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New immunochemical fecal occult blood test with two-consecutive stool sample testing is a cost-effective approach for colon cancer screening: Results of a prospective multicenter study in Chinese patients

Shirong Li[1]*, Huahong Wang[2], Jichun Hu[3], Nan Li[4], Yulan Liu[5], Zitao Wu[1], Yue Zheng[2], Honghua Wang[3], Kai Wu[4], Hui Ye[5] and Jianyu Rao[6,7]†

[1]*Department of Gastroenterology, Beijing Army General Hospital, Beijing, People's Republic of China*
[2]*Department of Gastroenterology, First Hospital of Beijing University, Beijing, People's Republic of China*
[3]*Department of Gastroenterology, Beijing Haidian Hospital, Beijing, People's Republic of China*
[4]*Department of Gastroenterology, 309 Hospital of People's Liberation Army, Beijing, People's Republic of China*
[5]*Department of Gastroenterology, Second Hospital of Beijing University, Beijing, People's Republic of China*
[6]*Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA*
[7]*Department of Epidemiology, School of Public Health, University of California at Los Angeles, Los Angeles, CA, USA*

The purpose of the study is to evaluate a new immunochemical fecal occult blood test method (Hemosure IFOBT), and compare it to the Guaiac-based chemical method (CFOBT) for colorectal cancer detection. A hypothetical sequential method (SFOBT), in which IFOBT was used only as a confirmatory test for CFOBT, was also evaluated. A total of 324 patients were recruited from 5 major hospitals in Beijing, China. For each patient, 3 consecutive stool samples were collected for simultaneous CFOBT and IFOBT tests, followed by colonoscopic examination. We compared the sensitivity and specificity of the 3 methods (CFOBT, IFOBT and SFOBT) in two settings, with the first 2 consecutive samples versus all 3 samples. Although the sensitivity for the detection of cancer and large (>20 mm) or multiple adenoma was similar for all 3 methods in the three-sample setting, in the two-sample setting IFOBT had higher sensitivity than SFOBT for detecting cancer (87.8% *vs.* 75.5%, respectively, $p < 0.05$) and large (>20 mm) or multiple adenomas (65.4% *vs.* 42.3%, respectively, $p < 0.05$). The IFOBT also had a higher specificity than the CFOBT (89.2% *vs.* 75.5%, respectively, $p < 0.01$) in ''normal'' individuals defined by colonoscopy in the three-sample setting. Comparing two-sample setting to the three-sample setting, both CFOBT and SFOBT showed significant loss of sensitivity for the detection of cancer as well as adenoma, whereas the sensitivity for IFOBT did not change significantly. Overall, IFOBT with two-sample testing showed compatible sensitivity and specificity to the three-sample testing, and had a lower relative cost per cancer detected than the three-sample testing. In conclusion, the new Hemosure IFOBT with two consecutive stool samples appears to be the most cost-effective approach for colon cancer screening.

Key words: colon cancer; fecal occult blood test; screening

In recent years, the incidence of colorectal cancer has increased rapidly in China, especially in major metropolitan areas such as Beijing and Shanghai.[1] The exact reason for this is unclear. The problem of colorectal cancer (CRC) in China is further compounded by the fact that more than half of patients with CRC are diagnosed at the advanced stage, which may be at least partly due to the lack of implementing screening measures.[2,3] Based on the data from randomized, controlled trials from developed countries, population-based screening of CRC may increase the detection rate of early cancer, and thus increasing the long-term survival rate of patients.[4–7]

In the United States, the Fecal Occult Blood Test (FOBT) is one of the most commonly recommended CRC screening methods by the National Cancer Institute, National Institute of Health and the American Cancer Society.[8] Currently, there are 2 major types of FOBT tests: Chemical Fecal Occult Blood Test (CFOBT) and Immunochemical Fecal Occult Blood Test (IFOBT). The CFOBT method is relatively inexpensive, but generates a higher false-positive rate and often requires a restriction of certain food types before and during the time of fecal sample collection. In contrast the IFOBT has better specificity, but has a relatively higher cost for testing.[9] For either CFOBT or IFOBT test, however, it is recommended that the test should be performed on 3 consecutive samples, and patients with any positive findings should be evaluated further.[8]

