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Association Between Colorectal Cancer Mortality and Gradient Fecal Hemoglobin Concentration in Colonoscopy Noncompliers

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Abstract

Background: To what extent the risk for colorectal cancer (CRC) death among noncompliers of colonoscopy is elevated following positive fecal immunological testing and whether the elevated risk varies with the fecal hemoglobin concentration (f-Hb) and location of CRC have not been researched.

Methods: We used data on 59 389 individuals (4.0%) among 1 489 937 Taiwanese screenees age 50 to 69 years with f-Hb 20 μg hemoglobin or more per gram of feces from 2004 to 2009. They were classified into 41 995 who received colonoscopy and 10 778 who received no confirmatory examination; the latter was categorized into three risk groups according to f-Hb (20–49, 50–99, and 100+). Mortality from CRC as the primary end point was monitored until December 31, 2012.

Results: A 1.64-fold (95% confidence interval [CI] = 1.32 to 2.04) increased risk for CRC death for the noncolonoscopy group as opposed to the colonoscopy group adjusting for differences in baseline characteristics. A gradient relationship was noted between cumulative mortality and age- and sex-adjusted f-Hb categories with 1.31-fold (95% CI = 1.04 to 1.71), 2.21-fold (95% CI = 1.55 to 3.34), and 2.53-fold (95% CI = 1.95 to 3.43) increased risk, respectively, for the 20–49, 50–99, and 100+ risk groups in the noncolonoscopy group compared with the colonoscopy group. The noncolonoscopy group led to a statistically significant 1.75-fold increased risk (95% CI = 1.35 to 2.33) for CRC of the distal colon but a statistically nonsignificant 1.11-fold increased risk (95% CI = 0.70 to 1.75) for the proximal colon, compared with the colonoscopy group. When the comparator was limited to subjects whose colonoscopy was completed to the cecum, the statistically significantly elevated risk for CRC mortality was seen for both distal and proximal colon in the noncolonoscopy group.

Conclusions: After a positive fecal immunochemical test, colonoscopy can reduce by about half the number of deaths from CRC. Among colonoscopy noncompliers, higher f-Hb is associated with an increased risk of mortality from CRC in a dose-response manner.

Colorectal cancer (CRC) accounts for 10% of all cancers worldwide (1). In an effort to reduce mortality rates, several countries have adopted mass screening for CRC using either the fecal occult blood test (2–5) or lower gastrointestinal endoscopy (6–8). The superior performance (9) and unique quantitative property of the fecal immunochemical test (FIT) (10) render it feasible for population-based screening.

Despite the widespread use of FIT in population-based screening, its effectiveness in reducing mortality from CRC is contingent upon the successful completion of a colonoscopic examination, a procedure that can directly reduce the mortality rate (3–5,11,12) for those with positive test results. Therefore, an evaluation of the efficacy of FIT in reducing CRC mortality essentially amounts to an evaluation of the efficacy of colonoscopy for FIT-positive patients, assuming the sensitivity of FIT and colonoscopy compliance are both 100%.

Unfortunately, in population-based screening programs, some 10% to 20% of people in whom FIT is positive decline subsequent colonoscopy (4,5,13–16), substantially reducing the effectiveness of screening. The best way to address this problem is to fully educate colonoscopy candidates about the risk of CRC if they do not receive this procedure. An alternative approach is to focus on individuals with the highest risk of developing CRC so that resources allocated to tracking and counseling patients may be used efficiently.

While a perfect scenario may be unachievable, FIT-positive patients not referred for colonoscopy may serve as a comparator group to evaluate the efficacy of colonoscopy following a positive FIT. In addition, there is a need to evaluate the effectiveness of colonoscopy in reducing the mortality rate of patients with cancers of the proximal colon (8,17–22). Furthermore, no evidence has been presented quantifying the benefit of colonoscopy in patients with positive FIT, considering that the screening test may diagnose the cancer earlier but with no effect on the outcome (ie, the lead time bias).

In light of the increased incidence of CRC (1), a nationwide screening program was launched in Taiwan in 2004 (3,5). The primary aim of this study was to quantify the increased risk in mortality in those who did not receive colonoscopic follow-up after a positive FIT compared with those who did. We also determined whether fecal quantities of hemoglobin could serve as a priority-setting tool for referral to colonoscopy (23–26).

Methods

Study Population

Details of the nationwide screening program have been reported elsewhere (3,5). In brief, residents age 50 to 69 years were invited to receive biennial FIT. The cutoff concentration for a positive test was 20 μg hemoglobin per gram of feces (Eiken Chemical Co, Tokyo, Japan or Kyowa Medex Co Ltd., Tokyo, Japan). The rationale for this cutoff was based on the cost-effectiveness analysis of a community-based pilot study (27), and the diagnostic accuracy has been validated previously (3). Screening test results were reported as "positive" or "negative" to the participants/physicians while the quantitative measures of f-Hb were stored in the central database without specific notification; these data were prepared for future assessment of clinical applications. From 2004 to 2009, a total of 1 489 937 subjects participated in the program, 59 389 (4.0%) of whom had a positive FIT. Among FIT-positive individuals, 41 995 (70.7%) received a colonoscopy and 10778 (18.2%) declined a confirmatory

examination. The 6616 subjects (11.1%) who received suboptimal examinations (eg, sigmoidoscopy or barium enema) were excluded from the study.

