Performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract

Tsung-Hsien Chiang MD MSc, Yi-Chia Lee MD PhD, Chia-Hung Tu MD MSc, Han-Mo Chiu MD PhD, Ming-Shiang Wu MD PhD

ABSTRACT

Background: Previous studies have suggested that the immunochemical fecal occult blood test has superior specificity for detecting bleeding in the lower gastrointestinal tract even if bleeding occurs in the upper tract. We conducted a large population-based study involving asymptomatic adults in Taiwan, a population with prevalent upper gastro-intestinal lesions, to confirm this claim.

Methods: We conducted a prospective cohort study involving asymptomatic people aged 18 years or more in Taiwan recruited to undergo an immunochemical fecal occult blood test, colonoscopy and esophagogastroduodenos-copy between August 2007 and July 2009. We compared the prevalence of lesions in the lower and upper gastrointestinal tracts between patients with positive and negative fecal test results. We also identified risk factors associated with a false-positive fecal test result.

Results: Of the 2796 participants, 397 (14.2%) had a positive fecal test result. The sensitivity of the test for predicting lesions in the lower gastrointestinal tract was 24.3%, the specificity 89.0%, the positive predictive value 41.3%, the

negative predictive value 78.7%, the positive likelihood ratio 2.22, the negative likelihood ratio 0.85 and the accuracy 73.4%. The preva-lence of lesions in the lower gastrointestinal tract was higher among those with a positive fecal test result than among those with a nega-tive result (41.3% v. 21.3%, $p < 0.001$). The prevalence of lesions in the upper gastrointesti-nal tract did not differ significantly between the two groups (20.7% v. 17.5%, $p = 0.12$). Almost all of the participants found to have colon can-cer (27/28, 96.4%) had a positive fecal test result; in contrast, none of the three found to have esophageal or gastric cancer had a positive fecal test result ($p < 0.001$). Among those with a negative finding on colonoscopy, the risk factors associated with a false-positive fecal test result were use of antiplatelet drugs (adjusted odds ratio [OR] 2.46, 95% confidence interval [CI] 1.21–4.98) and a low hemoglobin concentration (adjusted OR 2.65, 95% CI 1.62–4.33).

Interpretation: The immunochemical fecal occult blood test was specific for predicting lesions in the lower gastrointestinal tract. However, the test did not adequately predict lesions in the upper gastrointestinal tract.

The fecal occult blood test is a convenient tool to screen for asymptomatic gastro - intestinal bleeding.[1] When the test result is positive, colonoscopy is the strategy of choice to investigate the source of bleeding.[2,3] However, 13%–42% of patients can have a positive test result but a negative colonoscopy,[4] and it has not yet been determined whether asymptomatic patients should then undergo evaluation of the upper gastrointestinal tract.

Previous studies showed that the frequency of lesions in the upper gastrointestinal tract was comparable or even higher than that of colonic lesions[5–9] and that the use of esophagogastroduo-denoscopy may change clinical management.[10,11] Some studies showed that evaluation of the upper gastrointestinal tract helped to identify important lesions in symptomatic patients and those with

iron deficiency anemia;[12,13] however, others con-cluded that esophagogastroduodenoscopy was unjustified because important findings in the upper gastrointestinal tract were rare[14–17] and sometimes irrelevant to the results of fecal occult blood testing.[18–21] This controversy is related to the heterogeneity of study populations and to the limitations of the formerly used guaiac-based fecal occult blood test,[5–20] which was not able to distinguish bleeding in the lower gastrointestinal tract from that originating in the upper tract.

The guaiac-based fecal occult blood test is in-creasingly being replaced by the immunochemi-cal-based test. The latter is recommended for detecting bleeding in the lower gastrointestinal tract because it reacts with human globin, a protein that is digested by enzymes in the upper gastro-intestinal tract.[22] With this advantage, the occur-

rence of a positive fecal test result and a negative finding on colonoscopy is expected to decrease.

We conducted a population-based study in Taiwan to verify the performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract and to confirm that results are not confounded by the presence of lesions in the upper tract. In Taiwan, the incidence of colorectal cancer is rapidly increasing, and *Helicobacter pylori*-related lesions in the upper gastrointestinal tract remain highly prevalent.[23] Same-day bidirectional endoscopies are therefore commonly used for cancer screening.[24] This screening strategy provides an opportunity to evaluate the performance of the immunochemical fecal occult blood test.