The barriers for colon cancer screening in less developed countries such as China include not only the lack of financial resources, but also the inconvenience of the sampling method, for example the requirement of multiple stool samples. Thus, there is a need to find the most cost-effective testing and sampling protocol for colon cancer screening. In an attempt to reduce the cost barrier for CRC screening in China, a new IFOBT test (Hemosure IFOBT) that is easier to perform and potentially cheaper than IFOBT tests currently available in western countries, has been developed and used in clinical settings. To take a step further, we also developed a protocol termed ''Sequential Fecal Occult Blood Test'' (SFOBT), which combines the CFOBT and IFOBT tests together.[3,10,11] In SFOBT, with 3 consecutive samples, CFOBT is first tested on the first sample, and if it is positive, the result is confirmed by IFOBT. If the first sample is negative by CFOBT, or if the first sample is ''positive'' by CFOBT but negative by IFOBT, the second sample will be collected and tested again with CFOBT first, followed by IFOBT. The same sequence is repeated for the third sample. The testing will be stopped and patient will be evaluated by colonoscopy if a positive CFOBT is confirmed by IFOBT with up to 3 samples. In other word, only patients with at least one positive CFOBT, which is confirmed by IFOBT, are further evaluated by colonoscopy.

The goal of this multicenter study was to perform a direct comparison of the cost-effectiveness of the 3 FOBT protocols (CFOBT, IFOBT and SFOBT) for Chinese patients in an effort to determine the optimal method and number of samples needed for population-based colon cancer screening in China.

***Correspondence to:** Department of Gastroenterology, Center of Colon Disease, Beijing Army General Hospital, Beijing, 100700, China. Fax: +[8610640615 11]. E-mail: lishirong@263.sina.com or †Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, Jonsson Comprehensive Cancer Center, University of California at Los Angeles, Los Angeles, CA 90095, USA. Fax: +[310-825-7795]. E-mail: jrao@mednet.ucla.edu
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Material and methods

Patient population

The study was carried out in 5 hospitals: Beijing Army General Hospital, First Hospital of Beijing University, Beijing Haidian Hospital, 309 Hospital of People's Liberation Army, and Second Hospital of Beijing University. The patients who underwent colonoscopy for a variety of indications in these 5 hospitals were recruited from November 2003 to February 2004. There were no age, sex, or race restrictions. After obtaining an informed consent, each patient was instructed to collect 3 consecutive stool samples before colonoscopy. For the convenience of the patients, no specific restriction of diet was requested. The patients were excluded from the study if they did not provide 3 consecutive stool samples or if the appropriate procedure of FOBT was not followed, according to the protocol provided in the test kit. The Clinical Trial Ethics Committees of each participating hospital approved the study.

Performing FOBT tests

All submitted stool samples were tested for CFOBT and IFOBT simultaneously, according to the procedures provided by the manufacturers (CFOBT kits were produced by Baso Tech. Ltd. Company in China, and IFOBT were provided by Wanhua-Puman Biol. Tech Ltd. Company in China). In practice, SFOBT was a sequential method combining CFOBT and IFOBT, *i.e.*, with CFOBT performed first; IFOBT would only be performed as a confirmatory test for the sample positive for CFOBT. Therefore, SFOBT was interpreted as positive only if both tests were positive. However, in this study, since CFOBT and IFOBT were performed simultaneously on all samples, the data for SFOBT was generated hypothetically based on the 2 test results (CFOBT and IFOBT), rather than a separate test procedure itself.

Colonoscopic examination

Colonoscopy was performed on all the participants after the FOBT tests. An experienced gastrointestinal physician performed all colonoscopic examinations. No significant adverse events associated with colonoscopy were ever noted on the study subjects. A complete colonoscopy was defined as an endoscope reaching the cecum. A biopsy was taken from any lesions suspected for tumors or inflammation.

Histopathological examination

Surgery was performed for those diagnosed with CRC. One pathologist from each hospital examined the biopsy samples from the respective hospitals. The stage of cancer was determined according to the standard protocol. Each patient was classified based on the worst pathology.

