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# Prevention and Early Detection of Cancer – A Public Health View

Ljiljana Majnaric<sup>1</sup> and Aleksandar Vcev<sup>2</sup>

*Dep. of General Medicine, Dep. of Biomedicine, School of Medicine,  
University J.J. Strossmayer Osijek,  
Dep. Of Internal Medicine, School of Medicine,  
University J.J. Strossmayer Osijek,  
Croatia*

## 1. Introduction

Cancer is the second leading cause of death worldwide. According to the World Health Organisation (WHO), 12,5% of all deaths every year are caused by cancer (WHO, 2006). This is more than the total percentage of people who die from AIDS, tuberculosis and malaria, put together (International Union Against Cancer [UICC], 2007). Frightening fact is that deaths from cancer are projected to steadily rise. From about 7,5 million of cancer deaths, registered in 2005, this number will likely to reach 9 million, in 2015, and about 11,5 million, in 2030 (WHO, 2006). On the other hand, the knowledge about the causes of cancer and interventions to prevent and manage cancer are also growing up very fastly. At the current level of knowledge, it is estimated that up to one third of the cancer burden could be reduced if strictly implemented preventive strategies aimed at reducing the exposure to cancer risks, and another third of this burden could be cured if detected cancer early and treated adequately. The term “*cancer control*” was coined to unify public health actions aimed at implementing evidence-based strategies for cancer prevention, early detection and treatment, however adapted to different socioeconomic, cultural and resource settings (WHO, 2006). WHO and its cancer research agency, the International Agency for Research in Cancer (IARC), provide coordination and the leadership in these international actions (WHO, 2006).

## 2. Cancer as a common ageing disease; The risk factors paradigm

### 2.1 Cancer as a common ageing disease

Modern societies are characterised by a domination of chronic noncommunicable diseases in morbidity and mortality causes, including cardiovascular diseases, some cancers, chronic respiratory diseases, diabetes and dementia. This is partially a consequence of the decline in acute infectious diseases, due to improvements in life conditions, sanitation and medical care, and partially of the fast spread of modern lifestyles, due to urbanisation, globalisation and technology progress (Pearce, 1996, as cited in Majnarić-Trtica, 2009). Modern lifestyles include increased consumption of processed foods enriched in saturated fats and sugars, smoking cigarettes due to market orientation of tobacco industry, reduced leisure time, use of automobiles for transportation, and increased availability of electronic entertainment and

communication media, all contributing to a sedentary lifestyle and weight gain (American Cancer Society [ACS], 2002).

To prevent diseases, it is necessary to identify and deal with their causes. In the case of chronic noncommunicable diseases, that means identification of health risks that underlie these diseases (Venkat et al, 2010; WHO, 2009). Most important, in this issue, is that a particular disease is caused by multiple risk factors and that, in turn, many risk factors are associated with more than one disease. So, by targeting certain risks, it is possible to reduce the burden of several diseases (WHO, 2009). This observation is in line with the results of the Human Genome Project showing that there is no specific disease susceptibility genotype, yet numerous genetic variants account for many age-related phenotypes (Collins & McKusick, 2001, as cited in Majnarić-Trtica, 2009; Yang et al., 2003, as cited in Majnarić-Trtica, 2009). That means that the symptoms and signs of common chronic diseases arise from the complex interactions, taking place over time, among multiple genetic variants and environmental risk factors, shared between clinically related diseases (Buchanan et al., 2006, as cited in Majnarić-Trtica, 2009; Yang et al., 2005, as cited in Majnarić-Trtica, 2008a). The main mechanism through which an organism responds to external environmental signals was found to be an epigenetic control of genome function in somatic cells (Jaenisch & Bird, 2003, as cited in Majnarić-Trtica, 2008a; Sandovici, 2008).

## 2.2 The risk factors paradigm

Importantly, when planning preventive activities, is to understand that each risk factor has its own causes. In fact, there is a complex chain of events enabling many entry points for intervention (WHO, 2009). In the proximity, there are more direct causes of the diseases. Factors located further in the back, act through intermediary mechanisms, to produce these proximal factors. Causally most distal factors have their background in social conditions and are hardly recognisable. However, if modified, these background causes are likely to have amplifying effects, by influencing multiple proximal effects (WHO, 2009). Keeping this in mind can help health workers and policy makers to realise that besides individually oriented preventive measures, population-based strategies are of the greatest importance if they want to reduce health risks in a community (American Cancer Society, 2002; WHO, 2009). That means that an individual choice, regarding health-related behaviors, occurs within a community context that can be either facilitating, or interfering with these behaviors. For example, in order to disseminate healthy diet and increased physical activity patterns, policy makers should implement multiple strategies at the community level, to ensure that all population groups have access to healthy food choices and opportunities for physical activity (American Cancer Society, 2002).

Another important fact is that there is no simple correlation between economic development and the shift in a major disease burden, from acute infections to chronic noncommunicable diseases. Namely, as economic development occurs, tobacco and alcohol use and obesity increase, followed by the burden of chronic diseases, in decades later. However, mortality and morbidity from chronic diseases do not start to decrease until very high level of social and economic development is reached (Derek et al., 2011). In other words, only at a high level of awareness about chronic diseases, governments and policy makers are likely to respond on negative trends in health behaviors, by using a range of policy instruments to revert these trends. It is not surprisingly then, that in the coming decades, the burden from chronic diseases is projected to rise, particularly fast in the developing world (Daar et al.,

2007). However, chronic diseases do not simple replace acute infections; rather, developing countries experience double disease burden, that have a huge negative impact on their economies (Derek et al., 2011; Daar et al., 2007).

By attributing known risk factors, including behavioural, physiological, occupational and environmental ones, to the total number of deaths, or the burden of diseases (measured in DALYs - years of life lost due to premature mortality and disability), it is possible to estimate of how much the burden of diseases is attributable to these selected risk factors (Venkat et al. 2010; WHO, 2009). Based on such analysis, it was realised that more than one third of the world`s deaths can be attributed to a small number of risk factors. The five top-ranked risks include high blood pressure, tobacco use, high blood glucose, physical inactivity and overweight/obesity. They affect countries of all income groups: high, middle and low (Figure 1) (WHO, 2009). When taking into account the fact that two leading world`s causes of death include cardiovascular diseases and cancers, this is likely to suggest that avoiding tobacco and obesity, and using regular physical activity, can provide the greatest potential to minimise cancer risk (American Cancer Society, 2002; WHO, 2009).

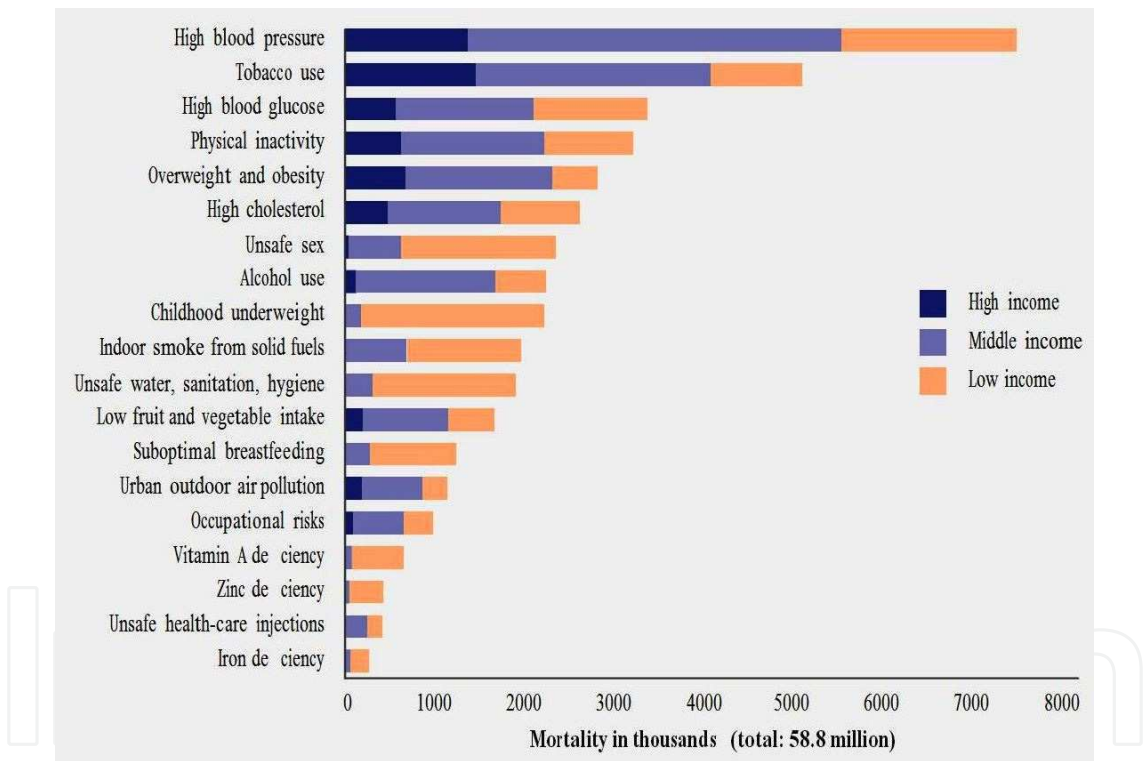


Fig. 1. Deaths attributed to leading risk factors, by country income level (2004)

3. Cancer with infectious origin

It is estimated that approximately 15% of all cancers can be attributed to viral infections. The oncogenic role of at least six viruses has strongly been established, including Epstein-Barr virus (EBV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), several Human Papillomavirus (HPV) types, Human T-cell Lymphotropic Virus type I (HTLV-I) and Human Immunodeficiency Virus type I (HIV-I) (Boccardo & Villa, 2011). Cells infected by these viruses may turn towards oncogenesis after many years of infection latency,

depending on the contextual, both the host-related, and the environmental factors - the fact that may complicate targeting potential preventive and therapeutic approaches (Butel, 1999; Weinberg, 1994). On the other hand, knowledge about the ways these infections are being spreaded on, is likely to provide directions for instituting adequate infection control practices. In relation to this, it is known that some of these infections are sexually transmitted and can be attributed to unsafe sex and non-use of contraception. Others are associated with using nonsterilised injection equipment, that is either related to unsafe health-care, or to opiates addiction (Boccardo & Villa, 2011; WHO, 2009).