Colonoscopic Examination

Colonoscopy was recommended to be performed within three months of a positive fecal test. Diagnostic details, including whether the subjects received the recommended colonoscopy; the thoroughness of examination; the anatomic site reached by colonoscopy; the number, size, location, and histopathology of colonic neoplasms; and whether the colonic neoplasms had been removed were recorded and transmitted to a central database via a virtual private network to generate performance indicators (3,5). The histopathology of colonic lesions was classified according to the criteria of the World Health Organization (28). For patients who had colorectal neoplasms, follow-up colonoscopy was recommended according to the guidelines of the US Multi-Society Task Force (29).

Study Design

Evaluation of the efficacy of colonoscopy for FIT-positive subjects was based on a cohort study design in which we classified referrals undergoing colonoscopy as the exposed group (colonoscopy group) and nonreferrals as the unexposed group (noncolonoscopy group) to compare the CRC mortality between groups. Because this was not a randomized controlled trial, we also compared the adjusted mortality rates from CRC by controlling for confounding factors, consisting mainly of age, sex, and baseline fecal hemoglobin concentration (f-Hb). A propensity score design was also used to adjust for selection bias resulting from the possible imbalance of baseline characteristics between the two groups.

This study was approved by the Health Promotion Administration, Ministry of Health and Welfare, prior to data retrieval and analysis (1049906162), and patient records/information were anonymized and de-identified prior to analysis. The Research Ethics Committee of National Taiwan University Hospital approved this project and granted a waiver of informed consent (201511034W) pursuant to the regulation of the Institutional Review Board.

Assessment of End Points

Study outcomes were evaluated by linking the screening data with the National Cancer Registry to determine the incidence of CRC and deaths from CRC from 2004 to 2012 (30). Cancer was staged according to the American Joint Committee on Cancer 7th staging system (31). The region of colon and more proximal to the splenic flexure was defined as the proximal colon.

Statistical Analysis

Differences in baseline characteristics between the colonoscopy and noncolonoscopy groups were assessed by Student's t or χ^2 test. Differences in the distribution of CRC stages were determined using the Poisson method. To assess whether the difference in socioeconomic status, access to healthcare, proximity to colonoscopists, etc., may affect colonoscopy completion, we used the geographic areas as a proxy variable (32) for the comparison of referral rates. To evaluate the magnitude of increased

risk in mortality associated with noncompliance to colonoscopy, we estimated the relative risk (RR) and the corresponding 95% confidence interval (CI) of the CRC-specific mortality rate of the noncolonoscopy group vs that of colonoscopy group using the Poisson method.

The above results could be also interpreted as the benefit of mortality reduction attributed to the colonoscopy, which was calculated as: $(1-1/RR) \times 100\%$.

To adjust for between-group differences in baseline characteristics, propensity scores for the probability of undergoing colonoscopy were developed using the logistic regression model. A multivariable Poisson regression model was then used to estimate the adjusted relative risk and the corresponding 95% confidence interval.

We also included the city/county clustering effect, reflecting the extent of similar socioeconomic status of patients living in the same area, in the regression model.

To test the hypothesis that higher f-Hb was associated with higher risk of CRC death, we categorized the f-Hb in tertiles (20–49, 50–99, and ≥100) according to the distribution of f-Hb in our population and also for the ease of use in clinical practice. We also used propensity scores to match referrals with nonreferrals in a 1:1 ratio and calculated the relative risk between the two groups.

To verify the above findings, we compared the stage-specific distribution of CRC and evaluated CRC-specific survival in patients diagnosed with CRC, adjusting for lead time (33–35), and with the results expressed as hazard ratios (or death rates) and their corresponding 95% confidence intervals (Supplementary Figure 1, available online).

We also performed subgroup analyses of the effectiveness of colonoscopy for cancers in the proximal vs distal colonic sites. Furthermore, we excluded those subjects who did not receive a complete colonoscopy and repeated the analyses so that the effectiveness of colonoscopy on the reduction in mortality rates in cancers of the proximal colon would be emphasized.

Finally, we applied a Cox proportional hazards regression model to identify risk factors for CRC-specific death among the noncolonoscopy group by using the regression coefficients of statistically significant risk factors to develop a risk score to stratify the noncolonoscopy group into different risk groups. The results are graphically presented with risk of CRC death over time. The proportional hazard assumption was verified by testing the statistical significance of the regression coefficient on time-by-group interaction using the time-dependent Cox proportional hazards regression model. All relevant results shown below met this assumption as the regression coefficients of interaction terms were not statistically significant ($P > .05$).

