Nutrition and Colorectal Cancer Pathogenesis

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1 Introduction

The common etiological factors for cancer are obesity, nutritional deficiencies, smoking, radiation, environmental toxins, sedentary lifestyle, and aging. These factors cause cancer by damaging genes in combination with existing genetic mutation within cells. Epidemiological studies have shown that diet containing fruits and vegetables reduce the risk of several types of cancer. High intake of fruits and vegetables has an active role in the prevention of chronic disease associated with oxidative stress-mediated carcinogenesis. World Health Organization projects 10,000,000 cases of cancer per year worldwide and 6,000,000 mortality from cancer per year worldwide. It also projected 15 million cases/year in 2020. Cancers vary on the basis of age, gender, race, and genetic predisposition.

Despite the continuous advances in cancer treatment and early diagnosis, yet colorectal cancer (CRC) is still worldwide afflicting large numbers of people of all social classes. The CRC incidence is increasing rapidly in many countries where previous rates were low in the past years, indicating the existence of a common etiological factor as being the trigger for CRC occurrence in susceptible subjects. CRC is one of the commonest cancers and the third leading cause of cancer death. CRC incidence has decreased as a result of effective intervention and lifestyle changes in the West. The risk of CRC increases with age as 91% of cases are diagnosed in individuals aged 50 and older. Several modifiable factors are associated with increased risk of colorectal cancer; among these are obesity, physical inactivity, a diet high in red or processed meat, heavy alcohol consumption, and possibly smoking and inadequate intake of fruits and vegetables.

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Prevention of CRC remains a theoretic possibility and ought to be pursued, especially for patients whose family histories place them at high risk. Identifying genetic predisposition, dietary modifications, cessation of alcohol and tobacco use, and chemoprevention represent the spectrum of primary preventive measures. The role of genetic predisposition in CRC is most prominent for patients with familial polyposis, inflammatory bowel disease, a family history of colon cancer, and a family history of adenomatous polyps. The first two categories require aggressive and regular surveillance to identify the development and removal of early adenomas up to and including total colectomy. This chapter addresses different aspects of cancer pathogenesis and the role of nutrition in colorectal cancer prevention.

2 Cancer Pathogenesis and Stages

Cancers represent a heterogeneous group of diseases characterized by uncontrolled growth and spread of abnormal cells in the body. Cancer may affect people at all ages, even fetuses, but the risk for most varieties increases with age. The disruptive behaviors of cancer cells reflect dynamic changes in their genomes and in genes that result in disruption of normal regulatory signaling circuits. Cancers vary on the basis of both the biologic features of the disease and the characteristics of the affected organism. The process by which normal cells are transformed into cancer cells is known as carcinogenesis. Cancers are multifactorial diseases, with environmental and endogenous factors contributing at a different level in determining cancer risk [1, 2]. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells [3]. There are many different forms of cancer. Their manifestation is a growth of cells and tissues, which differ in various aspects from the surrounding tissue. Cancers occur in all living things. All life forms share similar deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) blueprints and cell physiology. Therefore, the mechanisms for cancer development and methods for cancer treatment are similar [4].

Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries [3]. Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may be randomly acquired through errors in DNA replication, or are inherited, and thus present in all cells from birth. The heritability of cancers are usually affected by complex interactions between carcinogens and the host's genome. New aspects of the genetics of cancer pathogenesis, such as DNA methylation, and microRNAs are increasingly recognized as important. Genetic abnormalities found in cancer typically affect two general classes of genes. Cancer-promoting oncogenes are typically activated in cancer

cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments [5].

Cancer cells are formed from normal cells due to a modification, mutation of DNA and/or RNA. These modifications/mutations can occur spontaneously or they may be induced by other factors such as nuclear radiation, electromagnetic radiation (microwaves, X-rays, Gamma-rays, Ultraviolet-rays), viruses, bacteria and fungi, parasites (due to tissue inflammation/ irritation), heat, chemicals in the air, water, and food, mechanical cell-level injury, free radicals, evolution and aging of DNA and RNA, plus poor diet, stress, lack of proper exercise, and lack of sufficient rest and sleep. All these can produce mutations that may start cancer. Cancer can be called therefore "Entropic Disease" since it is associated with the increase of entropy of the organism to the point where the organism cannot correct this itself. External intervention is required to allow the organism to return to a stable entropic state [6]. Although the relatively small risks associated with low-level exposure to carcinogens in air, food, or water are difficult to detect in epidemiological studies, scientific and regulatory bodies throughout the world have accepted the principle that it is reasonable and prudent to reduce human exposure to substances shown to be carcinogenic at higher levels of exposure [6].