Statistical analysis

For each test type (CFOBT, IFOBT and SFOBT), sensitivity and specificity were calculated based on the findings of either the first 2 samples (for two-sample setting) or all 3 samples, using colonoscopic with histopathology findings as the gold standard. Sensitivity was calculated as a number with a true positive test/(number with a true positive + a false-negative test). Specificity was calculated as a number with a true negative test/(number with a true-negative test + number with a false-positive test). The χ^2 test was used to test the significance of difference among different FOBT methods. $p < 0.05$ was considered statistically significant and all tests were two-tailed. Ninety-five percent confidence intervals were calculated using methods for proportions.

Cost analysis

The total cost and the relative cost per each cancer detected were estimated for 3 different protocols, with 2 to 3 consecutive samples, in a hypothetical screening population of 100,000 subjects with CRC prevalence of 50 per 100,000. For each test, the sensitivity of cancer detection and the specificity of ''normal'' population (Table II) were used to calculate the number of cancers detected as well as the total number of positive cases that require colonoscopic examination. For example, with 3 consecutive CFOBT test, the sensitivity of cancer detection was 95.9%, which resulted in 48 cancer cases, and the specificity of 75.5%, which resulted in 24,488 false-positive subjects. The total number of subjects required for colonoscopy was 48 + 24,488 = 24,538. For the sake of simplicity, only the costs of the FOBT test (0.65 Chinese Yuan/test for CFOBT and 2.0 Chinese Yuan/test for IFOBT) and colonoscopy (300 Chinese Yuan/test) were included in the calculation, whereas other costs were not considered (*e.g.*, cost for sample collection, shipping, and so forth). The total cost = (0.65 × 3 [for 3 CFOBT tests] × 100,000) + (24,538 × 300) = 7,556,400 Yuan. There were 48 cancers detected, thus, the cost per cancer detected equals total cost divided by 48, which was 157,425 Yuan.

Results

Colonoscopic examination of the 324 patients who participated in the study showed 50 patients had CRC, 60 patients had chronic colitis, 60 patients had colorectal adenomas, 15 patients had hemorrhoids, and 139 patients had normal colons. The FOBT tests (CFOBT and IFOBT) were performed successfully on all except one colon cancer patient, in whom the IFOBT test protocol was not followed appropriately, and thus was excluded from the analysis. Table I shows the clinical and demographic information of the 323 patients eventually included in the analysis. Among them, 186 were men and 137 were women. The mean age was 53.47 ± 15.3 years and the age range was 18–68 years old (Table I).

Table II presents the sensitivity of various FOBT tests (CFOBT, IFOBT and SFOBT) for detecting colorectal adenomas, cancers, and the combination of both, in two- to three-consecutive sample test settings. In two-sample setting, IFOBT had significantly higher sensitivity than SFOBT for cancer detection (87.8% *vs.* 75.5%, respectively, $p < 0.05$ by χ^2 test). The IFOBT also had significantly higher sensitivity than the SFOBT for the detection of adenoma (46.7% *vs.* 28.3%, respectively, $p < 0.05$ by χ^2 test), or adenoma and cancer together (65.1% *vs.* 49.5%, respectively, $p < 0.05$ by χ^2 test). The sensitivity for detecting adenoma, cancer, or combined groups in three-sample setting was similar for different methods (CFOBT, IFOBT and SFOBT). However, when the two-sample setting was compared to the three-sample setting for each method, the sensitivities of IFOBT for detecting these lesions did not show significant differences; however, there were significant decreases of sensitivity for CFOBT or SFOBT for detecting cancer (95.9% *vs.* 77.5%, respectively, for CFOBT and 93.8% *vs.* 75.5%, respectively, for SFOBT, $p < 0.05$ for both by χ^2 testing) or

TABLE I – SUBJECT DEMOGRAPHICS AND CLINICAL INFORMATION (N = 323)

Characteristics	*N*
Sex	
Male	186
Female	137
Age	
Mean + SD	53.5 + 15.3
Range	18–68
Clinical indications for colonoscopy	323
Suspicious for colon cancer	37
History of colon cancer	10
History of polyps	34
History of bloody stool	80
Abdominal pain	62
Diarrhea	40
Asymptomatic	46
Other	14