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All P values were two-sided, and P values of less than .05 were considered statistically significant.

Results

Baseline Characteristics

A comparison of baseline demographic characteristics of the colonoscopy and noncolonoscopy groups is presented in Table 1. There were no statistically significant differences in the age or

Table 1. Baseline characteristics of the screened population

Baseline characteristics	Referrals (n = 41 995)	Nonreferrals (n = 10 778)	P^*
Demographic characteristics			
Age, mean ± SD, y	59.5 ± 5.8	59.6 ± 5.8	.26
Sex, No. (%)			.49
Male	19 871 (47.3)	5 060 (46.9)	
Female	22 124 (52.7)	5 718 (53.1)	
Geographic area, No. (%)			<.001
Northern area	15 316 (36.5)	4 499 (41.7)	
Central area	11 350 (27.0)	3 022 (28.1)	
Southern area	12 198 (29.0)	2 553 (23.7)	
Eastern area and offshore island	3 131 (7.5)	704 (6.5)	
Fecal hemoglobin concentration, μg Hb/g stool			<.001
20–49	16 155 (40.5)	4 510 (45.4)	
50–99	9 009 (22.6)	2 149 (21.6)	
≥100	14 727 (36.9)	3 268 (33.0)	
No. of subsequent screening (%)†	9 858 (23.5)	1 400 (13.0)	<.001
Propensity score, mean ± SD‡			
	0.80 ± 0.05	0.78 ± 0.04	<.001
Time to diagnosis of colorectal cancer, mean ± SD, y			
	0.21 ± 0.20	1.73 ± 1.35	<.001
Colonoscopy quality index, %			–
Cecal intubation rate	79.3	–	
Adenoma detection rate	44.7	–	
Advanced adenoma detection rate‡,§	12.5	–	
Resection rate of < 2 cm adenoma	85.0	–	

*Quantitative data were compared using the Student's t test, and categorical data were compared using the χ^2 test. All these statistical assessments were two-sided.
†The fecal immunochemical test (FIT)–based screening program was biennial in schedule, so participants may have received the FIT more than once during the study period. The initial screening was defined as: subjects who received the FIT for the first time and the results were positive. Subsequent screening was defined as: subjects who received the repeated FIT after the first screening (with negative FIT result) and the results were positive at subsequent screen.
‡Age, sex, fecal hemoglobin concentration, brand of FIT, and the prevalence/subsequent screen were included in the calculation of the propensity score using the logistic regression model.
§Advanced adenoma was defined as an adenoma 10 mm or larger in diameter or having a villous component or high-grade dysplasia.

sex. Small but statistically significant differences were noted, possibly as a result of the large sample size, between the two groups in geographic area and f-Hb. There were substantial differences in the proportion of initial vs subsequent screening and, as expected, the time to diagnosis of CRC. The number of hospitals that performed the confirmatory colonoscopy was 268, 236, 222, and 103, respectively, in the northern, central, southern, and eastern areas/offshore islands while the corresponding percentages of referrals were 77.3%, 79.0%, 82.7%, and 81.6%, respectively; a higher number of hospitals was not associated with better referral.

Incidence and Mortality of Colorectal Cancer

The numbers of deaths from CRC and mortality rate of CRC among the 59 389 participants over a mean period of 5.7 years are shown in Table 2. We identified 2424 cases of and 297 deaths from CRC among the colonoscopy group and 386 cases of and 129 deaths from CRC among the noncolonoscopy group. The incidence rates of CRC were 1085 (2424/223 473 person-years) and 592 (386/65 237 person-years) per 100 000 person-years for the colonoscopy and noncolonoscopy groups, respectively, yielding a 1.83-fold increased relative risk in detection of CRC (95% CI = 1.82 to 1.85) (Figure 1).The mortality rates from CRC were 128 (297/233 017) and 200 (129/64 560) per 100 000 person-years for the colonoscopy and noncolonoscopy groups, respectively. Analysis of these data indicated a statistically significant 1.56-fold increased risk of dying from CRC (RR = 1.56, 95% CI = 1.36 to 1.79) if the subject did not comply with colonoscopy (Table 3). The absolute mortality difference was 72 (95% CI = 37 to 112) per 100 000 person-years, yielding the number of subjects needed to do colonoscopy to prevent one CRC death at six years of follow-up (Figure 3A) estimated as 250 (95% CI = 162 to 480).

Stage Distribution of Incident Colorectal Cancer

The cumulative incidence rates (Figure 2) revealed that patients in the noncolonoscopy group had lower incidence rates of stage 0 to III cancers, but a higher incidence of stage IV cancers relative to patients in the colonoscopy group. Cancers were detected at an earlier stage in the colonoscopy group than in the noncolonoscopy group (P < .001).

