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Lifestyle Related Causes of Cancer and Chemoprevention through Phytonutrients

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Abstract: Cancer is a leading cause of death worldwide. There are a lot of cancer causing agents which are divided as physical carcinogens, chemical carcinogens and biological carcinogens. But most of the carcinogens or causes of cancer are related to our lifestyle like diet, habit, occupation, radiation and some infection, etc. Chemoprevention is highly necessary to prevent cancer related preterm death. For this besides avoiding the causes of cancer we should concentrate ourselves on our diet. Because, numerous phytochemicals derived from edible plants have been reported to interfere with a specific stage of the carcinogenic process. Many mechanisms have been shown to account for the anticarcinogenic actions of dietary constituents and recently attention has been focused on intracellular-signalling cascades as common molecular targets for various chemopreventive phytochemicals. In this study, we tried to describe lifestyle related causes of cancer and the molecular basis of cancer prevention through the phytochemicals.

Key words: Phytonutrients, carcinogen, chemopreventive, cell cycle

INTRODUCTION

Cancer is a leading cause of mortality in human and a growing health problem all around the world. Cancer is a generic term for a large group of diseases that can affect any part of the body. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries and which can then invade adjoining parts of the body and spread to other organs. This process is referred to as metastasis. Metastases are the major cause of death from cancer. According to IARC (International Agency for Research on Cancer) it was estimated that about 10 million new cases were registered while about 6.3 million people died from cancer worldwide (IARC, 2001). It appears that by 2020, cancer will kill over 10 million people globally (Sanyal, 2003). Moreover, in 2003 it was estimated that approximately 1.3 million new cases of cancer diagnosed and more than 550,000 people died from cancer in United States alone (Surh, 1999). Cancer is just not only the health problem but global social and economical problem also.

As there are no particular treatment of cancer, effective preventive measures and cancer awareness among the general population is essential. To treat a disease first we have to know the causes of the disease. In this study, we tried our best to describe the causes of cancer related to our eating habit, lifestyle and environmental pollution. Doll and Peto (1981) reported that 10-70% of human cancer mortality is attributable to diet. Sugimura (2002) reported that cigarette smoking, chronic inflammation and infection and nutrition accounts to one third of the total cause of cancer. That means our lifestyle and dietary factors are playing a complex multifaceted role in the etiology of cancer.

To prevent cancer besides avoiding the causes of cancer we should concentrate ourselves on our diet. Because, cancer preventive effect of nutritional supplements and modified diets (consumption of fruits and vegetables) have been supported by so many clinical and laboratory Studies (Surh, 1999). Fruits and vegetables contains a lot of phytochemicals that posses substantial anticarcinogenic and antimutagenic properties. This study describe the molecular basis of cancer prevention through the phytochemicals.

CAUSES OF CANCER

Cancer has a lot of causes, but here our main intention is to describe the lifestyle related causes of

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cancer like diet, habit, occupation, radiation and some infection, etc.

Diet related carcinogenesis: In our daily food habit we included various cereals, dried fruits, coffee and so on. At the time of long time preservation and for wrong preservation techniques various fungi and molds are grown on the preserved cereals and fruits. These fungi and molds produce various toxins such as aflatoxins, fumonisins and ochratoxins on preserved food items. Among these mycotoxins aflatoxins are highly dangerous to human health. AflatoxinB1, the commonest of the aflatoxins is produced by *Aspergillus flavus* Bradburn *et al.* (1993). Through both laboratory and epidemiological data the liver carcinogenic properties of aflatoxins has been established (Groopmann and Kensler, 1999). In many studies, it has been shown that aflatoxinB1 exposure occurs through the consumption of mold contaminated groundnuts and grains (Wogan, 1992), which can be transmitted transplacentally (Denning *et al*., 1990) and to newborns via breast feeding (Wild *et al*., 1987). AflatoxinB1 causes guanine nucleotide substitution (Lilleberg *et al*., 1992) specifically to codon 249 of the p^{53} gene (Aguilar *et al*., 1993; Greenblatt *et al*., 1994). And mutation in the P^{53} gene is a risk factor for the development of cancer (Soussi, 2005).