Methods

Study design

For this prospective cohort study, we enrolled consecutive patients aged 18 years or more who voluntarily underwent bidirectional endoscopies as part of a self-paid medical check-up at the Far Eastern Memorial Hospital in Taiwan between August 2007 and July 2009. They were recruited through advertisements for health promotion purposes. Before the examination, a self-administered questionnaire was used to collect information on the participants' demographic characteristics, social habits, clinical symptoms, and medical and medication histories. The examination protocol included an immunochemical fecal occult blood test, a face-to-face interview, blood chemistry tests, colonoscopy and esophagogastroduodenoscopy.

To ensure that the study population was asymptomatic and that bleeding was occult, we excluded people who had overt gastrointestinal symptoms (e.g., dysphagia or abdominal pain that normally would require an immediate medical evaluation) and overt gastrointestinal bleeding (e.g., hematemesis, tarry stool, melena and hematochezia). We also excluded people who reported a history of malignant disease, polyps in the colon, inflammatory bowel disease or bowel surgery.

The hospital ethics committee approved the study protocol (no. 97024), and people who met the inclusion criteria provided informed consent.

Fecal occult blood test

A one-step commercial immunochemical fecal occult blood test kit with a brush-type sampler (OC-Light, Eiken Chemical Co. Ltd., Tokyo, Japan) was given to all participants. The test has a positive cutoff level of 50 ng/mL. Participants were asked to collect stool samples within two days before the bowel preparation started for the screening endoscopies. They brought the stool samples to the hospital on the screening day; within 24 hours the samples were sent to the laboratory, where they were tested immediately.

Endoscopic examinations

Participants were given sodium phosphate (Fleet; C.B. Fleet Company Inc., Lynchburg, Virginia, USA) for bowel preparation, which they took at least four hours before the endoscopic examinations. The endoscopies were performed with the use of a standard colonoscope (CF-H260AZI; Olympus, Tokyo, Japan) and esophagogastroduodenoscope (GIF-H260Z; Olympus) by two of us (T.-H.C. and C.-H.T.), who were experienced endoscopists who had each performed at least 3000 colonoscopies. The two endoscopists were blinded to the results of the fecal tests.

Endoscopic findings were recorded on a standardized reporting form. They included information on the quality of bowel preparation; completeness of the colonoscopy; number, size and localization of lesions; and whether a biopsy was performed. Participants with an incomplete colonoscopy or poor bowel preparation were excluded from analyses.

Lesions that were identified as important were confirmed clinically. We defined important lesions in the lower gastrointestinal tract as colorectal cancer, colonic adenoma, carcinoid, colitis or ulcer, angiodysplasia and submucosal tumour. Hyperplastic polyps and hemorrhoids were not included in the definition. Important lesions in the upper gastrointestinal tract included cancer, esophageal varix, ulcer of at least 0.5 cm in diameter with a perceptible depth, angiodysplasia, submucosal tumour, and reflux esophagitis with a severity of at least Los Angeles class C or D.[25]

Statistical analysis

For descriptive findings, we present quantitative data as means and standard deviations, and categorical variables as percentages. Differences in demographic characteristics between participants with positive and negative fecal test results were determined using the Student t test or the χ^2 test.

To determine the performance of the immunochemical fecal occult blood test, we used the test results and the colonoscopic findings to construct a 2×2 table and calculated the sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, accuracy and corresponding 95% confidence intervals (CIs). Because the immunochemical fecal test is specific for detecting bleeding in the lower gastrointestinal tract, we hypothesized that its specificity for predicting lesions in the colon would be high.

We set a minimally acceptable level of speci-

ficity at 85%, a level achieved by the guaiac-based test (Hemoccult SENSA, Beckman Coulter Inc., USA) in our institution. Assuming that the specificity of an immunochemical-based test should reach at least 90%, we determined that a sample size of 750 participants with a negative finding on colonoscopy would be required to detect this difference at α = 0.05, β = 0.1 and a single-tail hypothesis. Knowing that the prevalence of colon lesions in our population is about 20%,[28] we determined that an overall sample size of 940 participants would suffice.