TABLE II – SENSITIVITY AND SPECIFICITY OF VARIOUS FOBT TEST BY COLONOSCOPIC FINDINGS BASED ON TWO TO THREE CONSECUTIVE STOOL SAMPLES (N = 323)

	n	+CFOBT (%)	+IFOBT (%)	+SFOBT (%)
Sensitivity				
Two-sample setting				
Adenoma	60	25 (41.7)*	28 (46.7)[1]	17 (28.3)
Cancer	49	38 (77.5)	43 (87.8)[1]	37 (75.5)
denoma + cancer	109	63 (57.8)	71 (65.1)[1]	54 (49.5)
Three-sample setting				
Adenoma	60	27 (45.0)	29 (48.3)	25 (41.6)
Cancer	49	47 (95.9)	47 (95.9)	46 (93.8)
Adenoma + cancer	109	74 (67.9)	76 (69.7)	71 (65.1)
Specificity				
Two-sample setting				
Normal	139	16 (88.5)**	5 (96.4)	2 (98.5)[2]
Colitis & hemorrhoid	75	35 (53.3)	42 (44.0)	27 (64.0)
Nor./colitis/hemorrhoid	214	51 (76.2)	47 (78.0)	29 (86.4)[3]
Three-sample setting				
Normal	139	34 (75.5)	15 (89.2)[4]	8 (94.2)[4]
Colitis & hemorrhoid	75	41 (45.3)	47 (37.4)	27 (64.0)[5]
Nor./colitis/hemorrhoid	214	75 (64.9)	62 (71.0)	35 (83.6)[5]

[1]$p < 0.05$ compared to SFOBT.–[2]$p < 0.05$ compared to CFOBT.–[3]$p < 0.05$ compared to either CFOBT or IFOBT.–[4]$p < 0.05$ compared to CFOBT.–[5]$p < 0.05$ compared to either CFOBT or IFOBT.–*Number of positive tests (sensitivity).–**Number of positive tests (specificity).

TABLE III – SENSITIVITY OF VARIOUS FOBT TESTS IN DIFFERENT SIZES OF ADENOMAS BASED ON TWO TO THREE CONSECUTIVE STOOL SAMPLES

	N	CFOBT (%)	IFOBT (%)	SFOBT (%)
Two-sample setting				
<5 mm	12	3 (25.0)*	4 (33.3)	0 (0)
5–10 mm	14	4 (17.4)	3 (21.4)	2 (14.3)
10–20 mm	8	4 (50.0)	4 (50.0)	4 (50.0)
>20 mm or multiple	26	14 (53.8)	17 (65.4)**	11 (42.3)
Three-sample setting				
<5 mm	12	3 (25.0)	4 (30.0)	3 (25.0)
5–10 mm	14	4 (28.6)	3 (21.4)	3 (21.4)
10–20 mm	8	4 (50.0)	4 (50.0)	4 (50.0)
>20 mm or multiple	26	16 (61.5)	18 (69.2)	15 (57.7)

*Number of positive tests (sensitivity).–**$p < 0.05$ compared to SFOBT by χ^2 test.

adenoma and cancer combined (67.9% *vs.* 57.8%, respectively, for CFOBT and 65.1% *vs.* 49.5%, respectively, for SFOBT, $p < 0.05$ for both by χ^2 test).

Table II also shows the specificity of these tests in normal individuals, patients with colitis/hemorrhoid, and the combination of both. As expected, compared to three-sample setting, the two-sample setting decreased false-positive findings for all 3 methods (CFOBT, IFOBT and SFOBT), although none of such differences reached the statistical significance. The IFOBT method had a significantly higher specificity in the normal group than the CFOBT (89.2% *vs.* 75.5%, respectively, $p < 0.01$ by χ^2 test) in the three-sample setting. With the two-sample setting, the SFOBT had significantly higher specificity than CFOBT for normal (98.5% *vs.* 88.5%, respectively, $p < 0.05$ by χ^2 test), and higher specificity than either CFOBT or IFOBT for combined normal/colitis/hemorrhoid (86.4% *vs.* 76.2% and 78.0%, respectively, $p < 0.05$ for both by χ^2 test). With the three-sample setting, the SFOBT also had significantly higher specificity than either CFOBT or IFOBT for the colitis/hemorrhoid group or combined normal/colitis/hemorrhoid groups ($p < 0.05$ for all by χ^2 test).

