

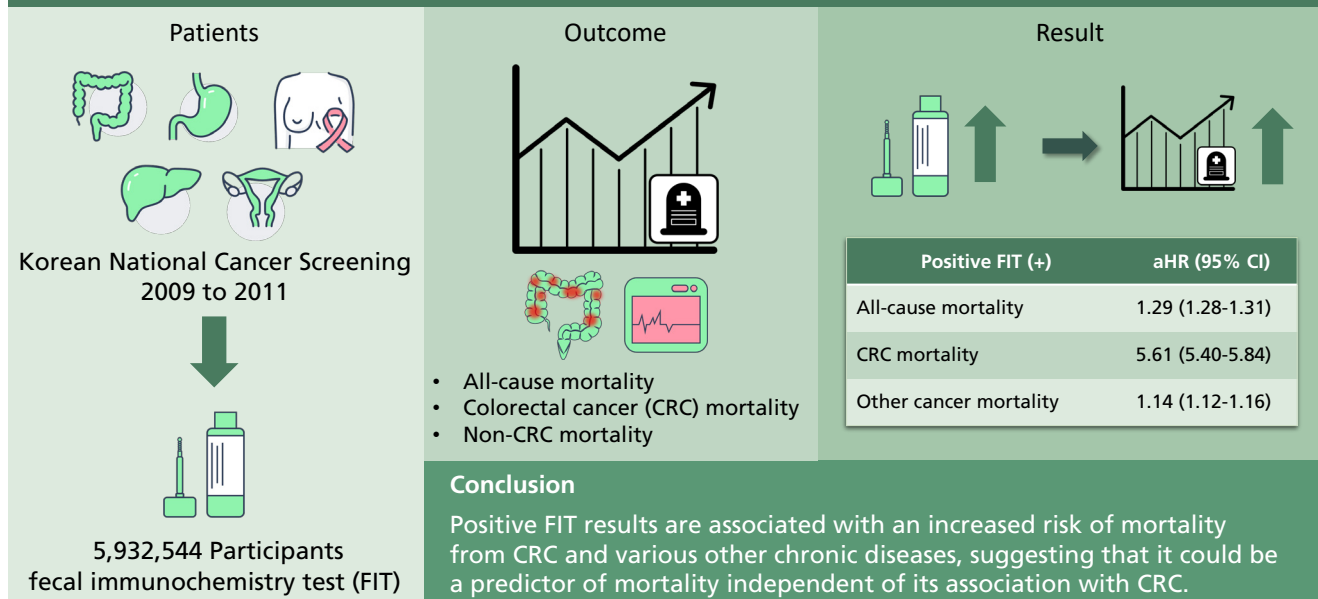


Positive fecal immunochemical test results are associated with non-colorectal cancer mortality

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Background/Aims: Studies have reported an association between fecal occult blood and increased all-cause, non-colorectal cancer (CRC) as well as CRC mortality. This study aimed to determine whether positive fecal immunochemistry test (FIT) results are associated with death from various causes in the South Korean population.

Methods: Using the Korean National Cancer Screening Program database, we collected data on patients who underwent FIT between 2009 and 2011.

Results: Of the 5,932,544 participants, 380,789 (6.4%) had positive FIT results. FIT-positive participants had a higher mortality rate than FIT-negative participants from CRC (1.33 and 0.21 per 1,000 person-years, $p < 0.001$, respectively) and non-CRC causes (10.40 and 7.50 per 1,000 person-years, $p < 0.001$, respectively). Despite adjusting for age, sex, smoking status, alcohol consumption habits, body mass index, comorbidity, and aspirin use, FIT positivity was associated with an increased risk of dying from all non-CRC causes (adjusted hazard ratio [aHR], 1.17; 95% confidence interval [CI], 1.15 to 1.18) and CRC (aHR, 5.61; 95% CI, 5.40 to 5.84). Additionally, FIT positivity was significantly associated with increased mortality from circulatory disease (aHR, 1.14; 95% CI, 1.11 to 1.17), respiratory disease (aHR, 1.14; 95% CI, 1.09 to 1.19), digestive disease (aHR, 1.57; 95% CI, 1.48 to 1.66), neuropsychological disease (aHR, 1.08; 95% CI, 1.01 to 1.16), blood and endocrine diseases (aHR, 1.10; 95% CI, 1.04 to 1.17), and external factors (aHR, 1.16; 95% CI, 1.11 to 1.20).

