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Risk and Protective Factors for Development of Colorectal Polyps and Cancer

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1. Introduction

CRC is one of the most frequently diagnosed neoplastic disorders in humans worldwide. According to the National Centre for Health Information of Bulgaria the prevalence of CRC for 2005 is 304.6/100 000 cases, and the incidence - 49.2/100 000 cases (Bulletin of the National Centre for Health Information, 2005). Colorectal polyps (CRP) are established precursors of CRC. Hence, elimination of precursors is a well-known strategy for reduction of risk. In the last decade the most extensively studied etiologic factors are the risk factors for colorectal cancer development, because of its growing incidence and the possibility for its prevention. Prophylaxis of CRC we can divide in primary, secondary and tertiary. The most widely used chemopreventive drugs are: acetylsalicylic acid, polyvitamins, calcium, folic acid, selenium and NSAID.

2. Risk and protective factors for colorectal polyps and cancer

Today it is widely accepted that colorectal polyps (CRP) are preneoplastic lesions of colorectal cancer (CRC). From the 3 major groups of polyps: adenomas, hyperplastic, and serrated polyps, with the first group having the highest malignant potential. Hyperplastic polyps are the most common benign lesions, possessing very low malignant potential, and therefore do not require colonoscopic surveillance. However, recent studies prove their role in the classical model of adenoma-carcinoma sequence, and reveal common molecular features between normal mucosa, colorectal polyps, and cancer: proliferation activity, p53 overexpression, hypomethylation of c-myc, and mutations in k-ras oncogene (Hamilton, 2001). Progression of adenomas to CRC has been proven by the 'multistep model' of carcinogenesis, proposed by Fearon and Vogelstein. According to this model the stepwise progression of aberrant crypt foci, small, middle and large adenoma to carcinoma is accompanied by accumulation of mutations in the genes APC, k-ras, DCC, and p53 (Fearon, Fogelstein, 1990). Serrated polyps are histologicaly characterized by 'saw-tooth' infolding of the crypt epithelium, and are seen in 1% of the cases (Longacre & Fenoglio-Preiser, 1990). Every adenoma of the colorectum has a 5% probability for malignant transformation (Winawer et al., 1997). The growth of small adenomas is slow, requiring 10 years on average for doubling of their size (Hoff, 1987). The percentage of transformation of small adenomas into carcinomas is 0.25% (Eide, 1986). CRC is caused by complex interactions between host genetic susceptibility and certain exogenous risk factors. Geographic variation underscores

the importance of environmental factors in CRC pathogenesis, since a 30-40 fold difference between regions with high and low incidence has been found (Parkin et al., 1999). It is famous that the main risk factors for CRC and CRP are obesity, high calories intake, high body mass index (BMI), and low physical activity, consumption of red meat and animal fats, and alcohol. Other risk factors include male gender, advancing age, use of laxatives, constipation, pathological gut flora, some occupations, and intake of Fe-containing supplements. There is association also between the risk of developing CRC or CRP and presence of some diseases like inflammatory bowel disease (IBD), acromegaly, diabetes mellitus, cholecystectomy, ovarian and breast cancer, history of survived cancer or availability of adenomatous polyps in the past. Many conditions increase the risk of development of CRC and the degree of their influence substantially varies, as is shown in Table 1.

Risk factor	Minimal	Moderate	Major
Dominant inheritance (FAP, HNPCC, Juvenile polyposis)			+
Diet			+
Recessive inheritance or low penetration (MAP)		+	
CRC in the past		+	
Colorectal villous adenoma in the past		+	
Low physical activity		+	
Age > 50 y.		+	
Male gender	+		
Obesity	+		
Tobacco smoking	+		
Chronic alcohol abuse	+		
Extensive IBD	+		
Acromegaly	+		
Diabetes mellitus	+		
Cholecystectomy	+		
Breast cancer, ovarian cancer, radiotherapy	+		

Table 1. Assessment of risk factors for CRC and CRP. FAP, Familial adenomatous polyposis; NHPCC, Hereditary non-polyposis colorectal cancer; MAP, MYH-associated adenomatous polyposis; IBD, inflammatory bowel disease.

3. Patients and methods (our study)

3.1 Characteristics of patients with colorectal polyps and cancer

One-hundred and sixty six patients diagnosed for large bowel polyps were included in the present study. Of the patients, 76 were female and 90 male, aged 60±13 years (range 19-86 years). Also, 107 patients with CRC (48 female and 59 male) aged 64±11 years (range 32-94 years), 3 patients with familial adenomatous polyposis (FAP), and 2 patients with

Peutz-Jeghers syndrome, aged 31±12 years were included in the study. As a control we used a group of 42 healthy individuals (18 female and 24 male), aged 55±12 years, to whom upper and lower endoscopy was performed at their will or as a screening procedure, but showed no changes. Careful personal history, including dietary habits, physical examination, and anthropometric data were taken from all patients. We studied some factors from the lifestyle and diet in our patients with CRC and CRP, and looked for any connection between these factors and the beginning of CRC and CRP. For the aim of our study, we divided food consumed from the patients into 13 groups as follows: I. Milk and dairy products; II. Eggs; III. Meat and meat products; IV. Fish and sea animals; V. Cereals and pasta; VI. Sugar and sweets; VII. Legumes; VIII. Nuts; IX. Fats; X. Vegetables; XI. Fruits; XII. Spices; XIII. Beverages. We tried to establish the preferred way of cooking and favorite drinks in the studied patients. We registered their dietary habits in qualitative and quantitative manner, until the moment of CRC or CRP occurrence. We analyzed family predisposition of the included patients and their exposition to deleterious exogenous factors. All information, including clinical data, endoscopic and histological results, surveillance, and treatment, was entered on personal cards and in a gastrointestinal register for polyps and cancer.

3.2 Statistical analysis

Logit-models were used for determining the possible risk or preventive factors, which combine regression and correlation analysis. We investigated the influence of these factors upon included patients with linear regression analysis to be able to associate the lifestyle and diet habits of population in our region. Depending on the value of the Exponent Exp(B), factors are classified in three groups: risk factors – Exp(B)>1, protective factors – Exp(B) <1 and indifferent factors – Exp(B)=1. Statistical analysis was performed using Microsoft Excel, Statistics 5. 13./W and SPSS 13.0 for Windows software programs. Values of $p<0.05$ were considered as statistically significant.

4. Risk factors for colorectal polyps according to our data

Our data find the following risk factors for colorectal polyps: consumption of red meat, meat products, sausages, fat food, high BMI, frequent use of laxatives, beer and alcohol intake, preserved foods, salty foods, grilled or barbecued meat, low physical activity, allergy, bacon, ham, margarine, fried food, preserved meat, sugar, marinated food, tobacco smoking, egg-fried food, working in heavy or petrol industry, presence of autoimmune disease, use of microwave oven, professional exposure to extremely low temperatures, passive smoking and elevated serum glucose level.

We concluded that the most important risk factors for the development of colorectal polyps are diet factors - consumption of sugar products, fried, grilled and preserved food, animal fats and margarine, egg-fried food and obesity. The most important life style and occupational risk factors for the development of colorectal polyps are: chronic alcohol intake, long lasting tobacco smoking, minimal physical activity, occupational exposure to petrol and metals. The chronic alcohol intake includes usage of beer, wine and strong drink. Substantial factors are and presence of autoimmune disease or allergy, frequent use of laxatives and elevated serum glucose level.

