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## Role of diet and gut microbiota on colorectal cancer immunomodulation

De Almeida CV *et al.* Diet and gut microbiota on immune system

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## Abstract

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers and it is characterized by genetic and epigenetic alterations, as well as by the infiltration of inflammatory cells among malignant and stromal cells. However, this dynamic infiltration, can be influenced by the microenvironment to promote tumor proliferation, survival and metastasis or cancer inhibition. In particular, the metabolites of cancer microenvironment are able to orchestrate the inflammatory cells, also developing a chronic inflammatory response that can be a predisposing condition for the CRC retention. In addition, some nutritional components might contribute to a chronic inflammatory condition, by regulating various immune and inflammatory pathways. Besides that, the diet strongly modulates the gut microbiota composition, which has a key role in maintaining the gut homeostasis and it is associated with the modulation of host inflammatory and immune responses. Therefore, diet has a fundamental role in CRC initiation, progression and mainly in prevention. In particular, functional foods as probiotics, prebiotics and symbiotics can have a potentially positive effect on health beyond basic nutrition and exhibit anti-inflammatory impacts. In this review, we discuss the influence of diet on the gut microbiota composition, focusing on its role on the gut inflammation/immunity. Finally, we describe the potential benefits of using probiotics and prebiotics in the modulation of host inflammatory response, as well as its application on the prevention and treatments of CRC.

**Key words:** Colorectal cancer; Diet; Inflammation; Immune response; Gut microbiota

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**Core tip:** The host immune system plays a central role in colorectal cancer (CRC) prevention and development. However, the immune response is deeply influenced by the gut microbiota composition, which in turn is modulated by the host diet. So, diet could be used as a strong ally to prevent CRC and to support its treatment.

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## INTRODUCTION

Inflammation consists of innate system with cellular and humoral responses to an injury induced by foreign organisms, dead cells or physical irritants stimulus. The aim is the attempting to inactivate the primary triggers and to regenerate the injured tissues. As a response to those injuries, a multifactorial network of chemical signals initiates and amplifies the recruitment of leukocytes (neutrophils, monocytes, and eosinophils) into the damage sites[1]. Nevertheless, when unregulated, the inflammatory process can become chronic with a persistent production of growth factors, reactive oxygen (RO) and nitrogen species (NS) that interact with the DNA of the cells. As result, we could identify permanent genomic alterations[2] that can lead the development of diseases, such as obesity[3], diabetes[4], and different cancer types[5,6].

Inflammation has been considered a predisposing condition for tumor development since 1863[7,8] and nowadays, at least 20% of all cancers are considered to be a direct consequence of chronic inflammatory process[9]. Besides that, many malignancy aspects, are affected by cancer-associated inflammation[10-12]. A chronic inflammation persistently promotes a pro- tumorigenic microenvironment, which is rich in cytokines, the mainly players in regulating the crosstalk between malignant cells and the surrounding stromal cells[13].

Chronic inflammatory disorders of the intestine, such as inflammatory bowel diseases (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), are considered to be a risk factor for colorectal cancer (CRC) since their initiation and progression are closely linked to the gene-environment and gene-gene interactions[14-17]. In this scenario, the inflammatory microenvironment is considered a crucial contributing factor to the CRC evolution[5,10,18,19]. Even being one of the most studied human malignancies; the CRC is still the third most common cancer worldwide with 140250 new cases estimated in 2018[20]. CRC occurs more frequently in high-income countries[21], mostly in sporadic forms, with only 25% of the cases having a familial feature[22]. Furthermore, the immune system also plays an important role in antitumor resistance[23].

Since some nutritional components, such as saturated fats, refined carbohydrates, and red meat, may have pro-inflammatory properties, the World Cancer Research Foundation and the American Institute for Cancer Research consider diet as one of the most important exogenous factors in the CRC etiology[24-28]. In addition, epidemiological studies demonstrated that diet-gene interactions could cause diverse somatic alterations known to be involved with gastrointestinal cancers development. These distinct alterations could be associated with the wide variation of CRC risk and progression, among different individuals[29]. Besides that, food and nutritional aspects have a major impact on the modulation of host gut microbiota (GM)[30-32] which in turn have a crucial symbiotic relationship with the host by regulating its physiology and immune system, which make them important factor in health and disease.

In this review, we point out the main aspects of CRC immunological scenario and the dietary impact on CRC-associated inflammation and GM modulation. Finally, we discuss the potential beneficial effects of probiotics and prebiotics administration to restore intestinal microbiota in the CRC prevention and as support of current anti-CRC treatments.

## IMPACT OF DIETARY HABITS AND LIFESTYLE IN CRC

Nowadays it is estimated that 30%-40% of the different cancers is caused by food, nutrition and other lifestyle factors, which make cancer a somewhat preventable disease. Overwhelming epidemiological data suggest that dietary factors, particularly those that result in overweight and obesity, influence risk, morbidity and mortality in multiple distinct cancers[33], especially CRC[29]. In sight of this assumption, the Department of Health and Human Services at National Institutes of Health and The Agency for Healthcare Research and Quality have attempted to implement lifestyle interventions among the population, aiming to alert the importance of diet and healthy lifestyle for the prevention of diseases, including cancer[34,35].

However, although being considered an important source of mutagenic compounds (that may lead to tumor development)[36], differently from other environmental factors, such as UV in melanoma (of which the role on cancer was already well established), the diet components’ association with cancer might well be not so linear (Table 1). The link between nutrition and cancer can be muddled by other health-compromising factors such as smoking and alcohol consumption, sedentary lifestyle and exposure to environmental toxicants, all well established as risk factors for cancer development[37]. Thus, even if it is hard to ‘isolate’ dietary risk factors in epidemiological studies, animal models have irrefutably demonstrated the nutrition influences on cancer evolution[38]. Besides that, as resumed on Figure 1, diet components could act in an indirect way on cancer initiation and progression, by increasing the production of endocrine factors, or changing inflammatory and immunological parameters, or by changing the GM composition[37].

Direct effects of dietary components on cancer development could be represented by the strong correlation between CRC incidence and excessive consumption of fats and proteins (mainly of animal sources), processed meat, and substantial alcohol consumption (more than 30 g/d)[39-41]. People are more susceptible to develop CRC when they have an increased intake of heterocyclic amines (HCA). The main HCA generated are 2-amino-1-methyl-6- phenyl-imidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f] quinoxaline (MeIQx), and benzo[a]pyrene (Bap) a polycyclic aromatic hydrocarbon (PAH), the first reported group of chemical carcinogens for human cells[42]. Otherwise, vegetarian diet seems to prevent cardiovascular diseases, type 2 diabetes and cancer[43], since fruits and vegetables invariably contain antioxidants, which scavenge free radicals and prevent DNA damages[44]. The vegetarian diet also includes a variety of nutrients associated with reduction of cancer development risk[45]. These compounds can protect cells by affecting the bio-transformation/detoxification pathways (phases I and II), the cell signaling and endogenous antioxidant system[46]. Some micronutrients, such as zinc[47] and selenium[48], have been extensively studied and seem to have important roles in cancer prevention, whereas complex compounds such as carotenoids[49], flavonoids[50], curcumin and silymarin[51], resveratrol[52], folate[53] and total oligomeric flavonoids[54] show both direct activity against tumor cells and *in vitro* immunomodulatory effects.

Besides that, nutrients such as glucose and amino acids increase the proliferative rate of tumor cells by activating the growth signaling proto- oncogenes such as IGF1R, PI3K, and AKT. In this way, deprivation of nutrients as well as nutrient-responsive growth factors seem to kill selectively high proliferative/resilient cancer cells by forcing their glycolytic asset toward an oxidative one. In fact, the calorie restriction (CR), defined as 30%–60% less of daily calorie requirement without malnutrition, is known to extend healthy life span with anticancer effects; being particularly effective in reducing the incidence, mass, and metastasis of breast cancer (due to the profound metabolic reprogramming that builds up adaptive stress responses)[55]. The controlled fasting also demonstrated to be a promising as adjuvant treatment in cancer therapy, mainly when associated with ketogenic diets (KD), that is low in carbohydrates and high in fats[56]. Moreover, short-term fasting exerts a beneficial impact on cancer immunosurveillance, since it induces the depletion of regulatory T cells, while an isocaloric diet with protein restriction has been demonstrated to induce an IRE1α-dependent UPR in cancer cells, enhancing cytotoxic CD8+ T cell (CTL). The presence of CTL in the tumor environment [tumor infiltrating lymphocytes (TIL)] is considered a positive outcome of the cancer treatment[55,57].

