

RESULTS OF FAECAL IMMUNOCHEMICAL TEST FOR COLORECTAL CANCER SCREENING, IN AVERAGE RISK POPULATION, IN A COHORT OF 1389 SUBJECTS

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Abstract

Aim. The aim of this study is to evaluate the usefulness of the fecal immunochemical test (FIT) in colorectal cancer screening, detection of precancerous lesions and early colorectal cancer.

Material and methods. The study evaluated asymptomatic patients with average risk (no personal or family antecedents of polyps or colorectal cancer), aged between 50 and 74 years. The presence of the occult haemorrhage was tested with the immunochemical faecal test Hem Check 1 (Veda Lab, France). The subjects were not requested to have any dietary or drug restrictions. Colonoscopy was recommended in all subjects that tested positive.

Results. In our study, we had a total of 1389 participants who met the inclusion criteria, with a mean age of 61.2 ± 12.8 years, 565 (40.7%) men and 824 (59.3%) women. FIT was positive in 87 individuals (6.3%). In 57/87 subjects (65.5%) with positive FIT, colonoscopy was performed, while the rest of the subjects refused or delayed the investigation. A number of 5 (8.8%) patients were not able to have a complete colonoscopy, due to neoplastic stenosis. The colonoscopies revealed in 10 cases (0.7%) cancer, in 29 cases (2.1%) advanced adenomas and in 15 cases (1.1%) non advanced adenomas from the total participants in the study. The colonoscopies performed revealed a greater percentage of advanced adenomas in the left colon compared to the right colon, 74.1% vs. 28.6% ($p < 0.001$).

Conclusions. In our study, FIT had a positivity rate of 6.3%. The detection rate for advanced neoplasia was 2.8% (0.7% for cancer, 2.1% for advanced adenomas) in our study group. Adherence to colonoscopy for FIT-positive subjects was 65.5%.

Keywords: screening, colorectal cancer, faecal immunochemical test, advanced adenoma, occult bleeding.

Introduction

Colorectal cancer (CCR) holds the third place in incidence and the fourth place among the most common causes of cancer death worldwide [1]. Detection in the early stages of colorectal cancer, detection of adenoma in apparently healthy subjects, in whom the disease progresses asymptotically, through screening is resulting in the decrease of incidence and mortality through colorectal cancer [2]. Non-invasive tests, stool tests for occult bleeding (FOBT), are accepted today by most researchers in CRC screening [3].

The faecal test for occult bleeding is the least expensive and easiest test recommended by international guidelines for colorectal cancer screening [4]. Screening with FOBT has been shown to be effective in reducing mortality by 13% to 20% of CCR, both in randomized trials and controlled trials [2]. The traditional faecal occult blood test uses guaiac to detect peroxidase activity of heme in feces, but with a lower specificity and sensitivity compared to the fecal immunochemical test (FIT) that is using specific antibodies to detect human hemoglobin. Performing the faecal immunochemical test does not require dietary restrictions, which makes it more compliant for the people integrated in screening programs. Globin being rapidly digested in the stomach and small intestine, this test

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is more selective than the guaiac-based in detecting just blood in the colon [2]. FIT is a more expensive test than the guaiac-based, but requires one sample of stool, compared to two or three samples from three consecutive stools that the guaiac-based test requires [5]. So far there is only one large randomized controlled study, which shows after eight years of follow up a statistically significant reduction in rectal cancer by 32%, and three controlled studies showing a reduction in CRC mortality from 23% to 81% [2,4].

Aim

The aim of this study is to evaluate the usefulness of the FIT in colorectal cancer screening, detection of precancerous lesions and early colorectal cancer.

Material and methods

Participants in the study

Participants (people recruited for screening and which sent the feces sample to the laboratory) were asymptomatic persons, aged 50 years and 74 years inclusive. We excluded from the program subjects with known inflammatory bowel disease, colonic adenomas or cancer, those with a family history, first degree relatives with colonic cancer or adenomas, subjects that performed in the last two years a FOBT, those that performed in the last 5 years barium enema, CT colonography, flexible sigmoidoscopy or colonoscopy in the last 10 years. We also excluded subjects with rectal bleeding, hematuria, women with menorrhagia or during menstrual cycle, patients with cancer, cardiac, neurological, pulmonary, renal or hepatic diseases whose evolution is supposed to lead to death within a period of less than 10 years.

