Improvements in colorectal cancer screening programmes – quantitative immunochemical faecal occult blood testing – how to set the cut-off for a particular population

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Objective. The aim of the study was to determine the optimum cut-off value of the quantitative immunochemical test (q-FIT) OC-Sensor® for colorectal cancer and advanced adenomatous polyps in a particular population.
Methods. 815 patients were referred for colonoscopy and were offered two q-FIT examinations at two different colonoscopy centers. The patients were classified according to the colonoscopic findings. Test sensitivity, specificity, and accuracy were statistically evaluated using one test and two tests at the levels of 50, 75, 100, 125, and 150 ng/mL of faecal hemoglobin in those patients with advanced polyps and colorectal cancer. The optimum cut-off test level for clinically significant neoplasia was determined using one test.
Results. The optimum cut-off value of q-FIT OC-Sensor® for the detection of clinically significant neoplasia in our particular population was determined as 75 ng/mL using one test. This value provides an optimum proportion of 73% sensitivity (±95% CI 60.3% – 83.4%) and 90% specificity (±95% CI 86.8% – 92.8%), PPV and NPV were determined as 54.76% and 95.43% respectively.
Conclusions. The first step in the implementation of q-FIT test in the screening program in our country is to determine the optimum cut-off level for a population, and to estimate the number of tests performed with respect to the optimum cost effectiveness and economical climate. Using one test, the optimum level of q-FIT OC-Sensor® in the Czech Republic was determined as 75 ng/mL. This study could serve as a model for further studies in other countries, where screening does not yet exist.

Key words: cut-off, quantitative immunochemical test, colorectal cancer, screening, Czech Republic

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INTRODUCTION

The epidemiology of colorectal cancer (CRC) in the Czech Republic (CR) is extremely unfavorable[1,2]. The Czech Republic has one of the highest incidences of and mortality from colorectal cancer in the world. An alarming incidence rate (79/100,000) and mortality rate (45/100,000) exists and has remained almost unchanged over the past few years. For this reason, the National Colorectal Cancer Screening Program was launched in 2000 (ref.[1]). It was focused on asymptomatic persons older than 50 years of age who were offered faecal occult blood test (FOBT), followed by colonoscopy in those cases with positive results.

Guaiac-based tests were solely used during the early years of the screening program[3]. Guaiac-based FOBTs (g-FOBTs) (ref.[3,4]) are based on the pseudoperoxidase reaction of hemoglobin with guaiac resin in the presence of hydrogen peroxide. These tests are only qualitative, thus giving only positive or negative results. They have low sensitivity for advanced adenomatous polyps and carcinomas (11% and 13%, respectively) and relatively low specificity for human hemoglobin. Therefore, a convenient low peroxidase diet should be introduced and maintained before testing.

G-FOBTs are still mostly used in Europe, but some European countries have changed to immunochemical tests (FIT) (ref.[5-7]) such as France and Italy while other

countries will introduce it ie. Slovenia, The Netherlands and Germany.

Immunochemical tests had already become available during the first years of the screening program, with the use of specific antibodies against human hemoglobin and without dietary restriction. FITs are specific for human hemoglobin and, moreover, they possess a sensitivity which is almost twice as high as g-FOBT[4,5,8]. FITs are qualitative tests as well and as some recent studies show, the quality of individual FIT testing varies markedly[6].

At the beginning of 2009, the method of the screening program in the Czech Republic was improved by the introduction of primary screening colonoscopy as the method of choice for patients age 55 years.

Recently, a new generation of quantitative FIT (q-FIT) (ref.[9]) testing has become available, the advantage of which is to obtain optimum test sensitivity and specificity for a particular population by setting a cut-off value. A new more sophisticated sampling technology in immunochemical testing may lead to the growing participation of the population in the screening programme as well[7]. Some studies have also indicated greater patient participation in screening using q-FIT than g-FOBT[10-12].

In our study performed in a Czech population with a high incidence of colorectal cancer, an optimum cut-off value of q-FIT was determined, and, with respect to the economic considerations, optimum parameters were set for performing one test. Thus, conditions for using q-FIT in our population within the ongoing screening program were prepared. This kind of clinical research could serve as a model for further studies in other European countries, where screening does not yet exist, before an expensive screening program is embarked upon nationwide.

