

Short communication

Positive predictive value of fecal immunochemical test for high-risk colonic adenomas and carcinoma: A health maintenance organization cohort screening study in Lebanon



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ABSTRACT

Background and Study Aims: Fecal Immunochemical Test (FIT) is one of the leading modalities for colorectal cancer screening. Studies show that FIT is highly sensitive for the detection of colorectal cancer (CRC) but not similarly accurate for detection of pre-cancerous advanced adenomas (AA). We studied the performance metrics of FIT for the detection of CRC and AA in a health maintenance organization (HMO) cohort screening program.

Patients and Methods: Retrospective cohort study of asymptomatic persons of screening age belonging to a HMO. Endoscopy and pathology reports of those who tested positive were used to calculate the positive predictive value (PPV) of FIT, and characterize endoscopic findings on colonoscopy.

Results: Between 1995 and 2017, 3000 persons had screening fecal occult testing as part of their Employee Health Care plan. Of those, 150 had a positive qualitative FIT (cutoff 10 Åµg hemoglobin/g feces). All underwent colonoscopy, and median time to colonoscopy was 27 days. 4 (2.6%) had carcinoma (2 stage IIIA and 2 stage IIIB), 106 (70.6%) had adenomas of which 40 (26.6% of the total cohort) had advanced adenomas (≥ 1 cm, villous features, or high-grade dysplasia) giving a PPV for AA and carcinoma of 29% and 3% respectively. When stratified by age, the PPV of AA; carcinoma was [50–59 (21.7%; 0.0%)], [60–69 (14.6%; 4.2%)], [70–79 (42.6%; 2.1%)], [80–89 (33.3%; 11.1%)].

Conclusion: The performance characteristics of FIT testing are acceptable for population screening in resource-limited settings. The results of this study are helpful when discussing expectations prior to colonoscopy in people with positive FIT.

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Introduction

Colorectal cancer (CRC) is a significant contributor to cancer-related mortality and morbidity, with more than 1,800,000 new cases diagnosed annually and more than 880,000 deaths worldwide [1]. Mortality is associated with stage at diagnosis [2], and earlier detection via screening has been shown to improve mortality and morbidity from CRC [3]. Screening tests for CRC fall into two categories: Fecal Occult Blood Testing (FOBT), which detect trace amounts of blood in stool, and tests such as colonoscopy and sigmoidoscopy that assess the colon visually for the detection of premalignant and malignant lesions. Three types of stool-based

tests are in use: Guaiac-based FOBT (gFOBT), Fecal Immunochemistry testing (FIT), and Multi-Target Stool DNA tests with FIT (FIT-DNA) testing, which combines FIT testing with DNA mutations associated with CRC. In the Multi-Society Task Force recommendations on Colorectal Cancer, these tests are acceptable alternatives to colonoscopy for CRC screening [4]. Compared to structural testing, FOBT tests are non-invasive, risk-free, and do not require sedation, bowel preparation, or transportation to and from the testing site [4]. One study that compared participation rates for sigmoidoscopy, gFOBT and FIT found that FIT had the highest participation rate (32.4%, 49.5% and 61.5% respectively) [5]. Furthermore, studies comparing FIT and gFOBT found FIT to be more accurate for the detection of CRC and advanced adenoma (AA) [6].

One study showed that FIT-based screening programs were associated with a reduction of 22% of CRC-related mortality [7]. A

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meta-analysis on the diagnostic accuracy of FIT showed that it is sensitive and specific for the detection of CRC [8]. However, studies on the detection rates of colonic adenomas are not as promising. A systematic review of 18 studies showed sensitivity rates of 6%-56% for the detection of AA [9]. The variation between sensitivity rates was explained due to the use of different brands of FIT tests, and different cutoff values to define a positive test [9]. One review found that the increased participation rate of FIT is offset by the number of AA missed compared to screening by colonoscopy [6]. Our study is a retrospective cohort study of individuals belonging to a health maintenance organization (HMO) presenting for colonoscopy following a positive screening FIT test. Herein, we examine the positive predictive value (PPV) of FIT for AA and carcinoma, and we characterize the lesions found on endoscopy in a middle-eastern population. This is the first study to assess the PPV of FIT screening for colonic lesions in the Arab world.

