

## EPIDEMIOLOGY AND SCREENING OF COLORECTAL CANCER

NATAŠA ANTOLJAK, MARIO ŠEKERIJA

Croatian National Institute of Public Health  
University Zagreb, School of Medicine, School of public health 'dr. Andrija Štampar',  
Zagreb, Croatia

---

### Summary

Colorectal cancer (CRC) is global problem with 1.36 million new cases each year. Moreover it is the third most common cancer in men worldwide (746,000; 10%) and second most common in women (614,000 cases; 9.2%). The main characteristic of colorectal cancer is slow development and long presymptomatic phase, so it make possible for early diagnose as well as prevention by removing polyps. Faecal occult blood testing (FOBT) for early detection of colorectal cancer is an evidence based, cost-effective screening strategy and is the most commonly chosen approach in organised population-based colorectal cancer screening programmes throughout the world. There are two main kinds of tests-one guaiac based which detects hem in haemoglobin and other, immunochemical directed to detect protein part globuline. All FOBT positive persons are sent to colonoscopy. CRC incidence and mortality data in Croatia still show high values, especially in males so national colorectal cancer screening programme started in Croatia under the auspices of the Ministry of Health and Welfare (now the Ministry of Health) at the end of 2007. All citizens age 50-74 years are invited to programme. First cycle lasted longer due to legal and financial difficulties related to the harmonization of legislation with EU law and finished in 2012. Response rate was 21%, so the second cycle started in September 2013<sup>th</sup> in reorganized form which includes educational and promotive campaign and participation of primary care physicians and field nurses.

KEY WORDS: *epidemiology, colorectal cancer, mortality, screening*

### EPIDEMIOLOGIJA I PROBIR KOLOREKTALNOG KARCINOMA

#### Sažetak

Rak debelog crijeva globalni je problem s 1.36 milijuna novih slučajeva svake godine. Štoviše, u muškaraca je to treće najučestalije sijelo (746,000; 10%) i drugo u žena (614,000 cases; 9.2%). Glavna osobina raka debelog crijeva je spori razvoj bolesti i dugo razdoblje do pojave prvih znakova, što ga čini pogodnim za rano otkrivanje kao i prevenciju uklanjanjem polipa. Testiranje na skrivenu krv u stolici za rano otkrivanje kolorektalnog raka je utemeljeno na dokazima i kost-účinkovita je strategija, pa je najčešći pristup provedbom organiziranih populacijskih programa diljem svijeta. Dvije su glavne vrste testova na skrivenu krv u stolici-gvajakov koji otkriva hem u hemoglobinu i imunokemijski temeljen na reakciji s globulin-skim dijelom. Sve osobe s pozitivnim testom upućuju se na kolonoskopiju. Pojavnost i smrtnost od raka debelog crijeva u Hrvatskoj još uvijek pokazuju visoke vrijednosti, osobito u muškaraca, te je 2007. god. započeo nacionalni program ranog otkrivanja u organizaciji Ministarstva zdravlja. Svi građani u dobi 50-74 godine pozivaju se u program. Prvi ciklus trajao je dulje od planiranog zbog zakonskih i financijskih problema vezanih uz harmonizaciju zakona sa zakonima EU, te je završio 2012. godine. Odaziv je bio 21%, a drugi ciklus počeo je u rujnu 2013. u reorganiziranom obliku što uključuje edukacijsku i promotivnu kampanju te učešće obiteljskih liječnika i patronažnih sestara.

KLJUČNE RIJEČI: *epidemiologija, kolorektalni karcinom, mortalitet, probir*

---

## INTRODUCTION

### Epidemiology

Colorectal cancer (CRC) is an important health issue throughout the world. The latest estimates of the International Agency for Research on Cancer (IARC) according to GLOBOCAN 2012 (1) are point to 1.36 million new cases of CRC in the world each year, 447,000 of which occur in Europe. It is the third most common cancer in men worldwide (746,000; 10%) and second most common in women (614,000 cases; 9.2%). There is a substantial geographical variation in the incidence and mortality rates, with the highest incidence rates attributable to Australia and New Zealand while the highest mortality rates are observed in Central and Eastern Europe. Incidence has been on the rise in recent years, owing to the rise of overall life expectancy and lifestyle changes related to diet factors. The most common risk factors include high fat and red meat consumption with low vegetable intake, overweight and obesity, physical inactivity and high consumption of alcohol (2). Family history of colorectal cancer is also an important predisposition for development of CRC, accounting for 15-20% of all cases (3), with hereditary syndromes accounting for 5% of the cases (4).

