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Feasibility of Colon Cancer Screening by Fecal Immunochemical Test in Iran

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Abstract

Background: Colorectal cancer (CRC) is the third most common cancer in Iran, where there is no mass screening for the disease yet. We aimed to measure the feasibility of a pilot CRC screening program based on fecal immunochemical test (FIT) in Iranian population and the implications for scaling-up at the national level.

Methods: A single quantitative FIT was offered by health navigators to individuals aged between 45 and 75 years in primary health centers in rural and urban areas in Tehran. Participants who had a positive FIT were referred for colonoscopy.

Results: A total of 1044 asymptomatic average-risk individuals were enrolled. The mean age (SD) was 54.1 ± 7.0 years and nearly 63.0% (n = 657) were female. Only a small fraction of the participants had a prior screening practice (2.2%) and were aware of colon cancer (13.7%). In sum, 1002 returned the FIT kit, of whom the stool sample was unsatisfactory for testing in six participants (0.6%). The FIT uptake was 96.0%, positivity rate was 9.1% and the detection rates were 11.9% for adenomas and 7.1% for advanced adenomas. No cancer was detected. The positive predictive value (PPV) of the FIT was about 17% for any colonic neoplasms.

Conclusion: This is the first study that reports minimal quality metrics within a CRC screening process. FIT modality as a test of choice for colon cancer screening in average-risk people is a safe and highly acceptable method of screening in Iranian people. The results of the current study may not be limited to Iranians, and could have implications to other developing countries with similar trends of CRC epidemic.

Keywords: Colorectal cancer, feasibility studies, patient navigation, population screening

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Introduction

Colorectal cancer (CRC) is the third-most common cancer in Iran, with an age-standardized rate of 11.1 per 10^5 person-years and an estimation of 7163 new cases and 4262 deaths, annually.[1,2] A rapid rise in CRC incidence has been reported in East Asian regions, such as Hong Kong, Taiwan, and Thailand, equal to the rates from Western countries.[3,4] Similar trends, although still relatively slow, have been observed in West Asian countries like Iran[5] and other counterparts in the region, including Saudi Arabia, Jordan, Yemen and Egypt, over the recent decades.[6-8] Mass screening of CRC is not yet available in Iran; however, our previous data from an opportunistic screening setting showed that the prevalence of adenoma in average-risk asymptomatic individuals is comparable to those in populations that are considered to have high incidence of CRCs.[9]

Although screening colonoscopy is an effective preventive method that is shown to reduce the incidence and mortality of CRC in developed nations,[10,11] the associated cost and resources required for organized colonoscopy prohibit its use as primary screening test in low-resource settings.[12] On the other hand, stool blood tests with non-invasive nature and desirable uptake can reduce unnecessary colonoscopies, thus preventing harms and lowering costs. In this context, a stool test with newer technology, fecal immunochemical test (FIT), appears to have an acceptable diagnostic yield for CRC in screened populations.[13,14] Therefore, developing countries with limited colonoscopy capacity may consider FIT as the initial screening test for CRC, with referral for colonoscopy for triage of FIT positive individuals.[12]

In Iran, opportunistic testing for screening is available, yet the majority of people are not informed of their cancer

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risk or the available screening tests, and/or never receive a physician recommendation for screening.[15,16] This calls for adopting effective strategies for CRC prevention in these populations. Among preventive strategies, health navigation has a substantial role in improving cancer screening[17,18] in which health providers work with patients to identify their individual health needs and reduce any barriers that make it difficult for patients to receive quality and timely follow-up diagnostic and treatment care.[19–21]

There is increasing interest in mass CRC screening programs among our expert advisory group in the Ministry of Health and Digestive Diseases Research Institute (DDRI) to make decision about whether Iran should have a national CRC screening program. But before implementing an organized CRC screening program in the nation, we need to collect information which could not be extrapolated from other countries such as test participation/acceptability, screening barriers, test positivity, preliminary data on cost, and health service implications. In this pilot project, we incorporated a health navigation system into screening program and aimed to measure the FIT uptake and performance in population aged between 45 and 75 years as the main outcome and determine the feasibility of the test for CRC screening in Iran before scaling-up at the national level.