Conclusions: Positive FIT results are associated with an increased risk of mortality from CRC and various other chronic diseases, suggesting that it could be a predictor of mortality independent of its association with CRC.

Keywords: Fecal immunochemical test; Mortality; Colorectal neoplasms

INTRODUCTION

Fecal occult blood test (FOBT) can detect a large proportion of colorectal cancers (CRCs) that occur in asymptomatic populations [1]. Randomized controlled trials have demonstrated that FOBT screening reduces CRC incidence and mortality, and accordingly, FOBT has been widely used for CRC screening worldwide [1-4]. Unlike direct examination of fecal hemoglobin (f-Hb), conventional guaiac FOBT (gFOBT) indirectly detects blood in human stool based on colorimetric detection of peroxidase activity; therefore, the test results can be influenced by foods with non-hemoglobin peroxidase activity [1]. In contrast to traditional gFOBT, the fecal immunochemistry test (FIT) directly assesses f-Hb using monoclonal or polyclonal antibodies directed against the globin moiety of human hemoglobin [1]. Given these features, it is not surprising that FIT is considered superior to gFOBT in detecting CRC. Compared to gFOBT, FIT is 31.7% to 61.5% more sensitive for CRC [5-8] and has a greater ability to detect CRC and advanced adenomas [9].

A recent study from Scotland revealed that the presence of detectable f-Hb was associated with increased all-cause and non-CRC mortality, suggesting that a positive f-Hb could potentially be used as a meaningful index to predict the mortality rate from various diseases [10]. However, this

study used gFOBT instead of FIT, and the number of patients with a positive gFOBT result ($n = 2,714$) was too small to evaluate the mortality rate [10]. Studies using FIT on a much larger scale are needed to clarify the association between f-Hb and mortality from various causes. It is also necessary to explore whether these associations are maintained among different ethnicities.

In South Korea, the Korean National Cancer Screening Program (NCSP) began FIT screening for all citizens over 50 years of age in 2004. Using this database, we aimed to evaluate the effect of FIT positivity on all-cause, CRC, and non-CRC mortality in the Korean population.

METHODS

Study population

The Korean government administers CRC screening examinations through the NCSP, which includes a free FIT once a year for all citizens over the age of 50 and a free colonoscopy for patients with positive FIT results. We extracted data from the National Health Information Database (NHID) of the National Health Insurance Service (NHIS), which operates the NCSP. The study population consisted of patients who received FIT through the NCSP from January 1, 2009,

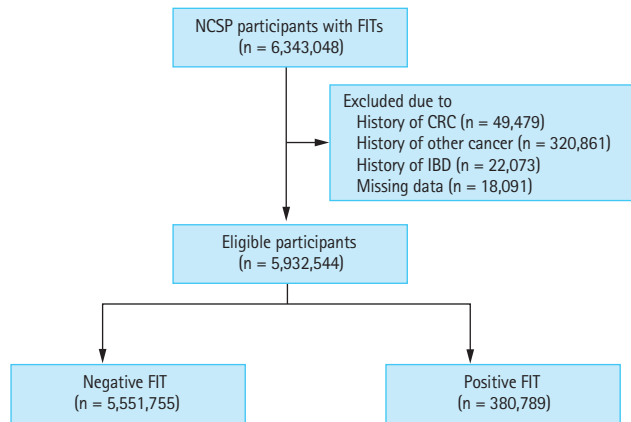


Figure 1. Flowchart of the study population. NCSF, National Cancer Screening Program; FIT, fecal immunochemistry test; CRC, colorectal cancer; IBD, inflammatory bowel disease.

to December 31, 2011. Only the initial FIT results were recorded for those who received two or more FITs during the study period.

