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Chapter 17

Nutrigenomics and Cancer Prevention

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Additional information is available at the end of the chapter

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1. Introduction

Cancer is fundamentally a genetic disease. At the beginning of the process is an alteration in the DNA of a single cell. This change in DNA can be caused by several factors, chemical, physical or biological phenomena. The stage of promotion is the second stage of carcinogenesis. The genetically altered cells, ie, "initiated," suffer the effects of carcinogens classified as oncopromotores. The initiated cell is transformed into a malignant cell, a slow and gradual process. For this transformation to occur, you need a long and continuous contact with the carcinogen promoter. The stage of progression is the third and final stage and is characterized by uncontrolled proliferation of cells and irreversibly changed. At this stage cancer is already installed, progressing to the emergence of the first clinical manifestations of the disease [1]. In this sense, the diet plays a key role in various stages of cancer development. The process of carcinogenesis may be affected by nutritional factors through mechanisms that promote or inhibit its development. Some foods can contain not only carcinogens, but also other substances that act to reduce the damage to the cell's genetic material caused by environmental mutagens. The observation of cancer in an individual does not identify the causative agent(s). However, epidemiological data on populations do indicate that a large fraction of human cancers are associated with lifestyle/diet. Such studies may also help identify the etiologic agents but unless there are good dose-response data for humans and/or animal models, the probability of identifying the agent is not high. Cancers may result from endogenous reactions, such as oxidations or from exogenous agents, such as tobacco smoke (lung cancer), sunlight exposure (skin cancer), aflatoxin (liver cancer), and relatively high doses of ionizing radiations (many types of cancers) [2].

The importance of nutrition in health is not a new idea. More than two thousand years ago, Hippocrates, the father of Western medicine, wrote: "Let food be thy medicine and medicine be thy food." What has changed since the time of Hippocrates is our understanding of the details of how nutrition affects our health. Researchers are getting more knowledge as to what foods or bioactive food compounds and how they can interact with our bodies promoting

health. The Human Genome Project was one of the key factors that enable the study of gene-food interactions and promotion of health. Discoveries in genetics make it possible to understand the effects of nutrients in processes at the molecular level in the body and also the variable effects of dietary components on each individual. Research has shown that the nutrients affect gene expression and formation of several proteins that are important in the formation and maintenance of tissues. So, faced with this interaction genomics and nutrition, emerges Nutrigenomics aiming to understand the functions of all genes and their interactions with food, in order to promote health and reduce the risk of developing diseases [3].

Nutrigenomics studies the modulating effect of the chemical compounds in foods and on the stability of DNA synthesis and gene expression. The nutrients are able to affect the genome and its expression through the synthesis of nucleotides, prevention and repair of DNA damage, or through epigenetic mechanisms including methylation of histones, proteins responsible for chromatin structure that play an important role in regulating gene expression. Those methodological approaches are based on nutrition, molecular biology, and genomics. Integration of these disciplines is leading to identification and understanding of individual and population differences and similarities in gene expression, or phenotype, in response to diet. We can consider nutrigenomics as a multidisciplinary science that applies the genomic techniques besides the biochemical and epidemiological aspects, with the aim to understand the etiologic aspects of chronic diseases such as cardiovascular diseases, diabetes, obesity and cancer [4].

An understanding of scientific information about the composition and functions of genomes, has created unprecedented opportunities for increasing our understanding of how nutrients modulate gene and protein expression and ultimately influence cellular and organismal metabolism. On that basis, the purpose of this chapter is to make a broad review study to evaluate the modulation between compounds found in nutrients and their interactions with on the genomic stability and control of gene expression.

2. Nutrition and epigenetics

All the cells in the body have identical genomes. However, each cell has one of many "epigenomes", unique sets of epigenetic instructions for establishing and maintaining lineage-specific expression profiles. The genome is programmed to express appropriate sets of genes, in particular tissues, at specific time points during the individual's life. Epigenetic events create a memory of cell identity, maintaining genomic functions such as the maintenance of cell identity after differentiation, the propagation of essential features of chromosomal architecture and dosage compensation [5]. Epigenetic mechanisms are capable of modulating gene expression through changes in the chromosomes structure. Chromosomes are formed from the condensation of the chromatin, which is formed by a complex of DNA, and unique proteins called histone. Examples of epigenetic mechanisms may be mentioned as DNA methylation and histone acetylation [3].

DNA methylation occurs at the cytosine bases of eukaryotic DNA, which are converted to 5-methylcytosine. The altered cytosine residues are usually immediately adjacent to a guanine

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nucleotide, resulting in two methylated cytosine residues sitting diagonally to each other on opposing DNA strands [6]. DNA methylation, which modifies a cytosine base at the CpG dinucleotide residues with methyl groups, is catalyzed by DNA methyltransferases (Dnmt) and regulates gene expression patterns by altering chromatin structures. Currently, 5 different Dnmt are known: Dnmt1, Dnmt2, Dnmt 3a, Dnmt3b and DnmtL [7]. The Polycomb group protein EZH2 directly controls DNA methylation (Figure 1). EZH2 serves as a recruitment platform for DNA methyltransferases, thus highlighting a previously unrecognized direct connection between two key epigenetic repression systems [8].

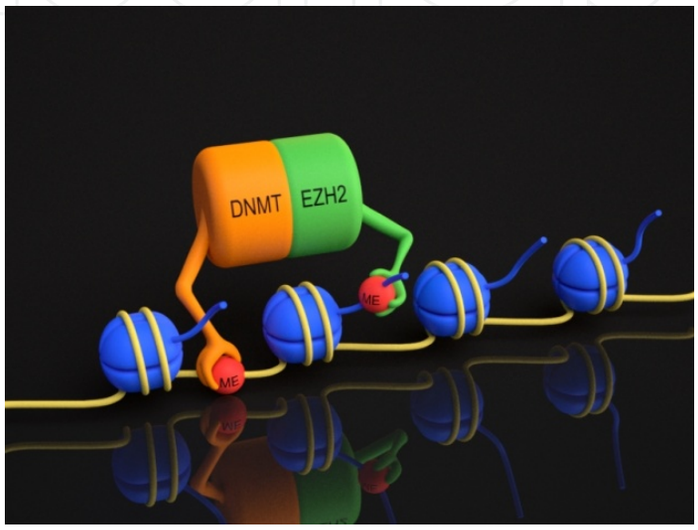

Figure 1. Polycomb Group (PcG) protein EZH2 serves as a recruitment platform for DNA methyltransferases (http://www.ulb.ac.be/medecine/fukslab/research.htm).

DNA methylation is essential for cell differentiation and embryonic development. Moreover, in some cases, methylation has observed to play a role in mediating gene expression. In mammals, methylation is found sparsely but globally, distributed in definite CpG sequences throughout the entire genome, with the exception of CpG islands, or certain stretches (approximately 1 kilobase in length) where high CpG contents are found. The methylation of these sequences can lead to inappropriate gene silencing, such as the silencing of tumor suppressor genes in cancer cells [6]. A large amount of research on DNA methylation and disease has focused on cancer and tumor suppressor genes. Tumor suppressor genes are often silenced in cancer cells due to hypermethylation. In contrast, the genomes of cancer cells have been shown to be hypomethylated overall when compared to normal cells, with the exception of hypermethylation events at genes involved in cell cycle regulation, tumor cell invasion, DNA repair, and other events in which silencing propagates metastasis. In fact, in certain cancers, such as that of the colon, hypermethylation is detectable early and might serve as a biomarker for the disease [6] (See Figure 2).

