CAMPARISON OF FIT TO gFOBT IN COLORECTAL CANCER SCREENING

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Summary
Most countries provide national screening programs for early detection and prevention of colorectal cancer (CRC). As a result, the incidence and mortality are becoming slightly divergent. Croatian colorectal cancer screening program has begun in 2007 with overall response rate about 20%. This response rate, may be explained by complexity of fecal occult blood test (FOBT) and availability of colonoscopy for positive results.

Recently, European countries started replacing FOBT test in national screening programs with fecal immunochemical test (FIT), which is based on immunochemical method performed by automatic analyzer using the specially designed highly specific antibodies that could detect human hemoglobin exclusively. The main advantages of FIT are higher sensitivity for detection of cancer and higher proportion of true negative.

The aim of the national screening program is to detect the disease as early as possible when CRC is curable. Providing information on colorectal cancer to general public, along with current national plan and through the application of current guidelines it is possible to increase response rate, early detection, improve quality of life and increase overall survival.

In this paper we discuss a possibility of replacing FOBT with FIT attributing to these goals.
KEYWORDS: fecal occult blood test (FOBT), Fecal immunochemical test (FIT), colorectal cancer, screening

USPOREDBA FIT-a I FOBT-a U PROBIRU ZA KOLOREKTALNI KARCINOM
Sažetak
Većina zemalja ima Nacionalni program za rano otkrivanje i prevenciju raka debelog i završnog crijeva (KRK). Kao rezultat, incidenca i mortalitet postaju divergentni. Hrvatski program ranog otkrivanja raka debelog crijeva započeo je 2007 s odazivom od oko 20%. Odaziv se može objasniti složenošću izvođenja testa na okultno krvarenje i dostupnošću kolonoskopijskoj nakon pozitivnog testa.

Odnedavno, Europske zemlje su počela zamijenjivati standardni test na okultno krvarenje imunohistokemijskim testom koji se temelji na protutijelima visokospecifičnim na hemoglobin. Glavne prednosti imunokemijskog testa su veća osjetljivost u otkrivanju raka i veći stupanj detekcije zaista negativnih uzoraka.

Cilj nacionalnog programa je rano otkrivanje bolesti, kada je kolorektalni karcinom izlječiv. Informiranost o kolorektalnom karcinomu, postojeći nacionalni program probira i njegova implementacija, te praćenje trenutnih smjerica omogućili bi povećani odgovor na program probira, raniju detekciju, poboljšali kvalitetu života i ukupno preživljenje.

U ovom radu razmatrano potencijalni doprinos zamjene, testa na okultno krvarenje s imunohistokemijskim testom u program probira.
KLJUČNE RIJEČI: test na okultno krvarenje (Hemokult), imunokemijski test (FIT), kolorektalni karcinom, probir
SCREENING PROGRAMS

Forming the framework and the network for systematic early colorectal cancer (CRC) detection in Croatia officially began in 2007, when the Proposal of the National Program for Early Colorectal Cancer had been accepted (1).

The accepted program was in line with the main guidelines of the former National Health Development Strategy 2006-11, as well as international strategic health documents: Resolution of prevention and control of the cancer by WHO from the 2005, and the European Union Council Recommendations from 2003(878/EZ) (2,3,4). The main goal of the program was implementing preventive procedures for early detection of malignant colorectal tumors at stage of limited pre-malignant lesions and early cancer, which is a basic requirement for increased survival rate.

The programs' holders were Croatian Ministry of Health and the Croatian Health Insurance Fund. Targeted groups were men and women over 50 years who were invited to participate by performing the fecal occult blood testing. Actions important for achieving the greatest possible response to the screening (preparing and distribution of brochures, media campaign, educations of the health staff and participants of the screening...) were defined. Designated goals of the program were mortality reduction for 15% in five years after initializing the program with response rate up to 60% (1).

Subsequent national strategic document – Plan for Development of the Public Health 2011-2015 in Croatia emphasizes the priority of increased response rate of the target population in comparison to the first round of screening (5). Without going in to specific causes, objective problem of the program was relatively low response rate (from 1056694 invited persons only 209763 of them returned samples) (6).

Systematic colorectal cancer prevention, implemented as annual or biannual screening program contributes significantly to statistically significant CRC mortality reduction of 15-40%, which confirms the efficacy of the secondary colorectal cancer prevention by detection in the early stage (7, 8) since transition from localized CRC curable stage (stage I) to metastatic disease (stage IV) is a slow process that can last up to ten years.

EPIDEMIOLOGICAL DATA, RISK FACTORS, AND METHODS OF PRIMARY AND SECONDARY PREVENTION

The most comprehensive global data on the assessment about tumors incidence, mortality and prevalence are provided by the International Agency for Research in Cancer (IARC) part of the World Health Organization through the GLOBOCAN Project. These are obtained from a total of 184 national registries worldwide (9, 10). When that data is converted to absolute numbers, the total number of new cases in Europe has almost reached the number of 450000, and almost 215000 have died (11).

