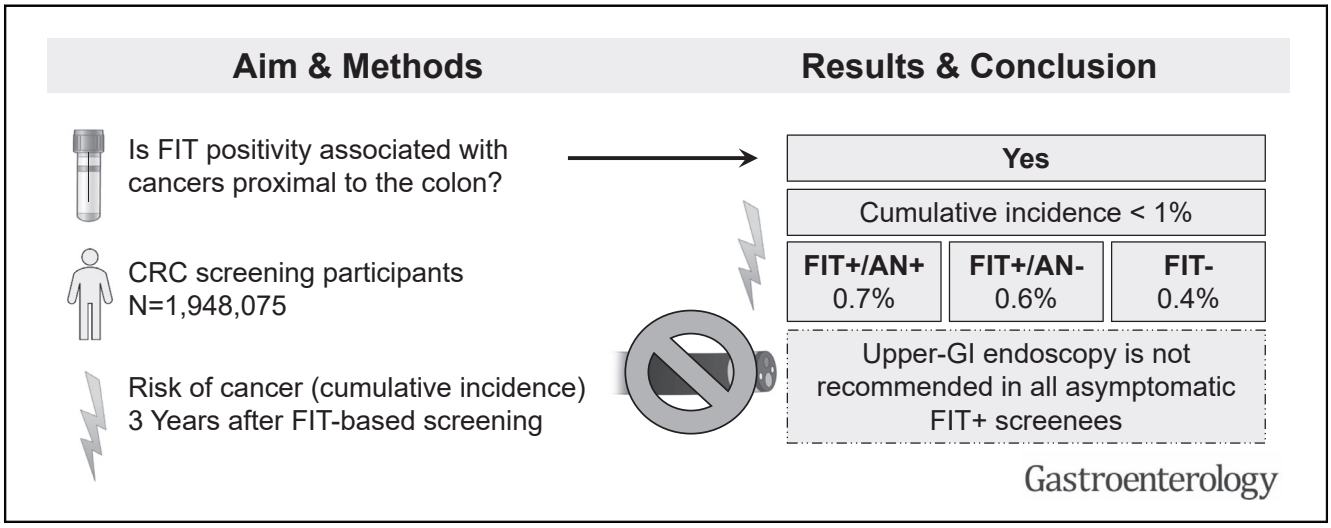

BACKGROUND & AIMS: In more than half of the colorectal cancer screening participants with a positive fecal immunochemical test (FIT) result, no advanced neoplasia (AN) is detected at colonoscopy. The positive FIT result could also be generated by cancers located proximal to the colon: upper gastrointestinal, oral cavity, nose, and throat cancers. We evaluated screenees' risk of being diagnosed with a cancer proximal to the colon within the 3 years and compared risks between those with a positive vs those with a negative FIT. **METHODS:** Data of Dutch colorectal cancer screening participants who underwent biennial FIT-based screening 2014–2018 were collected from the national screening database and linked to the National Cancer Registry. Screenees were classified into 3 groups: FIT-positives with AN (FIT+/AN+), FIT-positives without AN (FIT+/AN−), and FIT-negatives (FIT−). We compared the cumulative incidence of cancers proximal to the colon in each group 3 years after FIT. A Cox regression analysis with left truncation and right censoring, using FIT positivity as time-dependent variable and stratified for sex, was performed to compare the hazard of cancers proximal to the colon in participants who were FIT-positive vs FIT-negative. **RESULTS:** Three-year cumulative incidence of cancers proximal to the colon in FIT+/AN+ (n = 65,767), FIT+/AN− (n = 50,661), and FIT− (n = 1,831,647) screenees was 0.7%, 0.6%, and 0.4%, respectively ($P <$ .001). FIT-positives were older and more frequently male than FIT-negatives ($P <$ .001). Significantly more cancers proximal to the colon were detected among FIT-positives ($P <$ .001; hazard ratio, 1.55; 95% CI, 1.44–1.67). **CONCLUSION:** FIT-positive screenees were at significantly increased risk of being diagnosed with a cancer proximal to the colon within 3 years after FIT, although the 3-year cumulative incidence was still less than 1%.

Keywords: Advanced Neoplasia; Colorectal Cancer Screening; Fecal Immunochemical Test; Gastric Cancer; Esophagogastroduodenoscopy.

Over the past 10 years many countries have introduced colorectal cancer (CRC) screening programs based on fecal immunochemical tests (FIT). FIT-based

Abbreviations used in this paper: **AN, advanced neoplasia; CRC, colorectal cancer; EGD, esophagogastroduodenoscopy; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood testing; Hb, hemoglobin.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2024.04.028

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Fecal immunochemical tests are used in colorectal cancer screening. Cancers proximal to the colon, that is, upper gastrointestinal, oral cavity, nose, and throat cancers, might also lead to a positive fecal immunochemical test.

NEW FINDINGS

Screenees testing positive for the fecal immunochemical test have a significantly higher risk of being diagnosed with a cancer proximal to the colon within 3 years after their positive test, independent of the findings at colonoscopy.

LIMITATIONS

Symptoms related to cancers and benign diseases proximal to the colon were not evaluated. In addition, we could not adjust for all possible confounders (eg, smoking status), as this information was not available.

CLINICAL RESEARCH RELEVANCE

The 3-year cumulative incidence of cancers proximal to the colon is significantly higher in fecal immunochemical test–positive screenees but still low (<1%). These findings do not justify performing esophagogastroduodenoscopy as an additional procedure in all fecal immunochemical test–positive screenees.

