Effectiveness of Fecal Immunochemical Testing in Reducing Colorectal Cancer Mortality From the One Million Taiwanese Screening Program

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BACKGROUND: The effectiveness of fecal immunochemical testing (FIT) in reducing colorectal cancer (CRC) mortality has not yet been fully assessed in a large, population-based service screening program. METHODS: A prospective cohort study of the follow-up of approximately 5 million Taiwanese from 2004 to 2009 was conducted to compare CRC mortality for an exposed (screened) group and an unexposed (unscreened) group in a population-based CRC screening service targeting community residents of Taiwan who were 50 to 69 years old. Given clinical capacity, this nationwide screening program was first rolled out in 2004. In all, 1,160,895 eligible subjects who were 50 to 69 years old (ie, 21.4% of the 5,417,699 subjects of the underlying population) participated in the biennial nationwide screening program by 2009. RESULTS: The actual effectiveness in reducing CRC mortality attributed to the FIT screening was 62% (relative rate for the screened group vs the unscreened group, 0.38; 95% confidence interval, 0.35-0.42) with a maximum follow-up of 6 years. The 21.4% coverage of the population receiving FIT led to a significant 10% reduction in CRC mortality (relative rate, 0.90; 95% confidence interval, 0.84-0.95) after adjustments for a self-selection bias. CONCLUSIONS: This large, prospective Taiwanese cohort undergoing population-based FIT screening for CRC had the statistical power to demonstrate a significant CRC mortality reduction, although the follow-up time was short. Although such findings are informative for health decision makers, continued follow-up of this large cohort will be required to estimate the long-term impact of FIT screening if the covered population is expanded. Cancer 2015;121:3221-9. © 2015 The Authors. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: colorectal cancer, fecal immunochemical testing, mortality reduction, population-based screening.

INTRODUCTION
The efficacy of guaiac fecal occult blood test (gFOBT) screening at reducing colorectal cancer (CRC) mortality has been proven in previous randomized trials1-3 and with population screening.4,5 Fecal immunochemical testing (FIT) has advantages over gFOBT in several aspects. Studies comparing gFOBT and FIT in screening populations have shown that the former has higher sensitivity for both invasive cancers and advanced adenomas with comparable specificity.6-9 This is of utmost importance because the early detection of neoplasms is the key to obtaining a large survival benefit through a cancer screening program. The use of FIT also enables one to get the optimal cutoff value for follow-up colonoscopy through...
quantitative test results.\textsuperscript{10} This would be of great benefit for health care systems if, in light of the limited manpower and health care resources available, unnecessary colonoscopy could be avoided but a higher sensitivity could still be retained.\textsuperscript{17} These studies have also shown that public participation is higher with FIT because it removes the need for dietary restrictions before testing and provides a more user-friendly way of sample collection.\textsuperscript{8,9} For these reasons, screening with FIT is anticipated to be more effective than gFOBT at reducing CRC mortality, and many countries have already begun using it in regional or nationwide population screening programs.\textsuperscript{11} Nevertheless, there are few empirical data demonstrating its effectiveness at reducing CRC mortality and thus supporting its use.

In the Asia-Pacific region, where many countries have experienced a substantial increase in both CRC incidence and mortality over the past few decades, the development of effective screening programs for CRC is one of the most critical and urgent tasks facing public health policymakers.\textsuperscript{12} After a successful pilot population screening program, a nationwide CRC screening service program was launched in 2004 by the Taiwanese government, which offered biennial FIT to the general population between the ages of 50 and 69 years as a part of the National Cancer Control Program.\textsuperscript{13-15} In this study, we report the inaugural results of this nationwide screening service and, by taking advantage of the large population size, evaluate its effectiveness at reducing CRC mortality from 2004 to 2009.

\section*{Materials and Methods}

\textbf{Taiwanese Nationwide CRC Screening Program}

According to the household registry, Taiwan had 25 municipalities with a total population of 23,119,772 inhabitants in 2009. In this nationwide program, a budget was allocated by the government annually, and funds were distributed to the individual municipalities for this screening program. Residents who were 50 to 69 years old (\(n = 5,417,699\)) were considered eligible for this screening with biennial FIT. This nationwide screening program was implemented with a gradual expansion of the covered population (a phase-in approach) because of budgetary limitations and the clinical capacity for public health service and colonoscopy. We set a 20\% coverage rate as the goal for the initial 5 years and expected to reach up to 60\% by 2016.

