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Review article

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PHARMACOLOGICAL AND DIETARY FACTORS IN PREVENTION OF COLORECTAL CANCER

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Colorectal cancer (CRC) is the third most prevalent neoplasm worldwide and fourth most frequent reason of cancer-related death throughout the world. About 70% of malignant tumors are related to lifestyle and environmental factors, and better knowledge of their significance might reduce the prevalence of CRC. The cyclooxygenase-2 (COX-2) inhibitory and other direct and indirect pathways of aspirin are translated to inhibition proliferation and enhanced apoptosis of cancer cells. Many studies showed the benefits of aspirin in reducing the risk of CRC development, cancer-related mortality and adenoma prevalence rate in general population, but not in high risk populations. The role of sulindac in CRC prevention is uncertain and the use of this drug is rather uncommon. Celecoxib - COX-2 selective inhibitor- showed efficacy in decreasing of colon adenoma recurrence only in some studies. The protective role of microelements is controversial. The beneficial effects of supplementation of selenium, calcium, folic acid, methionine, antioxidant supplements and probiotics are still not certain. A high energy diet consisting of red meat, animal fat, highly processed foods and unsaturated fats increases the risk of CRC. Carcinogenic role of fat and cholesterol depends on increased production of primary bile acids. The importance of milk and dairy products in CRC prevention is controversial. Fruits, vegetables and grain are considered to have protective effects against adenoma and CRC. Excessive alcohol consumption, smoking, physical inactivity are considered as important CRC risk factors. This article briefly summarizes current state of knowledge about the role of pharmacological and dietary prevention of colorectal cancer. Moreover, it indicates that despite many studies some aspects of this issue are not clear and require future studies.

Key words: *colorectal adenocarcinoma, carcinogenic factors, prevention, preventive pharmaceuticals, diet, cyclooxygenase-2, microelements, life style*

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent neoplasm worldwide after lung and breast cancer (1). According to GLOBOCAN data, about 14.1 million new carcinoma (of all organs) cases and 8.2 million deaths related to this disease occurred in 2012 worldwide. CRC with about 1.3 million new cases and 0.7 million deaths each year is the fourth most frequent reason of cancer-related death throughout the world (2).

Main causes of an increased occurrence of CRC, irrespective of genetic factors (3) and family history (4) are: aging of the population (5), inflammatory bowel diseases (6), unhealthy diet, smoking, lack of physical activity (7) obesity (8) and diabetes (9). It is estimated that even 70% of malignant tumors are related to lifestyle and environmental factors (10, 11). Effective prevention by introducing some systems leading to diet and tobacco control, the use of early detection tests and providing appropriate education could be the way to decrease the incidence of CRC and death rate.

PHARMACOLOGICAL FACTORS IN COLORECTAL CANCER

Acetylsalicylic acid

The preventing role of aspirin in carcinogenesis possibly depends on the modification of the COX enzymes activity, responsible for the conversion of arachidonic acid to prostaglandins (12). It is known that COX-2 is up-regulated in CRC and in colorectal adenomas (13, 14). COX-2 plays a role in the development and growth of CRC by its effect on production of cytokines, control of cell apoptosis and migration or release of angiogenic factors (15, 16). The chemopreventive action of aspirin in CRC is direct, related to suppression of prostanoids by inhibition of COX-1, and also indirect - through its effect on platelets (17). The platelets are activated in response to mucosal injury and may interact with stromal cells. This phenomenon may lead to the release of several mediators involved in cell growth and

angiogenesis and may contribute to epithelial cell transformation in the gastrointestinal tract. Platelet-derived cytokines and growth factors may up-regulate COX-2 expression in intestinal mucosa cells; however, low-dose aspirin affects platelet COX-1, but coxibs are selective inhibitos of COX-2. The chemopreventive effect of low-dose aspirin depends on suppressing platelet activation at sites of intestinal mucosal injury (18).

Activated platelets release some important mediators such as thromboxane-A2 (TXA_2) and prostaglandin E2 (PGE_2) as well as angiogenic and antiangiogenic factors (19, 20). Increased COX-1 dependent PGE_2 levels reflect the suppression of the prostaglandin-catabolizing enzyme (15-prostaglandin dehydrogenase), which was described to play a role in the early stages of tumorigenesis (21). Enhanced PGE_2 production in epithelial cells leads to disfunction of apoptosis and promotes accumulation of genetic mutations what is the crucial factor for loss of proliferative control. Aspirin-mediated inactivation of platelets may also restore antitumor reactivity by blocking the release of paracrine lipid as well as protein mediators which can induce COX-2 expression in adjacent nucleated cells at sites of mucosal injury (13, 14). The anti-CRC activity of aspirin seems also to be independent of COX-related pathway by promoting apoptosis (22, 23) and inhibiting proliferation of cancer cells. These effects are dependent on: a) inhibition of nuclear factor kappa B (NF-κB) signaling, Wnt/β-catenin signaling (24, 25) and extracellular kinases signaling, b) the acetylation of extra-COX proteins (24), c) induction of caspases 8 and 9 (25). The beneficial effect of aspirin is also dependent on the diminution of microsatellite instability in CRC cells (26, 27) and modulation of polyamine synthesis by induction of spermidine/spermine N1-acetyltransferase (28, 29).

