Review Article

Cancer preventive role of selected dietary factors

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Abstract

Dietary behavior seems to be an important modifiable determinant for the risk of cancer. The evidences from several epidemiological studies suggest that higher intakes of fruits and vegetables have been associated with lower risk of cancer. Dietary phenolic and polyphenolic substances, terpenoids, dietary fibers, fish oils, some micronutrients present in foods of both plant and animal origin, and a reduction of caloric intake appear to inhibit the process of cancer development. Many dietary factors possess antioxidant and anti-inflammatory properties and cause induction of phase II enzymes like glutathione-*S*-transferases. It has been suggested that cruciferous vegetables play an important role in cancer prevention, and their chemopreventive effects are due to high glucosinolate content which under enzymatic hydrolysis produces bioactive compound isothiocyanates. Further, isothiocyanates of a wide variety of cruciferous vegetables are powerful inhibitors of carcinogenesis in experimental animal models. Several flavonoids present in fruits, tea, soya beans, etc. may be useful as cancer preventive agents. Similarly, ellagic acid, perillyl alcohol and resveratrol found in various fruits may have chemoprotective effect. Moreover, different vanilloids such as curcumin and gingerol have been shown to possess antioxidative properties. Nevertheless, in spite of several studies, still the effects of various ingredients are not clearly distinguished. In human, little convincing evidence has been established for the proposed protective effects of dietary constituents. It is an important future research goal to provide necessary evidences to support the chemopreventive role of different dietary factors, and also to clarify misunderstandings in this perplexing area.

Key Words: Cancer, diet, micronutrients, isothiocyanates, phenolic compounds

Introduction

This article is based on (however, not restricted to) the discussion of the meeting 'Dietary Factors and Cancer Prevention: Current Premises and Future Promises' which was held at the Mayo Clinic, Rochester (Minnesota, USA) on 23rd-25th September 2004. This review paper has covered all the relevant lectures of the said conference (which were about 70%). A total of 31 speakers including well-known personalities like Lee Wattenberg, John H. Weisburger, Akira Murakami and the other investigators participated in the meeting. All relevant lectures have been summarized in this article by quoting appropriate published papers of the concerned speakers. The remaining lectures (about 30%) in that meeting were on other issues of cancer such as pathology including natural history and diagnostic aspect, treatment and related US governmental policies.

Cancer is the second major cause of non-communicable deaths, contributing to 13% mortality and 22% of non-communicable disease mortality, worldwide; whereas cardiovascular disease is the leading cause of deaths.[1] Cancer is a multifactorial disease that develops over a long period of time and progresses through different stages. Perhaps nutrition is the most important aspect, which is intricately and intimately associated with the entire pathological process of cancer. In general, the

total mixed fat (i.e., different types of dietary fat) intake is probably associated with a higher incidence of several leading cancers such as carcinoma of the breast, colon, prostate, ovary, endometrium and pancreas.[2,3] Similarly, obesity increases the risk for different cancers and physical activity, the main determinant of energy expenditure, reduces the risk.[4] Moreover, it has been observed that caloric restriction inhibits carcinogenesis in many animal models.[5]

Epidemiological studies and animal experiments indicate that dietary fiber and *n*-3 fatty acids exert protective effects against some common cancers, especially cancers of the breast, colon and prostate.[6-9] Dietary fiber comprises a heterogeneous group of non-starch polysaccharides such as cellulose, hemicellulose, pectin and non-carbohydrate substances like phytic acid, with the protective effect of dietary fiber depending on the nature and source of fiber. Wheat bran appears to inhibit colon tumor development more consistently than do other dietary sources of fiber.[10] Human diet intervention studies have demonstrated that supplemental wheat bran in the diet decreased the formation of putative metabolites such as secondary bile acids and diacylglycerol in the colon, which have been shown to act as tumor promoters.[9] However, in a study conducted by Alberts et al., three years of dietary supplementation with wheat bran fiber did not protect against the recurrence of colorectal adenomas.[11] On the other hand, several studies have suggested that *n*-3 polyunsaturated fatty acids (PUFA) – especially long-chain *n*-3 PUFA, which are synthesized from α-linolenic acid, can prevent cancers. Generally, fish and seafood are the main dietary sources of long-chain *n*-3 PUFA in majority of populations. Whereas, *n*-6 PUFA, synthesized from linoleic acid, has been suggested to facilitate cancer development.[12]