Data concerning the incidence of CRC in Croatia show 3209 new cases in 2012: 1863 men and 1406 women. In 2012, 1149 men and 861 women died from colorectal cancer. Reviewed chronologically, numbers of CRC cases in Croatia also indicate a trend of continuous increase in the last two decades: 1990 (1648 new cases of CRC); 2000 – (2700 new cases of CRC); 2005 – (2846 new cases of CRC); 2010 – (3067 new cases of CRC) (12).

The same situation is globally present and is considered as particularly alarming. Despite the progress in diagnostic, surgical and therapeutic procedures, the incidence and mortality of CRC has an increasing trend (approximately 3% per year). Additionally, the risk increases significantly with age, especially after 40 years, and almost doubles with each subsequent decade of life. Every person older than 50 years carries 5% (1/20) risk of suffering and 2.5% (1/40) risk of dying before 74 years from CRC (12). Risk factors that contribute to the development of CRC can be classified in to several basic categories: genetic (family history is present in one quarter of the patients); environmental (diet, physical activity, obesity, diabetes, smoking...), other pathophysiological conditions (previous colorectal cancer, adenomas, polyps, ulcerative colitis, Crohn's disease...). Symptoms suggestive of CRC are occult or overt bleeding in the stool, a change in the cycle, shape and consistency of stools, abdominal pain and anemia (13, 14, 15).

Despite the fact that in 80% CRC patients, disease is detected in operable stage, 40-45% of them relapse in next five years, often with fatal outcome. It is therefore understandable that the
priority is to diagnose the disease in an earlier stage (stages I and II), before dissemination (stages III and IV). Studies have shown that the detection of CRC in the first stage provides a high probability of 5-year survival (95%) (16, 17).

Considering the above, as well as the significant contribution of genetic factors, The American Cancer Society categorized CRC screening algorithm and chose the optimal approach to prevention. It is tailored for: a) the general population (average risk); b) population with moderately increased risk; and finally c) high-risk population. In fact, a first relative who has been diagnosed with CRC increases the likelihood of developing CRC by 1.5; and two affected first relatives increase probability by 3-4 times compared to the general population (18).

Generally, CRC primary prevention methods are not systematized and organized. They are mostly focused to risk factors identification and correction, as well as general recommendations for proper diet (limited intake of refined sugar and red meat, fulfilling the need for carbohydrates mostly from fruit and vegetables, fulfilling the need for protein mostly from white meat and fish, reducing intake of saturated fatty acids...), supplement intake of essential nutrients (vitamin D, folic acid, selenium, calcium...), as well as recommendations for healthy living (maintaining ideal body weight, physical activity, reduce alcohol consumption and smoking).

The essence of successfully implemented CRC secondary prevention is diagnosis the bigger proportion of patients in early stages of the disease-increasing the number of patients treated with curative intent and subsequently increase the survival rate (19, 20).

gFOBT vs. FIT

By using guiaiac fecal occult blood test (gFOBT) testing presence of blood in the stool is detected based on pseudoperoxidative performance of haemoglobin, which in the presence of hydrogen peroxide converts guiaiacalplaacidor2,5-di-(4-hydroxy-3-methoxyphenyl) -3,4-dimethylphuran into blue colored quinone. Test qualitatively detects the presence of hemoglobin, but its objective limitation is the fact that is that reagent does not react and detects hemoglobin of human origin only, but also reacts with hemoglobin from food (like red meat), or peroxidase (usually from vegetables). Because of that it is necessary, before preforming the test, to inform the participants on proper diet (excluding those ingredients in food which significantly positively interfere with the method). Unlike qualitative gFOBT, fecal immunochimical test (FIT) is a quantitative immunochimical method which is performed by automatic analyzer using the specially designed highly specific antibodies that could detect human hemoglobin exclusively. Additional gFOBT limiting factor compared with FIT is the possibility of falsely positive results because of the drugs interference (NSAIDs, aspirin, vitamin C) (21, 22, 23).

