

# Clinical impact of the immunochemical fecal occult blood test for colorectal cancer screening in Brazil

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## Abstract

**Background** Colorectal cancer (CRC) screening programs based on the fecal occult blood test (FOBT) reduce CRC mortality. We carried out an observational prospective study to determine the accuracy of immunochemical FOBTs for the detection of CRC in individuals at average risk for the disease.

**Methods** This population-based study was performed between April 2015 and January 2016 in two gastroenterology referral centers in Southern Brazil. It included 1039 average-risk volunteers aged 50-75 years who were symptom-free for colonic disease. Participants underwent OC-Light immunochemical fecal occult blood test (i-FOBT, EIKEN chemical Co., Tokyo, Japan) as well as screening colonoscopy.

**Results** Nine hundred forty-eight (91.2%) of the 1039 participants completed and returned the i-FOBT (95% confidence interval [CI] 89.4-92.9). Among the 73 participants with a positive i-FOBT who underwent colonoscopy, advanced CRC was detected in 9 (12.3%). Two (2.7%) early CRCs, 7 (9.5%) high-grade dysplasia adenomas and 25 (34.2%) low-grade dysplasia adenomas were also diagnosed. Among the 243 negative i-FOBT cases who underwent colonoscopy, one (0.4%) advanced CRC and 91 (37.6%) low-grade dysplasia adenomas were detected. The detection rate of CRC considering the whole screened population (n=1039) was 1.05% (11/1039).

**Conclusions** The i-FOBT test in the CRC screening programs in Brazil showed a high compliance and high detection rates for cancers and high-risk adenomas. The i-FOBT test is feasible for CRC screening in an average-risk population.

**Keywords** Colorectal cancer, fecal occult blood test, screening, colonoscopy, adenoma, fecal immunochemical test

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## Introduction

CRC is the third most common neoplasia in the world and the fifth cause of cancer-related death in Southern Brazil [1]. There has been a significant increase in the global CRC incidence over the last 20 years and a still greater increase in CRC incidence is expected by 2025, due to population aging [2]. CRC screening by colonoscopy with detection and removal of pre-malignant lesions or early cancers is the gold standard for reducing cancer-related mortality and morbidity [3].

CRC screening by occult blood testing is also reported to reduce cancer-related mortality [4]. Occult blood testing has advantages in population screening programs in terms of patient's acceptance, availability, and cost-effectiveness, and because it is a risk-free procedure [4]. However, both negative and positive results require confirmatory colonoscopy for a definitive diagnosis.

The guaiac fecal occult blood test (g-FOBT) is a widely used test for detecting fecal occult blood. However, this test

has many drawbacks, such as the need for a diet in the days prior to the test, avoidance of some medications, and the need to avoid dental brush procedures up to three days before beginning the fecal collection for the test. Furthermore, it has a low sensitivity, specificity and positive predictive value [5]. In the last few years, the immunochemical fecal occult blood test (i-FOBT) has been demonstrated to have better reproducibility, as well as higher sensitivity, specificity and positive predictive value than the g-FOBT [6]. In addition, there is no need for a special diet prior to fecal testing or other special precautions [7]. Consequently, this method has found better acceptance among patients and physicians [5]. The OC-Light immunochemical fecal occult blood test (i-FOBT, EIKEN chemical Co., Tokyo, Japan) is a qualitative test that can detect 50 ng/mL of hemoglobin (Hb) [2,3]; furthermore, it is specific for human Hb, while upper digestive bleeding does not produce a positive test. The low level of detection of OC-Light provides high sensitivity, which is fundamental for improving the detection rate of CRC in population screening programs.

The aim of this study was to evaluate the feasibility, sensitivity, and specificity of the i-FOBT for colonic neoplasms in an average-risk population in Southern Brazil, considering colonoscopy as the diagnostic gold standard.

## Patients and methods

A population-based study was designed in which average-risk volunteers who were symptom-free for colonic disease were enrolled between April 2015 and January 2016 in two gastroenterology referral centers (Gastroenterology Foundation of Rio Grande do Sul, Fugast, Endoscopy Unit, and Santa Casa Hospital). A total of 1039 volunteers agreed to participate in the study. All volunteers agreed to take the test home and carry it out, but in case of non-compliance the participants were contacted by phone. Only 321 (30.9%) participants returned to undergo colonoscopy.