Faecal immunochemical test

Participants in the screening program received a stool container. They received instructions regarding the way the samples should be collected and handed to the laboratory within 24 hours of collection. We used a rapid immunochemical test HEM-CECK 1 (VedaLab, France). The immunochemical test contains antibodies for human hemoglobin, that does not react with animal hemoglobin, and is not influenced by vegetable food or fruit that have peroxidase activity.

Colonoscopy and the lesions

All patients with positive FIT were recommended to perform a colonoscopy under sedation-analgesia. Anesthesia was provided by an anesthetist who used midazolam, fentanyl and propofol. The patients were instructed on how they should prepare for colonoscopy and after being informed of the risks and the advantages of a colonoscopy, they gave a written consent accepting anesthesia and colonoscopy. The study was approved by the local Ethics Committee and was in accordance with the Helsinki Declaration of 1975.

Each person with positive FIT was informed about the importance and necessity of endoscopic examination

of the entire colon. Participants were recommended a colonoscopy if they have not taken treatment with anticoagulants, clopidogrel or nonsteroidal anti-inflammatory drugs in the last 5-7 days. Colonoscopies were performed by experienced gastroenterologists in our department, who also performed the biopsies and the polypectomies when it was necessary.

Colonoscopy was considered complete if caecum was reached (identification of the ileocaecal valve, appendiceal orifice). In every patient the type of lesion (adenoma, cancer) was identified, the number of lesions determined and a description was made stating the location, size and histology. Colon tumor lesions were biopsied and adenomas were removed using a polypectomy loop. Cancer was considered according to the revised Vienna classification, carcinoma invading submucosa or beyond. Dukes or TNM classification was used for advanced cancers.

Regardless of the histological structure, depending on the diameter or size, adenomas were grouped in adenomas ≤ 5 mm, adenomas with a diameter of 6 to 9 mm and adenomas ≥ 10 mm. Histologically, adenomas were classified as tubular, tubulo-villous or villous adenomas and dysplasia was classified as low grade or high grade. Cancer and advanced adenomas were analyzed separately but also together as clinically significant colorectal neoplasia or advanced neoplasia.

We defined advanced adenomas, colonic precancerous lesions at highest risk of malignancy, adenomas with at least one of these characteristics: size ≥ 10 mm and/or high-grade mucosal dysplasia and/or with a villous structure of $\geq 20\%$ (tubulovillous, villous) [6]. The term advanced neoplasia, includes cancer and advanced adenomas (there are studies that also include multiple adenomas, ≥ 3 adenomas) [7].

Non-advanced adenomas or simple adenomas are less than 10 mm, have tubular structure and low dysplasia. Depending on the size they were considered small simple adenomas if their diameter was 0-5 mm or large simple adenomas with a diameter between 6-9 mm [6].

The histopathologic outcome suggested further decisions: surgery, chemotherapy or radiotherapy according to location, stage of the cancer.

Statistical analysis

Statistical analysis was performed using the MedCalc Software, version 12.4.0 (MedCalc, Belgium). The distribution of the numerical variables was first tested by the Kolmogorov-Smirnov test. In case of numerical variables with normal distribution mean value and standard deviation were calculated, while in case of non-normal distribution median values and range interval were presented. Differences between numerical variables were analyzed by parametric (t-test) or nonparametric tests (Mann-Whitney test) according to the normal or non-normal distribution of variables. Qualitative variables were presented as numbers and percentages. The Chi-square (X^2)

test and Fisher's exact test were used for the comparison of two proportions expressed as a percentage. 95% confidence intervals was calculated for each predictive test. A *p*-value less than 0.05 was regarded as significant for each statistical test.

Results

In our study, we had a total of 1389 participants who met the inclusion criteria, with a mean age of 61.2±12.8 years, 565 (40.7%) men and 824 (59.3%) women. The number of participants from urban areas was significantly higher as compared with those from rural areas: 74% vs. 26%, *p*<0.001.