Diet can also contribute to cancer initiation and progression indirectly by favoring the obesity through over-nutrition and imbalanced diets. Obesity is closely linked to chronic inflammation, a significant cancer risk factor, as previously reported; since adipose tissue, when in a hyperplastic and hypertrophic status, is overloaded with a variety of pro-inflammatory immune cells, including classically activated macrophages, natural killer (NK) cells, mast cells, neutrophils, dendritic cells (DCs), B cells, CTL and T helpers 1 (Th1) cells[58]. These cells release pro-inflammatory factors, such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6), which lead to the increase of local and systemic inflammation and insulin resistance[33], becoming a strong promoter of tumor progression[59].

The presence of insulin resistance cells culminates to hyperinsulinemia and hyperglycemia, two important tumor-promoting effects; in fact, high concentrations of insulin, glucose, and non-esterified fatty acid (NEFA) are strong promoters of cell survival, growth, and proliferation and exert similar effects on tumor progenitors. In addition, high glucose concentrations favor glycolytic cancer cell metabolism characterized by enhanced glucose consumption[33]. Moreover, during obesity the adipose tissue macrophages (ATM), which in healthy conditions are skewed towards the M2 anti- inflammatory phenotype, are directed to pro-inflammatory M1 macrophages[60]. The M1 macrophages produce tumor-promoting cytokines (*e.g.*, TNF, IL-6, and IL-1b) and chemokines, such as Monocyte chemoattractant protein-1 (MCP-1) and Macrophage migration inhibitory factor (MIF)[61].

These data suggest that the diet modulation could be used as a form of cancer chemoprevention in healthy individuals. In pharmacology, chemoprevention is used to describe the “use of pharmacological or natural agents that inhibits the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of pre-malignant cells in which such damage has already occurred”[62].

Diet is also associated with the modulation of the gut microbiome that has a significant role in host metabolism, nutrition and physiological features (intestinal epithelial cell proliferation and differentiation, pH, function) as well as with the development of the immune system and protection against pathogens[63-65]. But, other than the diet, the GM is influenced by numerous and incompletely elucidated factors, such as host genetics, gender, age, anthropometric parameters, health/disease condition, geographic and socio- economic factors, exhibiting a huge diversity among individuals[66]. In healthy conditions, the GM plays a key role in the maintenance of the host physiological condition, by modulating the host’s immunity. The GM can influence the neutrophil migration and function[67] as well as the differentiation of T cell subsets into Th1, Th2, and Th17 or regulatory T cells (Tregs)[68-70]. By fermenting non-digestible complex carbohydrates such as dietary fiber, these commensal bacteria can produce short-chain fatty acids (SCFAs), which can cross the intestinal epithelium and reach the *lamina propria*, directly shaping the mucosal immune responses[71].

SCFAs modulate the phenotype and function of numerous immunologically relevant cells, such as colonic epithelial cells, macrophages, neutrophils and DCs[72]. Moreover, upon butyrate (one of the most produced SCAFs) stimulation, the CD4+ effector T cells increase the expression of T-bet and IFN-γ, being able to exert either beneficial or detrimental effects on the mucosal immune system, depending on its concentration and immunological milieu[73]. The presence of CTLs and IFN-γ-producing Th1 cells has been associated with prolonged survival[74,75], making some SCFAs as butyrate, propionate, or acetate being considered as a potential therapeutic tool to modulate inflammatory responses[76,77] including for CRC treatment[78]. Nevertheless, it is important to consider that SCFAs interact with the receptor GPR43 of colonic Tregs, as well as act as histone deacetylase (HDAC) inhibitors on the nucleus of mucosal peripheral Tregs, which in healthy conditions, helps to maintain intestinal immune homeostasis[79-81]. However, in the tumoral scenario (*e.g.*,CRC) it can impair the anti-tumor immunity, decreasing effectors T cells’ proliferation[82].

The role of the GM in the CRC progression deserves special attention since there is a strong interaction between GM, the intestinal barrier and the immune system’s cells[83-85]. Increased permeability of the epithelial layer, for example, allows the translocation of bacteria, antigens and toxins from the lumen to the *lamina propria* into the blood stream, which may initiate both local and systemic immune responses[86]. These changes can modify inflammatory cell response, requiring them to integrate signals (*e.g.*,cytokines) with cues, such as the local oxygen concentrations and other metabolites, promoting epithelial cells damages that can lead to tumor development[6].

Clinical, epidemiological and experimental data demonstrated that nutrition and foods have a central role in cancer onset, because it can change the tumor risk, the diagnosis after the onset and the life quality after treatment, other than contribute to ameliorate the adverse effects of chemotherapy and radiotherapy[87,88]. “Functional foods” and “nutraceuticals” are foods or food components that supply health benefits beyond basic nutrition, like peptides and proteins, amino acids, polyunsaturated fatty acids, dietary fibers, oligosaccharides, vitamins, minerals, antioxidants, probiotics and prebiotics, oils and fatty acids, carbohydrates and fibers[89]. In particular, we have focused on the immune-modulating ability of probiotics and prebiotics, which make them a potential adjuvant therapy on anti-CRC treatments.

## ADJUVANT ROLE OF PROBIOTICS AND PREBIOTICS IN CRC TREATMENTS

Probiotics are defined [(by the International Scientific Association for Probiotics and Prebiotics (ISAPP)] as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”[90]. They can excerpt health-promoting effects as antimicrobial activities against gut pathogens, decrease blood cholesterol levels, reduce colitis and inflammation, regulate of the host energy metabolism and modulate the immune system[91,92]. In the last years, the use of probiotics and prebiotics to control the onset/progression, or their application as adjuvant therapies in different diseases such as influenza[93], nonalcoholic fatty liver disease[94], pancreatitis[95], Parkinson disease[96] is being deeply investigated. In addition, their use is also being considered as a potential anti-cancer alternative or adjuvant therapy[97], since the pro/pre-biotics can improve the safety of and decrease the side effects of cancer treatment (as demonstrated in a few significant clinical trials)[98-100].

In addition to the direct role on GM modulation, probiotics present direct anti-cancer effects by the inactivation of carcinogens or mutagens, alteration of cell differentiation and by the production of immunomodulatory effects[101-103]. They increase the immunostimulatory activities, improving gut barrier actions by secreting anti-carcinogenic and anti-oxidative molecules[104,105], and finally activating mononuclear cells, lymphocytes and increasing immunoglobulin A production[106,107]. Probiotics’ administration also reduces the expression of certain Toll like receptors (TLRs), increasing the resistance of the epithelial barrier[102], and activate the phagocytes, which contribute to the maintenance of a vigilance state against tumor cells, especially in the early stages of progression[108].

The use of the *Lactobacillus rhamnosus* GG (LGG) strain decreased the cellular proliferation and carcinogenesis, since reduces β-catenin and Bcl-2 concentrations and increases p53 and Bax in rats. Moreover, this strain can reduce levels of pro-inflammatory molecules such as COX-2 and NF-κB-p65[103]. But, recently the administrated a mix of *Bifidobacterium spp and Lactobacillus spp* (the two main strains studied as probiotics in CRC therapies)[109], induced the secretion of anti-inflammatory cytokines and up-regulation of gene expression related to Treg and Th2 response[110]. However, we, in agreement and supported by other study, believe that Tregs can play protective roles prior to cancer initiation in “inflammation-prone” cancers but, after the tumor establishment, the Tregs can be co-opted by tumors, assuming a pro-tumorigenic role. In this way, we think that the use of specific probiotics should be applicate to prevent the early phases of CRC[111].