Among the other mycotoxins ochratoxin A has dose dependent carcinogenic, genotoxic, immunotoxic or teratogenic properties (Neal and Judah, 2000). It is produced as secondary metabolite by species of *Aspergillus* and *Penicillium* (Van Der Merwe *et al*., 1965) and found as contaminant in human foods, including various cereals, coffee, cocoa, wines and dried fruits. This mycotoxin usually found in the crops grown in semiarid and temperate region but not in tropics (Bankole and Adebanjo, 2003). IARC has classified it in group 2b as possibly carcinogenic to human (IARC, 1993). Fumonisin is another carcinogenic mycotoxin produced by *Fusarium verticillioides*, a common fungal contaminant of maize (Marasas *et al*., 2004). The maize contaminated with fumonisins causes esophageal carcinoma in some parts of South Africa and China (IPCS, 2000) and it also increases the lipid peroxidation, production of ROS (reactive oxygen species), caspase-3 like protease activity (Stockmann-Juvala *et al*., 2004) that are marked as the risk factor of cancer.

Polycyclic Aromatic Hydrocarbons (PAH) have been established experimentally as carcinogens. The major carcinogenic compounds among these are benzo(a)pyrene, 1,2,5,6-dibenzanthracene, 3-methylcholanthrene, 7, 12-dimethylbenz(a)anthracene and benz(a)anthracene (IARC, 1983). Further studies to underscore PAH exposure from diet are the findings that intake of charcoal-broiled meat is more correlated to blood PAH-DNA adducts than smoking (Rothman *et al*., 1990). The target organs for PAH are the lung, breast, oropharynx, genitourinary and gastrointestinal tracts (Goldman and Shields, 2003). In several animal species, administration of benzo(a)pyrene by different routes has been shown to result in the production of tumors (Huggins and Yang, 1962). In rodents, diets with PAH have been reported to consistently induce cancer of the foregut and lung tumors (Singh *et al*., 1998). Evidence abounds in humans that dietary exposure to PAH may induce colon cancer (Giovasnnucci *et al*., 1994).

Organic N-nitroso compounds such as nitrosamines have been shown to present serious health hazard. More than 80% of the nitrosamines tested in laboratory animals have been shown to be carcinogenic (Bartsch *et al*., 1987). In humans, dietary nitrosamines have been implicated in the etiology of gastric, esophageal, nasopharyngeal and other gastrointestinal cancer (Bartsch *et al*., 1987). N-nitrosamines are considered an important carcinogen in parts of China and Japan (Goldman and Shields, 2003). Nitrosamines have been detected in foods and local beverages in certain parts of Nigeria (Maduagwu and Uhegbu, 1986). Most of the processed meat was probably preserved with nitrite and nitrite in preserved meat may produce organic N-nitroso compounds (Mirvish *et al*., 2002). As meat remains a nutritionally important component of most Western diets processed meat might be a risk factor for the people of the Western countries (Truswell, 2001).

Heterocyclic aromatic amines are sometimes formed during the cooking of muscle meats (Sugimura, 1986) and their mutagenic and carcinogenic effects are of potential concern in the aetiology of human cancer (Knize *et al*., 1997). A number of HCAs have been purified and characterized and their carcinogenicity has been demonstrated in rodents and the liver, lung, urinary bladder, small and large intestines, fore stomach, skin, oral cavity, mammary glands, clitoral gland and prostate in the ventral lobe are found as the target organs of HCAs (Sugimura, 2002).

