

The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings

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Objectives: To study the performance of a single test using two fecal occult blood tests with colonoscopy for the detection of colorectal cancer (CRC) for the first time in Saudi Arabia to determine possible implications for the anticipated colorectal screening program.

Materials and methods: We compared the performance of guaiac and immunochemical fecal occult blood tests for the detection of CRC among patients of 50–74 years old attending two hospitals in the Eastern Region of Saudi Arabia. Samples of feces were collected from 257 asymptomatic patients and 20 cases of confirmed CRC, and they were tested simultaneously by the guaiac-based occult blood test and monoclonal antibody-based immunoassay kit. Colonoscopy was performed on all participants and the results were statistically analyzed with both positive and negative occult blood tests of both methods.

Results: Of the 277 subjects, 79 tested positive for occult blood with at least one method. Overall, the number of those with an occult blood-positive result by both tests was 39 (14.1%), while for 198 (71.5%), both tests were negative ($P < 0.0001$); 40 (14.4%) samples showed a discrepant result. Colonoscopy data were obtained for all 277 patients. A total of three invasive cancers were detected among the screening group. Of the three, the guaiac test detected two cases, while the immunochemical test detected three of them. Of the 20 control cases, the guaiac test detected 13 CRC cases ($P = 0.03$), while the immunochemical test detected 16 of them ($P < 0.0001$). The sensitivity of guaiac and immunochemical tests for the detection of CRC in the screening group was 50.00% (95% confidence interval [CI] = 6.76–93.24) and 75.00% (95% CI = 19.41–99.37), respectively. For comparison, the sensitivity of the guaiac fecal occult blood test for detecting CRC among the control group was 65.00% (95% CI = 40.78–84.61) while that of FIT was 80.00% (95% CI = 56.34–94.27). The specificity of the guaiac and immunoassay tests was 77.87% (95% CI = 72.24–82.83) and 90.12% (95% CI = 85.76–93.50), respectively. The positive likelihood ratio of guaiac and immunochemical tests for the detection of CRC was 2.26 (95% CI = 0.83–6.18) and 7.59 (95% CI = 3.86–14.94), whereas the negative likelihood ratio was 0.64 (95% CI = 0.24–1.71) and 0.28 (95% CI = 0.05–1.52), respectively. The positive predictive values of guaiac and immunochemical tests were 3.45% (95% CI = 0.426–11.91) and 10.71% (95% CI = 2.27–28.23), respectively. There was no marked difference in the negative predictive values for both methods. The sensitivity of the fecal occult blood test by FIT was significantly higher for stages III and IV colorectal cancer than for stages I and II ($P = 0.01$) and it was insignificant for the guaiac fecal occult blood test ($P = 0.07$).

Conclusion: In areas where other advance screening methods of CRC are not feasible, the use of FIT can be considered.

Keywords: fecal occult blood test, guaiac, immunochemical, endoscopy, colorectal cancer

Introduction

Colorectal cancer (CRC) is an important health concern and a leading cause of death among adults worldwide. In Saudi Arabia, a total of 4,201 cases of CRC were registered in the national Saudi Cancer Registry, with a noticeable increase in incidence rates between 2001 and 2006.¹ This cancer ranked first among the male population and third among the female population with an overall age-standardized incidence rate of 6.6 per 1,000,000.² Between 1994 and 2003, age-standardized rates for CRC in Saudi Arabia had increased almost twofold.³

Early detection of CRC is one of the best approaches to reduce related deaths. A broad spectrum of choices is available for CRC screening, including fecal occult blood (FOB) testing (FOBT), flexible sigmoidoscopy, and colonoscopy.^{4,5}

FOBT detects blood in the stool that is not visible on gross inspection, usually less than 50 mg of hemoglobin per gram of stool.⁶ The test is intended for the determination of gastrointestinal bleeding found in a number of gastrointestinal disorders including diverticulitis, colitis, polyps, and CRC. Three randomized controlled clinical trials showed that FOBT reduced the risk for death from CRC.⁷⁻⁹