Factor	Intensity	Exp. (B)
Chronic alcohol abuse	+ + +	9,256
Sugar and sweets	+ + +	8,917
Fried food	+ + +	7,258
Preserved food	+ + +	5,363
Heavy industry workers	+ + +	5,259
Beer	+ + +	5,025
Meat delicacy	+ + +	4,759
Bacon	+ + +	4,582
Long lasting sausages	+ + +	4,265
Fat food	+ + +	4,023
Margarine	+ +	3,707
Exposure to petrol	+ +	3,616
Weekly consumption of grilled meal	+ +	3,093
Presence of autoimmune disease	+ +	2,958
Strong drink	+ +	2,919
Low physical activity	+ +	2,843
Wine	+ +	2,827
Salty food	+ +	2,575
Allergy	+ +	2,566
Grilled meat	+ +	2,439
Preserved meat	+ +	2,345
Ham	+ +	2,241
Smoked food	+ +	2,144
Frequent use of laxatives	+	1,796
Marinated food	+	1,658
Preserved food	+	1,511
Egg-fried food	+	1,448
Tobacco smoking	+	1,444
Frequent meat consumption	+	1,349
Elevated serum glucose level	+	1,115
Years of alcohol consumption)	+	1,074
High body mass index (BMI)	+	1,047
Years of smoking	+	1,030

Table 2. Risk factors for colorectal polyps (4,01 – 10,00 + + +), (2,01 – 4,00 + +), (1,00 – 2,00 +).

5. Protective factors for colorectal polyps according to our data

According to our results fruits (apples, plumbs, raspberries, and pears), vegetables, rye- and whole-grain bread, green tea, vegetable food consumption, yoghurt, fasting, fish, lamb, hare, garlic, legumes and mineral water have a strong protective effect against large bowel polyps.

The most significant protective factors against colorectal polyps are again diet factors - consumption of fruit, vegetables, rye- and whole-grain bread, vegetable food, green tea, yoghurt and fasting. Protective role plays and frequent consumption of fish, lamb and hare. Probably, conditions of rural life are connected with reduction of the risk factors for development of colorectal polyps.

Factor	*Intensity*	*Exp. (B)*
Fruit	+ + +	0,033
Rare consumption of grilled food	+ + +	0,094
Apples	+ + +	0,122
Vegetables	+ + +	0,126
Rye bread	+ + +	0,199
Plumbs	+ + +	0,244
Raspberries	+ + +	0,258
Pears	+ + +	0,268
Rural life	+ +	0,318
Green tea	+ +	0,325
Vegetable food	+ +	0,345
Whole-grain bread	+ +	0,352
Yoghourt	+ +	0,367
Green vegetables	+ +	0,382
Fasting	+ +	0,385
Fish	+ +	0,428
Lamb	+	0,559
Hares	+	0,588
Legumes	+	0,595
Garlic	+	0,616
Low salt diet	+	0,668
Mineral water	+	0,895

Table 3. Protective factors for colorectal polyps (0,01 – 0,3 + + +), (0,31 – 0,50 + +), (0,51 – 1,00 +).

6. Risk factors for colorectal cancer according to our data

One of the most important aims of our study was to establish the risk factors for the CRC epidemic, which is observed now and in Bulgaria. We accomplished this study considering the specific conditions in our country and made comprehensive investigation of the diet habits of all included patients with colorectal polyps and cancer. We estimated and all other possible risk factors. Detailed list of risk factors for development of colorectal cancer is presented in Table 4.

The major risk factors for CRC are dietary as well: consumption of fat food, red meat and meat diet as a whole, smoked and egg-fried food, sugar and sweets, white bread, obesity. The lifestyle has also a significant effect: long lasting alcohol intake (beer, wine, and spirits), tobacco smoking, minimal physical activity, urban life. We noticed and other risk factors for CRC development: *H. pylori* infection, presence of adenomas, diabetes mellitus, and frequent use of laxatives. Probably, urban life increases the exposition to many of the presented risk factors and therefore it is a specific risk factor for development of CRC.

7. Protective factors for colorectal cancer according to our data

According to our results consumption of dairy products, fruit, garlic, onions, fish, plant oil, boiled food, vegetables, fowls, legumes and white meat has a strong protective effect for CRC. Low salt diet, fasting, usage of acetylsalicylic acid and rural life also possess protective

Factor	Intensity	Exp. (B)
Fat food	+ + +	11,034
Adenomas with severe dysplasia	+ + +	10,784
Smoked meat	+ + +	7,282
Egg-fried food	+ + +	6,334
Long lasting alcohol intake>10y	+ + +	5,939
Sub-products	+ + +	5,625
Fried food	+ + +	5,244
Short lasting sausages	+ + +	4,646
Pork	+ + +	4,368
Sausages	+ + +	4,255
Margarine	+ + +	4,214
Beer	+ + +	4,095
Bacon	+ +	3,366
Tobacco smoking	+ +	3,622
Meat delicacy	+ +	3,546
Low gr. dysplastic adenomas	+ +	3,541
Minimal physical activity	+ +	3,446
Sugar and sweets	+ +	3,281
Urban life	+ +	3,054
Exposure to petrol	+ +	2.898
Frequent use of laxatives	+ +	2,895
Preserved food	+ +	2,339
White bread	+ +	2,248
Helicobacter pylori	+ +	2,204
Red meat	+	1,805
Meat products	+	1,508
Wine	+	1,414
Tobacco smoking >10y	+	1,058
Strong drink	+	1,054
Villous component in adenoma	+	1,052
Overweight and obesity	+	1,045
Diabetes mellitus	+	1,040
Age	+	1,036

Table 4. Risk factors for CRC (4,01 – 12,00 + + +), (2,01 – 4,00 + +), (1,00 – 2,00 +).

effect against development of CRC. Our data is similar to the findings of other authors (Zaridze, 1983). Detailed list of protective factors against development of CRC is presented in Table 5.

The most important protective factors for CRC development are: consumption of fruit, vegetables, fasting, vegetable oil, fish, poultry, white meat, legumes, boiled food, and rare consumption of grilled meat. Regular use of acetylsalicylic acid and rural life are prominent protective factors for development of CRC. Obviously, diet regime in conditions of Bulgarian rural area is much closer to the healthy Balkan diet from the first half of the 20-th century, which plays protective role in the prophylaxis of cardiovascular, metabolic and neoplastic diseases.

Factor	Intensity	Exp. (B)
Low salt diet	+ + +	0,001
Melons	+ + +	0,051
Dairy products	+ + +	0,071
Pears	+ + +	0,114
Acetylsalicylic acid	+ + +	0,119
Garlic	+ + +	0,128
Fasting	+ + +	0,133
Fish	+ + +	0,137
Poultry	+ + +	0,165
Rural life	+ + +	0,197
Water melons	+ + +	0,200
Hares	+ +	0,202
Onions	+ +	0,228
Plant oil	+ +	0,231
Grapes	+ +	0,235
Peppers	+ +	0,264
Fruit	+ +	0,294
Vegetables	+ +	0,300
Green vegetables	+ +	0,318
Boiled food	+ +	0,343
Fowls	+ +	0,367
Legumes	+	0,418
Rare use of grilled meat	+	0,430
Fasting	+	0,457
White meat	+	0,665
Peaches	+	0,668

Table 5. Protective factors for CRC (0,01 – 0,2 + + +), (0,201 – 0,40 + +), (0,41 – 1,00 +).