Of the 6,343,048 participants, we excluded those with a previous CRC diagnosis ($n = 49,479$) or other types of cancer ($n = 320,861$). Another 22,073 patients were excluded due to a history of inflammatory bowel disease, and an additional 18,091 were excluded due to the absence of data regarding age, sex, or screening date. The final sample included 5,932,544 participants (Fig. 1).

The NHIS–NHID is encrypted and does not contain any personal identifiers. The study protocol was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (IRB no. EUMC 2020-07-024). Written informed consent by the patients was waived due to a retrospective nature of our study.

Definition of variables and mortality data

Age, sex, screening date, FIT results, smoking status, alcohol consumption, body mass index (BMI), medication use, and comorbidities of all patients according to the International Classification of Diseases 10th Revision (ICD-10) codes were obtained from the NHIS–NHID. Smoking status and alcohol consumption were assessed using data from medical questionnaires in the NHIS–NHID. Alcohol consumption was defined as alcohol consumption more than once per week. Aspirin use was defined as the total prescription days of aspirin for more than 180 days in the 2 years before FIT. The Charlson comorbidity index (CCI) was calculated based

on ICD-10 codes using the NHIS–NHID database (Supplementary Table 1) [11]. The ICD-10 code for CCI scoring was defined as one or more hospitalizations or two or more outpatient treatments under the corresponding ICD-10 code within one year before CRC screening.

The causes of death for participants of this study were retrieved from the Korea Statistical Office (<https://mdis.kostat.go.kr>) [12], recorded based on ICD-10 codes, and categorized based on previous studies [10,13]. Cancer-related mortality was separated into CRC (codes C18–C21, D01.0–D01.3) and all other cancers (all C codes excluding C18–C21). Non-cancer mortality was categorized as follows: circulatory diseases (code I), respiratory diseases (code J), digestive diseases (code K), neuropsychological diseases (codes F and G), blood and endocrine diseases (codes D and E), and external factors (codes S–Z). Any remaining deaths were categorized as “other cause (not classified).”

Statistical analysis

The baseline characteristics of FIT-negative and FIT-positive participants were compared using the chi-square test for categorical variables and Student’s *t* test for continuous variables. The follow-up time was defined as the time from the screening date to the date of death or the end of the study period (December 31, 2018). The cause-specific mortality rates per 1,000 person-years for FIT-negative and FIT-positive participants were then compared. Additionally, the cumulative mortality from all causes, all causes excluding CRC, and CRC were plotted by years since the screening date using the Kaplan–Meier method, and the differences between FIT-negative and FIT-positive patients were determined using the log-rank test.

We performed a Cox proportional hazards regression analysis to estimate the hazard ratio with the corresponding 95% confidence intervals (CIs) for mortality. Cause-specific and all-cause mortality for FIT-positive and FIT-negative participants using both univariable and multivariable models were compared. Subsequently, they were adjusted for potentially confounding variables, including age, sex, CCI, and aspirin use.

All reported *p* values were two-sided, and statistical significance was set at $p < 0.05$. All data analyses were performed using the SAS software program version 9.4 (SAS Institute, Cary, NC, USA).