The tests were analyzed in a laboratory in one of the Gastroenterology Units participating in the study (Gastroenterology Foundation of Rio Grande do Sul, Fugast, Endoscopy Unit). The samples were analyzed using the OC-Light™ by two independent investigators; Hb was detected and results were given automatically as 10 µg Hb/g feces. The OC-Light i-FOBT is an immunoassay that uses a blend of a polyclonal and monoclonal antibodies to specifically detect the presence of Hb in feces. The sample end of the test strip is dipped in the feces extract. The liquid feces wicks through a series of absorbent materials and contacts latex particles conjugated to an antibody specific to Hb. The sample and latex conjugate then wick through a membrane that contains zones of immobilized antibodies, a patient test zone of anti-Hb capture antibody and a control zone of anti-mouse antibody. If Hb is present in the sample it serves to link the latex conjugate to the capture antibody in the patient test zone. The control zone antibody binds the monoclonal antibody on the latex. The buildup of latex particles in the zones leads to the development of visible blue bands. The cutoff for a positive test is 10 µg Hb/g feces (50 ng/mL).

Colonoscopy screening was offered to all volunteers, regardless of whether they were positive or negative for i-FOBT. Lesion size and location were registered. The resected lesions were sent for histopathological analysis. Advanced CRCs, for which endoscopic resection was not feasible, were biopsied. All other colonic diseases were also evaluated and registered. Those performing the colonoscopy and histologic examinations were blinded to the i-FOBT results. The Ethics Committee of the Federal University of Health Science approved the study under number 41858515.8.0000.5345.

Statistical analysis was performed using SPSS software for Windows, version 18.0. Formal descriptive statistics for proportions and continuous variables were calculated with their respective confidence interval (95%CI). The acceptance and return percentage were registered. Once the colonoscopy was performed in positive and negative participants for i-FOBT, the sensitivity and specificity of the test could be estimated directly.

## Results

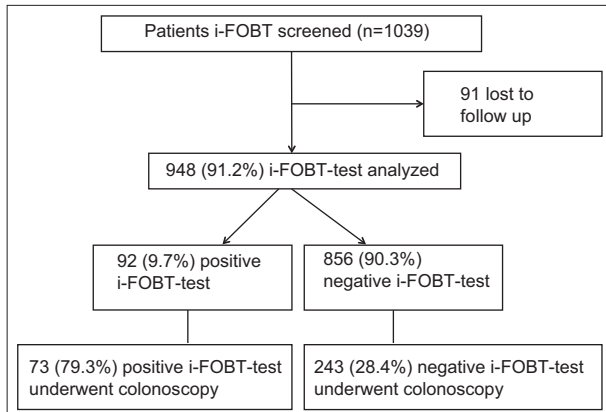
Overall, 1039 participants (675 female), with a mean age 60.5 years (range 50-75) were included in the study. Nine-hundred forty-eight (91.2%) returned with the i-FOBT (95%CI 89.4-92.9). Ninety-two (9.7%) were positive (95%CI 7.9-11.8) and of these 73 (79.3%) underwent colonoscopy. The remaining 19 (20.7%) participants refused to undergo a colonoscopy (Fig. 1). The cecal intubation rate was 100%.

Nine (12.3%) advanced CRCs were detected among the 73 participants with a positive i-FOBT. Two patients (2.7%) had early CRC, 7 patients (9.5%) had high-grade dysplasia adenomas and 25 (34.2%) patients had low-grade dysplasia adenomas. Thirty (41%) cases had a normal colon or no neoplastic lesions (Fig. 2). Of the 243 negative i-FOBT cases who underwent colonoscopy, one (0.4%) had advanced CRC and 91 patients (37.6%) had low-grade dysplasia adenomas. The remaining 151 (62%) had normal colonoscopy or no neoplastic lesions (Fig. 3).

