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Colorectal cancer screening: 20 years of development and recent progress

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Abstract

Colorectal cancer (CRC) is the second most common cancer in Europe and its incidence is steadily increasing. This trend could be reversed through timely secondary prevention (screening). In the last twenty years, CRC screening programs across Europe have experienced considerable improvements (fecal occult blood testing; transition from opportunistic to population based program settings). The Czech Republic is a typical example of a country with a long history of nationwide CRC screening programs in the face of very high CRC incidence and mortality rates. Each year, approximately 8000 people are diagnosed with CRC and some 4000 die from this malignancy. Twenty years ago, the first pilot studies on CRC screening led to the introduction of the opportunistic Czech National Colorectal Cancer Screening Program in 2000. Originally, this program was based on the guaiac fecal occult blood test (FOBT) offered by general practitioners, followed by colonoscopy in cases of FOBT positivity. The program has continuously evolved, namely with the implementation of immunochemical FOBTs and screening colonoscopy, as well as the involvement of gynecologists. Since the establishment of the Czech CRC Screening Registry in 2006, 2405850 FOBTs have been performed and 104565 preventive colonoscopies recorded within the screening program. The overall program expanded to cover 25.0% of the target population by 2011. However, stagnation in the annual number of performed FOBTs lately has led to switching to the option of a population-based program with personal invitation, which is currently being prepared.

Key words: Colorectal cancer; Population-based screening program; Colonoscopy; Fecal occult blood test

Core tip: The rising incidence rate of colorectal cancer (CRC) puts demands on systematic approaches towards secondary prevention. The National CRC Screening Program in the Czech Republic has been running for more than 13 years. Nowadays, guaiac and immunochemical fecal occult blood tests (FOBT) are used, as well as screening colonoscopy. The quality control system was devised with the introduction of CRC Screening Registry. Since 2006, 104565 preventive colonoscopies have been performed: 89752 FOBT+ colonoscopies (85.8%) and 14813 screening colonoscopies (14.2%). Adenomas were diagnosed in 30515 patients undergoing FOBT+ colonoscopy (34.0%), and in 3719 patients through...
screening colonoscopy (25.1%). In all preventive colonoscopies, a total of 4193 cancers were registered.

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INTRODUCTION

Colorectal cancer (CRC) poses serious health risks to the European population, mainly in the Central European region, where it is the second most common cancer as well as the second most common cause of cancer deaths[2,3]. This is an unfortunate fact knowing that CRC belongs to the group of preventable diseases, if diagnosed early[1]. CRC prevention includes two modalities: screening (early diagnosis of a disease in asymptomatic individuals) and surveillance[3] (long-term follow-up of high-risk individuals). Screening is focused on people aged 50 and over. Age represents a low risk factor for sporadic CRC, that is, carcinoma developing in patients with negative family or personal history of CRC or chronic inflammatory bowel disease; this type of carcinoma accounts for 80% to 95% of all CRC cases[4].

Screening procedures are performed in either one or two steps. One-step programs are represented by screening colonoscopy[5], flexible sigmoidoscopy[6-8], and CT colonography[9]. The initial method of two-step programs involves fecal occult blood tests (FOBT), which can be either guaiac-based (gFOBT)[10,11] or immunochemical (FIT)[12]. In cases of positive FOBT, examination with colonoscopy or flexible sigmoidoscopy follows. Recently, studies with other tests (such as capsule colonoscopy[13,14] or DNA testing[15]) have been performed, but their efficiency in practice has yet to be proved.

Guaiac FOBTs are the most frequently used test in screening programs worldwide. The malignant transformation of premalignant lesions (adenomas) lasts 8-10 years on average[16]. These lesions are often accompanied only by irregular and occult bleeding. However, with repeated and regular FOBT examination, the chances of detecting advanced adenomas or early cancers (followed by successful treatment) are high. It is documented that CRC diagnosis in an asymptomatic individual is associated with a 90% five-year survival rate, but this proportion decreases to 40% and 25% if the symptoms last for 5 or 7 mo, respectively[17]. Similarly, the five-year relative survival[18] can range between 90% and 15% for localized and advanced cancers, respectively[19].

The key point of the screening programs is to reach adequate target population coverage. Therefore, an organized population-based screening program based on early identification and followed by personal invitation to each individual from the target population is preferred[20].