Throughout history, many naturally occurring agents have been used for the prevention and treatment of cancer and other diseases.[13] The cancer preventive effects of fruits and vegetables have been observed in several epidemiological and experimental studies. However, these studies could not distinguish the effects of various dietary factors because of high collinearity of nutrients and food constituents. The majority of these naturally occurring substances possess antioxidative and anti-inflammatory properties which appear to contribute to their chemopreventive activity. The term 'chemoprevention' was first used by Sporn, who showed that retinoids hindered experimental carcinogenesis.[14] However, the conventional classification of chemopreventive agents was first proposed by Wattenberg,[15] who subdivided the chemopreventive agents into two principal groups: blocking agents and suppressing agents. Blocking agents such as isothiocyanates, ellagic acid and flavonoids are able to prevent initiation by either inhibiting the formation of carcinogens from precursor molecules or hindering carcinogens from interacting with cellular target molecules. On the other hand, suppressing agents such as β-carotene, gingerol, epigallocatechin-3-gallate (EGCG), are thought to prevent carcinogenic expression of cells in promotion or progression stage. Some agents such as curcumin and resveratrol act as both blocking and suppressing agents.[16]

The detoxifying/biotransformation enzymes play a vital role in deciding the final fate of carcinogens or procarcinogens and their subsequent influence on the process of carcinogenesis. Overall, the purpose of physiological system is to increase the water solubility of carcinogenic substances in order to facilitate their excretion; this purpose is achieved in two phases. Phase I enzymes (cytochrome P450 and flavin-dependent monooxygenases) convert lipophilic compounds into more hydrophilic intermediates. In certain cases, this process can also give rise to carcinogens from biologically inactive compounds (procarcinogens) and, thus, inhibition of phase I enzymes may be protective. Subsequently, phase II enzymes (e.g., glutathione-*S*-transferases, UDP-glucuronosyltransferases, sulfotransferases, *N*-acetyl-transferases) catalyze conjugation reactions with molecules such as glutathione, glucuronic acid, or sulfate to render the toxic substances even more water soluble; and eventually, they are excreted through urine or bile. A wide variety of phenolic compounds present in diet can modify the detoxifying enzymes. Induction of phase II enzymes in general leads to protection of cells against exogenous and/or endogenous carcinogenic intermediates.[17] Regulation of phase II enzymes by dietary chemopreventive compounds is mediated by the antioxidant or electrophile response element (ARE/EpRE), which is located in the promoter region of concerned gene. Many chemopreventive agents modulate several signal transduction pathways, including mitogen-activated protein kinase (MAPK), protein kinase C, and phosphatidylinositol 3-kinase pathways, leading to activation of the transcription factor nuclear factor E2-related factor 2 (Nrf2) that binds to the ARE sequence to initiate gene expression.[18]

Lifestyle Factors and Cancer

The process of carcinogenesis is a complex phenomenon, and several factors (both environmental including behavioral, and genetic) are associated with

the etiology. Among behavioral factors, tobacco use, diet, physical activity, and obesity/energy balance – are all linked with the pathogenesis of cancer.[19] Large international variation in cancer incidence and mortality rate, and an increase in cancer rates among populations who migrated from low to high cancer incidence areas are important evidence that lifestyle factors influence the development of cancer.[20,21] Further, human lifestyle factors are closely associated with various enzymes of the physiological system, including enzymes that metabolize exogenous environmental compounds and different nutrients. The genes encoding metabolic enzymes are polymorphically expressed and many polymorphisms have a functional consequence for the expressed protein. Therefore, the interaction of genetic polymorphisms with consumed nutrients or with promutagens could modulate cancer etiology.[22] For instance, studies have shown that glutathione-*S*-transferase genotypes GSTM1 and GSTT1 null allele are associated with an increased risk of several cancers.[23,24] Similarly, certain genetic variations of different enzymes such as cytochrome P450s, acetyltransferases, sulfotransferases, superoxide dismutase etc. have been suggested to be related to cancer risk.[22] Moreover, recent studies have documented that diets and energy balance influence carcinogenesis in genetically altered animals like p53-deficient mice.[25,26]