Patients and methods

This is a retrospective cohort study conducted to determine the probability of finding high-risk adenomas or carcinoma in persons with a positive screening FIT. The population consisted of members of a HMO at the American University of Beirut Medical Center for employees and their family members. Inclusion criteria included any patient over the age of 50 eligible for CRC screening who were referred for FOBT testing. Those with a positive result were subsequently referred for colonoscopy. Individuals who had received previous CRC screening by FOBT, colonoscopy or sigmoidoscopy, and those who had prior colonic surgery were also excluded from the study. The FIT test used was Hemosure © (W. H. P. M., Inc, El Monte, CA). Hemosure is a qualitative FIT test that uses monoclonal and polyclonal antibodies to detect human hemoglobin in stool samples. The cut-off for a positive test is 10 Åµg hemoglobin/g feces. All colonoscopies were performed by 6 experienced endoscopists who had performed more than 1000 colonoscopies each. FOBT kits were not mailed, and samples were collected at the American university of Beirut Medical Center laboratories, per hospital protocol. Patient demographics, endoscopy and pathology reports were obtained from the Electronic Health Records (EHR). The PPV of AA was calculated according to the following equation (True Positive/(True positive + False positive)), where true positive is defined as individuals with a positive FIT test who were found to have AA on colonoscopy, and False positives were individuals with a positive FIT test who did not have an AA on colonoscopy. The study was approved by the Institutional Review Board. Advanced adenoma (AA) was defined as tubular adenomas ≥ 1 cm, presence of high-grade dysplasia, or adenomas with villous histology [10]. PPV for both advanced AA and carcinoma was calculated for the overall study population as well as after stratification by age (4 different age groups: 50–59, 60–69, 70–79, 80–89).

Results

Between 1995 and 2017, 3,000 individuals underwent FOBT testing for first-time screening purposes at AUBMC. Those with a positive gFOBT test were excluded (28 people); 150 people had a positive FIT. Median time to colonoscopy was 27 days. Of the 150 people, 4 (2.6%) had carcinoma (2 stage IIIA and 2 stage IIIB), 106 (70.6%) had adenomatous polyps and 40 (26.6%) had non-adenomatous polyps (Fig. 1). Of the people with adenomatous polyps, 40 (37.7%) had AN: 39 had adenomas ≥ 1 cm, 5 had adenomas with villous features, and 1 patient had adenoma with high-grade dysplasia (Fig. 2). The PPV for AA and/or carcinoma was 29.3%, and the PPV for carcinoma was 2.7%. Excluding people with

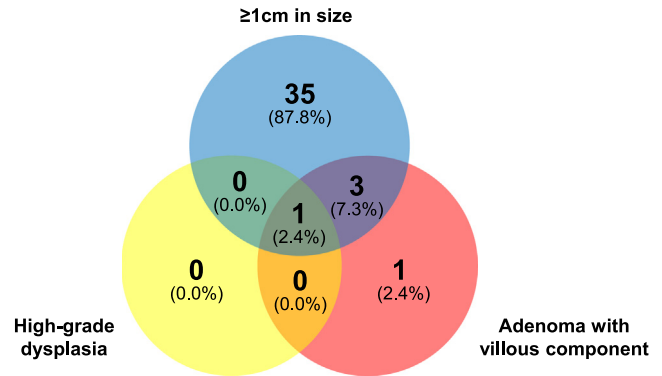


Fig. 1. Characteristics of high-risk adenomas identified on colonoscopy (N = 40).

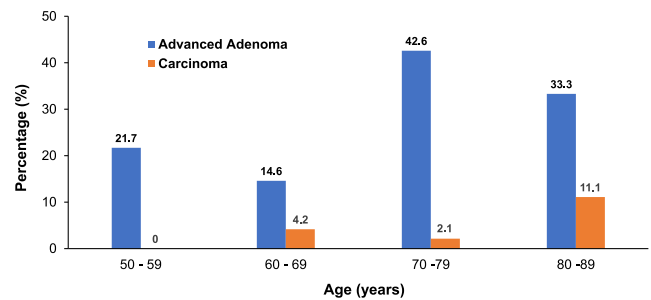


Fig. 2. Distribution of colonic lesions by age.

carcinoma, the PPV for AA was 27.4%. When the population was stratified by age groups, results were as follows [Age group] (PPV of AA);(PPV of carcinoma): [50–59 (21.7%; 0.0%)], [60–69 (14.6%; 4.2%)], [70–79 (42.6%; 2.1%)], [80–89 (33.3%; 11.1%)] (Fig. 3).