We then compared the prevalence rates of lesions in the lower and upper gastrointestinal tracts between participants with positive and negative fecal test results. To test our theory that the fecal test result is not confounded by the presence of a lesion in the upper gastrointestinal tract, we hypothesized that the prevalence of lesions in the colon would be higher among participants with a positive fecal test result than among those with a negative test result. In contrast, we hypothesized that the prevalence of lesions in the upper gastrointestinal tract would
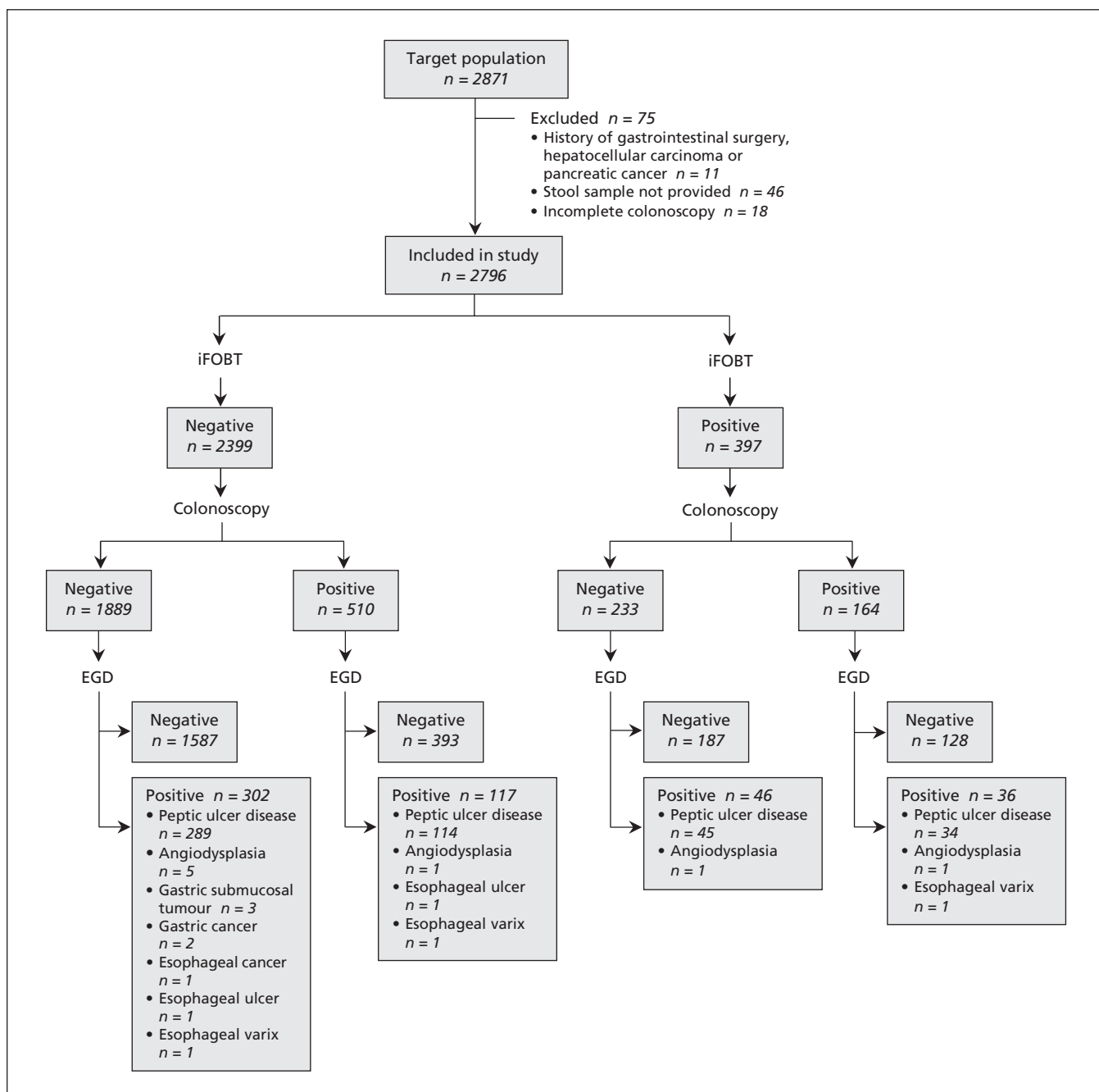

Figure 1: Study flow of asymptomatic participants undergoing immunochemical fecal occult blood test (iFOBT), colonoscopy and esophagogastroduodenoscopy (EGD).

be similar among those with positive and negative fecal test results. We assessed statistical differences using the χ^2 test.

We evaluated the association between a positive fecal test result and a positive finding on colonoscopy using multivariable logistic regression analysis and controlling for the presence of lesions in the upper gastrointestinal tract. Results were expressed as adjusted odds ratios (ORs) and 95% CIs. Because malignant disease commonly causes occult gastrointestinal bleeding, we compared rates of fecal test positivity between participants with colon cancer and those with esophageal or gastric cancer, expecting the former to be higher.