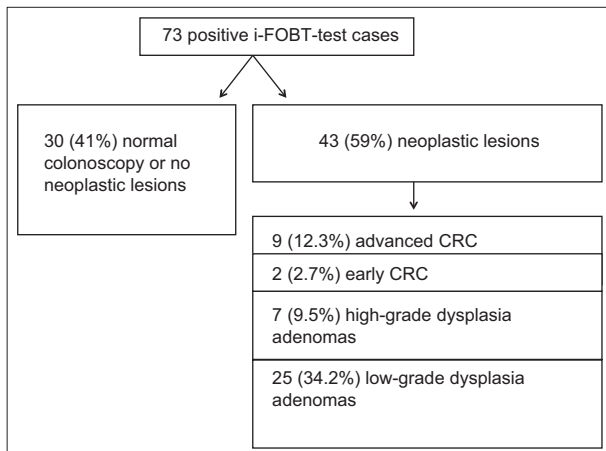
The detection rate of CRC considering the whole screened population (n=1039) was 1.05% (11/1039), and the detection rate for the population who underwent colonoscopy was 3.48% (11/316). High-grade dysplasia adenomas were detected in 0.67% (7/1039) of the screened population and 2.2% (7/316) of those screened by colonoscopy. The participation rate was 91.2% (948/1039). The positivity rate of the method was 9.7%. Table 1 shows the results of i-FOBT OC-Light analysis for the detection of CRC, adenoma and any neoplastic lesion in a Southern Brazilian population.

## Discussion

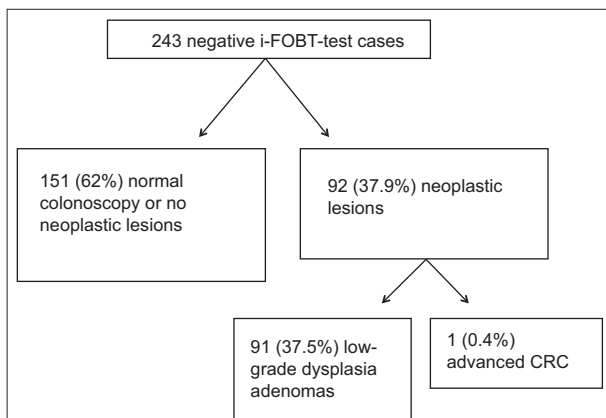
This is the first CRC screening study with OC-Light (i-FOBT) to be performed in a Brazilian population. i-FOBT screening programs have shown a significant reduction in CRC mortality



**Figure 1** Flow chart of the study  
i-FOBT, immunochemical fecal occult blood test



**Figure 2** Colonoscopy results of participants with a positive immunochemical fecal occult blood test (i-FOBT)  
CRC, colorectal cancer



**Figure 3** Colonoscopy results of participants with a negative immunochemical fecal occult blood test (i-FOBT)

and their impact on incidence rates has already been described in the literature [10,11]. The reduction in incidence rates associated with the removal of precancerous lesions may reflect an even greater reduction in mortality in the long term [9].

The applicability of this test to CRC screening was excellent, with a high acceptance rate among our patient population. Similar figures were observed in another South American CRC screening study, in which 90% of the participants returned with stool samples [4]. The high acceptance of this test supports our ongoing screening program. We believe that the absence of dietary restrictions is paramount for the acceptability of this test within our population, where people consume large amounts of meat.

The positivity rate of our study resembles that of other published results [4,5]. The most striking results of our study were the high sensitivity for CRC detection and the high negative predictive value of the test. However, the negative predictive value for harboring any neoplastic lesion was low. This high sensitivity demonstrates that the i-FOBT is a promising test for CRC screening in the general population older than 50 years. The OC-Light i-FOBT test is designed for preliminary screening.

Chemical tests, such as the guaiac method, have been reported to reduce CRC mortality in a cost-effective fashion. However, this method had a low specificity because the Hb detected is pseudoperoxidase activity Hb, not specific to human Hb. This gives this test a high false positive rate, besides the need for dietary restrictions and discontinuation of drugs and teeth brushing [8,9].