In large population study including 662,424 participants, reduced risk of CRC mortality was caused by aspirin given at least 16 times per month for 6-years (30). Similarly, in nationwide Health Professionals Follow-up Study (HPFS) and the US Nurses, Health Study (NHS) the regular use of aspirin reduced CRC prevalence respectively by 21% in men and 23% in women (31, 32). Daily aspirin intake is associated with a significant reduction in the incidence and recurrent colorectal adenomas in patients with previous colorectal cancer (33). Interestingly, in the Baron study the relative risk (RR) of adenoma reappearance was lower in patients who received 81 mg of aspirin than in these who received 325 mg of it (34). The clear benefits of aspirin in high risk populations like patients with Lynch syndrome or familial adenomatous polyposis (FAP) (35) have not been evidenced; however, in Colorectal Adenoma/Carcinoma Prevention Program 1 (CAPP1) a decline in polyp size in FAP patients treated with aspirin was found (36).

Meta-analysis of randomized trials showed that aspirin used for 5 years reduced incidence and mortality related to CRC by 30 – 40% after 20 years of follow-up (37). Aspirin reduces also the risk of obesity-related cancers, including CRC (38). This drug stimulates AMP-activated protein kinase (AMPK) and inhibits mTOR signaling in colon cancer cells (39). The same mechanisms are shared by several nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or diclofenac (40, 41).

Many clinical trials of III phase demonstrated decrease of adenoma prevalence rate after polypectomy or carcinoma resection, which was statistically significant already after one year of aspirin administration. The time of administration and the dose of aspirin correlated with reduction of relative risk of CRC development and death caused by this cancer (42). The results of uKCAP study on the group of 945 patients, assessing the impact of the administration of 300 mg of acetylsalicylic acid showed significant decrease of adenomas occurrence by 21% (43).

Low-dose aspirin administration was shown to reduce the incidence of cancers, but its role in the treatment of any type of cancer is uncertain (44). Some studies indicated that low-dose aspirin reduced the incidence and mortality of CRC (44-49). There is also the evidence that aspirin, used as an adjuvant treatment of cancer, may reduce metastatic spreading and may increase overall survival time of patients with cancer (46). The suggestions have been done that targeting platelet COX-1 with low-dose aspirin treatment decreased metastasis rate by averting the stem cell mimicry of cancer cells; this phenomen could be associated with enhanced pro-aggregatory effects induced by platelet-tumor cells crosstalk (4). The adjunct aspirin treatment leads also to an interruption of tumor growth and retardation of metastatic spread by inhibiting angiogenesis, enhancements of DNA mismatch repair and cellular apoptosis as well as an abrogation of invasiveness (44). Study by Elwood *et al.* (44) suggested that aspirin administration brings a reduction of CRC mortality by about 50%, but inhibition of cancer growth by aspirin was restricted to tumors expressing mutations in PIK3CA and HLA class I antigen or showing COX-2 overexpression. Among patients with CRC, these characteristics regarded 17%, 54% and 50%, respectively. Estimation of other authors suggest a reduction of only 30% of it (50). However, on the basis of these reports, it should be suggested, that aspirin benefit in CRC may be restricted to patients with tumors expressing certain genetic mutations. Moreover, other benefits of low-dose aspirin administration like reductions in metastatic spread, vascular events like venous thromboembolism may also vary inter-individually. This interindividual variability to low-dose aspirin therapy in CRC treatment needs further studies. Feasible, reliable biomarkers which will allow to characterize the genetic, pharmacokinetic and pharmacodynamic determinants in individual CRC patients are needed (51). In the light of mentioned above studies it seems, that the information about the benefits relevant presence to the administration of aspirin should be given for all patients with CRC, independently of the presence of biomarkers (44). However, U.S. Preventive Services Task Force Recommendation Statement (USPSTF) recommends initiating low-dose aspirin use for the primary prevention of CRC in adults aged 50 to 59 years who are not at increased risk of bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (B recommendation) (52). The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CRC in adults younger than 50 year and in adults aged 70 years or older (52).

