PUBLIC HEALTH

# SOME INTERNATIONAL EXPERIENCES FROM SCREENING FOR COLORECTAL CANCER

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## Abstract

Colorectal cancer (CRC) is an important public health problem, especially in Europe. Every year approximately 435,000 new cases are being diagnosed with colorectal cancer. Half of these people die, which makes this type of cancer a second-rated mortality cause in Europe. The main aim of this paper was to make a literature search related to colorectal cancer with a focus on the developed Western European countries and countries close to the Republic of North Macedonia.

This paper also intended to provide a picture of the early screening for colorectal cancer as the most efficient method for prevention and early detection of colorectal cancer and its application in some developed countries. For achieving the objectives set out in this paper, a survey of the available literature (both electronic and print) as well as of the grey literature was made. A systematic search of the following databases was made: PubMed, European Commission, and Google Scholar. The inclusion criteria were studies conducted between 2008 and 2020, with an emphasis on the newest studies and those published in the neighboring countries. According to the WHO recommendations and practices in modern countries, colorectal cancer should be identified as a serious public health problem. This includes unclear cause of its occurrence, as well as all possible risk factors which make it almost possible to implement an adequate prevention program.

The most acceptable sensitive test for implementation of the screening program for colorectal cancer is the utilization of the FOB test. It is of great importance to follow-up patients with a positive FOB test as well as to offer easy access to health services, i.e., screening program to the population.

ЈАВНО ЗДРАВЈЕ

# НЕКОИ МЕЃУНАРОДНИ ИСКУСТВА ОД СКРИНИНГ НА КОЛОРЕКТАЛЕН РАК

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## Извадок

Колоректалниот карцином (КРК) претставува многу важен јавноздравствен проблем со 435.000 нови случаи годишно. Овој вид карцином е на второ место по смртност во Европа. Главна цел на овој труд беше да се изврши преглед на постојната литература поврзана со скринингот за колоректален карцином (КРК) во развиените западноевропски земји, како и во Република Северна Макединија и земјите од нејзиното опкружување. Трудот укажува на почетоците и развојот на скрининг програмата за КРК, како најефикасна метода за превенција и рана детекција на колоректалниот карцином. Бидејќи сè уште во целост не се познати причините за настанувањето на карциномот на дебелото црево, како и можните фактори на ризик, единствено можна превенција е избегнувањето на веќе познатите ризици како и скринингот за рано откривање. За остварување на целите поставени во овој труд беше направен преглед на достапната литература (во електронска и печатена форма), како и преглед на „сивата литература“ (grey literature). Како извори на податоци (бази на податоци) за електронско пребарување беа користени PubMed, WHO, European commission, Google Scholar. Во истражувањето беа вклучени стидии публикувани во периодот 2008-2020 година, при што предност им беше дадена на поновите студии како и на студиите кои се однесуваа на земјите од регионот на Република Северна Македонија. Како најмногу применуван и најсензитивен тест при скрининг за КРК е ФОБ тестот. Неопходно е да се олесни пристапот на населението кон раното откривање на колоректалниот карцином преку здравствена услуга во форма на бесплатен скрининг за КРК со ФОБ тест.

## Introduction

Colorectal cancer (CRC) is a very important public health problem in Europe. Every year approximately 435,000 new cases are being diagnosed with colorectal cancer. Half of these people die, which makes this type of cancer a second-rated mortality cause in Europe[1]. According to WHO data, colorectal cancer is the third commonest cause of death from malignant diseases in men, and the fourth most common in women, responsible for 10% of overall death rate from malignant diseases in the developed countries.[3] CRC mortality rate in 27 Member States of the European Union varies, whereby Hungary takes the leading place and Cyprus is on the last place. This diversity in mortality is due to different life styles, screening models or the stage when the disease has been detected as well as to the range of sophisticated treatment and health care.

Colorectal cancer can be detected in its early stage. In the developed countries, approximately 40-50% of the population across lifetime develop one or more adenomas in the colorectal region1, and most of them do not progress to malignancy.[2] The average duration of the development of an adenoma to colorectal cancer has not been identified, but it is assumed to take at least 10 years.[3] This long latent phase provides an excellent opportunity for early detection of this disease. If it is detected in the phase of adenoma, its removal can prevent the incidence of colorectal cancer. But, even when cancer is detected in an earlier stage, prognosis is considerably better than in a more advanced stage.