Multivariable Analysis of Colorectal Cancer-Specific Mortality Rate

The result of multivariable analyses adjusting for the differences in baseline characteristics showed a statistically significant 1.64-fold (aRR = 1.64, 95% CI = 1.32 to 2.04) increased risk of CRC death without colonoscopy (Figure 3A). This was remarkably similar to the result obtained from univariate analyses (Table 3). Older age, male sex, and higher f-Hb led to a higher risk of CRC-specific mortality. For the colonoscopy group, there was no statistically significant difference in the mortality rates for the initial (131 per 100 000 person-years) and subsequent screens (114 per 100 000 person-years, P = .35), or between the two different brands of FIT (131 and 119 per 100 000 person-years, respectively, P = .55) (data not shown).
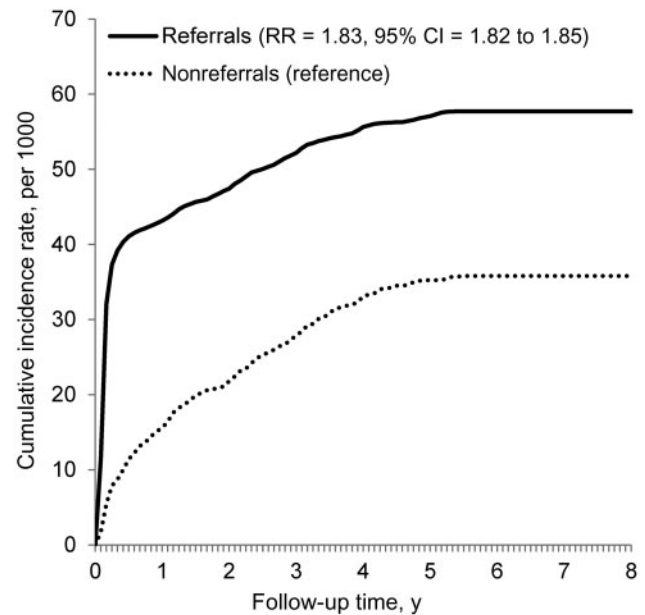

Figure 1. Cumulative incidence of colorectal cancer according to study group (referral n = 41 995 vs nonreferral n = 10 778). The difference between the two groups was assessed by using the Poisson method, two-sided. CI = confidence interval; RR = relative risk.

Table 2. Numbers of colorectal cancer deaths, person-years at risk, and colorectal cancer mortality rates

Characteristic	CRC death		Person-years at risk		CRC mortality*		Mortality rate difference	P†
	Referrals	Nonreferrals	Referrals	Nonreferrals	Referrals	Nonreferrals		
Male								
Age 50–59 y	62	18	50 472	14 069	122.8	127.9	5.1	.87
Age 60–69 y	114	46	58 926	15 634	193.5	294.2	100.7	.01
Subtotal	176	64	109 398	29 703	160.9	215.5	54.6	.04
Female								
Age 50–59 y	55	34	66 477	18 313	82.7	185.7	103	<.001
Age 60–69 y	66	31	57 141	16 544	115.5	187.4	71.9	.02
Subtotal	121	65	123 618	34 857	97.9	186.5	88.6	<.001
Both sexes								
Age 50–59 y	117	52	116 950	32 382	100.0	160.6	60.6	.004
Age 60–69 y	180	77	116 067	32 178	155.1	239.3	84.2	.001
Total	297	129	233 017	64 560	127.5	199.8	72.3	<.001

*Per 100 000 person-years. CRC = colorectal cancer.
†P values were calculated using the Poisson method, two-sided.

Table 3. Comparisons of colorectal cancer–specific mortality between the colonoscopy and noncolonoscopy groups using Poisson regression models

Variables	Relative risk (95% CI)
Univariate analysis	
Noncolonoscopy vs colonoscopy	1.56 (1.36 to 1.79)
Multivariable analysis*	
Noncolonoscopy vs colonoscopy	1.64 (1.32 to 2.04)
Noncolonoscopy vs complete colonoscopy†	2.31 (1.88 to 2.84)
Incomplete colonoscopy vs complete colonoscopy†	1.65 (1.26 to 2.16)
Age of attending screen, y	
60–69 vs 50–59	1.47 (1.22 to 1.77)
Sex	
Male vs female	1.29 (1.02 to 1.62)
Screening round	
First screen vs subsequent screen	1.37 (0.90 to 2.08)
Fecal hemoglobin concentration, μg Hb/g stool	
20–49	1.00 (reference)
50–99	2.10 (1.61 to 2.73)
$\geq$100	4.61 (3.61 to 5.89)

