Research paper

FAECAL IMMUNOCHEMICAL SCREENING TESTS FOR COLORECTAL CANCER: A SINGLE-CENTRE STUDY FROM THE CZECH REPUBLIC

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Abstract. The goal of this study is to describe the temporary state of faecal occult blood screening in the Czech Republic. Qualitative and quantitative methods of faecal immunochemical testing for haemoglobin were compared and evaluated retrospectively for a period of four years. Screening is actively offered to asymptomatic individuals within their preventive check-ups, starting at the age of 50. Two types of faecal immunochemical tests were used for screening: a qualitative and a quantitative method. Any positive tests detected during screening were followed up by a total colonoscopy. The research sample contained 454 persons; 191 individuals (42.07%) were tested using the qualitative method and 263 individuals (57.83%) were tested through the quantitative method. The qualitative test's specificity for our sample was 75.84%. Better results were yielded by the quantitative test, where the specificity of the sample reached 94.69%. The latter represented an improvement in faecal occult blood test (FOBT) screening in the Czech Republic that can result in more frequent detection of the disease and a lower mortality rate. Occult blood test screening is ideal for the successful prevention of colorectal cancer (CRC) developing from polyps.

Keywords: Colorectal cancer (CRC), faecal immunochemical tests for haemoglobin (FIT), faecal occult blood test (FOBT), prevention, screening

1 Introduction

The term colorectal cancer (CRC) describes the condition of the malignant transformation of the columnar epithelium of the large intestine and the rectum. In the Czech Republic, statistics for this condition are recorded under the International Classification of Diseases (ICD-10) codes

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C18, C19, C20, and C21, i.e. malignant neoplasms of the colon, recto-sigmoid junction, rectum, and anus (Institute of Health Information and Statistics of the Czech Republic, 2013). Incidence of CRC within the Czech Republic is still the highest in Central Europe. According to the Institute of Health Information and Statistics of the Czech Republic (2013), the incidence of the disease in the Czech Republic in 2012 was of 36.79 ASR-W (age-standardised rate - world) and mortality was of 16.38 ASR-W. Due to certain common dietary habits, a high mortality and increasing incidence of the disease were observed predominantly in Slovakia, the Czech Republic and Hungary.

The incidence of CRC in the Czech Republic has been rising since 1960. In the past 20 years, the Czech Republic and Hungary have been the leading countries in the list of CRC incidence (Fric et al., 1994). Unfortunately, CRC is often diagnosed at late stages with poor prognosis and negative social impact for the patients. Thus, the need for improved secondary prevention of CRC has been a main focus in the Czech Republic, including the implementation of faecal occult blood screening at two-year intervals for individuals aged 50 years and over. The secondary prevention plan has been divided into two steps:

(1) regular population screening whereby diagnostic testing is carried out by general practitioners and gynaecologists in asymptomatic individuals;

(2) follow-up surveillance including long-term observation of high-risk individuals.

Indeed, follow-up surveillance programmes are specified according to the individual's risk for CRC development (Zavoral et al., 2014).

Based on previous experience, the Ministry of Health of the Czech Republic (2009) started addressing the innovation and standardisation of the screening programme. At annual intervals, people aged between 50 and 54 years attended faecal occult blood test (FOBT) screening at the general practitioner's or gynaecologist's clinic. After reaching the age of 55, the intervals become biennial. The screening is free of charge for the target population. A primary screening colonoscopy could also be used as a screening method at the age of 55; this is performed in selected centres, and can

be repeated after 10 years in the case of a negative finding. However, colonoscopy centres may become overloaded with the demands of this procedure. Entire screening output data are evaluated by the National Reference Centre (Dušek, 2015).

Previously, the guaiac FOBT was used as a screening test for CRC. The guaiac FOBT has low efficacy, requires restriction in diet and must be repeated to confirm the result. For this reason, the faecal immunochemical test for haemoglobin (FIT) was used as it has higher sensitivity, but nonetheless also has a higher false positivity rate. Since 2009, FIT has been preferred over the guaiac FOBT (Zavoral et al., 2014). The qualitative FIT method uses one cut-off level as given by the manufacturer of the device and results are issued as positive or negative. The quantitative FIT provides results for the presence of haemoglobin in stools as μg Hb/g faeces. Nowadays, many medical centres use the quantitative FIT method, which reportedly detects around 81.8% of CRC (47.8% - 96.8%), is able to reduce false positive findings, and has a specificity of 96.9% (96.4% - 97.4%) (Allison et al., 2014).