In the nutritional field, epigenetics is exceptionally important, because nutrients and bioactive food components can modify epigenetic phenomena and alter the expression of genes at the transcriptional level. Nutrients can reverse or change epigenetic phenomena such as DNA

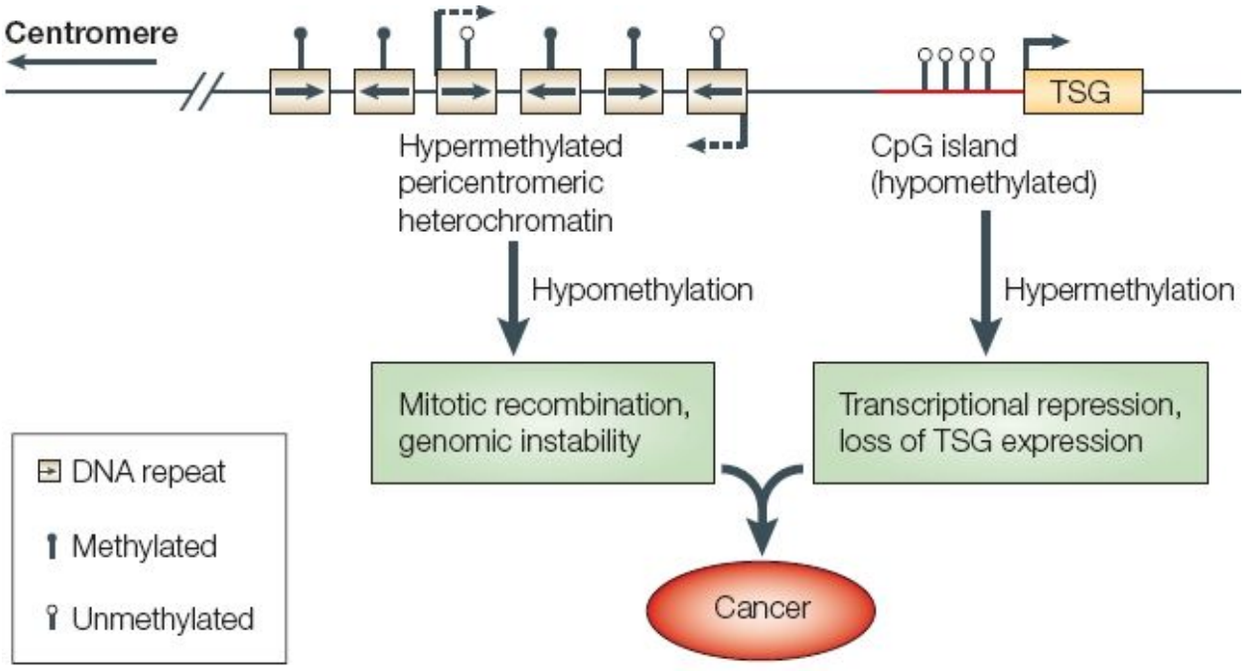

Figure 2. DNA methylation and cancer. This diagram shows a representative region of genomic DNA in a normal cell. The region contains repeat-rich, hypermethylated pericentromeric heterochromatin and an actively transcribed tumor suppressor gene (TSG) associated with a hypomethylated CpG island (indicated in red). In tumor cells, repeat-rich heterochromatin becomes hypomethylated, and this contributes to genomic instability (a hallmark of tumor cells) through increased mitotic recombination events. *De novo* methylation of CpG islands also occurs in cancer cells, and it can result in the transcriptional silencing of growth-regulatory genes. These changes in methylation are early events in tumorigenesis. (See reference [9].)

methylation and histone modifications, thereby modifying the expression of critical genes associated with physiologic and pathologic processes, including embryonic development, aging, and carcinogenesis [7].

The most interesting study linking diet and epigenetics was made by Kucharski et al. [10], about nutritional control of reproductive status in honeybees via DNA methylation. Fertile queens and sterile workers are alternative forms of the adult female honeybee that develop from genetically identical larvae following differential feeding with royal jelly. Royal jelly is a complex, protein-rich substance secreted from glands on the heads of worker bees. A larva destined to become a queen is fed large quantities of royal jelly inside a specially constructed compartment called a queen cup. The authors observed that larvae fed with royal jelly developed functional ovaries and a larger abdomen for egg laying, while worker bees remain sterile. She'll also develop the necessary behaviors to act as queen, such as killing rival queens, making communication sounds known as "piping," and going on "mating flights." The queen is fed royal honey exclusively for the rest of her life. They showed that royal jelly silences a key gene (Dnmt3), which codes for an enzyme involved in genome-wide gene silencing. When Dnmt3 is active in bee larvae, the queen genes are epigenetically silenced and the larvae develop into the default "worker" variety. But when royal jelly turns Dnmt3 off, certain genes jump into action that turn the lucky larvae into queens. The authors suggested that DNA

methylation in *Apis* is used for storing epigenetic information, that the use of that information can be differentially altered by nutritional input, and that the flexibility of epigenetic modifications underpins, profound shifts in developmental fates, with massive implications for reproductive and behavioral status.

During our lifetime, nutrients can modify physiologic and pathologic processes through epigenetic mechanisms that are critical for gene expression (summarized in Table 1). Modulation of these processes through diet or specific nutrients may prevent diseases and maintain health. However, it is very hard to delineate the precise effect of nutrients or bioactive food components on each epigenetic modulation and their associations with physiologic and pathologic processes in our body, because the nutrients also interact with genes, other nutrients, and other lifestyle factors. Furthermore, each epigenetic phenomenon also interacts with the others, adding to the complexity of the system [7].

	Nutrient or diet	Epigenetic mechanism
Embryonic development	Folate	DNA methylation, imprinting
	Choline	DNA methylation
	Protein restriction	DNA methylation, histone modifications
	Alcohol	DNA methylation
Stem cell	Butyrate	Histone acetylation, DNA methylation
	Retinoic acid	PRC
Aging	Folate	DNA methylation
	Calorie restriction	Histone acetylation
Immune function	Folate	DNA methylation
Cancer	Methyl-deficient diet	Histone modification, microRNA
	Genistein	DNA methylation, microRNA
	(-)-Epigallocatechin-3-gallate	DNA methylation, PRC
	Curcumin	microRNA
Obesity, insulin resistance	High-fat diet	DNA methylation, microRNA
	Methyl-deficient diet	DNA methylation
	Curcumin	Histone acetylation
Inflammation	Resveratrol	Histone acetylation
	AdoMet	Histone methylation
	Methyl-deficient diet	microRNA
Neurocognition	Choline	DNA methylation, histone methylation

Data in reference [7].

Table 1. Epigenetic roles of nutrition in physiologic and pathologic processes

2.1. Diet and genomic stability

Eukaryotic DNA replication starts at multiple sites throughout the genome and is necessarily coordinated with transcription, sister chromatid cohesion, nucleosome assembly and cell cycle progression. In addition to the complexity of the replication reaction it, during replication cells need to deal with DNA damage and stalled forks, originated inevitably by the action of exogenous and endogenous agents. The success of this process is crucial to preserve genome stability, and the inability to deal with DNA lesions during replication or to protect or restart stalled forks leads to DNA breaks, chromosomal rearrangements, and mutations that can cause the loss of cell viability, but in addition errors in DNA replication result in a large number of human syndromes, including premature aging, various cancer predispositions and genetic abnormalities. To solve or reduce these problems, cells use repair and detoxification pathways as well as surveillance mechanisms, called checkpoints, which serve to detect the problem and coordinate repair with chromosome segregation and progression through the cell cycle (see Figure 3. www.genomic-instability.org/).