Information regarding the availability of this screening program was publicized through the media, a CRC awareness campaign pamphlet, and an outreach screening service unit launched in each municipality (partially by telephone or letter invitation). Because this period was still in the pilot phase, only a small fraction of the areas adopted individual invitations by telephone or letter.

Participants were checked for eligibility and were asked to complete a questionnaire that collected basic demographic data. The screening workflow is diagramed in Figure 1, and the whole process of screening activity was under regular monitoring, which included the screening sites for the uptake of screening, repeated screening cycles, confirmatory examinations, clinical surveillance, and data retrieval on CRC cases and deaths. The mean follow-up time for this cohort was 3.09 years with a maximum follow-up of 6 years. Because of the fiscal budgetary limits and clinical capacity mentioned previously, 1,160,895 residents of 5,417,699 eligible subjects (21.4\% of the eligible population) were screened by 2009.

\textbf{Study Design and Samples}

To evaluate the effectiveness of this nationwide screening program, we used a prospective cohort study design. Participants who underwent 1 to 3 rounds of FIT (\(n = 1,160,895\)) were considered the exposed (screened) group, and the rest of the population was considered the unexposed (unscreened) group. Events were defined as diagnoses of CRC and deaths from CRC, and they were ascertained from the screening database (screen-detected cases) through linkage with the National Cancer Registry (interval cancers) and the National Death Registry, respectively. Because entry to the study was staggered by its gradual expansion, the person-years for each individual were calculated from entry to the end of follow-up (defined as the occurrence of an event or the end of the study [whichever was earlier]). This study was approval by the Health Promotion Administration of the Ministry of Health and Welfare prior to data retrieval and analysis.

\textbf{FIT and Referral for a Confirmatory Diagnosis}

FIT was performed with a single fecal sample. One of 2 separate FIT kits (Eiken OC-SENSOR or Kyowa HM-JACK) was selected by each municipality according to its own purchasing process. The hemoglobin cutoff points for the 2 tests were 100 (Eiken) and 8 ng/mL (Kyowa); they were both equivalent to 20 \(\mu\)g of hemoglobin per gram of feces. The rationale for this cutoff was based on the results of our previous community-based pilot study.\textsuperscript{16} All samples were submitted to qualified laboratories in each municipality for testing. A positive test was defined as a test result that was above the defined cutoff.
for the given test. Test results were reported to all participants by mail and telephone. Participants with positive tests were referred for either total colonoscopy or sigmoidoscopy plus a barium enema for a confirmatory diagnosis. These confirmatory examinations were reimbursed by National Health Insurance, which has a coverage rate of 99.9% for the entire population.

All municipalities were asked to report the results of all confirmatory examination findings and pathological results. The histopathology of colon neoplasms was classified according to the World Health Organization criteria. Cancers were staged with the 6th edition of the American Joint Committee on Cancer staging system.

Data relevant to this screening program, including the demographics of screened subjects, the results of FIT, endoscopic findings, and the results of histopathology, were all stored in a central database. This database was linked to the National Death Registry of Taiwan and the Taiwan Cancer Registry, from which the causes of death (either cancerous or noncancerous codes) could be obtained. In this death registry, the causes of death in the government computer files were coded according to International Classification of Diseases, Ninth Revision. The cancer registry is a nationwide program with a coverage rate of 98.6% and an accuracy greater than 99%, but the delay in reporting is typically approximately 2 to 3 years. The date of diagnosis and the date and cause of death of a subject could be obtained via the matching of the computerized data file of the screening program and the aforementioned registry database with a unique identification number. We ascertained data regarding the incidence of CRC and CRC deaths from these 2 databases.

**Statistical Analysis**

**Screening indicators**

Standard screening measures and indicators were calculated. The coverage rate was calculated as the ratio of the number of subjects who received FIT to the number in the target population. Positive predictive values were calculated according to sex and age. Detection rates for adenoma, advanced adenoma, and cancer were expressed per 1000 people screened and were adjusted by the confirmatory examination rates.

