Review paper
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DIETARY AND LIFESTYLE RISK FACTORS IN COLON CANCER DEVELOPING

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Abstract

Colorectal cancer, with the breast and bronchogenic cancers are leaders in the malignant diseases of the human population. It is life threatening disease worldwide. The aim of this study is to review the dietary and lifestyle risk factors for colorectal cancer (CRC) prevention among general population. We searched 346 articles published in last decade, concerning the dietary components, and lifestyle risk factors in relation to colorectal cancer. The reviewed articles were obtained from the PubMed data sources where the most important clinical information was available.

There is reliable evidence that vitamin B6, magnesium and garlic intake, may significantly protect against developing colorectal cancer. The additional factors such as active living, maintaining a healthy weight by sport activities and exercises and avoiding or reducing red meat, alcohol, and smoking, as well as hormone replacement therapy among women, may provide proper work of the intestinal system. Obesity and stress life are noted as main risk factors for colorectal cancer. Surprisingly, there was less consistent evidence that some spices, herbs, tea, fruit and vegetable intake as well as fish and Omega-3 fatty acids, selenium, dairy, calcium and vitamin D, may provide additional protective role in developing the colorectal cancer. Colorectal cancer can be prevented in general population through dietary and lifestyle interventions. Further investigations of some nutritional components and the way of food processing are necessary in order to provide reliable aspects of colon cancer developing.

***Key words**: Dietary factors, Lifestyle, Prevention, Colorectal cancer, General population.*

1. Introduction

Colorectal cancer (CRC), with the breast and lung cancers are leaders in the malignant diseases of the human population. CRC is the third most common cancer in men (746,000 cases, 10% of total) and the second in women (614.000 cases, 9.2% of the total) worldwide (Figure 1) [1]. There is wide geographical variation in incidence across the world. Incidence rates vary tenfold in both sexes worldwide, the highest estimated rates being in Australia and New Zealand (ASR 44.8 and 32.2 per 100.000 in men and women respectively), and the lowest in Western Africa (4.5 and 3.8 per 100.000) [1]. Because of the high incidence of colorectal cancer in Western countries, it is commonly regarded as a Western life-style disease. However, the incidence rates have been increasing in economically transitioning countries, including Eastern European countries, most parts of Asia, and some countries of South America [2].

In Macedonia, CRC is the second most common cancer in men (421 cases, 10.9 of total) behind the lung cancer, and the third most common in women (366 cases, 10.6%) behind the breast and endometrial cancers [1].

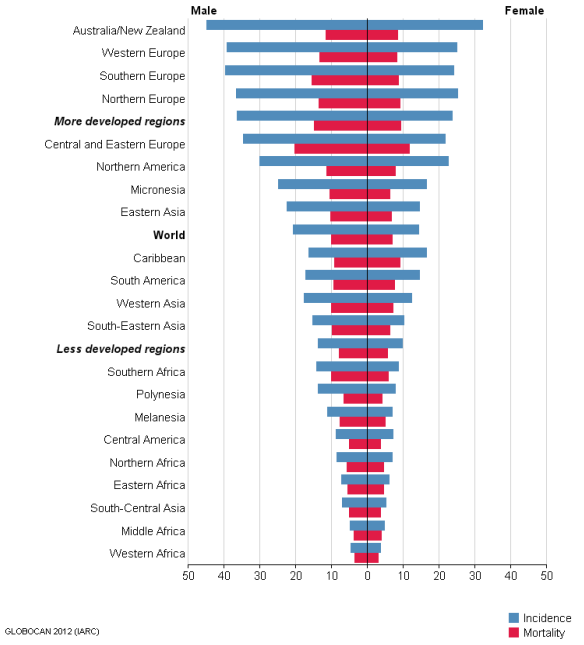

Figure 1. Age-standardized colorectal cancer incidence rates by sex and region of the world (Source: Ferlay *et al.* [1])

The role of diet and lifestyle factors has long been suspected and investigated in CRC development, with specific dietary constituents, in addition to excessive caloric intake, weight gain, physical inactivity, smoking, and heavy alcohol intake all thought to result in elevated risk [3]. The differences in rates by country, and elevated risk among immigrants from a low- to high-risk country, support the suspicion that environmental factors are important in CRC development [4].