Sulindac

Sulindac belongs to NSAIDs and its direct mechanism of antinflammatory action remains unknown, however it is thought to be an inhibitor of COX-1 and COX-2 enzymes, downregulating prostaglandin synthesis. This drug has a history of extensive investigations of his role as a potent chemotherapeutic drug for treatment of colon and other cancers. There are reports showing that sulindac (and its oxidation and reduction metabolites) have a pro-apoptotic activity in cancer cells in animal models (53-56). Mechanisms of anti-neoplastic activity is not clear. However, it was shown that sulindac induces apoptosis of colon cancer line cells *in vitro* by downregulation of survivin an anti-apoptotic protein overexpressed in CRC (55). Other study determining the possible mechanism of sulindac action in colon cancer has shown that sulindac indicates degradation of beta-catenin protein, which is another protein over-accumulated in CRC (56).

Sulindac administration was shown to decrease the number and size of polyps in patients with FAP. One study showed that sulindac at the dose of 150 mg twice a day given for nine months reduced the number and size of colorectal adenomas in patients with FAP, but after one year follow-up this treatment brought only partial efficacy (57). In the other study sulindac administered 400 mg once a day for six months brought a significant regression both in duodenal and rectal polyps (58).

Despite these findings, sulindac is not commonly recommended in this indication and total proctocolectomy is still the procedure of choice in patients with FAP. Sulindac, as other NSAIDs is generally well-tolerated. However, as other NSAIDs, it can cause pepitic-ulcer disease (59). There is also a risk of minor and major allergic reactions - including severe Stevens-Johnson syndrome/toxic epidermal necrolysis (60).

Summarizing, sulindac administration probably could have significance in CRC prophylaxis, however, due to unpredictable results and rare, but possibly relevant side effects the application of this drug is not recommended.

Selective COX-2 inhibitors

COX-2 expression and PGE_2 synthesis are elevated in CRC. The effectiveness of NSAIDs may be attributed to inhibition of cyclooxygenase (COX) enzymes. Moreover, NSAIDs could modify systemic inflammatory response in patients with primarily non-metastatic colorectal cancer (*Table 1*) (61).

The efficacy of celecoxib was proved in further smaller studies (62) but was challenged by others (63). Celecoxib was approved by FDA in 1999 as an adjunct to treat FAP. However, regulatory post-market clinical studies were not completed and the indication for FAP treatment was removed from celecoxib's product label (61).

The effects of NSAIDs on the development of colorectal cancer according to some studies are presented in *Table 2*.

Statins

In many clinical trials statins showed the protective effect on the development of CRC. In the large clinical study the morbidity of CRC during statin administration decreased by 47% compared to the control group (65).

In meta-analysis of six studies including 13,239 persons the median proportions of patients with any adenoma taking statins was 29.7% and not taking statins 31.2% (difference insignificant). However, with reference to advanced adenoma

Table 1. Effects of NSAIDs on cancer-related systemic inflammatory response in patients with primarily non-metastatic colorectal cancer, (according to Park J.H. *et al*. (61), modified).

Drug	Study type	Patient group	Duration (days)	Outcome measure	Outcome	Comment
Aspirin	Non-randomized, controlled study Sciulli (2005)	CRC (10)	5 preop	Platelet activation	↓COX-1 activity, platelet activity	Increase in platelet activation in CRC patients compared to controls
Ibuprofen	Non-randomized, controlled study McMillan (1995)	CRC (9) (3 Dukes D)	8 – 11	Acute phase reactants	↓CRP, Il-6, cortisol, platelet count; no change in albumin, insulin, CEA, WCC	
Indomethacin	*Ex vivo* and histopathologic study Yaqub (2008)	CRC (12) (5 Dukes D)	N/A	Tumor and lymph node Treg infiltration	↑Tumor and lymph node infiltration by Treg, COX-2 expression by lymph node Treg↓ activity ex vivo	NSAIDs may improve systemic and local immune responses by inhibiting circulating Treg activity and COX-2 expressing Treg cells identified in regional lymph nodes
Indomethacin	*Ex vivo* Han (1983)	CRC (29) (11 Dukes C)	N/A	MILPR	Increase in MILPR	MILPR impaired in up to 52% of CRC patients
Indomethacin	*Ex vivo* Balch (1984)	CRC (57)	N/A	MILPR	Increase in MILPR	MILPR impaired in CRC patients compared to controls
Indomethacin	*Ex vivo* Yaqub (2008)	CRC (12) (5 Dukes D)	N/A	Anti-CEA immune response	↑Anti-CEA immune resonse by inhibition of Treg activity	
Celecoxib	Non-randomized, age- and sex-matched controls Konturek (2006)	Rectal (10)	14 preop	Acute phase reactants, gastrin and progastrin	↓TNF□, Il-8 serum and tumor gastrin, serum progastrin	Effects mediated by NF□□ inhibition, increase in tumor COX-2 expression
Indomethacin Celecoxib	Randomized, controlled trial Lonnroth (2008)	CRC (28) (1 Dukes D)	3 preop	T1Ls	↑$CD4^+$, $CD8^+$, Tumor infiltration, ↓Treg tumor infiltration	

Abbreviations: CEA, carcinoembryonic antigen; COX, cyclooxygenase; CRC, colorectal cancer; MILPR, mitogen-induced lymphocyte proliferative response; preop, preoperatively; PTL, peritumoral lymphocytes; TIL, tumor infiltrating lymphocytes; Treg, regulatory T-lymphocytes.

