Colonoscopy-Related Mortality in a Fecal Immunochemical Test–Based Colorectal Cancer Screening Program

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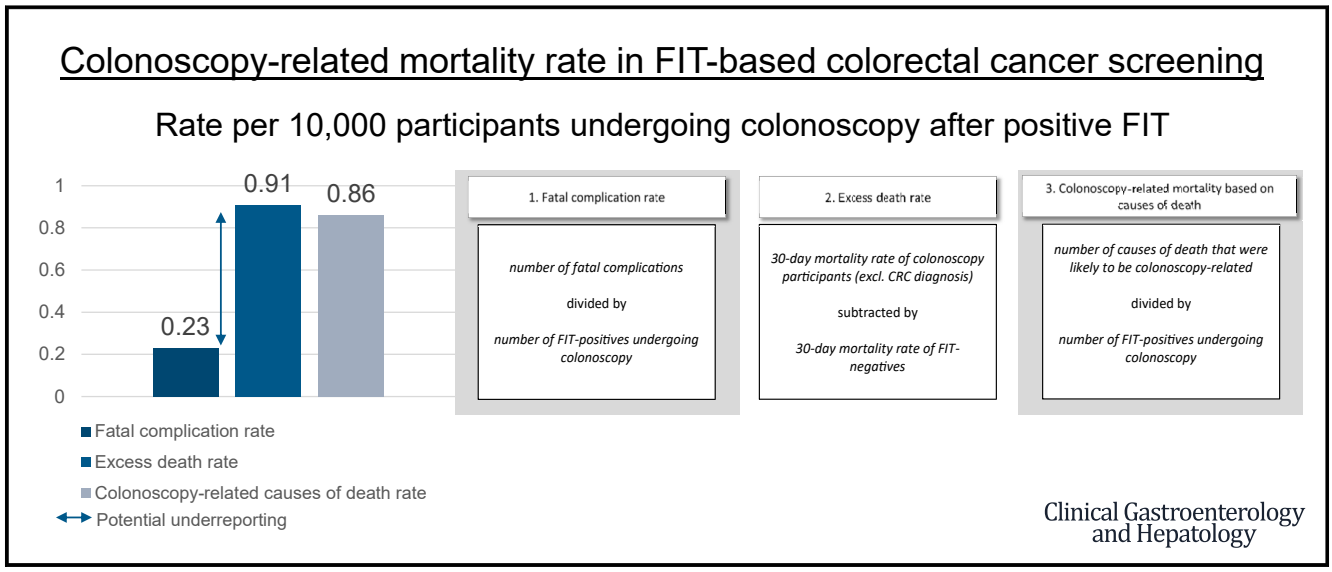

BACKGROUND & AIMS: **Many countries have introduced colorectal cancer (CRC) screening programs with fecal immunochemical tests (FITs), and follow-up colonoscopies for individuals with a positive FIT result. In order to make an informed decision to participate, individuals must be informed about the benefits and harms of FIT-based screening and subsequent colonoscopy. Colonoscopy-related fatal complications in FIT-based screening are understudied. We aimed to estimate the colonoscopy-related mortality in a national FIT-based CRC screening program.**

METHODS: **Colonoscopy-related mortality within 30 days after colonoscopy was assessed by analysis of data from national endoscopy complication databases in the Netherlands, determining the excess 30-day rate of death in FIT-positive individuals undergoing colonoscopy vs FIT-negative individuals (based on data from the national screening database), and determining the rate of likely colonoscopy-related deaths based on registered causes of death by the Statistics Netherlands.**

Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; FIT-negatives, participants with a negative FIT result; FIT-positives, participants with a positive FIT result.