Efficiently conducted screening technique can significantly reduce morbidity and mortality from CRC in the population. Several approaches for CRC control are available in healthy control subjects with or without familial or other risk of this disease. They include colonoscopy combined with sigmoidoscopy and FOB test. Screening with the FOB test is essential, but it is necessary to adequately implement it in practice, to have systems for appointment for early colonoscopy if there is a positive finding and to establish functional cancer registers.[4]

The main aim of this paper was to make a literature search related to screening for colorectal cancer with a focus on the developed Western European countries and countries close to the Republic of North Macedonia. The paper also describes the beginnings and development of CRC screening program as the most efficient method for prevention and early detection of colorectal cancer.

## Material and methods

In order to accomplish the objectives, set out for this paper, a systematic review of the available literature (electronic and print) was conducted as well as a survey of the "grey literature". Retrieval of the following databases PubMed, European Commission, and Google Scholar was made. The paper included studies conducted between 2008 and 2020, with an emphasis on the recent studies and those published in the neighboring countries of North Macedonia. The following keywords were used for retrieval of the electronic databases: colorectal cancer, screening for colorectal cancer, FOB test, algorithm of screening for col-

orectal cancer. The search of the "grey literature" comprised retrieval of web sites of relevant national institutions (Health Ministries, academic institutions, doctors' associations, non-governmental organizations) and it consisted of reviews of national annual programs, reports on implementation of programs, protocols and professional consensuses, national projects, etc.

## Results

In 2008, according to the WHO data, 450,000 newly diagnosed cases with colorectal cancer were registered and the estimated total number of deaths in the European Union was 232,000. About 65% of all new cases were in the high-income countries. The risk of onset of colorectal cancer across the lifespan depends on several factors such as age, eating habits/physical activity, personal and familial predisposition, and it ranges from 5% in patients with an average risk to more than 95% in patients with some hereditary/congenital syndromes.[5] It is important to stress the fact that one fourth of the diseased has a positive family history, of which 15% are first-degree relatives.[6]

According to the existing literature used for the needs of this paper, CRC is the third most common malignoma behind that in the lungs and prostate in the United Kingdom. It is the second most commonly diagnosed malignoma in women, right behind that of the breasts. CRC is always fatal if it is diagnosed in the advanced stage, but it can be cured, i.e., has a relatively long survival rate if it is diagnosed in the early stage.

In Europe, CRC is the second most common cause of cancer death in both men and women. It is the second most common malignoma encountered in women, right behind the breast cancer, and the third most commonly diagnosed cancer in men behind lung and prostate cancers. In the entire European Union, the death from colorectal cancer has decreased from 20.36/100,000 population in 1995 to 18.86/100,000 population in 2009.

Having in mind that in more than 90% of patients CRC develops based on previous existing benign adenomatous intestinal polyps by which removal carcinoma onset is prevented along with the fact that disease detection in the early phase results in a 5-year survival in more than 90% of patients, it is necessary to establish a preventive screening program for early detection of this disease.[7]

In 1968, WHO defined the first set of principles for population screening[8]: 1) its importance as a public health problem for the individual and for the community; 2) recognition of the latent or early symptomatic stage; 3) available facilities for diagnosis and treatment; 4) suitable screening tests; 5) promotion of tests among the populations; 6) adequate understanding of the disease history; 7) agreed policy for testing, treatment and care of patients diagnosed with this disease; and 8) financing of screening and treatment of CRC as a continuing process.

Accumulated knowledge for implementation of screening programs for cancer has been acquired through screening networks founded in the European Union and the ''Europe Against Cancer'' program.[9]

EU networks have shown that the entire outcome and quality from the screening depends on the performance of each and every step of the screening process. For achieving a potential benefit from CRC screening, the quality has to be optimal in every step of the process and has to include information, identification and personal invitation to the target population, adequate performance of the screening test, additional diagnostics of the lesions detected with the screening, treatment, surveillance and continuous care. This approach is essential regarding screening adjustment to those individuals who would benefit from it in terms of adequate monitoring, evaluation and subsequent improvement of its performance[10].

Later, all the above-mentioned principles were incorporated in the European Union policy about cancer screening and were embodied in the European Council Recommendations on Cancer Screening on 2nd December, 2003[11]. They showed that efficacy evaluation is an indispensable prerequisite for accepting the screening process by the population, but not sufficient by itself. Many other aspects such as adverse effects, cost and infrastructure should also be included in the screening process. Population screening is a process that starts with education of the population about the disease that is being screened and ends with follow-up of the disease and treatment of the patient if he/she tested positive.