Table 1. Baseline characteristics according to the FIT results

Characteristic	Total (n = 5,932,544)	FIT negative (n = 5,551,755)	FIT positive (n = 380,789)	p value
Sex				< 0.001
Male	2,609,985 (44.0)	2,411,853 (43.4)	198,132 (52.0)	
Female	3,322,559 (56.0)	3,139,902 (56.6)	182,657 (48.0)	
Age, yr	60.65 ± 8.23	60.60 ± 8.20	61.40 ± 8.57	< 0.001
50–59	2,938,401 (49.5)	2,761,549 (49.7)	176,852 (46.4)	
60–69	1,976,063 (33.3)	1,849,210 (33.3)	126,853 (33.3)	
70–79	900,122 (15.2)	833,366 (15.0)	66,756 (17.5)	
≥ 80	117,958 (2.0)	107,630 (1.9)	10,328 (2.7)	
Current smoking ^a	852,765 (14.4)	785,090 (14.1)	67,675 (17.8)	< 0.001
Alcohol consumption (≥ 1 time/week) ^b	1,968,636 (33.2)	1,828,320 (32.9)	140,316 (36.9)	< 0.001
BMI, kg/m ^{2c}	24.18 ± 3.01	24.18 ± 3.01	24.22 ± 3.10	< 0.001
Obesity (BMI ≥ 25 kg/m ^{2c})	2,091,385 (35.3)	1,955,118 (35.2)	136,267 (35.8)	< 0.001
Charlson comorbidity index	0.82 ± 1.22	0.82 ± 1.22	0.91 ± 1.31	< 0.001
Aspirin use	928,376 (15.6)	858,582 (15.5)	69,794 (18.3)	< 0.001
Died (as of December 31, 2018)	391,960 (6.6)	355,592 (6.4)	36,368 (9.6)	< 0.001

Values are presented as number (%) or mean ± standard deviation.

FIT, fecal immunochemistry test; BMI, body mass index.

^aMissing data in 371,038 patients (6.3%).

^bMissing data in 372,171 patients (6.3%).

^cMissing data in 353,632 patients (6.0%).

RESULTS

Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. The mean age of the study population was 60.6 ± 8.2 years, and 44.0% of this population were men. Of the 5,932,544 participants, 380,789 (6.4%) had positive FIT results. The proportion of men, mean age, current smoking, alcohol consumption, BMI, and CCI were higher in the FIT-positive participants than in the FIT-negative participants. The proportion of aspirin use was also higher in FIT-positive participants than in FIT-negative participants.

Mortality rates of FIT-positive and FIT-negative participants

According to the FIT results, the cumulative mortality rates from all causes, non-CRC and CRC, are shown in Fig. 2A, 2B, and 2C, respectively. FIT-positive participants had higher cumulative mortality from all causes, non-CRC and CRC, than FIT-negative participants (all *p* < 0.001).

The mortality rates from various causes in FIT-positive and FIT-negative participants are compared in detail in Table 2. Both the all-cause mortality rate (11.74 and 7.72 per 1,000 person-years, *p* < 0.001, respectively) and the mortality rate from all causes excluding CRC (10.40 and 7.50 per 1,000 person-years, *p* < 0.001, respectively) were higher in FIT-positive participants than in FIT-negative participants. Similarly, the mortality rate from cancers excluding CRC (3.54 and 2.65 per 1,000 person-years, *p* < 0.001, respectively) as well as CRC (1.33 and 0.21 per 1,000 person-years, *p* < 0.001, respectively) were higher in FIT-positive participants than in FIT-negative participants. Moreover, FIT-positive participants had higher mortality rates from all other causes than FIT-negative participants, including circulatory disease, respiratory disease, digestive disease, neuropsychological disease, blood and endocrine diseases, and external factors.