PATIENTS AND METHODS

Patients: Between February 2008 and March 2009 we invited 1000 ambulatory patients referred consecutively for colonoscopy at two endoscopy centers for participation in the study. Some patients were asymptomatic and were invited for elective colonoscopy, some patients were in the high risk category for colorectal cancer (from both centers), and some patients were symptomatic and were referred by their GPs (Table 1). Exclusion criteria were hematuria or menstruation at the time of the sample collection, a known diagnosis of IBD, visible rectal bleeding and an inability in stool collection. Patients on anticoagulant therapy (it was stopped for colonoscopy) and patients using non-steroidal anti-inflammatory drugs were not excluded[13] (Table 2). A complete colonoscopy was performed in 682 patients (83.7%) out of an initial number of 815 patients (410 males, 405 females, with a mean age 57.4 years). Study subjects with incomplete or inadequate colonoscopy examination were given contrast barium enemas or CT colonography and were additionally included. However patients having incomplete colonoscopies without the aforementioned additional investigations were excluded (Table 2). Complete colonoscopy was defined as intubation to the lower caecum or intubation up to an obstructing neoplasm.

The number and size of any polyps and their location were recorded; biopsies were taken of all abnormal lesions. Colonoscopies were performed by four experienced colonoscopists. Histological examinations of bioptic samples were reviewed by a pathologist and uncertain results were re-evaluated by a second pathologist. The degree of dysplasia of any resected polyps was determined according to the Vienna classification system[14,15].

Patients were then separated into three groups according to their colonoscopic and histological findings (Table 3).

A. The control group (group C): a group of healthy patients and patients with hemorrhoids – 445 patients (189 healthy persons + 226 persons with hemorrhoids).

B. The group with non-advanced polyps (group 1): a group of patients with polyps up to 1 cm with histology V1–V3 according to the Vienna classification system – 161 patients

C. The group with clinically significant neoplasia (group 2): this group of 63 patients consisted of those with advanced polyps, i.e. polyps of size ≥ 10 mm with V4 histology according to the Vienna classification system – 28 patients (group 2-V4) and patients with carcinomas, i.e. histology V5 according to Vienna classification system – 35 patients (group 2-V5). All the results are summarized in Table 3 and in Fig. 1.

Methods:

Tests and sample collection: The patients obtained two quantitative immunochemical tests OC-Sensor® (Eiken

Table 1. Basic sample characteristics.

Characterictic	Value [%]
Total Patients	815[100]
Men	410[50.3]
Women	405[49.7]
Mean age	57.4
Indications	**Value [%]**
Past colorectal neoplasia	295 [36]
Positive FOBT	122 [15]
Family history of CRC	65 [8]
Anaemia	81 [10]
Abdominal pain	57 [7]
Weight loss	73 [9]
Change of bowel habit	106 [13]
Other	16 [2]