BASIC RESEARCH RELEVANCE

Fecal immunochemical test positivity is associated with multiple cancer types. Literature suggests it might even be associated with a higher risk of other benign diseases. Consequently, future studies should evaluate which additional risk factors might justify esophagogastroduodenoscopy and which screenees would benefit from receiving additional lifestyle-related recommendations or other preventive measures to reduce their future risk of disease.

screening enables the detection of bleeding malignant or advanced benign colorectal lesions by measuring human hemoglobin (Hb) levels in stool.[1] As such, FIT-positive screenees have a higher likelihood of being diagnosed with advanced neoplasia (AN) (CRC or advanced adenomas) at colonoscopy than FIT-negative screenees.[2] Nevertheless, although FIT-based screening aims to detect individuals with AN, still more than half of the FIT-positive screenees are considered false positives, as no AN is detected at colonoscopy.[3–5]

Hypothetically, fecal Hb detected by FIT could also originate from lesions located more proximal in the gastrointestinal tract and oral, nose, and throat cavity (lesions proximal to the colon).[6,7] Yet, CRC is more prevalent than other gastrointestinal cancers and Hb is known to degrade while passing through the gastrointestinal tract.[8] Consequently, it is less probable that blood originating from more proximally located cancers can be detected in stool. Nevertheless, investigation by additional esophagogastroduodenoscopy (EGD) is frequently considered by both worried clinicians and FIT-positive screenees, especially in the absence of AN at colonoscopy. In addition, there is an increasing interest in studying FIT positivity in the context of other diseases, as it is hypothesized that FIT positivity might be associated with multiple diseases, due to shared underlying risk factors.[6,9–17]

Currently there is not enough evidence to recommend EGD in asymptomatic FIT-positive screenees without AN in the West.[18] Most studies that evaluated the cumulative incidence of cancers proximal to the colon after stool-based CRC screening were based on guaiac fecal occult blood testing (gFOBT).[6,19] Because gFOBT has a lower sensitivity for AN as compared with FIT and is not specific for human Hb, by detecting the heme component of hemoglobin instead of the human-specific globin component, the results of these studies do not immediately apply to FIT-based screening.[20] In addition, many studies, either gFOBT- or FIT-based, had sample sizes that were too small for sound conclusions.[6,19,21–28] A recent large-scale Korean study (n = 5,932,544) evaluated the risk of cancers proximal to the colon in the 3 years after FIT-based screening.[6] Already in the first year, FIT-positive screenees without CRC were found to have a higher risk of esophageal, gastric, small intestine, and overall cancers proximal to the colon as compared with FIT-negative screenees. As the incidence of cancers proximal to the colon in Asia is relatively high compared with the West, the results of this study may be less generalizable to other parts of the world.[29,30]

We aimed to evaluate whether FIT-positive participants in the national Dutch FIT-based CRC screening program are at higher risk of being diagnosed with cancers proximal to the colon and EGD-detectable cancers in the 3 years after a positive FIT, compared with FIT-negative screenees. In addition, as secondary analyses, we have also evaluated the incidence of 10 other types of cancers.

Materials and Methods

Study Design and Population

For this study, we analyzed prospectively collected data from the national Dutch FIT-based CRC screening program and linked these to the National Cancer Registry. The Dutch FIT-based CRC screening program was initiated by the Dutch Ministry of Health, Welfare, and Sport in 2014 and completely implemented in 2019. The Dutch Foundation of Population Screening is responsible for carrying out the screening program and is overseen by the National Institute for Public Health and the Environment. All citizens aged 55 to 75 years old are invited to perform a biennial FIT (FOB-Gold, Sentinel, Italy). FIT-positive participants (cutoff $\geq$ 47 μg Hb/g feces) are referred for colonoscopy.

We included data from screenees who participated at least once in the Dutch FIT-based CRC screening program between January 2014 and January 2018. Excluded were screenees with missing data, FIT-positive screenees with a colonoscopy of inadequate quality (Boston Bowel Preparation Score $<$ 6 and/or cecum not reached) without AN, FIT-positive screenees who underwent colonoscopy due to a temporary lower cutoff of $\geq$ 15 μg Hb/g feces, FIT-positive screenees who did not undergo colonoscopy and FIT-positive screenees for whom the

interval between FIT and colonoscopy was more than 3 years or the duration of the interval was unclear. For this study, informed consent was not required, as the Dutch Act on Medical Research Involving Human Subjects allows the analysis of data that are routinely collected, as long as it does not interfere with the standard of care. Our study protocol was approved by the Dutch Foundation of Population Screening and the Netherlands Comprehensive Cancer Organization.

Data Collection

Screening data were obtained from the national screening database (ScreenIT; Topicus, Deventer, the Netherlands) that is designed and managed by the Dutch Foundation of Population Screening. This is a comprehensive, high-quality database that prospectively collects screening data following standardized reporting procedures. Cancer data were provided by the National Cancer Registry. This registry includes detailed information on all Dutch citizens diagnosed with cancer from 1989 onward. It is designed and managed by the Netherlands Comprehensive Cancer Organization. More than 95% of all pathology-confirmed cancer diagnoses in the Netherlands are registered in this registry.[31] Screening data were linked to cancer data via the Dutch citizen service number. All data were pseudonymized before transmission to the research team, to comply with the General Data Protection Regulation Act.

Screening Data (FIT, Colonoscopy, and Histopathology)

Colonoscopies performed within the Dutch FIT-based CRC screening program are executed according to international quality standards.[32] Endoscopists performing these colonoscopies need to be certified; they are strictly monitored and audited, to ensure the quality of the colonoscopies.[33] For all colorectal lesions detected during colonoscopy, location, size, macroscopic aspect, and morphology are documented. All resected lesions are evaluated by gastrointestinal pathologists.