Table 2. NSAIDs and development of colorectal cancer (according to Dulai P.S. *et al*. (64), modified). Characteristics of trials included in review of chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia.

Design	Study group	Efficacy outcomes			Author
		Any neoplasia	Advanced neoplasia	Colorectal cancer	
Multi-center, double blind, placebo controlled, RCT, parallel, stratified randomization	Placebo	73/159	4/159	2/159	Ishikawa, 2014
	Aspirin 100mg	56/152	3/152	2/152	
Multi-center, double blind, placebo controlled, RCT, parallel, non-stratified block randomization	Placebo	58/218	7/218	1/218	Pommergaard, 2015
	Aspirin/vitamin D/calcium	52/209	5/209	1/209	
Multi-center, double blind, placebo controlled, RCT, factorial, stratified block randomization	Placebo	70/162	14/162	1/162	Baron, 2003 Cole, 2007
	Aspirin 81 mg	65/166	10/166	1/166	
	Aspirin 325 mg	71/158	18/158	1/158	
	Folate	87/168	27/168	0/168	
	Folate + aspirin	134/333	30/333	3/333	
Multi-center, double blind, placebo controlled, RCT, factorial, stratified block randomization	Placebo	56/204	30/204	3/204	Logan, 2008
	Aspirin 300	49/217	22/217	2/217	
	Folate	65/215	33/215	4/215	
	Folate + aspirin	50/217	19/217	1/217	
Multi-center, double blind, placebo controlled, RCT, parallel, stratified randomization	Placebo	264/557	56/557	1/557	Arber, 2006
	Celecoxib	270/840	42/840	6/840	
Multi-center, double blind, placebo controlled, RCT, parallel, stratified randomization	Placebo	354/608	99/608	3/608	Bertagnolli, 2006
	Celecoxib	465/1214	79/1214	4/1214	
Multi-center, double blind, placebo controlled, RCT, parallel, stratified block randomization	Placebo	53/129	11/129	2/129	Meyskens, 2008
	Sulindac	17/138	1/138	0/138	

Abbreviations: NSAIDs, non-steroid anti-inflammatory drugs; RCT, andomized controlled trial.

these proportions were 7.7% and 11.3% (difference significant). The conclusion from this meta-analysis was that prolonged use of statins is associated with a reduced risk of advanced adenoma, but not any adenoma (66). The other meta-analysis performed on Scottish cohort of patients with CRC indicated that statin use was associated with improved survival, but this association was weak and varied markedly between studies (67).

Summarizing, administration of statins has probably a weak prophylactic effect on CRC development. Moreover, the common use of these drugs may have impact on prevalence rate of CRC.

Sex-hormone substitution

A cohort of 214 162 postmenopausal women enrolled in the National Institutes of Health-American Association of Retired Persons Diet and Health Study. In this group 2014 incident cases of CRC that occurred over a mean follow-up of 8.2 years. Age at menopause and age at birth of first child were positively associated with the risk of CRC. In the subgroup of women with no history of hormone therapy use, age at menarche and parity were inversely associated with the risk of CRC. These data support a role of sex hormones in CRC tumorigenesis and indicate that greater endogenous estrogen exposure may increase the risk of CRC in postmenopausal women (68).

MICROELEMENTS AND OTHER COMPOUNDS

The results of the studies on role of microelement deficits in development of CRC are equivocal and the recommendations for dietary supplementation of microelements do not exist. The beneficial effects of selenium, magnesium and calcium (>1250 mg/day) or folic acid and methionine on CRC prevention were suggested, but have not been convincingly proven in clinical studies (43, 69).

Alpha lipoic acid

Alpha lipoic acid (ALA) is derived from octanoic acid, which is essential for aerobic metabolism. ALA inhibits the initiation and promotion stages of carcinogenesis. It also induces apoptosis

of human colon cancer cells by pro-oxidant mechanism that is triggered by an increased uptake of oxidizable substrates into mitochondria (70). The results of experimental studies suggest that ALA could be considered as a chemopreventive agent (71).