Materials and Methods

Study Plan, Setting, and Participants

Decisions on the screening parameters, such as target age and type of the stool test, were made by the expert advisory group in DDRI on the basis of the existing literature on the mortality benefit, participation, cost, resource, implications, sensitivity, specificity, and quality control as well as the potentials for long-term availability of the test to the nation. The primary care staff and physicians were also involved in developing the screening pathway and planning the study. Our study setting was Eslamshahr County in Tehran, because of its diverse ethnic population in both urban and rural areas with enough health care providers and capacity to deliver a screening service and to manage the requirements of the program.

We included all primary health care centers in Eslamshahr county in our sampling frame and 6 of them (3 in rural and 3 in urban settings) were randomly selected. We considered 1044 persons in total (174 per center) to be screened, assuming 60% uptake rate for FIT, as the main outcome of the study. As screening registry is not established in Iran, we utilized a population registry to identify and invite people eligible for screening, using either primary health care database or the municipal registries. Average-risk asymptomatic individuals aged between 45 and 75 were enrolled in the study. Individuals who met the following criteria were excluded from FIT testing: personal history of CRC or adenoma or inflammatory bowel diseases, or a family history of CRC (i.e. first degree relatives) or hereditary CRC syndromes, or having symptoms suggestive of CRC (e.g., rectal bleeding, anemia), or individuals who had been recently screened for CRC. Informed consent was obtained from all eligible participants.

Health navigation has proved to be successful in improving individual's access to the available health services[19,20]; therefore, we used a patient navigation system in order to replace a doctor consultation and thereby save the associated costs. The navigation system in this study addressed system and individual barriers that participants might face deciding to use FIT screening test and colonoscopy. For this purpose, native public health workers in urban and rural health centers (referred to hereafter as health navigators) were hired and participated in an 8-hour training workshop, reviewing basic information on CRC and screening tests and study protocol in details (e.g., the tasks and responsibilities such as participant recruitment, conducting interviews, risk-assessment, offering stool-based tests, reminder calls, administering educational sessions, and giving appropriate feedback). Invitation was both by in-person or phone call in rural areas, and by phone call or public announcement in urban areas. During the initial contact, individuals were assessed for eligibility by health navigators. High risk people identified through the feasibility study were referred directly to colonoscopy centers to follow their ongoing surveillance needs coordinated through the screening program. Eligible individuals were required to schedule for an in-person interview administered by health navigators at the selected health centers. During the interview, health navigators assessed participant's awareness using local language in a plain and understandable way to overcome language difficulties in communication. The health navigators spent about 30 minutes with each participant to address FIT testing barriers and cover basic information on CRC symptoms, risk factors and screening tests. They also addressed respondents worries, explained factual information against common myths about CRC (e.g., CRC only affects men), when needed.

Screening Tests

With regard to type of screening test, we used a quantitative immunochemical test, iFOBT German kit (Hemoglobin ELISA Kit) for *in vitro* determination of hemoglobin in stool. This test has been previously shown to be easy to handle and acceptable to service providers and requires no dietary restrictions for users.[22,23] Individuals were asked to keep buffer containing fecal samples at 4°C and return

them within 2 days after sampling to the health houses to be sent to the laboratory in health care system for analysis. At the end of the interview, the participants received a free of charge FIT kit plus an educational pamphlet in plain language on how to obtain stool specimens and were asked to return kits in person. Reminder calls were sent after one week if kits were not returned. Delivery of buffer containing samples to laboratory for analysis was managed by the health navigators in screening centers. In the laboratory, buffer-based samples were tested by trained lab experts after assessing and confirming the quality of FIT measurements following the manufacturer brochure. The cut-off to indicate test positivity was established at ≥20 μg Hb/g of feces (equivalent to ≥100 ng Hb/mL of buffer). We chose a relatively low cut-off level, yielding high sensitivity but low specificity, because our sample included asymptomatic average risk adults and we intended to detect all colonic neoplasms present on the first screen if possible. One week after sample collection, FIT results were sent back to the correspondent health centers from the laboratory. Health navigators notified all participants with a negative FIT of their results and that they should plan to receive FIT in the next year. They also notified individuals with a positive FIT result and recalled them to schedule a colonoscopy within 4 weeks. Health navigators delivered detailed instructions on bowel preparation for colonoscopy by taking three Bisacodyl tablets and 5 L of polyethylene glycol in divided doses on the day before colonoscopy. Participants were informed about the need for an escort and taking a day off from work for colonoscopy. Referral for colonoscopy by the health navigators was required in the screening program and facilitated by health navigators who personally contacted the colonoscopy center and made an appointment. Moreover, to avoid some common potential barriers like time restrictions and costs among referred participants, additional free colonoscopy services were provided -out of routine colonoscopy wait times- and free transportation to Shariati hospital designated as a colonoscopy center.