The great opportunity for cancer prevention, at the global scale, lies in the development and distribution of antiviral vaccines (Schiller & Lowy, 2010). Commercially available HBV and HPV vaccines are already in use, and the major focus is now on their delivery, especially to low-income countries (Dempsey, 2010; El-Serag, 2011). The reasoning is based on the fact showing that HBV infection accounts for about 60% of the total liver cancer in developing countries, while for only about 23% in developed countries. For cervical cancer (HPV infection was proved as a course), the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, more than 85% of all cases and deaths occur in developing countries (Ferlay, 2010; WHO, 2009).

#### 4. Environmental pollution and industrial carcinogenes

The discovery of smoking tobacco as a factor being strongly associated with lung cancer (more than 85% of lung cancers occur among smokers), has further emphasized the definition of other external factors that could probable cause cancer (that are termed "*carcinogenes*") (American Cancer Society, 2007, as cited in Majnarić-Trtica, 2009; Pearce, 1996, as cited in Majnarić-Trtica, 2009).

Accordingly, at least 150 chemicals and other agents, including ionizing radiation, occupational (workplace) and environmental airborne particles, some drugs, as well as foods and other consumer products, have been listed so far by IARC, as potential carcinogens (American Cancer Society, 2007, as cited in Majnarić-Trtica, 2009; WHO, 2009). It is estimated, for example, that occupational exposure to microscopic airborne particles accounts for 8% of lung cancer, that is the most frequent form of occupational cancer (compared to 12% of deaths due to chronic obstructive pulmonary disease) (WHO, 2009). The encouraging fact is, however, that the majority of occupational cancers can be prevented, through minimising exposure, substituting safer materials, and/or enclosing processes and ventilation. These all are measures within the domain of engineering manipulation, and policy and legislation changes (WHO, 2009).

Trends which deserve particular concern of the scientists, policy-makers and the public as a whole, are based on the growing number of evidence showing that long-term exposure to traffic-related air pollution is the risk factor which can contribute to overall and especially to specific respiratory and cardiovascular mortality in general population (Brunekreef et al., 2009). Even some consumer products, including food, cosmetics and household cleaners, owing to their overall use, are among the most significant sources of exposure to toxic and carcinogenic chemicals. Higher level of awareness is the first step to tackle more adequate legislation and adversiting options, as well as technology innovations (American Cancer Society, 2007, as cited in Majnarić-Trtica, 2009; WHO, 2009).

5. Global cancer statistics and calls for action

5.1 Global cancer statistics

Based on the GLOBOCAN estimates, about 12,7 million cancer cases and 7,6 million cancer deaths occurred worldwide in 2008 and this trend continues to rise (Jemal et al., 2011). Proposed major reasons include: 1) the ageing, alongside with growth, of the world population, as cancer affects older adults at the highest rates, and 2) an increasing adoption of cancer-causing behaviors, due to the processes of modernisation and globalisation (Jemal et al., 2011; WHO, 2009). Of this total cancer burden, 56% of the cases and 64% of the deaths have occurred in the economically developing world. Although overall cancer incidence rates in the developing countries are half those registered in the developed world, the cancer mortality is generally similar (Jemal et al., 2011). The main reason for this dysproportion is in cancer survival rates, which tend to be poor in developing countries, mostly because of a late stage at diagnosis and limited access to timely and standard treatment (American Cancer Society, 2007, as cited in Majnarić-Trtica, 2008b; Jemal et al., 2011; Ebling et al., 1993, as cited in Majnarić-Trtica et al., 2008b).

The most frequent cancer site diagnosed in females worldwide is breast cancer and it is also the leading cause of cancer death, comprising 23% of the total cancer cases and 14% of the cancer deaths. In general, the highest incidence rates are registered in the most developed regions, although 60% of the deaths occur in developing countries. Breast cancer is now the leading cause of cancer death among females in developing countries, a shift from cervical cancer which held this unfavorable position in the past decades. The second and the third most frequently diagnosed cancers in females are colorectal and lung cancers, the reverse order in cancer mortality (Table 1) (Jemal et al., 2011).

Estimated Age-standardized Incidence and Mortality Rates (per 100,000) by Sex, Cancer Site, and Level of Economic Development, 2008				
	Females			
	Developed countries		Developing countries	
	Incidence	Mortality	Incidence	Mortality
Breast	66,40	15,30	27,30	10,80
Cervix uteri	9,00	3,20	17,80	9,80
Colon & rectum	24,20	9,70	9,40	5,40
Corpus uteri	12,90	2,40	5,90	1,70
Liver	2,70	2,50	7,60	7,20
Lung & bronchus	18,60	13,60	11,10	9,70
Melanoma of skin	8,60	1,10	0,60	0,30
Ovary	9,40	5,10	5,00	3,10
Pancreas	5,40	5,10	2,10	2,00
Stomach	7,30	4,70	10,00	8,10
Thyroid	9,10	0,40	3,40	0,70
All sites*	225,50	87,30	138,00	85,40

Table 1. Leading cancer incidence and mortality rates, females, for more and less developed areas, world (GLOBOCAN 2008)

In males, the most common cancer site and the leading cause of cancer death is lung cancer, comprising 17% of the cancer cases and 23% of the cancer death (Table 2). Colorectal and prostate cancers are at the second and the third positions in cancer incidence and follow the same order in cancer mortality, with the addition of stomach cancer sharing the third position with prostate cancer (Jemal et al., 2011).

Estimated Age-standardized Incidence and Mortality Rates (per 100,000) by Sex, Cancer Site, and Level of Economic Development, 2008				
	Males			
	Developed countries		Developing countries	
	Incidence	Mortality	Incidence	Mortality
Bladder	16,60	4,60	5,40	2,60
Colon & rectum	37,60	15,10	12,10	6,90
Esophagus	6,50	5,30	11,80	10,10
Liver	8,10	7,20	18,90	17,40
Lung & bronchus	47,40	39,40	27,80	24,60
Pancreas	8,20	7,90	2,70	2,50
Prostate	62,00	10,60	12,00	5,60
Stomach	16,70	10,40	21,10	16,00
All sites*	300,10	143,90	160,30	119,30

Table 2. Leading cancer incidence and mortality rates, males, for more and less developed areas, world (GLOBOCAN 2008)

5.2 Calls for action

Based on the global cancer statistics, awareness is growing that a dramatic stride in fighting against cancer can be done only if initiatives are planned at the global scale. The framework for this call for a global action is provided in the form of basic documents, such as World Cancer Declaration 2006 (IUCC, 2006). According to this document, the aim is to increase the number of countries that have the national cancer control programs, including cancer prevention, early detection, treatment, palliative care and support for cancer patients. Cancer surveillance systems, including cancer registries, should be developed if they do not exist, to support data collection on cancer statistics, risk factors burden, and effects of measures done. Lower income countries will be especially encouraged to gain abilities for dealing with their growing cancer burden. In order to transfer the proclaimed aims into practice, international committees have established cancer control strategies (WHO, 2005, as cited in Majnarić-Trtica, 2008b).

5.3 The state in EU

In the European Union (EU27), 2,5 million of people were diagnosed with cancer in 2008 (Ferlay, 2010). During the past decades, cooperation at the EU level showed that it is possible to add value, beyond the national level, to reduce cancer burden in Europe. The goal, set under the Commission`s “Europe Against Cancer” programs (1987-2000), was a 15% reduction in cancer mortality by 2000 (Moss, 2000, as cited in Majnarić-Trtica, 2008b). Until 2003, the Program was at the half of this proposed pathway, with registered reduction of 9% (Boyle et

al., 2003). Until 2008, some of the Member States, like Finland and Luxemburg and Austria, have yet succeed in their efforts to reach this proclaimed goal (Cancer Society of Finland, 2010). The horizontal approach, aimed at tackling major health cancer-causing determinants, is being accomplished through documents such as “European Environment and Health Action Plan (2004)”, set up in order to minimise work-related exposures to carcinogens and mutagens, and “the European Code Against Cancer” (2003), set up to promote healthy lifestyles (as cited in Commission of the European Communities, 2009).

In general, although significant advances have been made in cancer control, cancer is still a major public health concern in EU, accounting for 29% (3 out of 10) of deaths in men and 23% (2 out of 10) of deaths in women (the facts for 2008) (European Commission, 2011).

Nowadays, the situation is characterised with substantial inequalities in cancer control among Member States, that is illustrated with the fact that mortality from cervical cancer is nearly four times, and mortality from lung cancer, in men - over three times higher, in the worst performing Member States, than in the best ones (European Commission, 2011). In order to strengthen efforts to share information, capacity and expertise in cancer prevention and control, the European Commission has recently proposed the “European Partnership for Action Against Cancer”, for the period 2009-2013 (Commission of the European Communities, 2009).

6. Preventive measures that can reduce the cancer burden

Based on the experience gained so far, it is considered that a substantial proportion of the cancer burden worldwide could be prevented if adequately implemented community-based programs for early cancer detection and treatment, tobacco control, cancer-related vaccination (for liver and cervical cancers), and health promotion campaigns (American Cancer Society, 2002; Commission of the European Communities, 2009; WHO, 2009) (Table 3).

<ul style="list-style-type: none"><li>• Implementation of principles of a healthy life-style, mainly by means of a healthy diet - low in saturated fats and carbohydrates and high in fruit and vegetable, regular physical activity, no smoking, and only moderate alcohol consumption</li><li>• Changes in sexual behaviour (including the number of partners, partners selection, the type of sex involved, knowledge on infection status of partners, use of barrier contraceptives)</li><li>• Immunization against Hepatitis B Virus (HBV) and Human Papilloma Virus (HPV) infection</li><li>• Taking the control over occupational hazards</li><li>• Avoidance of cancer-causing substances in the global environment and in consumer products</li><li>• Avoidance of attentive exposure to sunlight</li></ul>
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Table 3. Primary prevention measures (taken before any sign of a disease occurs) known to deal with the reduction in total cancer incidence

7. Screening protocols

The curability of cancer can be relatively high if it is detected in the early, localised stage (American Cancer Society, 2007, as cited in Majnarić-Trtica, 2008b; Ebling et al., 1993, as

cited in Majnarić-Trtica et al., 2008b). Results of randomised trials and experience of the countries where national programs for prevention and early detection of cancer have been implemented, showed that the implementation of such programs, especially when they are well prepared and monitored, is the most efficient and, in the long run, the least costly approach to fight cancer (Levin, B., et al., 2003, Nystrom, L., 2002, as cited in Majnarić-Trtica, 2008b). Based on these facts, respective agencies, such as the American Cancer Society, United States Preventive Services Task Force (USPSTF), WHO, and the European Union Advisory Committee on Cancer Prevention (EUACCP), set up recommendations for the early detection of cancer (American Cancer Society Guidelines for the Early Detection of Cancer, 2007, The Council of the European Union Recommendation of 2 December 2003 on cancer screening (2003/878/EC), 2003, WHO Program on Cancer Control, 2003, as cited in Majnarić-Trtica, 2008b).