Maintaining genomic stability in the face of replication and recombination requires a huge variety of different damage response proteins. A cell's ability to decide when and where to deploy this DNA repair kit is critical to prevent tumor development [11].

There is evidence that inappropriate nutrient supply can cause sizeable levels of genome mutation and alter expression of genes required for genome maintenance. Deficiencies in several micronutrients have been shown to cause DNA damage and are thought to be associated with a number of serious human diseases: folic acid, niacin, vitamin B6 and B12 deficiency may increase the risk of colon cancer, heart disease and neurological dysfunction due to chromosome breaks and disabled DNA repair [12]. On the other hand, as seen in reference [13], the authors believe that caloric restriction (CR) is an 'intervention' that alters the activation of specific 'stress response genes', key enzymes in DNA repair pathways, which then results in upregulation of 'DNA repair' capacity. Enhanced DNA repair reduces the levels of DNA damage, consequently reducing mutation frequency, which would result in maintenance of genomic stability.

Recommended dietary allowances (RDAs) of micronutrients have been traditionally defined as those levels necessary to prevent symptoms of deficiency diseases. There is increasing evidence that higher levels of many such micronutrients may be necessary for various DNA maintenance reactions, and that the current RDAs for some micronutrients may be inadequate to protect against genomic instability. Dietary imbalance may increase gene mutation and chromosome aberrations in human populations, similar to exposure to radiation, mutagens and carcinogens. Diet may well be a key factor in determining genomic stability since it impacts on all relevant pathways, i.e. exposure to dietary carcinogens, activation/detoxification of carcinogens, DNA repair, DNA synthesis and apoptosis, as mentioned previously. Many micronutrient minerals and vitamins act as substrates and/or co-factors in key DNA maintenance reactions, and the exact concentration of these in the cell may be critical. Sub-optimal levels of key micronutrients required for DNA maintenance will reduce genomic stability, producing similar effects to inherited genetic disorders or exposure to carcinogens [14].

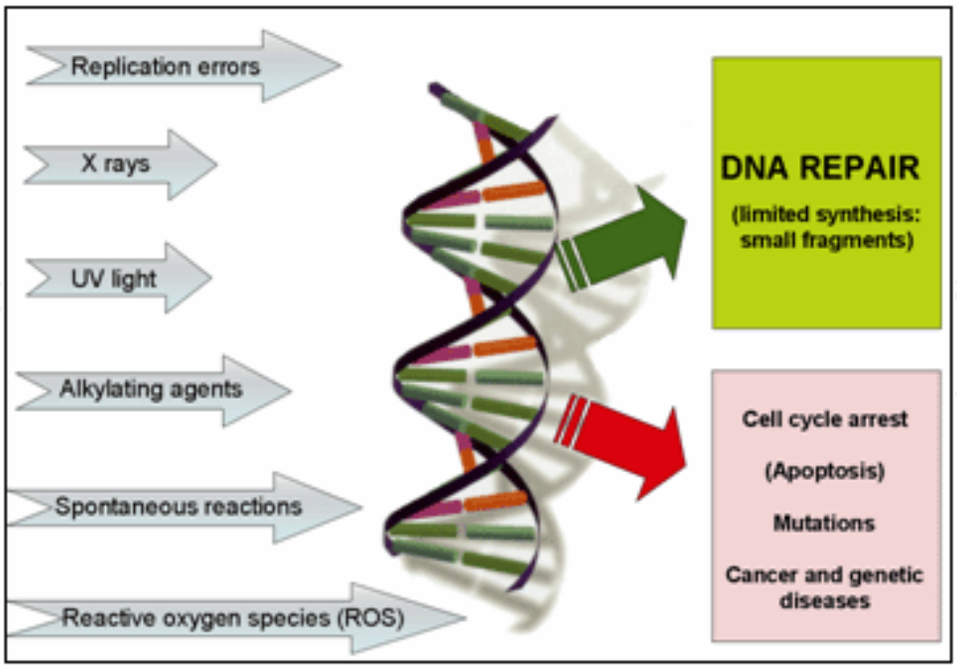

Figure 3. A general view of DNA insults and consequences on cell cycle and DNA repair (www.genomic-instability.org/).

3. Diet and cancer prevention

Current cancer models comprise those that are inherited through the germline and represent only ~5% of total cases of human cancers. These tumors originate because of mutational events. The remaining ~95% originate as sporadic events and evolve as a result of exposure to the environment, which includes exposure to both environmental contaminants and dietary agents. The multistage model of carcinogenesis identifies various phases, initiation, promotion, and progression, appears to be influenced by tissue microenvironment and organization. Significant opportunities in nutrition and cancer prevention exist in the early stages of initiation and promotion prior to clonal expansion of heterogeneous populations. Nutrigenomics represents a strategy that can be applied to the study and prevention of many diseases including cancer. DNA methylation and histone modifications are epigenetic events that mediate heritable changes in gene expression and chromatin organization in the absence of changes in the DNA sequence. The age-increased susceptibility to cancer may derive from accumulation of epigenetic changes and represents a potential target for therapies with bioactive compounds. Factors that mediate the response to dietary factors include nuclear receptors and transcription factors, which function as sensors to dietary components and determine changes in the profile of transcripts [15]. Milner and Romagnolo [15] affirm that the opportunity of targeting nutrients–gene interactions to influence the cancer process is modulated by genetic variations in human populations, epigenetic modifications that selectively and permanently alter gene expression, by complex interactions/associations among dietary components, and heterogeneity of cells within a certain tumor. Therefore, integration of information about gene polymorphisms, identification of gene targets that regulate cell and

tissue specific pathways, and development of diagnostic strategies to control for clinical heterogeneity are important to understand how nutrigenomics may be used in cancer prevention.

Berrino, Krogh and Riboli [16] were made a review which showed an epidemiology studies on diet and cancer (see Table 2 that summarizes the results of the randomized studies published). The authors summarized (Table 3) the results of the World Cancer Research Fund (WCRF) evaluation on major foods and nutrients and major cancer sites. The 'probable' and 'possible' judgements provide a frame of hypotheses to be addressed in further studies. The overall pattern indicates that vegetarian food, except sugar and alcoholic beverages, is usually associated with cancer prevention, whereas animal food is frequently associated with cancer risk. The first WCRF dietary recommendation to reduce cancer, indeed, is: "Choose predominantly plant-based diets rich in a variety of vegetables and fruits, pulses (legumes) and minimally processed starchy staple foods". This seems to open a new perspective in nutrition and cancer research: from chemoprevention studies based on a single or a few micronutrients to an experimental strategy requiring a comprehensive modification of dietary habits.

