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Dietary Cancer Chemoprevention: An Overview

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ABSTRACT Cancer is a major cause of mortality and morbidity worldwide. The majority of cancers are reported to be caused by environmental carcinogenic agents, occupational environment and dietary habits. Dietary habits are one of the major contributory factors for the genesis of cancer. The optimal way of dealing with any disease is by prevention, this is particularly relevant for cancer. Despite decade of basis and clinical research and trial of promising new therapy, overall cancer survival has only improved marginally. Molecular targeted agents are currently being studied in all treatment settings including chemoprevention, which is defined as the use of natural or synthetic agents to interrupt the process of carcinogenesis and to prevent or delay tumor growth. Epidemiological and experimental studies have indicated that dietary fat has an influence on carcinogenesis process. However, it has been observed that individuals who consume relatively large amounts of vegetables and fruits are at decrease risk of cancer of many organs. Several epidemiological studies suggest that consumption of cruciferous vegetables may be particularly effective in reducing cancer risk. Glucosinolates in crucifers are converted to isothiocyanates by plant myrosinase and gastrointestinal microflora, these are potent inducer of phase II proteins and is effective to block chemical carcinogenesis in animal models. Some dietary constituents are reported to act as naturally occurring cancer prevention agents and may explain some of the differences in cancer incidence seen in populations with varying dietary intake. Long term supplementation of the diet with folate, seems to lower the risk of colorectal cancer. Curcumin in the spice turmeric, genistein in soya, and catechins in tea have tumor-suppressing properties in rodent models of carcinogenesis. Although the results of clinical interventions trials of β-carotene to prevent lung cancer, and of dietary augmentation with fiber or fruits and vegetables to reduce the occurrence of colonic polyps have so far been negative, a structured path for the development of diet-derived constituents as cancer chemoprevention is emerging. By applying chemoprevention approaches from the use of single nutrients to multiple dietary constituents and functional foods, the scope of future cancer prevention strategies will be broadened. A new paradigm for diet, nutrient and cancer prevention can be developed using a multidisciplinary approach that includes lifestyle and environmental changes, dietary modification and physical activities consciousness to reduce the burden of cancer.

INTRODUCTION

Cancer is still a major cause of mortality and morbidity in developing as well as in developed countries. Overall survival rate has only improved slightly despite advances in surgery, radiotherapy, and chemotherapy. Molecular targeted agents are currently being studied in all treatment settings including that of chemoprevention, which is defined as the use of natural or synthetic non-essential dietary agents to interrupt the process of carcinogenesis and to prevent or delay tumor growth (Greenwald et al. 2002; Soria et al. 2003). Researches on the mechanisms of carcinogenesis have yielded a tremendous knowledge on cancer. Cancer cells are the result of single or multiple genetic defects resulting from exposure to environmental carcinogenic agents, occupational environment, dietary habit (Sugimura 1992) and infectious agents (Go et al. 2001). Dietary habits, in particular, are reported as the main determinant for the genesis of cancer (Shukla and Arora 2003). A considerable emphasis is being placed on the use of dietary constituents to prevent mutagenesis and carcinogenesis due to their relatively non-toxic effects (Shukla et al. 2003). Many of these substances including vitamins, soyabeans, curcumin, diallyl sulfide and indole-3-carbinol have been reported to effectively suppress carcinogen-induced neoplasia (Flora 1998; Singh and Shukla 1998a, b).

Our knowledge of transformation of a normal cell to cancer cell has greatly expanded over the past decade. The simplistic, stepwise concept of initiation, promotion and progression has matured

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to a better understanding of the serial genotypic changes that ultimately lead to cancer (Bishop 1991). Chemoprevention inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of pre-malignant cells in which such damage has already occurred (Hong and Sporn 1997). Many of the chemopreventive agents are antioxidants and might suppress carcinogenesis through: i.) inhibiting phase I enzyme; ii.) induction of phase II enzyme; iii.) scavenging DNA reactive agents; iv.) suppression of type-2 cell proliferation induced by carcinogens; and/or v.) inhibition of certain properties of neoplastic cells (Tanaka et al. 2001). Human diet contains a variety of compounds that exhibits chemo-prevention effect towards an array of xenobiotics (Shukla et al. 2003). Epidemiology studies have suggested that some dietary constituents may be acting as naturally occurring cancer prevention agents and may explain some of the differences in cancer incidence seen in populations with varying dietary intake (Willett and MacMohan 1984 a, b).