A positive colonoscopy after a positive FIT was defined as a colonoscopy in which AN was detected. AN was defined as CRC or advanced adenoma (adenoma $\geq$ 10 mm and/or with $\geq$ 25% villous component and/or with high-grade dysplasia). A negative colonoscopy after a positive FIT was defined as an adequate-quality colonoscopy (Boston Bowel Preparation Score $\geq$ 6 and cecum reached) in which no AN was detected.

Screenees were classified into 3 groups based on their FIT result and findings at colonoscopy: FIT-positives with AN (FIT+/AN+), FIT-positives without AN (FIT+/AN−) and FIT-negatives (FIT−). We used a FIT cutoff of $\geq$ 47 μg Hb/g feces.

Identification of Cancers

We collected data on cancer type, location, date of cancer diagnosis, and age at cancer diagnosis for all studied cancers that occurred within 3 years after FIT testing. Tissue typing and cancer localization were based on the International Classification of Diseases for Oncology (ICD-O). The codes used from the ICD-O can be found in Supplementary Table 1. All types of cancers that could occur proximal to the colon were included. The date of cancer diagnosis was defined as the first histological or cytological cancer diagnosis and was always within 3 months of the first clinical visit related to the cancer diagnosis.

Cancers proximal to the colon were classified as cancers in the oral cavity, nose or throat, esophageal, gastric, small bowel undefined, duodenum (including the papilla of Vater), jejunum, and ileum. In addition, esophageal, gastric, and duodenal cancers were classified as EGD-detectable cancers. In secondary analyses, we also analyzed cancers located in the lungs; liver; intra- and extrahepatic (bile) ducts; thyroid; bladder; lymphatic, hematopoietic, and reticuloendothelial system; pancreas; kidneys; prostate; breasts; and cervix uteri.

Statistical Analysis

We evaluated the 3-year incidence after FIT testing in each group: FIT+/AN+, FIT+/AN−, and FIT−. We only included cancers diagnosed within 3 years after FIT, as we assumed that such cancers could have been detectable at the time of FIT testing.

In the initial analyses, we calculated the cumulative incidence in each of the 3 groups. We only considered the last FIT result in each screenee whenever more than 1 FIT result was available within the inclusion period (January 2014 and January 2018). We assumed a 3-year observation time in all screenees, ignoring mortality and migration as competing events. Differences between groups were evaluated for statistical significance with the chi-square test statistic for categorical data and the Kruskal-Wallis test for quantitative data. To evaluate the impact of the FIT cutoff on cumulative incidence we repeated the analysis at different FIT cutoffs (15, 47, 80, and 100 μg Hb/g feces).

In addition, we analyzed the cumulative incidence for each cancer sub(type) separately. In the latter analyses, the time to a cancer diagnosis was not considered censored in case of a diagnosis of another cancer subtype. If there were multiple cancer diagnoses of the same subtype within 3 years, only the first diagnosis was considered.

Cancer risk increases with age. To adjust for confounding by age, we used Cox regression analysis to evaluate the relative hazard of the studied cancers in FIT-positive screenees compared with FIT-negative screenees. The baseline hazard was age-based and observation time was truncated at the left: the age of the first FIT result within the inclusion period. Here, FIT positivity and the detection of AN were defined as time-dependent variables: only the most recent FIT result was considered when comparing hazards. Time to event was considered censored in those without the studied cancer diagnosis 3 years after the last FIT testing. As male and female individuals differ in their cancer risk, we stratified for sex. In these analyses, we systematically evaluated whether the relative hazard differed significantly between FIT-positive screenees with and without AN, using the generalized likelihood ratio test statistic.

P values of less than .05 were considered to indicate statistically significant differences. All data analyses were performed with IBM SPSS statistics version 28 and R version 4.2.2. The R package "survival" was used for the Cox regression analysis.

Results

Baseline Characteristics of the Study Cohort

The national screening database identified 1,981,755 individuals who participated at least once in the Dutch CRC screening program between January 2014 and January

2018. Of those, 33,680 were excluded: 8 had missing or inconsistent FIT data, 5032 underwent a colonoscopy due to a temporarily lower cutoff of ≥ 15 μg Hb/g feces, 24,792 had a positive FIT but no follow-up colonoscopy, and 2869 underwent a colonoscopy of inadequate quality. Another 979 had either undergone a colonoscopy more than 3 years after FIT screening, or the timing between FIT screening and the colonoscopy was unclear.

The remaining 1,948,075 screenees were classified into 3 groups: 65,767 FIT-positive screenees with AN (FIT+/AN+), 50,661 FIT-positive screenees without AN (FIT+/AN−) and 1,831,647 FIT-negative screenees (FIT−). FIT-positive screenees (median 67, IQR 63–69) were significantly older than FIT-negative screenees (median 65, IQR 62–69; $P < .001$). In addition, more men had an FIT-positive result (64.7% vs 47.6%; $P < .001$). The median quantitative FIT result in μg Hb/g feces (IQR) in all screenees was 169.7 (90.0–211.5), 107.1 (66.2–186.1), and below the lower limit of quantification for FIT+/AN+, FIT+/AN−, and FIT− screenees, respectively. If we only looked at screenees without a cancer proximal to the colon, this was 169.6 (89.9–211.5), 107.1 (66.2–186.1), and below the lower limit of quantification for FIT+/AN+, FIT+/AN−, and FIT− screenees, respectively. There was a significant difference between groups (< .001).

