COLORECTAL CANCER SCREENING

Bohumil Seifert, M.D., Ph.D.

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Manual for general practitioners

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Bohumil Seifert
Prague
Czech Republic
16 June 2013

FOREWORD

150 000 European citizens die every year because of Colorectal Cancer (CRC).

I did not know this until 2010 when as a Member of the European Parliament I was approached by a group of United European Gastroenterology professionals to help achieve what the EU national governments had agreed in their Council Recommendations in 2003 but what had been lacking an effective execution.

This Council document stated that there is an undeniable need to introduce standardised screening programmes for Breast, Cervical and Colorectal Cancer in the European Union to secure early detection of these diseases. However the European Commission's implementation report from 2008 showed that it was the execution of Colorectal Cancer screening programmes, which has fallen behind the most.

Adoption of the Written Declaration on fighting Colorectal Cancer in the EU by the European Parliament was a key that opened doors to the EU Commissioner, national Health Ministers and others. In the Czech Republic the Declaration was instrumental to begin with our regular all-stakeholder meetings, where politicians, experts, patients and others get together and discuss the issues of CRC.

In 2012 we organised I. European Colorectal Cancer Days high level stakeholder conference in Brno, Czech Republic. During the conference political and public pressure developed, which moved the Czech Minister of Health to speed up the process leading to population based screening programme with personalised invitations and monitoring system, which is to be finally launched in the Czech Republic this year. If I had to point out two outcomes of the II. European Colorectal

Cancer Days 2013, which took place recently in Brno again, it would be (1) that a common networked European - wide approach to CRC screening programmes is an absolute must and (2) active, tireless and uneasy work of General Practitioners represents a key to the success of our common efforts - that is effective prevention and early diagnosis. GPs are indeed the prevention gatekeepers for everyday patients.

Prof. Bohumil Seifert contributed enormously to both European Colorectal Cancer Days conferences by providing the "GP insight" and did an excellent job by creating this very well structured and easy to read guide to Colorectal Cancer. This truly European material is not only for General Practitioners but for anyone interested in joining our fight.

Let me get back to the number of 150 000 CRC deaths annually. Imagine one hundred Titanics going down every year or one airplane full of passengers crashing every single working day. Wouldn't that deserve a proper media attention and help with raising awareness about CRC prevention? It certainly would, however, it is not the case here. The job is ours to do. Thank you for your help.

RNDr. Pavel Poc
Member of the European Parliament

Mariánské Lázně
Czech Republic
19 May 2013

COLORECTAL CANCER IN EUROPE: THE ROLE OF THE PRIMARY CARE PHYSICIAN

The role of Primary Care Physicians (General Practitioners; Family Physicians) is increasingly recognized as the backbone of any democratically caring regional and national healthcare organization. This is the reason why many countries have a strong organization of this profession, delegate important healthcare tasks and power to it and promote an excellent basic and continuous medical education of the discipline. Fortunately, in quite a number of EU countries, the medical primary care is also represented at university level and taking part of in healthcare research and development. These facts explain, why the United European Gastroenterology (UEG) is so pleased to have the European Society for Primary Care Gastroenterology (ESPCG) as one of its 15 member associations.

When the UEG initiated its campaign "Fight against Colorectal Cancer" in the European institutions (Parliament, Commission and Council and a multitude of other stakeholders), the ESPCG was present and active from the first moment on! The important UEG associations in this field (representing Endoscopy, Surgery, Oncology, Nutrition and Radiology) understood that the action against colorectal cancer in research, clinic and society would be abortive without the collaboration of the only category of physicians that knows the patients "from the cradle to the grave", regarding their physical and mental composition, their family habits and their individual lifestyle, their interest in health and wellbeing as well

as their means to maintain and improve these dimensions of life. Colorectal Cancer is conditioned by all these topics!

As the chairman of the Public Affairs Committee of the UEG, I am most grateful, that Prof. Bohumil Seifert, Prague/CZ, and outstanding practicing General Practitioner as well as academic teacher and researcher has gathered his knowledge and energy in order to compose this modern European manual about colorectal cancer screening, into an up-to-date information to his professional colleagues, but also to stakeholders in Public Health and other healthcare responsible in the community.

I am sure, that the ESPCG will do her best to update this manual periodically reflecting the continuous progression that is made in this field and that – well explained and promoted – will ease the suffering of the European Community from the plague that is called Colorectal Cancer.

Prof. Reinhold Stockbrugger

Ferrara, Italy
4 May 2013

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INTRODUCTION

The development of medical science is astonishing. We are now able to influence the prognosis and the quality of life of people with previously fatal diseases such as cancer. New findings are not only changing the process of diagnosis and treatment of oncologic diseases, but they are also pushing doctors to address their onset and development, and to examine and make interventions in healthy asymptomatic persons.

In this way, medicine is documenting its possibilities and perspectives, both present and future; but this also opens new ethical dilemmas. One issue is to set into process only those screening programs which are based on high quality medical research, fulfil the criteria for screening and are feasible in terms of capacity and cost.