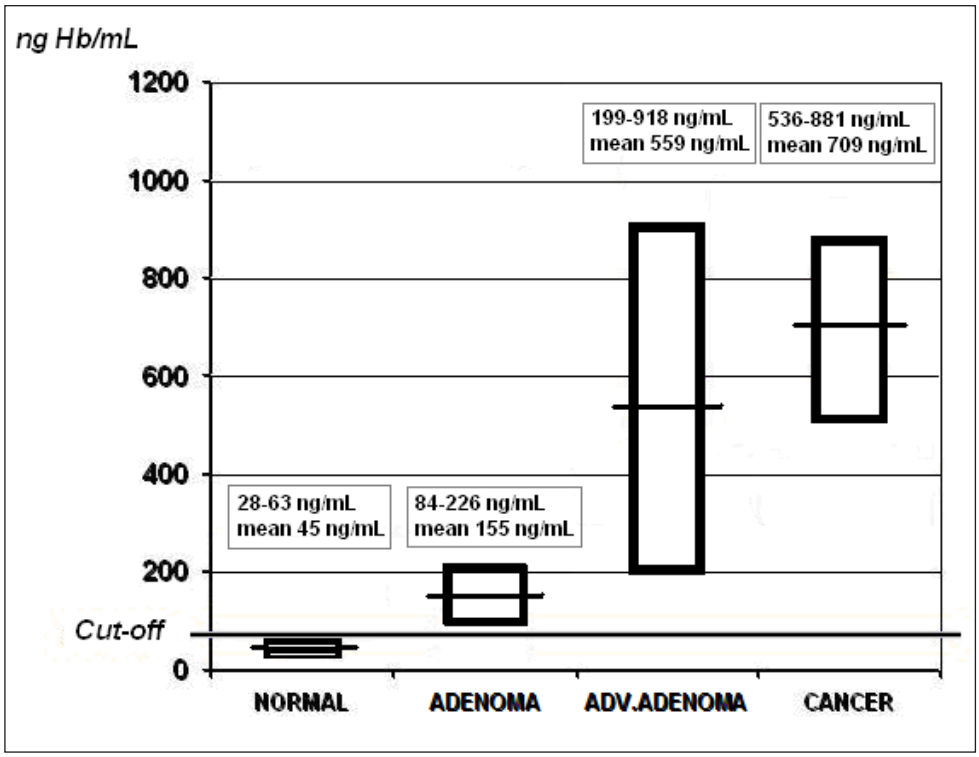

Fig. 1. Cut-off 75ng/mL for q-FIT and results of the first test in different groups of patients.

Table 2. Study flow chart.

Invited for participation in the study	1000		
Included (recieved FIT)	815 [100%]	Excluded	185
Completed	709 [87%]	Hematuria	15
Complete colonoscopy	682 [83.7%]	Menstruation	20
Incomplete colonoscopy + contrast barium enema or CT colography	27 [3.3%]	Rectal bleeding	74
Not completed (incomplete colonoscopy or poor preparation without next examination)	106 [13%] (82 [10.1%] + 24 [2.9%])	IBD	72
		Other	4

Chemical Co., Tokyo, Japan) (ref.[9]) at the time of colonoscopy scheduling[9]. All patients obtained both verbal as well as written instructions about the test. The samples were collected from two separate bowel movements at intervals of 1 to 5 days prior to preparation for colonoscopy using a special collecting stick on the kit cover. The collecting stick with attached stool was immediately inserted into a test tube and stored in the refrigerator. The date of stool collection was recorded and the tubes were delivered immediately prior to colonoscopy[16].

q-FIT analysis: A quantitative immunochemical faecal occult blood test OC-Sensor® was analyzed using the immuno-turbidimetric method with an OC-Sensor μ analyzer (Eiken Chemical Co., Tokyo, Japan). Monoclonal human HbA0 antibodies sensitized by latex, reacted with hemoglobin in the sample producing the subsequent latex-agglutination reaction. The optical density of the reaction solution increased together with the growing concentration of HbA0 in the sample, and the changes in optical density were subsequently analyzed.

Statistical evaluation: We compared areas under the ROC curve for both the first test (HGB1) and the highest value of the two tests performed (HGB2), using Z-statistics according to Hanley and McNeil[17]. This was to determine which of the values had the greater discriminative power and also to determine whether we needed only one test or two tests to adequately distinguish between healthy patients and those with significant neoplasia. Statistical analysis was performed at the levels of 50, 75, 100, 125, and 150 ng/mL. Software SPSS version17 (SPSS Inc.) and STATISTICA version 7.1 (STATSOFT Inc.) were used for statistical calculations. The statistical significance of all tests was determined at the level of $P \leq 0.05$.

The study was performed with the approval of the ethics committees of both participating centers. (The

Table 3. Results of measurement using one test (HGB1) and using two tests (HGB2).

	Patients n (%)	Mean ± SD[± 95% CI]	
Characteristic		HGB 1	HGB 2
A: Controls (n=415) – Group C			
Healthy	189 (25.82)	26.43 ± 82.23 [74.69 – 91.47]	48.50 ± 143.22 [130.095 – 159.32]
Hemorrhoids	226 (30.87)	61.26 ± 233.80 [214.05 – 257.60]	97.52 ± 338.31 [309.73 – 372.74]
All normal cases	415 (56.69)	45.40 ± 181.88 [170.29 – 195.18]	75.20 ± 268.54 [251.43 – 288.17]
Cases (total classified, n = 224)			
V1	34 (15.18)	258.32 ± 700.81 [565.26 – 922.46]	293.15 ± 733.38 [591.52 – 965.33]
V2	23 (10.27)	15.96 ± 32.31 [24.99 – 45.74]	21.91 ± 34.10 [26.37 – 48.27]
V3	104 (46.43)	152.15 ± 398.33 [350.57 – 461.57]	227.31 ± 534.77 [470.66 – 619.28]
B: All non advanced adenomas (V1 + V2 + V3) – Group 1	161 (71.88)	155.12 ± 456.77 [411.73 – 512.95]	211.87 ± 549.49 [495.31 – 617.08]
V4	28 (12.50)	558.87 ± 927.08 [732.96 - 1261.88]	722.86 ± 997.14 [788.36 – 1357.25]
V5 (Carcinomas)	35 (15.63)	708.80 ± 501.97 [406.03 – 657.68]	877.63 ± 640.44 [518.03 – 839.10]
C: Clinically significant neoplasia (V4+V5) – Group 2	63 (28.12)	642.03 ± 719.81 [612.41 – 873.25]	808.84 ± 814.82 [693.24 – 988.52]