The relatively low response rate to CRC screening programs might be due to uneasiness when performing the test. gFOBIT is performed on three consecutive days and requests direct stool manipulation by participants (smearing stool on the card). Performing FIT is easier for subjects, the

<table>
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<th>Table1. COMPARISON OF gFOBT AND FIT.</th>
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<td>gFOBT</td>
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<td>Qualitative test</td>
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<td>React sand gives false positive</td>
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<td>result with non-human hemoglobin</td>
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<td>vegetables</td>
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<td>Require several days of food</td>
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<td>Method is not automated and</td>
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<td>standardized</td>
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<td>Sensitivity: adenoma ≤ 5 mm: 1-5%</td>
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<td>mm: 8,9-27,5 % CRC: 25-50%</td>
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<td>CRC: 25-50%</td>
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<td>The negative predictive value for</td>
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<td>FIT</td>
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<td>Completely automated and standardized method</td>
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<td>Sensitivity: adenoma ≤ 5 mm: 2-7,5%</td>
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<td>adenoma 6-9 mm: 7,5-24% adenoma ≥ 10</td>
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<td>mm: 16-48 % CRC: 50-87%</td>
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<td>The negative predictive value for</td>
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<td>advanced adenoma sand CRC: 96%</td>
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sample is taken once or twice, without additional
direct manipulation with stool. After samples are
collected, participants bring the samples to the
collection site (for example primary medical care
ambulance) from where are the samples trans-
ported to the central laboratory where quantita-
tive and specific immunochemical measurement
on fresh samples is performed which remains the
same as for FOBT.

EXPERIENCE OF THE OTHERS COUNTRIES

The systematic implementation of national
screening program for CRC using FIT started in
Italy, in 2011. From 3.5 million invited persons
48% of them responded. At the initial screening,
5.5% were positive. 1000 cohort revealed a 2.4 in-
vasive tumors and 10.3 advanced adenomas (>10
mm in diameter and / or high grade dysplasia)
(24). The similar experiences was in Spain, where
pilot program of CRC screening with FIT began in
2009., and from 197.839 invited (Barcelona area)
has achieved the response rate of 43.5%, and the
proportion of 6.2% positive. They have detected
1639 high risk adenomas and 245 invasive CRCs.
The authors stated that CRC detection of using
FIT is comparable to colonoscopy (25). An impor-
tant argument for FIT implementation into the na-
tional screening programs in many countries (Ita-
ly, France, Netherlands, Spain, Slovenia, Japan,
Australia, New Zealand, United Kingdom) cer-
tainly was almost double diagnostic sensitivity of
FIT in the detection of advanced (greater diame-
ter) adenomas compared with gFOBT (48 vs. 27%,
5%), and higher sensitivity in the detection of can-
cer (25-50% with gFOBT vs. 50-87% FIT) (24, 25,
26, 27, 28).

Additional deficiency of gFOBIT in compari-
son to the FIT is a relatively high proportion of
false positive results, which complicates the whole
screening program by requiring a greater number
of unnecessary colonoscopies, with all the compli-
cations that those carry (29). In Ireland it is esti-
minated that the change from a gFOBIT to FITon
200000 participants could detect 500 CRC more
(309 by gFOBIT vs. 853 by FIT) (30). In The Neth-
erlands study on 20623 participants has detected
over twice as many adenomas and CRC using FIT
(5.5%) compared to gFOBIT (2.4%). One of the re-
commended items of the Guidelines for Colorectal
Cancer Screening of The American College of Gas-
troenterology is: FIT replaces older guaiac-based
fecal occult blood testing. FIT is the preferred can-
cer detection test (18).

Considering high negative predictive poten-
tial of the FIT (what is a direct consequence of the
higher proportion of truly negative, and lower
proportion of falsely negative results), it became a
test that The Europa Colon association preferred
to the gFOBIT. Europa Colon gives recommenda-
tions which are harmonized with the statement of
the European Cancer Society on its website. Un-
der the auspices of the World Endoscopy Organi-
zation, Colorectal Cancer Screening Committee is
working and meets every year, in 2013 for the
third time in a row, and has confirmed that the FIT
program is ideal for CRC screening (31, 32).

STRESSING THE OBJECTIVES
OF THE SCREENING PROGRAM

Achieving a successful screening program
for colorectal cancer is considered a key to achieve
higher survival rates for the colorectal cancer pa-
tients. For its success it is necessary to review all
involved and their perspectives with possible im-
provement on each phase. From a laboratory and
biochemical point of view FIT has better perfor-
mance than gFOBT. It has immediate financial im-
lications which might be neutralized when in-
corporating benefits into the calculus. However,
every implementation into a large scale system
needs time and adjustments and logistics. In the
meantime, the main point of all screening pro-
grams is population awareness of incidence and
symptoms of colorectal cancer as well as availabil-
ity of diagnostics and treatment that should be
stressed and worked on continously.

REFERENCES

1. Nacionalni program ranog otkrivanja raka debelog
    crijeva. Zagreb; Ministarstvo zdravstva i socijalne
    skrbi Republike Hrvatske, ; 2007.
    Narodne novine 2006; 72.
3. The 58th World Health Assembly, Resolution WHO
    58.22, Cancer Prevention and Control, World Health
    .int/ipcs/publications/wha/cancer_resolution.pdf?
    ua=1accessed on 15/07/2014
4. Council of the European Union (2003), Council Rec-
    ommendation of 2 December 2003 on cancer screening


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