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RESULTS: **Between October 2013 and December 2017, 172,797 participants underwent colonoscopy after a positive result from a FIT in the Dutch national CRC screening program; 13,848 participants received a diagnosis of CRC. The reported fatal complication rate was 0.23 per 10,000 FIT-positive participants (or 1 per 43,199; 95% CI, 0.090 – 0.60) undergoing colonoscopy, whereas this was 0.91 per 10,000 FIT-positive participants (or 1 per 10,961; 95% CI, 0.44 – 1.38) according to the excess death rate. Likely colonoscopy-related causes of death were reported in 0.86 per 10,000 FIT-positive participants (or 1 per 11,236; 95% CI, 0.48 – 1.63) who underwent colonoscopy, of which 50% considered cardiovascular events.**

CONCLUSIONS: **Colonoscopy-related mortality within the Dutch FIT-based CRC screening program was estimated to range from 0.23 to 0.91 per 10,000 FIT-positive participants undergoing colonoscopy. These findings indicate underreporting of fatal complications in registries and a noteworthy incidence of fatal cardiovascular adverse events that requires further investigation. Nevertheless, the harm of FIT-based CRC screening is vastly outweighed by the benefits.**

Keywords: Prevention; FOBT; Endoscopy; Adverse Event.

Cancer screening aims to reduce disease-related mortality, burden, and costs. However, cancer screening may also result in serious harms. It is important to ensure that these harms are outweighed by the benefits. Many countries worldwide have recently implemented colorectal cancer (CRC) screening programs based on fecal immunochemical testing (FIT).[1] An important harm of this form of screening is the risk of serious complications at the colonoscopy follow-up of participants with a positive FIT result (FIT-positives).

Although there are many data on colonoscopy-related complications, most originate from series of routine procedures instead of colonoscopies in FIT-positives. FIT-positives have a high prevalence of advanced neoplastic lesions requiring more often complex interventions.[2–4] Furthermore, most studies reported on nonlethal complications only. Studies that reported on fatal colonoscopy complications were often limited by their retrospective data collection or incomplete registration and underreporting of complications within the 30-day period after colonoscopy.[5–7] As a result of these limitations, the currently available information on harms of FIT-based screening is inadequate.

We therefore aimed to estimate the colonoscopy-related mortality in a FIT-based CRC screening program. The most straightforward method for this analysis is to use endoscopy complication registries. However, concerns about underreporting in particular because of lack of sufficient follow-up ask for additional independent methods. We therefore aimed to estimate the colonoscopy-related mortality by 3 different approaches using (1) endoscopists-reported fatal complications from national endoscopy complication registries, (2) 30-day mortality rates from the national screening database, and (3) registered causes of death within 30 days after colonoscopy from the national statistical office.

Methods

Setting

This study was performed in the setting of the Dutch FIT-based CRC screening program that was introduced in 2014. The design of the program has been described elsewhere.[3] The program targets individuals between 55 and 75 years old for biennial FIT-screening. We included all invited individuals from the start of the program until December 2017, including participants of the preceding pilot study (October to December 2013). The invited individuals in 2014 also contained persons aged 76 years because of a delayed implementation of the program. FIT-positives were invited for a precolonoscopy intake in an accredited colonoscopy center. During this intake, individuals were informed about the colonoscopy procedure and bowel preparation and assessed for eligibility. A participant was eligible for colonoscopy when colonoscopy was deemed proportional (ie, no impaired health or other severe diseases).

Outcome and Analyses

We estimated the colonoscopy-related mortality rate in a FIT-based CRC screening program in 3 independent ways using prospectively collected data from several sources:

1. The fatal complication rate among FIT-positives undergoing colonoscopy based on endoscopist-reported complications from national endoscopy complication registries.
2. The 30-days excess death rate in FIT-positives undergoing colonoscopy compared with a reference population not undergoing colonoscopy (FIT-negatives).

3. The rate of deaths among FIT-positives undergoing colonoscopy that were likely related to colonoscopy based on data on causes of death.

All 3 methods are visualized in Figure 1 and explained in detail next. Colonoscopy participants could undergo more than 1 colonoscopy. If this was the case, the most recent colonoscopy was included in the analyses.