V1 negative for neoplasia/dysplasia, V2 indefinite for neoplasia/dysplasia, V3 non-invasive low grade neoplasia (low grade adenoma/dysplasia), V4 non-invasive high grade neoplasia (high grade adenoma/dysplasia and non-invasive carcinoma), V5 invasive neoplasia (intramucosal carcinoma, submucosal carcinoma or beyond).

General Teaching Hospital and The Thomayer Teaching Hospital, both in Prague). The entire data were statistically processed, all patients gave their written informed consent and strict anonymity and confidentiality were maintained at all times.

RESULTS

In the group with clinically significant neoplasia (advanced polyps and carcinomas) (Group 2, V4+V5), sensitivity and specificity at the level of 50 ng/mL were 76.2% (±95% CI 63.8% – 86.0%) and 87.2% (±95% CI 83.6.3% – 90.2%), using one test, and 77.8% (±95% CI 65.5% – 90.2%) and 81.4% (±95% CI 77.3% – 85.0%), using the highest value of two tests. For the carcinoma subgroup (Group 2-V5), sensitivity and specificity at the level of 50 ng/mL was 88.6% (±95% CI 73.2% – 96.7%) and 87.2% (±95% CI 83.6% – 90.2%), using one test, and 88.6% (±95% CI 73.2% – 96.7%) and 81.4% (±95% CI 77.3% – 85.0%), using two tests. These results and the results for the levels of 75, 100, 125, and 150 ng/mL are summarized in Table 4. Based on these values, an optimum level was chosen for the clinically significant neoplasia group (V4 + V5). Using two tests at such a level when the sensitivity was sufficiently high, allowed assessment of the influence on the number of false positive results. Again, virtually similar results of sensitivity and specificity were found using one test.

The best results in the group with clinically significant neoplasia using one test were found at the level of 75 ng/mL with a sensitivity and specificity 73.0% (±95% CI 60.3% – 83.4%) and 90.1% (±95% CI 86.8% – 92.8%), respectively. Using one test at this level, a of sensitivity 85.7% (±95% CI 69.7% – 95.1%) and specificity of 90.1% (±95% CI 86.8% – 92.8%) were obtained in the carcinoma group (V5). The level of 75 ng/mL renders the best sensitivity/specificity ratio for q-FIT for performing one test.

For one test, the mean test value was 708 ng/mL [± 95 % CI 536.37–881.23] in the carcinoma group, 559 ng/mL [± 95 % CI 199.09–918.05] in the adenoma group and in the joint group of carcinomas and advanced adenomas, the mean value was 642 ng/mL [± 95 % CI 460.75–823.31]. The patients repeat this test each year in accordance with our screening program.

The area under the ROC curve for the first test (HGB1) was not significantly different from the area under the ROC curve for the two tests (HGB-Higher) (graph 2). The significance of the Z-test according to Hanley and Mc Neil[17] was *P*=0.86. Graph 2 shows that the curves

Table 4. Sensitivity, Specificity, Positive Likelihood Ratio (LR+), Negative Likelihood Ratio (LR-) and Area Under the ROC Curve of the HGB1 and the HGB2 in different groups.