Cumulative Incidence of Cancers Proximal to the Colon, EGD-detectable Cancers, and Other Cancers Within 3 Years After FIT

Linkage to the National Cancer Registry identified 7577 cancers proximal to the colon, and 4870 EGD-detectable cancers, between January 2014 and January 2021. The 3-year cumulative incidence of cancer proximal to the colon was 0.7% in FIT+/AN+ screenees, 0.6% in FIT+/AN− screenees, and 0.4% in FIT− screenees ($P < .001$). For EGD-detectable cancer these percentages were 0.4%, 0.4%, and 0.2% ($P < .001$) (Figure 1). Table 1 summarizes the characteristics of all screenees with cancer proximal to the colon within 3 years after FIT. The cumulative incidence of both cancers proximal to the colon and EGD-detectable cancers remained below 1%, independent of the FIT and colonoscopy result.

To evaluate if other FIT cutoffs would result in different findings, we have added Supplementary Tables 2 and 3. Supplementary Table 2 shows individuals who underwent an adequate-quality colonoscopy after a positive FIT at a temporarily lower cutoff of ≥ 15 μg Hb/g feces, either at the beginning of the Dutch screening program or during previous screening studies that used a lower FIT cutoff. As the number of individuals per group (FIT+/AN+ vs FIT+/AN−) is small, firm conclusions cannot be drawn. Based on these supplementary data, there was no significant difference in the cumulative incidence of cancers proximal to the colon in both groups. Supplementary Table 3 shows the cumulative incidence of cancers proximal to the colon based on different FIT cutoffs (15, 47, 80, and 100 μg Hb/g feces). Independent of the chosen FIT cutoff, we found FIT-positive screenees to have a significantly higher cumulative incidence of cancer proximal to the colon as compared with FIT-negative screenees ($P < .001$).

The number needed to scope to detect 1 EGD-detectable cancer after FIT-based screening is 255 if all FIT-positive screenees would undergo EGD. This is a lower limit, as this number needed to scope assumes that all EGD-detectable cancers would have been detectable at the moment of FIT screening.

Table 2 shows the cumulative incidence of the other cancer types in screenees diagnosed with cancer within 3 years after FIT (cutoff ≥ 47 μg Hb/g feces). We observed a significantly higher cumulative incidence of lung cancer, cancer of the liver, intra- and extrahepatic (bile) ducts, bladder cancer, cancer of the pancreas, kidney cancer, prostate cancer, and breast cancer in FIT-positive screenees. The cumulative incidence for most of the other cancer types did not significantly exceed 1%, except for the cumulative incidences of lung, prostate, and breast cancer, which were between 1% and 3%.

Cox Proportional Hazards Analysis of Cancers Proximal to the Colon, EGD-detectable Cancers, and Other Cancers 3 Years After FIT

The higher risk in FIT-positive screenees was confirmed in the Cox proportional hazards analysis (Table 3). Using FIT positivity as a time-dependent variable, the hazard rate ratio of a cancer proximal to the colon in FIT-positive screenees was 1.55 (95% CI, 1.44–1.67) compared with FIT-negative screenees. There was no significant difference in the relative hazard of cancers proximal to the colon in FIT-positive screenees in whom AN was found at colonoscopy (FIT+/AN+) compared with FIT-positive screenees without AN (FIT+/AN–) detected at colonoscopy (hazard rate ratio, 1.58; 95% CI, 1.44–1.74 vs 1.51; 95% CI, 1.34–1.70; $P = .527$).

The hazard rate ratio of an EGD-detectable cancer in FIT-positive screenees was 1.47 (95% CI, 1.34–1.63) compared with FIT-negative screenees. There was no significant difference in the relative hazard of EGD-detectable cancers in FIT-positive screenees with or without AN at colonoscopy (hazard rate ratio, 1.50; 95% CI, 1.33–1.70 vs 1.44, 95% CI, 1.24–1.67; $P = .637$).

For all studied cancer (sub)types, the hazard rate ratio for FIT-positives relative to FIT-negatives was below 2.0. Only for lung cancer and kidney cancer was there a significant difference in the relative hazard in FIT-positives with and without AN at colonoscopy.

Discussion

In this study within a national FIT-based CRC screening program, FIT-positive screenees were at higher risk of being diagnosed with a cancer in the upper gastrointestinal tract, oral cavity, nose, or throat within 3 years after FIT as compared with FIT-negative screenees. When focusing solely on EGD-detectable (esophageal, gastric, or duodenal) cancers, significantly more EGD-detectable cancers were detected within 3 years after FIT testing among FIT-positive screenees as compared with FIT-negative screenees.

Like for FIT-positive screenees with a cancer proximal to the colon ($P = .527$), in FIT-positive screenees with an EGD-