Colonoscopies were performed in Shariati hospital in Tehran by an experienced endoscopist (regularly having performed more than 200 procedures per year) under conscious sedation. Colonoscopy findings and any immediate complications of the procedure were documented in a standardized report form. If colonoscopy detected some cancers, they were referred to the tertiary care centers to be treated, and if found, polyps or lesions were biopsied or removed and sent in separate formalin containing jars to the pathology department. Specimens were evaluated by two experienced gastrointestinal pathologists.

Study Measures and Endoscopic Data

Data on participants' demographics, cancer risk and screening knowledge, and behavioral parameters, were collected in this study. We also measured the early indicators of effectiveness of the screening program including: participation rate, kit return rate, FIT positivity rate, colonoscopy referral rate, colonoscopy completion rate, adenomas and CRC detection rates. Participants were considered compliant if they completed and returned the FIT kit, and the uptake of individuals with positive FIT result who referred to the colonoscopy, was also reported. A false positive FIT in the participants was defined as a positive FIT result, but with no colonic lesions (i.e., polyps, adenomas, CRC) detected by total colonoscopy. We calculated the positive predictive value (PPV) for colorectal neoplasms as the number of participants with a positive FIT result who were detected with colonic neoplasms (i.e., polyps, adenomas, CRC) by colonoscopy divided by the total number of participants with positive abnormal FIT result who underwent total colonoscopy. Obesity and abdominal obesity were respectively defined as body mass index (BMI) ≥ 30.0 kg/m^2 and abdominal circumference ≥90 cm in men and ≥80 cm in women.

We documented the quality of bowel preparation and sedation, cecal intubation rate and serious complications requiring hospital admission. Lesion features (i.e., number, size, and location) were documented in the colonoscopy reports by the endoscopists. Advanced adenomas included adenomas sized ≥10 mm and/or with a villous component, and/or with high grade dysplasia. Detection rates were defined as the number of procedures with at least one colonic neoplasm detected divided by the total number of complete colonoscopies performed. We excluded incomplete procedures and those with inadequate bowel preparation from the calculations.

Statistical Analysis

We used mean and standard deviation for presenting quantitative variables, and percentages for describing qualitative variables. We divided participants into two groups (i.e., individuals who were aware and not aware about CRC and screening) and applied *t* test and χ^2 or Fisher exact tests for comparing means and proportions, respectively. We also assessed the adjusted effect of factors associated with cancer awareness using multivariate logistic regression model. The 95% CI was calculated for estimates, where needed. Two-tailed tests were applied with a *P* value of <0.05 considered statistically significant.

Results

Participants' Characteristics

We invited a total of 1542 adults aged 45–75 years. After assessing for eligibility criteria, 104 were not eligible due to

the following exclusion criteria: personal history of CRC or colorectal polyps (n = 36), history of inflammatory bowel diseases (n = 15), already having symptoms suggestive of CRC, e.g., rectal bleeding, anemia (n = 36), and having already undergone CRC screening within the past year (n = 17). Among eligible invited adults, a total of 1044 individuals, half living in rural areas and half in city, were randomly enrolled and agreed to participate in the FIT screening, all of whom were interviewed and given FIT kits. Demographic characteristics of the study sample are shown in Table 1. The mean age of the participants was 54.1 years, 62.9% (n = 657) were female and 90.2% (n = 942) were married. This study covered a poorly educated area, with only 9.1% having completed 12 or more years of schooling and 31.6% retired or employed. The vast majority of participants had health insurance (95.5%) and were invited to the study through phone calls (96.3%), except for 3.7% who could not be reached by telephone in rural centers, where a home visit was made. Over half of the individuals (55.4%) rated their general health status at the level of good to excellent. More than one fifth of participants had a family history of cancers other than colon cancer and diabetes. Overall, about 18.0% of respondents were smokers, 41.0% were obese and 33.4% regularly used nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin (Table 1).