In CRC, the probiotics’ administration (aiming to modulate the GM and immune response) has been proved a promising innovative approach to counteract CRC progression and increase the chemotherapy effectiveness[112]. In an animal model, the administration of combined *Bifidobacterium longum* and *Bifidobacterium breve* has improved cancer control, strongly reduced tumor development and increased the efficacy of a PD-L1 blocking antibody against cancers[113]. The administration of *Lactobacillus lactis* can reduce the concentration of hydrogen peroxide (H2O2) and the increment of the catalase activity, decreasing tissue inflammation and colonic damage in a BALB/c mouse model. These data suggest that bacteria are capable of affecting mediators of inflammation, such as cytokines[114]. However, the use of some bacterial strains as probiotics could have side effects. The *Lactobacillus acidophilus* induces the mRNA expression of CXCR4 (stromal-derived factor-1 receptor) and reduces the tumor growth by 50% in treated mice and improves the apoptosis of CT-26 cancer cells, showing a role in metastasis prevention; but its administration also suppressed MHC-class I expression, which is crucial in cancer surveillance[115]. Due to the heterogeneous immunomodulatory roles of probiotics, we believe that, to accurate the target in the anti-CRC battle, a specific selection of the bacterial strain is fundamental to have a probiotic effectiveness. The disease stage progression, for example, could be an important determining factor in the probiotic strains choice. Moreover, the probiotics’ use in cancer patients generates concern due to the risk of infection and the transfer of antibiotic resistance. Nevertheless, randomized clinical trials have not reported a significant increase in the risk of adverse effects following probiotic supplementation, when compared to patients who received a placebo, or even have been proven safe and beneficial in these patients[116].

As an adjuvant therapy, concomitant to chemo/radiotherapy in CRC patients, some clinical assays have proven that probiotics can be an efficacious treatment[117], since the supplementation with *Lactobacillus rhamnosus* decreased the frequency of diarrhea, abdominal distress and dose reductions due to intestinal toxicity, in comparison to patients with placebo[118]. A randomized clinical trial about the efficacy and tolerability of *Lactobacillus rhamnosus* in patients with radiation-induced diarrhea, showed that patients which receive probiotics had better fecal consistency and decreased bowel movements[119].

Furthermore, since diet is a crucial risk factor in CRC susceptibility[120-122], the administration of prebiotics (that are able to favor specific changes in the composition and/or GM activity), could confer benefits upon the hosts well- being and health[123]. Prebiotics are carbohydrate, principally oligosaccharides, including fructooligossacharides (FOS) xyloogliosaccharides (XOS), inulin, fructans, galactogliosaccharides (GOS)[124,125]. They are able to resist the digestion in the human small intestine and then reach the colon, becoming substrate to fermentation by the GM. Prebiotics’ administration inhibits aberrant crypt formation and SCFAs’ production[126], reduces caecal pH[127] and in addition, it shows anti-carcinogenic impact on the presence of resistant starch, inulin and other oligo-fructans[128,129]. Besides that, the prebiotics show anti-cancer properties by down regulating the expression levels of COX-2, iNOS, NF-kB, and gastrointestinal glutathione peroxidase, by their bifidogenic effects and immunomodulatory roles. Finally, the prebiotics are also able to modulate the GM, inhibit the pathogens’ multiplication and enhance the cell apoptosis[130-134].

Probiotics work synergistically with prebiotics (symbiotic) to exert a beneficial impact on GM and generally on intestinal health, which make them a potential therapeutic strategy in the CRC. *Lactobacillus* and *Bifidobacteria* combined with prebiotics, such as oligofructose and inulin, showed to counteract tumor progression. A pro/prebiotic cocktail of *Bifidobacterium infantum, Lactobacillus acidophilus*, *Bifidobacterium bifidum*, maltodextrin (LBB) and oligofructose increased intestinal ZO-1, MUC2, TLR2 and occludin, and reduced COX-2 and TLR4 in rats[102].

## CONCLUSION

The manipulation of nutrients could have potential implications for both the prevention as well as the treatment of CRC since it can affect a diverse range of mechanisms, such as cell signaling, apoptosis, and mainly immune system regulation, other than the overlying influence on the gut microbiome.

Diet has a great ability to modulate the cell responses to environmental stimuli, as well as a balanced nutritional regime can improve the immune metabolism, by enhancing the cytotoxic efficiency of CD8+ TIL within the tumor mass, showing a potential role in improving cancer prognosis. Furthermore, diet can modulate the GM; and since the intestinal immune system is constantly exposed to numerous xenobiotic and endobiotic metabolites (which shape mucosal immune function and inflammation), the intestinal microbiome along with the local immune system maintain the balance between mucosal tolerance and inflammation. In other words, the GM manipulation should be a promising treatment to improve the outcomes in CRC.

The fine mechanisms by which the dietary nutrients enhance the anti- cancer effects of standard anticancer therapies have not been fully elucidated yet.

But the actual scenario of poor prognosis for many cancer patients, in addition to the severe documented adverse events of current anti-cancer therapies, suggest the crucial need to find complementary treatments, that have limited patient toxicity and simultaneously enhance therapy responses in cancer versus normal cells. The data discussed in this review seem suggest that the investigation of the probiotic/prebiotic application as coadjutant anti-cancer treatments can give in the future interesting results; however, we believe that it is still necessary to plan different clinical trial in order to confirm these very promising results in humans.

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## REFERENCES

1 **Karin M**, Clevers H. Reparative inflammation takes charge of tissue regeneration. *Nature* 2016; **529**: 307-315 [PMID: 26791721 DOI: 10.1038/nature17039]

2 **Maeda H**, Akaike T. Nitric oxide and oxygen radicals in infection, inflammation, and cancer. *Biochemistry* (Mosc) 1998; **63**: 854-865 [PMID: 9721338]

3 **Ellulu MS**, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 2017; **13**: 851-863 [PMID: 28721154 DOI: 10.5114/aoms.2016.58928]

4 **Wellen KE**, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005; **115**: 1111-1119 [PMID: 15864338 DOI: 10.1172/JCI25102]

5 **Grivennikov SI**, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; **140**: 883-899 [PMID: 20303878 DOI: 10.1016/j.cell.2010.01.025]

6 **Hobson-Gutierrez SA**, Carmona-Fontaine C. The metabolic axis of macrophage and immune cell polarization. *Dis Model Mech* 2018; **11** [PMID: 29991530 DOI: 10.1242/dmm.034462]

7 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545 [PMID: 11229684 DOI: 10.1016/S0140-6736(00)04046-0]

8 **Schmidt A**, Weber OF. In memoriam of Rudolf virchow: a historical retrospective including aspects of inflammation, infection and neoplasia. *Contrib Microbiol* 2006; **13**: 1-15 [PMID: 16627956 DOI: 10.1159/000092961]

9 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**: 7-30 [PMID: 26742998 DOI: 10.3322/caac.21332]

10 **Mantovani A**, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038/nature07205]

11 **Balkwill F**, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* 2005; **7**: 211-217 [PMID: 15766659 DOI: 10.1016/j.ccr.2005.02.013]

12 **DeNardo DG**, Johansson M, Coussens LM. Immune cells as mediators of solid tumor metastasis. *Cancer Metastasis Rev* 2008; **27**: 11-18 [PMID: 18066650 DOI: 10.1007/s10555-007-9100-0]

13 **Landskron G**, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res* 2014; **2014**: 149185 [PMID: 24901008 DOI: 10.1155/2014/149185]

14 **Yi M**, Xu J, Liu P, Chang GJ, Du XL, Hu CY, Song Y, He J, Ren Y, Wei Y, Yang J, Hunt KK, Li X. Comparative analysis of lifestyle factors, screening test use, and clinicopathologic features in association with survival among Asian Americans with colorectal cancer. *Br J Cancer* 2013; **108**: 1508-1514 [PMID: 23470470 DOI: 10.1038/bjc.2013.97]