Study and year of publication	Agent	Primary end point	Relative risk	Relative risk for secondary end points
ECPOS, 2000	Ispaghula fiber	Colon adenoma	1.67**	
APPP, 1995	Beta-carotene	Colon adenoma	1.50**	
CARET, 1996	Beta-carotene	Lung cancer	1.28**	
APPP, 1995	Cereal fibre	Colon adenoma	1.20	
TPPT, 1994	Cereal fibre*	Colon adenoma	1.20	
ATBC, 1994	Beta-carotene	Lung cancer	1.18**	0.98 for colon adenoma 1.05 for colorectal cancer 1.26 for stomach cancer 1.23 for prostate cancer
NPCS, 1996	Selenium	Skin, squamous cell	1.14	0.50** for all cancers
NPCS, 1996	Selenium	Skin, basal cell	1.10	
PPS, 1994	Vit C + Vit E	Colon adenoma	1.08	
SWCPS, 1997	Retinol	Skin, basal cell	1.06	
Linxian, China, 1993	Vit C + Mb	All cancers	1.06	1.10 for stomach cancer
SCPS, 1990	Beta-carotene	Skin	1.05	
PPS, 1994	Beta-carotene	Colon adenoma	1.01	

Study and year of publication	Agent	Primary end point	Relative risk	Relative risk for secondary end points
Linxian, China, 1993	Retinol + Zn	All cancers	1.00	0.96 for stomach cancer
EUROSCAN, 2000	Retinilpalmitate	Lung cancer	1.00	
Alberts et al., 2000	Cereal fiber	Colon adenoma	0.99	
ATBC, 1994	Alpha tocopherol	Lung cancer	0.99	0.64** for prostate cancer 1.66** for colon adenoma 0.83 for colorectal cancer 1.26 for stomach cancer 1.18** for stomach cancer
Linxian, China, 1993	14 vitamins + 12 minerals***	Esophagus/cardias	0.98	
PHS, 1996	Beta-carotene	All cancers	0.98	0.95 for lung cancer
Linxian, China, 1993	Riboflavin+niacin	All cancers	0.95	1.04 for stomach cancer
Linxian, China, 1993	Se + Vit E + beta-carotene	All cancers	0.93	0.79** for stomach cancer 0.91** for total mortality
Baron et al., 1999	Calcium	Colon adenoma	0.83	
SWCPS, 1997	Retinol	Skin, squamous cell	0.74**	
ECPOS, 2000	Calcium	Colon adenoma	0.66	

*and low fat diet; **P < 0.05; ***including selenium, vitamin E and beta-carotene.
APPP, Australian Polyp Prevention Project; ATBC, Alpha Tocopherol Beta Carotene study; CARET, Carotene and Retinol Efficacy Trial; ECPOS, European Cancer Prevention Organisation Study Group; EUROSCAN, European Organization for Research and Treatment of Head and Neck Cancer and Lung Cancer Cooperative Group; NPCS, Nutritional Prevention of Skin Cancer; PHS, Physicians Health Study; PPS, Polyp Prevention Study Group; PPT, Polyp Prevention Trial; SCPS, Skin Cancer Prevention Study Group; SWCPS, Sothwest Skin Cancer Prevention Study; TPPT, Toronto Polyp Prevention Trial. Adapted from reference [16].

Table 2. Randomized controlled trials of dietary supplements to prevent cancer or colorectal adenomas, ordered by relative risk

American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention [17] says that many epidemiologic studies have reported a modest but significant association

	Vegetables	Fruits	Grains, fibers	Tea	Sugar	Alcohol	Salt & salting	Meat	Eggs	Milk & dairy
Mouth, pharynx	−−−	−−−			+++					
Nasopharynx							+++			
Esophagus	−−−	−−−	+			+++				
Stomach	−−−	−−−	−	−			++			
Pancreas	−−	−−	−						+	
Gallbladder										
Liver	−					+++				
Colon, rectum	−−−		−					++	+	
Larynx	−−	−−				+++				
Lung	−−−	−−−				+				
Breast	−−	−−	−			++		+		
Cervix	−	−								
Endometrium	−	−								
Ovary	−	−								
Prostate	−							+		+
Bladder	−−	−−								
Kidney	−							+		+
Thyroid	−									

Increased risk: +++, convincing; ++, probable; +, possible; decreased risk: −−−, convincing; −−, probable; −, possible. Data adapted from reference [16].

Table 3. Matrix summary of the WCRF/AICR judgments on the role of various foods in the risk of cancer

between high intakes of processed meats (such as bacon, sausage, luncheon meats) and red meats (defined as beef, pork, or lamb) and increases in cancer incidence and mortality as well as death from other causes. The American Cancer Society says that current evidence supports approximately a 15% to 20% increased risk of cancers of the colon and/or rectum per 100 grams (g) of red meat or 50 g of processed meat consumed per day, while the evidence for some other cancers (those of the esophagus, stomach, lung, pancreas, breast, prostate, stomach, endometrium, renal, and ovarian) is considered limited and suggestive. According to American Cancer Society meat contains several constituents that could increase the risk of cancer. Mutagens and carcinogens (heterocyclic amines and polycyclic aromatic hydrocarbons) are produced by cooking meat at high temperatures and/or by charcoal grilling. Nitrates/nitrites and salt used to process meat contribute to the formation of nitrosamines, which are known mutagens and carcinogens in animals. Iron from the heme group of myoglobin in red meat may act as a catalyst to nitrosamine formation, and generate free radicals that may damage DNA. It is also

possible that the fat content in meat contributes to risk through increasing the concentration of secondary bile acids and other compounds in the stool that could be carcinogens or promoters of carcinogenesis [17].

According to Davis [18] epidemiologic evidence suggests that regular consumption of fruits, vegetables, and whole grains may reduce cancer risk in some individuals. This association has been attributed to these foods being rich sources of numerous bioactive compounds. Plant foods contain a variety of components, including, but not limited to, essential nutrients, polyunsaturated fatty acids, and phytochemicals such as glucosinolates and flavonoids, many of which can inhibit cell proliferation and induce apoptosis, and which may act additively or synergistically when combined in the human diet.

3.1. Polyphenols

Polyphenols are common constituents of foods of plant origin and major antioxidants of our diet. The main dietary sources of polyphenols are fruits and beverages. Fruits like apple, grape, pear, cherry, and various berries contain up to 200–300 mg polyphenols per 100 g fresh weight. Typically, a glass of red wine or a cup of tea or coffee contains about 100 mg polyphenols. Cereals, chocolate, and dry legumes also contribute to the polyphenol intake [19]. Red wine polyphenols, which consisted of various powerful antioxidants such as flavonoids and stilbenes, have been implicated in cancer prevention and that promote human health without recognizable side effects. Experimental studies have shown that polyphenols from red wine, like resveratrol, quercetin, (+)-catechin and gallic acid, were potential cancer chemopreventive agents. However, red wine contains a wide range of different polyphenols and protective effects have not been assigned to a specific fraction or compound, so it is not yet clear which compounds present in red wine are endowed with protective activity [20]. Among the most highly cited class of polyphenols are the flavonoids, which comprise a large and diverse family of compounds synthesized by plants. Flavonoid subclasses include anthocyanidins in berries and grapes, flavanols in tea, flavanones in citrus fruits, flavonols in onions, flavones in herbs and peppers, and isoflavones in soy [21].

Zhou et al. [22] evaluated combined effects of soy phytochemical concentrate (SPC) and tea (green tea and black tea) components on the growth and metastasis of androgen-sensitive LNCaP human prostate cancer. The authors find that both black tea and green tea inhibited tumorigenicity rates of LNCaP tumors. For them the combination of soy phytochemicals and tea synergistically inhibited tumorigenicity, final tumor weight and metastasis to lymph nodes in vivo. This study supports further investigations using soy and tea combinations as effective nutritional regimens for prevention of prostate cancer. According to authors, studies of tea polyphenols suggest that epigallocatechin gallate (EGCG) is the major bioactive component in green tea and less is present in black tea. Black tea also contains other tea polyphenols such as theaflavins and thearubigins. They also affirm that chemopreventive properties of the soy isoflavone genistein have been the subject of extensive in vitro and in vivo.