*The multivariable regression model also adjusted for city/county clustering and propensity scores. CI = confidence interval.
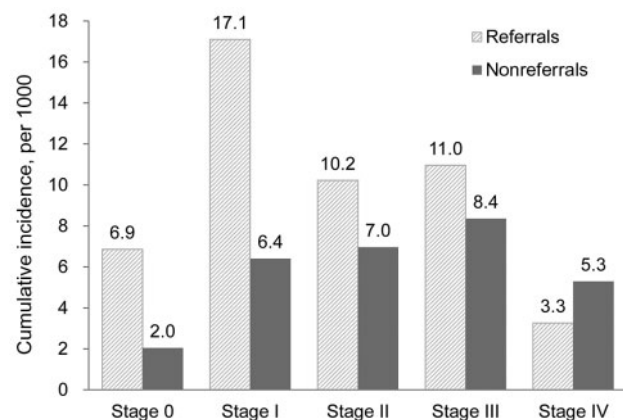†A multivariable model that introduced dummy variables to indicate the completeness of colonoscopy.

Figure 2. Cumulative incidence of colorectal cancer according to study group (referral vs nonreferral) and cancer stage.

Propensity Score Analysis

Before matching, patients in the colonoscopy group had statistically significantly higher propensity scores compared with those in the noncolonoscopy group. After matching, a 1.69-fold (95% CI = 1.47 to 2.08) increased risk for mortality from CRC was noted in noncolonoscopy group (data not shown).

Colorectal Cancer Survival with the Adjustment of Lead Time

Given our findings of 297 CRC deaths out of 2424 cases of CRC in the colonoscopy group, and 129 CRC deaths out of 386 cases of CRC in the noncolonoscopy group, the death rate from CRC was a 2.56-fold hazard ratio (95% CI = 2.08 to 3.23) for noncolonoscopy group compared with the colonoscopy group. Adjusting for the lead time (Supplementary Tables 1 and 2, available online)

gave a 1.67-fold (hazard ratio [HR] = 1.67, 95% CI = 1.35 to 2.04) increased risk for death from CRC, which was close to that estimated in the mortality-rate analysis (Figure 3B).

Proximal vs Distal Colon

The anatomical site distributions of CRC were similar for the two groups. There were 469 (19.3%) cases of proximal and 1446 (59.7%) cases of distal CRC in the colonoscopy group, and 80 (20.7%) cases of proximal and 250 (64.8%) cases of distal CRC in noncolonoscopy group. Anatomical data were missing for 509 (21.0%) and 56 (14.5%) cases in the colonoscopy and noncolonoscopy groups, respectively. There was a shift in distribution toward earlier stages in the colonoscopy group, and this was similar for cancers of the proximal and distal colon (Supplementary Table 3, available online).

The mortality rates for colonoscopy-group patients with CRC of the proximal and distal colon were 33 and 70 per 100 000 person-years, respectively, while those for noncolonoscopy group were 37 and 122 per 100 000 person-years, respectively (Supplementary Figures 2 and 3, available online). The elevated risk for CRC mortality for cancers of the distal colon was more remarkable (a statistically significant 1.75-fold increased RR, 95% CI = 1.35 to 2.33) than that for the proximal colon (a statistically nonsignificant 1.11-fold increased RR, 95% CI = 0.70 to 1.75) in noncolonoscopy group as opposed to the colonoscopy group. The similar findings were noted in the results of survival analyses, yielding statistically significant 1.82-fold hazard ratio (95% CI = 1.41 to 2.38) but statistically nonsignificant 1.35-fold hazard ratio (95% CI = 0.86 to 2.08) increased death rates for the distal and proximal location, respectively (Supplementary Figures 2 and 3, available online).

Completeness of Colonoscopy

When the analysis was limited to patients whose colonoscopy was completed to the cecum (33 302/41 995, 79.3%), higher mortality (a 2.39-fold increased RR, 95% CI = 1.91 to 2.98) and death rates (a 1.92-fold increased HR, 95% CI = 1.54 to 2.38) were seen in the noncolonoscopy group than in the colonoscopy group (Supplementary Figure 4, available online). Also, when we took into account the colonoscopy completeness in the multivariable model (Table 3), the statistically significantly elevated risks were noted in the noncolonoscopy group (a 2.31-fold increased RR, 95% CI = 1.88 to 2.84), and also for incomplete colonoscopy (a 1.65-fold increased RR, 95% CI = 1.26 to 2.16), compared with complete colonoscopy. The statistically significantly elevated risk for CRC mortality was seen for both cancers of the distal colon (a 2.63-fold increased RR, 95% CI = 2.00 to 3.57) and the proximal colon (a 1.82-fold increased RR, 95% CI = 1.11 to 2.94) in the noncolonoscopy group as opposed to the colonoscopy group. Similarly, the findings of survival analyses were both statistically significant, yielding 2.13-fold hazard ratio (95% CI = 1.61 to 2.78) and 1.64-fold hazard ratio (95% CI = 1.03 to 2.63) increased death rates for the distal and proximal location, respectively (Supplementary Figure 5 and 6, available online).