15 **Tung J**, Politis CE, Chadder J, Han J, Niu J, Fung S, Rahal R, Earle CC. The north-south and east-west gradient in colorectal cancer risk: a look at the distribution of modifiable risk factors and incidence across Canada. *Curr Oncol* 2018; **25**: 231-235 [PMID: 29962842 DOI: 10.3747/co.25.4071]

16 **Patel P**, De P. Trends in colorectal cancer incidence and related lifestyle risk factors in 15-49-year-olds in Canada, 1969-2010. *Cancer Epidemiol* 2016; **42**: 90-100 [PMID: 27060626 DOI: 10.1016/j.canep.2016.03.009]

17 **Wang X**, Chan AT, Slattery ML, Chang-Claude J, Potter JD, Gallinger S, Caan B, Lampe JW, Newcomb PA, Zubair N, Hsu L, Schoen RE, Hoffmeister M, Brenner H, Le Marchand L, Peters U, White E. Influence of Smoking, Body Mass Index, and Other Factors on the Preventive Effect of Nonsteroidal Anti-Inflammatory Drugs on Colorectal Cancer Risk. *Cancer Res* 2018; **78**: 4790-4799 [PMID: 29921691 DOI: 10.1158/0008-5472.CAN-18-0326]

18 **Feagins LA**, Souza RF, Spechler SJ. Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 297-305 [PMID: 19404270 DOI: 10.1038/nrgastro.2009.44]

19 **Lakatos PL**, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. *World J Gastroenterol* 2008; **14**: 3937-3947 [PMID: 18609676 DOI: 10.3748/wjg.14.3937]

20 **American Cancer Society**, Cancer Facts and Figures 2018. Atlanta: American Cancer Society, 2018 Accessed July 11, 2018

21 **Goldstein NS**. Serrated pathway and APC (conventional)-type colorectal polyps: molecular-morphologic correlations, genetic pathways, and implications for classification. *Am J Clin Pathol* 2006; **125**: 146-153 [PMID: 16483003 DOI: 10.1309/87BD0C6UCGUG236J]

22 **Carethers JM**, Jung BH. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. *Gastroenterology* 2015; **149**: 1177-1190.e3 [PMID: 26216840 DOI: 10.1053/j.gastro.2015.06.047]

23 **Grizzi F**, Di Ieva A, Russo C, Frezza EE, Cobos E, Muzzio PC, Chiriva-Internati M. Cancer initiation and progression: an unsimplifiable complexity. *Theor Biol Med Model* 2006; **3**: 37 [PMID: 17044918 DOI: 10.1186/1742-4682-3-37]

24 **World Cancer Research Fund**, American Institute for Cancer Research. In: Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007; p1-537

25 **Hardman WE**. Diet components can suppress inflammation and reduce cancer risk. *Nutr Res Pract* 2014; **8**: 233-240 [PMID: 24944766 DOI: 10.4162/nrp.2014.8.3.233]

26 **Dumas JA**, Bunn JY, Nickerson J, Crain KI, Ebenstein DB, Tarleton EK, Makarewicz J, Poynter ME, Kien CL. Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. *Metabolism* 2016; **65**: 1582-1588 [PMID: 27621193 DOI: 10.1016/j.metabol.2016.08.003]

27 **López-Alarcón M**, Perichart-Perera O, Flores-Huerta S, Inda-Icaza P, Rodríguez-Cruz M, Armenta-Álvarez A, Bram-Falcón MT, Mayorga-Ochoa M. Excessive refined carbohydrates and scarce micronutrients intakes increase inflammatory mediators and insulin resistance in prepubertal and pubertal obese children independently of obesity. *Mediators Inflamm* 2014; **2014**: 849031 [PMID: 25477716 DOI: 10.1155/2014/849031]

28 **Samraj AN**, Pearce OM, Läubli H, Crittenden AN, Bergfeld AK, Banda K, Gregg CJ, Bingman AE, Secrest P, Diaz SL, Varki NM, Varki A. A red meat-derived glycan promotes inflammation and cancer progression. *Proc Natl Acad Sci USA* 2015; **112**: 542-547 [PMID: 25548184 DOI: 10.1073/pnas.1417508112]

29 **Bingham SA**. Diet and colorectal cancer prevention. *Biochem Soc Trans* 2000; **28**: 12-16 [PMID: 10816091 DOI: 10.1042/bst0280012]

30 **De Filippo C**, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci USA* 2010; **107**: 14691-14696 [PMID: 20679230 DOI: 10.1073/pnas.1005963107]

31 **Kałużna-Czaplińska J**, Gątarek P, Chartrand MS, Dadar M, Bjørklund G. Is there a relationship between intestinal microbiota, dietary compounds, and obesity? Trends Food Sci Technol 2017; **70:** 105–113 [DOI: 10.1016/j.tifs.2017.10.010]

32 **Li W**, Dowd SE, Scurlock B, Acosta-Martinez V, Lyte M. Memory and learning behavior in mice is temporally associated with diet-induced alterations in gut bacteria. *Physiol Behav* 2009; **96**: 557-567 [PMID: 19135464 DOI: 10.1016/j.physbeh.2008.12.004]

33 **Font-Burgada J**, Sun B, Karin M. Obesity and Cancer: The Oil that Feeds the Flame. *Cell Metab* 2016; **23**: 48-62 [PMID: 26771116 DOI: 10.1016/j.cmet.2015.12.015]

34 **Ammerman A**, Lindquist C, Hersey J, Jackman AM, Gavin NI, Garces C, Lohr KN, Cary TS, Whitener BL. Efficacy of interventions to modify dietary behavior related to cancer risk. *Evid Rep Technol Assess* (Summ) 2000; : 1-4 [PMID: 11190254]

35 Theory at a glance: a guide for health promotion practice. 2nd ed. U.S. Dept. of Health and Human Services, National Institutes of Health, National Cancer Institute, 2005; p1-64

36 **Branca F**, Hanley AB, Pool-Zobel B, Verhagen H. Biomarkers in disease and health. *Br J Nutr* 2001; **86** Suppl 1: S55-S92 [PMID: 11520424 DOI: 10.1079/BJN2001339]

37 **Zitvogel L**, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. *Nat Immunol* 2017; **18**: 843-850 [PMID: 28722707 DOI: 10.1038/ni.3754]

38 **Deng T**, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, Inflammation, and Cancer. *Annu Rev Pathol* 2016; **11**: 421-449 [PMID: 27193454 DOI: 10.1146/annurev-pathol-012615-044359]

39 **American Cancer Society**, Cancer Facts and Figures 2008. Atlanta: American Cancer Society, 2008 Accessed September 29, 2018

40 **Norat T**, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer* 2002; **98**: 241-256 [PMID: 11857415 DOI: 10.1002/ijc.10126]

41 **Ognjanovic S**, Yamamoto J, Maskarinec G, Le Marchand L. NAT2, meat consumption and colorectal cancer incidence: an ecological study among 27 countries. *Cancer Causes Control* 2006; **17**: 1175-1182 [PMID: 17006723 DOI: 10.1007/s10552-006-0061-3]

42 **Butler LM**, Sinha R, Millikan RC, Martin CF, Newman B, Gammon MD, Ammerman AS, Sandler RS. Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. *Am J Epidemiol* 2003; **157**: 434-445 [PMID: 12615608 DOI: 10.1093/aje/kwf221]

43 **McEvoy CT**, Temple N, Woodside JV. Vegetarian diets, low-meat diets and health: a review. *Public Health Nutr* 2012; **15**: 2287-2294 [PMID: 22717188 DOI: 10.1017/S1368980012000936]

44 **Møller P**, Loft S. Dietary antioxidants and beneficial effect on oxidatively damaged DNA. *Free Radic Biol Med* 2006; **41**: 388-415 [PMID: 16843820 DOI: 10.1016/j.freeradbiomed.2006.04.001]

45 **Kelly JH Jr**, Sabaté J. Nuts and coronary heart disease: an epidemiological perspective. *Br J Nutr* 2006; **96** Suppl 2: S61-S67 [PMID: 17125535 DOI: 10.1017/BJN20061865]