The transformation of a normal cell to a cancer cell occurs through three distinct phases, initiation, promotion, and progression. Initiation of cancer occurs in the normal cells due to exposure of carcinogenic and mutagenic agents. The initiated cells are irreversibly altered and are at greater risk of neoplastic transformation. However, initiation alone is not sufficient for tumor formation [7]. In promotion phase, tumor promoters convert the initiated cells into neoplastic cells [8]. Progression involves a stepwise evolution of neoplastic cells into higher degree of malignancy [7, 8]. In clinical practice, cancer is divided into five stages: stage 0, 1, 2, 3, and 4. In stage 0 cancer cells are found in one tissue area and have not invaded normal surrounding tissue, whereas in stage 1 and 2, cancer is found only in the organ where it started to grow. Stage 3 is also known as regional and here cancer cells start to spread to the surrounding tissues or lymph nodes, metastasis [9]. Eventually it moves to other organs and systems of the body in stage 4, the last stage of cancer [9].

3 Colorectal Cancer

Cancer of the large bowel is a major health problem. Worldwide each year, over 900,000 new cases are diagnosed, and almost 500,000 people die from the disease [3]. About two-thirds of the incident cases occur in developed countries, where colorectal cancer is the third most common cancer in men and second most common in women [8]. Relatively few colorectal cancers occur in persons younger than 40. Rates increase rapidly with age thereafter, more markedly for colon than for rectal cancer [9]. The burden of colorectal cancer is, therefore, expected to increase in the

future as a result of population aging and increased life expectancy. This is particularly true for developing countries [3]. Colorectal cancer ranks second in terms of incidence and mortality in more developed countries. There is a significant geographical variation in age-standardized incidence rates that vary approximately 20-fold around the world with high rates occurring in countries of Europe, North America, Australia, and Japan. Although the colon and rectum have different etiological background, they are usually considered together. Migrants groups from low incidence countries rapidly reach the higher level of adopted country, suggesting that environmental factors play an important role in etiology [10].

Large bowel cancer is predominant in affluent societies and most frequent in North America, Western Europe, Australia, New Zealand, and the southern part of South America. CRC is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women in the USA [11]. Colon cancer is cancer that starts in the large intestine or the rectum. Such cancer is sometimes referred to as "colorectal cancer." Other types of colon cancer such as lymphoma, carcinoid tumors, melanoma, and sarcomas are rare. The term "colon cancer" refers to colon carcinoma and not these rare types of colon cancer. CRC ranks second in terms of incidence and mortality in more developed countries. There is a significant geographical variation in age-standardized incidence rates that vary approximately 20-fold around the world with high rates occurring in countries of Europe, North America, Australia, and Japan. Although the colon and rectum have different etiological background, they are usually considered together. Migrants groups from low incidence countries rapidly reach the higher level of adopted country, suggesting that environmental factors play an important role in etiology.

Many epidemiologic studies have indicated that the risks of CRC include genetic predisposition, modern lifestyle, environmental toxins, high consumption of red meat, alcohol, and low intakes of vegetables and fruits [12]. Among all of these etiological factors, the role of diet remains an effective approach for primary intervention for CRC. Recent case-control studies have shown that low or moderate intake of folate and B_{12} results in impairment of methylation reactions, including DNA hypomethylation which is thought to be the trigger of tumorigenesis in human cells [13]. In addition, low intakes of folate and vitamin B_{12} decrease the antioxidant capacity of human cells with a consequent reduction in glutathione, the major intracellular antioxidant. Oxidative stress has been associated with different types of cancers [14]. In developing countries, CRC account for just 2.5% of all cancers. Almost all colorectal cancers are adenocarcinomas. The incidence rate is a little higher in North Africa than in sub-Saharan Africa [15].

Environmental factors such as diet and alcohol intake also differ in their role in the development of tumors in the three segments, proximal colon, distal colon, and rectum. Proximal shift of colon cancer has been known for some time, and survival rates of colorectal cancer are higher when rectal cancers are excluded, both of which emphasize the three different segments of colorectal cancer and their

different properties [16]. Meanwhile, colonic and rectal cancers are distinctive therapeutic entities. The concept of three entities of colorectal cancer may be important in designing clinical trials or therapeutic strategies [17]. CRC is malignant cells found in the colon or rectum. Because colon cancer and rectal cancer have many features in common, they are sometimes referred to together as colorectal cancer. Colon cancer is cancer that starts in the large intestine (colon) or the rectum (end of the colon). Other types of colon cancer such as lymphoma, carcinoid tumors, melanoma, and sarcomas are rare [17].