It has been suggested that 5% of all cancers have genetic origin, smoking has an impact in about 30% and nutrition in about 35% of affected subjects.[27-29] However, in recent time, the evidence for a role of energy imbalance, physical inactivity, and obesity has been strengthened than dietary fat.[30] Energy balance, reflected in a low body weight and high level of physical activity, has been more convincingly related to lower cancer rates.[31] Different experimental studies have shown that animals on energy-restricted diets are relatively resistant to tumor development.[5,32] It has been observed that energy restriction augments apoptosis.[33] Further, the adverse effects of energy imbalance may be mediated through alterations in the metabolism of insulin and insulin-like growth factors.[34] Insulin regulates energy metabolism and increases the activity of insulin-like growth factor-I (IGF-I) by enhancing its synthesis and by decreasing several of its binding proteins (IGFBP-1 and 2). Both insulin and IGF-I stimulate anabolic process which can promote tumor development by inhibiting apoptosis, and by stimulating cell proliferation.[35] Evidence is accumulating, which shows that energy balance may affect carcinogenesis of various sites.

Anti-cancer Effects of Foods

Common food groups and cancer risk

In recent time, a high level of awareness/interest has been created among general people worldwide about the protective effects of fruit and vegetables against cancer risk. But, it should be clear that no protective effects have actually been firmly established. Although, a recent publication of the International Agency for Research on Cancer (IARC) has suggested to increase or maintain fruit and vegetable intake to improve nutrition for reducing the burden of cancer and other chronic diseases.[36] However, different studies have generally agreed that consumption of a diet rich in vegetables, fruits, and other plant food constituents; low in animal fats, along with maintaining a physically active healthy weight can reduce the risk of cancer and other chronic diseases.[13,28,37] Among animal foods, red or processed meat seems to enhance the risk of cancer, while it is not clear for white meat, and fish seems to be protective.[38] Furthermore, micronutrients present in animal foods such as calcium, vitamin D, folates, vitamin A and selenium can be protective (Table 1).[38,39] Milk and dairy products are the good source of calcium and vitamin D. Dairy products are a diverse food group comprising of various factors that could influence risk, e.g., relatively high saturated fat content, growth factors such as IGF-I, and chemical contaminants such as pesticide residues.[40] However, the calcium and vitamin D contents of dairy products have been hypothesized to reduce the cancer risk.[40-44]

Cruciferous vegetables

Cruciferous vegetables play an important role against the risk of cancer.[45,46] The Cruciferae (syn. Brassicaceae) are the family of plants that include a wide variety of familiar members of the species *Brassica oleracea* (e.g., broccoli, cabbage, cauliflower, parsnip, kale, kohlrabi, brussels sprouts, turnip, rutabaga) and many other plants which are commonly consumed in various parts of the world such as oriental cabbage, arugula, watercress, radish, daikon, wasabi, various mustards, horseradish, kai choi, etc. The role of cruciferous vegetables to protect against cancer is attributed to the fact that they are the unique source of glucosinolates (β-thioglycoside-*N*-hydroxysulfates) in our diet. Glucosinolate content is about 1% of dry weight of the Brassica vegetables; and it plays important roles in plants such as in allelopathy (suppression of growth of neighboring plants), and in protection against predators including nematocidal, microbicidal, antifungal

Table 1: Important micronutrients, present in foods of animal origin, which may have chemopreventive properties against cancer

Micronutrients	Animal sources	Plant sources
Calcium	Dairy products such as milk and cheese, fish-bones	Leafy vegetables (such as (spinach), beans, broccoli, kale, collard, turnip, mustard greens, fortified foods and beverages
Selenium	Fish, meat, eggs, milk, shell fish	Sources in plants vary with soil content
Vitamin A	Liver, fish, eggs, fortified milk	Carrots, spinach and other green vegetables, broccoli, sweet potatoes, mangoes, winter squash, tomatoes, romaine lettuce, apricots, peaches, cantaloupe, papaya
Vitamin D	Cholecalciferol or D_3 / Fish, fortified milk, butter, eggs, liver, synthesis in the skin during exposure to sun-light	Ergosterol or D_2 Raisin bran cereal
Folate	Liver, eggs	Spinach and other leafy vegetables, sprouts, broccoli, romaine lettuce, asparagus, orange, wheat germ, beans, legumes, sunflower seeds, cauliflower and cabbage

and insecticidal activities.[47] Glucosinolates are hydrolyzed by the plant enzyme myrosinase (a β-thioglucosidase) when the cells in plants are damaged due to cutting or chewing, releasing the biologically active isothiocyanates which are basically organosulfur compounds. If myrosinase has been inactivated due to cooking, glucosinolates are broken down by intestinal bacterial myrosinase in the colon.[48]

