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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, incidencija 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 kolonoskopije 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 smjernica 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 the2005, 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 premalignant 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 215 000 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 guiaiacolalphaacidor2,5-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 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 immunochemical test (FIT) is a quantitative immunochemical 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

Table1.

COMPARISON OF gFOBT AND FIT.

gFOBT	FIT
Qualitative test	Quantitative test
React sand gives false positive result with non-human hemoglobin (food)	Does not react and gives false positive result with non-human hemoglobin (food)
React sand gives false positive result with peroxidase from vegetables	Does not react and gives false positive result with peroxidase from vegetables
Require several days of food restriction prior to conducting the test	Does not require several days of food restriction prior to conducting the test
Positive interference NSAIDs, aspirin and vitamin C	Without drug interference
Require consecutive stool collection in three consecutive days	Does not require consecutive stool collection in three consecutive days
Screened persons should directly manipulate with the feces during the performance test	Screened persons should not directly manipulate with the feces during the performance test, they sent the sample for analysis
Method is not automated and standardized	Completely automated and standardized method
Sensitivity: adenoma ≤ 5 mm: 1-5% adenoma 6-9 mm: 5-13,7% adenoma ≥ 10 mm: 8,9-27,5 % CRC: 25-50%	Sensitivity: adenoma ≤ 5 mm: 2-7,5% adenoma 6-9 mm: 7,5-24% adenoma ≥ 10 mm: 16-48 % CRC: 50-87%
The negative predictive value for advanced adenoma sand CRC:84 %	The negative predictive value for advanced adenoma sand CRC:96 %

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 transported to the central laboratory where quantitative 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 invasive tumors and 10.3 advanced adenomas (>10 mmin 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 important argument for FIT implementation into the national screening programs in many countries (Italy, France, Netherlands, Spain, Slovenia, Japan, Australia, New Zealand, United Kingdom) certainly was almost double diagnostic sensitivity of FIT in the detection of advanced (greater diameter) adenomas compared with gFOBT (48 vs. 27%, 5%), and higher sensitivity in the detection of cancer (25-50% with gFOBT vs. 50-87% FIT) (24, 25, 26, 27, 28).

Additional deficiency of gFOBIT in comparison 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 complications that those carry (29). In Ireland it is estimated that the change from a gFOBIT to FITon 200 000 participants could detect 500 CRC more (309 by gFOBIT vs. 853 by FIT) (30). In The Netherlands 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 recommended items of the Guidelines for Colorectal Cancer Screening of The American College of Gastroenterology is: FIT replaces older guaiac-based fecal occult blood testing. FIT is the preferred cancer detection test (18).

Considering high negative predictive potential 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 recommendations which are harmonized with the statement of the European Cancer Society on its website. Under the auspices of the World Endoscopy Organization, 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).

STREESSING 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 patients. For its success it is necessary to review all involved and their perspectives with possible improvement on each phase. From a laboratory and biochemical point of view FIT has better performance than gFOBT. It has immediate financial implications which might be neutralized when incorporating 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 programs is population awareness of incidence and symptoms of colorectal cancer as well as availability 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.
2. Nacionalna strategija razvitka zdravstva 2006-2011. Narodne novine 2006; 72.
3. The 58th World Health Assembly, Resolution WHO 58.22, Cancer Prevention and Control, World Health Organisation, 2005. Available from: http://www.who.int/ipcs/publications/wha/cancer_resolution.pdf?ua=1accessed on 15/07/2014
4. Council of the European Union (2003), Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC), Off J Eur Union 2003;L 327:34-38.

5. Ministarstvo zdravstva i socijalne skrbi Republike Hrvatske. Plan razvoja javnog zdravstva za razdoblje 2011.-2015. Narodne novine 2011; 49.
6. Antoljak N. Nacionalni program rane dijagnostike raka debelog crijeva u Republici Hrvatskoj. 2008-2011. Hrvatski časopis za javno zdravstvo, 2011;7:28.
7. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348(9040):1467-71.
8. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328(19):1365-71.
9. Ferlay J, Soerjomataram I, Ervik M, et al.GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr , accessed on 15/07/2014.
10. Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013;132(5):1133-45.
11. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al.Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
12. Croatian National Cancer Registry. Cancer incidance in Croatia. Croatian National Institute of Public Health, 2014. Available from: http://www.hzjz.hr/rak_index.htm, accessed on 25/07/2014.
13. Nuako KW, Ahlquist DA, Mahoney DW, Schaid DJ, Siems DM, Lindor NM. Familial predisposition for colorectal cancer in chronic ulcerative colitis: a case-control study. Gastroenterology. 1998;115(5):1079-83.
14. Velayos FS, Loftus EV Jr, Jess T, e al. Predictive and protective factors associatedwith colorectal cancer in ulcerative colitis: A case-control study. Gastroenterology. 2006;130(7):1941-9.
15. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol. 2001;96(10):2992-3003.
16. Kahi CJ, Imperiale TF, Juliar BE, Rex DK. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol. 2009;7(7): 770-5.
17. Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M. Italian Multicentre Study Group. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut. 2001;48(6):812-5.
18. Levin B, Lieberman DA, McFarland B, et al. American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008;134(5):1570-95.
19. Vainio H, Miller AB. Primary and secondary prevention in colorectal cancer. Acta Oncol. 2003;42(8):809-15.
20. Price AS. Primary and secondary prevention of colorectal cancer. Gastroenterol Nurs. 2003;26(2):73-81.
21. Norfleet RG. 1,300 mg of aspirin daily does not cause positive fecal hemoccult tests". J Clin Gastroenterol.1983;5(2):123–5.
22. Jaffe RM, Kasten B, Young DS, MacLowry JD. False-negative stool occult blood tests caused by ingestion of ascorbic acid (vitamin C). Annals of Internal Medicine 1975;83(6): 824–6.
23. Bahrt KM, Korman LY, Nashel DJ. Significance of a positive test for occult blood in stools of patients taking anti-inflammatory drugs. Arch Intern Med. 1984;144(11):2165–6.
24. Senore C. The Italian experiance in CRC screening. Tumor Biol. 2014; 35(Suppl 1): S17.
25. Augee JM. FIT and colonoscopy. Competition and cooperation. Tumor Biol. 2014;35(Suppl 1): S17.
26. Raginel T, Puvinel J, Ferrand O, et al. A population-based comparison of immunochemical fecal occult blood tests for colorectal cancer screening. Gastroenterology. 2013;144(5):918-25.
27. Stegeman I, de Wijkerslooth TR, Stoop EM,et al. Risk factors for false positive and for false negative test results in screening with fecal occult blood testing. Int J Cancer. 2013;133(10):2408-14.
28. Tepeš B, Stabuc B, Stefanovič M,et al. Faecal immunochemical test-based colorectal cancer screening programme SVIT in Slovenia: pilot phase. Eur J Cancer Prev. 2014;23(4):235-9.
29. Allison JE, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). Gut Liver. 2014;8(2):117-30.
30. Sharp L, Tilson L, Whyte S,et al. Using resource modelling to inform decision making and service planning: the case of colorectal cancer screening in Ireland. BMC Health Serv Res. 2013;13:105.
31. Prevention and Screening. Europa colon website. Available from: http://www.europacolon.com/ accessed on 17/08/2014.
32. World Endoscopy Organization. Available from: http://www.worldendo.org/weo-crcsc-expert-working-group-fit-for-screening.html accessed on 17/08/2014.

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