Cancer chemoprevention is a desirable and important facet of biomedical research which in addition to provide a practical approach to identify potential useful inhibitors of cancer development, also offers an opportunity to study the mechanism of carcinogenesis (Wattenberg 1992). During the recent past a number of compounds, especially constituents of our diet, have been tested for their anti-carcinogenic potential. Many chemotherapeutic agents are products of bacterial or fungal metabolism (Aszalos and Berdy 1981; Antony et al. 2002). Higher plants, however, contains an extensive variety of compounds which are strong modifiers of chemical carcinogenesis (Shukla et al. 1999). Around 2000 natural and synthetic agents have been shown in experimental system to have chemopreventive activity. Agents that have been studied in clinical trials include retinoids, N-acetyl-cysteine, β-carotene, calcium, α-tocopherol, selinum, tamoxifen, finasteride, and NSAIDs (Soria et al. 2003).

Multistep Carcinogenesis

In multi-step carcinogenesis concept, cancer develops in a series of distinctive stages, with accumulation of molecular changes progressing through pre-invasive histological changes to invasive disease. The earliest events of this process are mutation, deletion, or polysomy at the genomic level (Mao et al. 1998). These mutations are either present in the cells (hereditary cancer) or, often, induced by an environmental factor (e.g., chemical carcinogens, ionizing radiation). Food may provide carcinogenic contaminants (xenobiotocs) or be a mutagen itself after some nutrient is transformed (e.g., heterocyclic aromatic amines in the meat overcooked at high temperatures). Genetic polymorphism renders some subjects more or less susceptible than others to environmental carcinogens. Oxidative stress is one of the main way by which DNA is damaged from either an exogenous or an endogenous source (inflammation etc.). Antioxidant micronutrients are reported to oppose this effect. Thus, food interacts in different ways with the initiation phase, and the protective effect of food is likely to be more important than food's contribution as a mutagen. The promotion step is the clonal proliferation of mutated cells that occurs as the result of genetic alteration and epigenetic modulations and thus achieve tumor growth. Reactive oxygen species (ROS) are necessary to intracell signaling for the synthesis of growth factor, and antioxidants which may interfere in this pathway. Not much is known about the effect of food at the invasion step. Food can interfere with the genetic and epigenetic alterations in this phase; for example, some experimental work suggests that dietary phenolic compounds can modify angiogenesis (Gerber 2001).

CHEMOPREVENTION STRATEGIES

Chemoprevention approaches target the carcinogenic process at early and potentially reversible stage, focusing on inhibition of one or many elements in the stepwise progression towards cancer. Chemoprevention can be organized into three strategies: *primary prevention*, preventing cancer in healthy individuals who are at high risk, for example, smokers; *secondary prevention*, preventing development of cancer in individuals with precancerous lesions like intraepithelial neoplasia, leukoplakia, dysplasia; and *tertiary prevention* to target patients who have had previous cancers and to prevent development of secondary primary tumor or recurrence (Soria et al. 2003).

Categories of Chemoprevention Agents

The optimal way of dealing with any disease is by prevention. This is particularly true for cancer, with all its complexities. A great strength of chemoprevention has been that a large number of compounds can prevent the occurrence of cancer and that a variety of mechanisms for producing such protective effects exist. Chemoprevention by natural products has been obtained in several hundred animal studies. Chemopreventive agents can be placed into three broad categories (Wattenberg 1997). The first category is "blocking agents". These compounds prevent carcinogenic agents from reaching or reacting with critical target site, thus act by exerting a barrier function. The second category of compounds which decreases the vulnerability of target tissue to carcinogenic stimuli. The third category is "suppressing agents". These compounds prevents the evolution of neoplastic process in tissue that otherwise would become malignant.