In principle, these programs may be two-way oriented. One way is promotion of the early diagnosis by recognising the early clinical symptoms and signs of cancer, based on health education programs performed for both, primary health care physicians and the population (WHO/Cancer, 2007, Wender, R.C., 2007, as cited in Majnarić-Trtica, 2008b). The other way is screening of an apparently healthy population, before clinical signs of cancer are detectable, in order to find individuals with the early cancer or pre-cancer stages (Moss, S., 2000, as cited in Majnarić-Trtica, 2008b). In this sense, screening procedures are considered as measures of a secondary prevention. There are two main approaches for targeting population: 1) targeting high-risk people (with a lifetime risk of getting a certain type of cancer of at least 20 to 25%), who are most likely to benefit from the intervention, and 2) targeting risk in the entire population, regardless of each individual's risk and potential benefit (WHO, 2009).

Fundamental for the screening is availability of effective (with the acceptable level of sensitivity and specificity), low-cost, simple for application, and safe tests. This is not possible for all cancer sites. Fortunately, screening tests proved so far as being feasible for wide implementation, correspond with some of the most frequent cancer sites. These tests include: high-quality mammography (for breast cancer), Pap cytology test (for cervical cancer) and testing for occult faecal bleeding (for colorectal cancer) (American Cancer Society Guidelines for the Early Detection of Cancer, 2007, as cited in Majnarić-Trtica, 2008b). The screening of prostate cancer by using prostate-specific antigen (PSA) testing has not yet been established routinely on a population base, although the increasing amount of evidence confirms that the early detection of this main form of cancer in men considerably reduces mortality, increases survival, and is likely to be cost-effective (American Cancer Society Guidelines for the Early Detection of Cancer, 2007; The Council of the EU, 2003, as cited in Majnarić-Trtica, 2008b; ESMO Guidelines Working Group, 2011).

Under the influence of the rapid technology progress and a large amount of randomised trials in which the validity of particular screening approaches have been assessed - screening methods and protocols are constantly being changed (Table 4) (American Cancer Society Guidelines for the Early Detection of Cancer, 2008). Efforts have also been made in looking for appropriate methods for the early detection of some other frequent and/or hazardous cancer sites, such as lung cancer, or pancreatic cancer (Harold, C.S., 2011; The Sol Goldman Pancreatic Cancer Research Center, 2011).

<b>Screening Guidelines</b> <b>For the Early Detection of Cancer in Asymptomatic People</b> <b>Site Recommendation</b>
<b>Breast</b> • Yearly mammograms are recommended starting at age 40. The age at which screening should be stopped should be individualized by considering the potential risks and benefits of screening in the context of overall health status and longevity. <ul style="list-style-type: none"><li>• Clinical breast exam should be part of a periodic health exam about every 3 years for women in their 20s and 30s and every year for women 40 and older.</li><li>• Women should know how their breasts normally feel and report any breast change promptly to their health care providers. Breast self-exam is an option for women starting in their 20s.</li><li>• Screening MRI is recommended for women with an approximately 20%-25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease.</li></ul>
<b>Colon &amp; rectum</b> • Beginning at age 50, men and women should begin screening with 1 of the examination schedules below: <ul style="list-style-type: none"><li>• A fecal occult blood test (FOBT) or fecal immunochemical test (FIT) every year</li><li>• A flexible sigmoidoscopy (FSIG) every 5 years</li><li>• Annual FOBT or FIT and flexible sigmoidoscopy every 5 years*</li><li>• A double-contrast barium enema every 5 years</li><li>• A colonoscopy every 10 years</li></ul> <i>*Combined testing is preferred over either annual FOBT or FIT, or FSIG every 5 years, alone. People who are at moderate or high risk for colorectal cancer should talk with a doctor about a different testing schedule.</i>
<b>Prostate</b> The PSA test and the digital rectal examination should be offered annually, beginning at age 50, to men who have a life expectancy of at least 10 years. Men at high risk (African American men and men with a strong family history of 1 or more first-degree relatives diagnosed with prostate cancer at an early age) should begin testing at age 45. For both men at average risk and high risk, information should be provided about what is known and what is uncertain about the benefits and limitations of early detection and treatment of prostate cancer so that they can make an informed decision about testing.
<b>Uterus</b> <b>Cervix:</b> Screening should begin approximately 3 years after a woman begins having vaginal intercourse, but no later than 21 years of age. Screening should be done every year with regular Pap tests or every 2 years using liquidbased tests. At or after age 30, women who have had 3 normal test results in a row may get screened every 2 to 3 years. Alternatively, cervical cancer screening with HPV DNA testing and conventional or liquid-based cytology could be performed every 3 years. However, doctors may suggest a woman get screened more often if she has certain risk factors, such as HIV infection or a weak immune system. Women aged 70 and older who have had 3 or more consecutive normal Pap tests in the last 10 years may choose to stop cervical cancer screening. Screening after total hysterectomy (with removal of the cervix) is not necessary unless the surgery was done as a treatment for cervical cancer. <b>Endometrium:</b> The American Cancer Society recommends that at the time of menopause all women should be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians. Annual screening for endometrial cancer with endometrial biopsy beginning at age 35 should be offered to women with or at risk for hereditary nonpolyposis colon cancer (HNPCC).
<b>Cancer-</b> For individuals undergoing periodic health examinations, a cancer-related checkup should include health <b>related</b> counseling and, depending on a person’s age and gender, might include examinations for cancers of the thyroid, <b>checkup</b> oral cavity, skin, lymph nodes, testes, and ovaries, as well as for some nonmalignant diseases. <small>American Cancer Society guidelines for early cancer detection are assessed annually in order to identify whether there is new scientific evidence sufficient to warrant a reevaluation of current recommendations. If evidence is sufficiently compelling to consider a change or clarification in a current guideline or the development of a new guideline, a formal procedure is initiated. Guidelines are formally evaluated every 5 years regardless of whether new evidence suggests a change in the existing recommendations. There are 9 steps in this procedure, and these “guidelines for guideline development” were formally established to provide a specific methodology for science and expert judgment to form the underpinnings of specific statements and recommendations from the Society. These procedures constitute a deliberate process to ensure that all Society recommendations have the same methodological and evidence-based process at their core. This process also employs a system for rating strength and consistency of evidence that is similar to that employed by the Agency for Health Care Research and Quality (AHCRO) and the US Preventive Services Task Force (USPSTF).</small>

Table 4. American Cancer Society, Cancer Screening Guidelines (2008)

7.1 Screening of breast cancer

Breast is the most prevalent cancer site in women in both developed and developing countries, accounting for a quarter of women worldwide diagnosed with cancer (Ferlay, 2010). The incidence continues to rise, as the combined effect of mammographic screening, ageing of population, and some risk factors burden, including postmenopausal hormone

replacement therapy, Western-style diet, obesity, and consuming alcohol and tobacco among women (Aebi, 2011; Warner, 2011). Although it is still the leading cause of cancer-related deaths in women, in most Western countries, the mortality trend has been decreasing in recent years, partly due to the screening programs implementation, and partly due to the improvements in treatment (Ferlay, 2010).

Risks Associated with Mammography	
Risk	Comments
False positive result leading to recall, with or without biopsy	<p>Inversely related to age; for women 40 to 49 yr of age, cumulative risk at 10 years is approximately 49% in the United States</p> <p>Higher risk is also associated with</p> <p>Prior breast biopsies</p> <p>Family history of breast cancer</p> <p>Current estrogen use</p> <p>No prior mammogram or a longer screening interval</p> <p>Individual radiologist</p> <p>May cause short-term anxiety and psychological distress</p> <p>May have small but significant long-term negative effects on health behaviors and psychological well-being</p>
False negative result leading to false reassurance	<p>Little research has been conducted to determine the effect of this finding; in one survey, more than 99% of women stated that they would not delay evaluation of a new abnormal physical finding despite a recent negative mammogram</p>
Overdiagnosis (and over- treatment)	<p>Increases with age; a review of five random- ized trials showed an excess of breast cancers (both invasive and in situ) in all studies, accounting for 4 to 32% of cancers found by screening</p> <p>Screening programs and simulation models report rates from 1 to 10%, depending on age, outcomes included (invasive vs. in situ disease), country, and whether cases are incident or prevalent</p>
Radiation-induced breast cancer	<p>Estimated risk is 86 cancers and 11 deaths per 100,000 women screened annually from 40 to 55 years of age and biennially there- after; ratio of benefit to risk is 4.5:1 for lives saved and 9.5:1 for life-years saved</p> <p>Level of exposure to radiation with digital mammography is the same as or lower than that with film mammography</p>

Table 5. Costs associated with mammography

It is estimated that over 90% of breast cancer in women can be cured if a disease is diagnosed in an early stage and adequately treated (American Cancer Society Guidelines for the Early Detection of Cancer, 2007, as cited in Majnarić-Trtica, 2008b). Several procedures are routinely used to diagnose breast cancer, including clinical (breast self-examination and bimanual palpation of the breasts and regional lymph nodes performed by health care professionals), radiological (bilateral mammography and ultrasound) and pathological examination (based on the core needle biopsy). Some advanced imaging techniques, such as MRI (magnetic resonance imaging) and digital mammography, have recently been added, because of high diagnostic sensitivity of these methods (Warner, 2011). However, mammography is the only screening method to date proved as to can reduce mortality from

breast cancer, and any other method can be used only as a supplement to mammography (Warner, 2011). For reading of mammograms, BI-RADS classification (stages 0-5) is used. Cases suspected on cancer (BI-RADS 4 or 5) are referred for follow up (Eberl, 2006).

Breast cancer incidence is strongly age-dependent, with only a quarter of cases occurring before age 50; less than 5% before age 35 (Ferlay, 2010). Based on these facts and on the results from randomised trials which consistently show a 14% to 32% reduction in mortality from breast cancer with annual or biennial mammography in women 50 to 69 years of age, screening mammography is universally recommended for women 50-69 years of age, with a 1-year, or 2-year screening interval (Nystrom, 2002, as cited in Majnarić-Trtica, 2008b; Warner, 2011). Some guidelines also include women aged 40-49, although data on the benefit to cost ratio have not yet been clarified (Table 4) (Mandelblatt, 2011; Warner, 2011).