Colorectal cancer (CRC) screening, together with breast and cervical cancer screening, fulfils these requirements and its implementation has been recommended by the Council of the European Union (2003/878/EC). In Europe the number of countries that are introducing national CRC screening programs is growing. CRC screening has been the subject of intensive research, and is characterized by dynamic development and increasing publicity. Primary care physicians can play an important role in CRC screening, not only by providing the tests themselves, but also in communicating the risks and benefits of screening to people in an appropriate way. Thus a population strategy is translated into personal medicine and individual care in the offices of primary care physicians.

This book is mostly designed for primary care doctors. European guidelines for quality assurance in colorectal cancer screening and diagnosis, launched in 2010, have been

a key resource. This publication describes the characteristics of colorectal cancer and gives the evidence for screening, together with the strategies and methods used in Europe. It describes the role of primary care doctors in screening and it gives information about current outcomes and perspectives of CRC screening.

1 COLORECTAL CANCER, EARLY DETECTION AND SCREENING

Colorectal cancer is one of the most important noncommunicable diseases worldwide, based on its insidious nature, epidemiology and costs.

The incidence and mortality of CRC in Western Europe, but also in other parts of the developed world, is forcing society to spotlight these problems. Entire teams devote themselves to the issue of CRC early detection and prevention; dozens of studies and discussions of this theme are regular parts of professional symposiums.

Despite diagnostics and treatment development, CRC mortality in the majority of European countries is not decreasing, even though cancer of the colon and rectum are the most preventable visceral organ cancers. The key to improving this situation is early disease discovery at the time when the symptoms have not yet appeared. Patients with cancer discovered at stage Dukes A (tumour penetrates into, but not through, the muscularis propria of the bowel wall) have 83 % five-year survival chance. Patients with cancer penetrating the lymph nodes have 38 % five-year survival chance and the chance of those with distant metastasis is even lower. Tumour usually stays asymptomatic for a long time, particularly when localized in the proximal part of the colon. Frequently, anaemia symptoms are manifested first. Despite the screening program effort, most CRC cases are still diagnosed in symptomatic patients, mainly in later stages of the disease.

The screening program is designed for asymptomatic individuals at average risk who are 50 years of age or more, based on national epidemiology characteristics and regarding the

capacity of the health care system. It is possible to identify groups of people at a high risk of colorectal cancer development in the population, for which specific follow up programs are designed. Screening should start at 40 years of age (or 10 years before the age of the youngest case of colorectal cancer in a family) for people at high risk, such as in cancer families, with polyposis or in presence of inflammatory bowel disease.

The colorectal cancer screening program is usually two staged, based on a faecal occult blood test (FOBT) for asymptomatic individuals, followed by indication of a colonoscopy if the test is positive. This is based on randomized studies which have shown evidence of decreasing the colorectal mortality by 15–30 %.

Stool-based tests, flexible sigmoidoscopy, and optical colonoscopy are acceptable screening options for people at average risk, while the gold standard, optical colonoscopy, is recommended as the first option for people at high risk.

2 ETIOPATHOGENESIS

Colorectal cancer originates in the mucosal cells of the colon and rectum, which are changed by gene defects (APC*, DCC**), antioncogenes (p53) or by higher expression of oncogenes (Ki-ras***). Nine out of ten colorectal cancers are preceded by a benign adenomatous phase that can be considered as precancerous, depending on its size and histological structure. Villous adenomas are in general at a higher risk of malignant change than tubular ones. In the early stage malignant cells are present only in the mucous membrane but subsequently they migrate through the muscularis mucosae of the bowel wall. At the intracellular level a multistep process of cancerogenesis takes place with accumulation of mutations and dysregulations in genes directing the cell cycle (especially proto-oncogenes and tumour suppressor genes), which leads to a loss of control over proliferation, uncontrolled cell division, invasive growth and metastasis.

- The malignant change into adenocarcinoma is a slow process that takes about 8–10 years. This long gestation provides opportunities for early detection and prophylaxis or treatment.

This can be facilitated and accelerated, if the genome of the given individual already includes inherited or newly formed mutations of one of the important gene alleles. The interindividual variability in the speed of cancer development

* *APC = adenomatous polyposis coli, gene determining eponymous protein*

** *DCC = deleted in colorectal carcinoma, gene determining eponymous protein*

*** *Ki-ras = Kirsten rat sarcoma viral oncogene, gene specifying the same-named protein, a predictor of poor response to biological treatment*

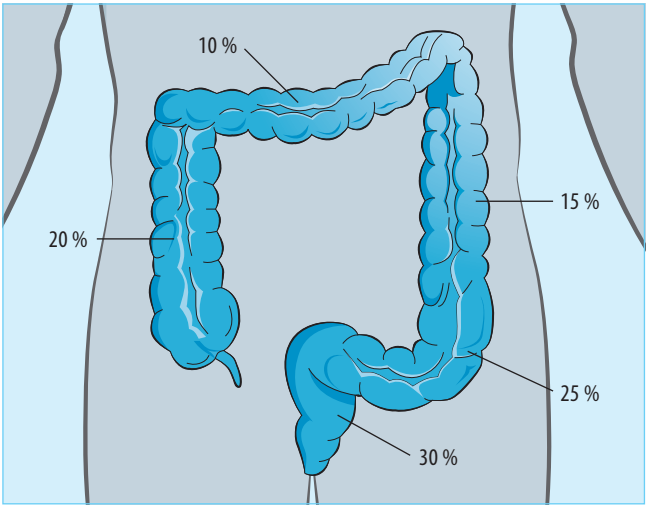

Fig. 2.1 The distribution of colorectal cancer incidence in colon and rectum (in %).

and the sensitivity to risk factors can be explained this way (Weston, 2003).