Blocking Agent

There are three major mechanisms by which blocking agents act. Some blocking agents prevent activation of carcinogens or tumor promoters requiring metabolic activation. A second group of blocking agents is effective by virtue of their capacity to enhance detoxification systems. Blocking agent that enhances the activity of system detoxifying carcinogenic chemicals is of special interest. Phase II enzyme, which are involved in conjugation and extraction reaction are particularly important in terms of their proactive capacities. Probably the single most critical system in this regard is glutathione-S-transferase (Wattenberg 1993). Many Phase II-inducing compound occur as non-nutrients in vegetable and fruits and may be responsible for some of the protective effect that are obtained as a result of consuming diets containing relatively large quantities of these type of food (Wattenberg 1992). A third group of blocking agents trap reactive carcinogenic species before they reach critical target sites (Wattenberg 1997). Endogenous thiols, particularly glutathione, are important in this regard. *N*-acetylcysteine is chemopreventive agent that has favorable attributes which potentially make it applicable for human use. The compound has efficacy as a trapping agent *in vivo* and has very low toxicity (DeFlora et al. 1992). The trapping of oxygen radicals has received a great deal of attention (Manson et al. 2000). These radicals are capable of attacking DNA. This is a very complex area because many antioxidants are multifunctional and have been used at high concentration in *in vivo* studies. The production of oxygen radicals is part of a complex process in which several events occur simultaneously, making it difficult to evaluate mechanism of inhibition by antioxidants particularly when it is used in high concentration (Wattenberg 1997).

Chemopreventive Agents Decreasing Tissue Vulnerability to Carcinogenesis

This group of chemicals makes tissue less vulnerable to carcinogenesis. The increased resistance can be brought about in at least three ways. One is by virtue of the compounds producing cellular maturation. A second is to decrease function or activity of target cells. A third is to decrease cell proliferation. The most extensively studied tissue for demonstrating protective effects of cellular maturation is the female breast. Decreasing the vulnerability of the breast to neoplasia has been studied in details in the rat (Russo and Russo 1994). The terminal end-buds of the mammary glands are vulnerable to carcinogenic stimuli. They can be matured by pregnancy or hormonal stimulation. The matured glands show a marked reduction in tumor formation resulting from administration of carcinogens (Grubbs et al. 1988). Epidemiological studies have shown that an early age of first pregnancy results in a lesser risk of breast cancer. It can be decreased by 50% or more when the first pregnancy occurs in very young women (Wattenberg 1997). A second way of increasing resistance of a tissue to carcinogenesis is to decrease tissue function. Castration results in prevention of cancer of sex hormone-dependent tissue. Data indicated that there is an approximately 50% decrease in ovarian cancer in women who use steroid contraceptive that contain estrogen. The third mechanism for potentially increasing resistance of a tissue to carcinogenesis is to decrease cell proliferation in the target tissue. Reduced cell proliferation can be brought about by dietary manipulation. When rat were fed with Western diet containing high fat, low calcium, marginal low phosphorous, and

low vitamin D showed high mitotic activity in the glands of the large bowel compared to animals fed with optimal diet (Newmark et al. 1990; Khan et al. 1994). Mitotic activity can be reduced by changing the dietary composition.

Suppressing Agents

Suppressing agents prevent the evolution of the neoplastic process in cell that otherwise would become malignant. A variety of compounds viz. vitamin A and retinoids, vitamin D, hormone antagonists, difluromethylornithine, polyphenolics, protease inhibitors, selenium, glucocorticoids, inositol and phytate, etc. have shown to act as suppressing agents. Whereas the conceptualization of mechanisms of action of blocking agents is clear, although many of the details are complicated, the mechanisms of action of suppressing agents are frequently poorly defined (Wattenberg 1997).

There is a fourth group of compounds, which does not fit into any of the above categories. This includes a large number of compounds that have as a common feature, the capacity to inhibit component of the arachidonic acid cascade (Yamamoto and Kato 1992). Some are medicinals, in particular nonsteroidal anti-inflammatory compounds. Numerous experiments in animals have been carried out in which the suppressing effects of nonsteroidal anti-inflammatory compounds such as piroxicam, sulindac, indomethacin, and aspirin was found to inhibit neoplasia when administered late in the premalignant stages of the carcinogenic process. Sulindac can produce regression of adenomatous polyps of the large bowel in human subjects with multiple polyposis (LaBayle et al. 1991).