Association between FIT positivity and mortality according to various causes

Despite adjusting for age, sex, CCI, and aspirin use, signifi-

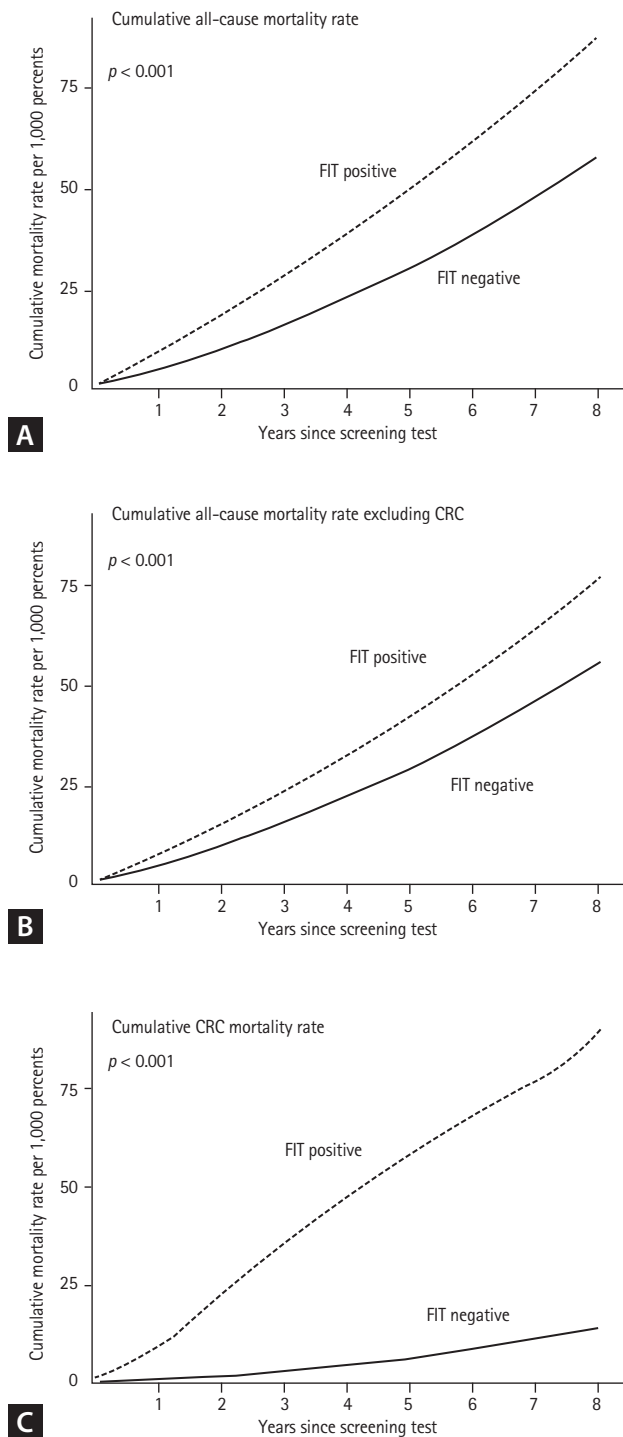


Figure 2. Cumulative mortality rate per 1,000 persons from all causes (A), all causes excluding colorectal cancer (CRC) (B), and CRC (C) in fecal immunochemistry test (FIT)-positive and -negative patients.

cant associations remained between positive FIT results and mortality from various causes, even though the impact was slightly reduced (Table 3). FIT positivity was associated with increased mortality from all causes (adjusted hazard ratio [aHR], 1.29; 95% CI, 1.28 to 1.31) and all causes excluding CRC (aHR, 1.17; 95% CI, 1.15 to 1.18). FIT positivity was also associated with increased mortality from CRC (aHR 5.61; 95% CI, 5.40 to 5.84) and from cancers other than CRC (aHR, 1.14; 95% CI, 1.12 to 1.16). Furthermore, positive FIT results were associated with higher mortality from other organ diseases. Specifically, FIT positivity was associated with higher mortality from circulatory disease (aHR, 1.14; 95% CI, 1.11 to 1.17), respiratory disease (aHR, 1.14; 95% CI, 1.09 to 1.19), digestive disease (aHR, 1.57; 95% CI, 1.48 to 1.66), neuropsychological disease (aHR, 1.08; 95% CI, 1.01 to 1.16), blood and endocrine diseases (aHR, 1.10; 95% CI, 1.04 to 1.17), and external factors (aHR, 1.16; 95% CI, 1.11 to 1.20). Among the various causes of mortality related to positive FIT results, the aHR (5.61) for CRC-related mortality was the highest, followed by aHR (1.57) for digestive disease mortality.

DISCUSSION

In this large-scale population-based study, we found that FIT-positive results were associated with increased mortality from CRC and from all causes excluding CRC. More specifically, FIT-positive results were significantly associated with increased mortality from several non-CRC diseases, such as circulatory, respiratory, digestive, neuropsychological, and blood and endocrine diseases. In addition, positive FIT results were associated with a higher risk of death from cancers, excluding CRC and external factors that were mainly trauma-related. These results suggest that a positive FIT can alert clinicians of the risk of mortality from various diseases regardless of the presence or absence of CRC.

