

## THE ROLE OF DIET AND NUTRITION TRENDS IN THE PREVENTION AND TREATMENT IN CANCER PATIENTS

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### Abstract

Numerous dietary products have been shown to possess cancer preventive effects, as well as to help recovery of cancer treated patients. The aim of this study is an attempt to summarize relevant data from recent scientific papers concerning the possible role and mechanisms by which certain dietary products can protect against carcinogenesis in normal human cells.

In this review of the available scientific literature, we conducted the association between dietary patterns and nutrition trends with the risk and/or treatment of cancer of all sites, through citation tracking identified in PubMed until recent date. "Mediterranean" dietary pattern plays one of the most important roles in cancer prevention as well as the food rich in vitamin B17 and flavonoids. Some patients may try special diets, in order to improve or to prevent side effects from cancer treatment by using vegetarian, macrobiotic or ketogenic diet. Dietary supplements such as: Vitamin C, probiotics, melatonin and glutamine may also be added to improve the symptoms of cancer treatment.

Dietary pattern suggested by many authors, plays an important role in prevention of many human cancers and can prevent side effects and nutrition problems caused by chemo/radiotherapy. However, important questions remain unexplained, concerning the mechanisms underlying differences by sex; life-course timing of exposure to dietary patterns; interaction of dietary patterns with the microbiome or with lifestyle factors

including physical activity; and elucidation of subsite differences.

**Key words:** Dietary pattern, Nutrition, Cancer prevention, Treatment.

### 1. Introduction

Cancer is one of main health public problems worldwide. It is the second leading cause of death with profound socio-economic consequences worldwide. Several factors are involved in beginning and development of cancer. Genetic and internal/external environmental factors can be as important agents that effect on emerging and development of several cancers [1].

Diet and nutrition may be as one of important factors in prevention or treatment of various cancers. Strong evidence supports the anticancer effects of: beetroot and its major compound betanin, cinnamon and cinnamaldehyde, barley and its products, extra-virgin olive oil, black pepper and its piperine, grapes and its compound resveratrol, ginger and its compound 6-gingerol, whey protein, fish, and honey.

A large number studies indicated that suitable dietary patterns may help to cancer prevention or could inhibit development of tumor in cancer patients. Moreover, some studies indicated that a variety of dietary

compounds such as: curcumin, green tea, folate, vitamin B17, selenium, and soy isoflavones show a wide range anti-cancer properties. It has been showed that these compounds via targeting a sequence of cellular and molecular pathways could be used as suitable options for cancer chemoprevention and cancer therapy [2].

The aim of this study is an attempt to summarize relevant data from recent scientific papers concerning the possible role and mechanisms by which certain dietary products can protect against carcinogenesis in normal human cells.

## 2. Dietary patterns in cancer prevention and treatment

### 2.1 Mediterranean diet

The Mediterranean diet (MD) is a dietary pattern associated with various health benefits including protection against: cardiovascular disease, diabetes, obesity, and various cancers. The MD eating pattern refers to dietary behaviors established through the blending of food, religious, economic and cultural practices by civilizations that have occupied the Mediterranean basin for millennia [3]. Twenty-two countries located across three continents are considered to have contributed to the MD eating pattern.

The five most important adaptations induced by the Mediterranean dietary pattern are: (1) lipid lowering effect, (2) protection against oxidative stress, inflammation and platelet aggregation, (3) modification of hormones and growth factors involved in the pathogenesis of cancer, (4) inhibition of nutrient sensing pathways by specific amino acid restriction, and (5) gut microbiota-mediated production of metabolites influencing metabolic health. Instead, this pattern can be described as one that (1) is abundant in plant-based foods such as: whole grains, legumes, nuts, seeds, fruits, and vegetables; (2) comprises olive oil as the main source of dietary fat; (3) limits intakes of red and processed meat, saturated fat, and refined sugars; (4) favors low-to-moderate intake of low-fat dairy and moderate consumption of fish; and (5) emphasizes regular, but moderate, alcohol (mostly red wine) consumption with meals [4]. The MD eating pattern also recommends the inclusion of water, tea, and herbal infusions as non-alcoholic beverages.

