Effectiveness of Multiple Consecutive Fecal Immunohistochemical Testing for Colorectal Cancer Screening

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Objective: The fecal immunohistochemical test (FIT) is a simple colorectal-cancer screening test. There are no recent studies evaluating the benefits of doing more than one a year. Our study aimed to evaluate the effectiveness of performing the test for 3 consecutive days in terms of detecting cancer and advanced adenomas.

Methods: This was a single-center retrospective review of records of patients who had daily tests for 3 consecutive days and had at least one positive during the period from 2009-2011.

Results: A total of 456 records were reviewed, 410 met the inclusion criteria. Most of the participants were men (95.9%), with the mean age of all the participants being 64.3 (±7.8) years. Regarding the FIT results, 18.8% had positive results on all 3 tests, 20.2% had 2 positive tests, and 61.0% had 1 positive FIT. There were 16 (3.9%) patients in the studied sample that had colon cancer. Their lesions were located predominantly in the distal colon (ratio of distal to proximal: 2:1). The patients with 3 positive FITs had a higher prevalence of advanced adenomas (33.3% vs. 13.4%, respectively; *P* < .05).

Discussion: Our study showed a low concordance between daily consecutive tests results. those patients with more than 1 positive FIT had a higher prevalence of advanced adenoma or adenocarcinoma than patients who had only one. Fewer than 4% of the patients in our study had colon cancer. Prospective studies would be needed to determine the effectiveness of more than 1 annual FIT in colon cancer prevention. [*P R Health Sci J 2022;41(3):117-122*]

Key words: Colon neoplasm, Cancer screening test, Fecal occult blood test

Among women and men, colorectal cancer (CRC) is the second and third (respectively) most common of all cancers, worldwide (1). It is the second leading cause of cancer death among men and women in the United States and is responsible for approximately 134,000 new cases each year and 49,000 CRC-related deaths; in addition, CRC accounts for approximately 8.3% of all cancer deaths and 3% of all deaths (2). In the United States, it has been determined that the average individual has a 4.4% lifetime risk of developing colorectal carcinoma (2). The incidence of CRC is higher in men than in women and is higher in African Americans (56.0 per 100,000 population per year) than in Hispanics (48.3 per 100,000 population per year) (2). As many as 75% of the newly diagnosed cases of colorectal carcinoma occur in individuals with no known risk factors for it, and approximately 1 in 3 people diagnosed with CRC will die of the disease within 5 years after having been diagnosed. For these reasons, CRC screening in average-risk individuals has been advocated by the American College of Gastroenterology, American College of Physicians/American Society of Internal Medicine, American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, and United States Preventive Service Task Force, as well as the American Cancer Society (3).

Multiple tests are available as options for CRC screening. The recommended strategies fall into 2 broad categories: stool-based tests (occult blood and fecal DNA testing) and structural examinations (flexible sigmoidoscopy, colonoscopy, and CT colonography). Each test has its strengths and weakness, sensitivity and specificity, evidence of effectiveness, safety, and associated costs. Currently there are randomized controlled trials comparing different screening strategies, since, to date, no screening method has proven to be superior when all aspects are considered.

Stool-based tests have been recommended as a screening method for CRC in average-risk healthy individuals. Having

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a yearly fecal occult blood test (FOBT) has been proven to reduce CRC deaths by up to 33%; the FOBT has been found to have an overall cancer-detection rate as high as 92% (4,5,6). It is ideal for mass population screening because it is simple, widely available, low in cost, and a proven cost-effective method.

The FOBT was developed to detect the microscopic bleeding caused by CRC before there are any signs or symptoms. It is done by collecting spontaneously passed stool samples that are then interpreted by qualified laboratory personnel. Its main advantages are that it does not require bowel preparation, sedation, or transportation to and from the screening examination. Initial stool tests were guaiac-based (gFOBT), which detected heme in stools by peroxidase-like activity but required 3 stool samples obtained on separate days and dietary restrictions that reduced compliance and increased false-positive results.