We found a relatively high adenoma detection rate, but our figures for CRC and high-grade dysplasia adenomas were in line with other published results [10,11]. Our study had the limitation that only a relatively small number of volunteers were evaluated by colonoscopy. However, we also evaluated those participants with a negative test, although in a smaller percentage than those with a positive-test. This allowed a more accurate evaluation in relation to sensitivity and specificity. Given that we offered colonoscopy to all volunteers, regardless of their i-FOBT result, the low rate of acceptance demonstrates that many volunteers are reluctant to undergo an invasive procedure. Thus, i-FOBT can also be a useful tool to reinforce the need for colonoscopy, mainly in those volunteers who are positive; this could increase the chance of CRC detection, expanding screening programs and hence reducing the incidence of CRC. On the other hand, the low acceptance of colonoscopy could make it difficult to analyze the sensitivity and specificity of the test.

One limitation of the method is that i-FOBT could be affected by certain medications, such as aspirin and non-steroidal anti-inflammatory drugs, because they may cause gastrointestinal erosions and subsequent bleeding in some patients, leading to positive results. However, a recent publication demonstrated that the positive predictive value of i-FOBT was not affected by ongoing antithrombotic therapy [12]. Another advantage of i-FOBT is that a positive test may be useful for predicting small bowel disease in patients with occult obscure gastrointestinal bleeding and negative colonoscopy [9].

Our findings confirm that i-FOBT is specific for predicting lesions in the lower gastrointestinal tract. The sensitivity for CRC detection is more than 90%. The acceptance rate was excellent, with 91.2% returning the i-FOBT. The detection rate of CRC was 1.05% and the positivity rate of the method

**Table 1** i-FOBT-test performance compared with colonoscopy

Predictive values	Any neoplastic lesions	Cancer	Adenoma
Sensitivity (%)	31.9 (24.1-40.4)	91.7 (61.5-99.8)	26.7 (19.0-35.5)
Specificity (%)	83.4 (77.2-88.5)	79.6 (74.6-84.0)	83.7 (77.6-88.7)
Positive predictive value (%)	58.9 (46.8-70.3)	15.1 (7.8-25.4)	51.6 (38.6-64.5)
Negative predictive value (%)	62.1 (55.7-68.3)	99.6 (97.7-100)	63.6 (57.2-69.7)
Positive likelihood ratio	1.92 (1.28-2.89)	4.49 (3.40-5.95)	1.64 (1.05-2.54)
Negative likelihood ratio	0.82 (0.72-0.93)	0.10 (0.02-0.68)	0.88 (0.77-0.99)
Prevalence (%)	42.7 (37.2-48.4)	3.80 (1.98-6.54)	39.5 (33.9-45.2)

Confidence Interval CI 95%

i-FOBT, immunochemical fecal occult blood test

**Summary Box****What is already known:**

- Guaiac fecal occult blood test screening has been shown to decrease the incidence and mortality of colorectal cancer
- Although long-term, large, programmatic trials with immunochemical fecal occult blood testing (i-FOBT) have not yet been completed, prospective data support the effectiveness of i-FOBT as a screening tool, including some evidence that programmatic testing reduces colorectal cancer (CRC) mortality
- There are several varieties of the new immunochemical test with different sensitivities in different populations

**What the new findings are:**

- This prospective study of 1039 symptom-free participants showed a high compliance and high detection rates for cancers and high-risk adenomas
- The OC-Light test is a practical method for CRC detection in an average-risk population
- The OC-Light test has a very high sensitivity and negative predictive value

was 9.7%, being similar to the findings of other studies that employed this technique [3,4]. Lesions in the lower gastrointestinal tract were more frequent among participants with a positive i-FOBT result than among those with a negative result. The OC-Light test is a practical method for CRC detection in an average-risk population, since it is an easy one-step procedure, with high sensitivity, no dietary restrictions, and the result can be ready within 5 min after the delivery of hygienic sampling bottles.

In summary, we suggest that the OC-light test could be offered to a population that refuses to be screened by colonoscopy, given its huge positive predictive value for CRC.

However, patients need to understand that the test has a low negative predictive value for any neoplastic lesion.

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