Habit related carcinogen: Many people around us have some bad habits like smoking and drinking. Both have bad impact on our body and are major cause of cancer. Among the carcinogenic hazards, tobacco use in the form of smoking or smokeless as chewing, etc. has been identified to be the most important one, since about 33% of all cancers are tobacco-related (Sanyal, 2003). On the other hand at the time of incomplete combustion of organic matter PAH are produced. Many PAH have been

established experimentally as carcinogens (Goldman and Shields, 2003). As the lung, breast, oropharynx, genitourinary and gastrointestinal tracts the target organs for PAH (Goldman and Shields, 2003) for this smoking has been firmly linked not only to lung cancer but also to oral, esophageal, bladder, pancreas, cervical, nasal, stomach cancers, etc. (Sanyal, 2003). Beside active smoking passive smoking is also very dangerous. Evidence suggests that nonsmoking women married to smokers experience an excess risk of developing lung cancer in the order of 20% (Sanyal, 2003).

Like smoking drinking also a risk factor of cancer. Excessive drinking causes liver, oral, pharynx, larynx and esophageal cancers and may increase the risks of colorectal and breast cancers. Simultaneous drinking and smoking habits are much more dangerous. Alcoholic beverages consumption potentiates the effects of tobacco smoking on cancers of the mouth, pharynx, oesophagus and larynx and has been estimated to account for about 3% of all cancer deaths (Sanyal, 2003).

Infections and cancer: Around the world, infection is one of the most important causes of cancer (Pisani *et al*., 1997). Links have already been established between some bacterial and viral infections and the development of cancers. It was estimated conservatively that in the year 2002, 18% of all malignancies were attributable to infectious agents (Parkin, 2006). From the result of the recent researches we may conclude the relation between infection with *Helicobacter pylori* and gastric adenocarcinoma (Helicobacter and Cancer Collaborative Group, 2001) or gastric lymphoma (Parsonnet *et al*., 1994; Chen *et al*., 2005), human papilloma virus (HPV) and cervical cancer in females (WHO/IARC, 1995), hepatitis B and C and hepatocellular (liver) carcinoma (The Global Burden of Hepatitis C (Working Group, 2004; Raza *et al*., 2007), Epstein-Barr virus and Burkitt lymphoma (Young and Rickinson, 2004), Human Immunodeficiency Virus (HIV) and higher incidence and death rates from malignancies like Kaposi's sarcoma, non-Hodgkin's lymphoma, etc. (Sanyal, 2003). Hence, awareness regarding infections is also very important to prevent various cancers.

Others causes of cancer: Exposure to radiation plays an important role in the development of cancer. Ionizing irradiation is the only proven initiating factor for human breast cancer. As such the breast, the thyroid and the bone marrow appear especially radiosensitive (Ullrich, 2001). On the other hand, ultraviolet radiation is a major risk factor for skin cancers. Among the known environmental risk factors for Squamous Cell Carcinoma (SCC) of the skin beside ultraviolet radiation from sunlight exposure, ionizing radiation, arsenic and the products arising from the combustion and distillation of coal and petroleum also responsible (Aubry and MacGibbon, 1985).

Although, sunlight is the major environmental risk factor for skin carcinomas, the relationship of skin cancer with sun exposure is not straightforward, nor is risk consistently higher among persons with outdoor occupations (Linet *et al*., 1995). Occupational factors such as employment in chemical-related industries certainly contribute some fraction to the total reported skin carcinoma cases (Linet *et al*., 1995). Although, most studies were designed to investigate malignant melanoma, some have focused on nonmelanoma skin cancers, indicating an association between occupation, work environment and the risk of carcinoma (Chase, 1998; Hansen and Olsen, 1994; Karlehagen *et al*., 1992).

CANCER PREVENTION WITH DIETARY PHYTOCHEMICALS

From the above discussion we knew about the causes of cancer related to our diet, habit, occupation and radiation. Besides avoiding the causes of cancer taking of cancer preventive phytochemicals are highly necessary to prevent cancer. Vegetables and fruits are excellent sources of cancer preventive phytochemicals.