Table 1. Characteristics of participants (n = 1044)

Parameters	
Age (mean ± SD)	54.1± 7.0
Females, No. (%)	657 (62.9)
Married, No. (%)	942 (90.2)
Residency area (rural), No. (%)	530 (50.8)
Ethnicity, No. (%)	
Fars	432 (41.4)
Azari	471 (45.1)
Kurd	68 (6.5)
Lur	73 (7.0)
Years of schooling, No. (%)	
Nil	297 (28.4)
Primary (1–5 years)	514 (49.2)
Secondary (6–11 years)	138 (13.2)
High School and University (12+ years)	95 (9.1)
Job, No. (%)	
Unemployed	659 (63.1)
Retired or employed	330 (31.6)
Farmer or workers	55 (5.3)
Invitation method, No. (%)	
Phone call	1005 (96.3)
In-person/home visit	39 (3.7)
Medical insurance, No. (%)	997 (95.5)
Self-rated general health (good-to-excellent), No. (%)	578 (55.4)
Family history of cancers other than colon cancer, No. (%)	226 (21.7)
Diabetes, No. (%)	211 (20.2)
BMI (kg/m^2)*, (mean ± SD)	29.4 ± 5.8
Obesity (BMI ≥ 30.0 kg/m^2), No. (%)	422 (41.0)
Abdominal obesity**, No. (%)	933 (90.6)
Current or ex-smoker, No. (%)	187 (17.9)
Opium use, No. (%)	92 (8.8)
Alcohol use, No. (%)	30 (2.9)
Regular use of aspirin or NSAIDs***, No. (%)	349 (33.4)
Cancer awareness, No. (%)	173 (16.6)
Colorectal cancer	143 (13.7)
Colonic polyps	87 (8.3)
Colorectal cancer screening	96 (9.2)
Fecal occult blood testing	31 (3.0)
Sigmoidoscopy/colonoscopy	72 (6.9)
Prior fecal occult blood testing, No. (%)	5 (0.5)
Prior colonoscopy, No. (%)	23 (2.2)
Source of medical information, No. (%)	
Media (e.g., TV, the internet, print magazines)	782 (74.9)
Medical staffs (e.g., physician, nurse, health provider)	219 (21.0)
Laypeople	43 (4.1)

*Data for BMI, obesity, and abdominal obesity were available for 1030 participants; **Abdominal circumference ≥90 cm in men and ≥80 cm in women; ***Nonsteroidal anti-inflammatory drugs.

Cancer Awareness and Prior Screening Practice

We noticed a very poor awareness about colon cancer (13.7%) or polyps (8.3%) or CRC screening (9.2%). Only 6.9% of the participants had heard about colonoscopy and 2.2% had undergone the procedure within the past 10 years. FOBT (fecal occult blood testing) as screening modality was known to only about 3.0% of participants with less than 1% having received a prior FOB testing for CRC screening. The majority of participants (74.9%) reported mass media (i.e., radio, TV, magazines, social networks, and the internet) as their main source for medical information, while only about 21.0% stated that they received health information from medical staff and 4.1% mostly relied on laypeople in this regard (Table 1).

We compared baseline characteristics according to awareness about CRC and screening tests and this analysis revealed some disparities between the two groups in terms of ethnicity, years of schooling, and family history of cancers; whereas other baseline characteristics did not differ between the study groups (Table 2). That is, awareness about colon cancer and screening tests significantly varied according to the ethnic groups ($P < 0.001$). We also recorded significantly higher cancer awareness by increasing years of schooling ($P < 0.001$). Likewise, there was greater cancer awareness in individuals who had a positive family history of cancers compared to those who did not ($P = 0.02$) (Table 2).

