Original Article

Clinical Factors Associated with a Positive Immunochemical Fecal Occult Blood Test and Negative Colonoscopic Findings

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Objective: To identify clinical factors associated with a positive immunochemical fecal occult blood test [iFOBT] followed by a negative colonoscopic finding in a colorectal cancer [CRC] screening program.

Materials and Methods: A retrospective study was performed of data collected from a CRC screening program in 2013. Participants were aged 50 to 65 years, with no previous history of colonoscopy. Their stool occult blood was tested at 0, 3, and 6 months, and if there was a positive result they underwent colonoscopy.

Results: There were 1,827 participants, among whom 379 cases had a positive iFOBT. The 356 cases that had complete data included 116 men (32.58%) and 240 women (67.42%). Their mean age was 57.56±4.38 years. In multivariate analysis, factors associated with a positive iFOBT and a negative colonoscopic finding were adjusted by sex, age, abnormal signs, and CRC family history. The presence of anemia was significantly associated with a positive iFOBT and a negative colonoscopic finding (adjusted OR, 1.44; 95% CI, 1.05 to 1.99; $p = 0.026$).

Conclusion: In patients with anemia who have a positive iFOBT and a negative colonoscopic finding, the physician should attempt to find possible causes of the unexplained anemia.

Keywords: Positive immunochemical fecal occult blood test, Negative colonoscopic finding, Hemorrhoids, Anemia

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Data from the Thailand Cancer Registry 2013 showed that in Thailand, colorectal cancer [CRC] is the third most common cancer in men and the fifth most common cancer in women. The incidence per 100,000 persons in 2013 was 8.9 for men and 8.2 for women(1).

Currently, colorectal screening is recommended for people at average risk who are older than 50 years and have never had a colonoscopy, have no history of CRC in their family, no other risk factors including a history of inflammatory bowel disease, and no abnormalities such as bowel habit changes, which should be assessed for the possibility of CRC. Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early and curable stage, and may decrease CRC incidence with polyp detection and removal during colonoscopy. There are many screening modalities and schedules that can detect CRC such as colonoscopy every 10 years, flexible sigmoidoscopy every 5 to 10 years, and CT colonography every 5 years to detect adenomatous polyps and cancer. One primary modality to detect cancer includes stool-base screening(2,3). In Thailand,

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fecal occult blood tests [FOBT] are often used as a non-invasive test in colorectal screening programs because of their low cost and rapid methodology. Nonetheless, a positive FOBT still requires further evaluation such as colonoscopy[2,3].

In terms of effectiveness, the sensitivity and relative specificity of immunochemical FOBT [iFOBT], guaiac FOBT, and fecal DNA FOBT are 93.6% and 99.1%, 35 to 67% and 90 to 98%, and 62 to 91% and 93 to 96%, respectively[4-6]. The FOB one Step Fecal Occult Blood Test Device is a rapid test for the detection of human occult blood in feces at 50 ng/mL or higher, or 6 μg/g feces[7,8]. However, colonoscopy is still the standard screening method for CRC since 1997[9].

The presence of blood in the stool may be a sign of an adenomatous polyp, a pre-cancerous lesion, or overt malignancy[10]. However, sometimes FOBT has been reported to show positive results while colonoscopic findings are negative[11].

There are many possible factors that can cause positive FOBT results in stool, such as colon cancer, inflammatory bowel disease, and ulcerative conditions in the upper or lower GI tract. In addition, less common causes like gastroesophageal cancer, hemosuccuspancreaticus, hemobilia, endometriosis, and infections also need to be considered. Meanwhile, hemorrhoids can sometimes lead to a positive fecal occult blood test[12]. Another recent study showed that hemorrhoids are significantly associated with positive FOBT results[13,14]. A previous study revealed that FOBT was inadequate to detect advanced colorectal neoplasia because of the low sensitivity of FOBT for overt cancer detection[11].