Selenium

Anticancerogenic effect of selenium depends on the protection of DNA against damage and improvement its reparative capabilities. A decrease in number of mutations (72), induction of apoptosis through the activation of caspase-3, and modulation of glutathione and mitochondrial functions were evidenced in experimental studies (73). An inverse association between serum selenium level and occurrence of advanced CRC was also found in active smokers (74). The risk of adenoma recurrence in patients who had undergone a polypectomy and were supplemented with preparations containing selenium and other antioxidants was pursued. A statistically significant role of antioxidants in reduction of the risk of adenoma recurrence was showed (75).

Calcium

The molecular role of calcium in carcinogenesis includes the control over cell proliferation, differentiation and apoptosis (12). Calcium is involved in the gene transcription through the cAMP response element-binding protein (CREB) (76). Many studies indicated relatively small prophylactic anticarcinogenic effect of calcium. The calcium had no effect either on the number, size and distribution of rectal polyps in patients with FAP (77) or the risk of adenomas recurrence (78). However, in other study involving 930 participants who received daily 1.2 g of calcium for 4 years the risk of adenoma prevalence and average number of adenomas were reduced (79). Protective role of calcium against formation of new adenomas was also supported by other study (80).

Population studies provide also inconsistent data. Sixty studies enrolling 26,335 CRC cases indicated protective role of calcium against CRC (81) and the study performed on 36,282 postmenopausal women receiving calcium 1 g/day plus vitamin D 400 IU/day for 7 years not showed its effect on CRC incidence (82).

Folic acid

Folic acid plays the role in prevention of carcinogenesis by regulating synthesis, repair and methylation of DNA (12, 83). Decline in folate supplementation has been suggested to increase the risk of colon carcinogenesis (12), however, the results of studies are ambiguous. Baron *et al.* (84) showed a protective effect of folic acid against CRC, but this effect disappeared after adjustment of dietary fiber and fat for intake. Chronic alcohol intake can reduce circulating folate levels, thus increasing risk of adenoma recurrence (84). Logan *et al.* did not support the beneficial effect of folic acid supplemented with 0.5 mg/day for 3 years in 945 patients with adenoma (43). In placebo controlled trial including patients with a history of CRC who received folic acid at a dose 1 mg/day with or without aspirin for 3 years the outcome was not different than placebo group (85). Also a meta-analysis including 13 randomized trials suggested that folic acid supplementation has not a chemopreventive effect on CRC (86). In summary, despite theoretical rationale for use of folic acid for prevention of CRC the clinical evidence seems to deny this hypothesis (87).

Probiotics

There is a growing number of evidence on the role of gut microbiota with carcinogenesis. A lot of of recently published basic and translational studies show that there is a link between dysbiosis, subsequent immunological responses and CRC-carcinogenesis. A systematic review of thirty-one original articles on the role of colon microbiota in colorectal carcinoma was published recently by Borges-Cahna *et al.* (88). This analysis has shown that some bacteria (Fusobacteria, Alistipes, Porphyromonadacae, Coriobacteridae, Staphylococcaceae, Akkermansia spp., Methanobacteriales spp) colonies are significantly increased or decreased (Bifidobacterium, Lactobacillus, Ruminococcus, Faecalibacterium spp., Roseburia, Treponema) in patients with CRC.

Potential bacterial metabolites, inflammatory pathways and effects of intraluminal intestinal events on carcinogenesis is currently matter of great interest. Recent next-generation sequencing studies of the intestinal microbiota now offer an unprecedented view of the etiology of sporadic CRC and have revealed that the microbiota associated with colorectal cancer contains bacterial species that differ in their temporal associations with developing tumors (89). Some bacterial metabolites *i.e.* secondary bile acids can promote carcinogenesis (90). On the other hand probiotics produce short chain fatty acids (SCFA) such as butyrate, acetate, propioniate and valerate - which are beneficial for colonocytes and have cancer-suppressive and anti-inflammatory effects (90). Altough further investigations are yet needed, probiotics producing SCFA seem to be safe and efficient in treatment of CRC. In recent clinical trial it was demonstrated that patients with CRC receiving probiotics had lower infection rate and shorter hospital stay (91).

DIETARY FACTORS

Consumption of various natural and synthetic substances for cancer prevention is hot topic discussed in the recent decades (79). Some authors claim that up to 70% of all cancers are associated with diet and even 90% of CRC may be preventable through dietary modifications (92). It is also known that dietary deficiencies may diminish the sensitivity to genetic damage and alter carcinogen metabolism (93).

Fat, meat and food processing

Many studies indicate that unhealthy diet has an important impact on the development of CRC, and an optimal diet could have preventive role (94-96). A high-energy diet consisting of red meat, animal fat, highly processed foods, and unsaturated fatty acids leads to overweight and obesity and increases the risk of CRC. Alimentary products that are formed during thermal conditioning at temperature above 100ºC have carcinogenic properties (97, 98). According to two large cohort studies, an intake of processed red meat was positively associated with risk of CRC, particularly located in distal colon (99).