Fatal Complication Rate

The fatal complication rate was defined as the number of endoscopist-reported fatal colonoscopy-related complications within 30 days after colonoscopy divided by the number of FIT-positives that underwent colonoscopy (Figure 1). Data were collected of all FIT-positives undergoing colonoscopy between October 2013 and December 2017 from the national screening database (ScreenIT). Colonoscopy-related (fatal) complications within 30 days after colonoscopy could until 2016 be registered in ScreenIT and/or in the complication registry of the Dutch Gastroenterology Association.[8] Duplicates were identified and excluded. From 2016 onward, all complications were reported in the Dutch Registration of Complications in Endoscopy.[9] Registration of colonoscopy-related complications by endoscopists was mandatory and an important item of the periodic audit to evaluate the quality of colonoscopies after positive FIT. Regional officials performed this audit per colonoscopy center every year. Completeness of such complication registries, however, depends on the endoscopists' compliance and, moreover, the extent in which colonoscopy-related complications are identified. Individuals are contacted 7 days postcolonoscopy to explain the final result and to inquire whether a complication did occur. There is no scheduled contact after 30 days postcolonoscopy.

Excess Death Rate

The excess death rate was defined as the difference in all-cause 30-day mortality rate between FIT-positives undergoing colonoscopy and a reference population not undergoing colonoscopy (Figure 1). We chose the FIT-negatives as reference population rather than the general Dutch population because people undergoing FIT for screening are generally healthier than the general population, and using the general population would have resulted in underestimation of the excess death rate.

All data were collected from ScreenIT. Apart from date of colonoscopy and date of FIT-analysis, this database also contained date of death through a daily updated linkage with the Personal Records Database. To get the 30-day mortality rate for FIT-positives that underwent colonoscopy, we divided the number of deaths within 30 days after the date of colonoscopy by the number of FIT-positives that underwent colonoscopy. To obtain the 30-day mortality rate for the reference population (FIT-negatives), we divided the number of deaths within 30 days after the date of FIT-analysis by the number of FIT-negatives.

We excluded FIT-positives undergoing colonoscopy diagnosed with CRC, because fatal complications in these participants may not be directly colonoscopy-related but could have been caused by surgical or systemic treatment of the cancer. We decided not to include FIT-positive participants who did not undergo colonoscopy as part of the reference population, because the reasons for not undergoing colonoscopy might be related to comorbidities.

All 30-day mortality rates were adjusted for differences in age- and sex-distribution between the 2 groups by applying the age- and sex-distribution of the Dutch population over 4 years (2014–2017) as standard population (using age-categories 56–60 years, 61–65 years, 66–70, years and 71–76 years). Standardization was then achieved by multiplying the observed 30-day mortality rates per sex- and age-category with their corresponding proportion of the standard population. Consequently, the estimated colonoscopy-related mortality would be representative for the target population of the screening program (55–75 years), instead of the relatively older population that had been invited during the first years of the program.

Colonoscopy-Related Mortality Based on Causes of Death

We identified all FIT-positives who died within 30 days postcolonoscopy through ScreenIT. Linkage with the Statistics Netherlands[10] allowed us to examine the