Very few studies have evaluated the association between fecal test results and mortality rates for diseases other than CRC. To date, only two studies have investigated this topic [10,14]. Similar to our results, a Scottish study including 134,192 individuals who participated in gFOBT screening demonstrated that the presence of detectable f-Hb was significantly associated with all-cause and non-CRC mortality [10]. In this study, participants with a positive gFOBT result had higher mortality from CRC (aHR, 7.79; 95% CI, 6.13

Table 2. Mortality rate per 1,000 person-years according to the FIT results

	FIT negative (n = 5,551,755)	FIT positive (n = 380,789)	p value
All-cause mortality	355,592 (7.72)	36,368 (11.74)	< 0.001
All-cause mortality excluding CRC	345,865 (7.50)	32,238 (10.40)	< 0.001
Mortality from CRC	9,727 (0.21)	4,130 (1.33)	< 0.001
Mortality from other cancers excluding CRC	122,027 (2.65)	10,966 (3.54)	< 0.001
Mortality from circulatory disease	71,732 (1.56)	6,530 (2.11)	< 0.001
Mortality from respiratory disease	33,799 (0.73)	3,191 (1.03)	< 0.001
Mortality from digestive disease excluding CRC	12,469 (0.27)	1,563 (0.50)	< 0.001
Mortality from neuropsychological disease	14,000 (0.30)	1,211 (0.39)	< 0.001
Mortality from blood and endocrine diseases	16,017 (0.35)	1,475 (0.48)	< 0.001
Mortality from external factors	34,943 (0.76)	3,185 (1.03)	< 0.001
Mortality from other causes (not classified)	40,878 (0.89)	4,117 (1.33)	< 0.001

Values are presented as number (mortality rate per 1,000 person-years)
FIT, fecal immunochemistry test; CRC, colorectal cancer.

Table 3. Cox regression analysis of mortality in patients with positive FIT results compared to those with negative FIT results

	Crude HR (95% CI)	p value	Adjusted HR (95% CI) ^a	p value
All-cause mortality	1.53 (1.51–1.55)	< 0.001	1.29 (1.28–1.31)	< 0.001
All-cause mortality excluding CRC	1.39 (1.38–1.41)	< 0.001	1.17 (1.15–1.18)	< 0.001
Mortality from CRC	6.34 (6.12–6.58)	< 0.001	5.61 (5.40–5.84)	< 0.001
Mortality from other cancers excluding CRC	1.34 (1.32–1.37)	< 0.001	1.14 (1.12–1.16)	< 0.001
Mortality from circulatory disease	1.36 (1.33–1.40)	< 0.001	1.14 (1.11–1.17)	< 0.001
Mortality from respiratory disease	1.42 (1.37–1.47)	< 0.001	1.14 (1.09–1.19)	< 0.001
Mortality from digestive disease excluding CRC	1.87 (1.78–1.97)	< 0.001	1.57 (1.48–1.66)	< 0.001
Mortality from neuropsychological disease	1.30 (1.22–1.38)	< 0.001	1.08 (1.01–1.16)	0.020
Mortality from blood and endocrine diseases	1.38 (1.31–1.45)	< 0.001	1.10 (1.04–1.17)	0.001
Mortality from external factors	1.36 (1.31–1.41)	< 0.001	1.16 (1.11–1.20)	< 0.001
Mortality from other causes (not classified)	1.51 (1.46–1.56)	< 0.001	1.26 (1.21–1.30)	< 0.001

FIT, fecal immunochemistry test; HR, hazard ratio; CI, confidence interval; CRC, colorectal cancer.