Finally, we identified risk factors associated with a positive fecal test result and a negative finding on colonoscopy using the backward elimination method in a multivariable logistic regression model. Odds ratios greater than 1.0 indicated an increased risk of a false-positive fecal test result. A two-tailed p value of less than 0.05 indicated statistical significance.

Results

Participant characteristics

Of the 2871 consecutive people who volunteered to undergo the screening endoscopies during the study period, we excluded 75 because they had a history of gastrointestinal surgery ($n = 8$), hepatocellular carcinoma ($n = 2$) or pancreatic cancer ($n = 1$), they did not provide a stool sample ($n = 46$), or they had an incomplete colonoscopy ($n = 18$) (Figure 1). The remaining 2796 participants (1654 men and 1142 women) were included in the study. The mean age was 49.0 (standard deviation 11.2) years. Overall, 397 (14.2%) of the participants had a positive result of the

immunochemical fecal occult blood test. The characteristics of the participants did not differ significantly between those with a positive fecal test result and those with a negative result except that a higher proportion of those with a positive result used antiplatelet drugs (Table 1).

Table 1: Demographic characteristics of 2796 study participants, by result of immunochemical fecal occult blood test

Characteristic	Fecal test result		Total n = 2796
	Positive n = 397	Negative n = 2399	
Age, yr			
Mean (SD)	50.5 (12.5)	48.7 (10.9)	49.0 (11.2)
Range	19–84	20–84	19–84
Male sex, no. (%)	244 (61.5)	1410 (58.8)	1654 (59.2)
Body mass index, kg/m²			
Mean (SD)	24.4 (3.6)	24.0 (3.4)	24.1 (3.4)
Range	16.5–39.0	13.9–41.4	13.9–41.4
Chronic comorbid disease,* no. (%)	101/364 (27.8)	461/1955 (23.6)	562/2319 (24.2)
Current smoker, no. (%)	95/364 (26.1)	431/1956 (22.0)	526/2320 (22.7)
Alcohol use, no. (%)	104/364 (28.6)	595/1956 (30.4)	699/2320 (30.1)
Use of antiplatelet drugs,† no. (%)	29/364 (8.0)	72/1954 (3.7)	101/2318 (4.4)
Hemoglobin, g/L			
Mean (SD)	145 (18)	147 (16)	146 (16)
Range	83–189	85–193	83–193
Platelet count, × 10⁹/L			
Mean (SD)	254.6 (67.2)	248.1 (58.6)	249.0 (60.0)
Range	109–570	76–695	76–695

Note: SD = standard deviation.
*Includes diabetes mellitus, hypertension and cardiovascular disease.
†Regular use of low-dose acetylsalicylic acid ($n = 77$), clopidogrel ($n = 13$), low-dose acetylsalicylic acid and clopidogrel ($n = 3$) or non-steroidal anti-inflammatory drug ($n = 8$).

Table 2: Performance of immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract among the 2796 participants

Outcome	Performance measure (95% CI)						
	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Positive likelihood ratio	Negative likelihood ratio	Accuracy, %
Colorectal cancer	96.4 (95.1–97.7)	86.6 (85.3–87.9)	6.8 (4.3–9.3)	99.9 (99.8–100)	7.21 (6.41–8.12)	0.04 (0.01–0.28)	86.7 (85.3–88.1)
Adenoma	21.4 (18.1–24.7)	88.9 (87.6–90.2)	34.9 (26.7–43.1)	80.3 (78.7–81.9)	1.93 (1.59–2.34)	0.88 (0.85–0.92)	74.2 (72.6–75.8)
Colorectal cancer or adenoma	24.8 (21.4–28.2)	88.9 (87.6–90.2)	39.2 (34.4–44.0)	80.2 (78.6–81.8)	2.23 (1.86–2.67)	0.85 (0.81–0.89)	74.4 (72.8–76.0)
Any important lesion	24.3 (21.1–27.5)	89.0 (87.7–90.3)	41.3 (36.5–46.1)	78.7 (77.1–80.3)	2.22 (1.85–2.65)	0.85 (0.81–0.89)	73.4 (71.8–75.0)

Note: CI = confidence interval.

Specificity of fecal test

Lesions were more prevalent in the lower gastrointestinal tract (24.1%) than in the upper tract (17.9%); colon cancer was more prevalent than upper gastrointestinal cancers. Performance of the immunochemical fecal occult blood test in predicting lesions in the lower gastrointestinal tract is shown in Table 2. The test's specificity was almost 90% for colorectal cancer, adenoma or any important lesion. The sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and accuracy of the fecal test were all significant for lesions in the lower gastrointestinal tract.