Based on accumulated evidence, the decision to screen, more and more involves weighting benefits against costs (Table 5) (Warner, 2011). In the case of screening mammography, the most important benefits include reduction in the risk of death and the number of life-years gained. Costs include the financial costs and the by-products of the screening regimen itself (radiation risk, pain, inconvenience and anxiety), false positive and false negative results, as well as overdiagnosis (leading to overtreatment) (Duffy, 2010; Warner, 2011). The ratio of benefit to cost varies significantly with the patient's age and depends on some other patient's characteristics, such as breasts density (Warner, 2011). New, revised guidelines for breast cancer screening therefore tend to be more individually oriented.

## 7.2 Screening of cervical cancer

Cervical cancer is the third most common cause of female mortality worldwide, with the mortality rate 10 times higher in developing countries, and 80% of new cases occurring in these regions, compared to the developed countries (Ferlay, 2010; Haie-Meder, 2010). This disparity is in connection with low level of knowledge about unsafe sex and inaccessibility to screening and treatment programs, for women in developing countries (Ferlay, 2010; WHO, 2009). The main problem, in developed countries, is still insufficient coverage of women in the generative age with the screening test (Commission of the European Union, 2007; Haie-Meder, 2010).

Cervical cytology based on Pap smears remains the cornerstone of cervical cancer prevention programs, although this field has rapidly been developing due to improved understanding of the natural history of the disease and technology innovations, such as liquid-based cytology, automated interpretation of Pap smears and testing for human papillomaviruses (HPVs) (American Cancer Society Guidelines, 2011; ESMO European guidelines for quality assurance, 2010). This, on the one hand, points up the necessity for establishing the uniform indicators for monitoring program performance, to enable data comparison across the countries, and on the other hand - leads to fast exchanges of practice guidelines (Table 4) (ESMO European guidelines for quality assurance, 2010).

It is now well known that a persistent infection with sexually transmittable human papillomaviruses is responsible for virtually all cases of cervical cancer (Haie-Meder, 2010). Early age at first sexual intercourse and early pregnancies have been recognised as risk factors. The evidence linking HPV infection to cervical cancer has initiated the development of HPV DNA testing, to support more accurate risk stratification, beyond the capacity of

conventional Papanicolaou smear testing (Figure 2) (American Cancer Society Guidelines, 2011; ESMO European guidelines for quality assurance, 2010). Also, primary prevention by prophylactic vaccination against the HPV types that are causally linked with most cervical cancers in Europe, HPV-16 and HPV-18, is now commercially available (Schiller & Lowy, 2010). The high efficacy of the vaccines is expected to dramatically decrease cervical cancer, by preventing up to 70% of newly diagnosed cases. However, prophylactic vaccination is performed in young girls and it will take a time until it provides the health gains. Therefore, cervical screening still remains the main preventive option (Figure 2). Nowadays, situation is that the high cost of the vaccine prevents its widespread implementation, which may further increase the gap in cervical cancer statistics between developed and developing countries (Haie-Meder, 2010).

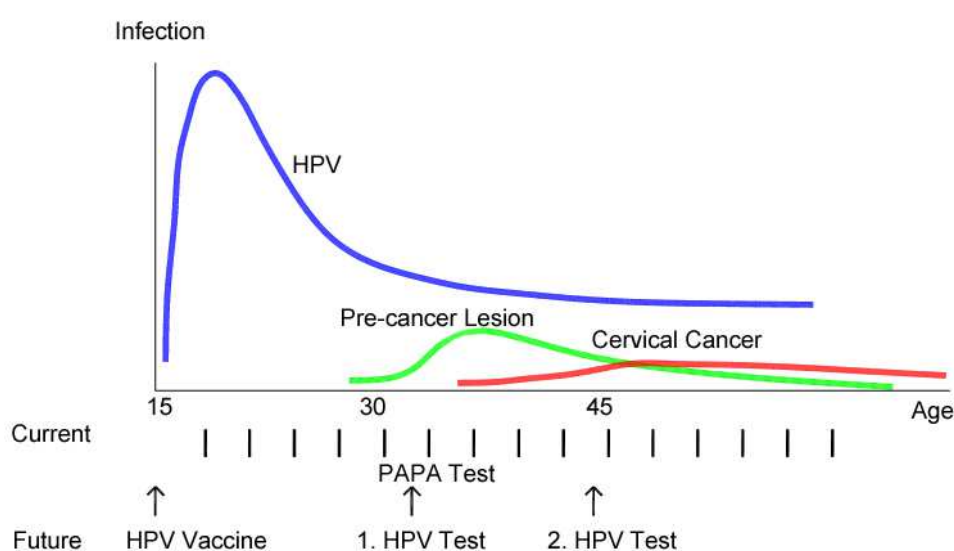


Fig. 2. Combined strategies to decrease cervical cancer

### 7.3 Screening of colorectal cancer

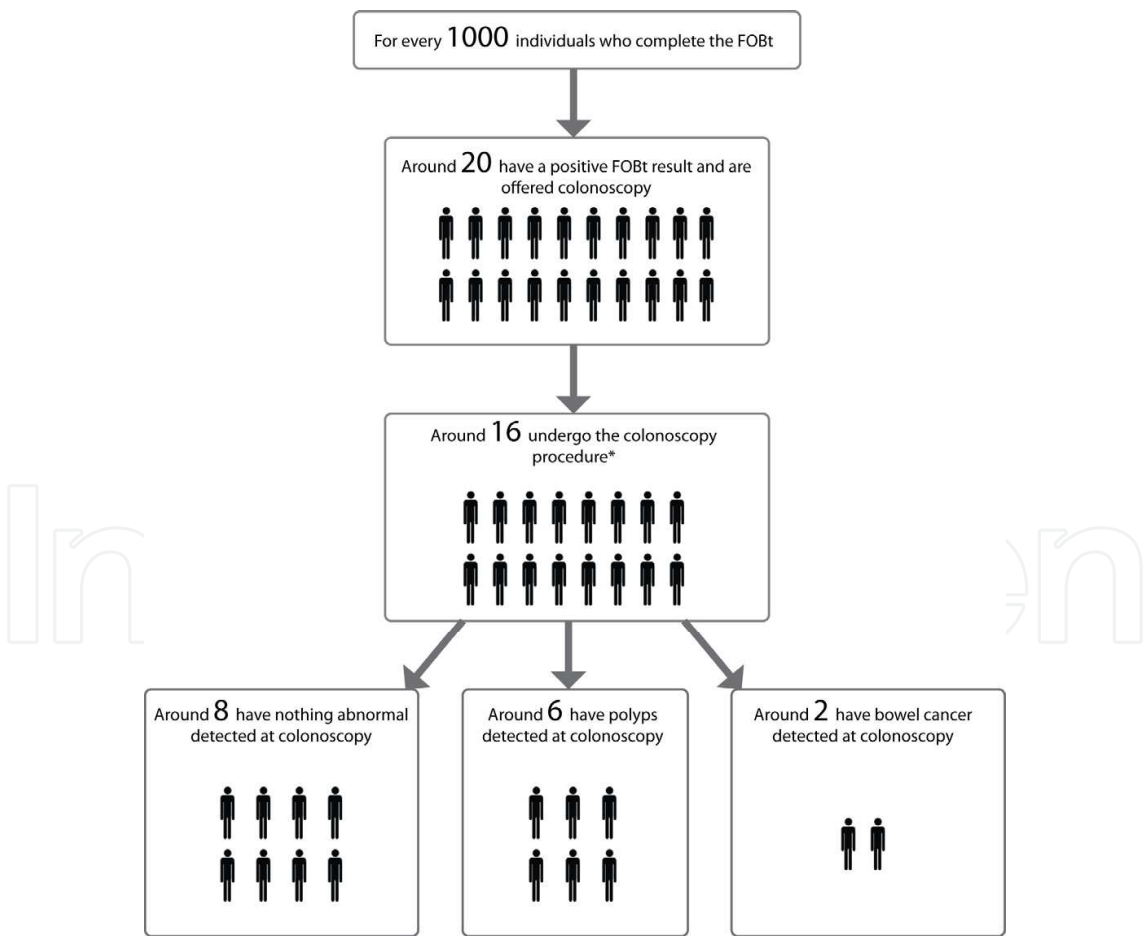
Cancers of the colon and rectum altogether are the third most common cancer type in the world and the most common newly diagnosed cancer in EU (Ferlay, 2010). In general, incidence is increasing along with industrialisation and urbanisation and is slightly higher in western and central, than in northern and southern and eastern Europe (Labianca, 2010).

Five-year survival rates, after the disease is detected, is much worse in the Eastern European countries, then in the developed countries (34%, compared to 54% and 65%, in the Western European countries and the USA, respectively) (Ferlay, 2010). As the result of the early detection programs implementation in many EU countries, in past decades, five-year survival rates show more favourable trends in all regions of Europe, compared to as it was before (Labianca, 2010).

Strong genetic influence can be attributed to only 5%-10% of colorectal cancers cases, due to either polyposis or non-polyposis syndromes, while the majority of cases occur sporadically (Balmana, 2010). The most important exogenous factors identified so far include: western-style diet and low physical activity, smoking tobacco and inflammatory bowel diseases,

while the effect of chronic use of non-steroidal anti-inflammatory drugs for the prevention or regression of colorectal adenomas, has not yet been strongly confirmed (Labianca, 2010).

If take into account fact that a 10-35 years long-lasting period is needed for the transformation of benign adenomas to cancer, it seems reasonable to expect that the systematic implementation of the programs of active searching for subjects with localised cancer or pre-cancer lesions, could substantially reduce colorectal cancer mortality rate in population. It is estimated that under these conditions, colorectal cancer could reach a high cure rate of 80% and more (Winawer, 2003, as cited in Majnarić-Trtica, 2008b). This makes colorectal cancer an ideal candidate for screening. Since about 70% of patients are >65 y of age and the disease is rare under the age of 45 (2 per 100 000/y), target groups for screening usually include population aged 50-74y, with the minimum recommendations for the age range 60-69y (American Cancer Society Guidelines, 2011; Labianca, 2010). In order to complement community-based screening programs for breast and cervical cancers, established in many EU countries several decades ago, the EU Commision set up in 2003 recommendations for early detection of colorectal cancer, and the action plan “Europe against Colon Cancer“, based on “the Brussels Declaration“ (IUCC/Interantional Union against cancer, 2007, WHO/WHO Cancer Control Strategy, 2005, as cited in Majnarić-Trtica, 2008b).