Therefore, a diet and lifestyle seems to be essential in incidence of CRC [4], and this review aims to summarize the most up-to-date evidence for some risk factors. This review evaluated and summarized scientific evidence on dietary and lifestyle risk factors of CRC developing. We searched 346 articles from the PubMed database in the last decade, for key epidemiological studies, large case-control and cohort studies, randomized controlled trials (RCTs), and meta-analyses of studies of risk factors of colorectal cancer in humans.

2. Nutritional components and lifestyle factors

2.1 Meat

Although the relation between red and processed meat intake and colorectal cancer has been reported in several epidemiologic studies, very few investigated the potential mechanisms [5]. Most of them have investigated prevalent events from a single screening, thus limiting the understanding of the role of meat and meat-related exposures in early colorectal carcinogenesis [5, 6]. In the study of Ferruci *et al*. [6], there are suggestive positive associations for red and processed meat intake and colorectal cancer; heme iron, nitrate/nitrite, and heterocyclic amines from meat may explain association with colon cancer.

2.2 Dietary fiber and folate intake

In the study of Dahm *at al*. [7], in the nested case-control study of 579 colorectal cancer case patients, they have found a statistically significant inverse association between dietary fiber intake and the risk of colorectal cancer. These findings strengthen existing evidence that supports recommendations to increase dietary fiber intake in populations to reduce colorectal cancer incidence. The same conclusion is related to the study of Lee and associates [8], who investigated the effect of folates. A higher folate intake is associated with a decreased colorectal cancer risk in observational studies. On the other hand, the recent evidence reported by Fujimori *et al*. [9], suggests that excessive folate supplementation may increase colorectal cancer risk in some individuals.

2.3 Garlic

The story of garlic's role in human history is an object of interest in many nutritional papers and its role as a natural medicament could fill a book, as indeed it has, many times. Garlic is widely used as an all-around treatment for preventing or slowing the progression of atherosclerosis and the use of garlic could enhance blood sugar control in diabetes [10]. Evidence from observational studies suggests that garlic may help prevent cancer, particularly cancer of the stomach and colon [11-14]. In one of the best of these trials, the Iowa Women's Study, a group of 41,837 women were questioned as to their lifestyle habits in 1986 and then followed continuously in subsequent years. At the 4-year follow-up, questionnaires showed that women whose diets included significant quantities of garlic were approximately 30% less likely to develop colon cancer [15]. In the study of El-Bayoumy *et al*. [16] is indicated that garlic with its organoselenium compounds are superior to their corresponding sulfur analogs in cancer chemoprevention.

2.4 Fish

In the population-based cohort study in Japan, reported by Kobayashi *et al*. [17] no significant associations was found between fish consumption and the incidence of colorectal cancer. In the other study from Finland reported by Knekt *et al*. [18] an increased incidence of colon cancer was attributed to smoked and salted fish, but the cooking methods may have influenced the results. Quite opposite of these findings are the studies of Jedrychowski and associates [19], based on a population of 548 CRC patients, which results indicate that increased fish intake may have a preventive effect on CRC and modulate the effect of meat consumption. The similar results are indicated from the cohort studies of Sugawara *et al*. [20].

2.5 Vitamin B6 and calcium

Vitamin B-6 plays an important role in one-carbon metabolism, which is essential for DNA synthesis and methylation. In addition, vitamin B-6 is involved in more than 100 coenzyme reactions and has also been shown to reduce oxidative stress, cell proliferation, and inflammation, all of which are associated with carcinogenesis. In contrast to a significant inverse association reported from a meta-analysis of case-control studies, in the study of Larsson and coworkers [21], there is no associations in the role of adulthood vitamin B-6 intake in colorectal carcinogenesis.

In the study of Carroll and associates [22], is suggested that calcium, with or without vitamin D, had no effect on the relative risk for colorectal cancer. Opposite of this, is the study of Galas and associates [23], based on 1556 patients that concluded the beneficial effect of dietary calcium depended on the level of dietary fiber, suggesting modification effect of calcium and dietary fibers and protective role against the CRC.

2.6 Selenium and magnesium

The role of selenium intake and the risk of CRC is a matter of objective in different studies [24], but the most analytical approach is presented in the study of Connelly-Frost and co-workers [25], where they observed a stronger association between selenium concentrations and colorectal tumor risk among studies that measured selenium after diagnosis of colorectal tumors than those measured before the diagnosis. The strength of this study includes the large number of cases, making it the largest observational study reported to date on serum selenium and colorectal cancer in women.