Nowadays, the Czech Republic does not have the highest rate of CRC incidence. Currently, Hungary holds the first position; the Czech Republic has the second highest incidence in men and the third in women. The second highest CRC incidence in women is held by Slovakia (Institute of Health Information and Statistics of the Czech Republic, 2010).

1.1 The nurse's role

The nurse has an essential role in the implementation of a CRC screening programme, most importantly in providing the necessary information to the patients in order to increase their knowledge of and participation in the screening programme. This will immensely improve primary, secondary, tertiary and quaternary prevention (Joseph, Vaughan & Stand, 2015). In addition, the nurse also has to be knowledgeable about the actual testing, as well as storage and transportation of the sample. It is the nurse who records the measurements and informs the doctor of the results, who subsequently determines the follow-up procedure. In some countries, the nurse also performs the screening colonoscopy (Joseph et al., 2015). This may be a solution for overloaded colonoscopy workplaces. However, an even better solution would be to optimise the screening methods, including decreasing false negative and false positive results (Tursi, 2013). In the Czech Republic, colonoscopy examinations are performed only by a medical doctor.

In January 2014, a direct invitation system, applicable also for FIT, was introduced. The system works on the principle of sending letters to individuals from the target population group. This is performed through health insurance companies or general practitioners. Direct invitation aims to reach a larger population through screening methods so as to prevent the late detection of tumours (Zavoral et al., 2014; Suchanek et al., 2014).

1.2 Research aims

The research aims of the present study were the following:

(1) to compare qualitative and quantitative FIT screening methods

(2) to establish which of the above methods produces the lower number of false positive results

(3) to compare colonoscopy results of patients with a positive FIT screen to the incidence rate of the Czech Republic.

2 Methods

A retrospective monocentric quantitative research method was employed. All the data originated from the office of a single general practitioner in a town of over 14,000 inhabitants where all the tests were performed between the 1st of January 2010 and the 1st of December 2014. All data was measured by a single nurse, with training provided by the manufacturer of the tests. Prior to the examination, the nurse provided instructions to patients on how to complete the FIT, collect the samples and transport them to the general practitioner's office.

2.1 Research sample and testing

The research sample contained 454 asymptomatic individuals (Table 1) who were examined using the qualitative or quantitative immunochemical FOBT during their check-ups. Participants were aged 50 years or older and none of them had undergone a colonoscopy or had been examined for the presence of blood in their stools within the last ten years. Furthermore, none of the research subjects reported a history of bowel problems, including chronic inflammation of the large intestines, or required surgical intervention to treat any intestinal problems.

A first group of 191 (42.07%) samples was analysed using the qualitative FIT method, whereas a second group of 263 (57.83%) samples was analysed using the quantitative FIT method. The threshold value for a positive FIT finding was set at 75 μg/l. According to Faecal Immunochemical Tests for Haemoglobin Evaluation Reporting (FITTER) standards (Fraser et al., 2015), the formula for the conversion of haemoglobin quantity from μg/l (ng/ml) to μg/g faeces is as follows: μg haemoglobin/g faeces = (ng haemoglobin/mL) x (volume of buffer in the device in mL) / (mass of faeces collected in mg). Our cut-off was 75 μg/l, which is equal to 13 μg Hb/g, allowing for the comparison of results from the pre-cancerous screening.

All examined individuals with a positive FIT were offered a follow-up colonoscopy with a prospective polypectomy. However, some participants (14 individuals) refused a follow-up procedure.

For research purposes, all data was anonymised. Research was conducted in accordance with the recommendations of the Helsinki Declaration and was approved by the Ethics Committee of the medical centre where the research took place.

2.2 Follow-up of the screening test results

Positive results of the qualitative and quantitative FIT were compared with the colonoscopy results as well as with the histology results from biopsies taken during colonoscopy. The latter acted as the gold standard for the diagnosis of pre-colon cancer and CRC. Colonoscopy and histological results were divided into five categories: non-adenomatous polyps, adenomatous polyps, carcinoma, without abnormalities, and other findings (including haemorrhoids, diverticula or inflammatory changes).