Firstly we have to know what carcinogenesis is. Carcinogenesis is generally recognized as a multi-step process in which distinct molecular and cellular alterations occur. From the study of experimentally induced carcinogenesis in rodents, tumour development is considered to consist of several separate, but closely linked, stages-tumour initiation, promotion and progression. Initiation is a rapid and irreversible process that involves a chain of extracellular and intracellular events. These include the initial uptake of or exposure to a carcinogenic agent, its distribution and transport to organs and tissues where metabolic activation and detoxification can occur and the covalent interaction of reactive species with target-cell DNA, leading to genotoxic damage. In contrast to initiation, tumour promotion is considered to be a relatively lengthy and reversible process in which actively proliferating preneoplastic cells accumulate. Progression, the final stage of neoplastic transformation, involves the growth of a tumour with invasive and metastatic potential (Surh, 1999).

On the other hand beside carcinogenic agents there are a lot of chemopreventive agents. According to the conventional classification originally proposed by Lee

Wattenberg, chemopreventive agents are subdivided into two main categories-blocking agents and suppressing agents (Wattenberg, 1985). Blocking agents prevent carcinogens from reaching the target sites, from undergoing metabolic activation or from subsequently interacting with crucial cellular macromolecules (for example, DNA, RNA and proteins). Suppressing agents, on the other hand, inhibit the malignant transformation of initiated cells, in either the promotion or the progression stage (Surh, 1999).

From some recently published articles it has been found that p^{53} plays an important role in tumor suppression and NF-kB and AP_1 play important role against apoptosis (Beg and Baltimore, 1996; Wang *et al*., 1998) and involved in cellular adaptation, differentiation and proliferation (Dong *et al*., 1997; Huang *et al*., 1998). Various scientific researches clear the critical role in cancer development and progression. NF-kB provides a mechanical link between inflammation and is a major factor controlling the ability of both pre-neoplastic and malignant cells to resist apoptosis based tumor surveillance mechanisms. NF-kB also involved in the regulation of tumor angiogenesis and in vasiveness (Karin, 2006). On the other hand AP_1 another transcription factor is involved in cancer cell differentiation and proliferation by regulating the MAPK signal cascade (Huang *et al*., 1996; Watts *et al*., 1998). In contrast to NF-kB and AP_1, p^{53} helps in cancer prevention by including cell cycle arrest or programmed cell death (Strahm and Capra, 2005).

So, it is an important question that, are there any phytochemicals that have cancer preventive activity by modifying the expression of p^{53}, NF-κB and AP_1? From many published articles it has been found that many natural food items have anti carcinogenic properties. The list of the natural food items with its cancer preventive phytochemicals are given in the Fig. 1 and the scientific explanations are given.

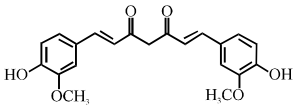
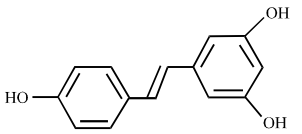
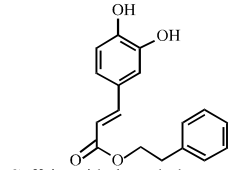
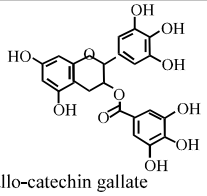
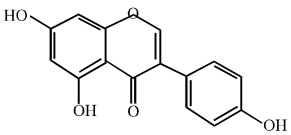
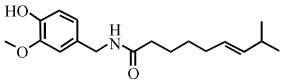
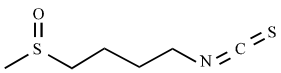
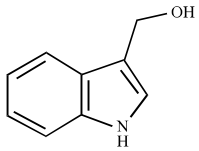
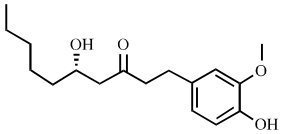
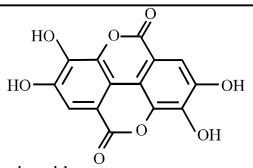
Natural source	Chemopreventive phytochemicals	Natural source	Chemopreventive phytochemicals
Turmeric 	 Curcumin	Grapes 	 Resveratrol
Honey 	 Caffeic acid phenethyl ester	Green tea 	 Epigallo-catechin gallate
Soybean 	 Genistein	Chilli pepper 	 Capsaicin
Broccoli 	 Sulphoraphane	Cabbage 	 Indole-3-carbinol
Ginger 	 [6]-Gingerol	Strawberry 	 Ellagic acid