8. Risk and protective factors for colorectal polyps and colorectal cancer - summary

Our data show that colorectal polyps and cancer share common risk and protective factors (Kotzev et al., 2008). This finding, paired with the high frequency of existence of colorectal polyps and CRC, could serve as an evidence of the role of the colorectal polyps as CRC precursors. Common risk and protective factors for colorectal polyps and colorectal cancer are summarized in Table. 6, where factors are divided into alimentary risk factors, nonalimentary risk factors and protective factors.

9. The mode of action of risk and protective factors for colorectal polyps and cancer

The mode of action of different risk and protective factors for CRC and CRP is associated with distinct pathogenetic mechanisms, which sometimes share similar pathways.

9.1 Alimentary risk factors for colorectal polyps and cancer

9.1.1 Obesity, high BMI and high caloric intake

Obesity, high BMI and high caloric intake are associated with increased risk for cancer formation, including CRC (Giovannucci et al., 1995). These risk factors are connected with

Risk dietary factors	Risk non-dietary factors	Protective factors
Overweight	Low physical activity	Carbohydrates (long chained)
Food additives and contaminants (heterocyclic amines)	Tobacco smoking	Fish
Contaminated water	Gender	Probiotics
Fats	Age	Fibers
Red meat	Laxatives	Flavonoids
Sugar	Helicobacter pylori	Dairy products
Alcohol	Occupational risks	Calcium
Eggs	Colorectal polyps	Fluids
Way of cooking - grilled meat	IBD, diabetes. mellitus, ovarian Ca, mammary Ca	Vitt. A, B, C, D, folic acid, Selenium, Calcium
Way of cooking – fried meat	Cholecystectomy	Fruit and vegetables
Way of cooking - high t°	Radiotherapy	Cereals
Polyamines	Colorectal cancer	Bioactive components

Table 6. Summary of all protective and risk factors tor CRC and CRP.

large bowel polyp formation as well. High caloric intake in combination with low physical activity leads to hyperinsulinemia and peripheral insulin resistance, which could result in high mucosal proliferative activity, reduced apoptosis, accumulation of free radicals, and mutagenesis. Being overweight could have an inappropriate influence on the immune system, could elevate the serum level of prolactine, and raise the sensitivity of the hypothalamo-hypophyseal axis. High BMI and high caloric intake are connected with elevated risk for development of CRC and colorectal adenomas according to different experimental animal studies and epidemiological studies (Ford, S. 1999).

9.1.2 Food additives and contaminants

Food contains various food additives, contaminants, fertilizers, herbicides, food dying agents, antibiotics and antimycotics. Increased mutageneity has been observed in faeces of patients with elevated risk for CRC formation (Villa et al., 1996). Food contains a lots of carcinogens and co-carcinogens such as free radicals, N-nitrous compounds, secondary bile acids, polyamines, and heterocyclic amines (used in food processing) (Parkin et al., 1999). Co-carcinogens usually need activation in the gut. Their activation and inactivation is maintained by the gut flora, some phytochemicals and metabolites. Meat processing leads to elevated carcinogen production. Meat and fish cooking leads to formation of heterocyclic amines, especially at high temperatures or when exposed to direct fire. Our study shows that grilled, fried and egg-fried foods are associated with high CRP formation, and fried and egg-fried foods are risk factors for CRC as well. We consider preserved food as a risk factor for CRP and CRC, while marinated food is associated with CRP. Some observations propose that gut bacteria could transform bile acids into secondary bile acids (deoxycholic and litocholic) which possess high toxicity and stimulate large bowel mucosal proliferation (Burnstein, 1993). Food fatty acids also alter the composition and the quantity of bile acids. Accelerated bowel transit time could diminish exposition time of mucosa to food carcinogens, and enlarged volume could dilute them. Thus food fibers bind, inactivate and carry out the luminal carcinogens.

9.1.3 Fats

The first announcement of the relationship between high intake of fats and CRC dates from 1969 (Wynder et al., 1969). The relationship between saturated/animal fatty acids and CRC risk is tight. Saturated fats play a crucial role in the initiation, promotion and progression of CRC. Saturated fats increase the bile excretion, which is followed by toxic impact upon colon epithelium and hyperproliferation (Burnstein, 1993). The current study proved that consumption of fatty foods, bacon, and margarine is strongly associated with CRP and CRC development. The results of animal studies report that in the animals, which are on high fat diet, elevated cell proliferation and free radicals are observed. Inflammation and oxidative stress play a significant role in human carcinogenesis, besuse DNA lesions and chromosomal instability could occur (Evans et al., 2004; Kryston et al., 2011; Sedelnikova et al., 2010). On the other hand omega-3 polyunsaturated fatty acids decrease inflammation, inhibit formation and progression of preneoplastic colorectal lesions (Anti et al., 1994). The so-called "Mediterranean" diet, which is rich in fish and sea products, reduces the risk for colorectal cancer. Our study proves that regular consumption of fish and sea products (more than twice a week) strongly prevents CRP and CRC. Probably, the protective effect of omega-3 polyunsaturated fatty acids is due to stimulation of apoptotic program, decrease of inflammation, mucous prostaglandins and decrease of the secondary bile salts concentration, which are promoters for CRC. There are data that omega-3 polyunsaturated fatty acids modulate the action of COX-2 and induce the expression of 15-hydroxyprostaglandin dehydrogenase, a physiologic COX-2 antagonist (Lim et al., 2008).

9.1.4 Carbohydrates

It is believed that decreased intake of carbohydrates reduces the risk for polyp formation (Lubin et al., 1997). Complex long-chained carbohydrates are considered highly protective in contrast to saccharose (World Cancer Research Fund and American Institute for Cancer Research, Food, Nutrition and the Prevention of Cancer: A Global Perspective., 1997). Some studies confirm that persistent hyperglicaemia and the subsequent insulin release are stimuli for hyperproliferation of colon epithelium and risk factors for the development of CRC (Calle & Thun, 2004). In contrast, other studies did not observe such an association (Weijenberg et al., 2008). Complex long-chained carbohydrates must supply 46-60% of all energy intake, while refined saccharose must supply <10% according to some recommendations (World Cancer Research Fund and American Institute for Cancer Research, Food, Nutrition and the Prevention of Cancer: A Global Perspective., 1997). The results of this study support the notion that saccharose and sweets are risk factors for CRP and CRC, while complex long-chained carbohydrates have protective effect.