**Distribution of CRC stages**

The distribution rates of stages among screen-detected cancer cases were determined and compared to those of non–screen-detected cancers identified through the cancer registry data released in 2005 (CRC cases diagnosed in 2003) with the chi-square test.

**Mortality with adjustments for the self-selection bias and increasing incidence of CRC**

Mortality data were ascertained to the end of 2009. As for the efficacy of the screening, the first measure was to compute the relative rate (RR) of CRC mortality between the
screened (exposed) subjects and the unscreened (unexposed) subjects, who included a substantial proportion of the uncovered population during the screening period from 2004 to 2009. The CRC mortality reduction was calculated as \((1 - \text{RR}) \times 100\%\). The second measure was the corresponding RR for the invited versus the uninvited after adjustments for the self-selection bias related to the screening rate on the basis of a methodology similar but not identical to an intention-to-treat analysis often used in randomized controlled trials.\(^{19-21}\) We selected the

\[
\text{Relative rate (RR) adjusted for self-selection bias} = \frac{P(\text{CRC death} | I)}{P(\text{CRC death} | T)}
\]

\[
= \frac{P(\text{CRC death} | I, S) \times P(S | I) + P(\text{CRC death} | I, \overline{S}) \times P(\overline{S} | I)}{P(\text{CRC death} | T)}
\]

\[
+ P(\overline{S} | I) \times \frac{P(\text{CRC death} | I, \overline{S})}{P(\text{CRC death} | T)}
\]

\[
= \text{(Screening rate [SR])} \times RR_{\text{screened/uninvited}} + (1 - \text{SR}) \times RR_{\text{unscreened/uninvited}}
\]

where \(P\) is the probability; \(I\) and \(T\) represent the invited group and the uninvited group, respectively; \(S\) and \(\overline{S}\) represent the screened group and the unscreened group, respectively; and SR is the screening rate. Note that \(P(\overline{S} | I) = 1 - P(S | I)\).

We estimated the aforementioned measures and their corresponding 95% credible intervals with a Bayesian acyclic graphic model underpinning the framework of a generalized linear model (as used in an evaluation for breast cancer screening in a previous study).\(^{21}\) A Poisson regression model was used to capture the RR of dying from CRC for the screened and unscreened groups versus the uninvited group. The 2 aforementioned measures were functions of the regression coefficients when they were weighted differently by the screening rate.\(^{20}\) The 2 cumulative mortality curves for the screened and unscreened groups were plotted after adjustments for both the self-selection bias and the increasing incidence trend with the follow-up time (Fig. 2A,B).

All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Screening Indicators

Table 1 shows the screening indicators of the screening program. There were 5,417,699 eligible subjects, and 1,160,895 participated in the first screening round from 2004 to 2009. Of the 1,160,895 subjects who attended the first screening, 329,042 attended the subsequent screenings; they included 157,545 with an interscreening interval of 2 years or less and 171,497 with an interscreening interval of more than 2 years. The overall coverage of the eligible population from 2004 until 2009 was 21.4%, and the rate of adhering to repeat screens was 28.3%. Of the 1,160,895 FIT cases that were completed at the first screen, 46,963 were positive, and this yielded an overall positivity rate of 4.0%. The positivity rate for those who attended subsequent screenings was 3.8%. Among those subjects who tested positive, 37,585 (80%) who were identified at the first screening and 11,026 (88.7%) who were identified at subsequent screenings underwent a confirmatory examination: 85.5% underwent total colonoscopy, 10.2% underwent sigmoidoscopy plus a barium enema, and 4.3% underwent an unspecified procedure. As a result of the confirmatory examinations, 19,398 colorectal adenoma cases (14,834 [16.0 per 1000] at the first screening), 5500 advanced adenoma cases (4284 [4.6 per 1000] at the first screening), and 2805 invasive cancers (2304 [2.5 per 1000] at the first screening) were detected. The positive predictive value of FIT was 39.5% for adenoma, 11.7% for advanced adenoma, and 6.1% for invasive cancers. The detection rate per 1000 subjects at the first screening was 16.0 for adenoma, 4.6 for advanced adenoma, and 2.5 for cancer. The corresponding figures for subsequent screenings were 15.6, 4.2, and 1.7, respectively. Table 2 shows the frequencies of age- and sex-specific screened...
and unscreened subjects in the screening period and eligible study subjects in the prescreening period. The corresponding person-years and deaths from CRC are also listed in Table 2.

