Original Article
Middle East Journal of Cancer; January 2023; 14(1): 162-169

Utility of Fecal Immunochemical Test in Screening for Colorectal Cancer in Egyptian Individuals with Family History of Advanced Colonic Neoplasia

Ahmed Alwassief*♦, MD, Ibrahim Sabry Bakr, MD, Hosam M. Dawod***, MD**

*Department of Internal Medicine, Gastroenterology Unit, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt
**Department of General Surgery, Al-Hussein University Hospital. Al-Azhar University, Cairo, Egypt
***Departement of Tropical Medicine, Zagazig University hospital, Zagazig, Egypt

Please cite this article as: Alwassief A, Bakr IS, Dawod HM. Utility of fecal immunochemical test in screening for colorectal cancer in Egyptian individuals with family history of advanced colonic neoplasia. Middle East J Cancer. 2023;14(1):162-9. doi: 10.30476/mejc.2022.91147.1610.

Abstract

Background: Colorectal cancer (CRC) has a presumable low incidence in Egypt which did not rationalize for the development of screening programs up till now. The fecal immunochemical test (FIT) can facilitate colonoscopy uptake and increase enrollment in CRC screening programs. We aimed to explore the attitude of Egyptian individuals towards screening colonoscopy and establish the accuracy of FIT to detect advanced colonic neoplasia (AN).

Method: In this cross-sectional study, we offered a questionnaire to 1470 subjects with a family history of AN to establish their attitude towards the use of either direct colonoscopy (group A) or 2 step screening strategy; utilizing FIT followed by colonoscopy (Group B). Eventually, all included individuals underwent both FIT and colonoscopy.

Results: A total of 547 persons of the interviewed population (37.3 %) agreed to participate in the study, and group A cohorts were more likely to accept colonoscopy invitations. A single cycle FIT had a sensitivity of 76.2% a specificity of 92.2%, a positive predictive value of 28.1.2%, and a negative predictive value of 99%. The incidence of AN among the screened population was 3.9%, and CRC was found in 2 patients (0.4%).

Conclusion: Uptake of colonoscopy is more likely, if the invitation strategy was a direct colonoscopy invitation. A single-round FIT test had good sensitivity and specificity to detect AN. Egypt has a low incidence of CRC in individuals with a family history of CRC.

Keywords: Colonoscopy, Colonic polyps, Adenomatous polyp, Colonic neoplasms

♦Corresponding Author:
Ahmed Alwassief, MD
Department of Internal Medicine, Gastroenterology Unit, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt
Email: ahmedelwassief@gmail.com

Introduction

Colorectal cancer (CRC) is among three most common cancers in developed countries.[1] The incidence of CRC in Egypt remains unestablished. In one study, CRC

Received: May 07, 2021; Accepted: June 22, 2022

represented only a proportion of 4.4% of newly diagnosed cancer compared with 13% in western countries.[2] According to the results of another research, 14% of symptomatic individuals undergoing colonoscopy had CRC.[3] This dearth of data might be explained by Egypt's ineffective reporting and monitoring system for cancer. A CRC screening program has not yet been justified due to Egypt's historically low prevalence of the disease. CRC can be effectively prevented, if adenomatous polyps were diagnosed early.[4] Fecal immunochemical tests (FIT), barium enema, and screening colonoscopy were all used as screening tools. However, effective screening faces many barriers. The cost of the procedure, social and cultural factors, and lack of symptoms were notable barriers to CRC screening and specifically for colonoscopy. It was reported that up to 20% individuals with CRC have a family history of CRC. Moreover, having a first- degree relative with CRC nearly doubles the risk of developing CRC.[5] Current guidelines state that patients with a family history of CRC should start their screening for CRC by the age of 40, or 10 years younger than the earliest diagnosis in their families.[6] In general, the individuals with above-average risk of CRC are recommended to utilize colonoscopy as the screening method for CRC.[7] FITs are tests which detect the haemoglobin via detecting globin chains in stool immunologically.[8] Commercially available tests are mostly qualitative with a few quantitative tests, and both reported high sensitivity and specificity.[7] A recommendation from the European Commission considered a minimum screening colonoscopy acceptance "uptake" of 45% in average-risk individuals as an acceptable goal and a rate of 65% as a favorable rate.[9]

The main goal of the study is to determine whether Egyptian cohorts prefer a direct invitation to a colonoscopy or a 2-step screening strategy (by determining the acceptance rate of a colonoscopy invitation by each group) and, as a result, to recommend the approach that the Egyptian population is most likely to accept. Our secondary objective, is to explore the diagnostic efficiency of FIT test as a screening test in Egyptian patients with a family history of AN.