46 **Collins AR**, Azqueta A, Langie SA. Effects of micronutrients on DNA repair. *Eur J Nutr* 2012; **51**: 261-279 [PMID: 22362552 DOI: 10.1007/s00394-012-0318-4]

47 **Ho E**. Zinc deficiency, DNA damage and cancer risk. *J Nutr Biochem* 2004; **15**: 572-578 [PMID: 15542347 DOI: 10.1016/j.jnutbio.2004.07.005]

48 **Jayaprakash V**, Marshall JR. Selenium and other antioxidants for chemoprevention of gastrointestinal cancers. *Best Pract Res Clin Gastroenterol* 2011; **25**: 507-518 [PMID: 22122767 DOI: 10.1016/j.bpg.2011.09.006]

49 **Astley SB**, Elliott RM, Archer DB, Southon S. Increased cellular carotenoid levels reduce the persistence of DNA single-strand breaks after oxidative challenge. *Nutr Cancer* 2002; **43**: 202-213 [PMID: 12588700 DOI: 10.1207/S15327914NC432\_11]

50 **Aherne SA**, O'Brien NM. Lack of effect of the flavonoids, myricetin, quercetin, and rutin, on repair of H2O2-induced DNA single-strand breaks in Caco-2, Hep G2, and V79 cells. *Nutr Cancer* 2000; **38**: 106-115 [PMID: 11341035 DOI: 10.1207/S15327914NC381\_15]

51 **Niture SK**, Velu CS, Smith QR, Bhat GJ, Srivenugopal KS. Increased expression of the MGMT repair protein mediated by cysteine prodrugs and chemopreventative natural products in human lymphocytes and tumor cell lines. *Carcinogenesis* 2007; **28**: 378-389 [PMID: 16950796 DOI: 10.1093/carcin/bgl155]

52 **Gatz SA**, Keimling M, Baumann C, Dörk T, Debatin KM, Fulda S, Wiesmüller L. Resveratrol modulates DNA double-strand break repair pathways in an ATM/ATR-p53- and -Nbs1-dependent manner. *Carcinogenesis* 2008; **29**: 519-527 [PMID: 18174244 DOI: 10.1093/carcin/bgm283]

53 **Williams JD**, Jacobson MK. Photobiological implications of folate depletion and repletion in cultured human keratinocytes. *J Photochem Photobiol B* 2010; **99**: 49-61 [PMID: 20211567 DOI: 10.1016/j.jphotobiol.2010.02.003]

54 **Bouhlel I**, Valenti K, Kilani S, Skandrani I, Ben Sghaier M, Mariotte AM, Dijoux-Franca MG, Ghedira K, Hininger-Favier I, Laporte F, Chekir-Ghedira L. Antimutagenic, antigenotoxic and antioxidant activities of Acacia salicina extracts (ASE) and modulation of cell gene expression by H2O2 and ASE treatment. *Toxicol In Vitro* 2008; **22**: 1264-1272 [PMID: 18515041 DOI: 10.1016/j.tiv.2008.04.008]

55 **Lettieri-Barbato D**, Aquilano K. Pushing the Limits of Cancer Therapy: The Nutrient Game. *Front Oncol* 2018; **8**: 148 [PMID: 29868472 DOI: 10.3389/fonc.2018.00148]

56 **Allen BG**, Bhatia SK, Anderson CM, Eichenberger-Gilmore JM, Sibenaller ZA, Mapuskar KA, Schoenfeld JD, Buatti JM, Spitz DR, Fath MA. Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism. *Redox Biol* 2014; **2**: 963-970 [PMID: 25460731 DOI: 10.1016/j.redox.2014.08.002]

57 **De Almeida CV**, Kaneno R and Amedei A. T Cells in Gastrointestinal Cancers: Role and Therapeutic Strategies. In: Frontiers in Anti-Cancer Drug Discovery, 8th ed. [DOI: 10.2174/97816810838961170801]

58 **Ferrante AW Jr**. The immune cells in adipose tissue. *Diabetes Obes Metab* 2013; **15** Suppl 3: 34-38 [PMID: 24003919 DOI: 10.1111/dom.12154]

59 **Grivennikov SI**, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann Rheum Dis* 2011; **70** Suppl 1: i104-i108 [PMID: 21339211 DOI: 10.1136/ard.2010.140145]

60 **McNelis JC**, Olefsky JM. Macrophages, immunity, and metabolic disease. *Immunity* 2014; **41**: 36-48 [PMID: 25035952 DOI: 10.1016/j.immuni.2014.05.010]

61 **Weisberg SP**, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*2003; **112**: 1796-1808 [PMID: 14679176 DOI: 10.1172/JCI19246]

62 **Hong WK**, Sporn MB. Recent advances in chemoprevention of cancer. *Science* 1997; **278**: 1073-1077 [PMID: 9353183 DOI: 10.1126/science.278.5340.1073]

63 **Guinane CM**, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. *Therap Adv Gastroenterol* 2013; **6**: 295-308 [PMID: 23814609 DOI: 10.1177/1756283X13482996]

64 **Korecka A**, Arulampalam V. The gut microbiome: scourge, sentinel or spectator? *J Oral Microbiol* 2012; **4** [PMID: 22368769 DOI: 10.3402/jom.v4i0.9367]

65 **Kurokawa K**, Itoh T, Kuwahara T, Oshima K, Toh H, Toyoda A, Takami H, Morita H, Sharma VK, Srivastava TP, Taylor TD, Noguchi H, Mori H, Ogura Y, Ehrlich DS, Itoh K, Takagi T, Sakaki Y, Hayashi T, Hattori M. Comparative metagenomics revealed commonly enriched gene sets in human gut microbiomes. *DNA Res* 2007; **14**: 169-181 [PMID: 17916580 DOI: 10.1093/dnares/dsm018]

66 **Ardissone AN**, de la Cruz DM, Davis-Richardson AG, Rechcigl KT, Li N, Drew JC, Murgas-Torrazza R, Sharma R, Hudak ML, Triplett EW, Neu J. Meconium microbiome analysis identifies bacteria correlated with premature birth. *PLoS One* 2014; **9**: e90784 [PMID: 24614698 DOI: 10.1371/journal.pone.0090784]

67 **Owaga E**, Hsieh RH, Mugendi B, Masuku S, Shih CK, Chang JS. Th17 Cells as Potential Probiotic Therapeutic Targets in Inflammatory Bowel Diseases. *Int J Mol Sci*2015; **16**: 20841-20858 [PMID: 26340622 DOI: 10.3390/ijms160920841]

68 **Francino MP**. Early development of the gut microbiota and immune health. *Pathogens* 2014; **3**: 769-790 [PMID: 25438024 DOI: 10.3390/pathogens3030769]

69 **Hooper LV**, Gordon JI. Commensal host-bacterial relationships in the gut. *Science* 2001; **292**: 1115-1118 [PMID: 11352068 DOI: 10.1126/science.1058709]

70 **Belkaid Y**, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; **157**: 121-141 [PMID: 24679531 DOI: 10.1016/j.cell.2014.03.011]

71 **Koh A**, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell* 2016; **165**: 1332-1345 [PMID: 27259147 DOI: 10.1016/j.cell.2016.05.041]

72 **Luu M**, Weigand K, Wedi F, Breidenbend C, Leister H, Pautz S, Adhikary T, Visekruna A. Regulation of the effector function of CD8+ T cells by gut microbiota-derived metabolite butyrate. *Sci Rep* 2018; **8**: 14430 [PMID: 30258117 DOI: 10.1038/s41598-018-32860-x]

73 **Kespohl M**, Vachharajani N, Luu M, Harb H, Pautz S, Wolff S, Sillner N, Walker A, Schmitt-Kopplin P, Boettger T, Renz H, Offermanns S, Steinhoff U, Visekruna A. The Microbial Metabolite Butyrate Induces Expression of Th1-Associated Factors in CD4+ T Cells. *Front Immunol* 2017; **8**: 1036 [PMID: 28894447 DOI: 10.3389/fimmu.2017.01036]