Priority-Setting Indicator for Colonoscopy

The multivariable regression model identified three statistically significant risk factors for CRC mortality, including older age, male sex, and higher f-Hb (Table 3). A gradient relationship was seen when the noncolonoscopy group was stratified into three
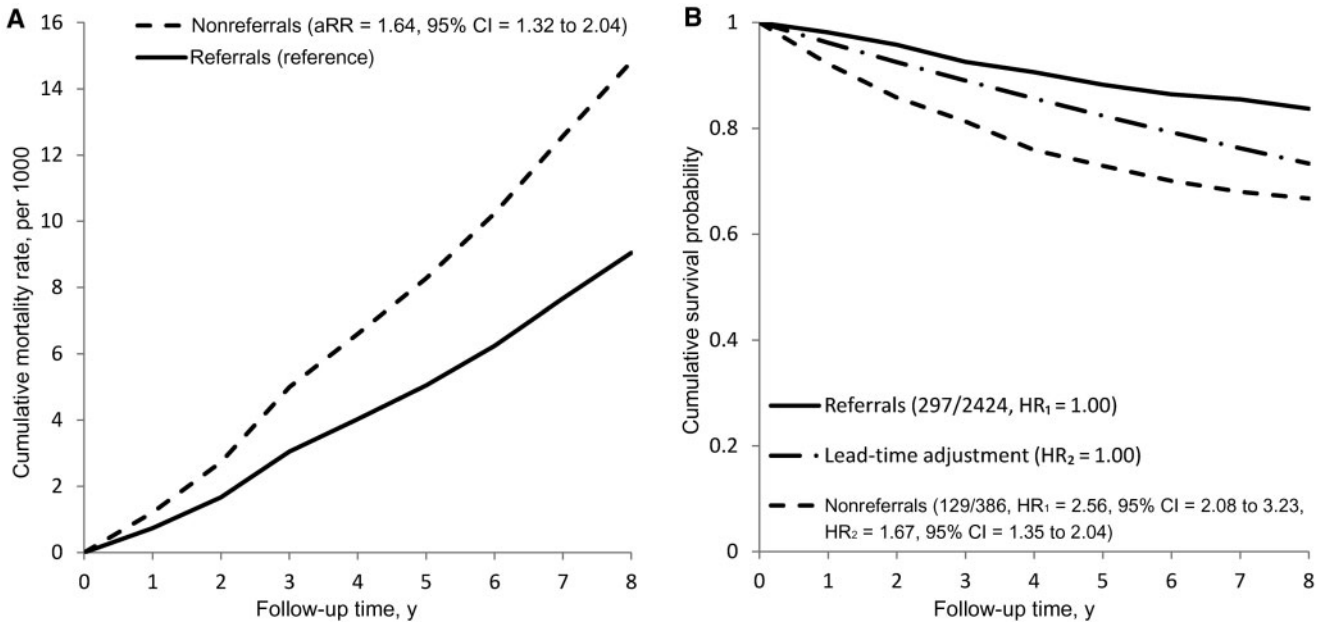
Figure 3. Cumulative mortality and survival of colorectal cancer according to study group. **A)** Cumulative mortality rates of colorectal cancer (CRC) according to the study group (referral vs nonreferral), adjusting for city/county clustering, age, sex, screening round, fecal hemoglobin concentration, and propensity score. **B)** Cumulative survival probability of patients with CRC according to the study group (referral vs nonreferral), adjusted for lead time in the referral group. aRR = adjusted relative risk; CI = confidence interval; HR = hazard ratio.
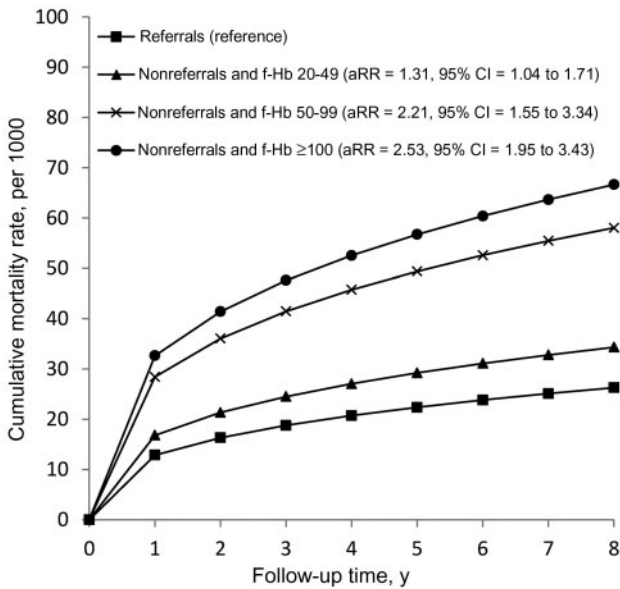