Materials and Methods

The research committee of the faculty of medicine, Al-Azhar University approved this cross-sectional study and ethical approval is part of the approval process committee. (code number: GM/gastro02; 3-1-2010). Verbal and written consent was obtained from all included individuals. Cohorts were identified using a questionnaire of patients referred to the gastroenterology and general surgery outpatient clinics of the hospital in the period from 1st of January 2010 to 1st of September 2019. The hospital provides medical care for a demographic population of about 80% of urban population and about 20% from the suburbs. At least one first-degree relative with colonic AN was present in every group. The youngest index patient was 34 years old, and none of the index patients had any inherited cancer syndromes identified. Cohorts were offered a questioner whether they prefer to perform colonoscopy directly or undertake a sequential screening procedure where step one would further stratify the risk of CRC by FIT test. Individuals were then interviewed and received a detailed description about the risk of CRC and the exact protocol of the study. It was clear that each person will undergo both FIT and colonoscopy in view of their initial above average risk assessment. In the initial analysis, patients were divided according to their response to the questionnaire into 2 groups. "Group A"; comprise those who chose to directly accept colonoscopy and "group B" are those who chose a 2-step screening protocol. The primary outcome of the study, measures the rate of colonoscopy uptake in the two groups to suggest the best screening strategy that would support the uptake of colonoscopy among Egyptians. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the FIT test are all measured by the secondary result. Patients' basic demographic data, including age and gender in addition to the number of family members with a history of advanced colonic neoplasia (AN), body mass index (BMI), life-style, history

Table 1. The effect of FIT test on colonoscopy uptake and risk stratification

Colonoscopy uptake	Patient preference		Total	*P*
	Group A	Group B		
	321/711 (45.1%)	226/759 (29.8%)	1470	0.000
Gender acceptance rate				
Male	336/751 (44.7%)		336/547 (61.4%)	
Female	211/719 (29.3%)		211/574 (38.6%)	
	FIT test accuracy/ performance			
Sensitivity	**Specificity**	**PPV**	**NPV**	**Total +ve**
16/ 21 (76.2%)	485/490 (99%)	16/57 (28.1%)	485/526 (92%)	57/547

FIT: Fecal immunochemical test; PPV: Positive predictive value; NPV: Negative predictive value

of alcoholism, tobacco smoking and NSAID treatment were all documented. Colonoscopy was repeated within a month for patients with suboptimal preparation or incomplete examination.

The qualitative FIT was assessed using the automated OC-sensor™ (Eiken Chemical Co, Tokyo, Japan) utilizing one stool sample following manufacturer instructions with a cut-off concentration of 20 µg hemoglobin per g feces. All individuals brought the sample on the day of colonoscopy.

Colonoscopy procedure

The colonoscopy procedure was performed blinded to the FIT result. Colonoscopy was done under conscious sedation using "2.5-7.5 mg midazolam" using Olympus colonoscope (CFQ240AL *Olympus* Optical Co Ltd., Tokyo, Japan or Pentax colonoscope EG-2731 PETAX medical Co Ltd., Tokyo, Japan). Lesion characteristics as site, size and morphology were all documented. Lesions were classified according to size into less than or equal to 1 cm, and more than 1 cm. Morphology of the lesion "Flat, ulcerative, polyploid or mixed polypoid/ ulcerative lesion" was recorded. The lesion's location was classified as proximal, if it was somewhere between the caecum and the transverse colon, or dista, if it was further away from the splenic flexure. Histological classification was either cancer, advanced lesions "adenomatous polyps with high grade dysplasia, larger than one centimeter or with significant villous component (>25%)" (9), and non-advanced lesions "adenomatous polyps with low grade dysplasia, hyperplastic polyps, bilharzial polyps or inflammatory polyps". Both CRC and advanced adenoma were combined as AN for collective risk stratification.