CANCER BURDEN IN CENTRAL EUROPE

In Europe in 2012, it is estimated that 3.45 million new cases of cancer were diagnosed and 1.75 million patients died from malignant diseases. Concerning CRC, the annual number stands at 447000 new cases, with 215000 fatalities[21]. The burden of CRC is not equally distributed across Europe. Central European countries, most notably Slovakia, Hungary, and the Czech Republic, rank among the countries with the highest CRC incidence and mortality rates in Europe, with values two to three times higher than countries with the lowest occurrence (e.g., Bosnia and Herzegovina, Greece, and Albania). The mortality to incidence (MI) ratio has been shown to be a good indicator of cancer-specific survival[22]. With a CRC MI ratio of 0.42, the Czech Republic is close to the EU-27 value (0.40). Within Central Europe, similar results were shown for Austria (0.41) and Slovakia (0.44).

Time trends in CRC incidence in the Czech Republic and neighboring countries show diverse patterns for the last two decades (Figure 1, Table 1; selected cancer registries with trends available over long periods of time were chosen to represent Germany and Poland). Whereas in 1990, Saarland in Germany was the area with the highest CRC incidence, followed by the Czech Republic and Austria, in 2000, the Czech CRC incidence rates ranked first, representing a 25% increase in incidence over a decade. An even sharper increase was seen in Slovakia (+33%) and in Kielce, Poland (+80%). Fortunately, these trends were not repeated during the most recent period: CRC incidence rates have decreased (Czech Republic, Germany, and Austria) or only moderately increased (Slovakia, Poland).

In the Czech Republic, 8265 new CRC cases were diagnosed in 2010 with 3991 deaths. CRC incidence has been increasing alarmingly from the start of cancer registration in the 1970s up to the early 2000s. Recently, CRC incidence dropped by 4.4% between the periods 1995-1999 and 2006-2010. An even more substantial decrease was observed in CRC mortality rates, which dropped by 20.8% between 1995-1999 and 2006-2010 (Figure 2). In 2010, 23.8% of the patients were diagnosed with stage 3 and 23.0% in the primary metastatic stage (Figure 3). However, the first positive trends in early diagnosis have been witnessed; whereas only 15.6% of patients were diagnosed with stage I CRC in 2000, this proportion increased to 23.3% in 2010.

The epidemiological situation has been a challenge in the designing of a more effective CRC screening program in the Czech Republic. The program has been developed in step by step phases.

CZECH NATIONAL CRC SCREENING PROGRAM

CRC screening pilot studies

Due to the unfavorable development of CRC incidence and mortality rates in the Czech Republic in the second
half of the 20th century, six pilot studies incorporating gFOBT were performed in the period 1979-1984, and their summary results were published in 1986.

These studies were followed by the subsequent phase, referred to as the “Czech Screening Program”, in the period 1985-1991. This program was conducted in all regions and involved more than 100000 asymptomatic individuals between 45 and 60 years. Compliance of the target population reached 83.1%. Cancers diagnosed within this screening program were detected in earlier stages than non-screening cancers.

To confirm these outcomes in a different political and medical care setting (national vs private health care), yet another prospective study was conducted under the label “The Prague Project” (1997-1998). Here, 68 general practitioners (GPs) were involved and 12600 asymptomatic individuals were examined, with 80% compliance.

Both studies confirmed favorable cost-benefit and cost-effectiveness results, interest of the target population, as well as readiness of health care professionals to support CRC screening.

**Introduction to the national program**

Based on these facts, negotiations among the Czech Society of Gastroenterology, the General Health Insurance Company, and the Czech Ministry of Health followed, leading to the introduction of the National CRC Screening Program on July 2000. At that time, the Czech Republic was only the second country to have a nationwide CRC screening program (with Germany being the first). In the two-step program, the biennial guaiac FOBT (three stool samples) was offered to asymptomatic individuals aged over 50 as part of preventive check-ups at GP clinics. In cases of a positive test, colonoscopy followed.

**Further development**

The two phases in the developmental course of the program can be distinguished. In the period 2000-2005, the program was implemented and established; from 2006 until now, it was continuously improved and evolved. Compared to the other widely recommended screening programs (focused on breast cancer and cervical cancer), the CRC program is a multidisciplinary issue. In the beginning, the organizational structure comprising of GPs and gastroenterologists was established. Over the first three years, specific financial support (approximately CZK 240 million, equivalent to EUR 9 million) was allocated, with the objective of substantial improvements in the equipment of endoscopy units. A media campaign was launched, and educational courses were held in all regions. The program has been monitored and evaluated by the CRC Screening Council, consisting of regional coordinators of all involved medical specialties, and by the CRC Screening Committee of the Czech Ministry of Health. Until 2005, the evaluation was only based on aggregated data (provided by health insurance companies). During this period, 977973 gFOBTs were performed, 19257 adenomas were removed, and 2797 cases of CRC were diagnosed.