Prevalence of gastrointestinal lesions by positivity of fecal test

Endoscopic findings are summarized in Table 3. Lesions in the lower gastrointestinal tract were more frequent among participants with a positive immunochemical fecal test result than among those with a negative result (41.3% v. 21.3%, $p < 0.001$). The frequency of lesions in the upper gastrointestinal tract was similar in both groups (20.7% and 17.5%, $p = 0.12$). Of the 397 participants with a positive fecal test result, 233 (58.7%) had a negative finding on colonoscopy; of these, 46 (19.7%) had an important lesion in the upper gastrointestinal tract, which was most often a peptic ulcer (97.8%).

The presence of a lesion in the lower gastrointestinal tract was significantly associated with positivity of the fecal test (adjusted OR 2.59, 95% CI 2.07–3.23). The presence of a lesion in the upper tract was not associated with the test's positivity (adjusted OR 1.14, 95% CI 0.87–1.49).

Among participants found to have a malignant lesion, almost all who had colon cancer had a positive fecal test result (27/28, 96.4%). In contrast, none of the three participants found to have esophageal or gastric cancer had a positive fecal test result ($p < 0.001$).

Risk factors associated with a false-positive fecal test result

Use of antiplatelet drugs and having a low hemoglobin concentration were the only factors associated with a positive result of the immunochemical fecal occult blood test among participants with a negative finding on colonoscopy (Figure 2). These risk factors remained significant after adjustment for confounding variables (adjusted OR 2.46, 95% CI 1.21–4.98 for use of antiplatelet drugs; 2.65, 95% CI 1.62–4.33, for low hemoglobin concentration).

Interpretation

We found that the specificity of the immunochemical fecal occult blood test was almost 90% for predicting colorectal cancer, adenoma or any important lesion in the lower gastrointestinal tract. These findings support those of previous studies showing that the immunochemical fecal test is a specific diagnostic tool.[26–34] Also, the test's sensitivity was 25% for neoplasms in the colon and 96% for colorectal cancer, findings that are consistent with most results of previous studies evaluating the immunochemical fecal test in either Eastern or Western populations (see Appendix 1 at www.cmaj.ca/lookup/suppl/doi :10.1503/cmaj.101248/-/DC1).

Previous studies invited asymptomatic participants with a negative result of the immunochemical fecal occult blood test to undergo

Table 3: Endoscopic findings among the 2796 participants, by result of immunochemical fecal occult blood test

Finding	Fecal test result; no. (%) of participants	
	Positive n = 397	Negative n = 2399
Lower gastrointestinal tract		
Lesion	164 (41.3)	510 (21.3)
Advanced colon cancer	10 (2.5)	0
Early colon cancer	17 (4.3)	1 (0.0)
Tubular adenoma	116 (29.2)	458 (19.1)
Tubulovillous adenoma	9 (2.2)	13 (0.6)
Villous adenoma	4 (1)	2 (0.1)
Carcinoid	0	1 (0.0)
Colitis or ulcer	6 (1.5)	19 (0.8)
Angiodysplasia	1 (0.3)	13 (0.6)
Submucosal tumour	0	3 (0.1)
Peutz–Jegher syndrome	1 (0.3)	0
No lesion	233 (58.7)	1889 (78.7)
Upper gastrointestinal tract		
Lesion	82 (20.7)	419 (17.4)
Advanced esophageal cancer	0	1 (0.0)
Advanced gastric cancer	0	1 (0.0)
Early gastric cancer	0	1 (0.0)
Esophageal varix	1 (0.3)	2 (0.1)
Esophageal ulcer	0	2 (0.1)
Gastric ulcer	57 (14.4)	293 (12.2)
Duodenal ulcer	11 (2.8)	70 (2.9)
Gastric or duodenal ulcer	11 (2.8)	40 (1.7)
Angiodysplasia	2 (0.5)	6 (0.3)
Gastric submucosal tumour	0	3 (0.1)
No lesion	315 (79.3)	1980 (82.6)

colonoscopy to validate the test results.[26–30] We took the additional step of adding esophagogastroduodenoscopy to clarify the effect of lesions in the upper gastrointestinal tract on the fecal test results. In our study, the prevalence of lesions in the upper tract was consistently about 20% whether among participants with a positive immunochemical fecal test result, a negative fecal test result, or a positive fecal test result and a negative finding on colonoscopy. In addition, the rate of positivity of the fecal test was substantially higher among participants with colon cancer than among those with malignant lesions in the upper gastrointestinal tract. Furthermore, regression analyses showed a lack of association between positivity of the fecal test and the presence of a lesion in the upper gastrointestinal tract. These findings indicate that the immunochemical fecal occult blood test cannot predict the presence of lesions in the upper gastrointestinal tract.