At least 120 different glucosinolates have been identified.[49] Glucobrassicin and glucoraphanin are generally found in high concentrations in broccoli. Chinese cabbage, radish and watercress contain high amount of gluconasturtiin; whereas, sinigrin is found in high concentrations in brussels sprouts, cabbage and cauliflower. As mentioned earlier, hydrolysis of glucosinolates by myrosinase produces various types of isothiocyanates. Hydrolysis of glucoraphanin results in sulforaphane, hydrolysis of sinigrin results in allyl isothiocyanate, gluconasturtiin produces phenethyl isothiocyanate (PEITC) and glucobrassicin produces indole-3-carbinol.[50] The isothiocyanates formed from indole glucosinolates are unstable, and decompose spontaneously to indole-3-carbinol, indole-acetonitrile, thiocyanate and 3,3'-diindolylmethane. Indole-3-carbinol may then spontaneously condense under the acidic conditions of the stomach to form compounds that closely resemble 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin), which is carcinogenic. In spite of this property, indole-3-carbinol has been investigated as a cancer chemopreventive agent.[49] A large amount of data demonstrate that isothiocyanates act as cancer chemopreventive agents by favorably modifying carcinogen metabolism via selective inhibition of cytochrome P450 enzymes involved in carcinogen metabolic activation and induction of phase II enzymes.[51] Interestingly, sulforaphane is an extremely potent inducer of phase II enzymes and effectively inhibits proliferation of cancer cells by causing caspase-9 and caspase-8 mediated apoptosis.[45,52]

Cruciferous vegetables can modulate estrogen metabolism and it has been hypothesized that they might lower the risk of estrogen-dependent cancers like breast cancer.[53] 16-α-hydroxylation yields potent estrogen that may play a positive role in the development of breast cancer; whereas hydroxylation at the 2-position lowers the biosynthesis of 16-α-hydroxylation product of estrogen. Therefore, the ratio between the products of these two major pathways of estrogen metabolism may be important in the pathogenesis, e.g., 2-hydroxyestrone:16-α-hydroxyestrone, an increase in the ratio is thought to be protective. Several studies have observed that indole-3-carbinol increased the level of 2-hydroxyestrogen and simultaneously decreased the concentration of 16-α-hydroxyestrogen.[54,55] Interestingly, cruciferous vegetables also contain other chemopreventive ingredients such as flavonoids and selenium.[50,56,57]

In this connection, it may be worthy to mention that in plants, selenium content varies with geographical areas. The products of plants grown in soils containing sufficient selenium are good sources. However, in general, foods providing the good sources of selenium are fish, grains such as wheat and oat, eggs, and meat (Table 1). It has been thought that selenium could protect against cancer through several mechanisms.[58]

Flavonoids and terpenoids

Flavonoids are a large group of plant's products that have a common C_6-C_3-C_6 structure consisting of two aromatic rings linked through an oxygenated heterocycle

(which is fused to one of these aromatic rings). Approximately, 8000 flavonoids have been characterized and the major classes (Table 2) are flavones (apigenin, luteolin), flavonols (quercetin, kaempferol), flavanones (hesperetin, naringenin), flavanols (epigallocatechin, EGCG), anthocyanins (cyanidnin, delphinidin) and isoflavones (genistein, daidzein).[59] Flavonoids possess free radical scavenging properties and have been reported to modulate cyclooxygenase-2 (COX-2) transcription in a number of different cell models.[60] There are two major isoforms of cyclooxygenase: COX-1 which does not change in response to stimuli, whereas COX-2 is overexpressed during inflammation and in the pathological process of cancer.[61] Liang et al. observed that apigenin was the most potent inhibitor of COX-2, inducible nitric oxide synthase (iNOS), and nuclear factor-κB (NF-κB).[62] On the other hand, Singh and Agarwal noticed that silibinin, a flavonoid isolated from milk thistle, inhibited mitogenic and cell survival signaling such as epidermal growth factor receptor (EGFR), insulin-like growth factor receptor type I (IGFRI) and NF-κB signaling.[63] Interestingly, isoflavones like genistein and daidzein possess estrogenic properties (phytoestrogens). In Asian nations, the staple consumption of phytoestrogen-rich food correlates with a reduced incidence of breast cancer.[64] Phytoestrogens compete with endogenous estrogens for binding to estrogen receptor. Therefore, they may have beneficial effects in prevention of steroid hormone dependent cancers such as breast and prostate cancer.