What You Need to Know

Background

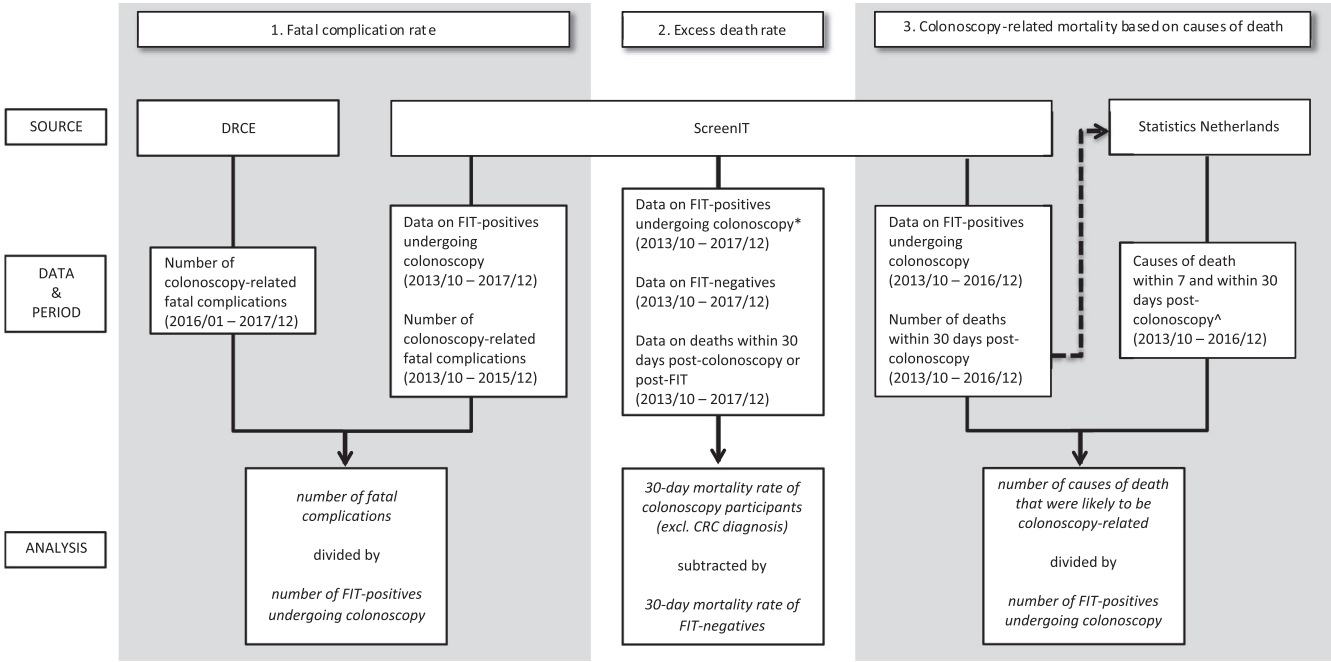
Colonoscopy-related fatal complications in fecal immunochemical test (FIT)-based screening are understudied. This study aimed to estimate the colonoscopy-related mortality in a national FIT-based colorectal cancer screening program.

Findings

Fatal complications occurred between 0.23 and 0.91 per 10,000 participants undergoing colonoscopy after positive FIT. Our results suggest that the colonoscopy-related mortality was underreported in complication registries.

Implications for patient care

Colonoscopy related-mortality is not higher than expected and this harm of FIT-based colorectal cancer screening is vastly outweighed by the benefits.



DRCE = Dutch Registration of Complications in Endoscopy; *Excluding FIT-positives with colorectal cancer diagnosis; ^Of all FIT-positives undergoing colonoscopy that died within 30 days post-colonoscopy, as derived from ScreenIT (dashed line)

Figure 1. Flowchart of the different methods to estimate colonoscopy-related mortality; an overview of the sources and periods of the used data. DRCE, Dutch Registration of Complications in Endoscopy. *Excluding FIT-positives with colorectal cancer diagnosis. ^Of all FIT-positives undergoing colonoscopy that died within 30 days postcolonoscopy, as derived from ScreenIT (*dashed line*).

registered causes of death of those individuals, subdivided for deaths within 7 and between 7 and 30 days postcolonoscopy. Because the Statistics Netherlands have a 1-year lag time, this method only included FIT-positives undergoing colonoscopy between October 2013 and December 2016.

The cause of death was defined by the Statistics Netherlands as the underlying event or disease that started the process that eventually resulted in death. Based on literature and expert opinion, we considered causes of death in the following categories and period of time likely to be colonoscopy-related: death by infection or cardiovascular disease within 7 days and death by (endoscopic) intervention within 30 days.[11,12] Infection can be caused by a bowel perforation, and cardiovascular events by the sedation or the required temporary stop of anticoagulant medication.