The protective effect of magnesium intake is described in the studies of Chen [26], and Wark [27], and their associates. They have found in the meta-analysis of their studies that every 100-mg/d increase in magnesium intake was associated with 13% lower risk of colorectal adenomas (OR: 0.87; 95% CI: 0.75, 1.00) and 12% lower risk of developing the colorectal cancer (RR: 0.88; 95% CI: 0.81, 0.97). According to these findings. the consumption of selenium and magnesium-rich foods may be a new avenue to explore further in the search for cancer-prevention strategies.

2.7 Obesity

The relationship between obesity and the risk of CRC has been assessed by a large number of studies and review papers that in summary were presented in the study of Moghaddam and associates [28]. However, the magnitude of the association has varied widely across studies and the findings have been inconsistent. The main increased risk factors in developing CRC in obese persons include elevated levels of insulin, insulin-like growth factor-1 (IGF-1), leptin, interleukin (IL)-6, IL-17, tumor necrosis factor (TNF)-alpha and decreased levels of adiponection. These factors in turn cause activation of multiple signal pathways which play key roles in obesity-associated colon cancer such as, phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), mitogen activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3). Among these mechanismas, the review of Ning *et al*. [29], focuses on the effects of green tea component (-)-epigallocatechin-3 gallate (EGCG) and turmeric component curcumin in the prevention of obesity-associated colon cancer and the mechanisms for such effects. They have found that both EGCG and curcumin, to have preventive effects on obesity-associated colon cancer. The mechanisms are their properties to inhibit multiple signalling pathway components especially that in PI3K/Akt and MAPK pathways.

2.8 Physical activity

Physical activity also has a role in the setting of advanced colorectal cancer, where impaired physical function due to disease progression and anticancer treatment is nearly ubiquitous [30]. As it was noted in the reports of Winzer *et al*. [31], current exercise guidelines for cancer patients recommend a base of prolonged aerobic exercise of low-to-moderate intensity, such as walking, carried out at least 150 minutes per week, in divided sessions. Also recommended is a small amount of resistance training. These guidelines are useful for many patients and should be liberally employed at present. However, the lack of major metabolic benefit for many persons adhering to this moderate-intensity regimen is of concern.

2.9 Alcohol

Several studies lend support, although inconsistently, to an association between increased intake of alcohol and risk of colorectal adenoma and adenocarcinoma [4,32,33]. A review of 27 epidemiological studies investigated by Boffetta and associates [32], showed that cohort studies reported risk estimates of 1·0–1·7 for colon cancer and the same for rectal cancer. The researchers concluded that such findings were consistent with either no increase in risk of colorectal cancer as a result of alcohol consumption, or a very moderate increase in risk. Investigations of Corrao and associates [33], recorded a dose-response relation between risk of colorectal cancer and amount of alcohol consumption. These analyses did not detect any differences in risk for type of alcoholic drink or in risk of colon cancer versus that for rectal cancer.

Dietary factors such as low folate intake are thought to increase the risk of colorectal cancer by 2 - 5 times, and alcohol adversely affects folate metabolism. Alcohol consumption and low folate intake might interact synergistically, or alcohol could act through folate metabolism to increase risk of colorectal cancer. Because the risk estimates suggest a moderate association between alcohol and risk of colorectal cancer, residual confounding by such dietary factors is of concern.

2.10 Smoking

Considerable evidence suggests that cigarette smoking is associated with a higher risk of colorectal cancer [34]. The recent IARC update (2010) concludes that smoking is a cause of colon cancer [1]. These findings are echoed by the World Health Organization and the Journal of the National Cancer Institute [35,36]. In the report of Gong *et al*. [37], current smokers (OR = 1.26, 95% CI = 1.11- 1.43) and former smokers (OR = 1.18, 95% CI = 1.09 - 1.27), relative to never smokers, showed higher risks of colorectal cancer. Former smokers remained at higher colorectal cancer risk, relative to never smokers, for up to about 25 years after quitting. The impact of time since quitting varied by cancer subsite: the excess risk due to smoking decreased immediately after quitting for proximal colon and rectal cancer, but not until about 20 years post-quitting for distal colon cancer.