We performed multivariate regression analysis including years of schooling, family history of cancers, and ethnicity in the model. Findings indicated that greater years of schooling was associated with higher cancer awareness (trend $P < 0.001$); also, family history of cancers was independently associated with cancer awareness with an adjusted odds ratio of 1.5 ($P = 0.036$). Moreover, adjustments slightly strengthened the relation for ethnicity, where Azari and Lur ethnics reported significantly poorer cancer awareness in comparison to

Table 2. Factors Associated With Cancer Awareness in Study Participants (n = 1044)

Variables	Yes (n = 173), No. (%)	No (n = 871), No. (%)	*P*
Age (y)			0.18
45–50	64 (37.0)	269 (30.9)	
55–59	75 (43.3)	384 (44.1)	
60–75	34 (19.7)	218 (25.0)	
Gender			0.29
Female	115 (66.5)	542 (62.2)	
Male	58 (33.5)	329 (37.8)	
Residency			0.07
Rural	77 (44.5)	453 (52.0)	
Urban	96 (55.5)	418 (48.0)	
Marital status			0.55
Married	154 (89.0)	788 (90.5)	
Single	19 (11.0)	83 (9.5)	
Ethnicity			**< 0.001**
Fars	104 (60.1)	328 (37.7)	
Azari	46 (26.6)	425 (48.8)	
Kurd	17 (9.8)	51 (5.8)	
Lur	6 (3.5)	67 (7.7)	
Job			0.24
Unemployed	116 (67.0)	543 (62.3)	
Farmer or worker	5 (2.9)	50 (5.7)	
Employed or retired	52 (30.1)	278 (32.0)	
Years of schooling			**< 0.001**
Nil	21 (12.1)	276 (31.7)	
Primary (1–5 years)	88 (50.9)	426 (48.9)	
Secondary (6–11 years)	30 (17.3)	108 (12.4)	
High School and University (12+ years)	34 (19.7)	61 (7.0)	
Smoking			0.13
Yes	24 (13.9)	163 (18.7)	
No	149 (86.1)	708 (81.3)	
Opium use			0.94
Yes	15 (8.7)	77 (8.8)	
No	158 (91.3)	794 (91.2)	
Alcohol use			0.61
Yes	6 (3.5)	24 (2.8)	
No	167 (96.5)	847 (97.2)	
Regular use of aspirin or NSAIDs			0.57
Yes	61 (35.3)	288 (33.0)	
No	112 (64.7)	583 (66.9)	
Family history of cancers*			**0.020**
Yes	49 (28.3)	177 (20.3)	
No	124 (71.7)	694 (79.7)	
Diabetes			0.99
Yes	35 (20.2)	176 (20.2)	
No	138 (79.8)	695 (79.8)	
Obesity (BMI ≥30.0 kg/m^2)**			0.48
Yes	75 (43.3)	347 (40.5)	
No	98 (56.7)	510 (59.5)	
General health			0.10
Fair to poor	86 (49.7)	379 (43.5)	
Good to excellent	87 (50.3)	492 (56.5)	
Source of medical information			0.34
Mass media	122 (70.5)	660 (75.8)	
Medical staffs	43 (24.9)	176 (20.2)	
Laypeople	8 (4.6)	35 (4.0)	

Abbreviations: BMI, body mass index; NSAIDs, Nonsteroidal anti-inflammatory drugs.
**Family history of cancers other than colon cancer; ***Data for obesity were available for 1030 participants.

the Fars participants (*P*'s < 0.01) (Table 3).

Screening Uptake and Findings

Screening results are presented in Table 4. In sum, 96.0% (1002/1044) returned the FIT kit, of whom stool sample was deemed unsatisfactory for testing due to leakage of the buffer in 6 participants (0.6%). Reminder calls were attempted in only 7.2% (n = 75) to return their samples. Overall, 95.4% completed one round of the test with only one stool sample, and FIT on the participants showed a positive rate of 9.1% (n = 91). Of the 91 participants with a positive FIT result, 82.4% were reachable and referred to colonoscopy center, of whom 45 (60.0 %) underwent colonoscopy (Table 4). None of the demographic data presented in Table 1 was found to be associated with FIT uptake, with the exception of the residency area. There was greater FIT uptake among participants in rural centers than urban areas (98.1% vs. 93.8%, respectively [*P* < 0.001]). Also, females had a slightly higher yet non-significant use of FIT than males (96.5% and 95.1%, respectively [*P* = 0.26]).