**CRC Stage Distribution Between Attenders and Nonattenders**

The age- and sex-specific numbers of subjects attending one-off and repeated screenings are listed in Table 3. There were 2805 CRCs detected in the screening population. Of these, 77% (2155/2805) had complete staging data; there were 286 cases (13.3%) of carcinoma in situ, 755 stage I cases (35.0%), 450 stage II cases (20.9%), 510 stage III cases (23.7%), and 154 stage IV cases (7.2%), as indicated in Table 4. The distribution rates with respect to tumor staging were different in the screened cohort versus the unscreened cohort. A remarkable difference in advanced cancers between the 2 groups was noted.

**Mortality Reduction**

The RR of cumulative CRC mortality between 2004 and 2009 for the screened subjects versus the unscreened ones...
was 0.38 (95% confidence interval, 0.35-0.42), and this yielded a significant 62% effectiveness of reducing deaths from CRC. The mortality rates were 13.77 per 100,000 persons in the screened group and 36.31 per 100,000 persons in the unscreened group. Figure 2A shows the difference in the corresponding cumulative CRC mortality curves for the screened and unscreened groups without adjustments for the self-selection bias.

It is interesting to note that the RR of cumulative mortality between the invited and uninvited groups was 0.90 (95% confidence interval, 0.84-0.95) with adjustments for the self-selection bias and CRC incidence change. This suggests a significant 10% mortality reduction from CRC attributable to the 21.4% coverage of the FIT screening. Figure 2B shows a comparison of the 2 curves with adjustments for the self-selection bias.

**DISCUSSION**

This large study cohort demonstrated that the administration of FIT screening led to a chance of reducing CRC deaths by 62% for screened subjects versus unscreened subjects. We further estimated a 10% mortality reduction from CRC as a result of FIT screening coverage of 21.4% (1,160,895/5,417,699 residents) after adjustments for the self-selection bias with an average follow-up of 3.09 years until 2009. Such findings may assist in convincing health decision makers that the continuous promotion of such a nationwide screening program is worthwhile.

Although the efficacy of gFOBT at reducing CRC mortality has been proven in previous randomized trials and evidence has demonstrated the advantages of FIT over gFOBT, organized service screening using FIT has been introduced in only a few countries, and its efficacy remains unknown.\(^\text{11}\) Our study supports the use of FIT for a number of reasons. First, the magnitude of the mortality reduction was significant and greater than that observed in trials using guaiac tests.\(^\text{1-3,22}\) It is worth noting that using available resources, we screened only 21.4% of the eligible population by 2009; we have estimated with a sensitivity analysis that the mortality reduction could reach 36% if the screening rate could be improved to 60% with our nationwide screening program, which continued to be run up to 2014 (see Table 5). Second, our results showed a reduction in advanced-stage cancers in the screened group versus the unscreened group (Table 4). This finding suggests a favorable impact on mortality reduction and overall costs of treating CRC, but long-term follow-up is still required to confirm this benefit after the lead-time bias is taken into account.

Evaluating effectiveness in a population screening service is of utmost importance for several reasons. First, from the perspectives of screening providers through an evaluation of effectiveness in mortality reduction, we can fully understand whether the screening strategy is feasible and what the utility of the screening program is in association with the incurred budget. Second, knowing that screening is effective

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**TABLE 2. Age- and Sex-Specific Numbers of Subjects and Colorectal Cancer Deaths in the Screening and Prescreening Periods**

| Age Group | Subjects | Prescreening | Screened | Unscreened |
|-----------|----------|--------------|----------|------------|
| Men       |          |              |          |            |
| 50-54 y   | 140,092  | 803,439      | 729,037  |
| 55-59 y   | 118,055  | 595,185      | 429,830  |
| 60-64 y   | 89,174   | 382,394      | 394,429  |
| 65-69 y   | 98,969   | 331,088      | 324,142  |
| Women     |          |              |          |            |
| 50-54 y   | 267,482  | 791,676      | 727,398  |
| 55-59 y   | 191,041  | 595,990      | 436,233  |
| 60-64 y   | 133,201  | 395,039      | 416,895  |
| 65-69 y   | 122,881  | 361,994      | 353,047  |