74 **Hirt C**, Eppenberger-Castori S, Sconocchia G, Iezzi G, Tornillo L, Terracciano L, Spagnoli GC, Droeser RA. Colorectal carcinoma infiltration by myeloperoxidase-expressing neutrophil granulocytes is associated with favorable prognosis. *Oncoimmunology* 2013; **2**: e25990 [PMID: 24244897 DOI: 10.4161/onci.25990]

75 **Niccolai E**, Cappello P, Taddei A, Ricci F, D'Elios MM, Benagiano M, Bechi P, Bencini L, Ringressi MN, Coratti A, Cianchi F, Bonello L, Di Celle PF, Prisco D, Novelli F, Amedei A. Peripheral ENO1-specific T cells mirror the intratumoral immune response and their presence is a potential prognostic factor for pancreatic adenocarcinoma. *Int J Oncol* 2016; **49**: 393-401 [PMID: 27210467 DOI: 10.3892/ijo.2016.3524]

76 **Thorburn AN**, Macia L, Mackay CR. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* 2014; **40**: 833-842 [PMID: 24950203 DOI: 10.1016/j.immuni.2014.05.014]

77 **Dorrestein PC**, Mazmanian SK, Knight R. Finding the missing links among metabolites, microbes, and the host. *Immunity* 2014; **40**: 824-832 [PMID: 24950202 DOI: 10.1016/j.immuni.2014.05.015]

78 **Gomes SD**, Oliveira CS, Azevedo-Silva J, Casanova M, Barreto J, Pereira H, Chaves S, Rodrigues L, Casal M, Corte-Real M, Baltazar F, Preto A. The Role of Diet Related Short-Chain Fatty Acids in Colorectal Cancer Metabolism and Survival: Prevention and Therapeutic Implications. *Curr Med Chem* 2018; Epub ahead of print [PMID: 29848266 DOI: 10.2174/0929867325666180530102050]

79 **Smith PM**, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 2013; **341**: 569-573 [PMID: 23828891 DOI: 10.1126/science.1241165]

80 **Furusawa Y**, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013; **504**: 446-450 [PMID: 24226770 DOI: 10.1038/nature12721]

81 **Arpaia N**, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, Liu H, Cross JR, Pfeffer K, Coffer PJ, Rudensky AY. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 2013; **504**: 451-455 [PMID: 24226773 DOI: 10.1038/nature12726]

82 **Sasada T**, Kimura M, Yoshida Y, Kanai M, Takabayashi A. CD4+CD25+ regulatory T cells in patients with gastrointestinal malignancies: possible involvement of regulatory T cells in disease progression. *Cancer* 2003; **98**: 1089-1099 [PMID: 12942579 DOI: 10.1002/cncr.11618]

83 **Takiishi T**, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. *Tissue Barriers* 2017; **5**: e1373208 [PMID: 28956703 DOI: 10.1080/21688370.2017.1373208]

84 **Russo E**, Taddei A, Ringressi MN, Ricci F, Amedei A. The interplay between the microbiome and the adaptive immune response in cancer development. *Therap Adv Gastroenterol* 2016; **9**: 594-605 [PMID: 27366226 DOI: 10.1177/1756283X16635082]

85 **Russo E,** Bacci G, Chiellini C, Fagorzi C, Niccolai E, Taddei A, Ricci F, Ringressi MN, Borrelli R, Melli F, Miloeva M, Bechi P, Mengoni A, Fani R, Amedei A. Preliminary Comparison of Oral and Intestinal Human Microbiota in Patients with Colorectal Cancer: A Pilot Study. *Front Microbiol* 2018; **8**: 2699

86 **Mu Q**, Kirby J, Reilly CM, Luo XM. Leaky Gut As a Danger Signal for Autoimmune Diseases. *Front Immunol* 2017; **8**: 598 [PMID: 28588585 DOI: 10.3389/fimmu.2017.00598]

87 **Chen Z**, Chen J, Collins R, Guo Y, Peto R, Wu F, Li L; China Kadoorie Biobank (CKB) collaborative group. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *Int J Epidemiol* 2011; **40**: 1652-1666 [PMID: 22158673 DOI: 10.1093/ije/dyr120]

88 **Wu QJ**, Yang Y, Vogtmann E, Wang J, Han LH, Li HL, Xiang YB. Cruciferous vegetables intake and the risk of colorectal cancer: a meta-analysis of observational studies. *Ann Oncol* 2013; **24**: 1079-1087 [PMID: 23211939 DOI: 10.1093/annonc/mds601]

89 **El Sohaimy SA**. Functional Foods and Nutraceuticals-Modern Approach to Food Science. *World Applied Sciences Journal* 2012; **20**: 691-708 [DOI: 10.5829/idosi.wasj.2012.20.05.66119]

90 **Hill C**, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 506-514 [PMID: 24912386 DOI: 10.1038/nrgastro.2014.66]

91 **Raman M**, Ambalam P, Kondepudi KK, Pithva S, Kothari C, Patel AT, Purama RK, Dave JM, Vyas BR. Potential of probiotics, prebiotics and synbiotics for management of colorectal cancer. *Gut Microbes* 2013; **4**: 181-192 [PMID: 23511582 DOI: 10.4161/gmic.23919]

92 **Liévin-Le Moal V**, Servin AL. Anti-infective activities of lactobacillus strains in the human intestinal microbiota: from probiotics to gastrointestinal anti-infectious biotherapeutic agents. *Clin Microbiol Rev* 2014; **27**: 167-199 [PMID: 24696432 DOI: 10.1128/CMR.00080-13]

93 **Yeh TL**, Shih PC, Liu SJ, Lin CH, Liu JM, Lei WT, Lin CY. The influence of prebiotic or probiotic supplementation on antibody titers after influenza vaccination: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther* 2018; **12**: 217-230 [PMID: 29416317 DOI: 10.2147/DDDT.S155110]

94 **Tarantino G**, Finelli C. Systematic review on intervention with prebiotics/probiotics in patients with obesity-related nonalcoholic fatty liver disease. *Future Microbiol* 2015; **10**: 889-902 [PMID: 26000656 DOI: 10.2217/fmb.15.13]

95 **Plaudis H**, Pupelis G, Zeiza K, Boka V. Early low volume oral synbiotic/prebiotic supplemented enteral stimulation of the gut in patients with severe acute pancreatitis: a prospective feasibility study. *Acta Chir Belg* 2012; **112**: 131-138 [PMID: 22571076 DOI: 10.1080/00015458.2012.11680811]

96 **Barichella M**, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, Pinelli G, Privitera G, Cesari I, Faierman SA, Caccialanza R, Pezzoli G, Cereda E. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: An RCT. *Neurology* 2016; **87**: 1274-1280 [PMID: 27543643 DOI: 10.1212/WNL.0000000000003127]

97 **Hendler R**, Zhang Y. Probiotics in the Treatment of Colorectal Cancer. *Medicines* (Basel) 2018; **5** [PMID: 30205429 DOI: 10.3390/medicines5030101]

98 **Russo E**, Amedei A. The Role of the Microbiota in the Genesis of Gastrointestinal Cancers. In: Frontiers in Anti-Cancer Drug Discovery, 7th ed. 2018 [DOI: 10.2174/97816810856231180701]

99 **Mego M**, Chovanec J, Vochyanova-Andrezalova I, Konkolovsky P, Mikulova M, Reckova M, Miskovska V, Bystricky B, Beniak J, Medvecova L, Lagin A, Svetlovska D, Spanik S, Zajac V, Mardiak J, Drgona L. Prevention of irinotecan induced diarrhea by probiotics: A randomized double blind, placebo controlled pilot study. *Complement Ther Med* 2015; **23**: 356-362 [PMID: 26051570 DOI: 10.1016/j.ctim.2015.03.008]

100 **Delia P**, Sansotta G, Donato V, Frosina P, Messina G, De Renzis C, Famularo G. Use of probiotics for prevention of radiation-induced diarrhea. *World J Gastroenterol* 2007; **13**: 912-915 [PMID: 17352022 DOI: 10.3748/wjg.v13.i6.912]