Lambert and Yang [23] affirm that although numerous health benefits have been proposed for the consumption of tea, the effectiveness of tea as a cancer preventive agent in humans remains unclear. Animal models of carcinogenesis may be different from the human situation (e.g., the

doses of tea and tea components used in animal studies are often much higher than those consumed by humans), and many confounding factors are involved in epidemiological studies. Interindividual variation in biotransformation and bioavailability may also affect the efficacy of tea as a cancer preventive agent. For them further studies on definitive mechanisms of cancer preventive activities of tea in animal models are needed. Although many possible mechanisms have been proposed, their relevance in vivo needs to be demonstrated. With some exceptions, the concentrations of catechins or theaflavins used in cell culture systems exceed the plasma concentrations obtained in animal studies by 10- to 100-fold. Mechanisms based on the use of such high concentrations may be relevant for cancers of the gastrointestinal tract but not for sites such as the lung, prostate and breast, which depend on systemic bioavailability. In spite of many in vitro and in vivo studies, the molecular mechanisms for the cancer preventive actions of these compounds are not clearly known. The relationship between tea consumption and cancer risk has not been conclusively demonstrated, and the relationship may become clearer if we consider the effects of specific types of tea, at defined doses, in populations with certain dietary patterns or genetic polymorphisms. Human intervention trials and large prospective studies are needed to further assess cancer preventive activities of tea constituents [24]. For the National Cancer Institute [25] more than 50 epidemiologic studies of the association between tea consumption and cancer risk have been published since 2006. The results of these studies have often been inconsistent, but some have linked tea consumption to reduced risks of cancers of the colon, breast, ovary, prostate, and lung. They also believe that the inconsistent results may be due to variables such as differences in tea preparation and consumption, the types of tea studied (green, black, or both), the methods of tea production, the bioavailability of tea compounds, genetic variation in how people respond to tea consumption, the concomitant use of tobacco and alcohol, and other lifestyle factors that may influence a person's risk of developing cancer, such as physical activity or weight status.

A double-blind intervention trial conducted in patients with oral mucosa leukoplakia using a mixed tea showed some direct evidence on the protective effects of tea on oral cancer. In this study developed by Li et al. [26] fifty-nine oral mucosa leukoplakia patients, diagnosed by established clinical and pathological criteria, were randomly divided into a treated group (3 g mixed tea oral administration and topical treatment) and a control group (placebo and glycerin treatment). After the 6-month trial, the size of oral lesion was decreased in 37.9% of the 29 treated patients and increased in 3.4%; whereas the oral lesion was decreased in 10.0% of the 30 control patients and increased in 6.7%.

3.2. Vitamins and micronutrients

Natural inhibitors of oxidizing agents that are found in the diet are important in preventing cancer and typically do not have the undesirable side effects of many xenobiotic compounds. Some vitamins, such as the antioxidant Vitamins A, E, and C, demonstrate these protective effects. The daily ingestion of antioxidants has the potential of not only protecting against cancer, but also cardiovascular disorders and neurological degenerative diseases [28]. Antioxidants nutrients such as vitamin E, vitamin C, vitamin A, and Beta-carotene are involved in detoxification of the Reactive oxygen species (ROS). Vitamin E, A, and Beta-carotene are

lipophilic antioxidants whereas vitamin C is hydrophilic antioxidant. Vitamin E function as a free radical chain breaker particularly it interferes with the propagation step of lipid peroxidation. Vitamin A and Beta-carotene have actions by quenching both singlet oxygen and other free radicals generated by photochemical reactions [28].

The changes in the DNA by a deficiency of some micronutrients (folic acid, vitamin B12, vitamin B6, niacin, vitamin C, vitamin E, iron and zinc) are considered as the most likely cause of some types of cancer [29].

Studies investigating the interactions between dietary exposure and genetic polymorphisms have the potential to clarify mechanisms and identify susceptible subgroups so that preventative strategies can be focused on the subgroups for maximum benefit. Red meat or meat cooking methods such as frying and doneness levels have been associated with the increased risk of colorectal and other cancers [30]. It is not clear whether it is red meat intake or the way meat is cooked that is involved in the etiology of colorectal cancer, as stated above. Both cooking methods and doneness level of red meat are thought to be surrogates for heterocyclic amines (HCA) consumption [31]. Sinha and Caporaso [31] affirm that genetics polymorphisms may interact with various dietary components and thus define subgroups of individuals who may be at a higher risk of getting cancer. For them there are also other polymorphic enzymes that may interact with various dietary components and play a role in human carcinogenesis. The authors describe categories of susceptibility genes, potential dietary carcinogens and anticarcinogens, and cancer sites in which they may be involved (see Table 4). Many studies are currently investigating the role of circulating vitamin D metabolites and dietary calcium. Because the vitamin D receptor is involved in vitamin D and calcium metabolism, the vitamin D receptor polymorphisms may also be important for colorectal cancers. Martinez et al. [32] investigated the associations between the intake of calcium and vitamin D and the occurrence of colorectal cancer. They found that vitamin D is suggestive of an inverse association, particularly for total vitamin D in relation to rectal cancer. However, since most of the support for this protective effect was seen for total vitamin D. They not rule out the possibility that something other than vitamin D in multivitamin supplements contributes to this apparent effect. The relation between vitamin D and colorectal cancer may be better elucidated with additional dietary measurements and further follow-up. They conclude that available evidence does not warrant an increase in calcium intake to prevent colon cancer, but longer-term studies of both calcium and especially vitamin D in relation to colorectal cancer risk are needed.

Carotenoids are the pigments that give fruits and vegetables such as carrots, cantaloupe, sweet potato, and kale their vibrant orange, yellow, and green colors. Beta-carotene, lycopene, and lutein are all different varieties of carotenoids. They all act as antioxidants with strong cancer-fighting properties. Preclinical studies have shown that some carotenoids have potent antitumor effects both in vitro and in vivo, suggesting potential preventive and/or therapeutic roles for the compounds. Since chemoprevention is one of the most important strategies in the control of cancer development, molecular mechanism-based cancer chemoprevention using carotenoids seems to be an attractive approach [33]. Epidemiologic studies have shown an

Dietary component	Polymorphic gene/phenotype[1]	**Cancer site**
Carcinogens		
Heterocyclic amines	NAT2, (NAT1), CYP1A2 (CYP1A1)	Colorectal, breast, other sites
Polycyclic hydrocarbons	CYP1A1, GSTM1	Gastrointestinal tract Nasophyrangeal, stomach
Nitrosamines	CYP2E1	
Aflatoxins	GSTM1, EPHX	Liver
Alcohol	ADH (ALDH, CYP2E1)	Colorectal, oral
Anticarcinogens		
Cruciferous vegetables	CYP1A2, GST	Colorectal, other sites
Fruits and vegetables	CYP1A2, GST	Many sites
Calcium/vitamin D	Vitamin D receptor	Colorectal, prostate
Retinoids	Retinoic acid receptor Variant	Acute promylocytic Leukemia, skin, Head and neck, breast
Folate, methionine	MTHFR, Methionine Synthase	Colorectal, cervix

1 Abbreviations used: NAT, *N*-acetyltminsferase; CYP, cytochrome p450; GST, glutathione-S-transferase; EPHX, epoxide hydrolase; ADH, alcohol dehydrogenase; MTHFR, metheylenetetrahydrofolate reductase. Adapted from reference [31].

Table 4. Polymorphic genes, dietary components and cancer: possible candidates

inverse relationship between the presence of various cancers and dietary or blood carotenoid levels. According to Tanaka, Shnimizu and Moriwaki [33] the epidemiologic observations of the possible protective effects of high dietary (not supplemental) β-carotene intakes against cancer, along with what is known about carotenoid biochemical functions, has led to further study of the effect of β-carotene on cancer risk. Long-term large randomized intervention trials were designed to test the efficacy of high doses of β-carotene (20–30 mg/day) in the prevention of cancer. These results are summarized in Table 5.