\*Based on an uptake rate of 78%

Fig. 3. Predicted outcomes of screening on colorectal cancer (according to NHS.UK, 2011)

Up to date, two strategies have been available: faecal occult blood test (FOBT) and endoscopy (colonoscopy or proctosigmoidoscopy) (American Cancer Society Guidelines for the Early Detection of Cancer, 2007, BMJ Clin Evid Concise/Colorectal cancer screening, 2006, as cited in Majnarić-Trtica, 2008b; Labianca, 2010). Experiences on using the conventional screening method, the Faecal Occult Blood Test (FOBT), applied in asymptomatic population at average risk, showed that 3-5% subjects with positive results are to be expected (Winawer, 2003; Bond, 2006, as cited in Majnarić-Trtica, 2008b). The rationale for its use is based on the fact that, at an early stage, a colorectal tumour causes minor bleeding which can not be seen with the naked eye. The purpose of the screening is to check for this hidden blood in the stool sample. Recently introduced, the Faecal Immunochemical Test (FIT), has been shown as simpler for use and of a better specificity, however, because of higher price and the lack of efficiency analysis, it has not been yet widely implementated (American Cancer Society Guidelines, 2011). In most recommendations, the FOBT is used as a standard screening method, and a colonoscopy - for follow-up of test-positive cases. Based on widely obtained data, 10-15% of those subjects referred to colonoscopy are expected to be diagnosed as cancer and 30-40% as adenomas (Figure 3) (American Cancer Society Five-Year Relative Survival Rates, 2007, as cited in Majnarić-Trtica, 2008b; NHS.UK, 2011). Experiences until now showed that if screening strategies are implemented as organised programs based on the screening interval of 1-2 years, it is possible to reduce mortality rate for 18% -33% (Achkar, 2006, as cited in Majnarić-Trtica, 2008b).

#### 7.4 Screening of prostate cancer

Prostate cancer is one of the three major cancer sites in men; commonly occurs after 50 years of age, with incidence progressively increasing in later decades of life. Only males with positive family history of a disease (at least one blood relative: father, grandfather, or brother) are at a higher risk even in age before 50 (American Cancer Society Guidelines for the Early Detection of Prostate Cancer, 2011; ESMO Guidelines Working Group, 2011).

Screening protocol include digitorectal examination (DRE) and PSA (prostate-specific-antigen) measuring in serum, in patients aged  $\geq 50$  years, in those who refer symptoms of prostatism and urinary tract disorders, or in those who require screening. The decision on whether or not to have a prostate biopsy (performed by transrectal ultrasound, TRUS) should take into account PSA parameters, such as free (f) PSA, fPSA/PSA ratio, DRE findings, prostate size, patient age, comorbidities, patient values and history of previous biopsy (American Cancer Society Guidelines for the Early Detection of Prostate Cancer, 2011; ESMO Guidelines Working Group, 2011).

Although there are evidence indicating that population-based screening may reduce prostate cancer mortality by approximately 20%, patients should have an opportunity to make an informed decision on whether to be screened or not, since there are some uncertainties associated with prostate cancer screening (American Cancer Society Guidelines for the Early Detection of Prostate Cancer, 2011; ESMO Guidelines Working Group, 2011). Namely, screening increases prostate cancer incidence, including subclinical forms that will not develop during life, leading to unnecessary manipulation and overtreating. Long prospective studies, and cost-effectiveness and quality of life analyses,

which are now under way, are expected to justify decisions on population screening on prostate cancer.

## 8. Programs of early cancer detection

In a general sense, screening program means systematic examination of the defined target population at average risk for developing some hazardous disease or undesirable medical event, or using scientifically justified tests that are appropriate to be applied as a public health measure (Table 6). Screening is organised periodically and at a long run, with the clearly defined aim to reduce the population burden of a disease and its unfavourable effects on the national health care system and economy. All activities in the program are fairly planned in an advance and performed according to the up to date standards of a medical care, with external finance assured. They include several subsequent steps, from promotional and educational activities, to screening, and a referral of subjects tested positive for further diagnostics and treatment. In concern to cancer, the early detection program is tending to become a part of more comprehensively shaped national strategies for cancer control, including also primary prevention and health promotion, as well as rehabilitation of cured patients, and palliative care for patients with infaust prognosis (WHO/Cancer, 2006). A programed approach has been proved as more efficient than the opposite one - an opportunistic approach - based mostly on patients demand, or performed in a diagnostic or clinical context. In the latter case, examinations may or may not be performed according to the public screening policy (Cancer screening in EU, 2007).

There is a wide consensus that a minimum degree of public responsibility, organisation and supervision, is required, for screening activities to be considered as within the context of a program, in opposite to a “non-program” screening. To qualify as a program, there should be a public screening policy documented in a law, or an official regulation, directive, or recommendation. As a minimum, the policy should define the screening test, the examination intervals, and the group of subjects eligible to be screened, including finance from public sources, or a co-payment. In a reality, substantially more organisational elements are needed to qualify screening activities as an “organised program”. These elements provide for supervision and monitoring of most steps in the screening process, as well as comprehensive guidelines and rules to define standard operation procedures. In fact, differentiation of “organised” from “unorganised” programs should take into account the continuous gradient, ranging from poorly organised to highly organised programs. Further, a team, or the body, declared as being responsible for program’s implementation and coordination, can be organised at the regional or national level. Programs may be further differentiated as to whether they are population-based or non-population-based. Population-based programs generally require a high degree of organisation and that, in each round of screening, subjects from the target population are individually identified and personally invited to screening. Finally, in the case of population-based screening, program implementation may be in various stages of development: planning phase, pilot phase, rollout ongoing, or rollout complete (i.e. fully established) (Figure 4) (Cancer screening in EU, 2007).

During last decades, evidence has been gained, in several countries in Europe, including Finland, Sweden, UK and Netherlands, which programs were performed to give possibilities for quality and effectiveness evaluation, on the benefits when implemented

organised programs for early cancer detection (Cancer Society of Finland/Screening programme, 2011).

- the condition is an important health problem
- its natural history is well understood
- it is recognisable at an early stage
- treatment is better at an early stage
- a suitable test exists
- an acceptable test exists
- adequate facilities exist to cope with abnormalities detected
- screening is done at repeat intervals when the onset is insidious
- the chance of harm is less than the chance of benefit
- the cost is balanced against benefit

Table 6. Ten principles which should govern a national screening program (by Wilson and Jungner of the WHO, 1968)

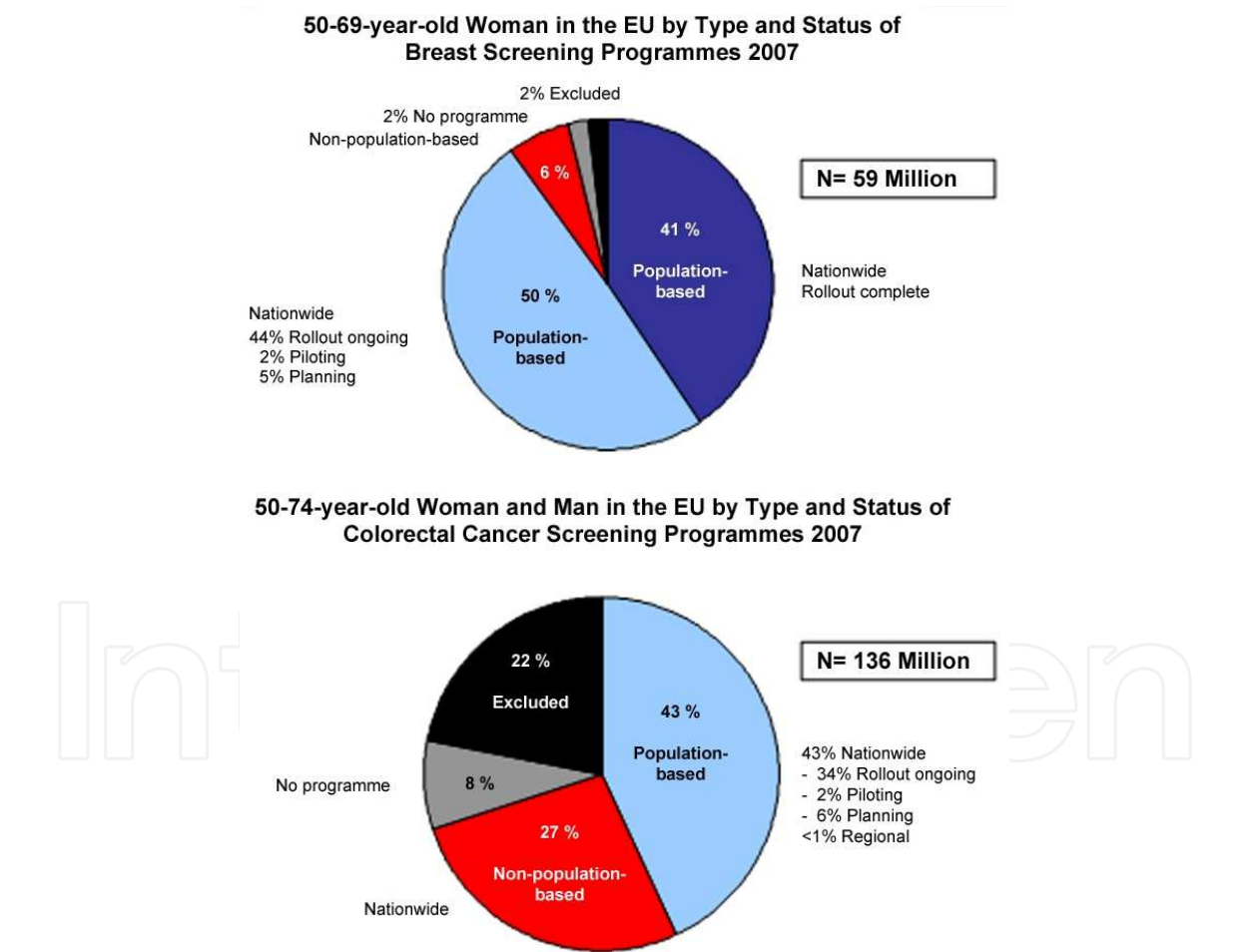


Fig. 4. Screening programs implementation in the EU, breast and colorectal cancers, for usual target groups

Until 2007, 22 Member States (out of 27) have adopted policies aiming for implementation of population-based screening programs, 11 of them in which nationwide rollout of

population-based programs is complete, 7 in which it is ongoing, and 4 in which it is being piloted or planned. Cervical cancer screening programs were running or being established in 25 of the Member States, but in comparison to the situation with breast cancer screening, program implementation varies more markedly and there is a substantial deviation from the recommendations of the Council of the EU. Compared to the prior two, colorectal cancer screening programs were running or being established in a smaller number of the Member States, program implementation was less advanced, and a smaller proportion of the population, specified in the Council Recommendations, was targeted (Figure 4) (Cancer screening in EU, 2010).