Two types of FOBTs of different analytical principles are available: the traditional guaiac (G)-FOBT; and the antibody-based fecal immunochemical test (FIT). The G-FOBT is based on the oxidation of phenolic compounds present in the guaiac (ie, guaiaconic acids), impregnated on the card that detects the pseudoperoxidase activity of the hematin portion of any hemoglobin, resulting in the production of a blue color.^{10,11} G-FOBTs are not specific for human hemoglobin and they detect any peroxidase found in feces (eg, plant peroxidases, heme in red meat), and they are affected by certain chemicals (eg, vitamin C).¹² It may also detect bleeding from any site in the gastrointestinal tract, including the stomach.¹³

Recently, an immunoassay for the FOBT has been introduced utilizing two monoclonal antibodies that specifically detect the presence of human globin in feces and is thus more specific for bleeding from the distal gut.

In the early 1970s, G-FOBTs were first proposed for the screening of CRC,¹⁴ and evidence has shown that they reduce both the incidence and mortality of CRC,^{7-9,15,16} although positive and negative predictive values were suboptimal.¹⁷ CRC screening by G-FOBTs had also been complicated by a high incidence of false-positive results, especially when patients do not follow a restricted diet before testing.¹¹

More recently, FIT has been widely used as an alternative to G-FOBT for CRC screening programs. Several methods of FIT exist including automated quantitative analysis.

Comparisons of different techniques to detect occult blood in the stool have been widely performed. Recent studies that compared G-FOBT and FIT in screening populations indicated superiority of the latter for the detection of both cancers and advanced adenomas.¹⁷⁻¹⁹ In the past few years, CRC screening has become more popular and colonoscopy has been postulated as the gold standard.²⁰

Although extensive literature concerning FOBT and CRC screening is available, these are mostly community based with only a few being hospital based. While community-based screening studies provide critical information on program sensitivity and the acceptability of a test in a large population, often only small numbers of CRCs are detected.²¹ In referral hospital-based studies, a higher prevalence of CRC will allow for better understanding of the performance of FOBTs for the detection of CRC as compared to colonoscopy. Most other study designs have included colonoscopy for positive FOBTs only.^{17-19,22} In order to directly measure the specificity of the FOBTs, the colonoscopy results of individuals with negative results should also be available. To allow for the better evaluation of the methods of FOBTs, a comparative study design that includes the performance of both tests in parallel on the same stool samples is needed.²³ The objective of this study is to compare the sensitivity, specificity, positive predictive value, and negative predictive value of G-FOBT and FIT in the same stool samples among patients attending hospitals who all underwent colonoscopy. To the best of our knowledge, no previous work has been done in Saudi Arabia for the detection of CRC by FOBT.

Materials and methods

Study design

The Research and Ethics Committee at the King Fahd Military Medical Complex (Dhahran, Saudi Arabia) approved this prospective cohort study protocol, including patients who reported to two tertiary hospitals in the eastern region of Saudi Arabia – King Fahd Military Medical Complex (Dhahran, Saudi Arabia); and King Faisal Specialist Hospital (Dammam, Saudi Arabia) from June 2012 through May 2013.

All asymptomatic participants that reported to hospital in this study were 50–74 years of age; they were tested once for FOB by two simultaneous methods, and they were scheduled for colonoscopy. Patients who reported symptoms of disease of the lower gastrointestinal tract were excluded. The medical record number of each of the participants was recorded. The results of the participants who were offered colonoscopy were taken from the medical record during the final 6 months of the

study period (ie, June 2013 through December 2013). Twenty confirmed CRC cases were recruited as a control.