**Assessment of quality control for program improvement**

In 2006, the Czech CRC Screening Registry for collecting anonymous individual data was established. This online database contains data from the nationwide network of high-quality endoscopy units (168 centers for screening colonoscopy) on all preventive colonoscopies. The term “preventive colonoscopy” covers both FOBT colonoscopies (performed after a positive FOBT) and screening colonoscopies (available to all individuals aged over 55 years). The centers are required to meet strict quality criteria, including adequate personnel, materials and equipment, the recommended annual volume of colonoscopies and endoscopic polypectomies, quality control system, and a plan for the management of complications. The registry includes demographic data, the type and date of FOBT applied, and the main findings of the performed colonoscopy. Records in the registry also involve information about the number, size and histology of adenomas, the preoperative staging and histology of cancers, as well as complications (severe bleeding, perforation) during diagnostic procedures and polypectomies. The collected data is centrally stored and analyzed at the
In all preventive colonoscopies, a total of 4,193 cancers were registered. The overall cecal intubation rate reached 94.7% in FOBT+ colonoscopies and 97.7% in screening colonoscopies. In the years 2006-2012, there were 92 cases of perforation (0.09% of all examinations) and 361 cases of bleeding during endoscopic polypectomies (0.76% of all therapeutic procedures) reported.

The Czech National Cancer Registry (CNCR) and the Czech National Reference Centre (CNRC) are additional sources for monitoring the quality of the screening program. The Czech National Cancer Registry, the data of which was made partly accessible via the www.svod.cz portal[29], is an essential source of cancer statistics data, covering the entire population of cancer patients.

Since 2006, a total of 104565 preventive colonoscopies have been performed: 89752 FOBT+ colonoscopies (85.8%) and 14813 screening colonoscopies (14.2%). Adenomas were diagnosed in 30515 patients undergoing FOBT+ colonoscopy (34.0%; 48.1% of them with advanced adenomas) and in 3719 patients undergoing screening colonoscopy (25.1%; 29.4% of them with advanced adenomas). In all preventive colonoscopies, a total of 4,193 cancers were registered. The overall cecal intubation rate reached 94.7% in FOBT+ colonoscopies and 97.7% in screening colonoscopies. In the years 2006-2012, there were 92 cases of perforation (0.09% of all examinations) and 361 cases of bleeding during endoscopic polypectomies (0.76% of all therapeutic procedures) reported.

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in the Czech Republic starting from 1977. CNCR is a population registry involving the following information: personal data, tumor diagnosis, treatment, and post-treatment follow-up entries. The population-based monitoring allows us to estimate the incidence and the mortality rates, distribution of the clinical stages, as well as cancer treatment and survival rates. Malignant neoplasms are recorded in accordance with the International Classification of Diseases for Oncology (ICD-O, 10th revision)\textsuperscript{[30]}. Tumor staging is performed on the basis of the TNM classification system\textsuperscript{[31]}. Standardized Death Certificates (internationally recommended by the WHO) are implemented to collect precise individual data on the cause of death\textsuperscript{[32]}. In the Czech Republic, all residents are covered by public health insurance. The Czech National Reference Centre aggregates complete information from all health insurance companies. As the insurance cover is practically universal, this data can be used to estimate the number of preventive and diagnostic colonoscopies, as well as the performed FOBTs. This information system is, therefore, an essential tool for monitoring early performance indicators within the Czech program. In the period 2006-2011, 2405850 FOBTs were performed, with an estimated overall positive result of 5.1%. However, this figure showed an upward trend until it reached 6.7% in 2011.

**Current design**

The CNRC data shows that the coverage of the target population (all individuals aged over 50) has been steadily increasing since the program’s introduction; however, this rise has been very slow and the coverage has been well under the target values as recommended by the European Guidelines (Figure 4). Therefore, in 2009, a new program design was launched with the implementation of FIT, screening colonoscopy, and the involvement of gynecologists. Currently, the program is offered to asymptomatic individuals aged 50 and over. As regards people aged between 50 and 54 years, annual FOBT is offered followed by FOBT\textsuperscript{+} colonoscopy in cases of a FOBT positive result. People aged 55 years and over can choose between FOBT (biannually) and screening colonoscopy (at 10-year intervals). Since early 2013, gFOBT has been phased out. All types of FIT are allowed, both qualitative and quantitative, without determining a uniform cut-off value. Participation of gynecologists in the screening program was beneficial, mainly due to the rise in FIT use. In 2011, 8% of FOBTs were performed by gynecologists; helping to increase the coverage notably in women aged less than 65.