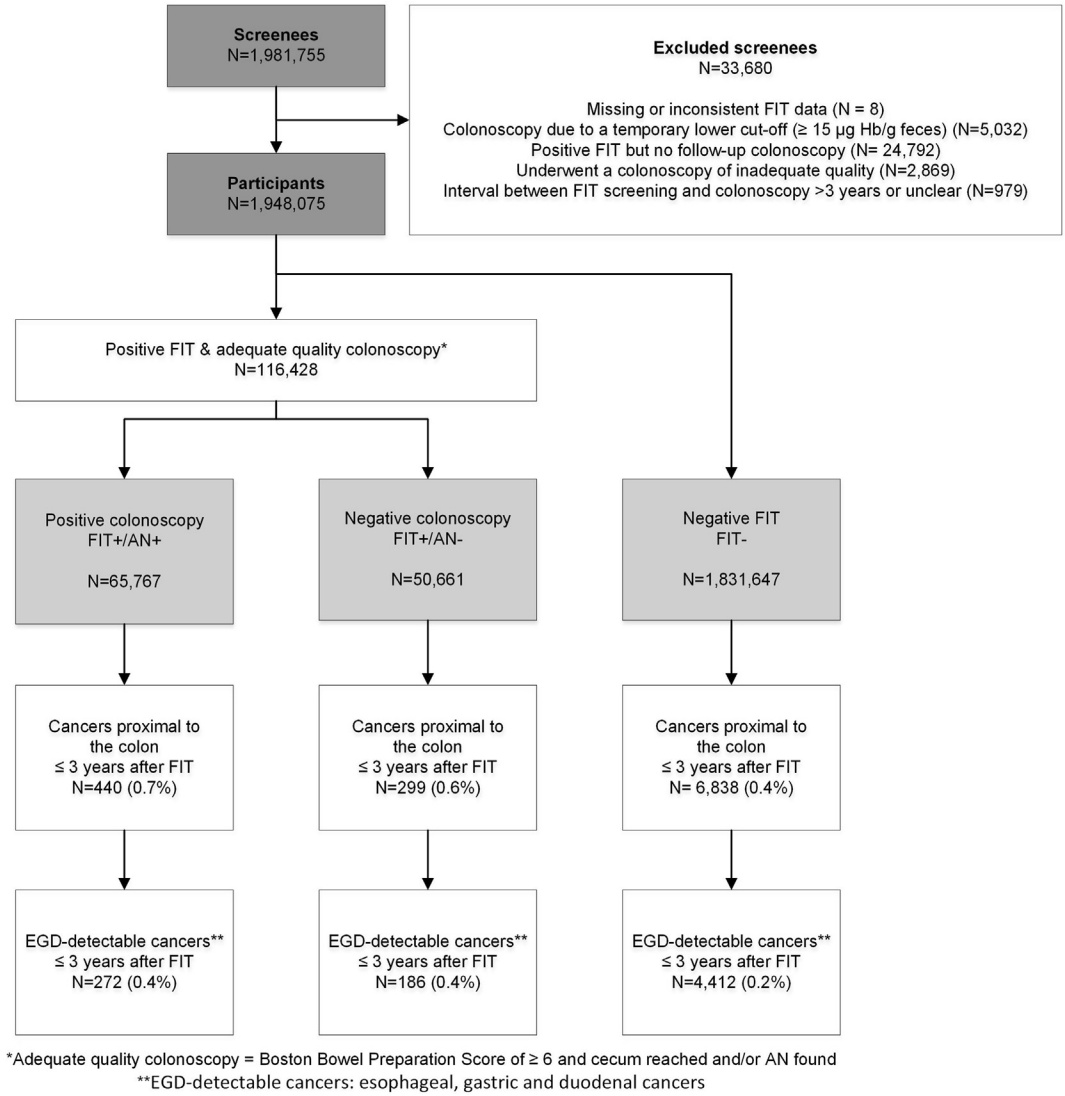

Figure 1. Flowchart of FIT-based study cohort 3 years after FIT.

detectable cancer we did not observe a significant difference in the relative hazard between FIT-positives with and without AN ($P = .637$). Assuming that all EGD-detectable cancers could have been detected at the moment of FIT screening, the number of FIT-positive screenees that would need to undergo an EGD to be able to detect 1 EGD-detectable cancer is at least 255. To put this number into context, the number of colonoscopies that need to be performed in those who are FIT-positive to detect 1 CRC is approximately 25 (in screenees $\geq$ 55 years at a cutoff FIT-value of $\geq$ 47 μg Hb/g feces).[34] In addition, we observed a significantly higher cumulative incidence of lung cancer; cancer of the liver, intra- and extrahepatic (bile) ducts; bladder cancer; cancer of the pancreas; kidney cancer; prostate cancer; and breast cancer in those who are FIT-positive. The relative hazard was significantly higher for FIT+/AN+, as compared with FIT+/AN− screenees, for lung and kidney cancer only. Nevertheless, as FIT positivity is most predictive for CRC, one should not forget that there is a considerable group of screenees that despite of having a positive FIT result refrain from follow-up colonoscopy. Efforts should be made to emphasize the importance of colonoscopy in these screenees.[34]

To our knowledge, this is the first study reporting the risk for cancers proximal to the colon and several other types of cancer in a very large cohort of screenees in a Western FIT-based CRC screening program, linking data from a national screening database to a National Cancer Registry with a follow-up of 3 years. Our study has several strengths. Our national screening database consists of high-quality data on invitees, participation, FIT results, and colonoscopy and pathology findings and thereby enables assessing AN as most advanced finding at colonoscopy. As it is known that the presence of advanced adenomas may attribute to a positive FIT result, we believe that not only CRC but also advanced adenomas should be included in the analysis. As the National Cancer Registry is continuously updated, linkage to this registry enabled us to identify almost all cancers proximal to the colon that occurred in the screenees. The registry includes all Dutch citizens diagnosed with cancer from 1989 onward, and has a coverage of 95%.[31] Last, we had a large sample size

Table 1. Characteristics of Screenees Diagnosed With Cancers Proximal to the Colon Within 3 Years After FIT (cutoff ≥ 47 μg Hb/g Feces) and the Corresponding Cumulative Incidences per Cancer (Sub)type