Among participants with a negative finding on colonoscopy, risk factors associated with a false-positive result of the immunochemical fecal occult blood test has rarely been addressed. Bleeding from hemorrhoids is one of the commonly speculated causes of a false-

positive result. However, in our study, the prevalence of hemorrhoids was similar among those with a positive fecal test result (61/397, 15.4%) and those with a negative test result (318/2399, 13.3%). In addition, the regression analyses showed a lack of association between positivity of the immunochemical fecal test and the presence of hemorrhoids among participants with a negative finding on colonoscopy. These findings indicate that hemorrhoids should not be used to explain a positive immunochemical fecal test result or hamper the indication for colonoscopy.

Recently, the effect of antiplatelet drugs on the performance of the immunochemical fecal occult blood test has attracted attention, because studies conducted in Western populations have shown that such use may increase the sensitivity of the test in detecting neoplasms in the colon with no or minimal change in specificity.[29,30,35] However, in our study, although a low proportion of participants used antiplatelet drugs, their false-positive test rate did increase, such that the sensitivity was increased (32.3% v. 24.3% for the whole study population), but the specificity was reduced (72.9% v. 89.0%) (see Appendix 1).
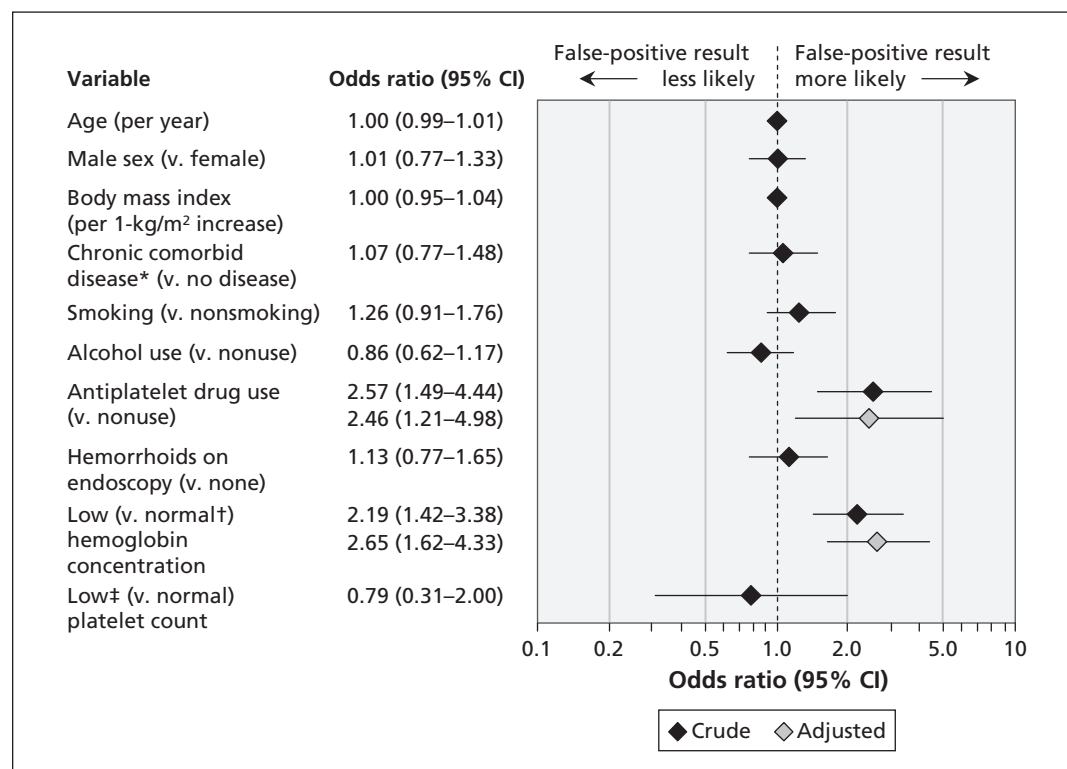

Figure 2: Risk factors associated with 233 false-positive results of the immunochemical fecal occult blood test among 2122 participants with a negative finding on colonoscopy. The multivariable model adjusted for all variables shown in the forest plot. An odds ratio greater than 1.0 indicates an increased risk of a false-positive result. CI = confidence interval. *Includes diabetes mellitus, hypertension and cardiovascular disease. †Normal hemoglobin concentration: < 120 g/L in women and < 130 g/L in men. ‡Low platelet count: < 150 × 10⁹/L.