Figure 4. Cumulative mortality rates of the nonreferral group, stratified by risk score. Based on age- and sex-adjusted f-Hb, the noncolonoscopy group was categorized into three risk groups of f-Hb 20-49 (n = 5361), f-Hb 50-99 (n = 2149), and f-Hb 100+ (n = 3268). The data was analyzed using the Cox proportional hazards regression model.

risk groups according to the regression coefficient-derived risk scores: A higher risk score was associated with a higher possibility of dying from CRC if the patient did not receive the colonoscopy (Figure 4). The cumulative CRC mortality increased by 1.31-fold (aHR, 95% CI = 1.04 to 1.71), 2.21-fold (95% CI = 1.55 to 3.34), and 2.53-fold (95% CI = 1.95 to 3.43), respectively, for the age- and sex-adjusted f-Hb categories of 20–49, 50–99, and 100+ as compared with colonoscopy group.

When the cumulative mortality curve of CRC was stratified according to the true tertile of population f-Hb distribution, similarly, the gradient relationship was noted (Supplementary Figure 7, available online). The baseline f-Hbs of stage II to IV CRCs in noncolonoscopy patients (noncompliance to colonoscopy and their CRCs were diagnosed at the time of developing clinical symptoms) were close to those of stage 0 to I CRCs in the colonoscopy group (compliance to colonoscopy and their CRCs were diagnosed at the time of screening) (Figure 5). Between the two groups, minimal difference was noted in cases without CRC whereas the difference widened in cases with CRC. As there was a time lag in cancer diagnosis between the two groups, this finding was in line with the delay in diagnosis of CRC in noncolonoscopy patients.

Discussion

This is the first study to quantify the magnitude of benefit attributed to colonoscopy in FIT-positive patients. The results indicate colonoscopy is associated with a statistically significant reduction in mortality rates for CRC through the detection of early-stage cancers. For those subjects who do not accept colonoscopy, their f-Hb levels may serve as a guide for priority setting in prompting them to undergo colonoscopy.

The benefit of colonoscopy screening in reducing the number of deaths from CRC remains unclear (36–38). Based on four studies, colonoscopy was associated with mortality reductions from CRC ranging from 37% to 88% (8,17,39–41). One study showed that complete colonoscopy was associated with 37% reduced mortality from distal CRC but found no reduction in deaths from proximal CRC (17). Another study showed the reduction in mortality rate was statistically significant for both distal (82%) and proximal (53%) CRCs (8). Based on the US Veterans Affairs system, colonoscopy was associated with a statistically significant 56% reduction in CRC death (42).
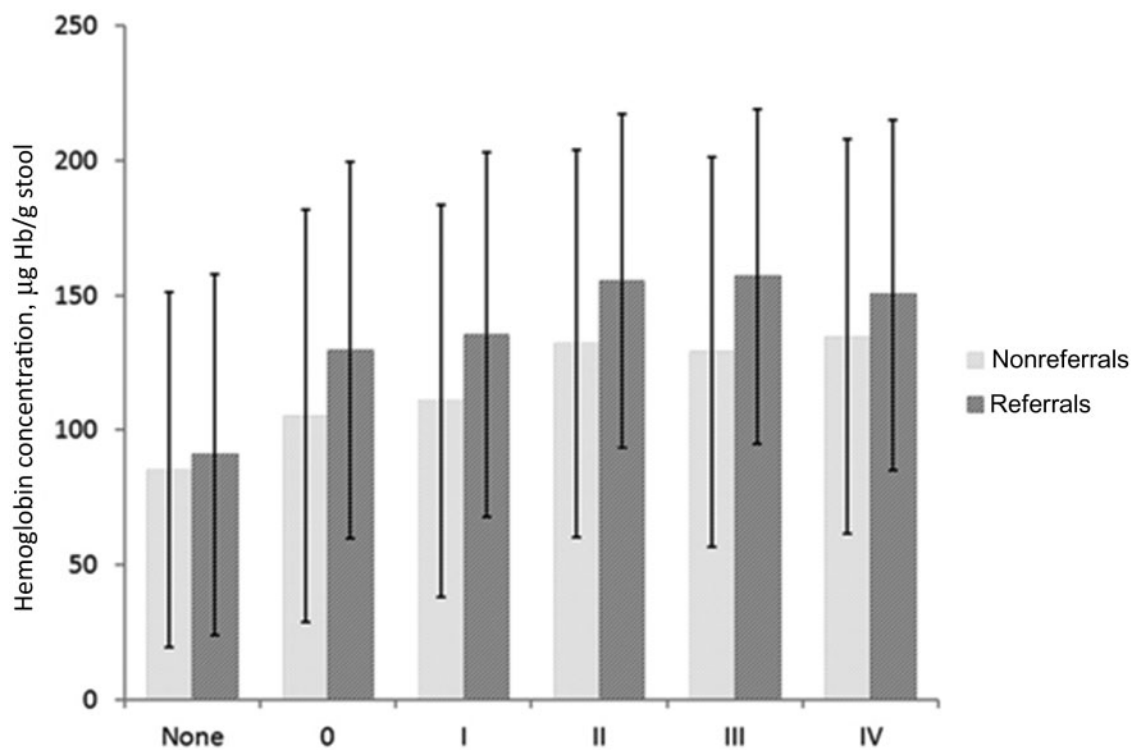
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Figure 5. Concentrations of f-Hb and standard deviation stratified by the stages of colorectal cancer (CRC). In referrals, the f-Hb denotes the quantitative measure at the time of screening for screen-detected colorectal cancer. In nonreferrals, the f-Hb indicates the quantitative measure at the time of screening associated with the staging of CRC when subjects did not comply with initial colonoscopy and their CRCs eventually developed clinical symptoms to raise medical attention. The **error bars** represent the standard deviation of the f-Hb concentration.