One of the most common causes of iron deficiency anemia is CRC[15]. Data from the Thailand National Cancer Institute showed that individuals with CRC may have anemia and 40 to 80% had a positive fecal occult blood test[3]. A previous study suggested that a complete blood count [CBC] can potentially be used as a tool to identify individuals who are at 10 to 20 times increased risk of harboring an occult CRC and may possibly be candidates for colonoscopy screening[16].

Hemorrhoids can be a possible cause of positive FOBT and lead to anemia. Thus, this study aimed to identify clinical factors like hemorrhoids and anemia that could be associated with positive FOBT results followed by negative colonoscopic findings, and to determine the prevalence of FOBT positive results in the CRC screening program at Chulabhorn Hospital, Thailand, starting from the year 2013.

Materials and Methods

A retrospective study was conducted at Chulabhorn Hospital in the CRC screening program starting in July 2013. We included 1,852 individuals aged 50 to 65 with no prior CRC. The design of this study was screening by iFOBT every three months during the first year. After screening by iFOBT, those with positive results underwent colonoscopic examinations. Those who underwent colonoscopy received complete blood count tests. Patient demographic data included sex, age, family history of CRC, and abnormal signs.

Anemia is the presence of a low complete blood count or low blood hemoglobin [Hb] concentration. According to the World Health Organization, anemia can be defined as a hemoglobin level with Hb lower than 13 g/dl in men and Hb lower than12 g/dl in non-pregnant women[17].

In this study, we defined CRC positive as a diagnosis of CRC or high-risk adenomas (villous, tubulovillous, or high-grade dysplasia or size of 1 cm or greater or 3 or more adenomatous polyps). All other results were defined as CRC negative.

Statistical analyses were performed with STATA version 12.1. Demographic data of the participants were reported as means and standard deviation for quantitative variables, and frequency and percentage for Categorical variables. Multi-level analysis with a cluster screening round was performed to determine factors associated with positive iFOBT results and negative colonoscopic findings. In multivariate analysis, age, sex, and abnormal signs of CRC, were adjusted. For each variable, the adjusted odds ratios [ORs] and 95% confidence intervals [CIs] were reported[18].

The protocol of this research was reviewed and approved by the Human Research Ethics Committee, Chulabhorn Research Institute No. 011/2560.

Results

Demographic data of participants with positive iFOBT

Of the 1,827 participants, 20.74 % (379 cases) of all fecal occult blood tests had positive findings. All cases of a positive fecal occult blood test (356) were followed by colonoscopy. There were 116 men and 240 women (32.58% and 67.42%, respectively) with a mean age of 57.56±4.38 years.

Approximately 90.17% of the participants had no abnormal signs and symptoms of CRC, and 85.11% did not have a family history of CRC (Table 1).

Screening round with positive iFOBT followed by negative colonoscopy findings

We compared the frequency of screening rounds every three months and within six months of a positive iFOBT followed by negative colonoscopic findings as shown in Table 2. The frequency of a positive iFOBT followed by negative colonoscopic findings in each round decreased gradually, 127 (43.05%), 109 (36.95%), and 59 (20%), respectively.

Positive iFOBT results and hemorrhoids

Of 356 cases with positive iFOBT results, 61 (17.13%) were CRC positive and 295 (82.87%) were CRC negative. Ninety-one cases (30.85%) had positive iFOBT results and negative colonoscopy results of hemorrhoids. In the multivariate analysis, hemorrhoids were not associated with a positive iFOBT followed by a negative colonoscopy result, adjusted by sex, age, abnormal signs, and CRC family history (Table 3).

Table 1. Demographic data of participants with positive iFOBT (n = 356)

Variable	n = 356	Percentage
Sex		
Male	116	32.58
Female	240	67.42
Age (years)		
Mean ± SD (range)	57.56±4.38 (50 to 65)	
CRC family history		
Yes	53	14.89
No	303	85.11
Abnormal sign		
Yes	35	9.83
No	321	90.17

SD = Standard deviation; CRC = Colorectal cancer

Positive iFOBT results and anemia

In the multivariate analysis, factors associated with a positive iFOBT and a negative colonoscopy result was adjusted by sex, age, abnormal signs, and CRC family history. The presence of anemia was identified as an independent factor of a positive iFOBT and negative colonoscopy result (adjusted OR, 1.44; 95% CI 1.05 to 1.99; $p = 0.026$) and was significantly associated with a positive iFOBT followed by a negative colonoscopy result (Table 3).