2.11 Hormone replacement therapy (HRT)

Estrogen/progestin replacement therapy is prescribed to women in menopause for purposes of postmenopausal symptom control or prevention of hormone deficiency–related diseases such as osteoporosis. Such treatments have formerly been shown to be associated with lower colorectal cancer risk in an as yet unknown mechanism [38]. In the study of Rennert and co-workers [38], 2460 peri/postmenopausal women were studied from among 2,648 patients with colorectal cancer and 2,566 controls. The self-reported use of HRT was associated with a significantly reduced relative risk of colorectal cancer (odds ratio [OR], 0.67; 95% CI, 0.51 to 0.89). This association remained significant after adjustment for age, sex, use of aspirin and statins, sports activity, family history of colorectal cancer, ethnic group, and level of vegetable consumption (OR, 0.37; 95% CI, 0.22 to 0.62). The same results are reported by Hoffmeister and associates [39], where body mass index (BMI) was not associated with risk of CRC among HRT users (P for interaction <0.01). In contrast to most other studies, a positive association of BMI and CRC risk was found among non-users of HRT, but not among users of HRT. The reasons for the inconsistency of results regarding the potential risk modifying effect of postmenopausal hormones in the association of BMI with CRC remain inconclusive and require further study.

3. Conclusions

- Regarding the above mentioned facts it is obvious that colorectal cancer is somehow "food induced cancer" [40].

- In order to protect ourselves from this disease some notes should be considered in the everyday diet according to the reports of Yi [41], and Russel [42]:

1. Eat less red meat.
2. Eat more garlic.
3. Eat a rainbow of plant antioxidants: blueberries, cranberries, pomegranates, carrots, apricots, cantaloupe, kale, broccoli, spinach, avocado, tomato, apples, red cabbage, red and purple grapes, pink grapefruit, turmeric, saffron, oregano, sage, rosemary. Colour signals the presence of anti-oxidant plant chemicals that turn on cancer suppressor genes and turn off cancer promoter genes.
4. Use olive oil. Olive oil reduces bile acid and increases enzymes that regulate cell turn over in the lining of the intestines promoting healthy tissue.
5. Include selenium rich foods. Foods rich in selenium include garlic and onions, sunflower seeds, mushrooms, whole grains (brown rice, oats, wheat germ), Brazil nuts, fish (tuna, halibut, sardines, salmon).
6. Include spices and herbs that inhibit colon cancer - garlic, ginger, turmeric, thyme, rosemary, sage, spearmint, and peppermint - all inhibit the growth of colon cancer cells.
7. Include Omega 3 oils. Omega 3 oils are found in cold water fish such as salmon, sardines, mackerel and cod as well as flax oil.
8. Drink Ginseng tea.

- Reflecting upon these recommendations for dietary choices, it is obvious that they are describing both traditional Mediterranean and traditional Asian Diets. These diets are naturally low in red meats and animal proteins, high in fish and omega-3 oils, high in olive oil and a wide variety of whole grains and fruits and vegetables as well as herbs and spices with known anti-cancer properties. Cultures where traditional diets are still eaten today have lower rates of colon cancer than countries such as the U.S. and some European countries, where a modern diet seems to promote and create higher risk for colon cancer.

4. References

[1] Ferlay J., Shin H. R., Bray F., Mathers C., and Parkin D. M. (2013). *Cancer Incidence and Mortality worldwide: IARC Cancer Base No. 10.* Lyon, France: International Agency for Research on Cancer. <URL:http://globocan.iarc.fr/Default.aspx. Accessed 12th April, 2014.

[2] Jemal A., Bray F., Center M. M, Ferlay J., Ward E., Forman D. (2011). *Global cancer statistics*. CA Cancer J Clin., 61, pp. 69-90.

[3] Center M. M., Jemal A., Ward E. (2009). *International trends in colorectal cancer incidence rates*. Cancer Epidemiol Biomarkers Prev., 18, pp. 1688-1694.

[4] Shike M. (1999). *Diet and lifestyle in the prevention of colorectal cancer: an overview.* Am. J. Med., 106, 11S-15S: Discussion, pp. 50S-51S.

[5] Cross A. J., Ferrucci L. M., Risch A., Graubard I. B., Ward H. M., Park Y., Hollenbeck R. A., Schatzkin A., and Sinha R. (2010). *A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association.* Cancer Res., 70. pp. 2406-2414.