## **8.1 Programs of some European countries**

### **8.1.1 Finland**

In Finland, population-based cancer screening has a long tradition, as started in the far 1963 with cervical cancer screening (Cancer Society of Finland/Screening programme, 2011). Over the years, this program has come under the scrutiny, and now serves as a gold standard for evaluation of screening programs' quality and effectiveness. Two other main cancer screenings, for breast and colorectal cancer, are also being carried out in a highly organised manner. The first started in 1987, and the latter in 2004, after the EU Commission set up in 2003 its recommendations for strengthening the efforts over early detection of colorectal cancer. The Mass Screening Registry provides evaluation of the impact of screening programs on cancer-related mortality and of the quality of the screening programs, and is a complementary to the Finnish Cancer Registry. The Finnish Cancer Registry is currently included in the European trial on prostate cancer screening.

Screening programs are centrally directed by the Cancer Society of Finland, but it does not exclude regional societies to work independently and to adjust programs to different local environments. These regional organisations provide a vast array of services, including counselling units, ambulatory cancer clinics, laboratories and hospices, as well as organisation of rehabilitation and recreational courses. Patient organisations and numerous volunteers, joined as members, provide the popular base to the Societies. The Cancer Society, together with the Cancer Foundation and the Foundation for Cancer Research, as private, non-profit investors, provide the sources of funds aimed at preventing cancer through research, health promotion and mass screenings. The Society also actively participates in creating health policy. In this way, the Cancer Society has become a vast forum for providing a support to comprehensive cancer control, by bringing together scientists, clinicians, decision-makers, financial experts, volunteers and patients, in the common mission of reducing the cancer burden in the population.

Specifically, Finnish smoking prevention and cessation campaigns, are worth mentioning details. Cigarette consumption in Finland was the highest in the world, in the period between two wars; consequently, the lung cancer incidence in men was one of the highest in the world. Due to combined effect of legislative measures, health promotion activities and strict monitoring, smoking decreased drastically over time, and nowadays is among the lowest in Europe.

By acting in this way, Finland has become one of the leading European countries in achieving an efficient cancer control, with the figures decline on cancer mortality and with

the five-year survival rates among the best in Europe. Overall, in performing public health activities, Finland experienced a long process of transition, from the prevailing implicit policies, determined by commercial and fiscal interest, to explicit - health-oriented policies. In this context, earlier, the risk behaviour and a disease concern was considered as a medical and individual problem, while nowadays it is primarily considered as a public health, social and political issue.

### 8.1.2 UK

National cancer screening programs in UK include cervical, breast and colorectal cancers. For prostate cancer, there is an informed choice program - for healthy men who requires screening, and the risk management program - for men at higher risk for developing disease, due to symptoms of prostatism, or a positive family history on prostate cancer (NHS.UK, 2011). Cancer screening programs in UK are characterised with a high level of quality performance, and a large coverage of the target population, for cervical cancer already reaching the expected 80% (Arbyn, 2008, as cited in NHS.UK, 2011). Further, these programs are strictly evidence based, by means of the screening intervals, recommended age groups and methods used for screening. To avoid disparities for screening, community-driven approach is preferred, while Primary Care Trusts and regional directors of public health are responsible for the quality assurance. The National Office for Cancer Screening provides the call/recall system and coordinate all other activities (NHS.UK, 2011).

The main shortage of this system is in using the lists of patients registered with general practitioners (GPs), allowing eligible individuals not covered by the health insurance, to drop out from the screening. The UK is an example of the cancer screening model which in a great part relies on the ordinary health care facilities and includes primary care teams to participate, by encouraging patients to screening and by keeping them informed on all the stages of the screening program. This model is termed as a "model service".

### 8.1.3 Hungary

Hungary, as a state in the process of transition, is typically faced with the growing burden of chronic noncommunicable diseases, especially concerning cancer (Kovacs, 2011, as cited in Hőjz/Health in Hungary). The life expectancy, of both men and women, is significantly below the average of most countries in EU, with cancer at the leading position in regard to "potential year of life lost" (PYLL). With the aim to reduce the overall mortality, and cancer mortality in particular, an organised cancer screening program, a part of the National Public Health Program, was launched in 2001. The official health care system is responsible for the program implementation, and finances are assured by the government. The program is coordinated and monitored by the Office of Chief Medical Officer.

Analysis made upon the program implementation, reveals some shortcomings, similar to ones found in other programs with small tradition. Some of these barriers to program's implementation include the lack of necessary prerequisites for screening, insufficient finances, and a fairly high number of screenings performed outside the organised screening settings. The latter phenomenon may be due to the low degree of awareness for mass screenings, and to the fixation upon traditional examination protocols. Further, there is a poor cooperation among actors within the programs, the problem in record linkage, between

various databases, and yet undeveloped laws on sensitive issues, such as data protection and patients rights (Kovacs, 2011, as cited in CJPH/Health in Hungary).

#### 8.1.4 Croatian national program of prevention and early detection of cancer

Croatia is a transitional country characterised with health problems such as unhealthy behavior of the population and a growing burden of chronic diseases. The situation is even worse than it could be expected, because Croatia has recently experienced a war and fast political and social changes (Ebling B., 2007; Majnarić-Trtica, 2009).

In cancer statistics, in comparison with the majority of European countries, Croatia takes high unfavourable position (Draft National Program, 2007). Cancer is the second mortality cause and accounts for every fourth case of death. Both cancer incidence and mortality rates are on the increase, with a sharp increase in incidence rates observed after 1997, consequently to the post war period (Figure 5). The most common cancer sites are the lung, the colon and the breast, with the prostate cancer prevailing in elderly men aged 75 and more.

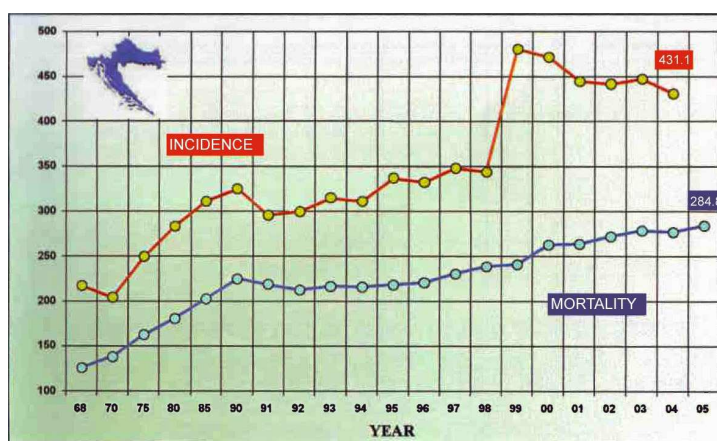


Fig. 5. Total cancer incidence and mortality rates, Croatia

In Croatia, primary prevention and early detection of cancer have not been systematically performed before, except for some separate actions, carried out by the non-governmental organisations or professional associations (Eljuga, 2006, as cited in Majnarić-Trtica, 2008b). The early detection of cervical cancer, by cervical cytology, has been performing for all sexually active women during their visits to gynecologists (Šamija, ed., 2000, as cited in Majnarić-Trtica, 2008b). Clinical examination on cancer and the FOBT have become a part of periodical medical checks, performed by family physicians for patients aged 50 and older.

Based on such situation and by taking into account unfavourable cancer statistics, the Croatian Oncology Society of the Croatian Medical Association initiated preparation of a Draft National Program for Prevention and Early Detection of Cancer (Draft National Program, 2007). The Program was published in early 2006. On behalf of the Ministry of Health and Social Welfare, the breast cancer screening program has started immediately that year. The National Program for Early Detection of Colorectal Cancer has started in late 2007. The Croatian Public Health Institute and its county departments coordinate and monitor program's implementation, including activities such as the central call/recall system, data

collection and evaluation. Family medicine teams are not actively included, only in keeping data on responsiveness of their invited patients to screening, and in follow up of those ones with positive tests.

General objectives, set up by the Program, are: to decrease prevalence of risk factors among the population by promotional and health educational activities, to reduce total cancer-related mortality rates by 15% within 5 years after the Program started, to increase the percentage of diagnosed pre-clinical and localised cancers compared to percentage of advanced stage disease and to increase the early detection coverage of the population. Specific objectives are oriented towards improvements in diagnostics and treatment and standardisation of protocols (Table 7).

CANCER SITE	RECOMMENDATIONS
Breast	<ul style="list-style-type: none"><li>• mammography for women aged 50-69, every two years</li><li>• special protocol for women with family history of first-degree relatives with breast cancer, with determined non-tumour or tumour breast disease and other risks (earlier controls start, more frequent examinations)</li></ul>
Cervix	<ul style="list-style-type: none"><li>• Pap test for women aged 25-64, every three years</li></ul>
Colon Rectum	<ul style="list-style-type: none"><li>• Fecal Occult Bleeding Test (FOBT) or Fecal Immunochemical Test (FIT) for persons &gt;50, every three years</li><li>• Colonoscopy for persons with positive FOBT results to determine bleeding cause</li><li>• Individuals at increased or high risk of colorectal cancer, including persons with history of colorectal adenoma or cancer, ulcerative colitis, Chron's disease, family history of polyposis syndromes (FAP, Gardner, Turcot, Peutz-Jaghers syndrome, familial juvenile polyposis, non-polyposis colon cancer, first-degree relative with colorectal cancer should be included in early cancer detection program at younger age.</li></ul>
Prostate	<ul style="list-style-type: none"><li>• digitorectal examination and PSA test once a year for;<ul style="list-style-type: none"><li>- males at increased risk aged 40 years and older</li><li>- males with prostatism symptoms aged 50 years and older;</li></ul></li><li>• males aged 50 years and older who request an examination</li></ul>
Health Awareness	<ul style="list-style-type: none"><li>• persons visiting family physicians should be distributed leaflets and brochures on prevention and early detection of cancer in the most frequent sites.</li></ul>

Table 7. Croatian National Program, Recommendations for screening

According to the Program for Early detection of breast cancer, women of the target population (50-69) are invited by surface mail to take preventive mammography every two years. Based on the planned coverage of 70%, it amounts about 280 000 women a year. BI-RADS classification and double-blind reading performed by two experienced radiologists are used as methods for checking up mammograms. Cases suspected on cancer (BI-RADS 4 and 5) are referred for follow up (Draft National Program, 2007; Ministry of health, 2006).