Several components of the MD such as: olive oil, fish, red wine, tea, fruits and vegetables, and other fiber sources contribute a myriad of bioactive compounds including antioxidants (i.e., proanthocyanidins, flavonoids, and other polyphenolic compounds); *n*-3 polyunsaturated fatty acids - PUFAs, such as eicosapentaenoic acid - EPA, docosahexaenoic acid - DHA; and short-chain fatty acids - SCFAs as for example butyrate). Given the diversity of available foods and dietary practices among Medi-

terranean countries, various definitions of the MD have been proposed such as one that favors higher intake of monounsaturated - MUFA and over saturated - SFA fatty acid; dietary fiber; antioxidants; and phytosterols. The MD has been extensively studied over several decades and suggested to provide protection against various chronic diseases and various cancers, including colorectal cancer [3, 4, and 5].

In a case control study of Spanish group with over thousand patients who evaluates the association between dietary patterns and risk of breast cancer (BC) in Spanish women, stratifying by menopausal status and tumor subtype, and comparing the results with those of Alternate Healthy Index (AHEI) and Alternate Mediterranean Diet Score - aMED, they have confirmed the harmful effect of a Western diet on BC risk, and add new evidence on the benefits of a diet rich in fruits, vegetables, legumes, oily fish and vegetable oils for preventing all BC subtypes, and particularly triple-negative tumors [6].

The same group explored the association of the previously described Western, prudent and Mediterranean dietary patterns with prostate cancer risk by tumor aggressiveness and extension. This population based, multicase-control study that was done in 7 Spanish provinces between September 2008 and December 2013 was based upon collected anthropometric, epidemiological and dietary information on 754 histologically confirmed incident cases of prostate cancer and 1,277 controls 38 to 85 years old. Three previously identified dietary patterns, including Western, prudent and Mediterranean, were reconstructed using MCC-Spain data. The results revealed that Mediterranean dietary pattern rich not only in fruits and vegetables but also in fish, legumes and olive oil was specifically associated with a lower risk of Gleason score greater than 6 prostate cancer or with higher clinical stage. This association was not observed with the prudent pattern, which combines vegetables and fruits with low fat dairy products, whole grains and juices. This study concludes that Mediterranean dietary pattern, was associated with a lower risk of aggressive prostate cancer, whereas Western and prudent dietary patterns, had no relationship with prostate cancer risk [7].

Other study from the Greek group report the similar results [8]. The prospective cohort study counted 23,349 patients, not previously diagnosed with cancer, coronary heart disease, or diabetes, with documented survival status until June 2008 and complete information on nutritional variables and important covariates at enrolment. After a mean follow-up of 8.5 years, 652 deaths from any cause had occurred among 12 694 participants with Mediterranean diet scores 0 - 4 and 423 among 10,655 participants with scores of 5 or more. Controlling for potential confounders, higher adherence to a Mediterranean diet was associated with a

statistically significant reduction in total mortality. The contributions of the individual components of the Mediterranean diet to this association were: moderate ethanol consumption 23.5%, low consumption of meat and meat products 16.6%, high vegetable consumption 16.2%, high fruit and nut consumption 11.2%, high monounsaturated to saturated lipid ratio 10.6%, and high legume consumption 9.7%. The contributions of high cereal consumption and low dairy consumption were minimal, whereas high fish and seafood consumption was associated with a non-significant increase in mortality ratio.