**Impact on long-term indicators**

Twelve years after its initiation, the Czech CRC screening program now extends coverage to about one in four of the target population. As it is far below the levels recommended by the European Guidelines, a significant impact of the program on CRC incidence and mortality in the target population cannot be expected. However, our data suggests a decrease in CRC incidence over the last decade: any slight decrease in the incidence is accompanied by a substantial fall in mortality and some increase in the proportion of the early stages. It is likely that the advent of CRC screening, combined with improvements in both the quality and capacity of endoscopy centers and increased CRC awareness, has had a positive impact on early diagnosis of CRC. Bearing in mind the slow spread of the screening cover, together with the sluggish natural progression of the adenoma to carcinoma, the impact of screening on CRC incidence is probably rather small, but may become more relevant in the years to come. The observed decrease in CRC mortality rates is the likely effect of both early diagnosis and a more successful treatment regime for CRC, as demonstrated by improvements in stage-specific CRC survival\textsuperscript{[33]}.

**DISCUSSION**

In the last twenty years, CRC screening programs across Europe went through considerable changes\textsuperscript{[34-37,38,39]}. The first country to implement an organized program was Germany in 1976, followed by the Czech Republic in the year 2000\textsuperscript{[35,36]}.
The development can be attributed to two main processes: fecal occult blood testing evolution and the transition from an opportunistic to population-based program setting. Initially, gFOBTs were used widely, mostly because of the favorable results of a randomized controlled study in 1993 that confirmed its 15%-33% CRC mortality reduction, low test cost, and easy handling. In the last decade, many trials showing the superiority of FIT were published. Higher sensitivity for colorectal neoplasia and higher target population compliance were detected. Some European countries (Great Britain, the Czech Republic, and Germany) have been replacing gFOBT by FIT; some started with FIT from the beginning (the Netherlands and Slovenia). The main issue is to find an appropriate cut-off level to balance the sensitivity and cost-effectiveness. Most studies prefer the cut-off level in the range of 75-100 ng/mL. In Finland, on the other hand, there is long tradition of using gFOBT, which has not changed over time, mainly because of the favorable results. The participation rate of 80% in women has been achieved for the second round. Poland remains the only country using colonoscopy in organized CRC screening program as the only screening modality. Colonoscopy is considered as a gold standard for CRC screening, but there has not been any randomized controlled trial confirming a reduction in CRC mortality by using this method. Therefore, an extensive international study (the NordICC Study) has started to prove this fact from a long-term perspective. In contrast, recent data from England points to a 43% reduction in CRC mortality with flexible sigmoidoscopy screening. Outside FOBT, colonoscopy, and flexible sigmoidoscopy, other methods have not yet been implemented as a regular part of screening programs as they are still under development (CT colonography, capsule colonoscopy, and molecular tests). In 2010, the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis were published based on the recent and evidence-based data focused on CRC secondary prevention and diagnosis. Concerning the program organization, it favors the population-based setting that can lead to adequate target population compliance (acceptable level of 45%, recommended level of 65%). Programs including personal invitations were successfully tested or implemented in many European countries and generally achieved very promising results regarding the participation rate of the target population.

The above developmental steps have been reflected in the colorectal cancer screening program in the Czech Republic. Based on the recent data, with a stagnating annual number of FOBTs, preventive colonoscopies, and diagnosed adenomas and cancers, it seems that the maximum limit of opportunistic screening has been reached. A switch to a population-based program is therefore essential and currently being prepared. This nationwide project (run by the Czech Ministry of Health) includes all three national screening programs (colorectal cancer, colorectal cancer, colorectal cancer).