Results

Between October 2013 and December 2017, a total of 3,746,307 individuals participated in the Dutch national CRC screening program and returned a FIT. The median age of participants was 65 years old and consisted of 48.1% men. Of the 214,284 (5.7%) FIT-positives, 172,797 (80.6%) underwent colonoscopy, which resulted for 8.0% (13,848 participants) in the detection of CRC.

Fatal Complication Rate

Among all 172,797 FIT-positives that underwent colonoscopy, 4 colonoscopy-related fatal complications were reported by the involved endoscopist in the complication registries. This resulted in a fatal complication rate of 0.23 (95% confidence interval [CI], 0.090–0.60) per 10,000 participants, or 1 fatal complication per 43,199 FIT-positives undergoing colonoscopy.

Excess Death Rate

The all-cause 30-day mortality rate among 158,949 FIT-positives undergoing colonoscopy (after exclusion of 13,848 participants with a CRC diagnosis) was 3.65 per 10,000 participants (Table 1). The all-cause 30-day mortality for the reference population of 3,532,023 FIT-negatives was 2.30 per 10,000 participants. After adjusting for age and sex, we estimated a 30-day excess death rate of 0.91 (95% CI, 0.44–1.38) per 10,000, or 1 excess death per 10,961 FIT-positives undergoing colonoscopy.

Colonoscopy-Related Mortality Based on Causes of Death

Within the time frame of cause of death availability (Oct 2013–Dec 2016), 112,634 FIT-positives underwent

Table 1. Characteristics and 30-Day Mortality Rates of Compared Populations to Estimate Excess Death Rate

Population	FIT-positives undergoing colonoscopy[a]	FIT-negatives not undergoing colonoscopy
Participants	158,949	3,532,023
Median age (IQR)	67 (63–70)	65 (62–69)
Male, %	59.2	47.4
Deaths within 30 d	58	811
30-d mortality rate	3.65	2.30
Adjusted rate[b]	3.22	2.30

NOTE. Rates per 10,000 participants.
FIT-negatives, participants with a negative fecal immunochemical test result; FIT-positives, participants with a positive fecal immunochemical test result; IQR, interquartile range.
[a]Excluding participants with colorectal cancer diagnosis.
[b]Adjusted for different age and sex distribution.

colonoscopy, of which 48 died within 30 days after colonoscopy (Table 2). Based on the registered causes of these deaths by the Netherlands Statistics, 10 (20.8%) deaths seemed likely to be associated with the colonoscopy. Three individuals died because of an infection (sepsis) and 5 after a cardiovascular event within 7 days. Besides, 2 individuals died because of an (endoscopic) intervention between 8 and 30 days. Consequently, the colonoscopy-related mortality based on data on cause of death was 0.89 per 10,000 (95% CI, 0.48–1.63), or 1 per 11,236 FIT-positives undergoing colonoscopy.

Discussion

We assessed the colonoscopy-related mortality in a nationwide FIT-based CRC screening program. Analyses of the endoscopist-reported fatal complications and the excess death rate among FIT-positives undergoing colonoscopy resulted in an estimated 30-day colonoscopy-related mortality between, respectively, 0.23 and 0.91 per 10,000 participants that underwent colonoscopy. Based on data on causes of death, half of the fatal complications concerned cardiovascular events.

Table 2. Registered Causes of Death Likely Related or Unrelated to Colonoscopy Within 7 Days and Within 8–30 Days Postcolonoscopy[a]

Period	Within 7 d	Within 8–30 d
Total	13	35
Likely colonoscopy-related		
Infection	3[b]	NA
Cardiovascular disease	5	NA
(Endoscopic) intervention	0	2
Unrelated to colonoscopy[c]	5	33[d]

NA, not applicable (not likely to be related to colonoscopy).
[a]Data only available for the period October 2013 to December 2016.
[b]Sepsis.
[c]Including such categories as nonnatural death causes, psychiatric disorders, or (nonvascular) neurologic diseases.
[d]Including death by infection or cardiovascular disease after 7 days.