In Croatia, a recent publication revealed increasing trends in incidence and mortality of CRC in men in the period 1988-2008, with estimated annual percent changes (EAPC) of +2.9% for incidence and +2.1% for mortality. In women, the increase in incidence rates was not statistically significant, while mortality rates showed an increase for the period from 1994-2008, with the EAPC of +1.1% (5).

The most recent data for Croatia (incidence for 2011 (6); mortality for 2012 (7) show that, in males, colorectal cancer is ranked third in incidence (1.648 new cases; crude incidence rate 79.8/100,000) and second in cancer causes of death (1.136 deaths; crude mortality rate 55.0/100,000). In females, colorectal cancer is ranked second in incidence (1.172 new cases; crude incidence rate 52.8/100,000) and second in cancer related mortality (868 deaths; crude mortality rate 39.1/100,000). The distribution of stages for CRC registered in the Croatian Cancer Registry in 2011 indicates that it was diagnosed at the localised stage in 19% of cases, with regional spreading or regional metas-

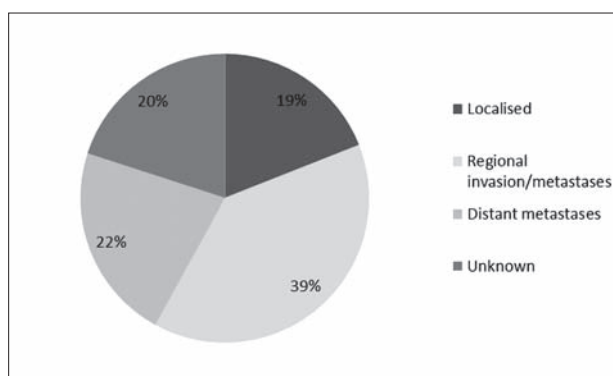


Figure 1 Stage at diagnosis in CRC patients diagnosed in 2011, Source: Croatian National Cancer registry (6)

tases in 39% of the cases, in 22% there were distant metastases at time of diagnosis, while for 20% of the cases the information on stage at diagnosis was missing.

According to the latest GLOBOCAN 2012 estimates, in males in Europe, Croatia is ranked 8<sup>th</sup> in incidence (age-standardized rate (ASR(W)) 44.2/100,000) and 3<sup>rd</sup> in mortality (ASR(W) 26.7/100,000). For women, Croatia is ranked 16<sup>th</sup> in incidence (24.7/100,000) and 2<sup>nd</sup> in mortality (ASR(W) 13.0/100,000). The estimated 5-year prevalence is 293.3/100,000 in males and 204.8/100,000 in females (1).

The recently published EURO CARE-5 study has provided data on cancer survival in European countries, and for the first time Croatian data were also included. The study showed that the 5-year relative survival of Croatian cancer patients diagnosed from 2000-2007 and followed-up until the end of 2008 was 49.6% for colon cancer, and 48.5% for rectal cancer (both sexes combined) (8). This was lower than survival in western European countries (Austria 61.2%/61.1%, Denmark 53.6%/54.6%), comparable to similar European countries (Slovenia 54.0%/49.7%, Slovakia 51.4%/44.7%) and higher than survival in Eastern European countries such as Bulgaria (45.2%/38.4%) and Latvia (42.9%/36.1%).

### Colorectal cancer screening

The main characteristic of colorectal cancer is slow development and long presymptomatic phase. A growth of tissue or tumor usually begins as a non-cancerous polyp on the inner lining of the colon or rectum and if not treated it can develop to