Table III shows the sensitivity of various FOBT tests in detecting adenomas of various sizes, in either two- or three-sample settings. IFOBT had a significantly higher sensitivity in detecting large (>20 mm) or multiple adenomas than SFOBT (65.4% *vs.* 42.3%, respectively, $p < 0.05$ by χ^2 test) in the two-sample setting. There were no significant differences of sensitivity between two- to three-sample settings in any of the 3 methods (CFOBT, IFOBT and SFOBT).

Table IV shows the sensitivity of 3 FOBT methods (CFOBT, IFOBT and SFOBT) for detecting different stages of cancers, when two- to three-sample settings were used. The performance was similar for all 3 methods, with either two- or three-sample settings. In the two-sample setting, IFOBT appeared to have higher sensitivity than CFOBT or SFOBT in all stages except in stage A. However such differences did not reach statistical significance due to the relatively small numbers in each stage category. For the three-sample setting, the sensitivity was 60% for the patients with cancer of Dukes' stage A (3 out of 5) and 100% for patients with stage B–D cancers. SFOBT missed one of the unstaged cancers.

The relative cost per each cancer detected was estimated, as described in the method section. As shown in Table V, when three-sample format was used, the relative cost per cancer detected for CFOBT, IFOBT and SFOBT were 157,400, 80,300 and 45,500 Chinese Yuan, respectively. With two-sample format, the relative cost per cancer detected for CFOBT, IFOBT and SFOBT were 92,000, 33,900 and 19,100 Yuan, respectively. The cost per cancer detected with two-sample IFOBT test was lower than three-sample based SFOBT test, but slightly higher than the two-sample based SFOBT. However, the two-sample based SFOBT missed 12 out of 50 cancers.

Discussion

The ultimate goal of cancer screening is to reduce the incidence and mortality of the disease by detecting cancer at its earliest pos-

TABLE IV – SENSITIVITY (%) OF VARIOUS FOBT TESTS IN DIFFERENT STAGES OF COLORECTAL CANCER BASED ON TWO TO THREE CONSECUTIVE STOOL SAMPLES

	Dukes' A (n = 5)	Dukes' B (n = 15)	Dukes' C (n = 16)	Dukes' D (n = 4)	Unstaged (n = 9)
Two-sample setting					
CFOBT	2 (40.0)*	13 (86.7)	14 (87.5)	3 (75.0)	6 (75.0)
IFOBT	2 (40.0)	14 (93.3)	15 (93.8)	4 (100.0)	8 (88.9)
SFOBT	2 (40.0)	13 (86.7)	13 (81.3)	3 (75.0)	6 (75.0)
Three-sample setting					
CFOBT	3 (60.0)	15 (100.0)	16 (100.0)	4 (100.0)	9 (100.0)
IFOBT	3 (60.0)	15 (100.0)	16 (100.0)	4 (100.0)	9 (100.0)
SFOBT	3 (60.0)	15 (100.0)	16 (100.0)	4 (100.0)	8 (88.9)

*Number of positive tests (sensitivity).

TABLE V – COST ANALYSIS OF VARIOUS FOBT METHODS (CFOBT, IFOBT AND SFOBT) WITH TWO OR THREE CONSECUTIVE SAMPLES IN A HYPOTHETICAL SCREENING POPULATION OF 100,000 SUBJECTS WITH COLORECTAL CANCER PREVALENCE OF 50 PER 100,000

Methods	Test modality	No. of cancers detected	No. of colonoscopy needed	Total cost (Yuan)*	Cost/cancer (Yuan)*
CFOBT	3	48	24,538	7,556.3	157.4
	2	39	11,533	3,589.9	92.0
IFOBT	3	48	10,843	3,852.9	80.3
	2	44	3,642	1,492.6	33.9
SFOBT	3	46	5,843	2,095.0	45.5
	2	38	1,837	726.8	19.1

*In thousands.