9.1.5 Red meat

Consumption of red meat is connected with development of CRC (Ferrucci et al., 2009). Our study also confirmed the fact that regular consumption of red meat, large amounts of meat and meat products, preserved meat, ham, long- and short lasting sausages, pork, sub-products, and meat delicacy, is strongly associated with CRP, and CRC initiation and progression. On the other hand intake of fish, hare, lamb, white meat and poultry are highly protective. The possible pro-carcinogenic effect of red meat could be explained by the elevated heme iron content which could serve as a source for production of free radicals and

mucosal hyperproliferation (Nelson, 2001). The results obtained by other studies deny the role of dietary Fe and iron status for CRC development (Tseng et al., 1997). N-nitrous compounds in the red meat and produced during the food processing with high temperature polycyclic carbohydrates and heterocyclic amines are also possible reasons for the harmful effect of red meat (De Meester & Gerber, 1995) Red meat consumption in elderly individuals should be limited to 70-80g/day.

9.1.6 Alcohol

We believe that chronic alcohol abuse is a major risk factor for gastrointestinal polyps and cancer formation in esophagus, stomach, colon and rectum. High alcohol intake (>21 units/week) of beer, wine and spirits significantly increases the risk for CRP and CRC. These findings are probably due to the effect of acetaldehyde, which damages colorectal mucosa and elevates cell regeneration. Folic acid and methionine deficiency in persons who chronically abuse with alcohol are also risk factors for development of CRC (Giovannucci et al., 1995). Alcohol is an inducer of cytochrome P-405 2E1, which contributes to increased production of free radicals (Seitz & Osswald, 1992). Alcohol diminishes the transformation of retinol into retinoic acid and as result cell proliferation is upregulated (Seitz et al., 1998).

9.1.7 Food processing

We found that fried and grilled food is a risk factor for CRC and CRP. Cooking of the food at high temperatures and usage of grill induces formation of heterocyclic amines in the meat, which own mutagenic and pro-carcinogenic activity (Sigimura et al., 2004; De Meester & Gerber, 1995). Biochemical interactions between proteins, carbohydrates and fats during food processing are also of great importance for the formation of carcinogenic compounds.

9.2 Nonalimentary risk factors for colorectal polyps and cancer

9.2.1 Physical activity

Five percent of cardiovascular mortality rate is caused by low physical activity. 13% is the estimated value for CRC (Slattery & Potter, 2002). This is probably due to the combination of low physical activity, nutrition, lifestyle, and their cross-interactions. The mode of action of physical activity upon CRC is not clear, but decrease in inflammation and insulin levels is supposed. A middle intensive physical activity 3-4 times per week with 1.5 h duration is advisable. Increased physical activities, especially in men, reduce the risk for CRC with 40-50% (Scottish Intercollegiate Guidelines Network. Management of Colorectal cancer. A national clinical guideline., 2003).

9.2.2 Tobacco smoking

Many authors consider CRC as tobacco-related, taking into account the duration of smoking. It is estimated that 12% of the cases of CRC are related to smoking (Courtney et al., 2004). The present study confirmed the role of tobacco smoking as a risk factor for CRP and CRC. The risk is elevated proportionally to the years of smoking. Tobacco smoking disrupts conjugation of glutathione, cytochromes and damages DNA (Pfohl-Leskowitcz et al, 1999). Inhalation of carcinogens from tobacco smoke could trigger microsatellite instability (Yang et al., 2000).

9.2.3 Gender

The incidence of CRC is almost always higher in men (Parkin et al., 1999). Our data support these findings, as the men/women ratio was 1.2/1 in patients with CRP and 1.23/1 in patients with CRC. These differences could be explained with different life style, diet habits, physical activity, tobacco smoking, and consumption of alcohol, usage of NSAID and iron stores. There are and speculations about the protective role of female sex hormones (Crandall, 1999). Hormone replacement therapy in women is not recommended, because of the risk of vascular damages, thromboembolism and breast cancer (Scottish Intercollegiate Guidelines Network. Management of Colorectal cancer. A national clinical guideline, 2003).

9.2.4 Age

The interacting reasons for neoplastic changes in the colon are clinically manifested as a CRC during the second half of life. The mean age of our patients with CRP is 60 years and the mean age of our patients with CRC is 64 year. The mortality rate is increasing in parallel with advancing age according to reported data (Crandall, 1999).

9.2.5 Laxatives use

Frequent use of laxatives is among risk factors according to our data. This result is supported by some other studies (Van Gorkom et al., 1999). Probably, laxatives exert direct toxic effect upon colon mucosa.

9.2.6 Iron and haemochromatosis

The presumable mechanism of iron influence as a risk factor for CRC is connected with the formation of the free radicals from the unabsorbed iron, which damage colon epithelium. Heterozygotic patients who have not developed haemochromatosis are at elevated risk of developing CRC (Altes et al., 1999). The high risk of developing CRP and CRC in our patients who have regularly consumed red meat could be partially explained with the high amount of organic iron, which is available in the heme molecule.

9.2.7 Occupation

Our data show that exposure to petrol and metal is a risk factor for CRP and CRC. It is possible that petrol derivates and metals exert harmful effect upon colonic mucosa. Other exogenous risk factors are: use of anthranoid laxatives, working in petrol industry, production of synthetic materials, wood- and metal processing. Ionizing radiation increases the risk for CRC in radiation treatment of small pelvis after latent period of 15 years (Levin et al., 2002).

9.2.8 Gut flora

Pathological gut flora could produce potential carcinogens, deconjugate bile acids and impair cell DNA molecule (Aries et al., 1969). Our study ascertained the fact that *H. pylori* infection serves as a risk factor for CRC development. Similar results are reported from other authors (Zumkeller et al., 2006). However, more extensive studies are needed to prove

this observation. *H. pylori* could exert negative effect not only on upper parts of gastrointestinal tract, but may be also on colorectal mucosa.

9.2.9 Association with other diseases

Chronic and extensive IBD is connected with increased cell turnover and elevated risk of developing CRC. The risk for development of CRC in patients with IBD depends on the duration (8-10 years) and the extent of disease (Ekbom et al., 1990). We observed malignant transformation in one patient with ulcer colitis and inflammatory pseudopolyposis with duration more than 10 years. Some big population based studies have found slightly elevated risk of developing CRC in right colon in women 15 years after cholecystectomy (Ekbom et al., 1993). Acromegaly is associated with elevated risk for CRC (Jenkins et al., 1997). We do not have any patient with acromegaly and CRP or CRC. We did not observe association between the patients who have undergone cholecystectomy and the frequency of CRC and CRP. The possible mechanism of this risk factor is associated with the constant free leakage of bile in the gut and with the toxic and carcinogenic effect of secondary bile salts.

9.3 The mode of action of protective factors for colorectal polyps and cancer

9.3.1 Probiotics

Our data confirm that Bulgarian yoghurt (containing *Lactobacilus acidophilus/bulgaricus* and *Streptococcus termophylus)* has a protective effect on large bowel polyp formation. Its use as a prophylactic seems perspective since it is traditionally present in Bulgarian national cuisine.

9.3.2 Fibers

According to our study the intake of large amounts of fibers is associated with reduced risk for CRP formation, although conflicting data exist. In a large prospective study, approximately 40% reduction of CRC risk in persons with high fiber consumption was reported (Bingham et al., 2003). The protective action of diet fibers is based on their capabilities to accelerate bowel transit time and enlarged volume, which could diminish exposition time of mucosa to food carcinogens and dilute them. Food fibers bind, inactivate and carry out the luminal carcinogens. Food fibers also decrease fecal pH and inhibit bacterial degradation of different alimentary compounds (Kritchevsky, 1995).