Role of Phase II Enzyme in Chemoprevention

Two types of DNA-damaging agents can evoke neoplastic transformations, i.e., electrophiles, largely of exogenous origin, and reactive oxygen species. Most electrophiles require metabolic activation, usually by phase II enzyme (cytochrome P-450); they convert generally innocuous procarcinogens to highly reactive electrophilic ultimately carcinogens that can damage susceptible centers of DNA bases and initiate carcinogenesis. DNA and other macromolecules are principally protected against damage by electrophiles and reactive oxygen species by a family of phase II enzymes. By a variety of mechanisms including conjugation with endogenous ligands (e.g., glutathione, glucuronic acid), a phase II enzyme inactivates carcinogenic agents and promotes their excretion. In addition, glutathione, the principal and most abundant small-molecule cellular antioxidant, which is also regulated by phase II enzyme, plays a major role in protection against electrophiles and ROS. Thus, whether malignancy will ensure when a cell is exposed to a potential carcinogen is determined largely by the balance of activities of phase I enzymes which activate carcinogens and phase II enzymes that detoxify reactive carcinogens (ultimate carcinogens). It is therefore of considerable importance that both families of enzymes are highly inducible in many tissues and chemical agents belonging to nine chemical classes (Talalay and Fahey 2001), among which dietary phytochemicals are essentially important. Furthermore, although some inducer elevate both phase I and phase II drug metabolizing enzymes (bifunctional inducers), other selectively induce only phase II enzyme (monofunctional inducers) (Prochaska and Talalay 1988). Among the most persuasive considerations is that compounds isolated from natural sources solely on the basis of their inducer activity have subsequently been shown to protect rodents against carcinogenesis (e.g., sulforaphane, terpenes from green coffee beans, resveratrol) and other compounds were predicted to have chemopreventive activity based on their phase II enzyme inducer properties (e.g., oltipraz and other 1, 2-dithiole-thiones, and a series of synthetic analogs of sulforaphane). Sulforaphane is an extremely potent inducer of phase II enzymes, perhaps the most potent naturally occurring inducer described so far (Talalay and Fahey 2001).

Additional and more complete evidence for the importance of phase II enzyme in regulating susceptibility to carcinogens and mediating chemoprevention has now been obtained by specific gene deletion. Many mono-functional inducers (Prochaska and Santamaria 1988), which selectively elevate phase II enzyme without inducing phase I enzymes, appears to do so by activating antioxidant response element (ARE) located in the 5'- upstream region of many of these enzymes (Hayes et al. 1999). Itoh et al. (1999) described an important mechanism of regulation of the ARE element by inducers that involves participation of *Nrf2*, a member of the

leucine zipper family of transcription factors. The binding of *Nrf2* to ARE signals the transcription of genes coding for phase II enzyme. Recent experiments showed that mice in which the *nrf2* gene was deleted had lower levels of glutathione transferases, quinine reductase and other phase II enzymes as well as depressed glutathione-synthesizing enzymes in a number of tissues (Itoh et al. 1999; Kwak et al. 2001). As expected, these enzymes were essentially not inducible by a variety of phase II inducers. When *nrf2* gene knock-out mice received benzo[a]pyrene by gavage, they developed 50% more tumors than did their wild-type control (Ramos-Gomez et al. 2001).

Chemoprevention by Fruits, Vegetables and Herbs

An interesting finding that has been observed repeatedly is that individuals who consume relatively large amounts of vegetables, fruits, grains and herbs, are at decrease risk of cancer of many organs (Park and Pezzuto 2002). A report (Block et al. 1992) of 24 epidemiological investigations showed that consumption of relatively large amount of vegetables and fruits was associated with decreased incidence of lung cancer. Multiple mechanism are undoubtedly involved in the protective effect of diets rich in fruits and vegetables (Steinmetz and Potter 1991a, b; Steinmetz and Potter 1996). However, it is difficult to identify the relative contribution of various components of a plant-based food to overall cancer risk reduction. The issue is further complicated by the recent demonstration of synergism among protectors (Brenner 2000; Torrance et al. 2000). Attention has recently been focused on intercellular-signaling as common molecular target for various chemopreventive phytochemicals (Surh 2003).