The fecal immunohistochemical test (FIT), unlike the gFOBT, detects antibodies specific to the globin portion of human hemoglobin. Human globin does not survive in gastric juice; thus, FIT is specific for lower gastrointestinal bleeding. Furthermore, it has the advantage that it does not require dietary restrictions prior to testing. For these reasons, it is widely used and endorsed by most professional (and pertinent) societies. The FIT was approved by the FDA as a single test, not 3 samples, as was the case with its predecessor.

In a large prospective study performed by investigators from Kaiser Permanente, the FIT had high sensitivity and specificity for detecting left-sided CRC, having a sensitivity of 81.8% for detecting colorectal carcinoma and 29.5% for advanced adenomas. Specificity was 96.9% for carcinomas and 97.3% for adenomas (7). In a study of 1,000 persons at high risk of CRC who had had both a colonoscopy and a FIT done with 3 bowel movements, the sensitivity and specificity for CRC were 94% and 87%, respectively; for advanced adenoma and CRC, the sensitivity and specificity were 67% and 91%, respectively (8). In another study, this one using a single FIT test, the sensitivity for CRC was 66%, and for advanced adenoma and CRC, the sensitivity was 27%, while the specificity was 95% (9). These sensitivities are much higher than the 13% to 39% sensitivity for CRC that is obtained when using gFOBT and when studied in a similar way (10,11).

Current guidelines for CRC screening recommend having a single FIT, every year (3). No recent studies provide definitive information about the effectiveness of doing more than 1 annual FIT.

Our institution, the Veteran Health Administration (VHA), was an early adopter of the FIT. Although approved by the FDA as a single test, the VHA national directive was to continue requesting 1 test each from 3 consecutive bowel movements.

The primary endpoint of the study was to evaluate the effectiveness of performing 3 FITs instead of 1 in the detection of colon carcinoma and advanced neoplasia. The secondary endpoint was to evaluate other causes of a positive FIT.

Methods

After receiving approval from the Institutional Review Board of the VHA, we conducted a single-center retrospective review of medical records of patients screened (from September 01, 2009, through October 15, 2011) for CRC with daily FITs for three consecutive days and who had at least 1 positive result. Included in the study were those aged 50 to 79 years old who had had a colonoscopy performed within 60 days after having tested positive. The exclusion criteria were having had a colonoscopy more than 60 days after a positive FIT, having fewer than 3 (FIT) tests in a row, and having the follow-up colonoscopy at a non-VA medical facility. The FIT kit used during the study period was the Polymedco OC-Auto Micro 80, with a detection threshold of 100 ng/mL.

Each patient's age; sex; smoking habits and alcohol use; use of aspirin (and/or other non-steroidal anti-inflammatory drugs, anticoagulants, and/or antiplatelets); and number of positive tests were recorded. The pathology and colonoscopy reports of each patient were reviewed for lesion location and histological type and size (< 1 or ≥ 1 cm). Neoplastic polyps/lesions were classified according to their histology as: tubular, tubulovillous, villous, and serrated adenomas; polyps with high-grade dysplasia; and/or CRC. The term advanced adenomas was used to identify polyps with higher risk of malignancy; these were: adenomas ≥ 1 cm in size, adenomas with villous histology, and/or an adenomas with evidence of high-grade dysplasia. The lesion's location was classified as proximal or distal to the splenic flexure. Other colonoscopy findings, including arteriovenous malformations, ulcers, colitis, diverticulosis, and hemorrhoids, were also recorded.

Statistical analysis

Data were analyzed using Stata 12.1 software (Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). The characteristics of the population under study were described using frequencies and percentages (for categorical variables) and means (±SD) (for continuous variables). The variables of interest, including demographics, lifestyles, medication use, and other conditions present, were compared by the status of the advanced adenoma, of the adenocarcinoma, or of both using Student's t test, a Chi-square test, or Fisher's exact test. Positive predictive values for the FIT's ability to detect intestinal disease were calculated. Furthermore, Poisson working models with robust variance estimators were employed to evaluate the association between having 1 or more positive FITs and advanced adenoma, adenocarcinoma, or both. Variables with a $P < .1$ on the bivariate analyses were included in the models. Crude and adjusted models were constructed, and the results are reported as prevalence ratios (PRs), with their corresponding 95% confidence intervals (95% CI). Finally, the correlation between FITs was determined by means of the Kappa statistic. All the analyses were 2 sided, and statistical significance was set at .05.