Screening can have two approaches: opportunistic – when patients themselves pay a routine check-up to their family physician, and proactive – when a target group that is going to be subjected to screening is identified. There are several screening modalities for early detection of CRC. They include: fecal occult blood test (FOBT), flexible sigmoidoscopy, colonoscopy and computerized tomographic colonography. Since one of the leading symptoms of colon cancer is occult or overt bleeding along with impaired intestinal (gastric) emptying, screening with the FOBT is a method of choice in a large number of countries.

The risk of developing CRC significantly rises above the age of 40, and 91% of all cancers have been detected at this age and primarily in individuals older than 50 years. It is assumed that every person at the age of 50 bears a 4.8% risk of developing CRC by the age of 74, i.e., 2.3% risk that he/she will die from CRC. That is why, the European Union recommends FOB screening for colorectal cancer in men and women aged 50 to 74 years.

Screening tests are available, but with different degrees of sensitivity and specificity. Prior to implementation of the national program in the United Kingdom, several sensitive and specific screening methods were identified and patient acceptance and financial implications were also investigated. CRC screening was conducted by using the FOB tests. There is evidence that this modality saves lives in a similar manner as the breast screening program in the United Kingdom. Single flexible sigmoidoscopy is an alternative to the FOB test screening and pilot data show that this technique is being logistically realized in the United Kingdom. Currently, the FOB test and

flexible sigmoidoscopy are rewarding, but they differ in sensitivity and specificity. Programs for education of the population are essential for reaching the effectiveness.[12]

In recent decades, the principles of WHO have been expanded and elaborated in the implementation of the national screening programs in the Netherlands and has been concluded that initiation of treatment in the early phase has more benefit than delayed treatment. In the Netherlands, population screening for colorectal cancer stared in 2014, the target group being aged 55-75 years. According to the experts' opinion in the Netherlands, in long-term perspective the national screening program could help about 2,400 people per year that would otherwise die from colorectal cancer. In the years 2014 through 2018, about 76 of 100 people responded to the invitation to participate in the screening program[14].

In the developed Nordic/Scandinavian countries colorectal cancer is the most common type of malignoma, ahead of breast and prostate cancer. By application of CRC screening and in line with the results they obtained, these countries have reduced death from this cancer by 23%. Denmark decided to conduct a feasibility study to assess whether population/community-based screening would have the same effect as it was demonstrated in randomized controlled trials.[15] In Danmark, all citizens between 50 and 74 years of age were invited to make a colon cancer screening every second year. A screening program looks for cancer precursors and cancer in people who do not have symptoms. Without a screening program colon cancer is usually discovered late, because symptoms appear late. In Danmark around 5,200 people a year develop colon cancer. Colon cancer is one of the most widespread types of cancer in the population. Approximately 1,800 people die from colon cancer every year. A screening kit is sent to every person by mail. This test kit is used to collect a small sample, and then it is returned to a laboratory by mail. The sample is then checked under a microscope for hidden blood, i.e., tiny amount of blood. Hidden blood can be a sign of colon cancer or polyps.[16] The earlier colon cancer is diagnosed, the greater the chances of being cured. In Norway, the Government has accepted the non-formal screening of the population. The reason behind this lies in the fact that this country has one of the world's highest incidence rates of colon cancer, especially in people aged 55 years and older. This country plans to offer every citizen free colorectal cancer screening before he/she turns 55 years. The program was started in 2019 with an aim to cover the entire population within a five-year period.[17] It was estimated that during the period 2013-2017 the final effect of this policy were 500 death cases. In Finland, the implementation of the national screening program was gradually introduced by using the FOBT as a method for screening in 2014[18]. In August of 2021 the Finish Government amended the Government Degree on Screening. Colorectal cancer screening will be performed on national level from 2022 onwards. The screening will be made for both men and women aged 60-68 years. It will be expanded by age group and will cover the entire

target population, that is, all people 56 - 74 years old in 2031. The screening will be made every two years.[19]

The National system in Italy (Passi) is organized as a telephone-interview surveillance system that collects information on population health, monitors behavioral health risk factors and diffusion of preventive health interventions. From 2010 to 2013, more than 151,000 of the population aged 18-69 years were interviewed. During 2013, 136 out of 147 Italian local health authorities participated in the survey. Information regarding screening included: test uptake (PAP test, HPV, mammography, FOB test, colonoscopy), date of the last test, reason for not participating in screening, screening promotion and results from the screening. Individual information about socio-economic characteristics was also available.[21]