Cecal intubation rate was 95.0% and repeat colonoscopy due to inadequate bowel preparation was performed in 4 cases within 1 month from the first procedure, of whom 3 did not have adequate bowel preparation at the second colonoscopy. There was no serious adverse event or complication related to the colonoscopy. Colorectal polyps were detected in 16.7% (n = 7/42) of participants who underwent colonoscopy, including 11.9% (5/42)

Table 3. Predictors of Cancer Awareness in Study Participants (n = 1044)

Variables	Odds Ratio	95% CI	*P*
Years of schooling			
Nil	Reference		
Primary (1-5 years)	2.33	1.39-3.91	
Secondary (6-11 years)	2.76	1.47-5.16	
High School and University (12+ years)	6.37	3.40-11.93	<0.001*
Family history of cancers* (yes vs. no)	1.50	1.03-2.22	0.036
Ethnicity			
Fars	Reference		
Azari	0.40	0.27-0.60	<0.001
Kurd	1.26	0.67-2.35	0.478
Lur	0.31	0.13-0.75	0.010

* *P* value of the trend; ** Family history of cancers other than colon cancer.

Table 4. Results of Colon Cancer Screening Program

Variables	No. (%)
Received FIT kits	1044 (100.0)
Returned FIT kits	1002 (96.0)
Unsatisfactory sample	6 (0.6)
Received reminder call to return FIT kit	75 (7.2)
Completed one round of FIT	996 (95.4)
FIT positive	91 (9.1)
Not reachable on phone	16 (17.6)
Referred to colonoscopy center	75 (82.4)
Underwent colonoscopies	45 (60.0)

adenomas and 7.1% advanced adenomas (n = 3). No cancer was detected. The false positive rate and the PPV of FIT for any colonic neoplasm were 83.3% and 16.7%, respectively.

Discussion

The overall uptake rate for the first round of FIT testing among our participants was 96.0% which is much higher than those reported in the previous studies varying from 48.2% in the United States,[24] 49.9% in Korea,[25] 56.9% in Canada,[26] to 57% in the Netherlands.[27] Another interesting finding of the current study is that only few samples returned (0.6%) were unsatisfactory for testing. Adherence or participation rate is one of the most important factors in any screening program, yet CRC screening is underused throughout the world due to client-, provider-, and system-level barriers.[13] On the other hand, the vast majority of the respondents (>90%) apparently expressed unfavorable screening practice and very poor awareness about CRC and screening tests, of whom almost 78% were either illiterate or had less than 6 years of primary schooling.

Although the efficacy of any health intervention should be tested against a control group, we believe that this high uptake rate could be associated, in part, with the efficacy of our health navigation system which targeted and eliminated barriers to FIT screening among people visiting a primary care center. There is no unique model for health navigation programs as each addresses particular health needs in different local settings and populations.[18] Strong evidence supports that health navigation and endorsement by the primary care providers improve individual's compliance with screening tests and follow-up testing rates,[18,28-30] in particular among participants who had not previously received any CRC screening tests. Our data is overall consistent with the prior studies that showed that incorporating health navigation into CRC screening program successfully increases screening uptake.[31,32]

Like other studies, we observed favorable cancer awareness among well-educated individuals and significant variations among different ethnics[33-36] as Azari and Lur ethnics had significantly lower level of awareness compared to Fars individuals and Kurds. Possible explanations for such result include language or cultural barriers among these ethnics. In other words, most of medical information on the media or in health care facilities are provided in Persian, which may not be easily understandable by other ethnic groups who are illiterate or do not speak Farsi language. It is crucial, therefore, to be conscious of the impact that language and cultural barriers might have on cancer awareness and participation rates and to address such ethnic diversities in awareness campaigns in particular in poorly educated areas. Also, we recorded higher cancer awareness in respondents with a family history of cancers other than CRC, comparable with the same data highlighting the role of having cancer in family members in enhancing cancer awareness among relatives.[36,37]

Participation rate in FIT screening could vary by residency area[38] and we found significantly greater FIT uptake in rural compared to urban centers. This is possibly due to the greater impact of hiring local health navigators in the rural health setting who are believed to build a trust-based relationship with participants and establish an emotional rapport as supported and confirmed by previous studies in Iran.[39] Although uptake of FIT was very high, colonoscopy compliance rate among individuals with a positive FIT was 60.0% which was lower than that in other studies.[25] This might be due to some personal or cultural barriers to colonoscopy such as fear, low-risk perception, or embarrassment which may eventually have led to avoiding the procedure.[16,40,41] This warrants more efforts to identify factors associated with non-uptake of colonoscopy after referral and suggests that an effective screening program requires significant actions towards patient motivation and education addressing specific barriers to colonoscopy and referrals.