## 2.2 Ketogenic diet (KD)

The KD is a high-fat low protein/carbohydrate diet used to treat refractory epilepsy. It has been shown to have neuroprotective effects and there are now studies to determine its efficacy for a number of neurological disorders, including: epilepsy, Alzheimer's disease, Parkinson's disease, sleep disorders, headache, traumatic brain injury, amyotrophic lateral sclerosis, pain and autism. The KD increases blood ketones and decreases blood glucose by simulating the physiological response to fasting, thus leading to high rates of fatty acid oxidation and an increase in the production of acetyl coenzyme A - acetyl-CoA. When the amount of acetyl-CoA exceeds the capacity of the tricarboxylic acid cycle to utilize it, there is an increase in the production of the ketone bodies  $\beta$ -hydroxybutyrate ( $\beta$ HB) and acetoacetate - ACA, which can be used as an energy source in the normal brain.

Since normal cells readily use ketones as an alternate energy source, they are unlikely to be adversely affected by reduced glucose. In contrast, the metabolic alterations found in cancer cells are generally thought to reduce their ability to be "flexible" regarding their primary energy source, and thus they require glucose. By reducing the glucose availability to cancer cells and providing ketones as an alternative energy source for normal cells, the KD may target the Warburg effect in highly glycolytic tumors, such as malignant gliomas [9].

One of the best illustrations of the influence of ketogenic diet upon cancer cells were described by studies of Nikolai and Schwartz in 2015 [10, 11]. Survival of the most aggressive brain tumor, glioblastoma multiforme - GBM with the current recommended treatment is poor. Reported median survivals are approximately 8 - 15 months. Based on recent publications from animal models, combining cancer drugs, radiation, and diet-metabolic treatments may be a new route to better survivals. In these studies, the clinical trial had enrolled 15 subjects using a ketogenic diet (KD) as an addition to current standard treatments that include surgery, radiation therapy, and chemotherapy. Of the 15 enrolled, 10 completed the protocol.

The authors emphasize that the diet selected, should be standardized within individual clinical trials, and more importantly, the patients' blood should be monitored for glucose and ketones twice daily so that the supervising dietitian can work with the patient and their caregivers to make appropriate changes in the diet. Compliance with the diet is best in highly motivated patients who have excellent home support from a family member or a friend who can help to overcome administrative, physical, and cognition deficiencies associated with the disease. Treatment of GBM using a KD represents a reasonable investigative approach. This perspective summarizes the challenges and lessons learned implementing and continuing KD therapy while the patients are concurrently being treated with radiation and chemotherapy.

## 2.3 Vegetarian diet and macrobiotics

Although plant-based diets including vegetarian and vegan diets are generally considered to be cancer protective, very few studies have directly addressed this question. Most large prospective observational studies show that vegetarian diets are at least modestly cancer protective (10 - 12% reduction in overall cancer risk) although results for specific cancers are less clear. No long-term randomized clinical trials have been conducted to address this relationship.

However, a broad body of evidence links specific plant foods such as fruits and vegetables, plant constituents such as fiber, antioxidants and other phytochemicals, and achieving and maintaining a healthy weight to reduced risk of cancer diagnosis and recurrence. Also, research links the consumption of meat, especially red and processed meats, to increased risk of several types of cancer. Vegetarian and vegan diets increase beneficial plant foods and plant constituents, eliminate the intake of red and processed meat, and aid in achieving and maintaining a healthy weight. The direct and indirect evidence taken together suggests that vegetarian diets are a useful strategy for reducing risk of cancer [12].

Many aspects of the dietary pattern promoted under standard macrobiotic dietary recommendations have been suggested to have anticancer effects. For example, whole grains have been emphasized as a centerpiece of macrobiotic dietary recommendations for many years. There is growing evidence that whole grain consumption decreases the risk of cancers at various sites. The effects of whole grains on cancer prevention are probably not limited to dietary fiber effects but may also involve effects on estrogen metabolism, glucose and insulin metabolism, and oxidative processes. A wide variety of vegetables are also recommended for regular consumption.