101 **Gamallat Y**, Meyiah A, Kuugbee ED, Hago AM, Chiwala G, Awadasseid A, Bamba D, Zhang X, Shang X, Luo F, Xin Y. Lactobacillus rhamnosus induced epithelial cell apoptosis, ameliorates inflammation and prevents colon cancer development in an animal model. *Biomed Pharmacother* 2016; **83**: 536-541 [PMID: 27447122 DOI: 10.1016/j.biopha.2016.07.001]

102 **Kuugbee ED**, Shang X, Gamallat Y, Bamba D, Awadasseid A, Suliman MA, Zang S, Ma Y, Chiwala G, Xin Y, Shang D. Structural Change in Microbiota by a Probiotic Cocktail Enhances the Gut Barrier and Reduces Cancer via TLR2 Signaling in a Rat Model of Colon Cancer. *Dig Dis Sci* 2016; **61**: 2908-2920 [PMID: 27384052 DOI: 10.1007/s10620-016-4238-7]

103 **Manuzak JA**, Hensley-McBain T, Zevin AS, Miller C, Cubas R, Agricola B, Gile J, Richert-Spuhler L, Patilea G, Estes JD, Langevin S, Reeves RK, Haddad EK, Klatt NR. Enhancement of Microbiota in Healthy Macaques Results in Beneficial Modulation of Mucosal and Systemic Immune Function. *J Immunol* 2016; **196**: 2401-2409 [PMID: 26826246 DOI: 10.4049/jimmunol.1502470]

104 **Kahouli I**, Tomaro-Duchesneau C, Prakash S. Probiotics in colorectal cancer (CRC) with emphasis on mechanisms of action and current perspectives. *J Med Microbiol* 2013; **62**: 1107-1123 [PMID: 23558140 DOI: 10.1099/jmm.0.048975-0]

105 **Chong ES**. A potential role of probiotics in colorectal cancer prevention: review of possible mechanisms of action. *World J Microbiol Biotechnol* 2014; **30**: 351-374 [PMID: 24068536 DOI: 10.1007/s11274-013-1499-6]

106 Scientific concepts of functional foods in Europe. Consensus document. *Br J Nutr* 1999; **81** Suppl 1: S1-27 [PMID: 10999022]

107 **Reig AD**, Anesto J. Prebióticos y probióticos, una relación beneficiosa. *Rev* *Cuba Aliment Nutr* 2002; **16**: 63-68

108 **Delcenserie V**, Martel D, Lamoureux M, Amiot J, Boutin Y, Roy D. Immunomodulatory effects of probiotics in the intestinal tract. *Curr Issues Mol Biol* 2008; **10**: 37-54 [PMID: 18525105]

109 **Ambalam P**, Raman M, Purama RK, Doble M. Probiotics, prebiotics and colorectal cancer prevention. *Best Pract Res Clin Gastroenterol* 2016; **30**: 119-131 [PMID: 27048903 DOI: 10.1016/j.bpg.2016.02.009]

110 **Salehipour Z**, Haghmorad D, Sankian M, Rastin M, Nosratabadi R, Soltan Dallal MM, Tabasi N, Khazaee M, Nasiraii LR, Mahmoudi M. Bifidobacterium animalis in combination with human origin of Lactobacillus plantarum ameliorate neuroinflammation in experimental model of multiple sclerosis by altering CD4+ T cell subset balance. *Biomed Pharmacother* 2017; **95**: 1535-1548 [PMID: 28946394 DOI: 10.1016/j.biopha.2017.08.117]

111 **Niccolai E**, Ricci F, Russo E, Nannini G, Emmi G, Taddei A, Ringressi MN, Melli F, Miloeva M, Cianchi F, Bechi P, Prisco D, Amedei A. The Different Functional Distribution of "Not Effector" T Cells (Treg/Tnull) in Colorectal Cancer. *Front Immunol* 2017; **8**: 1900 [PMID: 29375559 DOI: 10.3389/fimmu.2017.01900]

112 **Pandey KR**, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics- a review. *J Food Sci Technol* 2015; **52**: 7577-7587 [PMID: 26604335 DOI: 10.1007/s13197-015-1921-1]

113 **Sivan A**, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, Benyamin FW, Lei YM, Jabri B, Alegre ML, Chang EB, Gajewski TF. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 2015; **350**: 1084-1089 [PMID: 26541606 DOI: 10.1126/science.aac4255]

114 **de Moreno de LeBlanc A**, Matar C, Perdigón G. The application of probiotics in cancer. *Br J Nutr* 2007; **98** Suppl 1: S105-S110 [PMID: 17922945 DOI: 10.1017/S0007114507839602]

115 **Chen CC**, Lin WC, Kong MS, Shi HN, Walker WA, Lin CY, Huang CT, Lin YC, Jung SM, Lin TY. Oral inoculation of probiotics Lactobacillus acidophilus NCFM suppresses tumour growth both in segmental orthotopic colon cancer and extra-intestinal tissue. *Br J Nutr* 2012; **107**: 1623-1634 [PMID: 21992995 DOI: 10.1017/S0007114511004934]

116 **Mego M**, Holec V, Drgona L, Hainova K, Ciernikova S, Zajac V. Probiotic bacteria in cancer patients undergoing chemotherapy and radiation therapy. *Complement Ther Med* 2013; **21**: 712-723 [PMID: 24280481 DOI: 10.1016/j.ctim.2013.08.018]

117 **Wang YH**, Yao N, Wei KK, Jiang L, Hanif S, Wang ZX, Pei CX. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis. *Eur J Clin Nutr* 2016; **70**: 1246-1253 [PMID: 27329608 DOI: 10.1038/ejcn.2016.102]

118 **Osterlund P**, Ruotsalainen T, Korpela R, Saxelin M, Ollus A, Valta P, Kouri M, Elomaa I, Joensuu H. Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. *Br J Cancer* 2007; **97**: 1028-1034 [PMID: 17895895 DOI: 10.1038/sj.bjc.6603990]

119 **Urbancsek H**, Kazar T, Mezes I, Neumann K. Results of a double-blind, randomized study to evaluate the efficacy and safety of Antibiophilus in patients with radiation-induced diarrhoea. *Eur J Gastroenterol Hepatol* 2001; **13**: 391-396 [PMID: 11338068 DOI: 10.1097/00042737-200104000-00015]

120 **Kane KF**, Langman MJ, Williams GR. Antiproliferative responses to two human colon cancer cell lines to vitamin D3 are differently modified by 9-cis-retinoic acid. *Cancer Res* 1996; **56**: 623-632 [PMID: 8564982]

121 **Muscat JE**, Wynder EL. The consumption of well-done red meat and the risk of colorectal cancer. *Am J Public Health* 1994; **84**: 856-858 [PMID: 8179063]

122 **Le Marchand L**, Hankin JH, Wilkens LR, Pierce LM, Franke A, Kolonel LN, Seifried A, Custer LJ, Chang W, Lum-Jones A, Donlon T. Combined effects of well-done red meat, smoking, and rapid N-acetyltransferase 2 and CYP1A2 phenotypes in increasing colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 1259-1266 [PMID: 11751443]

123 **Roberfroid M**. Prebiotics: the concept revisited. *J Nutr* 2007; **137**: 830S-837S [PMID: 17311983 DOI: 10.1093/jn/137.3.830S]

124 **Gibson GR**, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr Res Rev* 2004; **17**: 259-275 [PMID: 19079930 DOI: 10.1079/NRR200479]

125 **Bruno-Barcena JM**, Azcarate-Peril MA. Galacto-oligosaccharides and Colorectal Cancer: Feeding our Intestinal Probiome. *J Funct Foods* 2015; **12**: 92-108 [PMID: 25584074 DOI: 10.1016/j.jff.2014.10.029]

126 **Femia AP**, Luceri C, Dolara P, Giannini A, Biggeri A, Salvadori M, Clune Y, Collins KJ, Paglierani M, Caderni G. Antitumorigenic activity of the prebiotic inulin enriched with oligofructose in combination with the probiotics Lactobacillus rhamnosus and Bifidobacterium lactis on azoxymethane-induced colon carcinogenesis in rats. *Carcinogenesis* 2002; **23**: 1953-1960 [PMID: 12419846 DOI: 10.1093/carcin/23.11.1953]