9.3.3 Flavonoids

Flavonoids are powerful antioxidants, which are found basically in fruit, vegetables, seeds, nuts, tea and wine (Middleton & Kandaswami, 1993). According to our data consumption of fruit and vegetables is protective factor for CRC and CRP, whereas regular consumption of tea is protective factor for CRP. Flavonoids inhibit cell proliferation and induce apoptosis (Wenzel et al., 2000).

9.3.4 Selenium

In supranutrtional doses selenium has protective effect against development of CRC, cancer of prostate and lung cancer (Schatzkin et al., 1996). Its mode of action is based on its antioxidant, antiproliferative, and proapoptotic properties (Zhu et al., 2000). Selenium is

basic part of the selenium-dependent glutathione-reductase, which removes free radical and protects the integrity of cell membrane and DNA stability. Selenium also activates tumor-suppressor gene p53 (Seo et al., 2002). Our data in patients who use selenium as prophylaxis confirm its protective role.

9.3.5 Calcium

Our data show that consumption of milk products has protective effect against developing CRC and CRP. Calcium in milk products bind luminal bile and fat acids in insoluble soaps and inhibits proliferation of colon cells (Bostick et al., 1995). Calcium also enhances cell apoptosis in colon mucosa (Fedirko et al., 2009). Probably, calcium has a modulating role in the western diet, rather than anticarcinogenic properties. Optimal intake of calcium in >50 year old persons is 1200 mg per day (Institute of Medicine, Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. Food and Nutrition Board, Washington, DC., 1997).

9.3.6 Fluid intake

Regular intake of mineral water is protective factor for CRP according to our data. Epidemiological studies showed that protective effect of fibers depends on the volume of drank fluids (Lubin et al., 1997). This phenomenon is associated with the decreased concentration of carcinogens, accompanied with a high amount of fluid intake.

9.3.7 Vitamins

There are data that vitamin D, alone or in combination with calcium plays protective role for CRC (Hawk et al., 2004). Vitamin D induces cell differentiation and inhibits cell proliferation and metastatic potential (Giovannucci, 2006). Vitamin A has similar properties as vitamin D, but there is no clear evidence of its protective role for CRC. Significant side effects of vitamin D and vitamin A restrict their usage. No convincing data exist and for the protective role of folic acid for CRC. Combined use of some vitamins with antioxidant properties, like vitamin C and vitamin E, and minerals, like selenium could enhance their impact (Patterson et al., 2000). Our data confirm this result, because we used combination formula composed of vitamin E – 80 mg, vitamin C – 100 mg, β-caroten – 10 mg and selenium – 250 μg) as a prophylactic drug in 12 patients for period of 5 years.

9.3.8 Bioactive compounds

A lot of foods containing bioactive compounds are with protective effect for CRC and CRP according to our data – garlic, tea, fruit, vegetables, onions, grapes, vegetable food, legumes etc. Bioactive compounds include numerous chemical substances, which own anticancer properties (Greenwald, 2002). Some of the most studied bioactive compounds are found in green tea, tomatoes, and different sorts of onions, carrots, lemons and garlic. There are flavonoids and polyphenols in green tea, fruit and vegetables, which possess antioxidant properties. Bioactive compounds d-limonen and perilil alcohol are found in citrus fruit and their impact is associated with the induction of glutathione S-transferase. Red grapes have antioxidant properties, because of the bioactive compound resveratrol. In cereals and in beans are found phytoestrogens, which change the metabolism of steroid hormones. A lot of

bioactive compounds present in traditional Bulgarian cuisine. Therefore, it is reasonable to keep the tradition of healthy Balkan (Bulgarian) diet from the first half of the 20-th century.

9.3.9 Cereals

Consumption of rye and whole grain bread are protective factors for CRP according to our data. Low incidence of CRC and other cancers is observed in countries with high consumption of complex long-chained carbohydrates, which is found in cereals (Gerber, 2003). This fact is based on the presumption that complex long-chained carbohydrates successfully substitute fats as a source of energy. Recommended dose of cereals is 600-800 gram per day.

9.3.10 Fruit and vegetables

Regular consumption of fruit and vegetables is a protective factor for CRC and CRP according to our data. Fruit and vegetables contain vitamins, minerals, biologically active substances and some insoluble fibers. All of them are regarded as protective. The suggested daily dose of fruit and vegetables is 400-800g/day divided in at least 5 meals. The protective role of regular consumption of fruits and vegetables is proven: the replacement of high calorie food with low calorie fruits and vegetables (cabbage and broccoli) decreases overall energy intake and reduce the risk for CRC. Compounds with hypothetical antiproliferative and anticancer action, which inactivate free radicals, are antioxidant vitamins (A, C, E), folic acid, thioethers (garlic, onions, leeks), terpens (citrus fruits), plant phenols (grapes, strawberries), carotenoids (carrots, sweet potatos, water melons), selenium, flavonoids, calcium, etc (Levin et al., 2002). With high consummation of fibres (cereals, fruits, vegetables) the risk for CRC is reduced with 40% (Guidance on Cancer Services. Improving Outcomes in Colorectal Cancers – Manual Update. National Institute for Clinical Excellence 2004). Protective effect of fibers is augmented from the fluid intake, calcium, etc. (Levin et al., 2002).

9.3.11 Dairy products

Our study confirms that dairy products and yoghourt are protective factors for CRC and CRP, but low-fat dairy products must be available, in order to prevent cardiovascular diseases. Low-fat dairy products supply calcium and vitamin D, both of which has protective effect for CRC. The contradictory data about the protective role of dairy products is associated with the quantity of the contained fat (World Cancer Research Fund and American Institute for Cancer Research, Food, Nutrition and the Prevention of Cancer, 1997).

In summary, the intake of fats cause increased influx of bile in the small intestine, whereas part of the fat and bile reaches the large bowel, where bacteria metabolize fat and bile into bile acids and fat acids. These products impair the epithelium of large bowel and stimulate cell proliferation, which is a prerequisite for carcinogenesis of large bowel. The secondary products of bile metabolism and by-products of some foods, which are cooked in certain way, could act like carcinogens, especially in persons with genetic predisposition for development of CRC. The food exerts effect upon intraluminal content and wall of the large bowel, but also part of the digested substances are absorbed and release of the local

hormones and peptides, like insulin and gastrin, is induced. These hormones and peptides could also promote epithelial hyperploliferation. Apoptosis and cell differentiation are suppressed too, and DNA abnormalities could occur (Fig. 1). Adenomatous, hyperplastic or mixed colorectal polyps are morphological sign of the blended influence of genetic and exogenous factors upon the colorectal epithelium. Occurrence and progression of these polyps are evidence for the readiness of the colorectal epithelium to react in this distinct way under the influence of exogenous risk factors and inherited predisposition. Diet fibers by their volume and fluids dilute large bowel content, shorten the bowel transit time and do not permit a long contact of large bowel content with large bowel wall. As a result of bacterial fermentation of the cereal fibers, short-chain fatty acids are produced, which are very important for the metabolism and proper state of large bowel epithelium and contribute to large bowel integrity (Hague et al., 1995). Changed low pH in the large bowel inhibits dehydroxylation and dehydrogenation of bile acids. Changed low pH in the large bowel plays protective role for occurrence of CRC, because dehydroxylation and dehydrogenation of bile acids could result in formation of carcinogenic substances.