In all locations of the colon and rectum adenocarcinoma is the most common histological finding, though carcinoid or sarcoma may rarely be seen. 60–70 % of tumours are located distally of the left flexure, 10 % in the range of digital palpation (Figure 2.1). In 3 % of cases there is a synchronous carcinoma, i.e. two malignancies occurring at the same time in different parts of the colorectum.

From the pathogenetic point of view we distinguish several types of colorectal cancer. The *sporadic form*, in which there is no hereditary basis, represents 80–85 % of all cases according to different literature sources. The risk of cancer increases with age, and incidence rises steeply after 50. The presence of CRC in a first degree relative (parents, siblings or children) increases the risk of cancer illness 2–3 times; a second affected first degree relative increases the risk by a further 25–35 %. The presence of CRC in a first degree relative under the age of 50 or 45, which increases the risk 3.9 times (Baglietto 2009,

Haggar 2009), provides special warning. The individual occurrence in higher degree relatives mainly affects the doctors' attitude and the patient's approach to the examination, but the risk is significantly increased only by multiple incidences in 2nd degree relatives. Positive family history is found in roughly 20 % of CRC diagnoses. Both sexes are threatened with a slightly higher incidence in men. 1–2 % of CRC cases occur in patients with inflammatory bowel disease, which should be considered a risk factor. The prevalence of ulcerative colitis ranges 70–150/100000 in Europe, while Crohn's disease affects 20–40/100000 inhabitants. A higher sporadic CRC incidence is seen in patients with type 2 diabetes (Deng 2012, Luo 2012).

A higher exposure to exogenous carcinogenic factors is assumed for sporadic cancer and there has been much interest in the etiopathogenesis of CRC without the exact mechanism being completely understood. It is not possible to reliably determine the degree to which the genetic factors (endogenous) and the influences of the external environment on the cancer onset are involved.

Among the influences of the external environment that can contribute to CRC development, diet has been extensively studied. Contributory dietary factors include high calorie intake, diet rich in saturated fat, that with low fibre content, and a high intake of alcohol, especially beer. Improperly heat treated (grilled, fried, smoked) animal proteins lead to the formation of significant amounts of substances with potentially carcinogenic effects.

Low fibre content diets and excessive consumption of short chain carbohydrates lead to inappropriate modulation of intestinal microflora, slow the intestinal content's passage and cause prolonged exposure of the intestinal wall to potential carcinogens. Fibre also neutralizes some carcinogenic substances including bile acids. Direct evidence of the effect of these mechanisms is not, however, available (Huxley 2009). However, these recommendations are the basis for counselling in primary care.

Smoking, prolonged stress, sedentary jobs and reduced physical activity have all been considered risk factors. Colorec-

tal cancer risk is also increased by occupational contact with chemicals like heavy metals, asbestos, and chlorinated hydrocarbons. Ionizing radiation to the abdomen or pelvis for therapeutic reasons, e.g. for the treatment of gynaecological malignancy, is also a risk factor.

A minority of cases have a genetic basis. In *Familial Adenomatous Polyposis* (FAP) an inherited allele mutation of the APC gene and obtaining another allele results in carcinogenesis. Polyps occur in the 2nd to 3rd decade of life and inevitably progress to malignancy. Relatives of affected individuals should undergo genetic testing and a colonoscopy before their 20th birthday. FAP forms less than 1 % of diagnosed CRC; other rare hereditary polyposis syndromes include Familial Juvenile Polyposis, Peutz-Jeghers and Turcot Syndrome.

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) associates a heterogeneous group of hereditary tumours, which represent 3–5 % of CRC. They are caused by defects in genes responsible for repair (mismatch repair genes) or for encoding enzymes to detoxify carcinogens. As a result, tumours arise in an accelerated manner. If polyps are present, they are not as scattered as in FAP. The so-called Amsterdam criteria (Vasen, 1999) require that for a diagnosis of Lynch syndrome there should be at least three cases in the affected person's relatives, of whom at least one has to be a first degree relative of the others, the tumour must occur before the age of 50 and in two consecutive generations, in at least one case. For relatives of patients with Lynch syndrome, the recommendation is to perform a colonoscopy at age 35, and then at intervals of 3–5 years; in the meantime doing faecal occult blood tests and monitoring of tumour markers (CEA, CA19-9). Lynch syndrome also increases the risk of cancer in other locations: the stomach, endometrium, ovaries, or the urogenital system.

Due to the unfavourable situation in the incidence and characteristics of CRC, which can hardly be attributed only to exogenous factors, we can might suspect a specific genetic load in the Central European population, which, however, has so far failed to be discovered.