Terpenoids are an extensive group of natural products whose structures are composed of isoprene units (synthesized from the five-carbon unit isopentenyl pyrophosphate). Therefore, the number of carbon atoms in different terpenoids is usually a multiple of five, which is the basis of their nomenclature such as hemiterpenes (one C_5 unit), monoterpenes (two C_5 units), sesquiterpenes (three C_5 units), diterpenes (four C_5 units), sesterterpenes (five C_5 units), triterpenes (six C_5 units), tetraterpenes (eight C_5 units), etc. In general, these are cyclic unsaturated hydrocarbons where oxygen molecules in the constituent groups are attached to the isoprene units. From the nutritional standpoint, the major subclasses are monoterpenes (e.g., limonene, menthol, perillyl alcohol), diterpenes (e.g., retinoids) and tetraterpenes (which include carotenoids such as β-carotene, lutein, lycopene and zeaxanthine).[65] Monoterpenes are present only in plants and usually they are volatile substances. Both limonene and perillyl alcohol (a hydroxylated analog of limonene) have anti-cancer effects and can cause induction of phase II enzymes such as glutathione-*S*-transferase.[66] Among diterpenes, vitamin A or retinol is the most important compound which is found in animals. The term retinoids refers to all analogs of retinol. Plant-derived carotenoids such as β-carotene, α-carotene, lutein, zeaxanthine and lycopene are thought to provide health benefits in decreasing the risk of certain diseases including cancers. β-carotene is a limited precursor of vitamin A. In part, the beneficial effects of carotenoids are due to their antioxidant properties.[67] An inverse relationship was recorded between the intake of lycopene from tomatoes and the risk of cancers of the prostate, lung and stomach.[68]

Table 2: Some common sources of flavonoids

Flavonoids	Major food sources
Apigenin (flavone)	Celery, parsley, thyme, sweet red pepper
Quercetin, kaempferol, myricetin (flavonol)	Onions, broccoli, kale, tomatoes, apples, plums, cherries, fennel, sorrel, cranberries, strawberries, grapes, tea
Hesperetin (flavanone)	Oranges, lemons, prunes
EGCG (flavanol or catechin)	Apples, plums, cocoa, green tea, black tea
Cyanidnin (anthocyanin)	Cherries, black grapes
Genistein, daidzein (isoflavone)	Soya beans, chickpeas, legumes, rye

Controversies exist on the question of supplementation with β-carotene. Both randomized chemoprevention trials in Finland and USA showed adverse effects of β-carotene.[69-71] In Finland study on male smokers, a higher incidence of lung cancer and 8% higher mortality were observed among the participants who received β-carotene.[69] The US study on heavy smokers and asbestos-exposed workers was stopped ahead of schedule time; because participants who received β-carotene and retinol were found to have a 28% increase in incidence of lung cancer, a 17% increase in incidence of death and a higher rate of cardiovascular disease mortality.[70,71] On the contrary, a reduction in the risk of death among head and neck cancer patients assigned to receive β-carotene was observed.[72] However, two other randomized trials of β-carotene supplementation did not find any effect.[73,74] On the other hand, Baron et al. noticed that β-carotene was associated with a marked decrease in the risk of recurrence of colorectal adenomas among subjects who neither smoked cigarettes nor drank alcohol.[75] Interestingly, they observed that β-carotene supplementation conferred an increase in the risk of recurrence among those who had the habit of cigarette smoking or taking alcohol or both. It is not clear, how the effects of β-carotene alter

in presence of predisposing factors like smoking or in high-risk individuals! In one of the most recent studies, Liu et al. observed that cigarette smoke exposure and/or pharmacological doses of β-carotene in ferrets increased the levels of cytochrome P450 enzymes, particularly CYP1A1 and CYP1A2, resulting in enhanced retinoic acid catabolism in the lung tissue.[76] On the other hand, Bendich has suggested several biologically plausible explanations such as an increase in lung function due to β-carotene supplementation leading to a greater exposure to tobacco carcinogens and other oxidative compounds, and alteration in immune responses.[77] This complexity underscores the need of more studies to identify pathways signaling chemopreventive effects.[78,79]