CRC is a disease in which cancerous growths (tumors) are found in the tissues of the colon and/or rectum. The colon is the upper five to six feet of the large intestine; the rectum is the last 15 inches of the colon [7, 8]. It usually develops slowly over a period of many years, and usually begins as a noncancerous polyp, which may eventually change into cancer. A polyp is a growth of tissue that develops on the lining of the colon or rectum. Certain kinds of polyps, called adenomatous polyps or adenomas, are most likely to become cancers, although most adenomas do not become cancerous. More than half of all individuals will eventually develop one or more adenomas. About 96% of colorectal cancers are adenocarcinomas, which evolve from glandular tissue. The great majority of colon and rectum cancers arise from an adenomatous polyp, which is visible through a scope or on an X-ray [18].

Globally CRC is one of the commonest cancers and the third leading cause of cancer death. CRC incidence has decreased as a result of effective intervention and lifestyle changes in the West. The risk of colorectal cancer increases with age; 91% of cases are diagnosed in individuals aged 50 years and older. Several modifiable factors are associated with increased risk of colorectal cancer. Among these are obesity, physical inactivity, a diet high in red or processed meat, heavy alcohol consumption, and possibly smoking and inadequate intake of fruits and vegetables. Studies indicate that compared to healthy-weight individuals, men and women who are overweight are more likely to develop and die from colorectal cancer. Colorectal cancer risk is also increased by certain inherited genetic mutations [familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome], a personal or family history of colorectal cancer and/or polyps, or a personal history of chronic inflammatory bowel disease [19].

The exact cause of most colorectal cancer is unknown, but the known risk factors are the most likely causes. Less than 10% of CRC are caused by inherited gene mutations. People with a family history of colorectal cancer may wish to consider genetic testing. The American Cancer Society suggests that anyone undergoing such tests have access to a physician or geneticist qualified to explain the significance of these test results. According to the American Cancer Society, colorectal cancer is one of the leading causes of cancer-related deaths in the United States (however, early diagnosis often leads to a complete cure). There is no single cause for colon cancer. Nearly all colon cancers begin as noncancerous (benign) polyps, which slowly develop into cancer [18, 19].

4 Nutrition and Colorectal Cancer

It has been estimated that 30–40% of all CRC tumors can be prevented with a correct lifestyle and diet [20]. CRC is a preventable disease. When people migrate from low incidence countries, such as Japan or Africa, to a high incidence country such as the United States, the rates of disease among their offspring increase to those of their adopted country. This indicates that there is something in the environment that is responsible. There is about a ninefold difference in the incidence of colorectal cancer in the highest risk countries compared to the lowest risk countries. Based on these differences in incidence and the experience of migrants, experts have estimated that as much as 80% of colorectal cancer might be explained by environmental factors. The term "environment" in this instance does not refer to air or water pollution, but rather to dietary and lifestyle factors that are part of our environment. Although the environment is central to the etiology of most colorectal cancers, individual genetically determined susceptibility is also important, as well as to understand gene-environment interaction as it relates to colorectal cancer risk. The implications of an environmental cause of colon cancer are clear. If we could identify and modify the relevant environmental factors, we could prevent most colorectal cancer.

Diet has received the greatest attention for obvious reasons—diet is a factor that changes markedly with migration and acculturation. Moreover, what we eat ends up in our colon, in one form or another. There have been a large number of studies of diet and colon cancer. It was summarized that the information on dietary and lifestyle factors that have been linked with colorectal cancer were qualitative and subjective [10, 20]. The comparison of CRC incidence in various countries strongly suggests that sedentarily, high caloric intake, and perhaps a diet high in meat (red or processed) could increase the risk of colorectal cancer. In contrast, a healthy body weight, physical fitness, and good nutrition decreases cancer risk in general. Accordingly, lifestyle changes could decrease the risk of colorectal cancer as much as 60–80% [21]. Fruits and vegetables have received much interest because they contain numerous substances (vitamins, minerals and fiber) with anticarcinogenic activity. Case-control studies concluded that diets high in fruits and vegetables were consistently associated with lower risk of some, but not all, cancers [22]. In addition, the world cancer research fund (WCRF) panel concluded that the consumption of fruits and vegetables has been consistently associated with a reduced risk of human cancers at many sites, reduced risk of adenomas and especially of colon cancer [23].