Table I. Distribution by age.

Age group (years)	Total number of subjects (%)	Number of subjects with advanced adenomas (%)
50-54	279 (20%)	5 (1.8%)
55-59	327 (23.5%)	3 (0.9%)
60-64	325 (23.4%)	8 (2.4%)
65-69	215 (15.5%)	7 (3.2%)
70-74	243 (17.5%)	6 (2.5%)
Total	1389	29 (2.1%)

Participants with positive FIT

FIT was positive in 87 individuals (6.3%) with a mean age of 62.3±12.3 years, 40 (2.9%) men and 47 (3.4%) women.

FIT positive rate was statistically similar in women and men: 54.1% vs. 45.9%, *p*=0.35. The mean age of women with positive FIT was similar with that of men with positive FIT: 62.6±11.4 years vs. 61.9±12.1 years, *p*=0.78.

Participants with positive FIT with colonoscopy

In 57/87 subjects (65.5%) with positive FIT, colonoscopy was performed. The rest of positive patients refused or delayed the investigation. A total colonoscopy was performed in 52/57 patients (91.2%). At 5 patients (8.8%), total colonoscopy could not be performed, because they had neoplastic stenosis.

In 39/57 participants (68.4%) who performed colonoscopy were detected lesions that could justify the test positivity were detected.

Among participants with positive FIT that performed colonoscopy, 10/57 patients (17.5%) had colorectal cancer, 29/57 patients (50.9%) had advanced adenomas, and 34 patients (59.6%) had advanced neoplasia (advanced adenomas ± colorectal cancer).

Table II. Participants with positive FIT.

	No.	(%)
Without colonoscopy	30	(34.5%)
With colonoscopy	57	(65.5%)
No cancer or adenomas	14	(16%)
Adenomas	35	(61.4%)
Non advanced adenomas	15	(26.3%)
Advanced adenomas	29	(50.9%)
Advanced neoplasia	34	(59.6%)
Cancer	10	(17.5%)

Table III. Characteristics of adenomas detected at colonoscopy.

	Adenomas no.	Percentage (%)
Size		
≤5 mm	9	16.7%
6-9 mm	13	24%
≥10 mm	32	59.3%
Histology		
Low dysplasia	30	55.5%
High displasia	24	44.5%
Tubular	37	68.5%
Tubulo-villous/villous	17	31.5%

Non-advanced adenomas (simple adenomas)

Colonoscopies performed at the 57 patients with positive FIT detected 15 patients (26.3%) with simple adenomas, with a mean age of 61.3±12.7 years. These 15 patients had 19 simple adenomas - 1.3 simple adenomas/patient. The percentage of simple adenomas detected was similar in men and women: 53.3% vs. 46.7%, *p*=0.60.

The majority of the simple adenomas were detected in the left colon (13 adenomas - 68.4%) and in the right sided colon only 6 adenomas (31.6%).

In our study, 68.5% of the non-advanced adenomas were large simple adenomas (6-9 mm), while only 31.6% were small simple adenomas (≤5 mm). Association of simple adenomas with advanced neoplasia was seen in 66.7% of patients diagnosed with simple adenomas, while in 33.4% of cases were detected only simple adenomas (*p*=0.14).

Advanced adenomas

Among the subjects who performed colonoscopy, 29/57 (50.8%) had advanced adenomas. In these patients 35 lesions were identified, with 1.2 adenomas/subject. The average age of this group was 63.2±13.2 subjects years. The majority were men, 18 patients (62.1%), and 11 patients (37.9%) were women. The mean age of men with advanced adenomas was similar with that of women 63.5±13.5 years vs. 62.6±12.6 years, *p*=0.85.

Analyzing the 3 characteristics of advanced adenomas, we observed in our study that 32/35 adenomas (91.4%) had sizes ≥10 mm, 17 adenomas (48.6%) were tubulovillous/villous and 24 adenomas (68.6%) had high dysplasia.