[6] Ferrucci L. M., Sinha R., Huang W. Y., Berndt S. I., Katki H. A., Schoen R. E., Hayes R. B., and Cross A. J. (2012). *Meat consumption and the risk of incident distal colon and rectal adenoma.* Br. J. Cancer, 106, pp. 608-616.

[7] Dahm C. C., Keogh R. H., Spencer E. A., Greenwood D. C., Key T. J., Fentiman I. S., Shipley M. J., Brunner E. J., Cade J. E., Burley V. J., Mishra G., Stephen A. M., Kuh D., White I. R., Luben R., Lentjes M. A., Khaw K. T., Rodwell Bingham S. A. (2010). *Dietary fiber and colorectal cancer risk: a nested case-control study using food diaries.* J. Natl. Cancer Inst., 102, pp. 614-626.

[8] Lee J. E., Willett W. C., Fuchs C. S., Smith-Warner S. A., Wu K., Ma J., Giovannucci E. (2011). *Folate intake and risk of colorectal cancer and adenoma: modification by time*. Am. J. Clin. Nutr., 93, pp. 817-825.

[9] Fujimori S., Gudis K., Takahashi Y., Kotoyori M. (2011). *Determination of the minimal essential serum folate concentration for reduced risk of colorectal adenoma*. Clin. Nutr., 30, pp. 653-658.

[10] Ngo S. N., Williams D. B., Cobiac L., Head R. J. (2007). *Does garlic reduce risk of colorectal cancer? A systematic review.* J. Nutr., 137, pp. 2264-2269.

[11] Fleischauer A. T., Poole C., Arab L. (2000). *Garlic consumption and cancer prevention: meta-analyses of colorectal and stomach cancers.* Am. J. Clin. Nutr., 72, pp. 1047-1052.

[12] Agarwal K. C. (1996). *Therapeutic actions of garlic constituents*. Med. Res. Rev., 16, pp. 111-124.

[13] Dausch J. G., Nixon D. W. (1990) *Garlic: a review of its relationship to malignant disease*. Prev. Med., 19, pp. 346-361.

[14] Dorant E., van den Brandt P. A., Goldbohm R. A., Hermus R. J., and Sturmans F. (1993). *Garlic and its significance for the prevention of cancer in humans: a critical view.* Br. J. Cancer, 67, pp. 424-429.

[15] Lau B. H., Tadi P. P., Tosk J. M. (1990). *Allium sativum (garlic) and cancer prevention*. Nutr. Res., 10, pp. 937-948.

[16] Steinmetz K. A., Kushi L. H., Bostick R. M., Folsom A. R, Potter J. D. (1994). *Vegetables, fruit, and colon cancer in the Iowa Women's Health Study.* Am. J. Epidemiol., 139, pp. 1-15.

[17] El-Bayoumy K., Sinha R., Pinto J.T., Rivlin R. S. (2006). *Cancer chemoprevention by garlic and garlic-containing sulfur and selenium compounds.* J. Nutr., 136, pp. 864S-869S.

[18] Kobayashi M., Tsubono Y., Otani T., Hanaoka T., Sobue T., Tsugane S. (2004). *Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study*. Nutr. Cancer., 49, pp. 32-40.

[19] Knekt P., Jarvinen R., Dich J., Hakulinen T. (1999). *Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study.* Int. J. Cancer., 80, pp. 852-856.

[20] Jedrychowski W., Maugeri U., Pac A., Sochacka-Tatara E., Galas A. (2008). *Protective effect of fish consumption on colorectal cancer risk. Hospital-based case-control study in Eastern Europe*. Ann. Nutr. Metab., 53, pp. 295-302.

[21] Sugawara Y., Kuriyama S., Kakizaki M., Nagai M., Ohmori-Matsuda K., Sone T., Hozawa A., Nishino Y., and Tsuji I. (2009). *Fish consumption and the risk of colorectal cancer: the Ohsaki Cohort Study*. Br. J. Cancer, 101, pp. 849-854.

[22] Larsson S. C., Orsini N., Wolk A. (2010). *Vitamin B6 and risk of colorectal cancer: a meta-analysis of prospective studies.* JAMA, 303, pp. 1077-1083.

[23] Carroll C., Cooper K., Papaioannou D., Hind D., Pilgrim H., Tappenden P. (2010). *Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis*. Clin. Ther., 32, pp. 789-803.

[24] Galas A., Augustyniak M., Sochacka-Tatara E. (2013). *Does dietary calcium interact with dietary fiber against colorectal cancer? A case-control study in Central Europe*. Nutr. J., 12, pp. 134.