Results

A total of 456 records were reviewed, of which 410 met the inclusion criteria. Of those patients who did not meet the criteria, 19 had had a colonoscopy more than 60 days after having had a positive FIT, 5 had fewer than 3 tests on record, 2 had had an incomplete colonoscopy, and 20 had had the endoscopic study performed outside of our institution.

Most of the participants were males (95.9%) with the mean age of all the participants being 64.3 (±7.8) years and a mean BMI in the range of overweight (28.8 [±4.7]). More than one-third (34.9%) of the patients were smokers, 44.6% used alcohol, and 39.3% were using ASA.

Regarding the FIT results, 18.8% had 3 tests with positive results, 20.2% had 2 positive tests (out of 3 performed), and 61.0% had 1 positive FIT (out of 3 performed). The most common colonoscopy findings were hemorrhoids (85.6%) and diverticulosis (49.0%) (Table 1).

There were 16 (3.9%) patients in the studied sample that had colon cancer. Their lesions were located mostly in the distal (left) portion of colon (ratio of distal to proximal: 2:1). Upon comparing those patients with cancer to those without it, we found that the cancer patients had a higher proportion of ASA use (68.8% vs. 38.1%, respectively; $P < .05$) and that they also had a greater number of positive FIT results (+++: 62.5% vs. 17.0%, respectively; $P < .05$) (Table 3).

Table 1. Description of population under study; n = 410

Variable	n (%)
Patient characteristics	
Sex, male	393 (95.9)
Age, years, mean (±SD)	64.3 (±7.8)
BMI, mean (±SD)	28.8 (±4.7)
Lifestyle	
Smokes	143 (34.9)
Uses alcohol	183 (44.6)
FIT result	
+++	77 (18.8)
++	83 (20.2)
+	250 (61.0)
Biopsy result	
TVA	13 (3.2)
VA	5 (1.2)
SA	4 (1.0)
TA + >1cm	71 (17.3)
Advanced adenoma	81 (19.8)
Adenocarcinoma	16 (3.9)
Location of tumor	
Proximal (right)	5 (31.2)
Distal (left)	11 (68.8)
Advanced adenoma or adenocarcinoma	88 (21.5)
Medication(s)	
ASA	161 (39.3)
NSAIDs	86 (21.0)
Antiplatelets	20 (4.9)
Anticoagulants	45 (11.0)
Other colonoscopy finding(s)	
AVMs	15 (3.7)
Ulcers	2 (0.5)
Colitis	5 (1.2)
Diverticulosis	201 (49.0)
Hemorrhoids	351 (85.6)
At least 1 other condition	381 (92.9)

BMI: body mass index; FIT: fecal immunohistochemical test; TVA: tubulovillous adenoma; VA: villous adenoma; SA: serrated adenoma; TA: tubular adenoma; ASA: aspirin; NSAIDs: non-steroidal anti-inflammatory drugs; AVMs: arteriovenous malformations

Table 2. Comparison of patients by adenocarcinoma status; n = 410

Variable	Adenocarcinoma n = 16	No adenocarcinoma n = 394
Patient characteristic		
Sex, male	16 (100%)	377 (95.7%)
Age, years, mean (±SD)	65.8 (±9.3)	64.3 (±7.7)
BMI, mean (±SD)	27.9 (±5.6)	28.8 (±4.7)
Lifestyle		
Smokes	3 (18.8%)	140 (35.5%)
Uses alcohol	9 (56.3%)	174 (44.2%)
Medication(s)		
ASA**	11 (68.8%)	150 (38.1%)
NSAIDs	4 (25.0%)	82 (20.8%)
Antiplatelets	2 (12.5%)	18 (4.6%)
Anticoagulants	0	45 (11.4%)
Other condition(s)		
AVMs	1 (6.3%)	14 (3.6%)
Diverticulosis	7 (43.8%)	194 (49.2%)
Hemorrhoids	12 (75.0%)	339 (86.0%)
At least 1 other condition	14 (87.5%)	367 (93.2%)
*FIT***		
+++	10 (62.5%)	67 (17.0%)
++	3 (18.8%)	80 (20.3%)
+	3 (18.8%)	247 (62.7%)

**P < .05. BMI: body mass index; ASA: aspirin; NSAIDs: non-steroidal anti-inflammatory drugs; AVMs: arteriovenous malformations; FIT: fecal immunohistochemical test

There were 81 patients with advanced adenomas, for an overall prevalence of 19.8%. Most of these (71/81 [88%]) were polyps greater than 1 cm in size. Ten patients had cancer and synchronous advanced adenoma.