Table 1. Demographic characteristics of the 454 participants

Characteristics	Valid *N*	Value
Females	275	60.57%
Males	179	39.43%
Age (years)		
Mean ± SD		61.86 ± 8.62
Range		50 – 86
Qualitative FIT	191	42.07%
Quantitative FIT	263	57.93%

FIT: faecal immunochemical tests for haemoglobin
SD: standard deviation

2.3 Statistical analysis

For statistical data processing, MS Excel 2010 and Statistica 12 software provided by DELL were used. Categorical variables were compared using the Fisher exact test with Freeman-Halton extension for 2x3 contingency tables, due to small sample sizes in some of the categories. A confidence interval of 95% was used. Specificity was calculated as the number of negative subjects divided by the number of negative subjects and the number of false positives.

3 Results

3.1 Participation in the screening programme

Between the 1st of January 2010 and the 1st of December 2014, 179 men (39.43%) and 275 women (60.67%) were examined for faecal occult blood (see Table 1). By the end of data collection, the medical centre where the research took place registered a total of 1,553 individuals aged 50 years and over. Out of the total, 25.64% men and 32.21% women attended the CRC screening. In total, 29.23% of the entire number of individuals was examined, which is higher than the regional average by 4.2%. A flow diagram of the study is seen in Figure 1.
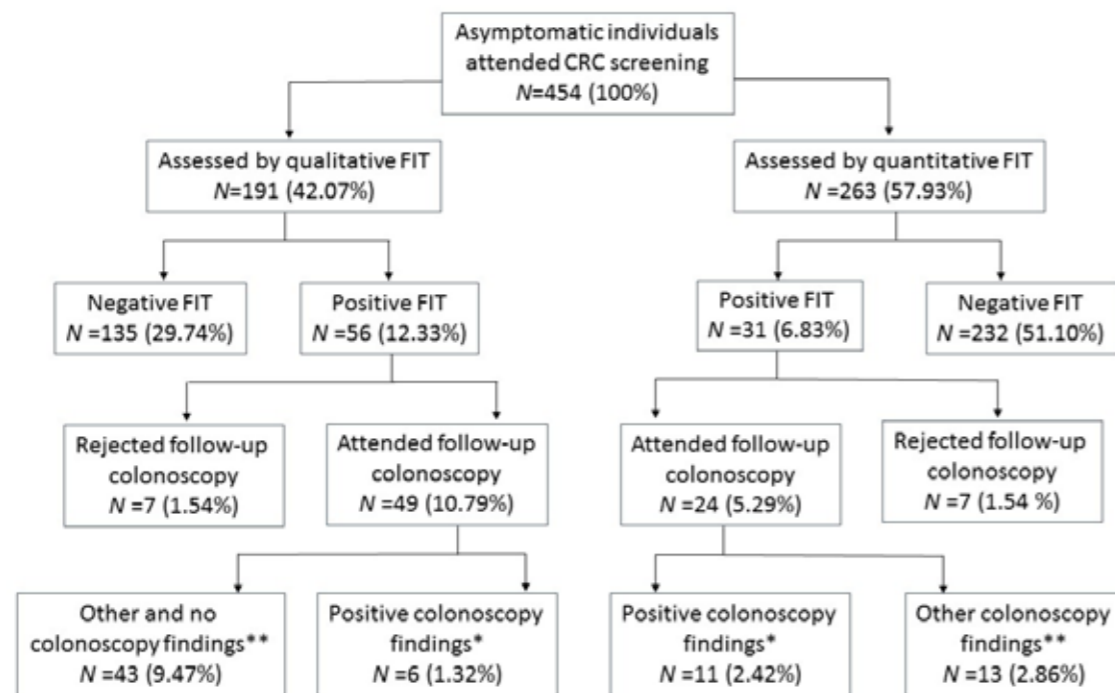

Figure 1. Flow diagram of the study
*'Positive findings' include polyps and carcinoma.
**'Other findings' include inflammation, diverticula and haemorrhoids.

3.2 Immunochemical screening test results

Out of 454 patients examined by the qualitative or quantitative immunochemical method, 87 (19.16%) findings were positive (Table 2), whereby 56 positive findings were detected by the qualitative FIT method and 31 positive findings by the quantitative FIT method. A total of 14 patients refused to attend a colonoscopy, and were thus missing in further statistical analysis. There was a decrease in the false positive results for the categories 'Other findings' and 'No abnormalities' when comparing results of the quantitative method with the qualitative method, implying that more of the positive results were due to the presence of polyps and malignant transformations. The calculated specificity when using the qualitative FIT method was of 75.84%, and it reached 94.69% when using the quantitative one; the false positive rate for the qualitative FIT was of 24.16% whereas that for the quantitative FIT was of 5.31%.