Fig. 1: Cancer preventive phytochemicals

Curcumin: Curcumin is a yellow pigment that is present in the rhizome of turmeric. The chemopreventive properties of curcumin have been extensively investigated. From various researches it has been found that curcumin has the ability to suppress tumor promotion in a mouse model of skin carcinogenesis and inhibited TNF-α-induced cyclooxygenase-2 (COX2) gene transcription and NF-κB activation (Plummer *et al*., 1999). Curcumin also suppress activation of NF-κB and gene expression regulated by NF-κB (Takada *et al*., 2004). Curcumin arrested coloncancer cells in the G2/M phase of the cell cycle and caused them to undergo apoptosis via impairment of cell adhesion and Wingless signaling pathways that are thought to drive colorectal cancer (Jaiswal *et al*., 2002). Antiangiogenic properties of curcumin can be seen in umbilical vein endothelial cells also. In these cells, curcumin induces G0/G1 or G2/M phase cell-cycle arrest by upregulation of the tumour suppressor P53 and the cyclindependent kinase inhibitors P21 and P27 (Park *et al*., 2002).

Resveratrol: Resveratrol is a phytoalexin that is present in grapes. It can induce apoptosis by upregulation of the proapoptotic proto-oncogenes BAX and BAK, which results in the release of cytochrome c from the mitochondria and activation of various caspases (Delmas *et al*., 2003) and able to suppress activation of NF-κB and gene expression regulated by NF-κB (Manna *et al*., 2000). Resveratrol also induced apoptosis via p53 mediated pathway and has been consistently associated with arrest of cells in S phase of the cell cycle (Joe *et al*., 2002; Avci *et al*., 2007).

Caffeic acid phenethyl ester: Caffeic Acid Phenethyl Ester (CAPE) is a phenolic compound and an active component of honeybee propolis (Banskota *et al*., 2001; Murad *et al*., 2002). It has antiviral, anti-inflammatory, immunomodulatory and antiproliferative effects occur in different conditions (Avci *et al*., 2007). Anti-proliferative and apoptosis inducing effect of CAPE (Nagaoka *et al*., 2002; Chen *et al*., 2001; Lee *et al*., 2000; Usia *et al*., 2002; Nomura *et al*., 2001) has been considered as a new anti-cancer treatment modality. From some recently published article it has been found that the anti-carcinogenic properties of the CAPE are likely to be mediated by up-regulation of p^{53} gene expression and by inducing apoptosis via p^{53} mediated pathway (Avci *et al*., 2007). It has been also found that CAPE treatment was associated with a strong inhibition of proliferation in a dose- and time-dependent manner, along with induction of G0/G1 arrest and apoptosis in HCT116 cells (Wang *et al*., 2005).

Epigallo-catechin gallate: Epigallo-Catechin Gallate (EGCG) is an antioxidant and chemopreventive polyphenol that is found in green tea. It has been shown to suppress malignant transformation in a PMA-stimulated mouse epidermal JB6 cell line, which seemed to be mediated by inhibiting activation of Ap1 (Dong *et al*., 1997) or NF-κB (Nomura *et al*., 2000) dependent transcriptional activation.

The tumor suppressor gene p53, as the 'guardian of the genome', protects cellular DNA from a variety of carcinogenic insults by blocking cell proliferation, stimulating DNA repair and eliminating damaged cells by promoting apoptosis. In a UV-induced mouse skin carcinogenesis model, the administration of EGCG increased the number of wild-type p53-positive, p21-positive and apoptotic sunburn cells, demonstrating *in vivo* up-regulation of tumor suppressor and cell cycle regulator genes by this polyphenol (Lu *et al*., 2001).