A recent meta-analysis reported a pooled estimate of 0.29 colonoscopy-related deaths per 10,000 colonoscopies.[5] A Canadian study that reviewed all medical charts of patients that died within 30 days postcolonoscopy found a (possibly) colonoscopy-related death rate (0.74 per 10,000 colonoscopies) also within our observed range.[13] Both studies, however, did not focus on colonoscopies after a positive FIT, the latter requiring relatively many therapeutic procedures because of high detection rates of advanced lesions.[2–4] It is known that the risk of complications increases substantially in therapeutic colonoscopies compared with diagnostic colonoscopies.[5] Therefore, our results are difficult to compare with pooled estimates or colonoscopies in different settings and with other indications. This was also the case for a Polish study that interestingly discovered no increased mortality rate in a population invited for primary colonoscopy screening compared with unscreened matched control subjects.[14] Apart from the difference in setting, this could also be explained by a lack of power. Only 16% of their invited population underwent colonoscopy. A substantial colonoscopy-related mortality would be needed to observe an increased mortality compared with the control subjects. Studies that reported on fatal complications within 30 days postcolonoscopy after a positive fecal occult blood test described 0–0.21 (95% CI, 0.0–1.16) fatal complications per 10,000 participants.[6,7,15–19] However, those studies included small sample sizes of between 3000 and 60,000 colonoscopies and some indicated a suspected underestimation caused by incomplete registration.

The current study corroborates concerns about underreporting of colonoscopy-related fatal complications. We found an approximate 4-fold higher colonoscopy-related mortality by estimating the death excess rate compared with the fatal complication rate reported in complication registries (0.91 vs 0.23 per 10,000 FIT-positives undergoing colonoscopy). This difference may indicate that within our endoscopy practices the follow-up system to report and evaluate the 30-day mortality is not adequate. In the Dutch screening program, participants undergoing colonoscopy are contacted 7 days postcolonoscopy through a telephone call to register any colonoscopy-related complaints or complications. To increase the completeness of the (fatal) 30-day complication registration, all deaths within 30 days postcolonoscopy should be evaluated on an association with the colonoscopy. At the same time, it could also be that the colonoscopy-related mortality is rather overestimated by the 30-days death excess rate. We excluded participants detected with CRC from this analysis, but the surgical removal of detected lesions, other than CRC,

within 30 days postcolonoscopy might also have caused fatal complications.[20] Furthermore, FIT-positives have more adenomas than FIT-negatives, which has been shown to be correlated to an unhealthier lifestyle.[21–23] Because the use of anticoagulants increases the FIT positivity rate,[24] FIT-positives might have more cardiovascular comorbidities compared with FIT-negatives. These factors could have increased the all-cause mortality within 30 days of colonoscopy, although not being related to the colonoscopy. However, FIT-positives undergoing colonoscopy may be healthier than the FIT-negative reference population, because FIT-positives with serious health conditions were excluded from colonoscopy during the precolonoscopy intake interview. While bearing in mind the previously uncertainties, the method of estimating excess death rate (0.91 per 10,000) still seems the most realistic estimate of the colonoscopy-related mortality. It is the least sensitive method for biases, such as underreporting or inaccurate registration.

Because of the Dutch data protection law, we were unable to retrieve data from medical charts to determine whether a registered death within 30 days after colonoscopy was related to colonoscopy. Instead, we collected data on the registered causes of death by Statistics Netherlands to get an indication of what caused the deaths after colonoscopy. Based on these data, half (5/10) of the causes of death we considered likely to be colonoscopy-related seemed to be associated with perforation or bleeding (cause of death: infection or [endoscopic] intervention) and the other half with cardiovascular events (cause of death: cardiovascular disease). A temporary stop in anticoagulant medication is common before colonoscopy to reduce the risk of (post-procedure) bleeding. This results in lower levels of anticoagulation, which can cause (fatal) cardiovascular events (eg, by thromboembolism or myocardial infarction).[25] The association between a cardiovascular event and the colonoscopy is probably easier to overlook compared with other severe colonoscopy complications, such as a bleeding or perforation. Perhaps the underreporting of colonoscopy-related fatal cardiovascular events might explain the difference in mortality between the endoscopist-reported complications (0.23 per 10,000) and estimated excess death rate (0.91 per 10,000).