Fecal occult blood test

During the study period, 277 samples of feces were collected and tested simultaneously using the guaiac-based ColoScreen® by Helena Laboratories (Cat no: 5073; Beaumont, TX, USA) and the monoclonal antibody-based immunoassay (RAPEPKT313) kit by DAsource© (DAsource ImmunoAssays SA, Nivelles, Belgium) using the 1-day method.

ColoScreen® was performed according to the manufacturer's instructions. In brief, using the applicator, very thin smears of stool from different sites were applied in boxes A and B, and they were allowed to air dry before the cover was closed. The perforated window on the back of the slide was then opened and two drops of ColoScreen developer was applied to the back of boxes A and B before reading the results after 30 seconds and within 2 minutes. Any trace of blue color, within or on the outer rim of the specimen, was reported as positive for occult blood.

RAPEPKT313 was performed according to the manufacturer's instructions. In brief, a stool specimen is collected into the sampling tube containing extraction solution. After mixing the stool sample, a test strip is screwed into the sampling tube by breaking the bottom seal of the sampling tube while maintaining a vertical position, and it was allowed to settle for approximately 1 minute. The extracted fecal solution flows into the bottom space of the test strip and triggers the start of the FOB immunoassay. If human hemoglobin is present at a level higher than 50 ng/mL in a fecal sample extract, a red colored band appears in the test region, which is located in the lower half of the test membrane. A similar colored band must appear in the control region located in the upper-half of the test membrane, indicating that the test strip is functioning properly and the result is valid.

Colonoscopy

All participants underwent complete colonoscopy in one of the two hospitals. Colonoscopies were performed in a standard fashion by experienced gastroenterologists. The location and size of all polypoid lesions were recorded and the tumor specimens were pathologically classified as previously described.²⁴

Statistics analysis

Statistical analysis was performed using SAS software version 9.1. Sensitivities, specificities, and predictive values of G-FOBT and FIT for CRC were calculated as previously

described.^{6,25} We used the chi-squared and *t*-test, and *P*-values >0.05 were considered statistically significant.

Results

Overall, 277 individuals between 50 and 74 years of age (mean: 63.8 years; standard deviation =7.9 years) (189 males and 88 females) were tested by the two methods, G-FOBT and FIT.

Table 1 shows that the FOBT positivity rates of the guaiac and immunoassay tests for the screening and control groups were 22.6%, 12.1%, 65%, and 80%, respectively. For the occult blood tests, 39 (14.1%) patients were positive for both tests, while 198 (71.5%) were negative by both tests. Overall, 40 (14.4%) samples showed a discrepant result.

Colonoscopy was successfully performed on all 257 patients in the screening group and three invasive cancers were detected. Of the patients endoscoped, 37 were occult blood-positive by both or at least one test, and the other 194 were negative by both methods. Among the 20 cancer cases in the control group, 13 and 16 tested positive by G-FOBT and FIT, respectively. Tables 2 and 3 indicated the performance characteristics of G-FOBT and FIT for the detection of CRC, respectively.

The sensitivity of G-FOBT and FIT for the detection of CRC among the screening group was 50.00% (95% confidence interval [CI] =6.76–93.24) and 75.00% (95% CI =19.41–99.37), respectively. The specificity of G-FOBT and FIT was 77.87% (95% CI =72.24–82.83) and 90.12% (95% CI =85.76–93.50), respectively (Table 4). The positive likelihood ratio of guaiac and immunochemical tests for the detection of CRC was 2.26 (95% CI =0.83–6.18) and 7.59 (95% CI =3.86–14.94), whereas the negative likelihood ratio was 0.64 (95% CI =0.24–1.71) and 0.28 (95% CI =0.05–1.52), respectively.

The positive predictive values of G-FOBT and FIT were 3.45% (95% CI =0.426–11.91) and 10.71% (95% CI =2.27–28.23), respectively. There was no marked

Table 1 Performance characteristics of FIT compared with G-FOBT among the screening and control groups

G-FOBT	FIT				Total
	Screening group		Control group		
	Positive	Negative	Positive	Negative	
Positive	26	32	13	0	71
Negative	5	194	3	4	206
Total	31	226	16	4	277

Note: Chi-squared =108.93; *P*<0.0001.