The evidence that vegetable intake is associated with decreased risk of cancer is large and consistent and was

reviewed in the American Institute for Cancer Research and World Cancer Research Fund report [13]. This report noted that increasing consumption of vegetables and fruits from ~250 to 400 g/d may be associated with a 23% decreased risk of cancer worldwide. It has been suggested that sea vegetables, promoted in macrobiotics and an important part of traditional East Asian cuisine, may decrease risk of breast cancer and endometrial cancer. These associations may be accounted for in part by the antitumor activities of fucoidan, a sulfated polysaccharide found almost exclusively in brown seaweed, and fucoxanthin, the carotenoid responsible for the brown color of brown seaweed.

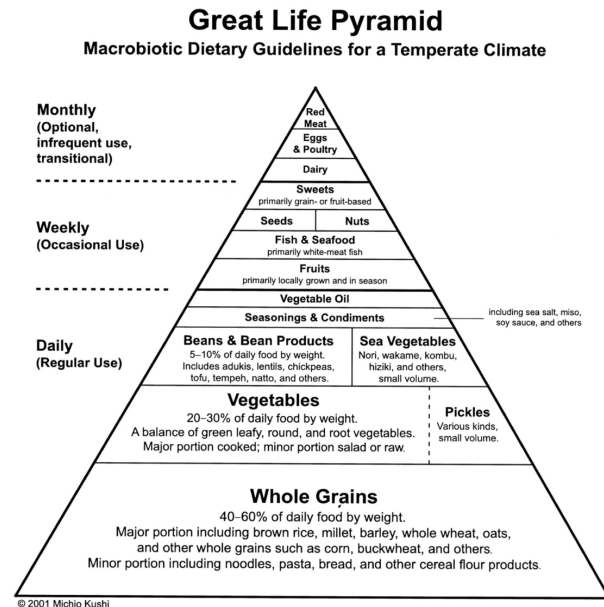
The role of beans and bean products, particularly soy foods, in cancer prevention continues to garner substantial interest. The interest in soy is based in part on the lower overall cancer rates in the Far East, where soy foods are a traditional part of the diet, compared with the USA and other Western countries, where soy foods are consumed in much smaller quantities [14]. Some evidence shows that soy intake is associated with decreased risk of hormone-dependent cancers such as those of the breast, endometrium and prostate [14, 15, and 16] and may also decrease risk of other cancers such as those of the stomach, although this may be limited to non-fermented soy foods [15].

Soy foods and other legumes may decrease risk of cancer because of the presence of various compounds that may have anticancer effects, including protease inhibitors and saponins [15]. There has been a particular interest in the role of phytoestrogens such as genistein and daidzein, which are found in high concentration in soybeans. These isoflavonoid compounds may not only influence estrogen metabolism but may also have antioxidant and antiangiogenesis effects and may influence signal transduction and inhibit the action of DNA topoisomerases [16].

Some foods that are linked to increased cancer risk are minimized in standard macrobiotic dietary recommendations. In contrast to the cancer-prevention effects of whole grains, refined grains, which are not recommended in macrobiotics, may actually increase risk of cancer.

With the exception of fish, animal food intake is generally minimized in macrobiotics. There is growing evidence that red meat intake increases the risk of cancers of the colon and rectum as well as cancers of the prostate, pancreas and perhaps other sites [17]. Eggs may be associated with increased risk of colorectal and ovarian cancer [15, 16], and dairy food intake is associated with increased risk of cancers of the prostate, kidney and ovary [17, 18]. A preference for natural, organically grown foods would minimize exposure to pesticides, herbicides and other such chemicals. Although the association of dietary exposure to such chemicals and

cancer risk is controversial, some reports have suggested that exposure to such compounds should be minimized. Macrobiotic dietary guidelines are briefly summarized in Figure 1 in so called "Great life Pyramid".