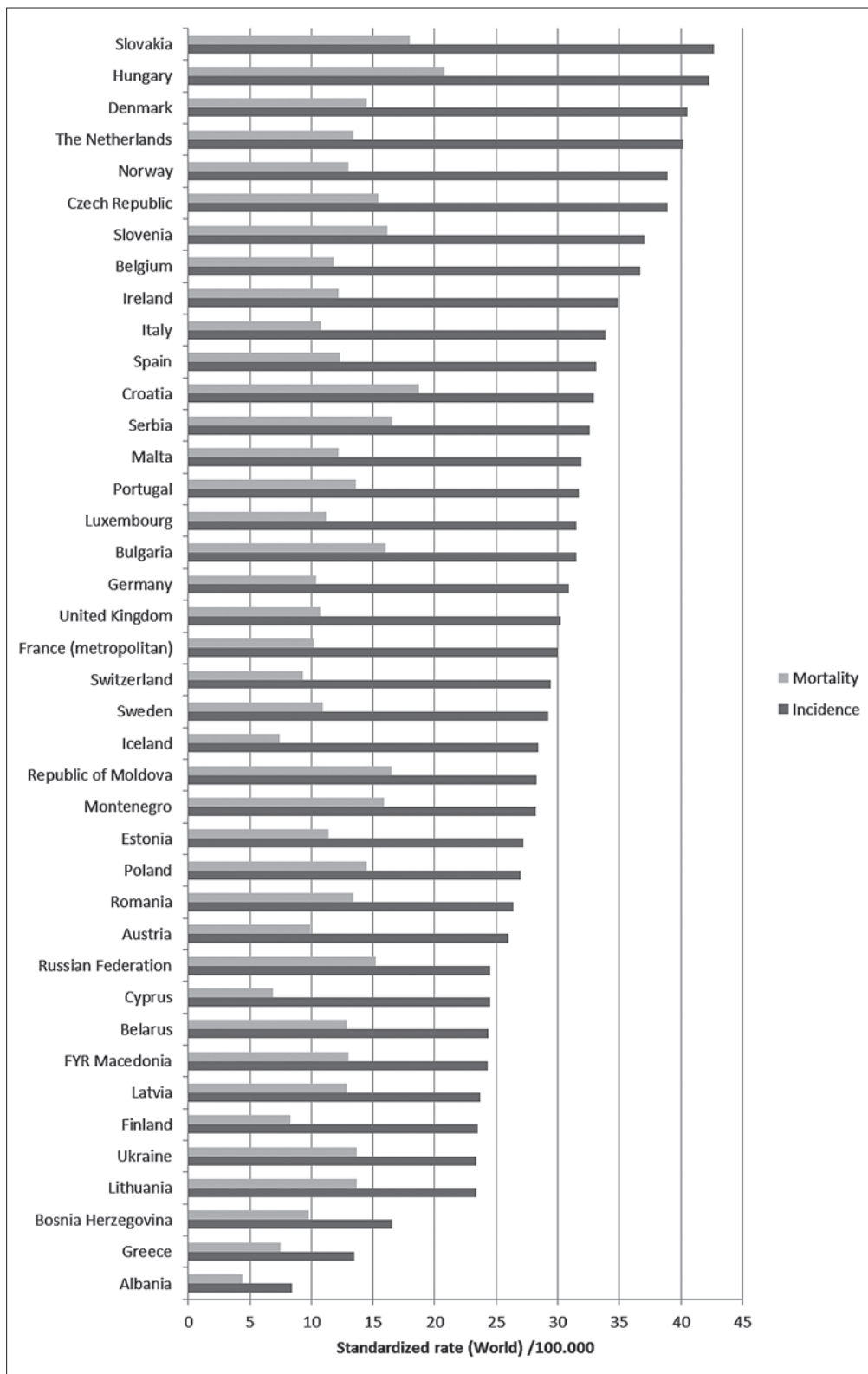


Figure 2 Incidence and mortality of colorectal cancer in Europe, Source: GLOBOCAN 2012 (1)

malignant lesion (9). The chance of changing into a cancer depends upon the kind of polyp, so adenomatous polyps can change into cancer and are called a pre-cancerous condition. Hyperplastic polyps and inflammatory polyps, in general, are not pre-cancerous. But some studies show that some hyperplastic polyps can become pre-cancerous or might be a sign of having a greater risk of developing adenomas and cancer, particularly when these polyps grow in the ascending colon (10). Another kind of pre-cancerous condition is called dysplasia. Dysplasia is an area in the lining of the colon or rectum where the cells look abnormal (but not like true cancer cells) when viewed under a microscope. These cells can change into cancer over time. Dysplasia is usually seen in people who have had diseases such as ulcerative colitis or Crohn's disease for many years. Both ulcerative colitis and Crohn's disease cause chronic inflammation of the colon (9).

Faecal occult blood testing (FOBT) for early detection of colorectal cancer is an evidence based, cost-effective screening strategy and is the most commonly chosen approach in organised population-based colorectal cancer national and regional screening programmes throughout the world (11, 12).