[25] Sanmartín C., Plano D., Sharma A. K., Palop A. J. (2012). *Selenium compounds, apoptosis and other types of cell death: an overview for cancer therapy.* Int. J. Mol. Sci., 13, pp. 9649-9672.

[26] Connelly-Frost A., Poole C., Satia J. A., Kupper L. L, Millikan R. C, Sandler R. S. (2009). *Selenium, folate, and colon cancer.* Nutr. Cancer, 61, pp. 165-178.

[27] Chen G. C., Pang Z., Liu Q. F. (2012). *Magnesium intake and risk of colorectal cancer: a meta-analysis of prospective studies.* Eur. J. Clin. Nutr., 66, pp. 1182-1186.

[28] Wark P. A., Lau R., Norat T., Kampman E. (2012). *Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis.* Am. J. Clin. Nutr., 3, pp. 622-631.

[29] Moghaddam A. A., Woodward M., Huxley R. (2007). *Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events*. Cancer Epidemiol. Biomarkers Prev., 16, pp. 2533-2547.

[30] Ning Y., Wang L., Giovannucci E. L. (2010). *A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies*. Obes. Rev., 11, pp. 19-30.

[31] Meyerhardt J. A., Heseltine D., Niedzwiecki D., Hollis D., Saltz L. B., Mayer R. J., Thomas J., Nelson H., Whittom R., Hantel A., Schilsky R. L., Fuchs C. S. (2006). *Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803*. J. Clin. Oncol., 24, pp. 3535-3541.

[32] Winzer B. M., Whiteman D. C., Reeves M. M., Paratz J. D. (2011). *Physical activity and cancer prevention: a systematic review of clinical trials.* Cancer Causes Control, 22, pp. 811-826.

[33] Boffetta P., Hashibe M. (2006) *Alcohol and cancer*. Lancet Oncol., 7, pp. 149-156.

[34] Corrao G., Bagnardi V., Zambon A., Arico S. (1999). *Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol related conditions: a meta-analysis.* Addiction, 94, pp. 551-573.

[35] Botteri E., Iodice S., Bagnardi V., Raimondi S., Lowenfels A. B., Maisonneuve P. (2008). *Smoking and colorectal cancer: a meta-analysis*. JAMA, 300, pp. 2765-2778.

[36] Liang P. S., Chen T. Y., Giovannucci E. (2009). *Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis*. Int. J. Cancer, 124, pp. 2406-2415.

[37] Gong J., Hutter C., Baron J. A., Berndt S., Caan B., Campbell T. P., Casey G., Chan T. A., Cotterchio M., Fuchs S. C., Gallinger S., Giovannucci E., Harrison T., Hayes R., Hsu L., Jiao S., Lin Y., Lindor M. N., Newcomb P., Pflugeisen B., Phipps I. A., Rohan T., Schoen R., Seminara D., Slattery L. M., Stelling D., Thomas F., Warnick G., White E., Potter J., and Peters U. (2012). *A pooled analysis of smoking and colorectal cancer: timing of exposure and interactions with environmental factors.* Cancer Epidemiol. Biomarkers Prev., 21, pp. 1974-1985.

[38] Rennert G., Rennert H. S., Pinchev M., Gruber B. S. (2009). *Use of hormone replacement therapy and the risk of colorectal cancer*. J. Clin. Oncol., 27, pp. 4542-4547.

[39] Hoffmeister M., Raum E., Winter J., Chang-Claude J., and Brenner H. (2007). *Hormone replacement therapy, body mass, and the risk of colorectal cancer among postmenopausal women from Germany*. Br. J. Cancer, 97, pp. 1486-1492.

[40] Randi G, Edefonti V, Ferraroni M, La Vecchia C., Decarli A. (2010). *Dietary patterns and the risk of colorectal cancer and adenomas*. Nutr. Rev., 68, pp. 389-408.

[41] Yi W., Wetzstein H. Y. (2011) *Anti-tumorigenic activity of five culinary and medicinal herbs grown under greenhouse conditions and their combination effects*. J. Sci. Food Agric., 91, (10), pp. 1849-1854.

[42] Russell W., Duthie G. (2011) *Plant secondary metabolites and gut health: the case for phenolic acids.* Proc. Nutr Soc., 70, (3), pp. 389-396.