Table 2. Colonoscopy findings for the positive results of the qualitative and quantitative FIT

Colonoscopy finding	Qualitative FIT value; N = 49 N (%)	Quantative FIT value; N = 24 N (%)
Non-adenomatous polyps	4 (8.16)	2 (8.33)
Adenomatous polyps	2 (4.08)	6 (25.00)
Carcinoma	0	3 (12.50)
Other findings*	35 (71.42)	13 (54.16)
No abnormalities	8 (16.32)	0

FIT: faecal immunochemical tests for haemoglobin
*'Other findings' include inflammation, diverticula and haemorrhoids.

Colonoscopy findings were grouped into three categories ('positive findings', 'other findings' and 'no abnormalities') for statistical evaluation using a Fisher's exact test (Table 3). A statistically significant difference was found between the different types of positive results detected by the qualitative and quantitative FIT method in relation to the results of colonoscopy examinations. The Fisher's exact test *p*-value was equal to 0.0027.

Table 3. The Fisher's exact test for colonoscopy findings in qualitative and quantitative FIT

Colonoscopy finding	Qualitative FIT value N (%)	Quantitative FIT value N (%)	*p*-value
Positive findings*	6 (12%)	11 (46%)	
Other findings** & No abnormalities	43 (88%)	13 (54%)	
Fisher's exact test			0.0027

FIT - faecal immunochemical tests for haemoglobin
*'Positive findings' include polyps and carcinoma.
**'Other findings' include inflammation, diverticula and haemorrhoids.

An overview of the measured values is depicted in the boxplot in Figure 2, where the small inner box represents the median statistic, accompanied by the lower and upper quartiles (25th and 75th percentiles), and the whiskers show the ranges. Using the quantitative FIT, haemoglobin in stools values ranged from 14.28 *µ*g Hb/g faeces to more than 170.00 *µ*g Hb/g faeces. The median was 52.19 *µ*g Hb/g faeces and the standard deviation was 56.78 *µ*g Hb/g faeces. The measured numerical value enabled one to estimate the severity of the findings and to optimise further diagnostics.
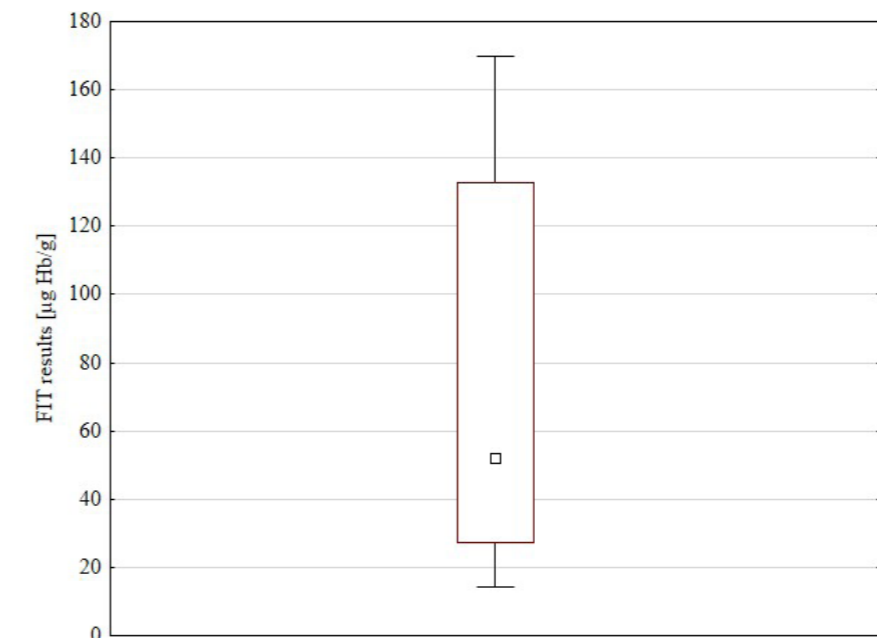

Figure 2. Boxplot representing the values obtained by quantitative FIT [*µ*g Hb/g]

When comparing the results of both methods according to age and gender, the highest incidence in men was found at the age of 71 and older, amounting to 29.41% of the examined individuals. The second highest incidence was in the age category 50 – 60 years (19.19%). In women, the highest incidence was detected in the age group 50 – 60 years, with 20.00% examined patients. The second highest incidence was in the age category of 71 years and higher, with 12.24%.