In analyzing the structure of the conducted screening programs in different regions of Italy, 38% of the participants aged 50-69 years reported having undergone CRC screening in the last two years prior to the interview. From 2010 to 2013, an increased coverage for all types of screening was registered: the trend was higher in the South of the country, and the increase was mostly due to the tests performed within the organized programs. In regions with people with a low level of education, economic problems and immigrants, a lower coverage of screening was observed. In regions with well-implemented organized screening programs, coverage for testing was higher. Also, differences regarding socio-economic factors were smaller than in regions with incomplete activation of the screening program. Between 2017 and 2020, about 47% of 50-69-years old in Italy underwent colorectal cancer screening. This statistic has highlighted regional variations. An obvious considerable geographic difference between the South and the North of the country was registered. In fact, in Northern regions, about 69% of residents underwent this kind of screening, while the average percentage in Southern regions was 27%. In Apulia, the prevalence rate of colorectal tests was as low as 10.6%.

With an aim to reduce death cases, CRC screening was established in the United Kingdom. The screening program was commenced in Northern Ireland in 2010, and then England and Scotland started its implementation. Its goal was to analyze and discuss the initial results from screening of the colon cancer in Northern Ireland and at the same time to compare data with other regions in the United Kingdom. The adenoma detection was higher than the expected one.[20]

A good example of a well-organized and effective colorectal cancer screening program from the region is the SVIT Program from Slovenia22 aimed for men and women aged 50 to 69 years. As a result of the screening program, each year in this country the number of new CRC cases is reduced for 300, and of death cases for 200. In the beginning, Slovenia conducted this CRC screening as a pilot project, which later proved to be very successful and hence was implemented on a national level.

In order to reduce CRC incidence and mortality, a population screen-

ing in the Republic of Serbia was organized. The goal was to assess the acceptability of the FOB test proposed by primary care physicians. From August to November 2013, a pilot study for CRC screening was realized. The screening was organized in individuals aged 50 to 74 years. Fifty primary healthcare centers from all 25 administrative regions of Serbia were included. A total of 50,894 individuals were invited to participate in the screening program. The participation rate was 67.8 and 3.4% of the FOB tests were positive. Of those with a positive test, 69.7% agreed to undergo colonoscopy. The positive prognostic value was 27.1% for adenoma and 14.6% for carcinoma. This was the first CRC screening program in the country and encompassed approximately one third of primary healthcare institutions in all regions across the country.[23]

According to the data of the National System for Electronic Health Records/Evidence – "My Term", the incidence of colorectal cancer in R. Macedonia in 2019 was 34.7/100,000 inhabitants, that is, 38.8/100,000 men and 30.6/100,000 women. In 2018/2019 the incidence of colorectal cancer in both genders was more than three times higher than in the period of 2015/2016. The prevalence of men was significantly higher compared to women (p=0.0001). The mean age was 64.7±10.9 years; the youngest diagnosed patient was 14 years old, and the oldest 94 years. The mean age of men versus women was 65.1±10.6 vs. 64.1±11.3, with a significant difference in favor of older age at first diagnosis in male patients (p=0.033). A total of 91.54% of diagnosed individuals were at the age ≥50 years. Diagnosis of colorectal cancer in younger age groups was significantly associated with life in the rural environment (p=0.0001). Since 2008, there is a national consensus on prevention, diagnosis, therapy and follow-up of CRC patients in R. North Macedonia. In a six-month period in 2012 (July – December), the first pilot CRC screening in the age group 50-74 years was organized. The results obtained showed that by using the FOB test there was a possibility of diagnosing this type of cancer in an early stage. In 2012, the first organized CRC screening was initiated, which in 2014 reached the highest coverage and fulfilled all steps of the screening program in R. North Macedonia. Screening and the need for its implementation in our country was included in the Strategy for Healthcare Development, Consensus on prevention, diagnosis, therapy and follow-up of patients with colorectal cancer in the Republic of North Macedonia has been made, and it is in line with the European recommendations against colorectal cancer as well as in line with the resolution on prevention and control of carcinomas adopted by the World Health Organization in Geneva in 2003.[24]

## Discussion

Although the mechanism has not yet been defined, a large number of studies have pointed out to stimulation of the proliferation of the normal colon mycosis that can turn to adenoma and CRC, probably due to the direct genotoxic effect of local metabolites (free oxygen radicals and sulfur reactions) in the colon. Advances in knowledge about molecular and genetic mechanisms, which play a key

role in the CRC pathogenesis, have stressed the importance of prevention and early detection by screening of people from 50 to 70 years of age.