### Table 2 Characteristics of selected fecal occult blood test colorectal cancer screening projects including personal invitations

| Country | Age group (yr), test | Time period | Procedure in personal invitation | Participation rate | Source |
|---------|---------------------|-------------|---------------------------------|--------------------|--------|
| England | 50-69 gFOBT         | 2000-2004   | Centralized invitations by the screening unit | F: 59%              | Weller et al[3], 2007 |
|         |                     |             | Sending fecal occult blood test (FOBT) test kits | SM: 48%             | UKCRCSPG[4], 2004 |
|         | 50-69               | 2003-2006   | Centralized invitations according to sickness fund database files | SW: 56%             |        |
|         | gFOBT               |             | Invitation to general practitioners (GP), reminder after 6 mo, FOBT kit reminder 4 mo later | FM: 54%             | Denis et al[5], 2007 |
|         |                     |             | Exclusions by GP: serious illness, recent colorectal cancer (CRC) screening, high CRC risk | FW: 57%             |        |
| Netherlands | 50-74 gFOBT, FIT    | 2006-2007   | Centralized invitations | gFOBT: 50%         | Hol et al[6], 2010 |
|         |                     |             | Exclusions: Inflammatory bowel disease (IBD), CRC, recent CRC screening |                      |        |
|         |                     |             | Pre-invitation, sending test kits after 2 wk, reminder after 6 wk | FIT: 62%             |        |
| Scotland | 50-69 gFOBT         | 2000-2007   | Centralized invitations by the screening center | FM: 50%, FW: 60%    | Steele et al[7], 2009 |
|         |                     |             | Sending FOBT test kits | SM: 49%, FW: 57%    |        |
|         |                     |             | Reminder-second kit-after 6 wk, (kit in first round only) |                      |        |
| Spain   | 50-69 gFOBT         | Since 2000  | Centralized invitations | FM: 17%, FW: 18%    | Peris et al[8], 2007 |
|         |                     |             | Exclusions: CRC, adenoma, high CRC risk | SM: 21%, FW: 24%    |        |
|         |                     |             | Invitation-reply-sending test kit, reminder after 6 wk |                      |        |
| Population-based screening programs |          |             |                              |                      |        |
| England | 60-69 gFOBT         | Since 2006  | Centralized invitations by the screening center | M: 50%              | Logan et al[9], 2012 |
|         |                     |             | People registered with a GP practice | W: 54%              |        |
|         |                     |             | Sending FOBT test kits |                      |        |
| Finland | 60-69 gFOBT         | Since 2004  | Centralized invitations by the national screening center | FM: 62%, FW: 77%    | Malila et al[10], 2011 |
|         |                     |             | using Population Register Center | SM: 68%, FW: 80%    | Malila et al[11], 2008 |
|         |                     |             | Sending FOBT test kits |                      | Malila et al[12], 2005 |

- F: First round of screening; S: Second round of screening; M: Men; W: Women; gFOBT: Guaiac fecal occult blood test; FIT: Fecal immunochemical test.

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breast cancer, and cervical cancer). It is based on an organized personal invitation of the eligible population sent to individuals by health insurance companies. Another topic of discussion focusing on further improvements in the program effectiveness includes the choice of a particular FOBT. Immunochemical methods currently used in the screening program differ in their analytical performance. The validation and selection of methods with an appropriate cut-off and quality control may be essential in the future. In a Czech initial study, the optimum cut-off level of quantitative FIT was determined as 75 ng/mL using one test[68]. However, further studies will be necessary for the implementation of an appropriate cut-off to the screening program.

Currently, the uniform design of the CRC screening program is used for asymptomatic individuals, but increased CRC risk has been proven in patients with cardiovascular diseases and diabetes mellitus, type II[69-71]. Therefore, an extensive Czech nationwide study is underway, focusing on the determination and stratification of metabolic risks in the development of colorectal neoplasia, and setting the specific intervals of CRC screening programs for these patients.

National screening programs may significantly improve the current state of public health. They require cooperation among health professionals, the Ministry of Health, and health insurance companies. In contrast to other national cancer prevention programs for breast and cervical cancers, the CRC screening program is aimed at both sexes, although women are statistically more likely to recognize the importance of the screening procedures. CRC screening is more complicated and partially invasive (colonoscopy). The publicity of the program has to be permanent, focusing on the entire population as well as on health professionals. It also needs the necessary support of prominent representatives of various professions from different segments of society. Since the beginning of this century, international scientific societies have drawn attention to the high CRC incidence and mortality rates prevalent in all developed European countries. In 2010, the European Society of Digestive Oncology, the International Digestive Cancer Alliance, the International Agency for Research on Cancer, the United European Gastroenterology, and the Munich Gastroenterology Foundation emphasized in the Barcelona Declaration that CRC is the second most common cause of cancer death. In the EU Parliament, a group of representatives headed by the Czech diplomat Pavel Poc opened a discussion on this topic, and the assembly finally approved the Written Declaration on Fighting Colorectal Cancer in the European Union. Therefore, CRC prevention is not only a medical topic; it is an issue of social policy as well. This fact should be reflected in CRC prevention at all levels, from the general public to the responsible authorities.

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