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NONNUTRIENTS AND CANCER PREVENTION

Cancer is a multifactorial, multifaceted and multi-mechanistic disease requiring a multidimensional approach for its treatment, control and prevention. Cancer involves fundamental biological processes concerning disorganised cell replication, cell death and disorganization of organ structure. For India, the annual estimate of cancer for the year 2001 is 0.98 million[1] and the annual mortality in 2000 is 0.7 million[2]. The incidence of cancer is on the rise, with multiple risk factors that involve an interplay between genetic and environmental components. Diet is a major environmental risk factor[3]. The contribution of diet and nutrition status to cancer risk and conversely to the prevention and treatment of cancer has been a major focus of research as well as public health policy[4].

In 1981 Doll and Peto[5] attempted the first relative quantification of the environmental contributions of a variety of factors such as diets, alcohol, tobacco, occupation and radiation. Diet is not only a source of antimutagens/ anticarcinogens but also a source of mutagens. The carcinogens in the diet may be exogenous in origin or formed as a result of the interaction of components of foods endogenously *eg* heterocyclic amines[6].

Doll and Peto[5] also estimated the contribution of diet, and identified some specific agents to have preventive influences on cancer. Throughout the 1930s and 1940s, the modifying effects of diet on cancer induced in animals by chemicals were very well demonstrated. Many hypothesis proposed centered on nutritional deficiencies, which were believed to be provoked by carcinogenic compounds.

Several epidemiological studies highlighted the role of vegetables and fruits in reducing the risk of cancer in a variety of organs and tissues[7]. Nutritients which show modulatory effects in experimental cancers include macronutrients such as fat, carbohydrates, proteins, fibre and micronutrients such as vitamins – folic acid, riboflavin, β-carotene, retinol, α-tocopherol, vitamin B12 and minerals such as selenium, zinc, magnesium and calcium. Recently, however, the focus and emphasis has shifted to a number of non nutritional components in our diet which possess anticarcinogenic and antimutagenic properties[8]. These are also known as bioactive compounds or chemopreventers[9]. Chemoprevention is considered as a strategy to block or reverse carcinogenesis from the very early stages[10]. It has been suggested that chemoprevention should be considered as an inexpensive, cost effective and easily applicable approach to cancer control[9].

CHEMOPREVENTERS/PHYTOCHEMICALS

Cereals, vegetables, fruits, pulses, spices and other plant foods contain many micro constituents other than vitamins and minerals that are known to be biologically active (Table I). The chemopreventers belong to over 25 classes of chemicals. They are safe and have low or no toxicity.

Table I. Food sources of phytochemicals.

Phytochemicals	Food source
Fiber (macronutrients)	Cereals (grains, fruits and vegetables)
Carotenoids	Yellow/orange vegetables, fruits and dark green leafy vegetables
Allium compounds	Onion, garlic, chives, leeks
Dithiolthiones/ glucosinolates	Cruciferous vegetables
Isothiocyanates	Cruciferous vegetables
Terpenoids	Oil of citrus fruit peel
Phytoestrogens	Cereals, pulses, sorghum, millets, soyabeans, fruits and berries
Protease inhibitors	Cereals, barley, wheat, oats, rye, soyabeans, kidneybeans and chick peas
Phytic acid	Cereals, nuts, seeds, seasame seeds, lima beans, peanuts, and soyabeans
Flavonoids	Fruits and vegetables
Phenolic compounds	Fruits, vegetables and tea
Plant sterols	Vegetables
Saponins	Soyabeans, yam and colacasia

Nutritive Chemopreventers

A number of micronutrients in diet have cancer preventive properties. These include vitamins A, C and E, β carotene, selenium and calcium. Most of these agents are antioxidants. Epidemiological studies have shown that the incidence of certain forms of cancer is highest in people with a low dietary intake of the above nutrients[1,2].

Nonnutritive Chemopreventers

There are many nonnutrients in diet with plausible cancer preventive effects. During the past few years, as research on the relationship between diet and cancer has increased[4], data from both epidemiological[8],[9] and experimental studies accumulated, indicating that cereals, vegetables, fruits and certain beverages contain a variety of potential cancer preventing substances[7].