Consumption of diets rich in cruciferous vegetables (broccoli, cabbage, and cauliflower) appears to be associated with a reduction in the risk of cancer of the colon and rectum. These vegetables are rich in isothiocyanate compounds. Animal studies have shown that diets rich in these substances are chemopreventive, when provided before chemical carcinogens, but when they are administered after the carcinogen they increase tumorigenesis [24]. Fruits and vegetables are rich in dietary antioxidants, vitamin C, and β-carotenoids. High consumption of foods rich in these

antioxidants results in a decreased risk for many cancers, including colorectal and lung [25]. A high intake of dietary fiber (from eating fruits, vegetables, cereals, and other high-fiber food products) has, until recently, been thought to reduce the risk of colorectal cancer and adenoma; it has been found that a fiber-rich diet does not reduce the risk of colon cancer [12]. The Harvard School of Public Health states: "Health Effects of Eating Fiber: Long heralded as part of a healthy diet, fiber appears to reduce the risk of developing various conditions, including heart disease, diabetes, diverticular disease, and constipation [12]. Despite what many people may think, however, fiber probably has little, if any effect on colon cancer risk" [12, 26].

Cohort studies concluded that diets high in total fat increases the risk of lung, colorectal, breast, and prostate cancers. Fat intake, owing to its high caloric density, increased risk of obesity, an indirect risk factor for endometrial, postmenopausal breast and renal cancers [27]. Total fat intake includes saturated, monounsaturated, and polyunsaturated fats. Saturated fats are derived from animal fat and are associated with greater risk of cancer, meanwhile monounsaturated fat intake, and the primary source is olive oil, has been hypothesized as a protective measure against cancer. Polyunsaturated fats include the n-3 fatty acids, conjugated linolenic acids (CLA) that are derived largely from fatty fish, and *trans* fatty acids present in variable quantities in hydrogenated oils and fast foods [28, 29]. CLA polyunsaturated fatty acids are well documented in preventing chemical carcinogens and are found mainly in dairy fats, milk, and cheeses. The CLA amounts in foods are not well documented in food composition tables, so human exposures are difficult to quantify in epidemiological studies [30, 31].

5 Conclusion

Regular screening examinations by a health care professional can result in the detection and removal of precancerous growths, as well as the diagnosis of cancers at an early stage, when they are most treatable. CRC is among cancers that can be diagnosed early through screening and early detection; this approach has been proven to reduce CRC mortality. In the majority of people CRC can be prevented with proper lifestyle modifications which include low-entropy diet, exercise, sleep, and stress reduction. In most cases cancer develops slowly over many years. With a positive change of lifestyle and healthy environment this trend can be reversed in the majority of CRC diagnosed patients. CRC etiology is complex and involves both genetic and environmental factors. Among the environmental factors, the dietary habits play a major role. Low intake of fibers, fruit, and vegetables and high intake of fat have been linked with increased risk of CRC. Therefore, dietary recommendations have been established to encourage people to change their dietary habits. Dietary fat and protein strongly correlate with the incidence of CRC, while low-fat, high-fiber, high-calcium diets, and diets with a high vegetable content appeared to be protective.

Dietary factors that have been studied for their possible role in the cause of colon and rectum cancer include high intake of red meat, alcohol, refined sugar, saturated/animal fat, and processed meat. Meanwhile high intake of fruits and vegetables acts as a preventive factor against colon and rectum cancer occurrence. Molecular biology studies indicate that micronutrients deficiencies, particularly folate and vitamin B_{12}, induce carcinogenesis in susceptible persons, via mechanisms that involve cell signaling, cell division, and DNA methylamines. There is robust evidence from cross-sectional and longitudinal studies to support that an energy-dense, high fat diet and physical inactivity are independent risk factors for weight gain and obesity. Overweight and obesity are established risk factors for CRC, as supported by both animal studies and human epidemiologic studies.

Many studies have revealed that dietary fiber contributes quantitatively to colorectal cancer risk or prevention. The protective effect of high intake of dietary fiber against colorectal cancer is mainly due to two major's mechanisms; firstly fiber decreases fecal transit time so it diminishes the exposure time of stool with toxins to epithetical cells. Secondly dietary fiber adsorbs stool toxins thus protecting the colonic epithelial cells. In the west the primary preventive measures for CRC include maintaining a healthy body weight, being physically active, and minimizing consumption of red meat and alcohol. In addition, early screening of colorectal cancer in the west results in early detection of the disease and removal of colorectal polyps before they become cancerous; therefore, the mortality rate of CRC in the west is lower than that in the developing countries.