Discussion

The most effective method for CRC screening is colonoscopy for detection and removal of adenomatous polyps at an early stage. The NCCN guideline suggests CRC screening in the average risk group (older then 50 years, no signs and symptoms of CRC, no family history) by one of many methods such as a FOBT every year, sigmoidoscopy every five years, or colonoscopy every 10 years. In Thailand, most of the population receives annual CRC screening with FOBT because it is a non-invasive screening method,

Table 2. Screening round with positive iFOBT followed by a negative colonoscopy result

FIT positive	n	iFOBT+, CRC-	iFOBT+, CRC+
Screening round 1 (day 0)	165	127 (76.97)	38 (23.03)
Screening round 2 (month 3)	121	109 (90.08)	12 (9.92)
Screening round 3 (month 6)	70	59 (84.29)	11 (15.71)
Total	356	295 (82.87)	61 (17.13)

CRC- = CRC negative with other pathology report; CRC+ = CRC positive (CA+ high risk); iFOBT+ = immunochemical fecal occult blood test positive

Table 3. Multivariate analysis of factors associated with a positive iFOBT and a negative colonoscopy result

Clinical factors	iFOBT+, CRC- (n = 295)	iFOBT+, CRC+ (n = 61)	OR (95% CI)	*p*-value
Hemorrhoids	91 (30.85)	25 (40.98)	0.65 (0.33 to 1.28)	0.213
Anemia	61 (20.68)	8 (13.11)	1.44 (1.05 to 1.99)	0.026

Adjusted by sex, age, abnormal signs, multi-level analysis with cluster (screening round)

has a low cost, and is included in their healthcare plan.

We found that a positive iFOBT can lead to patient anxiety about the test results. Some are concerned about the risks of a colonoscopy procedure. Thus, we studied two clinical factors including hemorrhoids and anemia that may be propable causes of a positive iFOBT. We found that a positive iFOBT was not associated with hemorrhoids. However, some studies have shown that positive iFOBT results are associated with hemorrhoids, sex, ethnicity, food, and aspirin or oral anticoagulant intake[11-13,15,19,20]. A limitation of this study is that it could not evaluate the characteristics of hemorrhoids and information on patients' feces that could be possible causes of positive fecal occult blood test.

Our data showed that a positive iFOBT followed by a negative colonoscopy result was associated with anemia. While there were other causes of occult blood in the digestive tract such as long-term use of non-steroidal anti-inflammatory drugs NSAIDs) that can irritate the bowel or digestive tract, in this study, the long-term use of NSAIDs was included in the analysis. Patients should be encouraged to stop NSAIDs use before iFOBT.

Conclusion

Patients with anemia are more likely to have a positive iFOBT and a negative colonoscopy. However, there are many factors that may result in the presence of blood in the feces. Hence, other clinical information must be considered and the physician should look for the possible causes of anemia.

What is already known on this topic?

From previous studies, hemorrhoids may be a cause of a positive FOBT, but our data indicates that anemia could be associated with a positive FOBT. Hence, this study aimed to determine clinical factors that could be associated with a positive FOBT followed by a negative colonoscopy result.

What this study adds?

Anemia, not hemorrhoids, could be associated with a positive fecal blood test followed by a negative colonoscopy result. Hence, further study is recommended on clinical factors that could be associated with hemorrhoids such as feces characteristics and types of hemorrhoids (internal or external hemorrhoids). In addition, the use of NSAIDs should also be studied as a possible cause of irritation and bleeding in the digestive tract.

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Potential conflicts of interest

None.

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