Study Designs				
Studies	**Population**	**Intervention**	**Duration**	**Cancer outcome**
ATBC	29,133 Finish male smokers (50–69 years of age)	β-carotene, 20 mg/day; vitamin E, 50 mg/day	5–8 years	18% increase in lung cancer; 8% increase in mortality
CARET	18,314 men and women and asbestoss workers (45–74 years of age)	β-carotene, 30 mg/day; vitamin A, 25,000 IU	<4 years	28% increase in lung cancer; 17% increase in deaths
PHS	22,071 male physicians (40–84 years of age)	β-carotene, 50 mg on alternate days	12 years	No effect of supplementation in incidence of cancer
Linxian	29,584 men and women, vitamin and mineral deficient (40–69 years of age)	β-carotene, 15 mg/day; selenium, 50 mg/day; α-tocopherol, 30 mg/day	5 years	13% decrease in total cancers; 9% decrease in overall deaths
Women's Health Study	39,876 female health professionals (over 45 years of age)	β-carotene, 50 mg on alternate days	4.1 years (2.1 years' treatment and 2.0 years' follow-up)	No effect of supplementation in incidence of cancer

Data adapted from reference [33].
CARET, Beta-Carotene and Retinol Efficacy Trial; ATBC, Alpha Tocopherol and Beta-Carotene Cancer Prevention; PHS, Physicians' Health Study.

Table 5. β-Carotene supplementation trials.

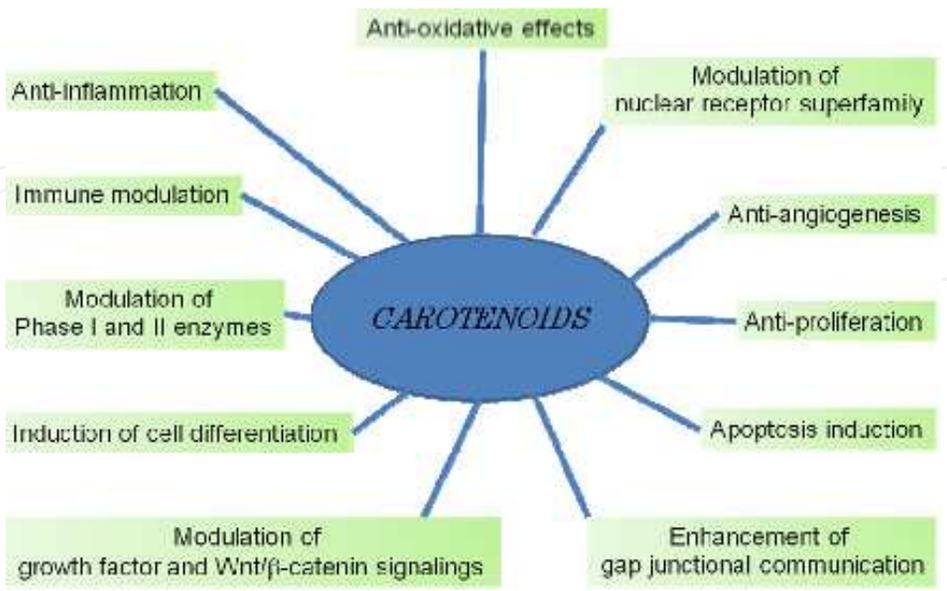

Figure 4. Proposed mechanisms by which certain carotenoids suppress carcinogenesis. Adapted from reference [33].

The authors [33] wrote an important review which showed a table (Table 6) about cancer prevention by means of carotenoids with dietary sources, function e effects. According to these authors the mechanisms underlying the anticancer and/or cancer chemopreventive activities of carotenoids may involve changes in pathways leading to cell growth or cell death. These include immune modulation, hormone and growth factor signaling, regulatory mechanisms of cell cycle progression, cell differentiation and apoptosis. In this sense the authors also showed an interesting figure proposing possible mechanisms by which certain carotenoids suppress carcinogenesis (see Figure 4 on the left).

Studies involving the use of vitamin C in cancer prevention are the most contradictory. Vitamin C is an essential vitamin the human body needs to function well. It is a water-soluble vitamin that cannot be made by the body, and must be obtained from foods or other sources. Vitamin C is found in abundance in citrus fruits such as oranges, grapefruit, and lemons, and in green leafy vegetables, potatoes, strawberries, bell peppers, and cantaloupe. American Cancer Society [34] wrote that many studies have shown a connection between eating foods rich in vitamin C, such as fruits and vegetables, and a reduced risk of cancer. On the other hand, evidence indicates that vitamin C supplements do not reduce cancer risk. This suggests that the activity of fruits and vegetables in preventing cancer is due to a combination of many vitamins and other phytochemicals and not to vitamin C alone. Clinical trials of high doses vitamin C as a treatment for cancer have not shown any benefit. High doses of vitamin C can cause a number of side effects.

According to Block [35] epidemiologic evidence of a protective effect of vitamin C for non-hormone-dependent cancers is strong. Of the 46 such studies in which a dietary vitamin C index was calculated, 33 found statistically significant protection, with high intake conferring approximately a twofold protective effect compared with low intake. 0f 29 additional studies that assessed fruit intake, 2 1 found significant protection. For cancers of the esophagus, larynx, oral cavity, and pancreas, evidence for a protective effect of vitamin C or some component in fruit is strong and consistent. For cancers of the stomach, rectum, breast, and cervix there is also strong evidence. Several recent lung cancer studies found significant protective effects of vitamin C or of foods that are better sources of vitamin C than of /3-carotene. It is likely that ascorbic acid, carotenoids, and other factors in fruits and vegetables act jointly.

Several lines of evidence suggest that vitamin C is a powerful antioxidant in biological systems in vitro. However, its antioxidant role in humans has not been supported by currently available clinical studies. Diets high in fruits and vegetables protect against cardiovascular disease and cancer, but such a protective effect cannot as yet be ascribed to vitamin C. In vivo markers of oxidative damage are being developed, and these have yet not shown major changes with vitamin C intake in humans [36]. The most important problem about vitamin C is that it can exert a pro-oxidant activity under certain conditions, particularly in the presence of transition metal ions or alkali. Thus, vitamin C *in vitro* reduces free ferric iron that generates hydrogen peroxide in the Fenton reaction and results in the production of hydroxyl radicals. The reactive hydroxyl radical quickly reacts with critical cellular macromolecules, including DNA, which may lead to mutagenesis and the initiation of cancer [37]. According to authors, the high

Carotenoids	Dietary Sources	Function	Effects
α-Carotene	Yellow-orange vegetables (carrots, sweet totatoes, pumpkin) and Dark-green vegetables (broccoli, green beans, spinach)	Provitamin A activity; Anti-oxidant	Immune- enhancement; Stimulate cell to cell communication; Decreases risk of some cancers
β-Carotene	Green leafy vegetables and orange and yellow fruits and vegetables (carrots, apricots, spinach, sweet potetoes, pumpkin, pepper, kale, cantaloupe)	Provitamin A activity; Antioxidant	Immune-enhancement; Decreases risk of some cancers and some cardiovascular events; high-dose supplementation may increase the risk of lung cancer among smokers
Lycopene	Tomatoes, water melon, apricot, peaches	Anti-oxidant	Decreases risk of some cancers and some cardiovascular events, diabetes, and osteoporosis
β-Cyptoxanthin	Orange fruits (mandarin orange and papaya, etc.), corn, peas, and egg yolks	Provitamin A activity; Anti-oxidant	Anti-inflammatory effects; Inhibits risks of some cancer and cardiovascular events; Immune enhancemen
Lutein/Zeaxanthin	Dark green leafy vegetables (spinach, kale), red peppers, maize, tomatoes, corn, and egg yolks	Anti-photosensitizing agent and photosynthetic pigment; Acts as antioxidants and blue light filters	Decrease age-related macular degeneration, cataract, and risk of cardiovascular disease and certain cancers
Astaxanthin	Green algae, salmon, trout, Crustacean	Antioxidant; Coloration	Prevent certain cancers, cataract, diabetes, and inflammatory neurodegenerative and cardiovascular diseases
Canthaxanthin	Salmon, crustacean	Antioxidant; Coloration	Immune enhancement; Decreases risk of some cancers
Focoxanthin	Brown algae, heterokonts	Antioxidant	Anti-cancer, anti-allergic, anti-obese, anti-inflammatory, and anti-osteoporotic activities

Adapted from reference [33].