We used a single quantitative FIT in average-risk individuals FIT and applied a cut-off of 100 ng Hb/mL buffer (equivalent to 20 mg of Hb/g of feces). In the current study, FIT positivity rate for the first round was 9.1% which compares favorably with findings of other programs (4.4% to 9.3%) applying the same cut-off.[26,38,42,43]

The PPV of FIT for any colonic neoplasms was about 17.0% in our series compared to 48.0% from other reports.[43,44] The detection rates for adenomas and advanced adenomas were nearly 12.0% and 7.1%, respectively, which was far below what we reported previously among average-risk Iranian population.[9] This might be attributable to our younger sample with almost one-third being under 50 years as well as the limited number of colonoscopies performed in this study. Moreover, due to our small and non-representative sample of colonoscopies, the PPV estimate is not precise and thus large longitudinal multi-center studies would be needed to better characterize the FIT clinical performance (e.g., PPV and false positive rate) in Iran.

This is the first population-based study from the region that reports the feasibility of stool-based CRC screening using a real-time health navigation in Iran's health care settings. The results of this pilot study underline the landmark impact of health navigation on screening uptake and suggest even greater uptake rates in real-world settings by engaging health navigators and

integrating CRC screening with other preventive services in primary health care system in the nation.[45] However, our study has several limitations. First, we only assessed the acceptability and safety of FIT method of screening while a feasibility study covers issues of efficacy, cost-effectiveness, and equity, as well. So, further research is required to evaluate the aspects of feasibility of FIT screening modality thoroughly before deciding to introduce it in a subsequent national program. Second, our study sample does not seem to be representative of the general population as females comprised nearly 63% of the participants. Finally, we used a 1-sample FIT which might have underestimated the sensitivity of the test for detecting colonic neoplasms. However, a recent study showed that the sensitivity and specificity of FIT in detecting advanced colonic neoplasms in 1-sample FITs were the same as those of 2-sample FITs.[46]

In conclusions, this is the first study that reports minimal quality metrics within a CRC screening process for the pilot phase before expanding into a national program. Based on our results, FIT modality as a test of choice for colon cancer screening in average-risk people is a safe and highly acceptable method of screening among Iranian. Therefore, we may suggest consideration of FIT as an initial CRC screening tool along with other preventive services in primary health care system in the nation. Indeed, the observed high uptake of FIT suggests that individual's acceptability will likely be achievable with different settings, representing the possibility of mass CRC screening by FIT in Iran. On the other hand, according to the current data in a mass screening scenario targeting Iranians aged 50–75 yrs. (n~12 000 000) approximately 9% will have a positive FIT, equal to 1 080 000 colonoscopies annually. Given the very limited number of trained endoscopists (n~300) and the fact that individuals subject to diagnostic clarification may expand even further, this will put our health care system and colonoscopy capacity under pressure leading to high logistic demands and high patient burden. For these reasons, we need to reinforce the current existing opportunistic approaches for CRC screening by increasing public awareness[9] and apply risk stratification tools to reserve endoscopic services only for those subjects who are at higher risk and most likely to benefit. Moreover, we need more investigations to identify potential alternative to FIT alone as screening modality by studying the clinical performance of the multi-target stool DNA test (Cologuard®) in combination with FIT to reduce false positive results. The results of the current study may not be limited to Iranians, and could have implications to other developing countries with similar trends of CRC epidemic.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Authors' Contribution

HS designed the study, carried out the implementation, analysed the data, and wrote the manuscript; FB and CS verified the analytical methods and helped in interpreting the results and revised the manuscript; MA performed screening procedures; GH and AN were involved in planning and supervised the work and processed the laboratory data; SM, AD, and RM helped design the study, supervised the findings, and verified the numerical results. All authors discussed the results and contributed to the final manuscript.

Ethical Statement

This study was approved by the ethical committee of Tehran University of Medical Sciences (Ethic code: 416/642).

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