^aValues were adjusted for age, sex, current smoking, alcohol consumption (≥1 time/week), and body mass index, Charlson comorbidity index, and aspirin use.

to 9.89) and all non-CRC causes (aHR, 1.58; 95% CI, 1.45 to 1.73) than those with a negative gFOBT result [10]. In addition, this study showed that a positive gFOBT result was significantly associated with an increased risk of death from circulatory, respiratory, digestive (excluding CRC), neuropsychological, and blood and endocrine diseases, and cancers excluding CRC [10]. However, this study used gFOBT, which is less sensitive in detecting CRC than FIT, and the sample

size was relatively small compared to our study (n = 134,192 vs. 5,932,544). Another study from Taiwan substantiated the claim that the impact of an incremental increase in f-Hb concentration on all-cause mortality and CRC mortality was dose-dependent [14]. The aHR for all-cause mortality increased from 1.03 (95% CI, 0.97 to 1.11) for a f-Hb of 20 to 49 ng Hb/mL to 1.35 (95% CI, 0.14 to 1.61), 1.73 (95% CI, 0.14 to 2.11), and 1.78 (95% CI, 1.54 to 2.17)

for an f-Hb of 150–249, 250–449, and ≥ 450 ng Hb/mL, respectively, compared to the risk associated with an f-Hb of 1 to 19 ng Hb/mL ($p < 0.001$ for trend test) [14]. Their study also revealed that the impact of f-Hb on non-CRC mortality was still statistically significant despite excluding CRC-related mortality ($p < 0.001$ for trend test) [14]. However, in their study, only age and sex were adjusted for, while medications that could cause gastrointestinal (GI) bleeding and affect FIT results as well as comorbidities that could affect mortality were not adjusted. Additionally, in their study, the cause of death was not analyzed in detail by disease type, and the sample size was relatively small compared to our study ($n = 185,743$ vs. $5,932,544$).

Given that FIT directly measures human f-Hb and is more sensitive to lower GI tract bleeding [1,15,16], it is not surprising that a positive FIT result would be associated with CRC mortality; among the risks of death from a range of causes, the risk of death from CRC (aHR, 5.61) was the highest. In addition, since GI bleeding is often associated with digestive disease, it could be assumed that a positive FIT result would be associated with an increased risk of mortality from digestive disease; the risk of mortality from digestive disease (aHR, 1.57) was the second-highest mortality risk.

Interestingly, however, positive FIT results were also associated with mortality from diseases other than CRC and digestive diseases, such as circulatory disease, respiratory disease, neuropsychological disease, blood and endocrine diseases, and cancers excluding CRC. Although the reasons behind these findings cannot be clearly elucidated, there are some possible explanations. First, f-Hb may reflect systemic inflammation, in addition to colon inflammation. Respiratory infectious diseases such as pneumonia can cause systemic inflammation [17]. In addition, it is known that ischemic heart disease, heart failure, atherosclerosis, the majority of solid tumors, and various chronic diseases, including diabetes mellitus, metabolic syndrome, and neurodegenerative diseases, are associated with systemic inflammation [18-22]. Systemic inflammation caused by these diseases may lead to subclinical gut inflammation and consequent occult bleeding. This hypothesis is supported by recent studies in which f-Hb was reported to be a useful marker of gut inflammation in patients with ulcerative colitis in clinical remission [23,24]. In addition, systemic inflammation has been reported to be associated with mortality. A recent meta-analysis demonstrated that elevated serum C-reactive protein (CRP) levels were associated with future cardiovascular and all-cause

mortality in patients with type 2 diabetes [25]. Another study also revealed that systemic inflammatory markers, including CRP level and neutrophil count, were predictive of all-cause, cancer, and cardiovascular mortality [26]. Our study suggests that f-Hb, similar to systemic inflammatory markers, may be a predictor of mortality from various causes.

Second, gut microbiota may also play a role in inducing occult bleeding in chronic diseases. Dysbiosis of the gut microbiota can damage the host intestinal epithelial barrier and alterations in the immune system [27,28]. Impaired intestinal barrier function can cause enteric bacterial translocation, which leads to an increase in circulating levels of bacterial structural components and microbial metabolites that can promote the development and progression of various chronic diseases, including metabolic and cardiovascular diseases, dementia, and several cancers, including extra-intestinal cancers [27-30]. One of the mechanisms linking a positive FIT result to mortality from chronic diseases and cancers may be intestinal epithelial barrier disruption caused by dysbiosis. Obesity and poor lifestyle habits such as a high-fat diet, physical inactivity, and smoking have also been associated with systemic inflammation and dysbiosis [28,31-34]. In this context, f-Hb may be a modifiable marker that could be used to assess the effect of an improved lifestyle on the reduction in overall mortality.