127 **Rowland IR**, Rumney CJ, Coutts JT, Lievense LC. Effect of Bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats. *Carcinogenesis* 1998; **19**: 281-285 [PMID: 9498277 DOI: 10.1093/carcin/19.2.281]

128 **Aachary AA,** Prapulla SG. Xylooligosaccharides (XOS) as an emerging prebiotic: microbial synthesis, utilization, structural characterization, bioactive properties, and applications. *Comp Rev Food Sci Food Saf* 2011; **10**: 2e16 [DOI: 10.1111/j.1541-4337.2010.00135.x]

129 **Birt DF**, Boylston T, Hendrich S, Jane JL, Hollis J, Li L, McClelland J, Moore S, Phillips GJ, Rowling M, Schalinske K, Scott MP, Whitley EM. Resistant starch: promise for improving human health. *Adv Nutr* 2013; **4**: 587-601 [PMID: 24228189 DOI: 10.3945/an.113.004325]

130 **Wijnands MV**, Schoterman HC, Bruijntjes JB, Hollanders VM, Woutersen RA. Effect of dietary galacto-oligosaccharides on azoxymethane-induced aberrant crypt foci and colorectal cancer in Fischer 344 rats. *Carcinogenesis* 2001; **22**: 127-132 [PMID: 11159750 DOI: 10.1093/carcin/22.1.127]

131 **Hsu CK**, Liao JW, Chung YC, Hsieh CP, Chan YC. Xylooligosaccharides and fructooligosaccharides affect the intestinal microbiota and precancerous colonic lesion development in rats. *J Nutr* 2004; **134**: 1523-1528 [PMID: 15173423 DOI: 10.1093/jn/134.6.1523]

132 **Bauer-Marinovic M**, Florian S, Müller-Schmehl K, Glatt H, Jacobasch G. Dietary resistant starch type 3 prevents tumor induction by 1,2-dimethylhydrazine and alters proliferation, apoptosis and dedifferentiation in rat colon. *Carcinogenesis* 2006; **27**: 1849-1859 [PMID: 16597648 DOI: 10.1093/carcin/bgl025]

133 **Gourineni VP**, Verghese M, Boateng J, Shackelford L, Bhat NK, Walker LT. Combinational Effects of Prebiotics and Soybean against Azoxymethane-Induced Colon Cancer In Vivo. *J Nutr Metab* 2011; **2011**: 868197 [PMID: 21961059 DOI: 10.1155/2011/868197]

134 **Hijova E**, Szabadosova V, Strojny L, Bomba A. Changes chemopreventive markers in colorectal cancer development after inulin supplementation. *Bratisl Lek Listy* 2014; **115**: 76-79 [PMID: 24601699 DOI: 10.4149/BLL\_2014\_016]

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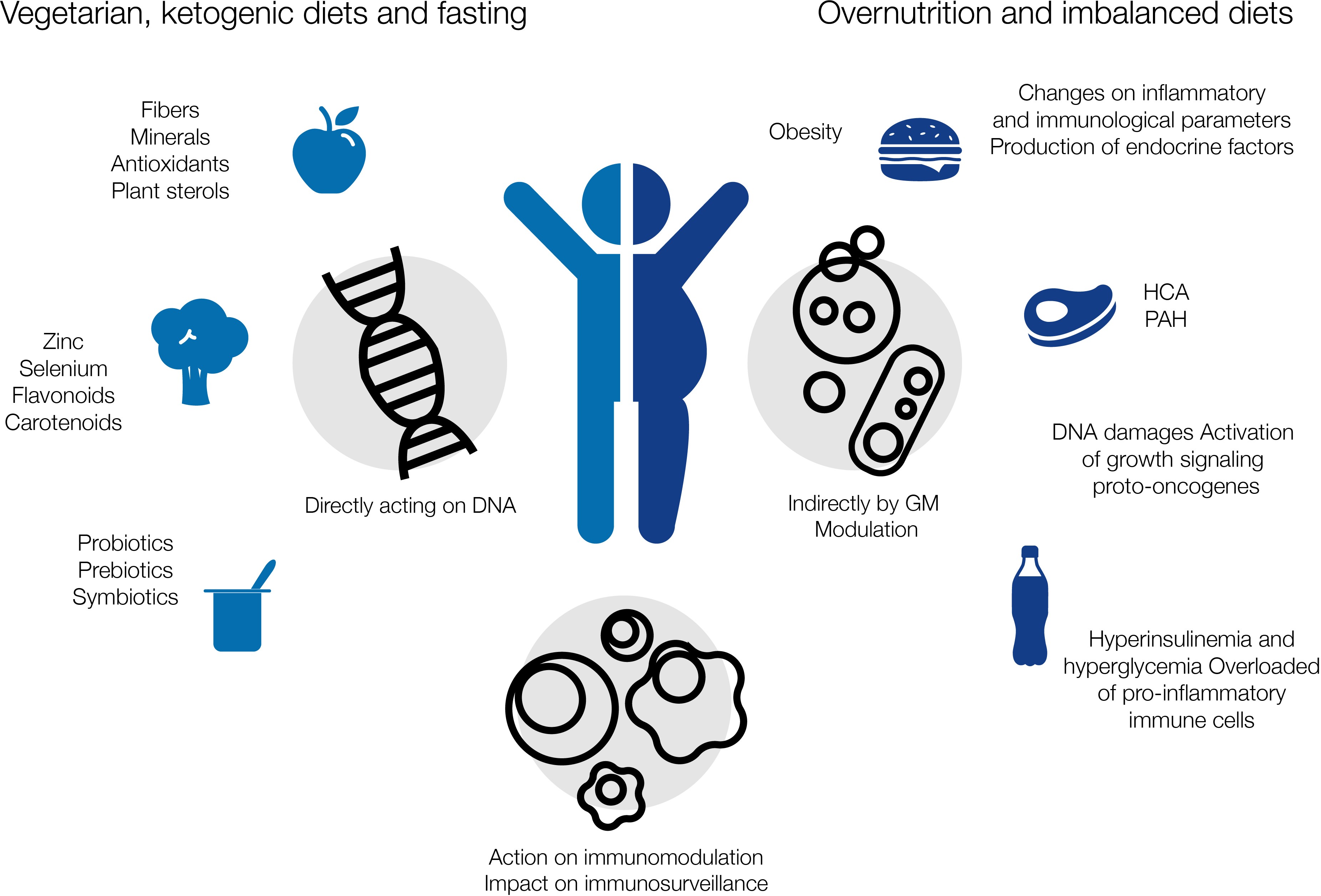
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Grade E (Poor): 0

**Table 1 Summarized the main references used in this review, which pointed diet as a harmful or protective to host health**

|  |  |  |
| --- | --- | --- |
| **Pathways** | **Ref.** | |
| **Harmful** | **Protective** |
| High ratio saturated fat | [27,34,39,40] |  |
| Obesity and cancer | [3,32,34,40,63] |  |
| Meat intake | [29,39,41-44,123,124] | [32,45] |
| Alcohol intake | [41] |  |
| Carbohydrates intake | [25,28,58] | [26,73] |
| Host microbiota and cancer | [65,87,100,133] | [70,72,100,105] |
| Probiotics and prebiotics supplementation |  | [69,93-96,98,99,101,102,104,106,107,110,111,116-119] |



**Figure 1 Diet components can act directly or indirectly on the prevention or initiation/progression of cancer.** Beneficial direct actions are exemplified by nutrients, which can direct protect the cells from DNA damage, and decrease the oxidative stress, while the harmful directly effect could be exemplify by DNA damage, activation of growth signaling proto-oncogenes and changes on proinflammatory cytokines. The indirect beneficial and harmful effects are represented by the modulation of gut microbiota and obesity induction respectively. HCA: Heterocyclic amines; PAH: Polycyclic aromatic hydrocarbon.