Moreover, in three different research articles the chemopreventive activity of EGCG through blockade of cell cycle in different stages is also supported. Two of these articles showed that EGCG causes G_0/G_1 (Masuda *et al*., 2001; Ahmad *et al*., 2002) blockade and another in G_2/M phase (Fujiki *et al*., 2000).

Genistein: Genistein is an isoflavone compound and found in soy bean and related products such as Tofu, soy milk and soy sauce (Fotsis *et al*., 1995). Genistein has been shown to inhibit tumor growth in mouse models of breast, prostate and skin cancers (Barnes, 1995; Lamartiniere *et al*., 2002). In the light of recent progress in cell cycle regulation of estrogen, especially in hormonal dependent tissues, the effects of genistein on cell cycle regulation have been extensively investigated. Genistein arrests cell cycle at the G2/M phase in breast (Choi *et al*., 1998), prostate (Davis *et al*., 1998), gastric (Matsukawa *et al*., 1993) and lung (Lian *et al*., 1998) cancer cells. Some other article also showed blockade of cell cycle at G1/S stage by genestein (Kuzumaki *et al*., 1998; Shen *et al*., 2000).

Capsaicin: Capsaicin (8-methyl-N-vanillyl-6-noneamide), the major pungent ingredient found in red pepper, has long been used as spices, food additives and drugs (Cordell and Araujo, 1993; Biro *et al*., 1997). One studies in murine myeloid leukemia cells suggested that capsaicin inhibits the activity of the transcription factor NF-κB by blocking the degradation of IκBα (Singh *et al*., 1996). Other studies showed that topical application of capsaicin inhibited PMA-induced mouse-skin tumour formation (Park *et al*., 1998) and activation of NF-κB (Han *et al*., 2001; Patel *et al*., 2002).

Indole-3-carbinol: Indole-3-carbinol (I3C) is produced by the breakdown of the glucosinolate glucobrassicin, which can be found at relatively high levels in cruciferous vegetables. Apoptosis in response to I3C was observed *in vivo* in initiated mammary glands with activation of caspases-8, -9 and -3 (Zhang and Malejka-Giganti, 2003) and in cervical epithelium of transgenic mice (HPV16), developing cervical cancer in response to estrogen (Chen *et al*., 2001). Few studies have investigated the effect of either agent on signal transduction intermediates *in vivo*, but one study reported that dietary I3C (0.5%) caused a significant decrease in total tyrosine phosphorylation and ornithine decarboxylase activity in the rat liver (Manson *et al*., 1998). Many of the signaling events modulated by I3C *in vitro* involve tyrosine phosphorylation, but interestingly, changes in ornithine decarboxylase activity in breast and colon cells *in vitro* were only observed at relatively high concentrations (>100 μmol L^{-1}) (Manson *et al*., 1998; Hudson *et al*., 2003). The downregulation of NF-κB-regulated genes by I3C occurring in a variety of cancer cells *in vitro*, was also observed in mouse xenografts of MDA-MB231 cells (Takada *et al*., 2005; Rahman *et al*., 2006).

Sulphoraphane: Sulforaphane, a potent cancer preventive agent, is a dietary isothiocyanate compound found as a precursor glucosinolate in cruciferous vegetables such as cauliflower, broccoli and Brussels sprouts (Fahey *et al*., 2001). Some previously reported observations on effects of isothiocyanates a G2-M arrest was observed in the sulforaphane-treated pancreatic cancer cells (Hasegawa *et al*., 1993; Gamet-Payrastre *et al*., 2000; Xiao *et al*., 2003; Keck *et al*., 2002). However, another study suggested a more complex mechanism involving cell cycle deregulation, apoptosis and an oxidative stress pathway that seems to reflect differences in degree of sulforaphane-induced toxicity between the cell lines (Pham *et al*., 2004).