After excluding all the patients with cancer, we compared the patient characteristics of those with and without advanced adenomas (Table 3). Patients with 3 positive FITs had a higher prevalence of advanced adenomas than did patients with fewer than 3 positive FITs (33.3% vs. 13.4%, respectively); this difference was significant ($P < .05$). Moreover, the prevalence of advanced adenomas was higher in patients with diverticulosis than it was in those without it (59.7% vs. 46.9%, respectively).

When patients with advanced adenoma and adenocarcinoma were classified together and compared to all the other patients, we found statistically significant differences in the presence of hemorrhoids and the number of positive FITs. Patients with advanced adenoma or adenocarcinoma were less likely to have hemorrhoids (78.4% vs. 87.6%, respectively) but had more positive FIT results (+++: 38.6% vs. 13.4%, respectively; ++: 28.4% vs. 18.0%, respectively; +: 33.0% vs. 68.6%, respectively) (Table 4).

Patients with 2 positive FIT results in 3 tests had a higher prevalence of advanced adenoma than did those patients

Table 3. Comparison of patients with and without advanced adenomas; n = 394 (16 patients with adenocarcinoma were excluded).

Variable	Advanced adenoma n = 72	No advanced adenoma, n = 322
Patient characteristic		
Sex, male	70 (97.2)	307 (95.3)
Age, years, mean (±SD)	64.4 (±7.7)	64.3 (±7.8)
BMI, mean (±SD)	29.1 (±4.7)	28.7 (±4.7)
Lifestyle		
Smokes	24 (33.3)	116 (36.0)
Uses alcohol	38 (52.8)	136 (42.2)
Medication(s)		
ASA	23 (31.9)	127 (39.4)
NSAIDs	11 (15.3)	71 (22.1)
Antiplatelets	3 (4.2)	15 (4.7)
Anticoagulants	5 (6.9)	40 (12.4)
Other condition(s)		
AVMs	2 (2.8)	12 (3.7)
Diverticulosis**	43 (59.7)	151 (46.9)
Hemorrhoids*	57 (79.2)	282 (87.6)
At least 1 other condition	66 (91.7)	301 (93.5)
*FIT***		
+++	24 (33.3)	43 (13.4)
++	22 (30.6)	58 (18.0)
+	26 (36.1)	221 (68.6)

*.05 < P < .1, **P < .05. BMI: body mass index; ASA: aspirin; NSAIDs: non-steroidal anti-inflammatory drugs; AVMs: arteriovenous malformations; FIT: fecal immunohistochemical test

with only 1 positive FIT, after controlling for the presence of diverticulosis and hemorrhoids (+++: PR_{adj} = 3.4, 95% CI: 2.1–5.4; ++: PR_{adj} = 2.6, 95% CI: 1.6–4.3) (Table 5). Similarly, patients having 3 positive FIT results had a significantly higher prevalence of adenocarcinoma than did patients with 1 positive test, adjusting for ASA use (+++: PR_{adj} = 11.0, 95% CI: 3.1–38.7) (Table 6). Finally, patients with more than 1 positive FIT had a higher prevalence of advanced adenoma or adenocarcinoma in comparison with those patients with only 1 positive result, even when controlling for alcohol use, anticoagulant and antithrombotic use, and the presence of diverticulosis and hemorrhoids (+++: PR_{adj} = 3.6, 95% CI: 2.4–5.5; ++: PR_{adj} = 2.5, 95% CI: 1.6–4.0, respectively).