Several plant constituents, which include polyphenols appears to be potent antimutagens and antioxidants (Ren et al. 2003). Flavonoids and Procyanidins are two major classes of polyphenolic phytochemicals demonstrating a wide range of biochemical and pharmacological effects. The flavonoids such as apigenin and quercetin have been shown to inhibit melanoma growth and metastatic potential. When tested for the ability to inhibit lung colonization, these polyphenols decrease the number of B16-BL6 colonies in lung in a dose dependent manner (Caltagirone et al. 2000). The phenolic compounds of *Lonicera japonica* have an inhibitory effect on platelets activation and cytoprotective effect on hydrogen peroxide induced cell injury (Chang and Hsu 1992). Dragsted et al. (1997) have found that polyphenol in fruits, vegetables, herbs and spices inhibit tumor formation in experimental animals exposed to carcinogens. The role of dietary plant polyphenol has been emphasized in relation to health maintenance. The various polyphenols have been shown to posses antiatherogenic and anticarcinogenic properties, inhibiting oxidative destruction of various oxylabel biological structures, inhibitory effect on processes of bioactivation of carcinogens, blocking LDL oxidation and stimulate the activity of antioxidant and detoxification enzymes (Zloch 1996). Several reports indicate polyphenols to be the inhibitors of carcinogenesis and especially of lung and esophageal cancer (Yang et al. 1997; Stoner and Morse 1997). Grape seed polyphenols or procyanides are shown to have anti-carcinogenic and/or antitumour promoting agent. Zhao et al (1999) have shown anti-tumor promoting effect of a polyphenolic fraction isolated from grape seed employing the 7, 12-dimethylbenz(a)anthracene (DMBA) initiated and 12-*O*-tetradecanoyl phorbol 13-acetate (TPA) promoted SENCAR mouse skin two stage carcinogenesis protocol as model system. They act as potent antioxidants and/or modulate key biological pathways *in vivo* in mammals (Rice-Evans and Packer 1997). Administration of 1% grape seed extract in the diet inhibited APC mutation-associated intestinal adenoma formation in *Min* mice (Arii et al. 1998).

Tea (C*amellia sinensis*) is a popular natural beverage consumed worldwide. Green tea has been reported to inhibit tumor formation in various experimental and epidemiological studies (Katiyar and Mukhtar 1996). Tea contains a variety of polyphenolic ingredients including theaflavins, thearubigins, epigallocatechin gallate (EGCG), Epicatechin (EC), Epicatechin gallate (ECG) and Epigallocatechins (EGC) in addition to some amount of caffeine and proteins (Graham 1992). EGCG the major component of tea has been reported to scavenge free radicals generated by Benzo(a)pyrene (BaP), Dimethyl benzanthracene (DMBA) and nitrosoamines. Tea polyphenols are known to exhibit cytotoxicity towards various human tumor cell lines as well as growth inhibition that is accompanied by cell

cycle arrest (Roy et al. 2001). Studies conducted in our laboratory have shown that aqueous black tea extract reduced DMBA induced solid skin and transplantable tumor (Javed and Shukla 2000). In long term skin tumor bioassay black tea phenol was observed to exibit both antitumor initiating and antitumor promoting activity (Javed et al. 1998). Black tea extract (BTE) was also effective in inhibiting tobacco specific carcinogen Diethylnitrosoamine (DEN) induced pulmonary tumorigenesis (Shukla and Taneja 2002a). The frequency of pulmonary adenomas and adenocarcinomas were reduced in animals treated with different concentrations of BTE.

Garlic (*Allium sativum*) is a common spicy flavoring agent has been shown to posses many medicinal properties including anti-mutagenic andanti-neoplastic effects (Shukla and Taneja 2002 b; Arora and Shukla 2003). Fresh and grounded garlic has been shown to inhibit cancer, caused by polycyclic aromatic hydrocarbons and nitrosoamines (Siegers et al. 1999). The protective effect of garlic has been attributed to the presence of organosulfur compound like diallyl sulfide (DAS), diallyl disulfide (DADS), ajoene, allixine, allyl mercaptans and allyl methyl sulphides (Fanelli et al. 1998). DAS is reported to reduce DMBA and aflatoxin-induced skin and hepatic tumors (Soni et al 1997). It is also known to suppress BaP and *N*-nitrosomethyl-benzylamine induced oesophageal tumors in rodents (Wargovich et al. 1992). Moreover, allium vegetables are known to inhibit mutagenic potential of various compounds in *Salmonella typhimurium* and *Escherichia coli* assay (Shukla and Taneja 2002a).