Analyzing advanced adenomas by its location we observed that most of them were found in the left colon as compared with the right colon: 71.4% vs. 28.6%, *p*=0.0008.

Cancer

Cancer was detected in 10/57 patients (17.5%) that performed colonoscopy, with a mean age of 60.3±11.7 years, 60% being men and 40% women.

According to the location, 50% of cancers were located in the left colon and 50% in the right colon.

In our study, the association of cancer with advanced adenomas was the most common, being found in 5/10 patients (50%) compared to the association of cancer with simple adenomas, which was evidenced in one patient (10%). In 4 patients (40%) cancer was not associated with adenomas.

Discussion

CRC screening was introduced in order to reduce morbidity and mortality from this disease [8]. Studies were performed on several populations depending on the degree of risk for CRC, the symptomatic/asymptomatic characteristic and age of participants. In our study the participants recruited were asymptomatic, with average risk and aged between 50 and 74, years because they could benefit the most from screening.

Colonoscopy is the only method that can be used for diagnostic and therapeutic purpose (for adenomas and cancer in situ) throughout the entire colon [9]. However, it cannot be used as a first choice method in wide population based screening programs, in all countries, because costs are higher and require specialized personnel. Regarding colonoscopy, in our study we obtained a colonoscopy rate of 4.1%, which is an acceptable value for Romania, knowing that a colonoscopy performed after a positive FIT increases significantly the positive predictive value [14]. In addition, low compliance and especially the risks involved by this method (perforation, bleeding) enhances the disadvantages for colonoscopy [10]. In our study we performed the CRC screening using FIT which is the most recommended and effective test for occult bleeding [2].

In the screening performed on 1389 subjects, fecal immunochemical test was positive in 87 people, representing a 6.3%, positivity rate found in most studies on asymptomatic population, where the percentage of positivity of the FIT ranged from 4.7% to 6.9% [11]. Morikawa et al., based on a study of 21,805 asymptomatic individuals who underwent a single FIT, obtained a positivity rate of 5.7% [6]. A Dutch study conducted on a population at average risk, aged 50-74 years, using FIT had a positive rate of 8.5% [12]. Adherence to colonoscopy among positive FIT participants was 65.5% in our group. Similar values were observed in other studies of screening, Levi et al. showed in a 2010 study on a group of 1224 participants a compliance for colonoscopy of 70% [13].

We observed that sex and age increase the risk of detection of advanced adenomas. They were more frequently detected in men and their frequency increased with age (the greatest value was obtained between 65-69 years). Similar data was obtained in other studies [15,16,17]. Published data demonstrated that detection rate for advanced adenomas and cancer is at least double in screening with FIT compared to screening with gFOBT (3% vs 1.2%) [2,18]. Among the 1389 participants, who performed the immunochemical test in our screening study, 2.8% had advanced neoplasia (0.7% colorectal cancer, 2.1% advanced adenomas). The detection rate for advanced adenomas and cancer in other studies in screening using FIT varied depending on populations that were included in the study. Our data are comparable with those of Levin who performed screening on an average risk population and aged between 50 and 75 years. Detection

rate in Levin's study compared with our study for cancer was 0.5% vs. 0.7%, slightly higher for advanced adenomas (2.4% vs. 2.1%) and almost equal for advanced neoplasia (2.9% vs. 2.8%) [13].

Colonoscopies performed revealed a greater percentage of advanced adenomas in the left colon compared to the right colon, 74.1% vs. 28.6% ($p < 0.001$), as demonstrated by numerous studies that have shown greater efficiency in detecting neoplasms in the left colon than in the right colon, studies justified by the fact that there are differences in the stool consistency, blood is distributed homogeneously in the right colon and in the left colon is located more superficially [19]. A study of 42,000 subjects at average risk, showed a FIT sensitivity of 31% for advanced adenomas located in the left colon and 16% for those located in the right colon and a specificity of 95% [14].

Conclusions

Our study using a qualitative FIT, with a positivity rate of 6.3%, allowed the identification of advanced adenomas and detection of cancer in a significant percentage of positive participants. Then, FIT can be used as a screening method in a Romanian national program to detect CCR, in our socioeconomic conditions.

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