Limitations

Our study has limitations. First, although we identified antiplatelet use and low hemoglobin concentration as risk factors associated with a false-positive immunochemical fecal test result, the performance of our multiple logistic regression model remains limited in accurately predicting the possibility of such a false-positive result. Also, low hemoglobin concentration appears to be a result rather than a cause. Therefore, it is worthwhile to investigate whether the participants, especially those who were using antiplatelet drugs, had other sources of bleeding, such as small-bowel lesions.

Second, the immunochemical fecal occult blood test does not adequately predict lesions in the upper gastrointestinal tract. Such lesions were present in 20% of the participants in our study who had a false-positive fecal test result and in 6% to 42% of participants in previous studies (see Appendix 2, at www.cmaj.ca/lookup /suppl/doi:10.1503/cmaj.101248/-/DC1). A pan-detecting assay based on stool samples is a recent development that offers an intriguing research opportunity for simultaneous multiple cancer screenings.[36] A combination of immunochemical fecal occult blood test and a stool antigen test for *H. pylori*[37] is an approach that may help to realize this goal in a population in which lesions in both the lower and upper gastrointestinal tracts are equally prevalent.[38,39] This topic warrants further investigation.

Conclusion

Our findings confirm that the immunochemical fecal occult blood test is specific for predicting lesions in the lower gastrointestinal tract but it does not adequately predict lesions in the upper tract. Among participants who had a negative colonoscopy, a false-positive result of the immunochemical fecal test was associated with the use of antiplatelet drugs and a low hemoglobin concentration.

References

1. American Gastroenterological Association medical position statement: evaluation and management of occult and obscure gastrointestinal bleeding. *Gastroenterology* 2000;118:197-201.
2. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997;112:594-642.
3. Davila RE, Rajan E, Baron TH, et al.; Standards of Practice Committee, American Society for Gastrointestinal Endoscopy. ASGE guideline: colorectal cancer screening and surveillance. *Gastrointest Endosc* 2006;63:546-57.
4. Bini EJ. Use of upper endoscopy to evaluate patients with a positive fecal occult blood test and negative colonoscopy: Is it appropriate? *Dig Liver Dis* 2006;38:507-10.
5. Geller AJ, Kolts BE, Achem SR, et al. The high frequency of upper gastrointestinal pathology in patients with fecal occult blood and colon polyps. *Am J Gastroenterol* 1993;88:1184-7.
6. Alemayehu G, Järnerot G. Same-day upper and lower endoscopy in patients with occult bleeding, melena, hematochezia, and/or microcytic anemia. A retrospective study of 224 patients. *Scand J Gastroenterol* 1993;28:667-72.
7. Rockey DC, Koch J, Cello JP, et al. Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood tests. *N Engl J Med* 1998;339:153-9.
8. Bini EJ, Rajapaksa RC, Valdes MT, et al. Is upper gastrointestinal endoscopy indicated in asymptomatic patients with a positive fecal occult blood test and negative colonoscopy? *Am J Med* 1999;106:613-8.
9. Velez JP, Schwesinger WH, Stauffer J, et al. Bidirectional endoscopy in patients with fecal occult blood. *Surg Endosc* 2002;16:117-20.
10. Zuckerman G, Benitez J. A prospective study of bidirectional endoscopy (colonoscopy and upper endoscopy) in the evaluation of patients with occult gastrointestinal bleeding. *Am J Gastroenterol* 1992;87:62-6.
11. Hsia PC, Al-Kawas FH. Yield of upper endoscopy in the evaluation of asymptomatic patients with Hemoccult-positive stool after a negative colonoscopy. *Am J Gastroenterol* 1992;87:1571-4.
12. Thomas WM, Hardcastle JD. Role of upper gastrointestinal investigation in a screening study for colorectal neoplasia. *Gut* 1990;31:1294-7.
13. Urquhart J, Eisen G, Faigel DO, et al. A closer look at same-day bidirectional endoscopy. *Gastrointest Endosc* 2009;69:271-7.
14. Chen YK, Gladden DR, Kestenbaum DJ, et al. Is there a role for upper gastrointestinal endoscopy in the evaluation of patients with occult blood-positive stool and negative colonoscopy? *Am J Gastroenterol* 1993;88:2026-9.
15. Rasmussen M, Kronborg O. Upper gastrointestinal cancer in a population-based screening program with fecal occult blood test for colorectal cancer. *Scand J Gastroenterol* 2002;37:95-8.
16. Ali M, Yaqub M, Haider Z, et al. Yield of dual endoscopy for positive fecal occult blood test. *Am J Gastroenterol* 2003;98:82-5.
17. Zappa M, Visioli CB, Ciatto S, et al. Gastric cancer after positive screening fecal occult blood testing and negative assessment. *Dig Liver Dis* 2007;39:321-6.
18. Bini EJ, Rajapaksa RC, Weinshel EH. Positive predictive value of fecal occult blood testing in persons taking warfarin. *Am J Gastroenterol* 2005;100:1586-92.
19. Stray N, Weberg R. A prospective study of same day bi-directional endoscopy in the evaluation of patients with occult gastrointestinal bleeding. *Scand J Gastroenterol* 2006;41:844-50.
20. Hisamuddin K, Mowat NA, Phull PS. Endoscopic findings in the upper gastrointestinal tract of faecal occult blood-positive, colonoscopy-negative patients. *Dig Liver Dis* 2006;38:503-7.
21. Levi Z, Vilkin A, Niv Y. Esophago-gastro-duodenoscopy is not indicated in patients with positive immunochemical test and non-explanatory colonoscopy. *Eur J Gastroenterol Hepatol* 2010;22: 1431-4.
22. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130-60.
23. *Cancer Registry annual report, 2008.* Taiwan: Bureau of Health Promotion, Department of Health, the Executive Yuan; 2010.
24. Chiu HM, Lin JT, Shun CT, et al. Association of metabolic syndrome with proximal and synchronous colorectal neoplasm. *Clin Gastroenterol Hepatol* 2007;5:221-9.
25. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172-80.
26. Morikawa T, Kato J, Yamaji Y, et al. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology* 2005;129:422-8.
27. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst* 2007;99:1462-70.
28. Chiu HM, Lin JT, Chen CC, et al. Prevalence and characteristics of nonpolypoid colorectal neoplasm in an asymptomatic and average-risk Chinese population. *Clin Gastroenterol Hepatol* 2009;7:463-70.
29. Levi Z, Rozen P, Hazazi R, et al. Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. *Am J Gastroenterol* 2009;104:933-8.
30. Brenner H, Tao S, Haug U. Low-dose aspirin use and performance of immunochemical fecal occult blood tests. *JAMA* 2010;304:2513-20.
31. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008;135:82-90.