Early detection of disease or screening in the healthy population is one way of improving health, and also the basis of epidemiology as a profession which aims preventing diseases in population or target group. The diseases that have a relatively long period between the beginning of the disease development and the first signs, and if there is an appropriate test for the early detection, it is possible and reasonable to implement screening (13). Test or examination that is used must also satisfy the criteria for clinical validity (corresponding sensitivity and specificity), and the risk of examination shall be the minimum and must be safe for the patient. It is important to have a robust digitalized system for monitoring patients and screening procedures for assessment (14). The final result of screening must be absolute prolongation of life not just earlier detection of disease (15). Moreover, the ultimate goal of every screening is reducing mortality and improving quality of life for patients, so quality care must be provided as well as treatment of newly diagnosed patients. There is scientifically based and multi-practically

confirmed evidence that screening for colorectal cancer contributes to early and timely detection, and consequently to greater survival as well as improved quality of life for patients, which is very important (16). A satisfactory response according to EU quality assurance guidelines is 45%, and the desired 65% (14). It should be noted that in some countries only after 10 or more years of implementation the response rate has been increased to 25%, but in countries with already developed knowledge of the population about the usefulness of prevention or those countries with extensive educational and promotional campaign, a significant increase of the response rate is as it has been done in the neighbouring Slovenia (17).

According to the recommendations of the Council of the European Union (2003/878/EZ), and based on published data and experience at that time, the national colorectal cancer screening programme started in Croatia under the auspices of the Ministry of Health and Welfare (now the Ministry of Health) at the end of 2007. The program is implemented in accordance with the resolution on the prevention and control of cancer (WHA, 58.22, Cancer prevention and control), adopted by the World Health Assembly at its 58<sup>th</sup> session in Geneva 2005<sup>th</sup>.

The network of Public Health Institutes, the Croatian National Institute of Public Health, hospitals, clinics, polyclinics and primary health care are included in implementation of the program. The first cycle lasted longer due to legal and financial difficulties related to the harmonization of legislation with EU law (from 2008-2012.) In September 2013<sup>th</sup> the second cycle started in the reorganized form.

### **The objectives of the Croatian National Colorectal Cancer Screening Program**

Program objectives are to detect cancer in its beginning stages, detect and remove polyps of the colon and thereby increase the possibility of healing, and improve the quality of life for affected individuals. Furthermore, the aim is to strengthen the network of colonoscopy units and to improve the organization of the program. So, the target is to increase the current response. The long-term goal is to reduce the mortality of colorectal cancer by 15% , 10-13 years after the start of the program.

## Target Group

The target group for this screening program are all women and men aged 50-74 years (approximately 1,400,000 persons). One cycle of invitations lasts 2 years.

## Method

Guaiac-based hypersensitive FOB test is used to test the occult (hidden) blood in the stool. For persons who have positive FOBT, a colonoscopy is a method of making a definitive diagnosis but also treatment in the event of finding polyps.

## The organization of the first cycle

In the first cycle of the program implementation it was organized in such a way that the test-cards were sent to the home addresses of the members of target population. The respondents received three test-cards and were asked to take samples of their stool successively for three consecutive days and send back in the enclosed envelope. The analysis of the samples was conducted in the Public Health Institutes. Persons whose test findings were positive were then invited for colonoscopy. The invitation also included a referral voucher and instructions on how to prepare for colonoscopy.

## Results of the first cycle

In the first cycle a samples from 1,419,639 persons were received for testing, among those 15,339 people were ineligible for testing. The Institutes received 288,935 of the sent test packages (21%) with correctly applied specimens which is in accordance to the response rate according to EU guidelines (17.2 to 70.8% ) in the first round.

Within the program, more than 10,000 colonoscopy examinations were conducted (80% response rate) and 576 people with colon cancer were discovered (2.3‰ of total number of tested persons, which is consistent with the expected: EU guidelines 1.2-2,3/1000). In 4223 people polyps were found (39.7% of incurred colonoscopy) and removed.

## Changes during the reorganization process of the program

The reorganization of the program aims to increase the response rate and at the same time

raise the level of knowledge and awareness of the population about colon cancer. The reorganization of the program is done due to rationalization, and in the first phase public health institutes send invitation letters, and then send test packages to responders who want it. We created a series of activities aimed at improving the organization and quality of the program. Written protocols that specify the basic epidemiological indicators of the quality control and indicators of implementation results are an obligatory part of the program. The European guidelines for quality assurance of screening are translated and will be published soon on the web. Coordinators in public health institutes (specialists in epidemiology and public health) within their teams are responsible for monitoring and implementation of the first part of the diagnostic process, as well as a timely provision of colonoscopy appointments for positive patients and for collaboration on continuous quality improvement program. They also participate in the organization of educational and promotional activities throughout Croatia. A very important factor for the successful implementation is continuous education of the personnel, i.e. professionals who are specifically trained to implement screening. Other measures for increasing participation rates are also implemented (i.e. napkins that can be placed on the toilet seat, clear and simple instructions for test performance as well as bowel cleaning and preparation for colonoscopy etc.).