Statistical analysis

The statistical analysis was performed using a statistical software package (SPSS 17.0 version for Windows; SPSS Inc., Chicago, IL, USA). Descriptive statistics were recorded as percentage (%) in relation to the total number. Student t-test "results were recorded as mean and standard deviation" compared the mean values of continuous variables. Either chi-square x^2, or Fisher exact extract test were used for the analysis of categorical data. We used chi-square x^2 to assess the sensitivity and specificity of selected tests. A *P* values below 0.05 were considered statistically significant. All values were presented as the mean ± standard deviation unless mentioned otherwise.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Within the period from 1-1-2010 to 1-9-2019, "1470" subjects were identified with a family history of AN. Out of them, 711 persons chose to do colonoscopy directly and 759 chose a sequential screening pathway. A significantly more proportion of individuals who chose a single test strategy complied with doing colonoscopy as 45.1% of group A, eventually conformed to colonoscopy appointments, while 29.8% of group B complied with colonoscopy appointment ($P < 0.05$). Finally, 547 were eligible for this study and underwent both colonoscopy and FIT (Table 1).

About 10.4% (57 patients) of patients had detectable blood in the stool. A single cycle FIT

Table 2. The demographic characteristics of screened population

Factor	Mean or %	
Rate of colonoscopy uptake	37.3%	
Age	49 ± 9	
Sex		
Male	(336/547)	61.4%
Lesions Total	**(69/547)**	**12.6%**
Hyper-plastic polyps	(9)	1.6%
Non-specific inflammatory lesions	(10)	1.8%
Bilharzial polyp	(2)	0.4%
Benign adenoma	(27)	4.9%
Advanced adenoma	(19)	3.5%
Carcinoma	(2)	0.4%
Advanced adenoma and carcinoma	(21)	3.9%

exhibited a sensitivity of 76.2%, a specificity of 92.2%, a PPV of 28.1.2%, and an excellent NPV of 99% (Table 1).

The mean age of the screened population was 49 ± 9, and about 61.4% of them were of the male gender. 69 patients (12.6%) had abnormal colonoscopic findings (Table 2). Two out of 69 (0.4%) patients had adenocarcinoma, 3.5 % had advanced adenoma, 4.9% had benign adenoma, 3.9% had AN, 1.8% had inflammatory lesion, 1.6% had hyperplastic polyp, and 0.4 % had bilharzial polyp" (Table 2).

40% of the participants were in the age group (40-50 years old). Both groups [above 60-year-old and between 40–50-year-old] had the highest incidence of AN 6.8% and 4.6%, respectively, while the other 2 age groups recorded an identical rate of 2.1% ($P > 0.05$). (Table 3)

The mean age of cohorts with AN did not significantly differ from those with benign adenomas. Even though most of the ANs were located distally 71.4% that was of no statistical significance. The mean size of AN was significantly larger than benign adenomas 19 ± 11 mm versus 5.2 ± 2.2 mm ($P < 0.05$) (Table 4).

Two male cases of adenocarcinoma (0.4%) were discovered in the age group over 60 years old ($P < 0.05$) and both lesions were found distally and were of a size >1 cm ($P < 0.05$). In respect of gross morphology, 33.3% of mixed lesions were malignant versus 1.9 % of polypoid and 0% of both flat and pure ulcerative lesions ($P < 0.05$). Neither history of significant smoking, nor the number of family members with a history of CRC was related to CRC detection (Table 4).