Abbreviations: FIT, fecal immunochemical test; G-FOBT, guaiac fecal occult blood test.

Table 2 Performance characteristics of G-FOBT for detecting colorectal cancer

G-FOBT	Screening group		Total	Control group
	Colorectal cancer			
	Positive	Negative		
Positive	2	56	58	13
Negative	2	197	199	7
Total	4	253	257	20

Note: Chi-squared = 1.75; $P=0.19$.

Abbreviation: G-FOBT, guaiac fecal occult blood test.

difference in negative predictive values for both methods, being 98.99% (95% CI =96.42–99.88) and 99.56% (95% CI =97.59–99.99), respectively.

Table 5 shows the sensitivity of FOB by FIT, which was significantly higher for stages III and IV CRC than for stages I and II ($P=0.01$) and insignificant for G-FOBT ($P=0.07$).

Discussion

We compared the sensitivity and specificity of a guaiac test and a monoclonal antibody-based immunoassay performed on 277 older patients reporting to the King Fahd Military Medical Complex and King Faisal Specialist Hospital for the detection of occult blood and the prediction of CRC in a hospital setting.

In this study, the occult blood positivity rates of the same samples were 22.6% and 12.1% by guaiac and immunoassay tests, respectively. The high incidence of false-positive test results by guaiac-based testing is largely due to the lack of proper dietary restrictions for several days prior to testing. In another study, even with properly prepared patients, the incidence of false-positive results with G-FOBT was found to be as high as 10%.²⁶ Red meat, fruits, and vegetables high in peroxidase, high doses of ascorbic acid (vitamin C, 250 mg/day or more), oral medications such as aspirin or other nonsteroidal anti-inflammatory drugs, heavy alcohol consumption, and some others may interfere with the test.²⁷

Table 3 Performance characteristics of FIT for detecting colorectal cancer

FIT	Screening group		Total	Control group
	Colorectal cancer			
	Positive	Negative		
Positive	3	25	28	16
Negative	1	228	229	4
Total	4	253	257	20

Note: Chi-squared = 17.20; $P=0.00$.

Abbreviation: FIT, fecal immunochemical test.

Table 4 Sensitivity, specificity, and predictive values and 95% CI (between parenthesis) of G-FOBT and FIT for colorectal cancer (n=277)

	G-FOBT	FIT
Sensitivity	50.00% (6.76–93.24)	75.00% (19.41–99.37)
Specificity	77.87% (72.24–82.83)	90.12% (85.76–93.50)
Positive likelihood ratio	2.26 (0.83–6.18)	7.59 (3.86–14.94)
Negative likelihood ratio	0.64 (0.24–1.71)	0.28 (0.05–1.52)
Positive predictive value	3.45% (0.42–11.91)	10.71% (2.27–28.23)
Negative predictive value	98.99% (96.42–99.88)	99.56% (97.59–99.99)

Abbreviations: CI, confidence interval; G-FOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test; n, number.

The number of observed agreements between the two test methods is 240 (86.6%), whereas 37 (13.4%) samples showed a discrepant result between the two methods. Because there is no “gold standard” reference method for FOBT, we could not resolve which method gave the “correct” results among the discrepant cases.