Figure 3. toilet-seat napkin for easy stool sampling

## CONCLUSIONS

In the upcoming period we plan to strengthen the implementation and ongoing promotional

educational campaign organized by the Ministry of Health, Institutes of Public Health and the associations of interested patients, of which the most important one in Croatia is ILCO, association of patients with colostomy.

#### ACKNOWLEDGMENTS

Thanks to all the participants of the National Programme for early detection of colon cancer in Croatia:

The Committee for the organization, professional monitoring, evaluation and quality control of the National Programm for early detection of colon cancer: President asist. prof. Mirjana Kalauz, PhD; members: prof. Miroslava Katičić MD PhD, prof. Nataša Antoljak MD PhD, prof. Strnad Pesikan MD PhD, prof. Milan Kujundzic MD PhD, prof. Davor Stimac MD PhD, prof. Mirko Šamija MD PhD, prof. Zdravko Ebling MD PhD, Valerija Stamenić MD PhD, Slavica Conjar MD, Štefica Sipek Bacc Med Tech, Višnja Družak MD.

Members of the committee in the first cycle: Danica Kramarić MD, Dunja Skoko Poljak MD, prim. Tomislav Brkić MD PhD.

Thanks to all coordinators and members of the sanitary-epidemiological and public health teams in county Department of Public Health and Institute of Public Health “ Dr. Andrija Stampar “ (previously members of the Commission for the implementation of the first cycle), as well as all staff in endoscopic teams, specialists, gastroenterologists, surgeons and pathologists involved in implementing the program.

#### REFERENCE

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. 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 10/03/2014.
2. Herszenyi L, Tulassay Z. Epidemiology of gastrointestinal and liver tumors. *Eur Rev Med Pharmacol Sci*. 2010;14(4):249-58.
3. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000;343(2):78-85.
4. Allen BA, Terdiman JP. Hereditary polyposis syndromes and hereditary non-polyposis colorectal cancer. *Best Pract Res Clin Gastroenterol*. 2003;17(2): 237-58.
5. Kirac I, Sekerija M, Simunovic I, Zgaga L, Velimir Vrdoljak D, Kovacevic D, et al. Incidence and mortality trends of gastric and colorectal cancers in Croatia, 1988-2008. *Croat Med J*. 2012;53(2):124-34.
6. Croatian National Cancer Registry. Cancer Incidence in Croatia 2011. Zagreb: Croatian National Institute of Public Health; 2013.
7. Poljicanin T, Benjak T, editors. Croatian Health Service Yearbook 2012. Zagreb: Croatian National Institute of Public Health; 2013.
8. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. *Lancet Oncol*. 2014;15 (1):23-34.
9. Capel MS. The pathophysiology, clinical presentation, and diagnosis of colon cancer and adenomatous polyps. *Med Clin N Am* 2005; 89: 1-42.
10. Hyman NH, Anderson P, Blasyk H. Hyperplastic polyposis and the risk of colorectal cancer. *Dis Colon Rectum*. 2004; 47: 2101-4.
11. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol*. 2008;103(6):1541-49.
12. Kerr J, Engel J, Eckel R, Hölzel D. Survival for rectal cancer patients and international comparisons. *Ann Oncol*. 2005;16(4):664-72.
13. The epidemiologic approach to evaluating screening programs. In: Gordis L. *Epidemiology*. Philadelphia: Saunders; 2009.
14. Segnan N, Patnick J, von Karsa L. European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis. Luxembourg: Publications Office of the European Union; 2010. doi.10.2772/1458.
15. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.
16. Kerr J, Engel J, Eckel R, Hölzel D. Survival for rectal cancer patients and international comparisons. *Ann Oncol*. 2005;16(4):664-72.
17. Novak Mlakar D, Bračko M, Maučec Zakotnik J, Keršič Svetel M, Metličar J. Presejanje za raka na debelem črevesu in danki - program SVIT. *Onkologija* 2013; 1: 21-5.

*Author's address: Mario Šekerija, Croatian National Institute of Public Health, University Zagreb, School of Medicine, School of public health 'dr. Andrija Stampar', Mirogojska 16, 10000 Zagreb, Croatia. E-mail: mario.sekerija@hzjz.hr*