Discussion

Among the initially evaluated individuals, 37.3% agreed to enroll in this study and complied to do the colonoscopy. Our cohorts were neutral in terms of choosing either one-step or 2-step screening strategy, However, those who choose a one-step colonoscopy approach were more likely to eventually undertake the test as 45.1% of this group eventually accepted colonoscopy, which fulfils the European Commission standards.[9] Consequently, the data supports limiting the design of a future screening colonoscopy program to rely solely on direct colonoscopy invitation. The total uptake rate of colonoscopy (37.3%) is higher than that reported by Lisi et al., 2010, who reported a 10% compliance rate.[10] Indeed, in their study, cohorts were of average-risk individuals, while our cohorts were above average risk. In general, it was observed that the patients with higher risk participate more frequently in CRC screening than those with average risk.[11] However, our reported uptake rate is still lower than the desirable required rate.[9]

The acceptance for colonoscopy was notably higher among males than females (44.7% versus 29.3%) (Table 1) [$P = .000$]. 61.4% of the participants in that study were males, resulting from social and cultural barriers (Table 1). Other studies pointed that female are less likely to approve on undergoing sigmoidoscopy mostly, because of social factors.[12] On the other hand, females were more likely to accept colonoscopy

Table 3. Age distribution of lesions

Factor		% of total lesions	Total	% within groups	*P*
Age distribution of AN	All ages	100.0%	21/547	3.8 %	
	<40	17.7%	2/97	2.1%	
	40-50	39.5%	10/216	4.6%	
	50-60	26.7%	3/146	2.1%	
	>60	16.1%	6/88	6.8%	NS

NS: Not significant; AN: Advanced neoplasia

invitation in Nordic populations.[13] It is established that many factors affect the decision to accept an invitation for colonoscopy. Economic, cultural, and social factors like violation (among men) and embarrassment (among women) were all barriers to the participation in colonoscopy.[14]

A single round of the FIT tests showed good sensitivity and specificity in detecting AN, 76.2% and 92%, respectively. Furthermore, the NPV of 99% points out that it would be a good screening test for those risk groups. The sensitivity and specificity of FIT was a subject of scrutiny in a multitude of studies with variable reported sensitivity ranging from 15.1% to 78.8% and relatively high specificity ranging from 96.8% to 85.7%.[15-16] In general, the more sensitive the test, the less specific it is. In one study, the test largely depended on the blood concentration as represented by µg of blood /g of stool. Using different cut-offs, yielded variable sensitivity and specificity with an observed linear increased in sensitivity parallel to the decrease of the threshold of detection of stool hemoglobin, being most sensitive 74.3% at a threshold of 10 µg/g. The researchers reported that at a detection threshold of 20 µg/g, which is identical to the one used in our study, a sensitivity, and a specificity of 79.0% and 93.5% were established, respectively. Moreover, the diagnostic performance of quantitative FIT test was better than qualitative tests as the odds ratio for detection of "suspicious cancer and cancer" versus "normal" sample by the quantitative FIT was about three times higher than that of the qualitative FIT.[17] Even though we used a qualitative FIT, the lower detection limit of the test was 20 µg/g, a threshold that showed a sensitivity and a specificity of 74.3% and 92.6% in a recent study.[16] We believe that when using a single cycle test a lower threshold should be used as it allows for a higher NPV as evidenced in our results. Despite the fact that those who choose the FIT test as a screening policy complied least to do colonoscopy, the good performance of the FIT test can be used as a real-time screening strategy by general practitioners in primary health care facilities.

12.6% percent of people had anomalies identified. The age group older than 60 years had the highest frequency of abnormalities (18.2%), whereas the age group younger than 40 years had the lowest prevalence of abnormalities (7.2%) [Table 2]. AN was found in 3.9% of individuals. Variable incidence rates of colonic AN were reported worldwide, for example, it was 7% in patients with family history of CRC in a German study.[18] The age group above 60 years old had the highest incidence of AN 6.8%. Moreover, the age group between 40–50 year-old showed also a high rate of AN of 4.6%. The high rate of detection in this age group might be in terms of the selection bias with the large number of patients in the 40-50 years old age group "almost 40% of all studied population versus 16% in the persons above 60 years old, consequently their results might have been more representative of the extent of the problem. On the other hand, there is mounting evidence that CRC is more common among younger people in Egypt. In one research, 38% of CRC patients from Egypt were under the age of 40.[19] Another research group concluded that the patients with CRC had the youngest mean age reported among gastrointestinal neoplasms in Egypt (44.11 +/- 14.08 years) and that the incidence of CRC had risen in patients between 40-60 years compared with other age groups within the preceding decade of the study.[20] Further evidence was provided by Abou-Zeid et al., reported that familial cancer syndromes are not the cause of the pattern of CRC age distribution in Egypt which have a predilection to younger