References

1. Dereu D, Savoldelli GL, Combescure C, Mathivon S, Rehberg B. Development of a simple preoperative risk score for persistent pain after breast cancer surgery: a prospective observational cohort study. Clin J Pain. 2017. https://doi.org/10.1097/AJP.0000000000000575.
2. Lee AYY. When can we stop anticoagulation in patients with cancer-associated thrombosis? Hematology. Am Soc Hematol Educ Program. 2017;2017(1):128–35.
3. Hughes LAE, Simons CCJM, van den Brandt PA, van Engeland M, Weijenberg MP. Lifestyle, diet, and colorectal cancer risk according to (epi)genetic instability: current evidence and future directions of molecular pathological epidemiology. Curr Colorectal Cancer Rep. 2017;13(6):455–69.
4. Fagunwa IO, Loughrey MB, Coleman HG. Alcohol, smoking and the risk of premalignant and malignant colorectal neoplasms. Best Pract Res Clin Gastroenterol. 2017;31(5):561–8.
5. Boscolo-Rizzo P, Furlan C, Lupato V, Polesel J, Fratta E. Novel insights into epigenetic drivers of oropharyngeal squamous cell carcinoma: role of HPV and lifestyle factors. Clin Epigenetics. 2017;9:124.
6. Yahyapour R, Motevaseli E, Rezaeyan A, Abdollahi H, Farhood B, Cheki M, Najafi M, Villa V. Mechanisms of radiation bystander and non-targeted effects: implications to radiation carcinogenesis and radiotherapy. Curr Radiopharm. 2017. https://doi.org/10.2174/1874471011666171229123130.
7. Vela CM, Grate LM, McBride A, Devine S, Andritsos LA. A retrospective review of fall risk factors in the bone marrow transplant inpatient service. J Oncol Pharm Pract. 2017. https://doi.org/10.1177/1078155217697485.