Curcumin (diferuloyl methane), the major pigment from the rhizome of *Curcuma longa* L., has been widely studied for its antimutagenic and tumor-inhibiting properties (Kuttan et al. 1985; Shukla et al. 2002; Ray et al 2003; Shukla and Arora 2003). Curcumin has shown to modify cell receptor binding and to effect intracellular signaling reactions. Curcumin has been shown to inhibit TPA-induced proliferation of epidermal cells (Kakar and Roy 1994), EGF-induced growth (Huang et al 1991) and EGF-stimulated activation of EGF-R tyrosine phosphorylation in a dose-dependent manner (Korutla et al. 1995). Curcumin – treated B16F10 melanoma cells formed eight-fold fewer lung metastases in C57BL6 mice (Sengupta et al 2000). Curcumin-treated cells showed a marked reduction in the expression of $\alpha_5\beta_1$ and $\alpha_v\beta_3$ integrin receptors. In addition, curcumin treatment inhibited pp125 focal adhesion kinase (FAK), tyrosine phosphorylation of a 120 kD protein, and collagenase activity (Ray et al 2003). In a recent study curcumin was found to enhance tumor necrosis factor related apoptosis-inducing ligand-induced apoptosis in LNCaP prostate cancer cells (Deeb et al. 2003). The inhibitory effect of curcumin on development of diethylnitrosamine induced altered hepatic foci has been reported by our group in medium term carcinogenicity bioassay (Shukla and Arora 2003).

The consumption of cruciferous vegetables such as cabbage, broccoli and Brussels sprouts has been shown to have cancer chemoprevention effects in human and experimental animals (Srivastava and Shukla 1998; Kim et al. 2003). A striking and characteristic chemical property of cruciferous plants is their high content of glucosinolates, which often approaches 1% or more of their dry weight. Glucosinolates and their isothiocyanates hydrolysis products are well-known protectors against carcinogenesis (Talalay and Fahey 2001). Indole-3-carbinol found in these cruciferous vegetables has shown to have cancer chemopreventive influence in liver, skin, colon, and mammary tissue when given before or concurrent with exposure to a carcinogen (Srivastava and Shukla 1998; Kim et al. 2003). The topical application of indole-3-carbinol resulted in a significant protection in DMBA initiated and TPA promoted mouse skin carcinogenesis (Srivastava and Shukla 1998). Lycopene, a natural antioxidant found predominantly in tomato, is also reported as a cancer preventive agent. Serum and dietary lycopene levels have been found to be inversely related to the incidence of cancer. Although the antioxidant properties of lycopene are thought to be primarily responsible for its apparent beneficial affects, other mechanisms may also be involved (Hwang and Bowen 2002).

Diet and Chemoprevention

Along with tobacco use, diet has great impact on the development of cancer. The effect of diet does not occur through the addition of a single nutrient; rather each food combines many nutrients that allow for a synergistic action when present in a certain balance. Moreover, several

foods constitute a meal and may reinforce a protective effect or be antagonistic. A large body of evidence related high caloric intake to the risk of colon cancer is based on epidemiological and laboratory animal studies (Gatof and Ahnen 2002; Reddy 1994). An association between high dietary intake of cooked meat and increased risk of cancer of the colon and breast was demonstrated in several but not all studies suggesting that heterocyclic aromatic amine may play a major role in the etiology of these diseases (Edenharder et al. 2002). Diet with especially high fat content but low in certain fibers, are generally associated with an increased risk of developing colon cancer (Kune 1996). Several epidemiological studies suggest that mortality from colon cancer is somewhat lower in areas where olive oil is the predominant type of fat consumed, and also in areas where fish or other marine animals is highly common (Caygill et al. 1996; Reddy 1995). The high levels of monounsaturated fatty acid, namely oleic acid in olive oil and highly polyunsaturated N-3 fatty acids, such as elcosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in marine oils, appears to have rather unique effects. There is a considerable interest in the relationship between total caloric intake and colon cancer risk. Several case-controlled studies have shown that high caloric intake is a risk factor (Kune 1996). From animal model studies it is conceivable that increase in colon tumor promotion due to high fat intake may be based on the alteration of membrane phospholipids turnover and prostaglandin synthesis (Rao et al 1996). Slattery et al. (1998) introduced principle component analysis in a case-controlled study of food-related colon cancer risk. With this type of analysis, they identified several dietary patterns, among them the Western diet (high intake of processed and red meats, fast food, refined grain, added sugar, high fat dairy food and low intake of yogurt), a prudent diet (high intake of fish, fresh fruits, legumes, cruciferous, carrot, tomatoes and other vegetables) and a "drinker" diet (high intake of fish, liquor and wine). The Western diet is shown to increase colon cancer risk whereas the prudent diet appears to be protective.