Table 4. The characteristics of AN and CRC

Factor	Lesion/Total	% or Mean + SD	*P*
Location			
Distal	15/21	71.4%	ns
Age			
Advanced adenoma	19/547	49 ± 9	
Non-advanced adenoma	526/547	51 ± 9	ns
Size			< 0.001
AN	21	19 ± 11	
Non-advanced neoplasia	47	5.2 ± 2.2	
Characteristics of CRC lesions			
Age groups			
<40	0/97	0%	
40-50	0/216	0%	
50-60	0/146	0%	
>60	2/88	2.3%	0.019
Sex			
Male	2/336	0.59%	
Female	0/211	0%	ns
Location of cancer			
Distal	2/46	4.3%	
Proximal	0/23	0%	ns
Morphology			
Polyploidy	1/54	1.9%	
Ulcerative	0/4	0%	
Mixed	1/3	33.3%	
Flat	0/8	0%	0.015
Size			
<1cm	0/48	0%	
>1cm	2/21	9.5%	0.03
Family members			
One	2/535	0.4%	
More	0/12	0%	ns
Smoking			
Yes	2/467	0.4%	
No	0/60	0%	ns

NS: Not significant; CRC: Colorectal cancer; AN: Advanced neoplasia

generations.[21] Collectively, these data point out that the current perception of low incidence of AN in the colon is a mere perception of the tip of the iceberg. We noticed that AN was more in the distal colon 68.4%, which is comparable to the classically reported data.[22]

In our study, CRC occurred in 0.4% of screened individuals "two patients". In one German study, the rate of CRC in relatives of patients with CRC was 1.2%.[18] Another Spanish study reported a CRC rate of 1.9% in 1st-degree relatives of CRC patients;[23] however, in that study, 14.8% of the participants had criteria of lynch syndrome which was not fulfilled in any of our screened individuals. A French study reported the rate of carcinoma in relatives of patients with large adenoma to be 4.2%.[24] Another Iranian study detected CRC in 2.2% of relatives of CRC patients.[25] However, it still supports the idea that the prevalence of CRC is low in Egypt, especially in the above-average risk category. This fluctuation in the rate of detection may reflect epidemiological and methodological discrepancies between various studies. Male patients with distal lesions and CRC diagnoses were both older than 60 years old. Age-specific incidence of cancer colon in males showed a progressive rising reaching a maximum in patients over 70.[2] Both lesions had a polypoid proportion which is in agreement with Kaku et al., who reported that most CRCs had polypoid morphology.[26] The observation that smoking was not a significant risk of CRC should be cautiously interpreted as the number of smokers in the sample was only 60 persons "less than 10% of the sample size". Moreover, the lack of association between the number of family members with the history

of CRC and the occurrence of CRC should be interpreted with caution, as only 12 persons had more than one family member with CRC. We are aware that the lack of a control group of individuals with average risk is a limitation of this study, but recruiting individuals with average risk for screening colonoscopy was difficult in view of the reported low incidence in Egypt, health literacy and fatalism. We only ran one round of the FIT test, which is another drawback. This was a preliminary research to look at how Egyptian cohorts behaved, while selecting AN screening test. Respect of real facts on the ground that Egypt does not have an active screening program necessitated that we select the least economically burdening strategy that can be accepted by both health authorities and patients as well.

Conclusion

We conclude that the direct invitation to colonoscopy strategy is more successful than two steps invitation policy to facilitate colonoscopy uptake in Egyptians. However, the good diagnostic performance of single-round FIT, supports its use as a real-time CRC screening test in primary health care facilities. Regarding the incidence of CRC, Egypt is a country with a low-risk of CRC that affects mainly older individuals.

Conflict of Interest

None declared.

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