Carcinogenic role of the fat and high-cholesterol meals depends on increased liver production and biliary excretion of primary bile acids as well as a consecutive rise of concentration of toxic secondary bile acids in the colon (due to decomposition of primary bile acids by microbiota). Together with increased synthesis of triglycerides and fecal pentanes, the colon may be exposed to several different carcinogens. Total amount of consumed meat has the minor importance, but the intake of red meat (beef, pork, lamb) and pure fat has considerable significance on CRC risk. The technique of meal preparation has also the great importance. The baked and barbecued meat releases many carcinogens in high temperature. Besides, treating the meat with curing, smoking or ripening and using fragrances, flavors and coloring agents are in relation to increased risk of CRC (100-107).

Consumption of products rich in omega-3 like fish and omega-6 like olive oil (108-110) could decrease the prevalence of CRC.

It is not clear if milk and dairy products are associated with a reduction of CRC risk (83, 111). Alkaline intestinal pH, which is common in persons using diet low in plant fibers and rich in animal fats, also may increase the carcinogenic and toxic effects. Some protein fermentation products such as ammonia, phenols and hydrogen sulphide can also be toxic and increase the risk of carcinogenesis (112, 113). The large geographical differences of CRC might be dependent on the amount of red meat consumed within given population, however, large epidemiologic studies did not confirm these assumptions.

Obesity itself also is considered as an important risk factor of CRC (114). Recently published large meta-analysis of nineteen prospective cohort studies identified a total number of 12,837 CRC cases among 1,343,560 participants (115). Authors stated that greater waist circumference and waist-to-hip ratio are significantly associated with increased risk of total colorectal cancer, colon cancer as well as rectal cancer. Current concepts on mechanisms underlying association between CRC and obesity include the role of obesity-induced insulin resistance, obesity-related inflammation and deregulation of immune system (116, 117). Insulin and insulin-like growth factor-1 (IGF-1) are active mitogens, which can promote growth of cancer cells and their elevated levels correspond with increased risk of CRC.

Fruits, vegetables, grain

In retrospective clinical studies the consumption of fruits, vegetables and grain showed protective effects on development of adenoma and CRC. From this point of view, fruits and vegetables including soft fruits such as berries may be taken into account to prevent CRC due to their chemopreventive or even chemotherapeutic properties (118). Berries are rich in natural compounds including minerals, vitamins, fibers and polyphenolic phytochemicals (118-121). In recent years the polyphenolic compounds of berries are largely investigated due to their antioxidant effects (122-124). Generally, it was evidenced that berries and their bioactive components suppress inflammation, oxidative stress, angiogenesis and proliferation through the modulation of multiple signaling pathways such as NF-κB, Wnt/β-catenin, PI3K/AKT/PKB/mTOR, and ERK/MAPK. Certain human studies have shown that consumption of berries can prevent from CRC, especially in high-risk patients with inflammatory bowel diseases, FAP or aberrant crypt foci (125). European clinical study including 500,000 subjects from 10 European countries (EPIC - Study) showed significant relationship between development of CRC and daily consumption of the fiber-reached diet after 5 years of follow-up. Nonetheless, an evidence of association between intake of fruits and vegetables and the decreased risk of CRC is still insufficient (126-129).

OTHER CARCINOGENIC FACTORS

Excessive alcohol consumption, smoking and physical inactivity are considered as important CRC risk factors.

Alcohol and smoking

Clinical studies regarding alcohol abuse are ambiguous. Total amount of consumed alcohol independently of its kind may be crucial for accumulated risk of CRC. In persons drinking 25, 50 and 100 g of alcohol daily an estimated relative risk of CRC development is 1.14, 1.21, 1.32, respectively. The deficiency of folic acid and methionine additionally increase the risk of cancer (38).

Clinical studies indicate, that smokers have 2 – 3 times greater risk of development of adenomatous polyps of large bowel than non-smokers. American studies showed 50% increase of CRC prevalence risk in smokers > 20 cigarettes/day and 40% increase of risk in patients with 35 package-years. This rise of risk is probably dependent on genetic polymorphisms of N-acetyltransferase and cytochrome P450 (42).

Meta-analysis of 42 studies and the trials performed by Botteri *et al.* showed that the risk of adenomas is increased not only in the current but also former smokers as compared with persons who never smoked (130, 131). The association was stronger for high-risk adenomas than for low-risk adenomas (130). Paskett *et al.* suggested that smoking increases the risk of cancer of the rectum but not of other parts of the colon (132). In other studies (9, 133, 134) the long-term smoking increased the risk of CRC with no specific location.