	FIT+/AN+ n = 65,767	FIT+/AN− n = 50,661	FIT− n = 1,831,647	*P* value
Cancer proximal to the colon,[a] n (cumulative incidence)	440 (0.7)	299 (0.6)	6838 (0.4)	<.001
EGD-detectable cancer,[b] n (cumulative incidence)	272 (0.4)	186 (0.4)	4412 (0.2)	<.001
Cancer subtypes, n (%)				
Oral cavity, nose, or throat	151 (34.3)	91 (30.4)	2145 (31.4)	<.001
Esophageal	168 (38.2)	94 (31.4)	2441 (35.7)	<.001
Gastric	78 (17.7)	75 (25.1)	1595 (23.3)	<.001
Small bowel undefined	4 (0.9)	6 (2.0)	87 (1.3)	.076
Duodenum	23 (5.2)	16 (5.4)	364 (5.3)	.007
Jejunum	2 (0.5)	4 (1.3)	67 (1.0)	.293
Ileum	14 (3.2)	13 (4.4)	139 (2.0)	<.001
Median age at cancer diagnosis, years (IQR)	68.0 (65.0–72.0)	69.0 (65.0–72.0)	68.0 (65.0–72.0)	.601
Age at cancer diagnosis subcategories, n (%)				
55–64	89 (20.2)	60 (20.1)	1526 (22.3)	.741
65–74	267 (60.7)	182 (60.9)	4002 (58.5)	
≥75	84 (19.1)	57 (19.1)	1310 (19.2)	
Male, n (%)	334 (75.9)	199 (66.6)	4685 (68.5)	.003
Median quantitative FIT result, μg Hb/g feces (IQR)	172.5 (94.9–216.3)	115.1 (65.0–186.4)	<LLoQ	<.001

NOTE. Data are presented as median (interquartile range), n (%), or mean ± standard deviation.
LLoQ, lower limit of quantification.
[a]Cancers proximal to the colon: cancer in the oral cavity, nose, or throat, esophageal, gastric, small bowel undefined, duodenum (including the papilla of Vater), jejunum and ileum.
[b]EGD-detectable cancers: esophageal, gastric, and duodenal cancers. We analyzed the cumulative incidence for each cancer sub(type) separately. Therefore the total number of EGD-detectable cancers is not the sum of the esophageal, gastric, and duodenal cancers.

Table 2. Cumulative Incidence of Other Cancer Types Within 3 Years After FIT (cutoff ≥ 47 μg Hb/g Feces)

	FIT+/AN+ n = 65,767	FIT+/AN− n = 50,661	FIT− n = 1,831,647	*P* value
Other cancer types in males and females, n (%)				
Lung	1029 (1.6)	653 (1.3)	14,324 (0.8)	<.001
Liver, intra- and extrahepatic (bile) ducts	109 (0.2)	65 (0.1)	1417 (0.1)	<.001
Thyroid	26 (0.04)	15 (0.03)	534 (0.03)	.314
Bladder	199 (0.3)	122 (0.2)	3194 (0.2)	<.001
Lymphatic, hematopoietic, and reticuloendothelial system	362 (0.6)	298 (0.6)	9294 (0.5)	.015
Pancreas	148 (0.2)	100 (0.2)	2910 (0.2)	<.001
Kidney	214 (0.3)	115 (0.2)	2970 (0.2)	<.001
	FIT+/AN+ n = 42,522	FIT+/AN− n = 27,984	FIT− n = 872,748	*P* value
Other cancer types in men, n (%)				
Prostate	1053 (2.5)	598 (2.1)	19,639 (2.3)	.004
	FIT+/AN+ n = 23,245	FIT+/AN− n = 22,677	FIT− n = 958,899	*P* value
Other cancer types in women, n (%)				
Breast	431 (1.9)	414 (1.8)	14,837 (1.5)	<.001
Cervix uteri	2 (0.01)	5 (0.02)	232 (0.02)	.309

Table 3. Cox Proportional Hazards Analysis: Cancer Risk Within 3 Years After FIT

Cancer types	Hazard rate ratio relative to FIT−			
	FIT+ (CI 95%)	FIT+/AN+ (CI 95%)	FIT+/AN− (CI 95%)	*P* value[a]
Proximal to the colon[b]	1.55 (1.44–1.67)	1.58 (1.44–1.74)	1.51 (1.34–1.70)	.527
EGD-detectable[c]	1.47 (1.34–1.63)	1.50 (1.33–1.70)	1.44 (1.24–1.67)	.637
Lung	1.83 (1.74–1.92)	1.96 (1.84–2.09)	1.65 (1.53–1.79)	<.001
Liver, intra- and extrahepatic (bile) ducts	1.83 (1.56–2.14)	1.96 (1.61–2.39)	1.65 (1.28–2.11)	.263
Thyroid	1.33 (0.97–1.83)	1.52 (1.03–2.26)	1.09 (0.65–1.82)	.290
Bladder	1.36 (1.21–1.52)	1.43 (1.24–1.65)	1.25 (1.04–1.50)	.235
Lymphatic, hematopoietic and reticuloendothelial system	1.04 (0.96–1.13)	0.99 (0.89–1.10)	1.12 (0.99–1.25)	.138
Pancreas	1.35 (1.19–1.54)	1.42 (1.20–1.67)	1.26 (1.03–1.54)	.364
Kidney	1.58 (1.41–1.78)	1.77 (1.54–2.04)	1.32 (1.09–1.60)	.011
Prostate	1.02 (0.97–1.07)	1.08 (1.02–1.15)	0.92 (0.84–1.00)	.001
Breast	1.20 (1.12–1.28)	1.21 (1.10–1.34)	1.18 (1.07–1.30)	.678
Cervix uteri	0.66 (0.31–1.39)	0.37 (0.09–1.48)	0.96 (0.39–2.32)	.228

NOTE. Cells indicate hazard rate ratio relative to FIT negatives (cutoff $\geq$ 47 μg Hb/g feces).
[a]Chi-square likelihood ratio test, comparing difference in hazard rate ratio between FIT+/AN+ and FIT+/AN−.
[b]Proximal to the colon: cancer in the oral cavity, nose, or throat; esophageal; gastric; small bowel undefined; duodenum (including the papilla of Vater); jejunum; and ileum.
[c]EGD-detectable: esophageal, gastric, and duodenal cancers.

available to reliably compare cumulative incidences among groups, which is essential as some cancers are very rare.