Third, chronic diseases related to mortality and colorectal neoplasia share common risk factors. Although advanced adenoma, a precursor of CRC, was not investigated in our study, a significant proportion of patients with a positive FIT result may have had advanced adenoma and not CRC. Indeed, previous studies have shown that the positive predictive value of FIT for advanced adenomas ranges from 22% to 48% [1]. Considering that the perceived risk factors for advanced adenoma include smoking, obesity, metabolic syndrome, and physical inactivity [35-37], the higher non-CRC mortality in FIT-positive individuals compared to FIT-negative individuals may be due in part to the association between these shared risk factors and chronic diseases that resulted in death.

Fourth, another explanation for our results may be that patients who died from circulatory diseases may have been more likely to take antiplatelet agents or anticoagulants than the general population, which may have caused GI bleeding. However, we found that correcting for aspirin use had minimal effect on the association between FIT positivity and mortality from non-CRC causes.

This is the largest study to demonstrate a significant association between FIT positivity and an increased risk of mortality from non-CRC causes. Nevertheless, this study has several limitations. First, various brands of FITs with varying cutoff points were used. Accordingly, the effect of f-Hb concentration on mortality from various causes was not assessed, despite using quantitative FITs. Second, the impact of dynamic changes in FIT results on mortality was not assessed because we considered only one-time FIT results. Further studies are necessary to determine if certain levels or changes in f-Hb concentration are useful modifiable biomarkers that could reflect life expectancy. Third, there may have been a detection bias. In the present study, the proportion of individuals who underwent colonoscopy within 1 year after FIT was significantly higher in FIT-positive individuals than in FIT-negative individuals (23.0% [n = 87,752/380,789] and 8.4% [n = 463,801/5,551,755], $p < 0.001$). This may have affected the higher incidence of CRC and the resulting higher CRC-related mortality in FIT-positive patients. Fourth, the use of anticoagulants or antiplatelet agents other than aspirin was not considered. Lastly, since only patients who participated in FIT screening were studied, there may be some degree of selection bias.

In conclusion, positive FIT results were associated with an increased risk of mortality from CRC and non-CRC causes. Our results suggest that FIT positivity may potentially be a prognostic biomarker for predicting life expectancy, independent of its association with CRC. Although the current indication for FIT is for CRC screening, FIT positivity may provide important information about health beyond CRC.

KEY MESSAGE

1. Positive fecal immunochemistry test (FIT) results were associated with an increased risk of mortality from non-colorectal cancer (CRC) causes as well as CRC.
2. FIT positivity may potentially be a prognostic biomarker for predicting mortality, independent of its association with CRC.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Charlson Comorbidity Index based on the ICD-10 codes

	ICD-10 codes ^a	CCI score
Myocardial infarction	I21, I22, I25.2	1
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43, I50, P29.0	1
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	G45, G46, H34.0, I60-I69	1
Dementia	F00-F03, F05.1, G30, G31.1	1
Chronic pulmonary disease	I27.8, I27.9, J40-J47, J60-J67, J68.4, J70.1, J70.3	1
Rheumatic disease	M05, M06, M31.5, M32-M34, M35.1, M35.3, M36.0	1
Peptic ulcer disease	K25-K28	
Mild liver disease	B18, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73, K74, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	1
Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	1
Diabetes with chronic complication	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	2
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0-G83.4, G83.9	2
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	2
Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97	2
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K71.2, K72.9, K76.5, K76.6, K76.7	3
Metastatic solid tumour	C77-C80	6
AIDS/HIV	B20-B22, B24	6

ICD, International Classification of Diseases; CCI, Charlson Comorbidity Index; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

^aThey were defined as one or more hospitalizations or two or more outpatient treatments under the corresponding disease code within 1 year prior to colorectal cancer screening.