Table 6. Sources, function, and effects of different carotenoids.

consumption of vitamin C–rich fruit and vegetables is not likely to be harmful. In general, data from in vitro and in vivo experiments and population-based studies do not indicate that high doses of vitamin C are linked to increased oxidative DNA damage or an elevated risk of cancer.

Lee et al. [37] believe that the cancer preventive effects of vegetables and fruit may result from multiple combined effects of various phenolic phytochemicals, vitamins, dietary fibers, indoles, allium compounds, and selenium rather than from the effect of a single active ingredient. For them, many dietary phenolic phytochemicals may have stronger antioxidant and antitumor promotion effects than do antioxidant vitamins, which may contribute to the chemopreventive effects of the phytochemicals in carcinogenesis. However, these authors suggest that the chemopreventive effects of vitamin C in carcinogenesis may be linked to the protective effects of vitamin C against epigenetic mechanisms, such as the inflammation and inhibition of gap junction intercellular communication (GJIC), as well as to antioxidant activities (see Figure 5).

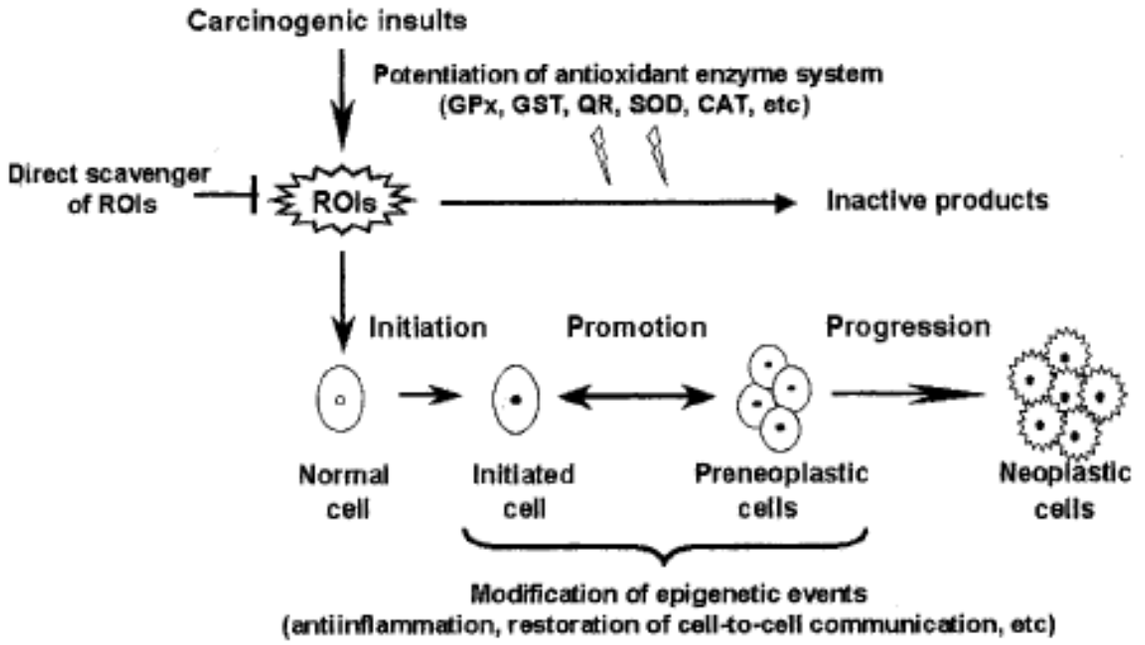

Figure 5. Possible chemopreventive mechanisms of vitamin C in carcinogenesis. ROIs, reactive oxygen intermediates; GPx, glutathione peroxidase; GST, glutathione *S*-transferase; QR, quinone oxidoreductase; SOD, superoxide dismutase; CAT, catalase. Adapted from reference [37].

Regarding the use of vitamin C in cancer patient the results were not promising. In a double-blind study 100 patients with advanced colorectal cancer were randomly assigned to treatment with either high-dose vitamin C (10 g daily) or placebo. Overall, these patients were in very good general condition, with minimal symptoms. None had received any previous treatment with cytotoxic drugs. Vitamin C therapy showed no advantage over placebo therapy with regard to either the interval between the beginning of treatment and disease progression or patient survival. Among patients with measurable disease, none had objective improvement. On the basis of this and our previous randomized study, it can be concluded that high-dose

vitamin C therapy is not effective against advanced malignant disease regardless of whether the patient has had any prior chemotherapy [38].

The terms folic acid and folate are often used interchangeably for this water-soluble B-complex vitamin. Folic acid, the more stable form, occurs rarely in foods or the human body but is the form most often used in vitamin supplements and fortified foods. Folic acid is essential to numerous bodily functions ranging from nucleotide biosynthesis to the remethylation of homocysteine. The human body needs folate to synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in biological reactions involving folate.

Considerable epidemiological evidence suggests that a low-folate diet is associated with an increased risk of colorectal neoplasia. Much animal data support an antineoplastic effect of folate. However, in some animal studies, folate deficiency protects against, and supplementation increases, experimental carcinogenesis. Cole et al. [39] developed a double-blind, placebo-controlled, 2-factor, phase 3, randomized clinical trial conducted at 9 clinical centers between July 6, 1994, and October 1, 2004. Participants included 1021 men and women with a recent history of colorectal adenomas and no previous invasive large intestine carcinoma. Participants were randomly assigned in a 1:1 ratio to receive 1 mg/d of folic acid (n=516) or placebo (n=505), and were separately randomized to receive aspirin (81 or 325 mg/d) or placebo. Follow-up consisted of 2 colonoscopic surveillance cycles (the first interval was at 3 years and the second at 3 or 5 years later). In this double-blind, placebo-controlled, randomized clinical trial, was found that folic acid supplementation did not decrease the risk of adenoma occurrence among participants with a recent history of adenomas. The authors concluded that folate, when administered as folic acid for up to 6 years, does not decrease the risk of adenoma formation in the large intestine among individuals with previously removed adenomas. For them, the evidence for an increased risk of adenomas is equivocal and requires further research.

In March of 1996, the U.S. Food and Drug Administration mandated that all enriched flour and uncooked cereal grains sold in the United States should be fortified with 140 μg folic acid/100 g of flour no later than January of 1998. Following the institution of fortification population-based studies showed the effectiveness of this measure: plasma levels of folate in the adult population increased ~2-fold as a result and the incidence of births complicated by neural tube defects was variously reported to decline by 20% to 50%. However, analyses of several cereal grains that were purchased after the institution of fortification showed that in many instances the actual amount of folate was 150% to 300% greater than the mandate, suggesting that in this early era of fortification, manufacturers often included ''overage'' to ensure that they were meeting the minimal level of mandated fortification [40]. Thus, the authors hypothesize, by means of an epidemiological study, that the institution of folic acid fortification may have been wholly or partly responsible for the observed increase in colorectal cancer rates in the mid-1990s. The authors affirm that wish to highlight the potential complexity of the response to this nutrient and emphasize prior observations that have been made in both preclinical and clinical studies that indicate that administering high doses of folic acid to susceptible individuals or in an inappropriate time frame may accelerate the growth of existing neoplasms.