Physical inactivity

Regular physical activity has positive effects on general health and is associated with lowering risk of CRC (135). A meta-analysis of 52 studies published by Wolin *et al.* (136) has shown a significant reduction of CRC risk in physically active women (21% reduction of CRC incidence) and men (24% reduction of CRC incidence) in comparison to inactive population. What is more, recently it was suggested that lifestyle recommendations concerning physical activity could improve survival after CRC treatment. Ratjen *et al.* has evaluated physical activity in a group of male and female (n = 1376) CRC survivors, showing that physical activity was inversely related to all-cause mortality (137). Sedentary lifestyle as well as a higher amount of TV viewing were associated with higher mortality. These findings suggest that CRC survivors should be recommended to keep active.

Lifestyle and dietary factors in perspective of molecular pathological epidemiology studies

Molecular pathological epidemiology (MPE) is a relatively new field of research which combines epidemiological investigations with pathological and molecular research to explore (epi)genetic molecular pathways leading to disease (138). This multidisplinary field explores also the interrelationship between exogenous and endogenous factors, tumoral molecular signatures and tumor progression (139). A wide variety of endogenous and exogenous factors like drugs, diet, alcohol, obesity, environment, smoking and microbiota, individually or in combination, can modify phenotypes of cancer, leading to interpersonal heterogenity (140). According to MPE research, an exposure or risk factor can be connected to specific pathogenic signatures (141). MPE approach can yeald a more accurate risk measure (139, 140).

There is a number of MPE studies showing the importance of diet and lifestyle factors for CRC occurrence and survival. Moreover, future worldwide studies considering epidemiology of colorectal cancer should focus on researching nutrient-gene interactions towards the goal of improving personal treatment as well as prevention strategies (142). Interactions between genetic factors and environmental factors, like obesity, aspirin administration, alcohol consumption, vitamin D or polyunsaturated fatty acids intake are considered in respect of this issue. For example increase of body mass index (BMI) increases risk of colorectal cancer in CTNNB1-negative but no in CTNNB1 - positive patients (143). Independently of this finding, greater colorectal cancer survival was observed in those who were CTNNB1-positive (143) and for individuals carrying the mutated PIK3CA gene (144, 145).

Aspirin chronic administration has been associated with a lower incidence of colorectal cancer for subjects with the wild-type BRAF gene. It was observed a strong beneficial effect of aspirin for PIK3CA-mutated colorectal cancer but this effect was not observed for PIK3CA-wild-type cancer (145). It was suggested, that PIK3CA mutation in colorectal cancer may be a predictive biomarker for response to aspirin; however, its prognostic role may not be significant (146).

Colorectal cancer risk was lower in aspirin users with high expression of 15-PGDH (147). Reduction risk of colorectal cancers, particularly with activated CTNNB1 is observed among patients with rs6983267 GT/TT genotypes but not among individuals with GG genotypes (148). Chemopreventive effect of aspirin and also other anti-inflammatory drugs (NSAIDs) on colorectal cancer risk is also dependent on genetic variation at two single nucleotide polymorphisms (SNPs) at chromosomes 12 (rs-2965667) and 15 (rs16973225) (149).

Regular alcohol drinkers with low IGF2 DMR0 methylation have an increased risk of colorectal cancer (150).

Although traditional epidemiological studies show a link between smoking and CRC, this association is even more convincing and complex when we use molecular classification in MPE studies (151). These studies support the data that the risk of CRC is increased up to two-fold for tumors driven by microsatellite-instability pathway (MSI) and chromosomal-instability pathway (CIN), while there are weak associations for tumors not exhibiting these phenotypes (*i.e.* tumors of the traditional adenoma-carcinoma pathway) (152-155). These data may suggest that MPE studies show new light on patterns of association of CRC and smoking.

MPE data about the association between alcohol intake and CRC is conflicting and heterogenous. Study by Bongaerts *et al.* proved that alcohol had not relationship with tumors associated with mutations in the KRAS gene (156). On the other hand, study published by Jayaskera *et al.* concluded that alcohol increased risk of KRAS mutated and BRAF wildtype/KRAS wildtype tumors driven by adenoma-carcinoma pathway, but not with BRAF mutated tumors driven by serrated adenoma pathway (157). One of the reasons of mentioned discrepancies may be that there are some genes in relation to alcohol metabolism not accounted in MPE studies (158).