32. Wong BC, Wong WM, Cheung KL, et al. A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. *Aliment Pharmacol Ther* 2003;18:941-6.
33. Wong WM, Lam SK, Cheung KL, et al. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. *Cancer* 2003;97:2420-4.
34. Chen LS, Liao CS, Chang SH, et al. Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16). *J Med Screen* 2007;14:191-9.
35. Mandelli G, Radaelli F, Paggi S, et al. Anticoagulant or aspirin treatment does not affect the positive predictive value of an immunological fecal occult blood test in patients undergoing colorectal cancer screening: results from a nested in a cohort case–control study. *Eur J Gastroenterol Hepatol* 2011;23:323-6.
36. Ahlquist DA. Next-generation stool DNA testing: expanding the scope. *Gastroenterology* 2009;136:2068-73.
37. Shimoyama T, Oyama T, Matsuzaka M, et al. Comparison of a stool antigen test and serology for the diagnosis of *Helicobacter pylori* infection in mass survey. *Helicobacter* 2009;14:87-90.
38. Sung JJ, Lau JY, Goh KL, et al.; Asia Pacific Working Group on Colorectal Cancer. Increasing incidence of colorectal cancer in Asia: implications for screening. *Lancet Oncol* 2005;6:871-6.
39. Leung WK, Wu MS, Kakugawa Y, et al.; Asia Pacific Working Group on Gastric Cancer. Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol* 2008;9:279-87.

Affiliations: From the Departments of Internal Medicine (Chiang, Lee, Tu, Chiu, Wu) and Primary Care Medicine (Wu), and the Graduate Institute of Clinical Medicine (Chiang, Wu), College of Medicine, National Taiwan University, Taipei, Taiwan; the Department of Internal Medicine (Chiang), Far Eastern Memorial Hospital, Taipei, Taiwan; and the Division of Biostatistics (Lee, Tu) and the Institute of Preventive Medicine (Chiu), College of Public Health, National Taiwan University, Taipei, Taiwan