Our study also has several limitations. Because we did not evaluate participants' symptoms at the moment of FIT-based CRC screening, we cannot rule out that some participants had cancer-related symptoms (eg, weight loss, hot flashes or night sweats). We could not adjust for all confounders, as for example the smoking status and alcohol consumption of screenees was unknown as this information is not available in the national registries. As we did not perform EGD in all participants and the National Cancer Registry only identifies cancers, we were unable to identify other benign diseases, like severe esophagitis or gastric ulcers, that may also have caused blood loss possibly explaining the positive FIT. However, benign diseases of the colon (eg, inflammatory bowel disease or hemorrhoids) are not included when evaluating FIT for CRC screening.

A recent Korean study reported that FIT-positive screenees without CRC had a higher risk of cancers proximal to the colon 1, 2, and 3 years after the positive FIT, as compared with FIT-negative screenees. However, the authors did not include colonoscopy findings. Instead, they used the International Statistical Classification of Diseases and Related Health Problems, 10th Revision codes in the government cancer registration program. As this registration program solely focusses on cancers, the authors were not able to include advanced precursor lesions in their analysis. In addition, they only included the initial FIT result for those who underwent more than 1 FIT during the study period, and their follow-up ended in 2014. The observed cumulative incidence of cancers proximal to the colon in the Korean study is much higher than observed in our study group. Three years after FIT-based screening, a cumulative incidence of cancers proximal to the colon of 3.2% for FIT+/CRC+ screenees, of 1.2% for FIT+/CRC− screenees and 0.8% for FIT− screenees was observed, as compared with, respectively, 0.7%, 0.6%, and 0.4% in our study population. The higher cumulative incidences are most likely explained by the much higher cumulative incidence of gastric cancers in the Korean study. Three years after FIT-based screening, gastric (2.6%) and hepatopancreatobiliary cancers (3.5%) were more prevalent than esophageal cancers (0.2%) in the Korean study, whereas in our study esophageal cancers (0.3%) were the most prevalent.[6] This was to be expected because the prevalence of cancers proximal to the colon differs in Asia compared to Western Europe.[35–37]

Over the past years there has been an increased interest in the clinical implications of a positive FIT for detecting diseases other than CRC. In our study we have shown that FIT positivity is associated with multiple cancer types. However, other studies have also looked at the association between FIT and benign diseases, such as cardiovascular diseases. The rationale for studying the association between FIT positivity and other diseases comes from the fact that several diseases have overlapping or similar risk factors as CRC, such as advanced age and smoking. Hence, a positive FIT might also indicate a higher risk of other diseases with similar underlying risk factors.[6,9–17] Given that FIT positivity is associated with multiple cancer types, discussing lifestyle-related recommendations may be considered for FIT-positive screenees, to reduce their future cancer risk.

In addition to FIT, other noninvasive stool-based CRC screening tests have been developed over the past 10 years, such as the multitarget stool DNA test (mt-sDNA test) and the more recently developed nonautomated research-use-only multitarget FIT (mtFIT).[38,39] A recent small study (n = 1216) evaluated the incidence of aerodigestive (lung or digestive tract) cancers in screenees with false-positive and true-negative mt-sDNA tests, based on whether or not AN was observed during a high-quality colonoscopy, and did not observe a significant difference between the groups. Consequently, further examination of screenees without AN at a high-quality colonoscopy was not advised based on these findings.[40]

Because *Helicobacter pylori* is the most important risk factor for intestinal-type gastric adenocarcinoma, some researchers suggest an *H pylori* test combined with FIT, or other noninvasive screening tests, as a screening strategy for combined upper and lower gastrointestinal (pre-) cancerous screening.[41,42] However, such a strategy would probably appear only (cost-)effective in regions with a high incidence of gastric cancer and *H pylori*. Based on the low cumulative incidences of gastric cancers in our screening population and the low prevalence of *H pylori* in most Western countries, screening all participants for *H pylori* is unlikely to be a cost-effective and justifiable strategy in our country.[43–45] Nevertheless, future studies should prospectively evaluate the added diagnostic value of such an approach in organized screening programs.

Currently multicancer early detection tests, which focus on the detection of multiple cancer types, are being developed. As these tests can detect multiple cancer types, they require additional testing, which is likely to result in a high burden and uncertainties on cost-effectiveness of such screening programs. Consequently, many questions still need to be addressed before multicancer early detection tests are ready to be used for population screening.

In conclusion, FIT-positive screenees have a higher risk of cancer proximal to the colon; EGD-detectable cancer; lung cancer; cancer of the liver, intra- and extrahepatic (bile) ducts; bladder cancer; cancer of the pancreas; kidney cancer; prostate cancer; and breast cancer. As the cumulative incidence for these cancers is still low, additional screening measures currently do not seem warranted. Considering the less than 1% 3-year cumulative incidence of EGD-detectable cancers and the fact that EGD is not perfectly sensitive for EGD-detectable cancers, we believe that these results do not justify performing EGD in all FIT-positive screenees in the West. Future studies should evaluate which additional risk factors might justify EGD or other additional tests.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.04.028.

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Received June 27, 2023. Accepted April 16, 2024.

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Acknowledgements
The authors thank F. van Maaren-Meijer and H. 't Mannetje from the Dutch Foundation of Population Screening and H. Bretveld from the Netherlands Cancer Registry for their contributions to this study.

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Conflicts of interest
These authors disclose the following: Evelien Dekker has endoscopic equipment on loan from FujiFilm, and received a research grant from FujiFilm; has received honoraria for consultancy from Olympus, Fujifilm, Ambu, InterVenn, and Exact Sciences, and speakers' fees from Olympus, GI Supply, Norgine, IPSEN, PAION and FujiFilm; and is a supervisory board member of the eNose Company. Manon C.W. Spaander has received research support from Sentinel, Sysmex, and Norgine. Manon van der Vlugt has received an honorarium for educational courses from Tillotts. Willemijn de Klaver has received consulting fees as member of the Dutch Post-polypectomy surveillance guideline committee. The remaining author discloses no conflicts.