Before initiation of the national screening program, fatal complications were expected to occur once per 10,000 colonoscopies,[26] derived from a quality indicator formulated by the American Society for Gastrointestinal Endoscopy that was based on expert opinions.[27] The same rate was used by several modeling studies that were carried out to predict the cost-effectiveness of a CRC screening program.[28,29] Apart from the need to adequately inform participants, colonoscopy-related mortality should be evaluated because it might influence the (cost-) effectiveness of a screening program. From 2019 onward, around 2.2 million individuals are invited in the Netherlands yearly.[3] Based on participation and positivity rates of the last 4 years,[30] approximately 80,000 FIT-positives will undergo colonoscopy per year. When using the initially expected fatal complication rate (1 per 10,000), this means that almost 8 colonoscopy-related deaths would occur per year within the screening program. According to our results, the number of colonoscopy-related deaths could be up to 7 deaths (0.91 per 10,000) per year. The initially expected fatal complication rate can therefore be considered a safe assumption. Besides, our data show that almost 14,000 participants were diagnosed with a screen-detected CRC. Previous results have shown that screen-detected CRCs after a positive FIT are more often detected in an early stage compared with symptomatically detected CRCs (67% vs 40%).[31] In time, FIT-based CRC screening can potentially prevent 2250–2400 deaths per year.[26,30,32] When weighing the benefits and harms of screening, the colonoscopy-related mortality only has a limited impact on this balance, which still seems clearly in favor of screening.

Important strengths of our study are the large sample size and 3 different, complementary analytic approaches. These increase the validity of our findings. However, some limitations also have to be taken into account. This study was mainly limited by restricted data collection because of privacy legislations. The accuracy of data from the Netherlands Statistics on causes of death can be disputed and because of the very broad stratification, we could only assume a likely association with colonoscopy. Because we were unable to retrieve the causes of death of a matched control group, adjusting for background risk was not possible. Also when comparing the 30-day mortality rates between FIT-positives undergoing colonoscopy and the reference population (FIT-negatives), we could only correct for a different age- and sex-distribution because other risk factors were not recorded in the national screening database (ScreenIT). Furthermore, we could not determine the precolonoscopy fatal complications. Precolonoscopy complications could be caused by the temporary stop of anticoagulant or the use of bowel preparation.[33] Finally, not all follow-up colonoscopies were systematically registered in the national screening database. This could mean that we missed fatal complications caused by follow-up colonoscopy after the 30-day period of the index colonoscopy.

To mitigate these limitations in future studies, it is important to try and contact all patients 30 days after the colonoscopy. Moreover, access to individual medical records of FIT-positives that died within 30 days postcolonoscopy in future studies is essential. Especially the high prevalence of postcolonoscopy fatal cardiovascular events calls for careful evaluation.

In conclusion, because screening aims for an optimal balance between harms and benefits, all harms should be

comprehensively evaluated, including fatal adverse events caused by the intervention. Evaluation of the first 4 years of a national screening program resulted in an estimated colonoscopy-related mortality rate of 0.23–0.91 deaths per 10,000 colonoscopy-participants after a positive FIT. The differences between outcomes suggest that fatal complications have been underreported in complication registries and data on causes of death indicated a noteworthy role of cardiovascular disease in the fatal events. Our results strongly suggest that the colonoscopy-related mortality is not higher than expected (1 per 10,000 colonoscopy participants) and that this harm of FIT-based CRC screening is vastly outweighed by the benefits.

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Conflicts of interest

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