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**TABLE 3. Age- and Sex-Specific Numbers of Subjects and Colorectal Cancer Deaths in the Screened Population**

| Age Group | One-Off | Repeated | One-Off | Repeated |
|-----------|---------|----------|---------|----------|
| Men       |         |          |         |          |
| 50-54 y   | 16/406,882 | 804/4,820,631 | 119/729,037 |
| 55-59 y   | 47/348,685  | 1009/3,571,107 | 106/429,830 |
| 60-64 y   | 48/285,636  | 1156/2,294,363 | 174/394,429 |
| 65-69 y   | 99/326,632  | 1588/1,986,527 | 266/324,142 |
| 70-74 y   | 64/85,171   | 1264/768,034  | 390/309,833 |

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**TABLE 4. Age- and Sex-Specific Numbers of Subjects and Colorectal Cancer Deaths in the Screened Population**

| Age Group | Subjects, No. | Colorectal Cancer Deaths, No. |
|-----------|---------------|-------------------------------|
| Men       |               |                               |
| 50-54 y   | 113,412       | 26,680                        |
| 55-59 y   | 93,631        | 24,424                        |
| 60-64 y   | 66,198        | 22,976                        |
| 65-69 y   | 81,730        | 17,239                        |
| 70-74 y   | 64            | 0                             |
| Women     |               |                               |
| 50-54 y   | 202,882       | 64,600                        |
| 55-59 y   | 141,464       | 49,577                        |
| 60-64 y   | 93,390        | 39,811                        |
| 65-69 y   | 100,731       | 22,150                        |
| 70-74 y   | 39            | 8                             |
TABLE 4. Frequencies and Distribution Rates of Tumor Stages by Detection Modes

| AJCC Staging | Subjects, No. (%) | Rate per 10^5 | Subjects, No. (%) | Distribution Rate per 10^5 | Subjects, No. (%) | Distribution Rate per 10^5 | Subjects, No. (%) | Distribution Rate per 10^5 | Subjects, No. (%) | Distribution Rate per 10^5 |
|--------------|------------------|---------------|------------------|---------------------------|------------------|---------------------------|------------------|---------------------------|------------------|---------------------------|
| 0            | 286 (13.3)       | 24.6          | 77 (10.4)        | 6.6                       | 77 (7.4)         | 6.6                       | 440 (11.2)       | 37.9                      | 928 (5.0)        | 21.8                      |
| I            | 755 (35.0)       | 65.0          | 190 (25.6)       | 16.4                      | 216 (20.9)       | 18.8                      | 1163 (29.5)      | 100.2                     | 3009 (16.1)      | 70.7                      |
| II           | 450 (20.9)       | 38.8          | 141 (19.0)       | 12.1                      | 281 (26.9)       | 24.2                      | 872 (22.1)       | 75.1                      | 5188 (17.8)      | 121.9                     |
| III          | 510 (23.7)       | 43.9          | 220 (29.6)       | 19.0                      | 321 (30.8)       | 27.7                      | 1051 (26.7)      | 90.5                      | 5935 (31.8)      | 139.4                     |
| IV           | 154 (7.2)        | 13.3          | 115 (15.5)       | 9.9                       | 146 (14.0)       | 12.6                      | 415 (10.5)       | 35.7                      | 3579 (19.2)      | 84.1                      |
| Total        | 2155 (100.0)     | —             | 743 (100.0)      | —                         | 1043 (100.0)     | —                         | 3941 (100.0)     | —                         | 18,639 (100.0)   | —                         |

Abbreviation: AJCC, American Joint Committee on Cancer.

TABLE 5. Effectiveness of Fecal Immunochemical Test Screening at Reducing Colorectal Cancer Mortality in Terms of the Crude Relative Rate and the Adjusted Relative Rate Between the Screened Group and the Unscreened Group With a Bayesian Approach to Making an Allowance for the Self-Selection Bias and Increasing Incidence

| Current Data and Sensitivity Analysis | Crude Relative Rate (95% Confidence Interval) | Adjusted Relative Rate (95% Confidence Interval) |
|--------------------------------------|----------------------------------------------|-----------------------------------------------|
| Empirical data                       | 0.38 (0.35-0.42)                             | 0.90 (0.84-0.95)                              |
| Sensitivity analysis                 |                                              |                                              |
| 20% SR and 30% RSR                  | 0.90 (0.85-0.96)                             |                                              |
| 40% SR and 30% RSR                  | 0.77 (0.73-0.82)                             |                                              |
| 60% SR and 30% RSR                  | 0.64 (0.60-0.68)                             |                                              |

Abbreviation: SR, screening rate; RSR, repeat screening rate.