4   Discussion

The results of this study imply that using the quantitative method of occult blood testing significantly reduces false positive findings and thus, fewer patients are referred for a colonoscopy. This reduces costs and, in turn, more effort is directed towards the detection of CRC and pre-cancerous conditions. Chauvin, Josselin and Heresbach (2013) report the same findings and add that the waiting time for a diagnostic procedure is significantly reduced due to fewer false positive findings. Chauvin et al.'s (2013) study was aimed at comparing guaiac FOBT and FIT. Furthermore, the replacement of the qualitative FIT by the quantitative FIT has caused a decrease in findings in the category 'Other findings' from 71.42% to 54.16%, meaning that there was an improvement in the test specificity of our research sample to 94.69%. The quantitative FIT specificity detected in this study was 1% lower than that reported by Dušek et al. (2014). Similarly, the high positivity rate detected by the qualitative FIT over the quantitative FIT in the study by Park et al. (2012) is comparable to that reported in this study. In 2013, Ou et al. confirmed that the quantitative FIT was able to accurately detect the presence of advanced colorectal neoplasms and that the quantitative FIT offered a much higher sensitivity in detection of CRC when compared to the qualitative FIT. According to Chen et al. (2012), testing of transferrin levels in faeces could aid and improve the screening programme of faecal occult blood by quantitative FIT in the high-risk population. Another advantage of the quantitative FIT is the possibility to prioritise patients based on the level of μg Hb/g faeces detected, thus accelerating the diagnostic process, facilitating earlier treatment options and improving survival outcomes of individuals with higher levels (Rozen et al., 2009). Comparison of the ASR-W incidence statistics for ICD-10 diagnoses C19 – C21 in 2010 in the Czech Republic with European and global averages leads to the conclusion that Czech figures are above average. In the Czech Republic, the incidence in the general population (men and women) was 39.2, while the European average was 31.7. In the United States, the average is even lower at 29.2. Recently, however, the Czech Republic has been very successful in decreasing mortality related to these conditions; this is where early detection is essential. In 2004, in the Czech Republic, C19 – C21 ASR-W mortality was 24.7 for the general population (men and women). In 2010, the values dropped to 17.8 for the general population (Institute of Health Information and Statistics of the Czech Republic, 2010). Thus, there is clear proof that implementation of regular periodic screening can act as an effective tool for the early diagnosis and treatment of CRC.

The future goal is to screen a higher percentage of the population aged 50 years and over, in order to increase the efficiency and benefit of the screening programme. This can be achieved by direct invitation of registered persons attending clinics and hospitals, increasing the awareness of CRC within the population and motivating individuals to participate in the screening programme. In our research sample, the overall screened population percentage was 29.2%, regardless of gender, which is 4.5% higher than the regional average (Institute of Health Information and Statistics of the Czech Republic, 2010). There is a limitation in our research because of the different sample size tested in the two screening methods and, unfortunately, both FIT methods were not performed on every sample.

5   Conclusion

Apparently, FOBT is the focus of CRC diagnostics in the Czech Republic. It is the improvement in screening methods and management which enables detection of pre-cancerous conditions or cancer in the early stages of the disease.

The most important results of our study are that firstly, from the positive results detected by the quantitative FIT method, none of the samples fell in the 'No abnormalities' category when confirmed by the follow-up colonoscopy, contrasting with the outcomes of the qualitative FIT method; secondly, a lower percentage of the positive results detected by the quantitative FIT (51.46%) as opposed to the qualitative FIT (71.42%) method were due to benign conditions such as inflammation, diverticula and haemorrhoids; lastly, specificity when using the quantitative FIT was higher than the qualitative FIT method. The essential role in this preventive-diagnostic-treatment process is held by the nurse. The nurse educates the patients before and during examination, performs the test, reads the measurements, and informs the doctor of the result, who subsequently determines the follow-up procedure. Another contribution of nurses could be within primary CRC prevention, by providing nutrition tips and advice. Finally, increasing the number of examined individuals might increase the five-year relative survival rate, which is one of the main goals of our preventive programme.

6   Funding

7   Conflicts of Interest

The authors report no conflicts of interest.

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