On the other hand, FIT methods are specific for human hemoglobin and require no dietary preparation, although medications that may cause minor gastrointestinal bleeding will potentially produce positive results. In normal subjects, a small amount of blood is lost in the intestine each day. It has been stated before that a blood loss of 2–3 mL (approximately 0.3 mg hemoglobin/g of stool) is the lower limit of blood loss that may be associated with gastrointestinal pathology.²⁸ It has been indicated before that performing two FOBT tests does not improve diagnostic accuracy; rather, it increases costs.²⁹

Unlike many previous studies,^{17,19,22} the colonoscopy results were also available for all those that were tested for occult blood, including those with negative results, which allowed for the improved detection of specificities. The sensitivity of G-FOBT and FIT for the detection of CRC was 50.00% (95% CI =6.76–93.24) and 75.00% (95% CI =19.41–99.37), respectively. The specificity of G-FOBT and FIT was 77.87% (95% CI =72.24–82.83) and 90.12% (95% CI =85.76–93.50), respectively.

A number of studies have reported clinical evaluations of various FOBT methods, and guidelines have been published for CRC screening with varying levels of sensitivities and specificities for detecting CRC, depending on the study design. Generally, the sensitivity of FOBT for CRC is relatively low, between 30% and 80%, in most population-based studies,^{30–33} while specificity has been reported to be between 87% and 98%.³² In agreement with our findings, a systematic review of the literature on repeated annual or biennial ColoScreen or G-FOBT revealed that the reported sensitivity

Table 5 The sensitivities and 95% CI (between parentheses) of a single G-FOBT and FIT by different anatomic stages of colorectal cancer

	n	G-FOBT positive cases	G-FOBT sensitivity % (95% CI)	FIT positive cases	FIT sensitivity % (95% CI)
Stage I	2	1	50.0 (1.26–98.74)	1	50.0 (1.26–98.74)
Stage II	15	8	53.33 (26.59–78.73)	9	60.0 (32.29–83.66)
Stage III	3	2	66.67 (9.43–99.16)	2	66.67 (9.43–99.16)
Stage IV	3	2	66.67 (9.43–99.16)	3	100.00 (29.24–100.00)
P-value		t=3.68; P=0.066		t=2.83; P=0.005	

Abbreviations: CI, confidence interval; G-FOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test; n, number.

for CRC varied from 51% to 100%, and specificity varied from 90% to 97%.²⁶ Furthermore, the positive predictive value (the percentage of positive tests that are true-positive results) ranged from 2.4% to 17.0%.³³ Low sensitivity for detecting CRC using guaiac-based tests was also reported in a population-based study.^{17,34} Immunochemical tests for FOBT have been studied as an alternative to guaiac-based tests.³⁵

Many studies have shown that FIT has better performance characteristics when compared to most G-FOBTs, and it also detects advanced adenomas, with a sensitivity for advanced adenomas ranging from 20% to 40%.^{17–19,36} FIT testing has been shown to facilitate compliance and it improves specificity for CRC screening, but at an increased cost compared to guaiac-based FOBT.³⁷ FITs are moderately sensitive, highly specific, and they have high overall diagnostic accuracy for detecting CRC.³⁸ However, different brands of quantitative FITs, even those using the same cutoff hemoglobin concentration, perform differently in mass screening.³⁹ Comparisons of different techniques to detect occult blood in stool have been widely performed.

This study, which is in agreement with some others,^{40–42} indicated the higher sensitivity, specificity, and predictive values of FIT for the screening of CRC when compared to community-based studies.⁴³

We detected only a few cases of CRCs among the screening group that resulted in a wide range of 95% CIs for sensitivity. However, specificity was well detected with a high degree of confidence. Moreover, the positive likelihood ratio of FIT for the detection of CRC was 7.59 (95% CI =3.86–14.94), indicating good performance of the test.

When classifying the tumors according to the different stages, the sensitivity of FOB by FIT was significantly higher for stages III and IV CRC than for stages I and II, which is in agreement to what was reported before.⁴⁴

Conclusion

We believe that FIT may offer advantages over G-FOBT in hospital settings because its higher sensitivity, combined with

its low incidence of false-positive test results, could improve screening programs for CRC.

It is worth mentioning that our sample size was only modest, we had a limited follow-up period, and the FOBT was administered once.

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Disclosure

The authors report no conflicts of interest in this work.

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