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin. Unlike most mammals and other animals, humans do not have the ability to make their own vitamin C. Therefore, we

must obtain vitamin C through our diet. Vitamin C is required for the synthesis of collagen, an important structural component of blood vessels, tendons, ligaments, and bone. Vitamin C also plays an important role in the synthesis of the neurotransmitter, norepinephrine. Neurotransmitters are critical to brain function and are known to affect mood. Vitamin C is also a highly effective antioxidant. Even in small amounts vitamin C can protect indispensable molecules in the body, such as proteins, lipids (fats), carbohydrates, and nucleic acids (DNA and RNA), from damage by free radicals and reactive oxygen species that can be generated during normal metabolism as well as through exposure to toxins and pollutants (e.g., cigarette smoke). In the U.S., the recommended dietary allowance (RDA) for vitamin C was revised in 2000 upward from the previous recommendation of 60 mg daily for men and women. The RDA continues to be based primarily on the prevention of deficiency disease, rather than the prevention of chronic disease and the promotion of optimum health. The recommended intake for smokers is 35 mg/day higher than for non-smokers, because smokers are under increased oxidative stress from the toxins in cigarette smoke and generally have lower blood levels of vitamin C (see Table 7 – reference [41]).

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	40 (AI)	40 (AI)
Infants	7-12 months	50 (AI)	50 (AI)
Children	1-3 years	15	15
Children	4-8 years	25	25
Children	9-13 years	45	45
Adolescents	14-18 years	75	65
Adults	19 years and older	90	75
Smokers	19 years and older	125	110
Pregnancy	18 years and younger	-	80
Pregnancy	19 years and older	-	85
Breast-feeding	18 years and younger	-	115
Breast-feeding	19 years and older	-	120

Data from reference [41].

Table 7. Recommended Dietary Allowance (RDA) for Vitamin C

The relations between the intake of beta-carotene, vitamin C, selenium, and 25-yr mortality from lung cancer and total cancer were analyzed within the Zutphen Study, a cohort study on diet and chronic diseases [42]. The Zutphen Study is a prospective study on the relations between diet, other risk factors, and the incidence of chronic diseases. The results of this study suggest that vitamin C intake may be more important for prevention of lung cancer than beta-carotene. It can, however, not be ruled out that substances present in fruit other than vitamin C (eg, phenols, flavones, and terpenes) may also be of importance in lung cancer prevention. The results suggest that a vitamin C intake of ≥ 70 mg/d may be of importance in lung cancer

prevention. Due to the role of vitamin C in the formation of N-nitrosocompounds, this may also be of importance for stomach cancer prevention. Another hand, 8 prospective studies does not suggest that intakes of vitamins A, C and E and folate reduce the risk of lung cancer. The results were similar with different analytic approaches and across studies, sex, smoking status and lung cancer cell type [43].

Data on intake of specific carotenoids and breast cancer risk are limited. Furthermore, studies of vitamins A, C, and E in relation to breast cancer risk are inconclusive. Zhang et al. [44] were made studies, using multivariate analysis, demonstrated associations between intakes of specific carotenoids, vitamins A, C, and E, consumption of fruits and vegetables, and breast cancer risk in a cohort of 83,234 women (aged 33-60 years in 1980). Through 1994, they identified 2,697 incident cases of invasive breast cancer (784 premenopausal and 1913 postmenopausal). The results demonstrated that intakes of beta-carotene from food and supplements, lutein/zeaxanthin, and vitamin A from foods were weakly inversely associated with breast cancer risk in premenopausal women. Strong inverse associations were found for increasing quintiles of alpha-carotene, beta-carotene, lutein/zeaxanthin, total vitamin C from foods, and total vitamin A among premenopausal women with a positive family history of breast cancer. An inverse association was also found for increasing quintiles of beta-carotene among premenopausal women who consumed 15 g or more of alcohol per day. Premenopausal women who consumed five or more servings per day of fruits and vegetables had modestly lower risk of breast cancer than those who had less than two servings per day (relative risk [RR] = 0.77; 95% confidence interval [CI] = 0.58-1.02); this association was stronger among premenopausal women who had a positive family history of breast cancer (RR = 0.29; 95% CI = 0.13-0.62) or those who consumed 15 g or more of alcohol per day (RR = 0.53; 95% CI = 0.27-1.04). The author concluded that consumption of fruits and vegetables high in specific carotenoids and vitamins may reduce premenopausal breast cancer risk [44].

In recent years, the intake of vitamins, minerals and herbs as a dietary supplement has increased dramatically. The supplementation with vitamins and minerals are used more often than the herbs. The most common supplements among users in the U.S. are multivitamins (75%), followed by vitamin C (38%), and iron (38%) [45]. Food supplementation with vitamins is a polemic question and it differs among authors. There are evidences that dietary supplementation with vitamin C may reduce the incidence of gastric cancer in certain populations, but it is unclear whether it was the antioxidant, vitamin or other property, responsible for this action [46]. However, the author states that it does not justify, in terms of cancer prevention to make a diet supplemented with vitamin C if the person has a good diet. Claycombe and Meydani [47] were made a review reporting the protective effect of vitamin E against chromosomal alterations induced by oxidation of DNA. However, the authors call attention to the careful supplementation, simultaneous with C vitamin E, considering a possible genotoxicity in the association of the two vitamins. Although most animal studies have shown cancer-preventive effects, a few recent studies suggest that soy phytoestrogens may stimulate breast cancer cell growth under certain circumstances. Before recommendations regarding phytoestrogen supplements can be safely made, we must have more information on the effects of the extracts on bone, heart and breast health. Until safety with respect to breast cancer is established, phytoestrogen supplements should not be recommended, particularly for women at high risk of breast cancer [48].

Cancer prevention can be done with a diet rich in vegetables, fruits, and low in red meat, saturated fats, salt and sugar. Carbohydrates should be consumed in the form of cereals - wheat bread and brown rice. The addition of fats should be in the form of fats dehydrogenated [49]. The types of vegetables or fruit that most often appear to be protective against cancer are allium vegetables, carrots, green vegetables, cruciferous vegetables, and tomatoes. Substances present in some vegetable and fruit may help cancer prevention and they include dithiolthiones, isothiocyanates, indole-3-carbinol, allium compounds, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, vitamin C, D-limonene, lutein, folic acid, beta carotene, lycopene, selenium, vitamin E, flavonoids, and dietary fiber. Current US vegetable and fruit intake, which averages about 3.4 servings per day, is discussed, as are possible non-cancer-related effects of increased vegetable and fruit consumption, including benefits against cardiovascular disease, diabetes, stroke, obesity, diverticulosis, and cataracts [50].

4. Conclusion

Cancer incidence is projected to increase in the future and an effectual preventive strategy is required to face this challenge. Alteration of dietary habits is potentially an effective approach for reducing cancer risk. Assessment of biological effects of a specific food or bioactive component that is linked to cancer and prediction of individual susceptibility as a function of nutrient-nutrient interactions and genetics is an essential element to evaluate the beneficiaries of dietary interventions [51]. We know that diet is an important factor both to minimize, as to increase the risk of cancer development. But diet is not the only factor. There are several risk factors that can trigger a process of tumor formation. Sedentary life, environmental issues, viruses, smoking, alcohol in excess, are factors that contribute to and are also strategic points that should be worked in cancer prevention.

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