	Sensitivity % (95% CI)		Specificity % (95% CI)		Positive Predictive Value %		Negative Predictive Value %		Positive LR %		Negative LR %		AUC	
	HGB1	HGB2	HGB1	HGB2	HGB1	HGB2	HGB1	HGB2	HGB1	HGB2	HGB1	HGB2	HGB1	HGB2
Controls [N = 415] vs. all clinically advanced neoplasia (V4+V5) [N = 63]														
50	76.2 (63.8-86.0)	77.8 (65.5-87.3)	87.2 (83.6-90.2)	81.4 (77.3-85.0)	47.53	38.89	96.00	96.00	5.94	4.17	0.27	0.27	0.869	0.854
75	73.0 (60.3-83.4)	74.6 (62.1-84.7)	90.1 (86.8-92.8)	84.7 (80.9-88.1)	54.76	42.72	95.63	95.63	7.36	4.89	0.30	0.30		
100	71.4 (58.7- 82.1)	74.6 (62.1- 84.7)	91.0 (87.9- 93.6)	86.9 (83.3-90.0)	54.88	46.54	95.43	95.73	7.97	5.71	0.31	0.29	Difference between areas: 0.015	
125	68.3 (55.3-79.4)	73.0 (60.3-83.4)	92.7 (89.8-95.0)	89.1 (85.7-91.9)	59.15	50.55	94.82	95.58	9.40	6.70	0.34	0.30	95% CI: -0.018 to 0.048	
150	63.5 (50.4- 75.3)	69.8 (57.0- 80.8)	93.5 (90.6- 95.6)	89.6 (86.2- 92.4)	59.70	50.58	94.15	95.12	9.71	6.71	0.39	0.34	Significance level *P*: 0.369	
Controls [N = 415] vs. cancer (V5) [N = 35]														
50	88.6 (73.2-96.7)	88.6 (73.2-96.7)	87.2 (83.6-90.2)	81.4 (77.3-85.0)	36.90	28.70	98.90	98.82	6.90	4.75	0.13	0.14	0.937	0.927
75	85.7 (69.7-95.1)	85.7 (69.7-95.1)	90.1 (86.8-92.8)	84.7 (80.9-88.1)	42.25	32.25	98.67	98.59	8.63	5.62	0.16	0.17		
100	85.7 (69.7-95.1)	85.7 (69.7-95.1)	91.0 (87.9-93.6)	86.9 (83.3-90.0)	44.78	35.71	98.69	98.62	9.57	6.56	0.16	0.16	Difference between areas: 0.010	
125	80.0 (63.1-91.5)	85.7 (69.7-95.1)	93.0 (90.1-95.2)	89.1 (85.7-91.9)	49.15	37.50	98.45	98.66	11.39	7.87	0.22	0.16	95% CI: -0.030 to 0.049	
150	80.0 (63.1-91.5)	85.7 (69.7-95.1)	93.5 (90.6-95.6)	90.1 (86.8-92.8)	50.91	42.25	98.22	98.67	12.24	8.63	0.21	0.16	Significance level *P*: 0.635	

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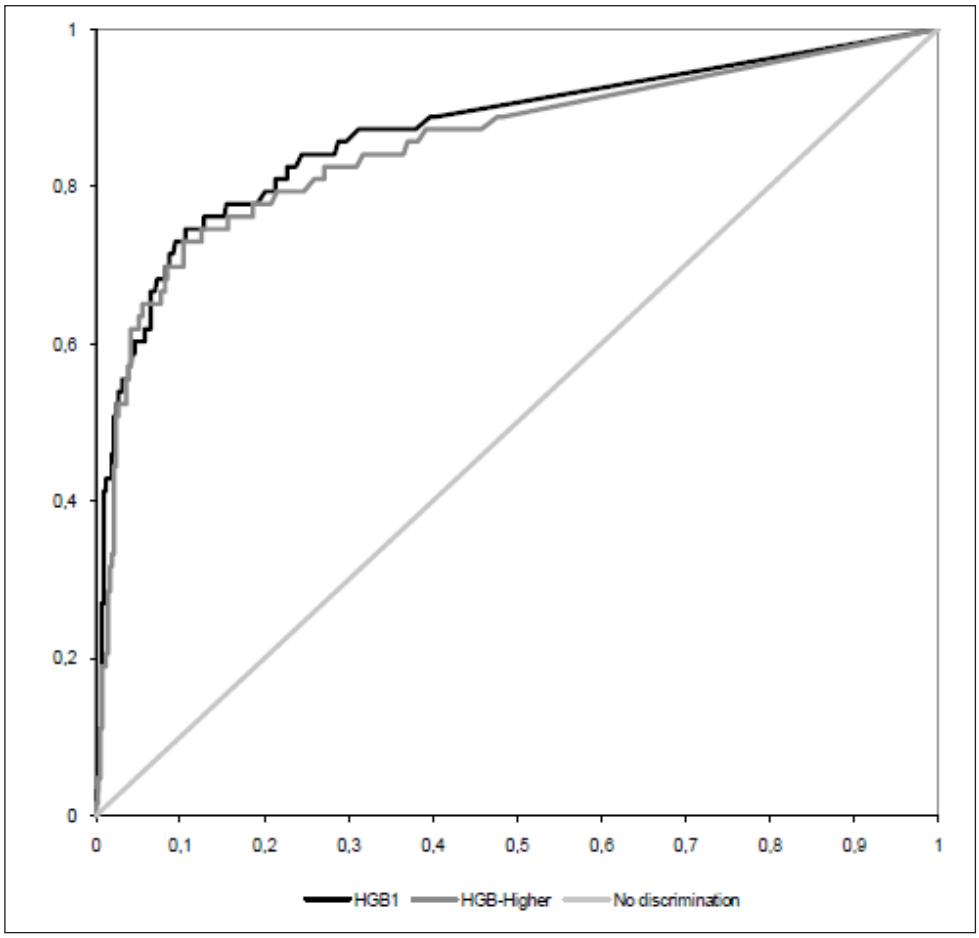