Fruits

A high fruit intake has also been considered to decrease the risk of most of the cancers.[36,80] There are evidences that different berries such as black raspberries, blackberries and strawberries inhibit carcinogen-induced malignancy in animal models. Some of the known chemopreventive agents in berries include vitamin C, E and folic acid; small amount of calcium and selenium; β- and α-carotene; polyphenols such as ellagic acid, ferulic acid, *p*-coumaric acid, quercetin, several anthocyanins and phytosterols (triterpenes) such as β-sitosterol and stigmasterol. It has been observed that berries could inhibit the growth of premalignant cells through down-regulation of COX-2 and also expression of other genes associated with tumor development such as iNOS and VEGF. Moreover, berries might have the ability to inhibit tumor development by impairing signal transduction pathways mediated through the activation of AP-1 and NF-κB.[81] Amongst various chemopreventive ingredients in berries, ellagic acid (a polyphenol and an abundant component) appears to accumulate selectively in the epithelial cells of the aerodigestive tract and has been demonstrated to be preventive for esophageal cancer in animal models both at the initiation and promotion stages.[82]

Resveratrol is a phytoalexin (i.e., inhibitor of phytopathogenic organisms) and is present in grapes, berries, peanuts and several other plants. It is one of the best known natural food microcomponents with potent chemopreventive properties towards several important human diseases such as cardiovascular disorders, cancer and neurodegenerative pathologies.[83] Reveratrol has various pharmacological properties which include inhibition of arachidonate metabolism in leukocytes and platelets, modulation of lipid metabolism, inhibition of platelet aggregation and lipid peroxidation, suppression of expression and activity of COX-2, induction of cell-cycle arrest at the S/G2 phase transition and pro-apoptotic cell death in many types of cancer cells. All these biological effects help to explain the vasorelaxing, anti-cancer and anti-inflammatory activity of resveratrol.[84] Perillyl alcohol, a monoterpene and an analog of *d*-limonene found in citrus peel, is another important chemopreventive agent. It has been observed that perillyl alcohol inhibited AP-1 activation and Ras farnesylation.[85] Similarly, Ding et al. noticed that apple peel extract inhibited AP-1 transactivation and strongly scavenged hydroxyl and superoxide radicals.[86] Further, the fruit juice of noni (*Morinda citrifolia*), a plant originally grown in the Hawaiian and Tahitian islands, was found to be effective in suppressing 12-*O*-tetradecanoylphorbol-13-acetate (TPA)- and EGF-induced cell transformation and associated AP-1 activity.[87] Also, it has been found that garcinol, a polyisoprenylated benzophenone derivative of *Garcinia indica* fruit rind, inhibited the expression of iNOS and COX-2.[88] Thus, different chemopreventive agents of various fruits have antioxidant and anti-inflammatory properties, and may exert inhibitory action on tumor promoter–induced carcinogenesis and associated cell signaling.

Other Nutrients or Dietary Compounds

Tea

There are mainly two popular types of tea: green and black tea, which are used worldwide as a common beverage. Although, it has been suggested that consumption of tea may have a protective effect against the development of several cancers, but the epidemiological findings are inconsistent,[89,90] like many other food constituents. Nevertheless, some recent studies have recorded beneficial effects of green tea against cancer. In Japan Public Health Center (JPHC)-based prospective study, an inverse association between green tea consumption and risk of gastric cancer was observed among women.[91] Zhang et al. observed a trend of better survival among ovarian cancer patients who were tea drinkers than non-drinker patients.[92] They concluded that increasing the consumption of green tea after diagnosis might be helpful in the prognosis of ovarian cancer.