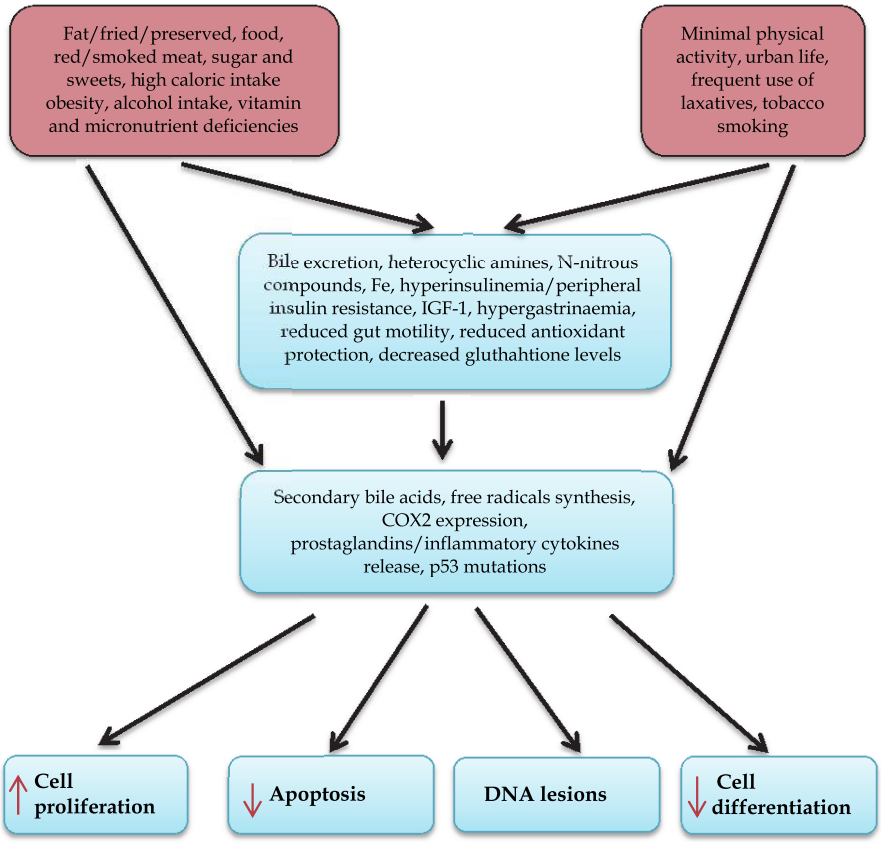

Fig. 1. Possible mechanisms of influence of diet and lifestyle upon pathogenesis of colorectal cancer. IFG-1, insulin-like growth factor-1; COX-2, cyclooxygenase-2.

Micronutrients and bioactive compounds complete their protective role by several mechanisms – in systemic way promote cell differentiation and apoptosis, and support the large bowel integrity, while intraluminally, micronutrients and bioactive compounds participate actively in detoxification of diet and metabolite carcinogens. Influence of the environmental risk factors, especially diet risk factors, could facilitate the clinic expression of recessive alleles for CRC or alleles with low penetration. Diet risk factors could also modulate the time of expression of recessive alleles for CRC. This statement could explain some of the cases of CRC in patients from a generation, which has been migrated from countries with low incidence of CRC in countries with high incidence of CRC (USA, Australia). Often, systemic genetic variations (polymorphisms) could affect the speed of detoxification or the activation of environmental carcinogens. This is happening in the process of the culinary food treatment, during tobacco smoking or from the alcohol metabolites. At the same time, shortage of anticarcinogens could be available in the regular diet.

We must not forget that from the two known etiological risk factors, the first is acquired – diet and lifestyle, and the second one is inheritable – susceptibility. Large bowel polyposis is a very good example of the interactions between exogenous and endogenous factors that take part in large bowel carcinogenesis with different rate of progression. In patients with FAP the progression from benign adenomas to cancer is rapid (2-4 years) due to inherited genetic changes; in other cases longer exposure to certain exogenous factors is needed to cause genetic changes that lead to cancer (the mean age of CRC patients in our group was 64 years); however, in certain subjects the time for neoplastic transformation exceeds life duration. Therefore a good differentiation between these groups and early prophylaxis and screening methods are needed. The most frequently used screening methods include: flexible sigmoidoscopy, fecal occult blood test, large bowel capsule endoscopy (if cheaper), double contrast barium enema, virtual colonoscopy, fibrocolonoscopy, endoscopic polypectomy, histological evaluation of all removed polyps, assessment of risk factors, and genetic testing if possible. In conclusion about 15% of the cases with CRC are hereditary, while the remaining 85% are sporadic. However, in 30% of cases a stronger correlation with dietary habits and lifestyle is suspected, while in 55% a close interaction between host susceptibility and environmental factors is more probable. The above fact leads us to the hypothesis that prevention of CRC is a possible task, which can be achieved by correction of certain exogenous factors.

10. Chemoprevention

Chemoprevention is defined as a usage of a medication or natural substances, which can prevent occurrence of benign or malignant tumor (Hakama, 1998). Chemoprevention is used in every stage of CRC prevention and includes three major groups: medications, non-medications and biologically active substances. Medications include non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, inhibitors of cyclooxigenase-2 (COX-2), 5-aminosalicylic acid (5-ASA), folic acid, ursodeoxycholic acid, difluoromethylornithine (DFMO), dithiolethionine (oltipraz), acetilcystein, etc. Non-medications are: selenium, fibers, calcium, vit A, B, C, D, β-carotene, other retinoids, minerals, etc. Biologically active substances include: limonene and perillyl alcohol (in citruses), resveratrol (red grape), diallyl disulfide (garlic), lycopene (tomatoes), flavanols (green tea), isoflavones – genistein

(soya), dithiolthiones, squalene (olive oil), ferulic and phytic acids (rice). Chemoprevention plays a substantial role in secondary and tertiary prevention of CRC. Also, it could be used for prophylaxis in patients after polypectomy of adenomas with high-grade dysplasia, polyps with invasive carcinomas, patients with familial history for cancer. Patient with IBD and inflammatory pseudopolyposis and require constant chemoprevention with 5-ASA. The most widely used medications include: acetylsalicylic acid, polyvitamins, folic acid, selenium, NSAID. So far, the most consistent data for reduction of polyp recurrence exist for acetylsalicylic acid and folic acid. Still, more large studies, examining the exact medications and possible role, are needed.