sible stage so that the treatment can be most effective.[12] The FOBT has widely been used as an effective screening tool for colon cancer in Western countries. Prospective, randomized controlled trials have demonstrated a 15–33% reduction in CRC mortality with FOBT screening.[5–7,13] There are currently 2 major types of FOBT: chemical and immunochemical tests. The chemicals-based test (CFOBT) reacts positively to pseudoperoxidase activity of heme in the feces and is not specific for human blood. False-positive tests can be due to the presence of plant and animal materials. In contrast the IFOBT is designed to detect the human hemoglobin and is also specific for blood in the large intestines rather than for blood originating from other sources higher up in the gastrointestinal tract.[14] Studies have shown that the IFOBT has better specificity than CFOBT in cancer detection in western countries and in Japan.[9,14,15] However, there has been no head-to-head comparison reported in the Chinese population in Mainland China. Furthermore, while 3 serial samples are generally recommended for the screening, there have been few studies that analyzed the cost effectiveness of the optimal number of samples that are needed for screening with various types of FOBT.

This study compared directly the sensitivity and specificity of traditional chemical Guaiac-based FOBT (CFOBT) and a new immunochemical-based FOBT (Hemosure IFOBT) developed by a Chinese company for the detection of colon cancer and adenomas in Chinese patients referred for colonoscopy. In addition, we also examined a combined sequential protocol hypothetically, *i.e.*, CFOBT followed by IFOBT for CFOBT-positive samples (SFOBT). With SFOBT, IFOBT is used only as a confirmatory test for CFOBT, and only if both tests were positive, the patient was scored as positive. A colonoscopy was performed for all subjects and used as the gold standard. The study showed that, with the three-sample setting, SFOBT and IFOBT had favorable specificity for colon cancer detection over CFOBT (94.2% and 89.2% *vs.* 75.5%), with similar sensitivity (93.8% and 95.9% *vs.* 95.9%, $p > 0.05$). With the two-sample setting, IFOBT had a higher sensitivity (87.8%) and specificity (96.4%) than either CFOBT or SFOBT.

Using the colonoscopy as the gold standard, the reported sensitivity of CFOBT for colon cancer detection is around 80% and specificity in the range of 85–94% (for review see reference 14). For IFOBT, the sensitivity is in the range of 80–87% and the specificity ranges from 87 to 97%.[14,16,17] Compared to other studies, our results showed that with the three-sample setting, the CFOBT test has lower specificity in the colonoscopic normal group (75.5%), but had a similar level of sensitivity. The lower specificity of our results may be explained by the fact that the Chinese diet often contains components that may cause a false-positive CFOBT.[18] It appears that the third sample had more false-positive finding than the first 2 samples combined. The reason for that is unclear. The finding that the IFOBT has a substantially higher specificity than the CFOBT test in our study (89.2% *vs.* 75.5% respectively, $p < 0.01$ by χ^2 test) supports this hypothesis. As one would expect, the specificity of various FOBT tests (CFOBT, IFOBT and SFOBT) in patients with colitis and hemorrhoid is low (ranging from 37.4% to 64%). When the specificity was calculated for the combined normal and colitis/hemorrhoid group, the specificity ranges from 64.9% (three-sample setting for CFOBT) to 86.4% (two-sample setting for SFOBT). However, it should be noted that in actual screenings, we would not recommend performing FOBT tests of any kind in patients with active colitis or bleeding symptoms (for example due to hemorrhoid) for the obvious reasons.

How can our findings from this hospital-based study be extrapolated in actual population-based screening? First, since most of the subjects in our study were symptomatic with various clinical indications for colonoscopy, and only a handful individual were asymptomatic (40 out of 323, Table I), the specificity might be underestimated, especially when patients with colitis/hemorrhoid were included in the calculation (Table II). In actual screening, the population is presumably mostly healthy and asymptomatic. Although it is theoretically possible to extrapolate the observed specificity under such a circumstance, to do so one needs to know exactly the prevalence of these symptoms in general population. It should be noted, however, that even with the inclusion of symptomatic patients, the specificity of IFOBT testing with a two-sample setting reaches 96.4% in colonoscopically normal individuals. For CFOBT, some of the false-positive findings might be related to diet factors, and in actual screening, diet restriction might improve the specificity of the test than what was observed in our study. Second, again because our study involves mostly symptomatic patients, the sensitivity of the tests for detecting cancers may be

overestimated. As seen in Table IV, most cancers detected in our study were Duke's stage B or above cancers, and both CFOBT and IFOBT methods showed over 85% sensitivity with two-sample testing and 100% sensitivity with three-sample testing. However, in our study there were 60 patients with adenomas of various sizes. The rate of a very small adenoma being cancerous has been estimated as only 1 in 500; for a l-cm diameter adenoma it is around 10%; and for a adenoma over 2 cm it may be 50%.[19] Therefore, finding adenoma over 2 cm in size is an important element of screening. Our study shows that with two-sample setting, IFOBT is able to detect 65.4% of such adenomas, significantly higher than SFOBT (42.3%, Table III).