In our study, the 1.64-fold increased risk of CRC death in the noncompliers could be interpreted as about 40% (1–1/1.64) mortality reduction of CRC if the subjects received colonoscopy, and for those who received complete colonoscopy the magnitude could reach about 60% (1–1/2.39). Only when colonoscopy was complete could statistically significant mortality reduction be seen for both distal (1–1/2.63, 62%) and proximal CRC (1–1/1.82, 45%).

The risk level and staging of CRCs for those with positive fecal test results are different from those of the average-risk population. Under such circumstances, detection of CRC through screening does not guarantee a better survival because the earliest detectable time (ie, the lead-time) may vary with different stool-based screening methods. It is expected that if the same analysis used for positive FITs were applied to positive guaiac-based tests, the efficacy of colonoscopy in reducing mortality rates among the referral group would be smaller because the lower sensitivity of guaiac-based tests may lead to smaller gains in lead time. This is supported by four randomized controlled trials that have shown an overall efficacy of approximately 14% in reducing mortality from CRCs based on guaiac-based tests (2,43–46). This may be smaller than that using FIT, albeit the effect of FIT has not been confirmed in randomized controlled trials; nevertheless, the larger benefit has been corroborated by recent cohort studies (4,5).

In patients with a positive FIT, the main target of colonoscopy is early-stage CRC, for which there is a sensitivity of approximately 79% (10), rather than colonic adenoma, for which the sensitivity is only about 20% (47). In the latter, primary colonoscopy trials may require decades of follow-up to show a reduction in incidence and mortality of CRC (36–38). A follow-up period of approximately six years in our study was sufficient to quantify the benefit of colonoscopy on mortality, and this was attributed to the early detection of CRC. The benefit regarding the detection and removal of colon adenoma on reduction of CRC incidence required a longer observation time.

We found that only complete colonoscopy was associated with a statistically significant reduction in the mortality rate for cancers in the proximal colon. Furthermore, we found that, as for proximal CRC, complete colonoscopy was associated with a modest, statistically nonsignificant increase in benefit of reducing mortality from cancers of the distal colon. This may be related to the better detectability of complete colonoscopy (Supplementary Table 4, available online).

Strengths of the present study include the large sample size and long follow-up time. Studying high-risk patients allowed us to gather outcomes in a shorter period of time and allow our results to be tested in other countries where mass screening is in place. The phenomenon of colonoscopy noncompletion prompted us to emphasize the usefulness of f-Hb on risk stratification (23–26).

Our study has some limitations. First, random assignment to groups was not possible, and residual confounding from unmeasured factors cannot be excluded. The risk prediction according to gradient f-Hb should be validated with updated data. Second, reasons for colonoscopy noncompliance were not thoroughly addressed; it would be more appropriate to focus on the attitudes and health beliefs of individuals. Third, our study used data from the inaugural period, so the quality of colonoscopy may not have met the highest standards such as occurrence of interval cancers. The cumulative CRC incidence of the referral group increased rapidly within the first year (due to colonoscopy

referral and early detection) and after the first year a slowly increasing trend was seen (due to postcolonoscopy interval cancer) (48). However, taking this opportunity, our study supports the use of self-reported cecal intubation as a definite indicator. Finally, a FIT-based program is aimed at detecting an early "bleeding phenotype" of CRC, different from that detected in primary colonoscopy-based screening (37–39). Our results on the efficacy of colonoscopy for subjects with positive FIT cannot replace those from the ongoing randomized controlled trials.

In conclusion, our study provides compelling evidence that FIT-positive patients have a high risk of CRC and shows there is an approximately 50% statistically significant reduction in mortality among those who undergo follow-up colonoscopy. The study also documents the value of f-Hb as a priority-setting indicator for colonoscopy. Both findings may help physicians encourage subjects with poor adherence to undergo follow-up colonoscopy.

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Author contributions

Yi-Chia Lee and Hsiu-Hsi Chen have full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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