10.1 NSAIDs

Mechanisms of chemoprevention with NSAIDs include: inhibition and deactivation of possible carcinogens, inhibition of cell proliferation, promotion of cell differentiation and apoptosis, correction of genetic damages and inhibition of angiogenesis (Gustafson-Svard et al., 1996). Epidemiological studies have shown that NSAIDs and especially acetylsalicylic acid have chemopreventive properties (Lang, 2003). Regression of polyps to 28% is detected in FAP patients, who are treated in a long period with NSAIDs (Steinbach et al., 2000). The regular intake of acetylsalicylic acid and other NSAIDs reduce the incidence of CRC with 30-50% according to retrospective and prospective studies (Janne & Mayer, 2000). However, adenomas are observed in some patients, who are treated with acetylsalicylic acid, which means that chemoprevention cannot substitute completely screening colonoscopy (Sandler et al., 2003). The dose of acetylsalicylic acid is still debatable. Some studies show that reduction of the risk for colorectal polyp occurrence is achieved with lower doses of acetylsalicylic acid (Baron et al., 2003). Side effects of long intake of acetylsalicylic acid, like gastrointestinal hemorrhage and brain hemorrhage restrict the usage of acetylsalicylic acid. There is a need for development and usage of new forms of acetylsalicylic acid and NSAIDs agents, which are much safer, like NO-acetylsalicylic acid (Fiorucci & Del Soldato, 2003). Another possibility is the usage of products and substances of natural origin. For example, natural COX-2 inhibitors are yellow pigment curcumin, resveratrol (in grapes) and omega 3-fatty acids in the fish.

10.2 Folic acid

The presumable protective mechanism of folic acid is not clear, but it is supposed, that the lack of folic acid is associated with hypomethylation of DNA and oncogenic activation. Regular intake of folic acid for at least 15 years reduces the risk of development of CRC (Giovannucci et al., 1998). A study showed reduction of CRC incidence in genetically predisposed persons who use folic acid in high doses. Probably, these persons are vulnerable to methyl group deficiency, as a result of DNA aberrations with low penetration (Fuchs et al., 2002). The risk for CRC is vastly reduced if folic acid is used for a prolonged time, especially from smokers (Scottish Intercollegiate Guidelines Network. Management of Colorectal cancer. A national clinical guideline. 2003). However, there are data from animal studies that folic acid can promote the impact of some carcinogens (Kim, 2003). Moreover, no large studies are available to sustain the chemopreventive role of folic acid.

10.3 Calcium

Protective role of calcium is confirmed in different trials. A result from a study claims that regular daily intake of 3 g calcium as supplement reduce the risk of colorectal adenomas relapse 1 year after their removal. This fact is an evidence of protective action of calcium in the early stages of colorectal carcinogenesis (Baron et al., 1999). Another study reported that high calcium intake is associated with vastly lower risk of development of distal CRC, but not proximal CRC (Wu et al., 2002).

10.4 Ursodeoxycholic acid

The protective role of ursodeoxycholic acid for CRC is probably due to the reduced absorption of the secondary deoxycholic acid, which increases epithelial proliferation and promote carcinogenesis. A study proved that use of synthetic ursodeoxycholic acid is associated with reduced risk of development of CRC in patients with ulcerative colitis and primary sclerosing cholangitis (Peng et al., 1995). Other authors found that administration of ursodeoxycholic acid in patients with primary biliary cirrhosis, who have undergone polypectomy, is connected with vastly reduced risk of CRP relapse (Serfaty et al., 2003).

10.5 Selenium

Abundant data for the role of selenium as a prophylactic substance for the CRC are constantly accumulating. Epidemiological studies have shown anticancer role of selenium since 1970. In some parts of Europe there is low amount of selenium in the soil and European population show tendency of lower intake of selenium in the last 25 years (Rayman, 2000). A lower risk for CRC was detected in persons who take 200 μg selenium daily (Clark et al., 1996). Some authors found lower serum levels of selenium in patients with CRC (Scieszka et al., 1997).

We can conclude that the choice of proper chemopreventive tool is difficult. Such a tool must be effective, cheap, safe and easy to use. It is calculated, that up to 80% of the cases with CRC could be prevented by alteration of diet habits (Cummings & Bingham, 1998). These data oblige us to fully clarify the role of chemoprevention in colorectal neoplasms. Combination of chemoprevention with screening endoscopy is of great importance for reduction of the CRC mortality. The most significant chemopreventive agents are the acetylsalicylic acid and other NSAIDs, antioxidants, calcium and selenium.

10.6 Chemoprevention in our patients

The main indications for applying chemoprevention in our patients were: patients with adenomatous polyposis of large bowel; patients who have undergone endoscopic polypectomy; operated for CRC patients, IBD patients and patients with hereditary syndromes of CRC. 70 of our patients took chemopreventive agents: acetylsalicylic acid, polyvitamins, folic acid, selenium, NSAID, calcium, 5-ASA, ursodeoxycholic acid.

11. Primary prophylaxis of colorectal adenomatous polyps and CRC

Colorectal cancer prevention is divided into three groups: primary, secondary and tertiary. Diet and lifestyle are considered as targets in primary CRC prevention, which includes

modification of the established risk factors for colorectal polyps. These are: limitation of certain foods, beverages and habits; improved physical activity; consumption of protective foods; eradication of *H. pylori*. Important question is whether it is possible to apply primary prophylaxis in CRC and its precursor – adenomatous colorectal polyposis and if risk factors for CRC and CRP are avoidable and at what extent? Considering the growing epidemic of CRC this issue is waiting its prompt answer. What kind of healthy style of life we can offer to threatened people, similarly to the primary prevention in other diseases like cardiovascular disease, ischaemic heart disease and arterial hypertension, and distinct type of cancers? A great part of risk factors for CRC and CRP are associated with the diet, the lifestyle, exogenous carcinogens, some diseases and disease-like conditions. However, some protective factors for CRC and CRP are famous and could be recommended. As a primary prevention in healthy persons change of diet habits, reduction of body weight, refusal of tobacco smoking and alcohol intake are recommended. Preventive role of calcium, magnesium, β-carotene, vitamins, folic acid and selenium for CRC and CRP is still disputable. Acetylsalicylic acid and other NSAIDs for this purpose are not commonly used, because of their adverse side effects (Sandler, 2004). However, if new and convincing data are available, we can try to restrict influences of known risk factors and to cure precancerous conditions and will be able to perform proper primary prevention for CRC and colorectal adenomatous polyposis.

12. Secondary prophylaxis of colorectal adenomatous polyps and CRC

Secondary CRC prevention is used for early detection of premalignant adenomas and cancer in its curative stage. It includes: screening colonoscopy; polypectomy; optimal treatment of IBD patients; chemoprevention and follow-up (Hawk, 2004; Rex, 2000). The aim of secondary prophylaxis or screening is to diminish the mortality of CRC by early detection and treatment of premalignant adenomas and cancer in its curable stage. European and national gastrointestinal and digestive endoscopy societies recommend screening to comprehend all healthy and risk groups of people. CRC screening consists of: digital rectal examination, fecal occult blood test, fecal immunochemical test for haemoglobin/haptoglobin, barium enema, sigmoidoscopy, sigmoidoscopy with fecal occult blood test, colonoscopy (with polypectomy), chromoendoscopy, NBI and high-resolution colonoscopy, virtual colonoscopy - CT or MRI, fecal DNA test (Geissler & Graeven, 2005). A useful test is invented for early detection and follow-up of CRC, similar to the noninvasive serological and fecal tests used for detection of infection with *H. Pylori*. This test is based on the idea, that proliferating cells, especially malignant cells, are expressing special isoenzyme of pyruvate kinase (PK), which plays a significant role in glycolysis. This isoenzyme consists of 4 subunits in healthy cells, while in neoplastic cells there are 2 subunits. This dimeric form M2-PK is found in gastrointestinal neoplasms. Tumor marker M2-PK is found in the blood of 47.8% of patients with CRC, while fecal test is sensible in 80% of cases with CRC (Hardt et al., 2004).