8. Kolak A, Kamińska M, Sygit K, Budny A, Surdyka D, Kukiełka-Budny B, Burdan F. Primary and secondary prevention of breast cancer. Ann Agric Environ Med. 2017;24(4):549–53.
9. Jabir NR, Anwar K, Firoz CK, Oves M, Kamal MA, Tabrez S. An overview on the current status of cancer nanomedicines. Curr Med Res Opin. 2017;26:1–22.
10. Gigic B, Boeing H, Toth R, Böhm J, Habermann N, Scherer D, Schrotz-King P, Abbenhardt-Martin C, Skender S, Brenner H, Chang-Claude J, Hoffmeister M, Syrjala K, Jacobsen PB, Schneider M, Ulrich A, Ulrich CM. Associations between dietary patterns and longitudinal quality of life changes in colorectal cancer patients: the colocare study. Nutr Cancer. 2018;70(1):51–60.
11. Hu Y, Ding M, Yuan C, Wu K, Smith-Warner SA, Hu FB, Chan AT, Meyerhardt JA, Ogino S, Fuchs CS, Giovannucci EL, Song M. Association between coffee intake after diagnosis of colorectal cancer and reduced mortality. Gastroenterology. 2017. pii: S0016-5085(17)36368-0. https://doi.org/10.1053/j.gastro.2017.11.010.
12. van Zutphen M, Kampman E, Giovannucci EL, van Duijnhoven FJB. Lifestyle after colorectal cancer diagnosis in relation to survival and recurrence: a review of the literature. Curr Colorectal Cancer Rep. 2017;13(5):370–401.
13. Beeken RJ, Croker H, Heinrich M, Obichere A, Finer N, Murphy N, Goldin R, Guppy NJ, Wilson R, Fisher A, Steptoe A, Gunter MJ, Wardle J. The impact of diet-induced weight loss on biomarkers for colorectal cancer: an exploratory study (INTERCEPT). Obesity (Silver Spring). 2017;25(Suppl 2):S95–S101.
14. de Vries E, Quintero DC, Henríquez-Mendoza G, Herrán OF. Population attributable fractions for colorectal cancer and red and processed meats in Colombia—a macro-simulation study. Colomb Med (Cali). 2017;48(2):64–9.
15. Asadi K, Ferguson LR, Philpott M, Karunasinghe N. Cancer-preventive properties of an anthocyanin-enriched sweet potato in the APC(MIN) mouse model. J Cancer Prev. 2017;22(3):135–46.
16. Mehra K, Berkowitz A, Sanft T. Diet, physical activity, and body weight in cancer survivorship. Med Clin North Am. 2017;101(6):1151–65.
17. Reblin M, Birmingham WC, Kohlmann W, Graff T. Support and negation of colorectal cancer risk prevention behaviors: analysis of spousal discussions. Psychol Health Med. 2017;6:1–7.
18. Fan Y, Jin X, Man C, Gao Z, Wang X. Meta-analysis of the association between the inflammatory potential of diet and colorectal cancer risk. Oncotarget. 2017;8(35):59592–600.
19. Egnell M, Fassier P, Lécuyer L, Gonzalez R, Zelek L, Vasson MP, Hercberg S, Latino-Martel P, Galan P, Druesne-Pecollo N, Deschasaux M, Touvier M. Antioxidant intake from diet and supplements and risk of digestive cancers in middle-aged adults: results from the prospective NutriNet-Santé cohort. Br J Nutr. 2017;118(7):541–9.
20. Donovan MG, Selmin OI, Doetschman TC, Romagnolo DF. Mediterranean diet: prevention of colorectal cancer. Front Nutr. 2017;4:59.
21. Akinyemiju T, Moore JX, Pisu M. Mediating effects of cancer risk factors on the association between race and cancer incidence: analysis of the NIH-AARP Diet and Health Study. Ann Epidemiol. 2017;17:S1047–2797.
22. Jain A, Tiwari A, Verma A, Jain SK. Vitamins for cancer prevention and treatment: an insight. Curr Mol Med. 2017;17(5):321–40. https://doi.org/10.2174/1566524018666171205113329.
23. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Laure Preterre A, Iqbal K, Bechthold A, De Henauw S, Michels N, Devleesschauwer B, Boeing H, Schlesinger S. Food groups and risk of colorectal cancer. Int J Cancer. 2017. https://doi.org/10.1002/ijc.31198.
24. Tollosa DN, Van Camp J, Huybrechts I, Huybregts L, Van Loco J, De Smet S, Sterck E, Rabâi C, Van Hecke T, Vanhaecke L, Vossen E, Peeters M, Lachat C. Validity and reproducibility of a food frequency questionnaire for dietary factors related to colorectal cancer. Forum Nutr. 2017;9(11):pii:E1257. https://doi.org/10.3390/nu9111257.
25. Zhao Z, Feng Q, Yin Z, Shuang J, Bai B, Yu P, Guo M, Zhao Q. Red and processed meat consumption and colorectal cancer risk: a systematic review and meta-analysis. Oncotarget. 2017;8(47):83306–14.

26. Song M, Wu K, Meyerhardt JA, Ogino S, Wang M, Fuchs CS, Giovannucci EL, Chan AT. Fiber intake and survival after colorectal cancer diagnosis. JAMA Oncol. 2018;4(1):71–9. https://doi.org/10.1001/jamaoncol.2017.3684.
27. Sasso A, Latella G. Dietary components that counteract the increased risk of colorectal cancer related to red meat consumption. Int J Food Sci Nutr. 2017;2:1–13.
28. Brandão D, Ribeiro L. Dietary fatty acids modulation of human colon cancer cells: mechanisms and future perspectives. Int J Food Sci Nutr. 2017:1–14.
29. Watson H, Mitra S, Croden FC, Taylor M, Wood HM, Perry SL, Spencer JA, Quirke P, Toogood GJ, Lawton CL, Dye L, Loadman PM, Hull MA. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. Gut. 2017. pii: gutjnl-2017-314968. https://doi.org/10.1136/gutjnl-2017-314968.
30. Lee JY, Sim TB, Lee JE, Na HK. Chemopreventive and chemotherapeutic effects of fish oil derived omega-3 polyunsaturated fatty acids on colon carcinogenesis. Clin Nutr Res. 2017;6(3):147–60.
31. Zhang LJ, Chen B, Zhang JJ, Li J, Yang Q, Zhong QS, Zhan S, Liu H, Cai C. Serum polyunsaturated fatty acid metabolites as useful tool for screening potential biomarker of colorectal cancer. Prostaglandins Leukot Essent Fatty Acids. 2017;120:25–31.