In the first screening cycle (until the end of 2006), about 720 000 women were invited, the number exceeded the planned number of 280 000 invitations a year, with more than 1500 newly diagnosed cases. (Experience from other European countries also showed increase in the cancer incidence during the first year of screening program implementation). Although achieved response rate of 58,5% was comparable to that in other European countries, the authorities are not completely satisfied with the results (Strnad, 2010). As the main barriers

to program implementation, wrong addresses and insufficiently checked patients lists, were addressed. The rate of suspicious results was lower than expected, which indicates that women with BI-RADS 0 should also be taken into consideration for referral to diagnostics. Continuous education of radiologists in reading the mammograms and acquisition of new equipments for the diagnostic centres, are planned improvement measures. Educational activities, with the aim to increase the level of awareness for screening among the population, and further strengthening the knowledge and companionships, as much among different sectors and participants included in the Project, as among local communities, will be essential (Samardžić, 2007; Strnad, 2010).

The screening protocol for colon cancer includes asymptomatic men and women aged 50-74 years, as according to the international recommendations, in two-year check-up by the FOBT, and the coverage rate of at least 60%. Test-positive individuals are referred to colonoscopy, to determine the cause of occult faecal bleeding. Individuals from the high risk groups are managed following the special protocols. Specialists colonoscopists and surgeons from clinical hospitals, and laboratory workers and coordinators from the counties' Public Health Institutes, are responsible for the Program implementation. Invitation letters are sent by mail to home addresses. In an envelope, there are three testing-cards, instructions for their use, questionnaire about risk factors and an educational brochure. Invited persons are asked to mail testing-cards back, after they used them, together with a filled questionnaire, the purpose of which is to obtain information on risk factors spreading in the population (Draft National Program, 2007; Ministry of health, 2007).

From the end of 2007 to the beginning of 2010, a total of 808 913 tests were distributed, of which only 19% were returned, 7,7% of these positive. Colonoscopy yielded 77,5% of pathologic findings, including 388 (5,99%) carcinomas; others were polyps (38,46%), hemorrhoids and diverticula (Strnad, 2010).

## 8.2 How to increase screening coverage?

One of the main problem, in mass screening programs, is how to increase the screening rates (*coverage*). This is two-sided problem. On the one side, there are problems of supply (program's implementation performans), including necessary equipment, professionals, implement of evidence, establishment of the call-recall system, and strictly managed follow up (screening policy). On the other side, there is the problem of motivation of subjects from the target groups for screening (*patients' compliance with screening*). Two steps of the motivation process can be recognised: 1) a decision to enter the screening cycle (*up-take*) and a decision to stay in (*adherence*) (Flight, 2008; Smith, 2004). It is possible to affect patients' motivation (an internal mental process) by psychological transfer, including *patients' empowerment and education*, provided by physicians or other actors in the program (Masterson, 2006).

### 8.2.1 Promotional and educational activities

It has been recognised that the rate of up-take and adherence to screening may have a long-term effect on screening programs effectiveness (Smith, 2004) and that both processes, inherent in decisions for screening, are subjected to changes, by educational and motivational activities (O'Neill, 2008). This is why it is important that promotional and educational activities precede to and/or follow mass screening programs implementation.

Media campaigns and promotional activities can be organised at the national or the local community level, initiated by policy-makers, local community authorities, or public health services. These activities have multifaceted aim to inform the community on: 1) risk factors for the most frequent cancer sites, 2) early symptoms of a disease, 3) early detection methods, 4) the importance of acceptance of screening (Ebling, 2006, as cited in Majnarić-Trtica, 2008b). More focused educational activities, oriented towards specific population groups, such as high-risk groups, adolescents, or workers in industry, as connected with occupational risk factors exposure - can be initiated and organised by non-governmental organisations, local public health institutions, health professionals' associations, or cancer patients support groups (Eljuga, 2006, Ebling, 2006, as cited in Majnarić-Trtica, 2008b).

Individually-oriented educational activities, for patients' groups or individuals, can be mostly effective if performed by primary health care workers, especially family physicians. In the latter case, educational activities tend to be transformed into more subjective cognitive tools, close to what is known as "encouragement" and "empowerment" of patients for screening. In this way, some elements of a self-decision making process, connected with reasoning thinking, can be tackled to change (Fig. 6) (Ackerson, 2009). In this context, it is important to know that there are elements of a self-decision making process that are less prone to change. They come from intuitive thinking, complementary to more conserved psychologic structures, such as the values and attitudes.

### **8.3 The role of family physicians in programs of early cancer detection**

In terms of organization, two extreme early cancer detection program forms are possible, either that supplied by governmental and public health institutions, or that based on the central role of family physicians in program's implementation. By working at the interface of the health care system and the population, family physicians are in the specific position that enables them an opportunity to promote a vast array of preventive activities, in a proactive and a patient-oriented manner (Summerton, 2002). That means that the doctor recognises medical needs of the groups and individuals, encourages them to take preventive measures and manages the screening protocols, in contrast to the approach where the doctor generally responds to the patient's requests. Moreover, the possibility of having an insight into specific characteristics of each patient, enables family physicians to select an appropriate way to present the preventive measures to a patient, and to create activities, in order to improve patient's uptake and adherence to screening (Figure 6) (NHS.UK, 2011).

There is a general assumption that prevention and early detection of cancer is insufficiently implemented in practice of family physicians. In most countries, family physicians are only partially involved, mainly through opportunistic screening (subjects are referred by a physician for screening outside the program supplied by public services), or only under certain conditions, such as rural and distant areas (Moss, 200, as cited in Majnarić-Trtica, 2008; NHS.UK, 2011). Randomised studies in which screenings on cancer, managed by family physicians, were explored, are scarce and not of a large-scale, to allow general conclusions to be drawn on (Jellema, 2010).

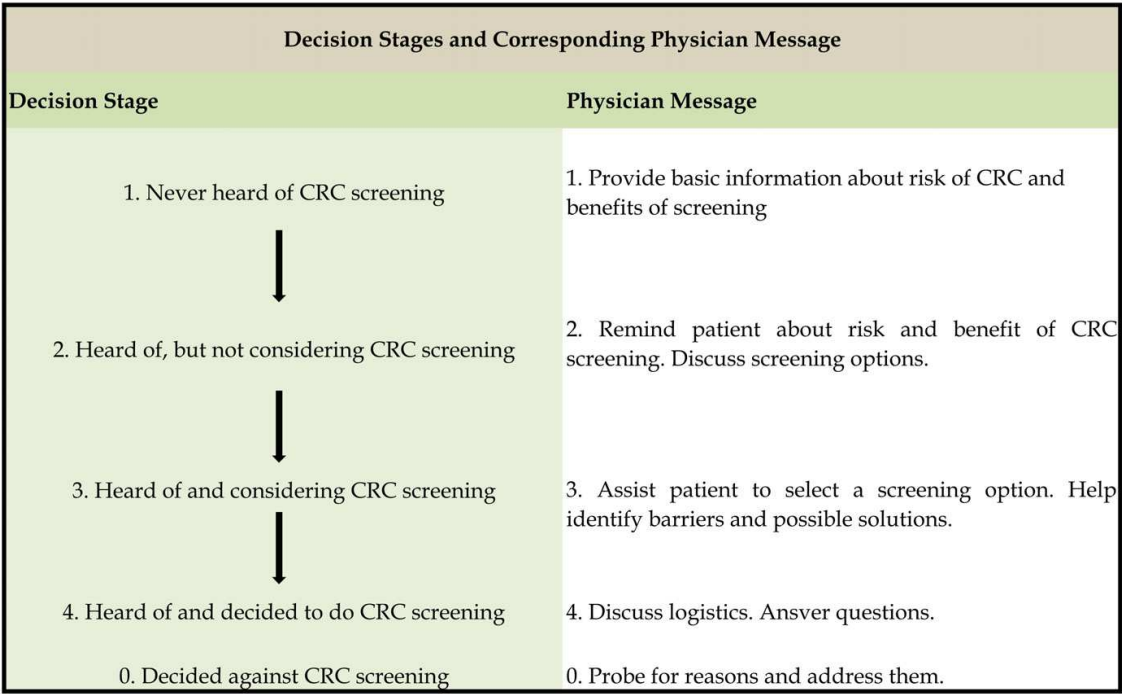


Fig. 6. Decision stages for colorectal cancer (CRC) screening

8.3.1 Experiences from Croatia in involving family physicians in programs of early cancer detection

The leaders of the Department of Family Medicine of the Osijek University School of Medicine and the Health Center Osijek, have recently introduced the project “*A Model of Early Cancer Detection Integrated in Practice of Family Physicians*“, to test the idea that screening and early diagnosis of cancer are more efficient if integrated in practice of family physicians, compared to the National Program, centrally directed and supplied by the public services (Ebling/Project, 2007, as cited in Majnarić-Trtica, 2008b). The Project has started after two years of preparations and education of subjects from the target groups and family physicians, included in the Project, on screening and early detection methods. The computer program, specifically designed for keeping the records on data and for follow up of patients with positive screening tests, was installed into a total of twenty GP offices included in the Project. This program has allowed the continuous recruitment of new patients into the surveillance system automatically, by using personal data on sex and age only (Majnarić-Trtica, 2008b). Up to date, the Project has yielded its results in colorectal and breast cancer screening.

8.3.1.1 The Project of early detection of colorectal cancer

To avoid overalpping with the National Program, subjects were included in the Project for early detection of colorectal cancer to belong to either the 5-year lower age class (45-49) or the 5-year upper age class (75-79), than it is recommended according to the National Program (50-74). These defined target groups encompassed approximately 4 000 people, randomly selected from the large sample of a total of 27 000 subjects, recorded on the lists of family physicians included in the Project (Majnarić-Trtica, 2008b; Pribić, 2011).

The screening protocol can be described as follows. Family physicians call the patients from the defined target groups by phone, deliver them letters of invitation in envelopes together with three testing cards, brochure for their use and a questionnaire on risk factors. A physician also provides instructions on how to correctly apply the testing cards and other issues the patients may be interested in. A physician reads the applied testing cards when patients return them back and keeps a record on the results. Patients with positive tests are referred for further diagnostics by colonoscopy. A physician also keeps a record on the results of follow up and treatments (Pribić, 2011).