**Figure 1. The Great Life Pyramid, showing macrobiotic dietary guidelines for a temperate climate. Note that these are guidelines that may be adjusted for climate and environment, cultural or ethnic heritage, gender, age, activity level, individual health concerns and personal needs and other considerations. Food consumed should be of natural quality, organically grown as much as possible and traditionally or naturally processed [18]**

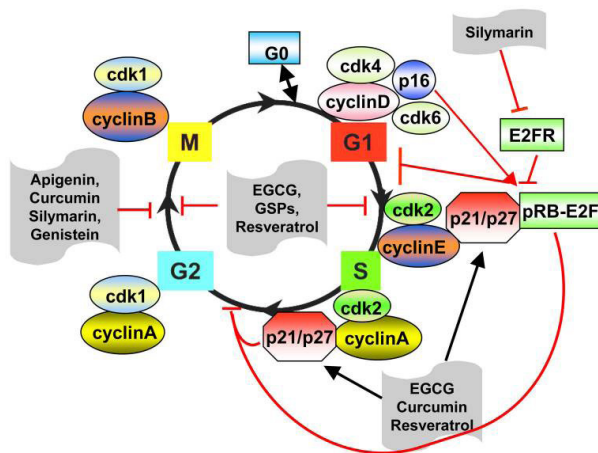
## 2.4 Cancer cell cycle

Cancer is a complex disease, in which there is genetic variability among not only different types of cancer but also among different patients with the same type of cancer, and even among different cells within the same tumor. Tumors also represent the culmination of multiple genetic abnormalities. As a consequence, the targeting of a single molecular target for therapeutic purposes might not be sufficient to elicit the desired outcome. Different nutrients, specifically dietary botanicals, carotenoid lutein [19] can play a role in the regulation of both normal and pathologic processes. An improved understanding of the regulatory role of these nutrients on cell cycle regulatory checkpoints may help in the prevention and treatment of various cancers [20]. For more than a decade, there has been considerable interest in the use of naturally occurring botanicals for the prevention of disease including prevention of various cancers [21].

Although several dietary agents or nutrients have been shown to affect the cell cycle regulation on treatment with cancer cells, the role of some common



dietary agents as an example are evidence that dietary agents can interfere with the abnormal progression of cell cycle regulation of cancer cells. The agents which have main effects on cell cycle include: grape seed proanthocyanidins - GSPs, green tea polyphenol, epigallocatechin-3-gallate - EGCG, resveratrol (red grapes, peanuts and berries), silymarin/silibinin (milk thistle), genistein (soybean), curcumin (turmeric) and apigenin (celery, parsley). Their effects on cancer cells *in vivo* and *in vitro* studies emphasize their multiple roles in the regulation of cell cycle proteins/checkpoints [22]. Their sources and structures are summarized briefly in Figure 2.



**Figure 2. A simplified schematic representation of the various cell cycle phases, and the different cyclins and their kinases that control progression through the cycle. At the core of this control is the cyclin dependent kinase (Cdk) family of serine/threonine kinases, which regulate cell cycle progression through phosphorylation of proteins that function at specific phase of the cell cycle. Different Cdk's act at different phases of the cell cycle and their activity is dependent on association with a member of the cyclin family of regulatory sub-units. Different dietary agents, such as EGCG, GSPs, silymarin, apigenin, resveratrol, genistein and curcumin act at different checkpoints as illustrated in the Figure. Some of them act on multiple checkpoints or targets. The arrows indicate activation and blocked signs indicate inhibitory effects [22].**

## 2.5 Dietary supplements and cancer malnutrition

A dietary supplement is a product that is added to the diet. It is usually taken by mouth, and usually has one or more dietary ingredients. Cancer patients may take dietary supplements to improve their symptoms or as additional remedy in cancer treatment [23].

### 2.5.1 Vitamin C

Vitamin C is a nutrient that the body needs in small amounts to function and stay healthy. It helps fight infection, heal wounds, and keep tissues healthy. Vitamin

C is found in fruits and vegetables. It can also be taken as a dietary supplement.