Laboratory animal studies and international correlations of fat intake by humans and their breast cancer mortality provide strong evidence for a tumor promoting effect of dietary fat in postmenopausal breast cancer (Wynder et al. 1986; Cohen 1986). In contrast, the result of large-scale cohort studies has consistently failed to demonstrate a low risk of breast cancer in women who eat a low-fat diet (Hunter et al. 1996). Van'T Veer et al. (1991) worked out two hypothesis; first, based on the effect of foods, was concerned with providing or avoiding oxidative stress at the initiation phase, namely, a high intake of antioxidants and a low intake of lipoperoxidable substrate, polyunsaturated fatty acid (Shatzkin et al. 2000). The second hypothesis was based on the metabolism of estrogens with a high intake of fat capable to increase adipose store and on the action of fiber and fermented milk in facilitating the excretion of conjugated estrogens. It was shown that combining a low intake of fat and high intake of fermented milk and fiber decreased breast cancer risk (Gerber 2001).

Macrobiotics is one of the most popular alternative or complementary comprehensive dietary and lifestyle approach to cancer (Kushi et al. 2001). The centerpiece of macrobiotics is a predominantly vegetarian, whole-food diet that has gained popularity because of remarkable case reports of individual who attributes recoveries from cancer with poor prognosis to macrobiotics. Bean and bean products, particularly soyfoods are a major component of macrobiotics. Some evidence shows that soy intake is associated with decreased risk of hormone-dependent cancer such as those of the breast (Shu et al. 2001), endometrium (Goodman et al. 1997) and prostate cancer (Kolonel et al. 2000). Soyfoods and other legumes may decrease risk of cancer because of the presence of various compounds that may have anticancer effect, including protease inhibitors and saponins (Steinmetz and Potter 1991b). There has been a particular interest in the role of phytoestrogens such as genistein and daidzein, which are found in high concentration in soybeans. These isoflavonoid compounds may not only influence estrogen metabolism but may also have antioxidant and antiangiogenesis effect and may influence signal transduction and inhibit the action of DNA topoisomerases (Messina et al. 1994).

Dietary Habits and Cancer Chemoprevention

Tobacco and alcohol drinks are established major risk factors for oral cancer. Women who smoke are at significantly higher risk than men who smoke. There is evidence that deficiencies in vitamins, especially in antioxidant vitamins,

and trace minerals are also involved in the etiology of oral cancer. Laboratory studies with animals have corroborated that supplementing feed with retinoids and vitamin C and E exerts chemopreventive effects on chemically induced oral carcinogenesis. Clinical trials in humans with such supplements are aimed in preventing second primary cancers (El-Bayoumy et al. 1997). Results to date demonstrated an effectiveness of *13-cis* retinoic acid, in reversing or preventing oral leukoplakia (Garewal et al. 1993). Recently, dietary black raspberries was found to have chemopreventive activity of the oral cavity in animal model (Costo et al. 2002).

Chemoprevention Clinical Trials

Of over 200 case-control and cohort studies, nearly 80% have reported significant inverse relationship between consumption of plant food and the risk of developing most types of cancer (Talalay and Fahey 2001). Although conclusion with respect to the overall extent to which diet contributes to cancer incidence, or to be more explicit, the degree to which dietary modification might be expected to reduce cancer risk, vary considerably, a reasonable estimate is about 30-40 % (World Cancer Research Fund 1997). Recent, several large prospective cohort studies have failed to demonstrate the presumed protective effect of fruits, vegetables and dietary fiber consumption on cancer risk (Terry et al. 2001; Flood et al. 2002). On the other hand it is known from studies of migrants that migrants tend to adopt the cancer pattern of their host country within 10 to 20 years for colorectal cancers and within few generations for cancer of the breast, stomach and prostate (Adami et al. 2001).