Fig. 2. Comparison of two ROC curves for the First and the Higher Measurements of two q-FITs (Controls vs. advanced neoplasia (cancer and advanced polyps)).
Area under the ROC curve = 0.869. 95 % Confidence interval = 0.835 to 0.898
HGB Higher: Area under the ROC curve = 0.854. 95 % Confidence interval = 0.819 to 0.884
Difference between areas = 0.015. Standard error = 0.017. 95 % Confidence interval = - 0.018 to 0.048. Significance level *P*=0.369

for both variables almost overlap, i.e. both variables possess the same resolving power. This observation was confirmed by means of the t-test ($P>0.05$; Fig. 2).

DISCUSSION

The incidence and mortality rates for colorectal cancer differ markedly in the populations of individual European countries, each having different eating habits and genetic predispositions[2]. For this reason, each population, not only Europeans, should be assessed with respect to possible diversity. Therefore we decided, prior to the introduction of q-FIT into the screening program, to test our population, which is remarkable for its very high incidence of colorectal cancer and mortality, and to determine a cut-off limit for the Czech population. Considering economic aspects, we took advantage of q-FIT to achieve an increase in test sensitivity by decreasing the cut-off value and, with respect to specificity; we chose the best cut-off point using a q-FIT. The technology of q-FIT ensures ideal sensitivity/specificity ratio by virtue of the quantitative results[18-21].

The lower proportion of complete colonoscopies in our survey was due to the exclusion of patients with poor preparation who were not willing to undergo repeated colonoscopy within the specified time-frame.

The patient population is not absolutely identical to the screening population. Therefore, the results of this study are to be verified in the future within a large population including the screening population.

q-FIT is a cheap method compared to colonoscopy. In the case of false positive tests, subsequent colonoscopy is feasible because patients in this country undergo primary screening colonoscopy (ie.colonoscopy without previous faecal occult blood test in patients older than 55 years)[2]. On the other hand, delayed diagnosis due to false negative tests may have serious impact on patient survival and subsequent quality of life. Hence, test sensitivity was strongly emphasized when the correct cut-off value as 75 ng/mL was determined. Relatively low specificity 90% is tolerable in a country with alternatively proceeding primary colonoscopy screening. Slightly better results were obtained by performing two tests and the results were corrected by lowering the cut-off level when performing one test[21,22]. If the capacity of the endoscopic centers is sufficient, the value 75 ng/mL is optimum and can be recommended.

A number of studies have reported the advantages of q-FIT[23-27]. The advantage of q-FIT over g-FOBT lies in the recognition of a larger number of early cancers and adenomatous lesions[25]. Better results from this newer test will also play a favorable role in the psychological influence of both general practitioners and patients, which may help to decrease the relatively high proportion of unperformed colonoscopies despite a positive FOBT[28,29].

In the processing of liquid q-FIT kits, time-dependency is an important consideration compared to g-FOBT dry kits[16]. In addition, the storage temperature, which is im-

portant for both types of tests, is logistically more demanding in the case of q-FIT and will require changes in the organization of the screening programme.

Despite primary colonoscopy screening being available in the Czech Republic as a "gold standard" for persons older than 55 years, FIT performed on an annual basis from the age of 50 years may be the next option. We expect a significant portion of the screening population will use the q-FIT (ref.[30]). With respect to the high quality of colonoscopic procedures, a high-quality but less invasive alternative should be offered.

CONCLUSION

The number of tests performed in each country will be determined by its economic viability.

Determination of an optimum cut-off point for a particular population should be the first step toward the introduction of q-FIT into the screening programme. For the Czech Republic, this level was determined as 75 ng/mL using one test. It could serve as a model for further studies in other countries where colorectal screening does not yet exist.

The next step in the verification of the results should be the use of q-FIT within a large study including the screening population of a particular country.

The final goal is a marked improvement in epidemiological parameters, i.e. colorectal cancer incidence and mortality, than was accomplished by g-FOBT.

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