Funding
None.

Data Availability
De-identified individual participant data that support the findings in this study are available on reasonable request from Evelien Dekker.

Supplementary Table 1. Overview of the Cancer (Sub)types and International Classification of Diseases for Oncology (ICD-O) Codes

Cancer (sub)types	ICD-O codes
Oral cavity, nose, or throat	C019, C020, C021, C022, C023, C024, C028, C029, C030, C031, C039, C040, C041, C048, C049, C050, C051, C052, C058, C059, C060, C061, C062, C068, C069, C079, C080, C081, C089, C090, C09, C098, C099, C100, C101, C102, C103, C108, C109, C110, C111, C112, C113, C118, C119, C129, C130, C131, C132, C138, C139, C140, C142, C148, C300, C310, C311, C312, C313, C318, C319, C320, C321, C322, C329
Esophageal	C150, C153, C154, C155, C158, C159
Gastric	C160, C161, C162, C163, C164, C165, C166, C168, C169
Small bowel undefined	C178, C179
Duodenum	C170, C241
Jejunum	C171
Ileum	C172, C173
Lung	C340, C341, C342, C343, C348, C349
Liver, intra- and extrahepatic (bile) ducts	C220, C221, C240, C242, C243, C244
Thyroid	C739
Bladder	C670, C671, C672, C673, C674, C675, C676, C677, C678, C679
Lymphatic, hematopoietic, and reticuloendothelial system	C770, C771, C772, C773, C774, C775, C778, C779, C420, C421, C422
Pancreas	C250, C251, C252, C253, C254, C257, C258, C259
Kidney	C641, C642, C643, C644, C648, C649
Prostate	C619
Breast	C500, C501, C502, C503, C504, C505, C506, C508, C509
Cervix uteri	C530, C531, C538, C539

Supplementary Table 2. Screenees Who Had a Colonoscopy Due to a Temporary Lower Cutoff ($\geq$ 15 μg Hb/g Feces) With Adequate Colonoscopy Quality Who Were Diagnosed With a Cancer Proximal to the Colon Within 3 Years After FIT

	FIT+/AN+ n = 1769	FIT+/AN− n = 3100	*P* value
Cancers proximal to the colon,[a] n (cumulative incidence)	14 (0.8)	25 (0.8)	.955
EGD-detectable cancers,[b] n (cumulative incidence)	10 (0.6)	18 (0.6)	.946

NOTE. Data are presented as n (%).
[a]Proximal cancers: cancer in the oral cavity, nose, or throat; esophageal; gastric; small bowel undefined; duodenum (including the papilla of Vater); jejunum; and ileum.
[b]EGD-detectable cancers: esophageal, gastric, and duodenal cancers.

Supplementary Table 3. Screenees Diagnosed With Cancer Proximal to the Colon Within 3 Years After FIT Presented for Different FIT Cutoffs (≥ 15, ≥ 47, ≥ 80, and ≥ 100 μg Hb/g Feces)

FIT cutoff ≥ 15 μg Hb/g feces	FIT+/AN?[a] n = 67,535	FIT+/AN+ n = 65,767	FIT+/AN− n = 50,661	FIT− n = 1,764,112	*P* value
Proximal cancers,[b] n (cumulative incidence)	478 (0.7%)	440 (0.7)	299 (0.6)	6360 (0.4)	<.001
EGD-detectable cancers,[c] n (cumulative incidence)	285 (0.4%)	272 (0.4)	186 (0.4)	4127 (0.2)	<.001
FIT cutoff ≥ 47 μg Hb/g feces	**FIT+/AN?[a] n = 0**	**FIT+/AN+ n = 65,767**	**FIT+/AN− n = 50,661**	**FIT− n = 1,831,647**	***P* value**
Proximal cancers,[b] n (cumulative incidence)	NA	440 (0.7)	299 (0.6)	6838 (0.4)	<.001
EGD-detectable cancers,[c] n (cumulative incidence)	NA	272 (0.4)	186 (0.4)	4412 (0.2)	<.001
FIT cutoff ≥ 80 μg Hb/g feces	**FIT+/AN?[a] n = 0**	**FIT+/AN+ n = 52,034**	**FIT+/AN− n = 32,381**	**FIT− n = 1,863,660**	***P* value**
Proximal cancers,[b] n (cumulative incidence)	NA	352 (0.7)	192 (0.6)	7033 (0.4)	<.001
EGD-detectable cancers,[c] n (cumulative incidence)	NA	214 (0.4)	120 (0.4)	4536 (0.2)	<.001
FIT cutoff ≥ 100 μg Hb/g feces	**FIT+/AN?[a] n = 0**	**FIT+/AN+ n = 47,006**	**FIT+/AN− n = 26,846**	**FIT− n = 1,874,223**	***P* value**
Proximal cancers,[b] n (cumulative incidence)	NA	323 (0.7)	164 (0.6)	7090 (0.4)	<.001
EGD-detectable cancers,[c] n (cumulative incidence)	NA	195 (0.4)	102 (0.4)	4573 (0.2)	<.001

NOTE. Data are presented as n (%).
NA, not applicable.
[a]Individuals did not have a colonoscopy because Hb 15-46 μg Hb/g feces; therefore, their AN status is unknown.
[b]Cancers proximal to the colon: cancer in the oral cavity, nose, or throat; esophageal; gastric; small bowel undefined; duodenum (including the papilla of Vater); jejunum; and ileum.
[c]EGD-detectable cancers: esophageal, gastric, and duodenal cancers.