We propose stratification of healthy population in *three* groups: patients with *moderate risk* for development of colorectal polyps and cancer; patients with *elevated risk* for development of colorectal polyps and cancer; patients with *extremely high risk* for development of colorectal polyps and cancer;

The *first* group includes all patients who have no family history for cancer and no personal history for polypectomy or cancer in the past.

The *second* group includes patients with family history for CRC or related neoplasia (stomach, mammary gland, endometrium, ovary, adrenal glands), patients with polypectomy of polyps with low-grade dysplasia, patients with large bowel resection due to CRC (5 years post-surgery), male gender.

The *third* group includes patients: with familial adenomatous polyposis (FAP), with polypectomy of polyps with high-grade dysplasia, patients with large bowel resection due to CRC (up to 5 years post-surgery), with Peutz-Jeghers syndrome, juvenile polyposis, Cowden`s disease, HNPCC, IBD patients, with acromegaly and ureterosigmoidostomy.

The most appropriate follow-up method of patients, who have undergone polypectomy, is colonoscopy. The intervals according to the patients` risk and starting age are summarized in Table 7.

№	Patients	Starting age for screening colonoscopy	Interval for control colonoscopy
1	With average statistical risk for development of CRP and CRC	50 years	10 years
2	With moderately elevated risk for CRC	40 years	5 years
3	With extremely high risk for CRC	10-30 years	1-3 years

Table 7. Starting age and intervals for screening colonoscopy.

13. Tertiary prophylaxis of CRC

Follow-up, chemoprevention and polypectomy are cornerstones of tertiary CRC prvention. Tertiary prevention is performed after surgical treatment for CRC and its aim is elongation of the survival and improvement of the quality of life of patients who have been treated with resection for curable CRC. This purpose can be achieved by treatment of the patient's complaints, which are connected with the primary disease or with the systemic chemotherapy, as well and by disclosure of relapses in early and curable stage. We have not to forget, that occupational and psychosocial rehabilitation are very important in these patients. Large studies, which offer standard approach to these patients, are missing. Nevertheless, the following factors must be considered: tumor stage, general condition of the patient and life expectancy, and the patient's gain from treatment with a new, potentially curable surgeon intervention in case with proven relapse of CRC. 8,4 % of our patients develop metachronous CRC with mean age 69±11 years. The mean difference between diagnosis (CRC) of first and second localization is 6 years (2-15). This is the time for tertiary prophylaxis of CRC.

Follow-up of patients with CRC is achieved by: personal history, physical examination, carcinoembryonic antigen (CEA) test, lab tests, fecal occult blood test, chest X-ray, abdominal ultrasound, echo-endoscopy, CT, MRI, colonoscopy and PET-CT.

In conclusion, primary prophylaxis of the disease is the ultimate aim of every clinical physician. Can we apply the primary prophylaxis in colorectal adenomas and CRC?

Encouraging examples for this possibility exist. Low physical activity, high uptake of saturated fats and arterial hypertension were recognized as risk factors for cardiovascular diseases. For a few years broad public campaigns resulted in dramatic reduction of mortality from coronary heart disease. Similar results are obtained and in some countries, in which restrictive government politics for tobacco smoking exists. No single factor is responsible for CRC carcinogenesis, but combination of some important factors, which are associated with the diet and lifestyle, is crucial.

May be the true pathway is to seek some average healthy diet and lifestyle, which play preventive role for many diseases. This recommendation is especially useful for the persons who are genetically predisposed, because the environmental risk factors can promote faster carcinogenesis.

Revival of the healthy Balkan (Bulgarian) feeding habits from the first half of the 20-th century seems reasonable (Ribarova et al., 2004). More protective foods must be included in our daily meal and this task looks feasible. We have to consume regularly fruit, vegetables, cereals, low-fat dairy products, legumes, poultry, fish, sea products, fibers and to reduce the intake of animal fats, red meat and preserved food. We have to be physical active, restrict alcohol usage, and to avoid tobacco smoking and usage of grilled and fried food.

Many countries introduced a large scale programs for reduction of risk factors and promotion of protective factors for CRC. Besides that, such programs are useful and for prophylaxis of cardiovascular diseases, some other cancers and important metabolite diseases, like diabetes mellitus II type and obesity.

14. Recommendations for prophylaxis of CRC according to our data

You must follow these rules to be protected from colorectal cancer:

1. Do not eat fatty food, smoked meat, fried foods, margarine, pork, red meat and egg-fried food
2. Do not drink alcohol
3. Do not smoke
4. Sustain high physical activity and do not be obese
5. Restrict the intake of refined sugar and white flour products
6. Use plant oil, but not margarine
7. Legumes, fish, low-fat dairy products and Bulgarian yoghourt are good source of proteins
8. Consume at least 5 times per day fruits and vegetables (pears, melons, water melons, grapes, peaches, onion, garlic, pepper)
9. Prefer poultry, white meat, hares and fish from the meat
10. Healthy cooking includes decrease of the fat added in the food, reduction of the cooking temperature and refraining from the use of grilled food
11. Do not use regularly laxatives
12. Avoid contact with petrol
13. Avoid usage of preserved foods and prefer local, season`s, fresh or frozen fruits and vegetables

14. Fasting is good
15. Do endoscopic polypectomy if you have adenomatous colorectal polyps
16. Eradicate Helicobacter pylori if you are infected
17. Use daily acetylsalicylic acid if you do not have any contraindications
18. Make a screening colonoscopy after you reach 50 years, and if you are in risk group (familial predisposed to colorectal cancer or associated localization – stomach, endometrium, breast, ovary or if you have preceding polypectomy) – after you reach 40 years. Consider genetic testing if you are in risk groups

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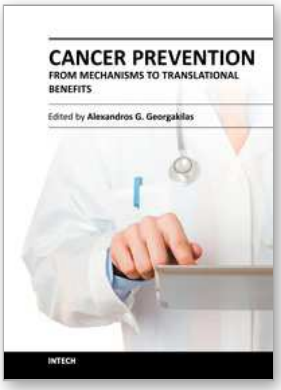

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This unique synthesis of chapters from top experts in their fields targets the unique and significant area of cancer prevention for different types of cancers. Perspective readers are invited to go through novel ideas and current developments in the field of molecular mechanisms for cancer prevention, epidemiological studies, antioxidant therapies and diets, as well as clinical aspects and new advances in prognosis and avoidance of cancer. The primary target audience for the book includes PhD students, researchers, biologists, medical doctors and professionals who are interested in mechanistic studies on cancer prevention and translational benefits for optimized cancer treatment.

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