The FIT results were also evaluated to determine the agreement between them. It was found that the concordance between tests was low (% of agreement: range, 44.6 to 48.3; Kappa: range, -0.11 to -0.04) and increased when 2 tests were added and compared to the other one (i.e. FITa positive vs. FITb & FITc positive) (% agreement: range, 58.3 to 60.2; Kappa: range, 0.18 to 0.22).

Discussion

Multiple test options are available for screening to detect either early-stage cancer or precancerous polyps. FIT has gained popularity and acceptance based on its showing higher sensitivity and specificity for the detection of advanced adenoma and CRC than gFOBT does (12). However, there are not many randomized controlled trials evaluating the ideal number of samples for a given screening period.

In this retrospective analysis of daily FIT for 3 consecutive days, with at least 1 of the tests being positive), the prevalence of advanced adenoma, colon cancer and both advance adenoma and CRC were 19.8% (n = 72), 3.9% (n = 16), and 21.5% (n = 88), respectively. In our study cohort, colon cancer was most commonly located in the distal colon 68.8% (n = 11). In a large Chinese cohort, researchers found that FIT was more sensitive at detecting distal than proximal advanced adenoma and CRC (13). This may be because right-sided lesions may bleed less than left-sided lesions do or because hemoglobin degrades during its transit through the colon.

Of the 16 patients identified with colon cancer in our study sample, the majority (62.5% [n = 10]) had 3 positive tests, 18.8% (n = 3) had 2 positive tests and 8.8% (n = 3) had just one. Similarly, the patients with advanced adenoma were more likely to have 3 positive tests than their counterparts without advanced adenomas (33.3% vs. 13.4%, respectively). Moreover, subjects with more than 1 positive FIT had a higher prevalence of advanced adenoma or CRC that did those subjects with only 1 positive result. In our review of 1 meta-analysis, we found that 1-time FIT sensitivity was approximately 80% for detecting CRC; for the detection of advanced adenoma, that sensitivity has been estimated to be 68%. Our study findings suggest that while undergoing more than 1 FIT improves sensitivity, doing so might also decrease specificity (14). In our study, 6 (37.5%)

Table 4. Comparison of patients with adenocarcinoma and/or advanced adenoma with all others (n = 410).

Variable	Advanced adenoma/ adenocarcinoma n = 88	No advanced adenoma/no adenocarcinoma n = 322
Patient characteristic		
Sex, male	86 (97.7)	307 (95.3)
Age, years, mean (±SD)	64.7 (±7.9)	64.3 (±7.8)
BMI, mean (±SD)	28.9 (±4.9)	28.7 (±4.7)
Lifestyle		
Smokes	27 (30.7)	116 (36.0)
Uses alcohol*	47 (53.4)	136 (42.2)
Medication(s)		
ASA	34 (38.6)	127 (39.4)
NSAIDs	15 (17.1)	71 (22.1)
Antiplatelets	5 (5.7)	15 (4.7)
Anticoagulants	5 (5.7)	40 (12.4)
Other condition(s)		
AVMs	3 (3.4)	12 (3.7)
Diverticulosis*	50 (56.8)	151 (46.9)
Hemorrhoids**	69 (78.4)	282 (87.6)
At least 1 other condition	80 (90.9)	301 (93.5)
*FIT***		
+++	34 (38.6)	43 (13.4)
++	25 (28.4)	58 (18.0)
+	29 (33.0)	221 (68.6)

(1)% per column,*.05 < *P* < .1, ***P* < .05, BMI: body mass index; ASA: aspirin; NSAIDs: non-steroidal anti-inflammatory drugs; AVMs: arteriovenous malformations; FIT: fecal immunohistochemical test

of the 16 patients with colon cancer had at least 1 negative test; therefore, the cancer of these patients could have been missed if they had been tested only once. The lack of reproducibility of the test results supports the theory that malignant lesions bleed intermittently and that a single FIT can miss a malignant neoplasm of the colon. Some investigators have reported that approximately 15% of CRC will be missed during screening, and our findings support that contention (3).

The use of low-dose ASA for the primary or secondary prevention of cardiovascular disease is very common among patients who are at the appropriate age for CRC screening. The effect of the use of ASA on the outcome of a FIT has been evaluated in at least 3 trials. The consensus is that the drug increases FIT sensitivity for detecting advanced neoplasia with only slightly lower specificity (15,16,17). In our study, the positive predictive value of having 3 positive FITs (+++: 62.5% vs. 17.0%, respectively; $P < .05$) in colon cancer increased with the use of ASA (68.8% vs. 38.1%, respectively; $P < .05$) (Table 3).