Initial optimism regarding cancer chemoprevention by dietary constituents has been dampened by the outcome of recent large trials that failed to detect any benefits (Gescher et al. 2001). Two of these trials explored the potential of β-carotene to decrease incidence of lung cancer in about 50, 000 individuals (Omenn 1998). The outcome of these trials suggested that in high-risk groups of smokers, and workers occupationally exposed to asbestos, the intervention increased, rather than decreased, the risk of developing the disease. Subgroup analysis of these two trials showed that the risk of lung cancer was highest among individual who continued to smoke at least 20 cigarettes per day and among those in the highest quartile of alcohol consumption. A conceivable explanation is that β-carotene suppresses tumor only in individuals in whom the initiating stimulus has been removed, but not in those who are still exposed to it, although the underlying mechanism is unknown. A pooled analysis of the unweighted results of the α-Tocopherol, β-Carotene Lung Cancer Prevention Study (ATBC), the β-Carotene and Retinol Efficacy Trial on Lung Cancer (CARET) and the Physicians' Health Study (PHS) yielded a relative risk of 1.16 (95% CI=1.05 – 1.29) for lung cancer incidence and 1.07 with (95% CI=1.05-1.29) for all-cause mortality (Omenn et al. 1996). In the European study on Chemoprevention with Vitamin A and N-Acetylcysteine (EUROSCAN), over twenty five hundred patients with a history of non-small cell lung, oral or laryngeal tumors who receive either of the following: i.) retinyl palmitate, ii.) N-Acetylcysteine, iii.) both retinyl palmitate and N-acetylcysteine (vanZandwijk et al. 2000), showed no significant changes in the risk of tumor recurrence, second primary tumors, or survival benefits of treatment (Lamson and Brignall 2001).

Many epidemiological studies have shown an inverse relation between selenium concentration in serum and the incidence of human cancer (Clark and Alberts 1995). In the Linxian Cancer Prevention Trials, the treatment groups receiving selenium, β-carotene, and α-tocopherol had significantly lower incidence and lower mortality from stomach cancer than the placebo group (Li et al. 1993). Moreover, the outcome of a recent clinical intervention trial in the United States supports that selenium protects against cancer of the prostate, colon, and lung (Clark et al. 1996).

Epidemiological studies suggest a lower incidence of colorectal cancer among individuals with the highest intake of dietary folate (Lamprecht and Lipkin 2003), whereas people with diets low in folate, or with high alcohol intake, seem to have an increased risk of colorectal adenomas and carcinomas (Janne and Mayer 2000). In the Nurses' Health Study, supplementation with folate was protective against colorectal cancer, with the great risk reduction among women taking daily doses of more than 400 μg folate; this reduction reached statistical significance only after 15 years of use (Giovannucci et al. 1998). Furthermore, the protective role of folate supplementation may be greatest for individuals who are genetically predisposed to colorectal cancer (Chen et al. 1998).

Future Prospect of Chemoprevention

Research on carcinogenesis has yielded a tremendous knowledge based on cancer and the role of diet constituents on the tumorigenesis process. It is now widely accepted concept that cancer is mostly a preventable disease. Though considerable efforts have been made to prove the preventive effect of different kinds of fruits and vegetables but randomized chemo-prevention trials have failed to prove this presumed effectiveness of their single ingredients (Tadjalli-Mehr et al. 2003). The conclusive demonstration of a cancer-protective effect of a high consumption of fruits and vegetables is considered to be impractical. Despite disappoint-ment, research in clinical cancer chemoprevention has produced encouraging results. Dietary constituent have intriguing properties that strongly suggest the potential for beneficial effect. Epidemiological studies suggest positive correlation between consumption of tea and a lower incidence of gastric and esophageal cancer. There is no comparable evidence for curcumin consumption, although Asian countries in which turmeric is a major dietary component have low incidence rates for colorectal cancer (Gescher et al. 2001). Both tea catechins and curcumin are currently under clinical evaluation. Phytochemicals may be useful to develop "designer food" or "functional food" for cancer prevention (Nishion et al. 2000). A new paradigm for diet and cancer prevention, research and strategy must be developed to include the nutrition modulation of the carcinogenesis pathway by nutrients, micronutrients and phytochemicals. The pathway includes nutrition modulation of DNA damage and repair mechanism; DNA methylation pathway influencing gene expression and cellular phenotypes; antioxidants rearranging and oxidative stress modulation; target receptors and signaling pathway; cell cycle control and check point; and antiangiogenic properties (Go et al. 2001). This knowledge will allow us to set the framework for diet and cancer prevention research that includes biomarkers of the consumption of key dietary compounds, research on biological mechanism underlying putative diet and the cancer relationship, identification of molecular targets of action by dietary constituents and development of the new paradigm for diet and cancer prevention research.

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