The implementation of screening programs includes also a structure responsible for delivery of services, quality of the service and evaluation. Population programs, in general, ask for a high level of organization in terms of identification and invitation of each and every individual that belongs to the target group. A large number of experts and professionals are undertaking further steps regarding the improvement of the screening standards.[25]

On 2nd of December 2003, the Health Ministers of the European Union unanimously adopted recommendations on cancer screening based on the evidence and experience of the "Europe Against Cancer" program.[25] The European Council Recommendations include fundamental principles of best practice in early detection of cancer and invites EU Member States to undertake joint actions in implementation of national colorectal cancer screening programs, with an organized population-based approach and with adequate quality assurance at all levels.

The adoption and subsequent implementation of the Council Recommendations on Cancer Screening has also been supported by various initiatives of the European Parliament and has been documented in resolutions of the Parliament.[26] Efforts for implementation of EU Council Recommendations also include continuous update of quality assurance guidelines suggested by the Council as a conclusion during the Slovenian Presidency.[27] The Council recommendations and European guidelines also stress the need for efficient communication with population groups, most commonly identified as persons with a limited access to screening or vulnerable social-economic groups. This, in return, should enable informed decisions about participation, based on objective, balanced information about the risks and benefits of the screening.[28]

Screening program efficacy is seen in the qualitative functioning of the individual components of the screening. The success of the program is seen not only in the impact on public health but also on the organization, implementation and adaptation. In order to determine the efficacy of the program, that is, its impact on morbidity and mortality, a continuous monitoring of the target population in defined timeframe is necessary. The key to evaluation of the population screening program is in the collection and timely and precise analysis of the data.

Short-term estimation on the success of conducting a screening program is evaluated by the population response, the speed of reporting a positive finding and referral to colonoscopy, the attitude of the people with a positive test towards further investigations, extent of the utilization of engaged resources (colonoscopy, analgosedation, endoscopic interventions – a successfully conducted examination, follow-up of the pathological finding and treatment).

Long-term estimation on the success of conducting a screening program refers to the decrease of mortality and morbidity rate from CRC.

Since 2007, several EU Member States

are in a process of implementation of a national population screening. This type of screening is being conducted in five countries: Finland, France, Italy, Poland and United Kingdom. Some of these countries are running non-population-based CRC screening program (Austria, Bulgaria, Czech Republic, Germany, Greece, Latvia, Slovak Republic). Other five countries have realized a pilot CRC screening program (Hungary, Cyprus, Portugal, Romania and Slovenia). Ten of these 17 countries have adopted the FOB test alone, 6 use a combined FOB test and endoscopy, and one uses colonoscopy, too. Ten of them have developed or upgraded the CRC screening program (Czech Republic, France, Ireland, Lithuania, Portugal, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom). Danmark and the Netherlands are in the phase of implementation of the CRC screening program.[29]

## Conclusions

According to the WHO recommendations and good practices in modern countries, CRC has to be identified as a public health problem. By applying a high-quality screening program that would comprise a large number of participants, the decrease in mortality percentage is generally accepted to be similar in all countries. Each country should give priority to the benefits of the CRC screening over the benefits of alternative programs. CRC incidence rate in Europe shows that the potential benefit from CRC screening is important for all European countries.

Currently, only the FOB test (for detection of occult bleeding) for men and women aged 50-74 years is recommended by EU as a valid screening test for early detection of CRC. Direct harmful effects related to this test are minimal. The guidelines, in general, contain information about establishing screening programs with excellent quality using the most common modalities in Europe, which are FOBT, flexible sigmoidoscopy and colonoscopy. Stool-based tests, such as FOBT and FIT (fecal immunochemical test), have been recognized as effective, but it is assumed that quantitative FIT is superior in terms of specificity and sensitivity. FOB tests should be repeated at annual or biannual basis or at least every three years if FIT is used. The guidelines emphasize the lack of high-quality evidence for assessment of colonoscopy. Nevertheless, according to the authors, current evidence supports the 10-year surveillance if colonoscopy is used, which indicates that the extended interval up to 20 years can be appropriate.

In the Republic of North Macedonia, the FOB test has been accepted for implementation in the screening program for early detection of CRC and hence European guidelines are met, but it has to be taken into consideration that upgrading is necessary for development of protocols and guidelines for screening.

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