This study had some limitations. Being a retrospective analysis, there were variables that could not be controlled. The lack of a control group made it impossible to calculate the sensitivity and specificity of the test. Furthermore, the population was mostly men, overweight, and veterans, with all of them attending a single center.

This study emphasizes the importance of prospective randomized trials exploring how many FIT tests would be optimal to evaluate the number of FITs that could be used to improve CRC screening. In populations for whom access to colonoscopy is a limiting factor, the strategy of using 3-test FIT screening may help identify those who are more likely to have colon cancer or an advanced neoplasia.

Table 5. Positive predictive value of FITs and relationship between having advanced adenoma and selected variables (n = 394).

Variable	Advanced adenoma		PPV (%)	Crude PR (95% CI)	Adjusted# PR (95% CI)
	Yes	No			
Diverticulosis					
Yes	43	151	---	1.5 (1.00, 2.35)	1.5 (1.01, 2.31)**
No	29	171	---	Ref	Ref
Hemorrhoids					
Yes	57	282	---	0.6 (0.38, 1.01)	0.6 (0.39, 1.00)
No	15	40	---	Ref	Ref
FIT					
+++	24	43	35.8	3.4 (2.09, 5.53)**	3.4 (2.08, 5.43)**
++	22	58	27.5	2.6 (1.57, 4.35)**	2.6 (1.57, 4.28)**
+	26	221	10.5	Ref	Ref

#Adjusted for all variables included in the table. **$P < .05$. PPV: positive predictive value

Table 6. Positive predictive value of FITs and relationship between having adenocarcinoma and the use of aspirin (n = 410).

Variable	Adenocarcinoma		PPV (%)	Crude PR (95% CI)	Adjusted# PR (95% CI)
	Yes	No			
ASA use					
Yes	11	150	---	3.4 (1.20, 9.62)**	3.5 (1.25, 9.58)**
No	5	244	---	Ref	Ref
FIT					
+++	10	67	13.0	10.8 (3.05, 38.39)**	11.0 (3.11, 38.69)**
++	3	80	3.6	3.0 (0.62, 14.67)	3.1 (0.65, 14.96)
+	3	247	1.2	Ref	Ref

#Adjusted for all variables included in the table. **$P < .05$. PPV: positive predictive value

Resumen

Objetivo: La prueba immunohistoquímica de sangre oculta es una prueba simple de cernimiento para cáncer de colon. No hay estudios recientes evaluando los beneficios de hacer más de una prueba al año. El propósito del estudio era determinar la efectividad de hacer la prueba por tres días consecutivos en la detección de cáncer y pólipos avanzados. Métodos: Estudio retrospectivo de revisión de expedientes de pacientes que se hicieron una prueba diaria por 3 días consecutivos y al menos una de ellas fue positiva en el periodo del 2009 al 2011. Resultados: Se revisaron un total de 456 expedientes, de los cuales 410 llenaron los criterios de inclusión. La mayoría de los sujetos eran hombres (95.9%), con una edad promedio de 64.3 (±7.8) años. El 18.8% tuvo las 3 pruebas positivas, 20.2% dos and 61.0% solo una. Hubo 16 (3.9%) pacientes del estudio que se diagnosticaron con cáncer de colon. Este estaba predominantemente localizado en el colon distal (distal a proximal, 2:1). Los pacientes con 3 pruebas positivas tenían una mayor prevalencia de pólipos avanzados. [(33.3% vs 13.4%) ($P < .05$)]. Discusión: Este estudio demostró una baja concordancia entre los resultados de las pruebas diarias. Aquellos pacientes con más de una prueba positiva tuvieron mayor riego de tener cáncer y pólipos avanzados que aquellos con solo una. A solo un 4% de los pacientes se les diagnosticó cáncer. Se necesitan estudios prospectivos para determinar la efectividad de más de 1 prueba al año en la prevención de cáncer de colon.

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