Sources of Nonnutritive Chemopreventers

Cereals

Cereals like wheat, rice, maize, millet, sorghum are principle constituents of food. They provide protein, vitamins, trace elements and varying amounts of non-starch polysaccharide (NSP)/dietary fibre. Although dietary fibre is not a supplier of calories or essential nutrients, it is important for intestinal functioning. The dietary fibre lowers the intestinal pH, binds to bile acid and shortens the intestinal transit time. Bile acids are believed to be one of the factors involved in colon carcinogenesis by regulating gene expression[11]. The prevalence of colon cancer in India is much lower as compared to Western population, probably because of higher unprocessed cereal intake with more fibre.

Vegetables

Green leafy vegetables, beans of all varities, cruciferous vegetables namely cabbage, brussels sprouts, cauliflower and broccoli are rich in anticarcinogens. Umbelliferae vegetables like carrots, celery, parsnips, alliums namely onions, garlic and chives, solanaceaous vegetables like potato, tomato and brinjal have significant levels of cancer protecting nonnutrients[7,8].

Fruits

All the citrus fruits, grapes, apples, strawberries, plums, pineapple, melons have high levels of protective phytochemicals. All the other fruits and dried fruits also possess some amounts of anticancer agents[7,8].

Spices

Spices and condiments which are a part of the Indian diet have chemical constituents which have antioxidant, antimutagenic and anticarcinogenic properties[12]. Some of them have many other beneficial effects like hypocholesterolaemic, hypoglycaemic, antiinflammatory and antimicrobial properties. Turmeric, cloves, ginger, thyme, anise, mustard, cinnamon have been reported to have antioxidant and antimutagenic properties.

Mechanisms of Action of Chemopreventers

The mechanism of action of chemopreventers is complex; it is classified according to the site of action or by specific type of action. The activity could be the result of simultaneous action of several factors on the same event[13]. It appears that most chemopreventers act primarily as antioxidants, antimutagens, immunomodulators and anticarcinogens[13] (Table II).

Table II. Nonnutrient chemopreventers – Mechanism of action.

Category	Mechanism
Inhibitors of carcinogen formation Caffeic acid, ferulic acid	Inhibit *in situ* formation of carcinogen *eg* nitrosamines formation
Blocking agents Isothiocyanates, diallylsulphide, ellagic acid, ferulic acid, dithiocarbamates	Inhibit the activity of enzymes (cytochrom P 450) which convert procarcinogens to carcinogens
Inducing agents Isothiocyanates, sulpharaphane d-limonene, terpenoids, curcumin	Stimulate enzymatic system which are involved in detoxification of carcinogens
Trapping agents Ellagic acid, N-acetylcysteine	Physically react with carcinogens and detoxify them
Suppressing agents/ selenium, soya products Isoflavones, phytoestrogens, epigallocatechin gallate (EGCG)	Suppress different steps in metabolic pathways required for tumour development

Source: Refs. 12 and 13

Broadly, the chemopreventers may act through detoxification mechanism or by antimutagenic processes at both the initiation and promotion steps of carcinogenesis.

Detoxificants

These phytochemicals induce drug metabolising enzymes in the body and act by detoxifying the harmful substances capable of producing harmful effects. The antineoplastic effects of inducing and inhibiting agents in foods focus on specific monooxygenases like the aryl hydrocarbon hydroxylase (AHH), uridine diphosphate (UDP) - glucuronyl transferase (UDPGT), and glutathione-S-transferases[12].

Antimutagens

Carcinogens bind to the cell macromolecules namely, DNA, RNA and proteins and result in mutagenic events leading to cell transformation and neoplastic changes. Some phytochemicals prevent these changes from occurring either by directly binding to the carcinogens/ their metabolites or by metabolising and eliminating toxic xenobiotics[12]. These are known as antimutagens/ anticarcinogens.

At the National Institute of Nutrition (NIN), Hyderabad extensive research has been carried out on some of the nonnutritive chemopreventers such as garlic, onion, turmeric, green leafy vegetables (spinach, amaranth, *gogu*) and cabbage. The results of NIN studies are highlighted here.