Tea contains large quantities of polyphenolic compounds known as catechins. The leading catechins in green tea are epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and EGCG. Green tea contains catechins up to 40% of its dry weight; whereas black tea contains up to 10% catechins, about

5% theaflavins and more than 20% thearubigins.[93] Several studies based on cell culture and animal models have demonstrated the cancer preventive role of tea. Numerous mechanisms have been proposed for the cancer preventive activity of tea constituents. Both EGCG and theaflavins have been shown to inhibit the growth, induce cell cycle arrest, and apoptosis in different cancer cell lines.[94] Studies have also demonstrated that tea polyphenols can inhibit activator protein 1 (AP1) which is a multifaceted transcription factor that affects a wide range of biological responses.[95] Moreover, Masuda et al. observed that EGCG suppressed the activation of EGFR and HER-2, and thereby inhibited related downstream signaling pathways.[96] This phenomenon was associated with the inhibition of signal transducer and activator of transcription 3 (Stat3) activation, inhibition of c-fos and cyclin D1 promoter activity, decreased cellular levels of cyclin D1 and Bcl-XL proteins, inhibition of cellular production of vascular endothelial growth factor (VEGF) and inhibition of constitutive NF-κB activation.[97]

Spices

Curcumin (diferuloylmethane) is a yellow colored pigment isolated from the rhizome of the plant *Curcuma longa*, commonly called turmeric; it has been widely used in different Asian countries without any recorded toxic effects. Extensive research over the last 50 years has indicated that this yellow colored polyphenol could prevent cancer and might contribute to the lower rate of some types of cancer in these countries.[98] Curcumin possesses anti-inflammatory and antioxidant properties.[16] Also, curcumin could induce apoptosis by targeting mitochondria, affecting p53-related signaling and blocking NF-κB activation.[99] In addition, it has been thought to inhibit lipooxygenase activity, COX-2 expression, initiation of carcinogenesis by suppressing cytochrome P-450 enzyme activity and increasing the levels of glutathione-*S*-transferase.[100] Moreover, a number of targets of curcumin have been identified such as aryl hydrocarbon receptor, matrix metalloproteinases, tyrosine kinases, etc.[99] Like curcumin, the oleoresin from rhizomes of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) contains [6]-gingerol, a pungent ingredient that has been found to exert various pharmacological effects such as anti-inflammatory, analgesic, antipyretic and antioxidant activity.[101,102] Gingerol is converted into shogaol during dehydration (shogaol is thus present in dried or powdered form). Ginger also contains gingerdiol, zingerone and [6]-paradol. The bioactive ingredients of different spices such as curcumin, gingerol, paradol, capsaicin etc. are the members of vanilloid compounds (which contain the vanillyl moiety, i.e., 4-hydroxy-3-methoxybenzyl). The chemopreventive effects exerted by these phytochemicals are often associated with their antioxidative and anti-inflammatory activities.[103] Interestingly, data in the literature suggest that capsaicin (the major pungent principle of hot chili pepper) has dual effects on carcinogenesis. Capsaicin might increase the risk for gastric cancer.[104] However, many other factors such as excessive salt intake, diet and Helicobacter pylori infection play an important role in the development of gastric cancer.[2,105] On the contrary, capsaicin apparently protects against experimentally induced mutagenesis and tumorigenesis in various model systems.[106]

Conclusions

In recent years, cancer prevention by botanicals has received considerable attention. Different phenolic substances present in various types of vegetables, fruits and plants possess antioxidant and anti-inflammatory properties, which can function in our physiological system in order to act as cancer chemopreventive agents. It is thought that oxidative damage to the cell has an important etiological role in cancer. In our physiological system, spontaneous generation of free radicals such as superoxide, hydrogen peroxide and hydroxide radicals occurs every day. These hazardous events are effectively counteracted by different mechanisms like antioxidants, DNA repair, apoptosis and immunological surveillance. Dietary ingredients may modulate these tools of the body's defence. However, all natural dietary substances act in a complex and diverse manner. Unlike deficiency of vitamins and other micronutrients, still no clear clinical disorder has been detected due to deficiencies of various dietary ingredients that are supposed to prevent the process of cancer development. Also, the results of many epidemiological studies could not prove a beneficial role of high vegetable and fruit consumption with reference to cancer. Moreover, some glucosinolates may have goitrogenic effects. Despite this complexity, different studies have suggested an advantage from the use of some selective phytochemicals in the chemoprevention of cancer. Murakami et al. advocated an intake of various phytochemicals in combination as individual food phytochemicals have complex interactions that can be antagonistic, additive or synergistic depending upon many factors including concentrations and interactions or co-existence with other compounds.[107] However, more well-designed studies are needed to expand our current understanding on bioavailability, pharmacological action and adverse effects of different phytochemicals.

Further, appropriate human interventional studies may be helpful to evaluate these dietary factors as proper chemopreventive agents for human cancer.

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