Lifestyle factors indicating energy balance including: BMI, waist and hip circumference, adult-attained height, caloric intake and physical activity have been investigated in MPE research with respect to markers of the serrated neoplasia pathway (159-162). There are no strong proofs of association between APC, KRAS and CIN driven CRC and body growth as well as obesity; however, overweight and obesity strongly increase risk of CRC tumors. Taller individuals have an increased risk of developing tumour with a BRAF mutation or MSI (159). Body size, especially central adiposity increases the risk of both CIMP and non-CIMP tumors (160). Body fat at younger individuals may also influence this risk. Physical activity appears to decrease the risk of CRC regardless of these molecular subtypes (160). There have been shown the data on the association of BMI and microsatellite instability in CRC and they could suggest a link between overweight and obesity with sporadic MSI-high colorectal cancer in women (161). Other authors suggested that despite multiple pathways to colon cancer development, data did not support a unique role for dietary folate, alcohol, vitamins B6 and B12 as well as methionine in CpG island methylator phenotype (162).

In future, MPE studies could be a valuable source of information concerning patterns of epigenic instability in CRC pathophysiology. Evaluating high quality studies and pooling data from large groups of patients may improve our knowledge about carcinogenesis of CRC.

OTHER ASPECTS OF MOLECULAR PATHOLOGICAL STUDIES

There is a lot of pathways and cellular signals influencing carcinogenesis. The Hippo pathway in one of them and it is the major regulator of organ growth and proliferation. The important target of the Hipo core kinases is the mammalian transcriptional activator Yes-asociated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). The Hippo signaling is inactivated in cancer and YAP as well as TAZ are activated and free to translocate into the nucleus to promote cell proliferation (163). Hippo pathway components are associated with colorectal cancer differentiation and TNM stage. The expression of YAP and phosphorylated YAP could be an independent prognostic indicator of colorectal cancer (163). YAP activation is characteristic for tubular adenomas in familial adenomatous polyposis (163). A positive feedback loop between activated YAP and increased EGFR/KRAS is associated with the CRC progression and also resistance to epidermal growth factor receptor (EGFR) inhibitors. The expression level of YAP in wild-type KRAS CRC could be used as a marker of cetuximab therapy effectiveness (163). TEAD4 is a nuclear target of YAP. It controls genes responsible for induction of cell adhesion and up-regultion of the epithelial-mesenchymal transition-related changes in CRC cells. YAP/TAZ and Ki-67 are coactivators of liver metastases in CRC. High level of YAP/TAZ correlates with the proliferation marker Ki-67. YAP/TAZ plays an important role in the control of the proliferation/quiescence switch in liver metastases (163).

Treatment of CRC is very complex and the analysis of it is not the aim of this short review. However, pain is the the very common symptom of this disease and the mention about it semms to be argued in this place due to many clinical, pharmacological and ethical problems accompanying it. CRC for a long time develop locally and at the beginning - without pain. The pain in CRC is commonly associated with bowel obstruction. In this cases pain may be relieved by a surgical intervention, which restores gastrointestinal passage. Advanced tumors of the rectum with infiltration of surrounding nerve structures and sacral bone may induce severe pain with neuropathic component (164). The management of many symtopms accompanying CRC and monitoring of effetivenes of pain therapy with possible drug interactions should be taken into account (164).

So, surgical treatment should be considered not only as the main way to define the essential treatment but also palliative therapy leading to relief of pain. However, physical forces such as pressure and shear stress have profound effects on cancer cell biology. In the perioperative setting, tumor manipulation by the surgeon, surgical site irrigation subject tumor cells to pressure and shear stress. Laparoscopic surgery generally increases intraperitoneal pressure by 15 mmHg. Even relatively brief exposure to such pressure can trigger an intracellular signal cascade that increases the adhesive potential of suspended colon cancer (165). Increased extracellular pressure or shear stress activate a complex signal pathway that stimulates integrin binding affinity and potentiates metastatic cell adhesion. It was demonstrated, that independently expressing the F1 domain in human Cacco-2 or murine CT-26 colon cancers by transient or stable inducible plasmid expression respectively prevents the stimulation of cancer cell adhesion by increased extracellular pressure (165). This advance shows that inhibiting of this prometastatic signal cascade might have substantial benefits for reducing perioperative tumor dissemination and long term metastasis from unresectable tumours (165).

SUMMARY

Many factors contribute to the development of CRC, however, exact mechanisms and pathophysiological pathways are complex and not precisely recognized. Several epidemiological and clinical studies suggested the anti-tumoral effects of aspirin, but further studies should be performed to elucidate the mechanisms underlining these effects. On the other hand, the impact of some microelements and vitamins as well as probiotics are ambiguous. By contrast, it is well known that red animal meat and highly processed food prepared in thermal conditions have unfavorable effect on carcinogenesis. In contrary, fruits and vegetables have protective effects against CRC development. Molecular pathological studies could be in near future a valuable source of data on patterns of CRC development. Further research in the field of basic sciences as well as large clinical studies are required to decrease the prevalence of CRC.

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