[6]-Gingerol: [6]-gingerol, a major pungent ingredient present in ginger, has potent anti-angiogenic activity *in vitro* and *in vivo* (Kim *et al*., 2005). These results points towards a possible role of [6]-gingerol in preventing cancers from becoming malignant, presumably by selective inhibition of angiogenesis formation at the tumor site. Gingerol suppressed experimental metastases in tumor-bearing mice and results suggested that [6]-gingerol may inhibit tumor growth and metastasis via its anti-angiogenic activity (Kim *et al*., 2004, 2005). Furthermore, [6]-gingerol has been shown to inhibit pulmonary metastasis in mice implanted with B16 melanoma cells, probably through stimulation of the host's immune functions (Suzuki *et al*., 1997). Gingerol also inhibited the growth of human colorectal cancer cells, (Bode, 2003). Johji *et al*. (1988) reported that crude acetone extract of ginger, isolated zingiberene (the main terpenoid from acetone extract), as well as [6]-gingerol significantly inhibited gastric lesions induced by HCl and ethanol in rats.

Ellagic acid: Ellagic acid ($C_{14}H_6O_8$) is a polyphenolic compound present in fruits and berries such as pomegranates, strawberries, raspberries and blackberries. It has anticarcinogenic, antioxidant and antifibrosis properties (Mukhtar *et al*., 1998; Thresiamma and Kuttan, 1996; Osawa *et al*., 1987; Stoner and Gupta, 2001). The anticarcinogenic effect of ellagic acid was shown in several types of cancers including skin, esophageal and colon cancers (Stoner and Gupta, 2001; Larrosa *et al*., 2006).

DISCUSSION

Among various diseases attributed to mortality in humans all over the world, cancer is a leading cause. Dietary factors continue to play a complex and multifaceted role in the aetiology of cancer (Sugimura, 2002). Cancers most commonly associated with diet include esophageal, stomach, colon, liver and the prostate. It is well known that most communities feed on substances of plant and animal origin which most of the times contain before processing chemicals, which are toxic. Of particular interest to toxicologists and nutritionists world wide particularly in the underdeveloped nations are the mycotoxins such as aflatoxins, which are metabolites of certain strains of fungi (Visconti, 2001). Other specific diet related compounds of concern are the polycyclic aromatic hydrocarbons from roasted and charcoaled grilled meats, N-nitroso compounds that are found in cooked or cured meat and emanating from nitrites. These substances have been identified and shown to act as carcinogens in initiating early stages of cancer (Ferguson, 2002). In light of the considerable complexity of dietary substances, it is not surprising that in addition to mutagenic and carcinogenic components present in the diet, there may exist anticarcinogenic and antimutagenic substances. Thus, certain plant-derived and dietary agents have been identified to play a role in the chemoprotection and chemoprevention.

Humans are unavoidably exposed to carcinogenic agents such as the heterocyclic amines, mycotoxins and other dietary carcinogens such as the nitrosamines. Although, each one of these examples only occurs at low

levels but the presence of these genotoxic substances may result in synergistic effects leading to cancer in humans. Chemopreventive strategies designed to limit both exposure to and the adverse health effects from dietary carcinogens are important public health goals to attenuate the incidence of diet-related neoplastic diseases since the complete elimination of exposure to these agents is not possible. In the light of recent progress in cell cycle regulation of estrogen, especially in hormonal dependent tissues, the effects of genistein on cell cycle regulation have been extensively investigated. Genistein arrests cell cycle at the G2/M phase in breast (Choi *et al*., 1998). It is reassuring that many food constituents consumed by the population contain potentially cancer preventive agents which are effective in preclinical models owing to their intrinsic antioxidant and anti-inflammatory properties. In view of the multifaceted action of these naturally occurring chemopreventive agents, clinical application should be considered. However, one of the aspects that pose serious challenge to the future is to find, validate and introduce appropriate biomarkers for evaluating the results of cancer chemopreventive treatments carcinogens.

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