Discussion

This is the first study in the Arab world examining the PPV of FIT testing for colonic adenomas or carcinoma as part of a CRC screening program. We found that the overall PPV of FIT for advanced adenoma and carcinoma is 29% and 3% respectively. Several studies from the rest of the world have assessed the PPV of FIT for the

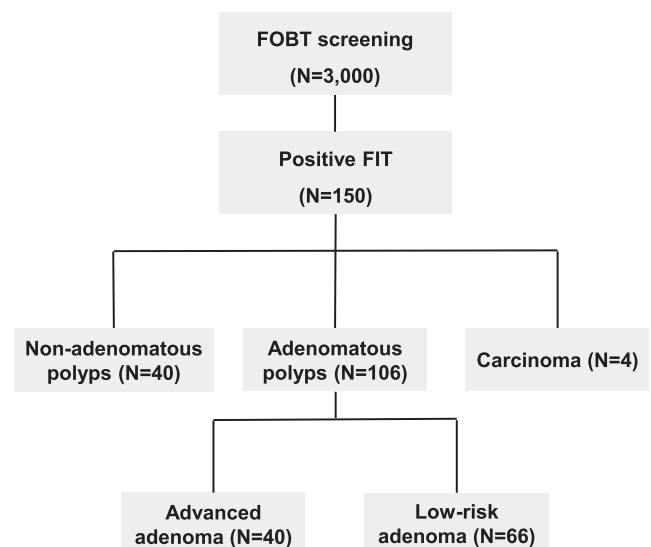


Fig. 3. Flow chart of patients.

detection of AA and carcinoma showing that the PPVs for AA ranged from 10 to 50%, and PPVs for carcinoma ranged from 5 to 15% [11]. Our reported PPV are on the lower end of this range. PPV is a parameter that is directly proportional to the prevalence of the disease in the studied population. However, in the Lebanese population, the prevalence of AA is 6%, and is comparable to European and American populations [12] while the prevalence of CRC is lower than developed nations, and this may account for the lower PPV of CRC [1,13]. The incidence of AA and CRC also increases with age, and this explains the increasing trend of the PPV and AA with age found in our study. PPV is also a function of sensitivity of the device used. The sensitivity of FIT tests is determined by the kind of FIT test used [14], as well as the cut-off used to define positive tests [8]. De Wijkerslooth et al. showed that for different cut-offs of the same test, increasing PPV of AA and CRC will be detected [15]. Furthermore, Chubak et al. showed that even at same cut-offs, different brands of FIT tests may have different PPV [11].

The use of screening colonoscopy in an average-risk population has an average yield of 0.3% for carcinoma and 5.7% for advanced adenoma. In our cohort, the use of FIT testing on an average-risk population provided a much larger yield of 3% and 29% respectively. Recently published guidelines by the American Society of Clinical Oncology have recommended that in limited or basic settings, gFOBT or FIT testing annually be used [16], and this study provides evidence that FIT testing may be used to increase the yield of screening colonoscopy. Furthermore, the PPVs found in this study may be used when counseling patients to ensure that they complete colonoscopy screening following FIT testing.

The strength of this study are the completeness of the HMO data set, the ascertainment of all relevant outcomes, as well as an exceptional timely access time from FIT results to colonoscopy. It is also the first study of its kind in the Arab world examining the value of FIT testing and findings on colonoscopy thereby providing real-world information on a preferred screening test for a common disease with an important health burden. Our study does however have a few limitations. It is a retrospective study, and so may be susceptible to selection bias. The study was conducted on members of an HMO, and the results may not be generalizable to the rest of the Lebanese population. This study also had a relatively small sample size, which means that the percentages discovered may not be representative of the population. However, this is unlikely as the numbers found are similar to those found in other studies. Individuals with negative FIT did not undergo colonoscopy, and so we could not calculate the number of false negatives and cannot contextualize the PPV found in this study with the performance characteristics (sensitivity, specificity, etc.) of the test at our institution. Furthermore, we did not assess whether colonoscopy identified causes of positive FIT tests other than AA. These include findings such as hemorrhoids, diverticular disease.

In an average-risk population, the performance characteristics of qualitative FIT testing are acceptable as population screening strategy in resource-limited settings. A positive FIT screening has a positive predictive value of 29% for advanced adenoma and 2.6% for carcinoma with an age-specific risk relationship. The

results of this study are helpful when discussing general expectations prior to colonoscopy in individuals with positive FIT screening.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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