From the beginning of April to the end of May 2009, a total number of 516 testing sets on occult faecal blood were delivered to patients from these two defined target groups. A high responding rate of 69,76% (360 cases) was recorded. This was an advantage in comparison with low responding rates of about 20%, obtained by the National Program. In the Project, there were in average 2,5% (13 cases) with positive tests, predominantly in the older age group, 3,5% (11 cases), compared to 1% (2 cases) recorded in the younger age group. These results showed that in the middle age population groups (45-49), a very low rate of positive tests, in systematically and non selectively performed screening on occult faecal bleeding, might be expected (1% positive tests). This further indicates that, for younger population groups, a selection of subjects at higher risk for the development of colon cancer should be made, prior entering the screening cycle.

#### **8.3.1.2 The Project of early detection of breast cancer**

The study group comprised the women from ten GP offices who have not yet been invited by the County Institute of Public Health to screening with mammography (Pribić, 2010). These women were invited during their visits for reasons other than mammography (opportunistic screening), or actively, by surface mail or phone. Women who did not respond at the first invitation, were included in the four-phased motivation program, carried out by a family physician and a home visiting nurse. If their decisions remained unchanged after the period of three months of follow-up, they were classified as resisted the screening with mammography. Although a high level of responsiveness, of 80%, was achieved, a critical appraisal upon this study includes a suggestion for the post-hoc testing, to decide on whether a long-lasting and highly suggestive motivation activities are applicable as a routine advising procedure. In addition, results obtained here indicate, similar as in the case with the Project of early detection of colorectal cancer, that there is a need for more thoroughly prepared selection procedure, before someone starts motivating women to screening.

#### **8.3.2 Concluding remarks**

A central role of family physicians, in implementation of preventive programs, has been recognised as an advantage, in terms of achieving better screening coverage and decreasing the costs, as compared to the strictly centrally controlled programs. However, as with the respect to the above results - even those who advocate for this approach, must point out that some kind of technical and professional support to family physicians should be assured, to allow the program to maintain and to achieve high quality norms (Wender, 2007).

## 9. Current trends

### 9.1 Personalised screening

There is no doubt that the early detection of cancer is effective, but no clear attitudes on which strategy is more efficient than another, in a real situation within the framework of the current health care system organisation. Awareness has been increasing that variables such as “a benefit-to-risk” and “a benefit-to-cost” ratio, or „a quality of life measures“, should be taken into consideration when planning screening strategies (WHO, 2009; Aebi, 2011). New, more specific screening tests, such as a digital mammography, or immunochemical tests for testing on occult faecal bleeding, are now available and increase our chance to detect cancer early. However, higher prices of these tests, compared to conventional ones, require more specifically elaborated screening strategies, including a precise definition of who should be included in screening, by using which tests, and under which conditions (Jellema, 2010; Schousboe, JT, 2011; Warner, 2011). Evidence also suggests that variables such as the patient's context, including co-morbid health disorders, and patient's values, regarding specific benefits and harms from screening, are to be taken into account (Warner, 2011).

### 9.2 Cancer risk prediction models

The average risk of getting a cancer (for a 5-years, or a 10-years time period, or expressed as a lifetime risk) are estimated on the basis of the incidence data for the population. Many factors that can change these estimates to the higher or to the lower, for some of the most common cancers sites, have been identified (known as cancer risk factors) (US National Cancer Institute, 2010, 2011). Knowledge on this issue allows personalisation of risk assessments, based on the estimates such as the score charts, or mathematical risk prediction models, which can help physicians and policymakers to identify individuals who might benefit, more than some others, from the screening.

Multivariable risk prediction models for some usual cancer sites have been established so far, based on using easily available epidemiologic and clinical data and identified risk factors. It has been realised, however, that the model's precision can further be improved, if some biochemical or molecular biomarkers are added into the model or, more recently - information on a personal genome analysis (Barlow, 2006; Rosenbaum, 2010; Spitz, 2007, 2008; Wang, 2007). Risk prediction models are expected to support a decision-making, beyond the traditional screening protocols, by more accurately identifying subjects of the target groups.

### 9.3 Genetic risk estimates

Two Mendelian genetic tests, appropriate to add value to the cancer risk assessment, have been established so far, including BRCA1 and BRCA2, highly penetrant breast and ovarian cancer predisposition genes, and a set of the mismatch repair (MMR) genes, carriers of which have a high risk of the most common hereditary colorectal cancer and/or endometrial cancer, and a lower risk of urinary tract, small intestine, ovary, gastric, pancreas, biliary tract and brain cancers (Balmana, 2010; 2011).

The costs of the genetic tests were the main problem in the past, making the barriers for implementing these tests in routine practice. Nowadays, when the costs of these tests

rapidly fall down, the dominant problem is a lack of the clinical assessments of genetic risk estimates. For example, higher prevalence of BRCA 1/2 genes can be found in association with a family history of breast or ovarian cancer and a young age at onset (Balmana, 2011). Is there an added value of systematic testing on these genes, in women with a positive family history of breast cancer, beyond the standard screening with mammography, if familial susceptibility to breast cancer accounts for less than 25% of all breast cancer cases? This further arises some additional questions. Namely, carriers should advise close family members to obtain genetic counseling and/or testing (American Cancer Society/ A manual Cancer and Genetics, 1997/98; Balmana, 2011). This is associated with some ethical and moral issues addressing both, potential carriers and physicians who provide counseling for them. The major concern addressing potential carriers includes living under the pressure of having an increased susceptibility for cancer. Concerns addressing physicians include low level of knowledge on variation in penetrance and expression of cancer-prone genes, and a lack of evidence of how a genetic counseling might have an impact on issues from the ethical domains (American Cancer Society/ A manual Cancer and Genetics, 1997/98).

#### **9.4 The personalised approach in early cancer detection - the role of genomics and proteomics**

The rapid progress in biotechnology has been expected to provide huge benefits in prevention and early detection of chronic noncommunicable diseases, notably cancer, by implementing genomics, proteomics and other -omics techniques in practice. The main principle, these techniques relies on, is a possibility of identifying subjects at an early clinical or subclinical phase, during the course of developing a chronic disease, by obtaining the whole-genome sequencing (genomics), or by characterising the protein and peptide profiles of various biological fluids or tissues (proteomics) (Yang, 2003, Khoury, 2007, as cited in Majnarić-Trtica, 2009).

These techniques have attracted the attention of both, the scientists and the public as a whole, in recent times, for their potential to stimulate the adoption of the personalised approach in medical practice, with expectancies for the improvements, equally in prevention, prognosis, diagnosis and treatment. For the reason that these techniques were developing far more rapidly than their clinical utility could be evaluated, there is no clear understanding yet, of what would be reasonable expectations of implementing these techniques in the real-life settings, and which obstacles need to be overcome. Although some early results of their clinical applications seem promising, such as the use of serum proteomics in screening for ovarian cancer, providing sensitivity of 100% and specificity of 95% - to date, there are no visible results yet, capable to bring substantial changes into the standard routine (Evans, 2010; Ioannidis, 2011).

### **10. Challenges for the future**

#### **10.1 Integrated knowledge translation**

In spite of the huge advances in understanding the natural course of development of some common cancers, as well as in methods for their prevention and early detection, there are still difficulties in translating this knowledge into practice. The problem is especially emphasized in developing countries. Some of the main reasons include: separation between

public health and clinical medicine, poor coordination between the health care and science - on the one hand, and the health care and politics and social welfare - on the other, and the rapid progress in health care technology and biotechnology, leading to a rapid rise in health care costs and the disparity in access. In addition, there is a need for better integration of the new, individually-oriented approaches into the established early detection programs (Evans, 2010; Hudson, 2011; Majnarić-Trtica, 2009; Pigeot, 2010).

There are initiatives to bridge these gaps, by favouring a collective approach to problems and questions concerning health. It is believed that this might be achieved through a leadership shift (from a traditionally top-down to a coalition leadership between practitioners and researchers/scientists), and the process of integration of the knowledge bases, among multiple health care and other social sectors. Namely, an awareness is growing up that the issues of public health are intimately embedded in the socioenvironmental context and should be managed within this context. For this reason, researches, public health professionals and policy decision-makers, should collaborate in searching for “better”, “faster” and “cheaper” interventions, aimed at improving the health in the community. The development of the common information and communication technology infrastructure are expected to facilitate these common initiatives (Lapaige, 2010; majnarić-Trtica, 2009; Patridge, 2011).

## 10.2 The chronic care model

Improvements in the early detection, diagnosis and treatment of cancer enable people with cancer living longer and managing their cancers as a chronic illnesses. This considers a long-term surveillance, including prevention, early detection, diagnosis, treatment, care after the treatment, and survivorship. Demands are put on patients and their families, in managing care on their own, and on family physicians, in providing them education and support, as well as a follow up (McCorkie, 2011).

## 11. Conclusions

Experiences gathered up-to-date show that the programs for early cancer detection are best performed if well organised and coordinated, independently on whether they are conducted by governmental and public health institutions, or predominantly supplied by family medicine teams. In highly income countries, with long tradition in organising early cancer detection programs, expected curing and survival rates have been achieved. These favourable results can not be attributed only to a large number of professionals employed, good technical facilities and government officials coordinating the programs, but, even partially, to the comprehensively performed and sustainable driven strategies aimed at cutting the common risks factors burden for the most important chronic diseases, including cardiovascular diseases, diabetes and cancer. In this sense, the best way to invest in populations` health, would be by ensuring health protective working and living environment (Cancer Society of Finland, 2011; WHO/Health 2020, 2011). In case of lower income countries, strong orientation towards primary health care in performing programs of prevention and early detection of cancer, could be the best solution, as it has been proved that better primary care resources considerable contribute to reducing the adverse impact of social inequalities on health (Starfield, 2011). However, good primary care (practice)

depends on good primary health care (system), that means that primary care is reflective of a specific health care system policy. This reasoning was in the background of the recent initiative of the European Member States, to potentiate a wave of health reforms across Europe (WHO/Health 2020, 2011).

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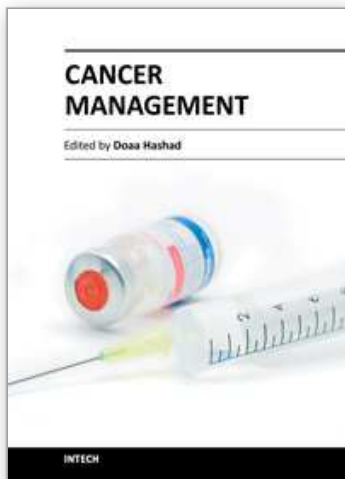
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Phone: +86-21-62489820  
Fax: +86-21-62489821

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