### 2.5.2 Probiotics

Probiotics are live microorganisms used as dietary supplements to help with digestion and normal bowel function. They may also help keep the gastrointestinal tract healthy. Studies have shown that taking probiotics during radiation therapy and chemotherapy can help prevent diarrhea caused by those treatments. This is especially true for patients receiving radiation therapy to the abdomen for combined chemo- and radiation therapy for colorectal or gastric cancer [24].

### 2.5.3 Melatonin

Melatonin is a hormone made by the pineal gland (tiny organ near the center of the brain). Melatonin helps control the body's sleep cycle. It can also be made in a laboratory and taken as a dietary supplement. Several small studies have shown that taking a melatonin supplement with chemotherapy and/or radiation therapy for treatment of solid tumors may be helpful. It may help reduce side effects of treatment. Melatonin does not appear to have side effects.

### 2.5.4 Oral glutamine

Oral glutamine is an amino acid that is being studied for the treatment of diarrhea and mucositis (inflammation of the lining of the digestive system, often seen as mouth sores) caused by chemotherapy or radiation therapy. Oral glutamine may help prevent mucositis or make it less severe. Cancer patients who are receiving radiation therapy to the abdomen may benefit from oral glutamine. Oral glutamine may reduce the severity of diarrhea [25]. This can help the patients to continue with their treatment plan.

### 2.5.5 Malnutrition, anorexia and cachexia

Cancer and cancer treatments may affect taste, smell, appetite, and the ability to eat enough food or absorb the nutrients from food. This can cause malnutrition, which is a condition caused by a lack of key nutrients. Alcohol abuse and obesity may increase the risk of malnutrition.

Malnutrition can cause the patient to be weak, tired, and unable to fight infection or finish cancer treatment. Malnutrition may be made worse if the cancer grows or spreads. Eating the right amount of protein and calories is important for healing, fighting infection, and having enough energy [26].

Anorexia is the loss of appetite or desire to eat. It is a common symptom in patients with cancer. Anorexia may occur early in the disease or later, if the cancer

grows or spreads. Some patients already have anorexia when they are diagnosed with cancer. Most patients who have advanced cancer will have anorexia. Anorexia is the most common cause of malnutrition in cancer patients.

Cachexia is a condition marked by weakness, weight loss, and fat and muscle loss. It is common in patients with tumors that affect eating and digestion. It can occur in cancer patients who are eating well, but are not storing fat and muscle because of tumor growth. Some tumors change the way the body uses certain nutrients. The body's use of protein, carbohydrates, and fat may be affected, especially by tumors of the stomach, intestines, or head and neck. A patient may seem to be eating enough, but the body may not be able to absorb all the nutrients from the food. Cancer patients may have anorexia and cachexia at the same time [26].

Side effects from chemotherapy may cause problems with eating and digestion. When more than one chemotherapy drug is given, each drug may cause different side effects or when drugs cause the same side effect, the side effect may be more severe. The most common side effects are loss of appetite, nausea, vomiting, dry mouth, sores in the mouth and throat, changes in the food taste, trouble swallowing, feeling full after eating a small amount of food, constipation and diarrhea.

### 3. Conclusions

- Dietary pattern suggested by many authors, plays an important role in prevention of many human cancers and can prevent side effects and nutrition problems caused by chemo/radiotherapy. However, important questions remain unexplained, concerning the mechanisms underlying differences by sex; life-course timing of exposure to dietary patterns; interaction of dietary patterns with the microbiome or with lifestyle factors including physical activity; and elucidation of subsite differences.

- However, additional pharmacological studies and clinical trials are needed to elucidate their molecular and cellular mechanisms of actions, frequency, and amount of consumption, possible adverse effects, and optimum preparation methods. Moreover, studying mechanisms of actions of the bioactive compounds present in the discussed food items can be helpful in identifying and development of new anticancer agents.

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