The American Cancer Society Guidelines do not recommend a combined IFOBT and CFOBT approach for colon cancer screening in United States.[8] In the past, we have adopted a serial approach (SFOBT) in clinical and population-based screening of colon cancer in part of China as a cost-saving gesture.[10–12] This is proposed with the assumption that CFOBT has at least the same, if not better, sensitivity but probably lower specificity than IFOBT to detect significant colonic neoplasia (large adenoma and carcinoma). However, the finding that (at least in the two-sample setting) SFOBT had significantly lower sensitivity than IFOBT for detecting large or multiple adenomas (Table III) may not support such a hypothesis. Another potential problem with the SFOBT approach is the fact that some CFOBT formats used sample cards submitted by the patient, not the actual stool sample, and thus IFOBT may not be able to be performed on the card.

Our results showed that the two-sample based Hemosure IFOBT is the more cost-effective approach than other protocols. While numerous studies have examined the various FOBT tests, few directly analyzed the optimal number of samples needed for the screening. This is important not only for the cost-effectiveness consideration, but also for the consideration of subject compliance, regarding stool sample collection, which is also a major barrier for colon cancer screening.[3] A study from Wong in the Hong Kong Chinese population also demonstrated the effectiveness of the two-sample setting of IFOBT method using a different product, the Magstream 1000/Hem SP from Japan.[17] However, the IFOBT used in their study was a different type, and there was no data from Wong's study to compare to the three-sample setting. It should also be noted that there are different IFOBT products throughout the world, and whether they all have similar testing characteristics remains a question.

There are several limitations for our study. First, as discussed earlier, the study was carried out in a hospital-based setting, and the patient population recruited into the study had various types of symptoms or had substantially higher risks for colon cancer than general population, thus the results (sensitivity and specificity) derived from this study might not be readily applicable to actual screening, which in general targets low risk population. However, the main purpose of our study was to compare the test performance characteristics of different methods (CFOBT, IFOBT and SFOBT) and optimal number of samples needed for the screening. This design, although not ideal, provided sufficient data that would allow us to determine the optimal protocols for the actual screening setting—which is to use two sample-based IFOBT testing. Second, in our study the patients were not asked to restrict their diets ''for convenience.'' This might result in higher false-positive rates than otherwise expected if diet restriction was used, especially for CFOBT. Third, again because the hospital-based setting of the study and the involvement of many symptomatic patients, most cancers detected in our study were Duke's stage B or above, with only 5 Duke's stage A cancer, whereas finding early cancer is the ultimate goal of the screening. To circumvent the problem, our study also included 60 adenomas of various sizes. Comparing the testing characteristics of different methods in the adenomas, some of which may be precancerous, would provide important information to determine the optimal method for screening. As seen in our study, IFOBT with two-sample setting had comparable sensitivity and specificity to three-sample setting for detecting adenomas, and IFOBT had significantly higher sensitivity than SFOBT and similar specificity compared to CFOBT. This again led us to conclude that two-sample setting of IFOBT is the favored method for screening. Finally, for cost-effectiveness analysis, obviously the ultimate variable is the cost per year of life saved, rather than cost per cancer detected. However, our study design would not allow us to calculate that. Caution should also be taken when interpreting the cost-analysis, since there might be overestimation of sensitivity and underestimation of the specificity associated with the hospital-based design in comparison to actual screening population involving mostly healthy subjects.

Taken together, our study showed that Hemosure IFOBT has a better specificity than the CFOBT in colonoscopically normal populations. The hypothetical SFOBT approach with 3 consecutive stool samples may further increase the specificity and reduce the cost, overall, whereas the IFOBT with 2 consecutive stool samples appears to be the most cost-effective approach of colon cancer screening. Further prospective trials will be needed to confirm such an observation.

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