The results of the calculation using empirical data were based on the current SR of 21.4%. These results were also adjusted for a projected 1.97% increase in the incidence rate per year (based on data from the Taiwan Cancer Registry, 1998-2003).

in reducing CRC mortality, the public will be more willing to go for screening tests, and further improvement in participation in either fecal testing or colonoscopy thus can be anticipated. Third, distinct from randomized trials, service screening is apt to be influenced by a self-selection bias. Our current study well demonstrated how one could deal with this problem of bias and provide a population-based (rather than selected group-based) estimate of effectiveness in a nonexperimental study. In addition to the estimation of mortality reduction via screening based on screening rate/repeat screening rate empirical data, we also provided the results of a sensitivity analysis based on 3 scenarios of screening rates (Table 5) to provide results that could convince health decision makers to continue to support this population-based FIT screening program on the basis of the current evidence from a short period of follow-up and the projection of possible long-term effects when the program is expanded.

We believe that such a self-selection bias adjustment is very conservative because we treated those who were not available for FIT (because the capacity for screening was gradually expanded) as if they had been invited and had refused FIT screening. Because these estimates were projected under a Taiwanese scenario (rather than through a literature review), we believe that the true benefit of FIT screening may not be exactly the same as the projection but may lie between 10% and 36% if the screening rate could be enhanced gradually to 60%.

Our study may have limitations. First, because this is a nationwide service screening program and the coverage rate of this nationwide service screening program has expanded over the years, one would not expect a formal invitation rate and attendance rate as reported in previous experimental trials and other organized screening programs.23,24 There are 2 reasons for the unavailability of the attendance rate. Both resulted in an inability to differentiate those who refused FIT when invited from those who were unavailable for FIT. The first is related to the invitation methods (eg, mass media and pamphlets), which precluded us from getting the denominators of invitees. The second reason is the gradual expansion of this nationwide screening program due to budgetary limitations; this yielded only 21.4% coverage of the eligible population by 2009. However, the coverage rate would be expected to increase with time.

Aside from budgetary support for the screening program from the government, to improve the coverage rate, we have to pay attention to the following aspects. First, the improvement of public awareness of CRC and the
promotion of screening by physicians are likely to be helpful and play pivotal roles.25 Second, with a significant reduction of mortality by FIT in this program, interval cancers still exist. Our recent study also showed a lower sensitivity of FIT for early-stage cancers and proximal advanced neoplasms.26 Further study is needed to improve the detection of these lesions. Third, not all FIT-positive subjects underwent colonoscopy; instead, some underwent a barium enema plus sigmoidoscopy or another examination as a confirmatory examination in this program. Although colonoscopy was recommended as the first-choice confirmatory examination in our program, it was not necessarily available in some rural areas. Moreover, the fee for sedation during colonoscopy has yet to be subsidized by the National Health Insurance, so this might have also hindered the acceptance of colonoscopy in some FIT-positive subjects. Finally, although we demonstrated a significant reduction in CRC mortality during the short follow-up period, the main cause is probably the large cohort size because the required follow-up time for estimating the impact of screening on mortality from CRC in population-based randomized controlled trials is often longer than ours. Longer follow-up of our service screening program is, therefore, required to estimate the true long-term effect of FIT screening on mortality.

In conclusion, FIT is a feasible and effective test for use in population screening programs; 1,160,895 Taiwanese residents were covered. The large cohort data presented herein provide the statistical power for demonstrating a significant CRC mortality reduction even though the follow-up time was short. However, continued follow-up of this large cohort is required to assess the true long-term effect of FIT screening if more of the population is covered in a continuing nationwide screening program.

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CONFLICT OF INTEREST DISCLOSURES
The authors made no disclosure.

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