Turmeric as Anticancer Agent

Among the spices, turmeric is the most extensively used for its colour, taste and flavour. It is also added to foods as a preservative. In traditional medicine, it has been used as a potent antiinflammatory agent, carminative and antiseptic agent. Curcumin, the active principle in turmeric, has strong antioxidant and antiinflammatory potency. The NIN studies on turmeric consisted of its *in vivo* and *in vitro* evaluation as a potential chemopreventive agent[14]. Its potent antimutagenic effects were demonstrated against well known carcinogens in *in vivo* rat model[15]. In order to understand the underlying mechanisms, experiments were conducted to study the levels of tissue xenobiotic metabolising enzymes in animals fed turmeric through diet. The results suggested that there was stimulation of detoxifying enzymes *viz.* glutathione-S-transferases (GSTs) and UDP glucuronyl transferases (UDPGT)[16]. Although drug metabolising enzymes are important in the carcinogen activation/deactivation pathway, the propensity of DNA to bind itself to the toxic metabolites of carcinogens is equally important. Turmeric/ curcumin feeding to rats for 4 weeks prior to carcinogen exposure decreased the binding of liver DNA to the carcinogen benzo(a)pyrene [B(a)P] as quantitated by ^{32}P post label assay[17].

Turmeric/curcmin in experimental tumourigenesis

As oral cancers occur commonly in India, the effects of curcumin and turmeric were assessed in experimental tumourigenesis using Syrian golden hamster cheek pouch model. Cheek pouches were painted with the carcinogen dimethyl benanthracene (DMBA) with or without turmeric/ curcumin for induction or retardation of tumours along with feeding turmeric/curcumin through diet. At the end of 14 weeks, it was found that the animals given turmeric/

curcumin through diet or painted with curcumin had a lower percentage of microscopic tumours as compared to controls which did not receive turmeric through diet.

In animals which received curcumin, most of the tumours did not go beyond grade 1. The binding of tissue DNA to carcinogen was found to be significantly reduced in the experimental groups given turmeric/curcumin either through diet or locally painted[18]. These findings suggest that turmeric/curcumin may act as anti proliferators and antipromoters.

Turmeric anti-initiator or anti-promoter

To know exactly at what stage turmeric acts, forestomach tumours were induced by B(a)P in mice which were simultaneously fed turmeric/curcumin during the various stages of carcinogenesis[19]. While turmeric and curcumin treatment during initiation inhibited papillomas by 67 and 50% respectively, the inhibition was 50 to 100% post initiation. While turmeric can act in the both phases, curcumin can act only in post initiation process[19].

Curcumin on DNA repair

DNA repair is one of the important mechanisms of protecting the system from the onslaught of genotoxic agents. Therefore, the effect of curcumin was studied on the single strand breaks (ssb) in the DNA of yeast, *Saccharomyces cerevisiae* exposed to UV radiation, 8-methoxypsoralen and benzo(a)pyrene. The single strand breaks in DNA as estimated by alkaline elution technique were reduced in yeast cells in the presence of curcumin (Polasa *et al:* unpublished observations).

Studies to assess the repair capacity of curcumin against DNA damage induced by B(a)P in lymphocytes of smoking and non smoking men and in women, showed that it was effectively counteracted suggesting that in addition to anti-initiating, detoxifying and antioxidant activities, curcumin also has the ability to repair DNA[20].

Turmeric as antimutagen in humans

Antimutagenicity effect of turmeric was evaluated in human smokers who are known to excrete mutagens. The excretion of urinary mutagens was reduced at the end of 15 days of turmeric ingestion (1.5 g/day orally for 30 days) and further by 30 days time. The liver and kidney function tests were not altered[21]. A clinical trial in reverse smokers who are at a high risk of palatal cancers in a specific area of Andhra Pradesh showed that turmeric administration (1g/day for 9 months) had a significant impact on the regression of precancerous lesions such as red and white patches over the palatal regions and decreased the micronuclei and DNA adducts in oral epithelial cells which are markers for genomic damage[12].

Turmeric/curcumin as antioxidant

Turmeric and curcumin have been shown to be antioxidants. Studies in the animal model where oxidant damage was induced by paracetamol and DMBA showed that the levels of TBARS and SGOT and SGPT were reduced in liver of carcinogen treated rats, demonstrating its antioxidant property[14].

Effect of cooking on turmeric/curcumin

As turmeric in the Indian culinary practices is usually boiled or fried, it was considered essential to assess its antimutagenic properties after heating or frying. A short term assay was used to measure the genotoxic response to a commonly present food mutagen 4 nitroquinoline oxide in *E.coli PQ37*. In the presence of boiled or fried curcumin this response was decreased indicating that cooking conditions are unlikely to destroy the antimutagenic property of turmeric[22].

Turmeric as a functional food

In view of its wide spectrum of action, turmeric is an ideal functional food for prevention of cancer. Toxicological studies on turmeric have indicated that curcumin taken orally in doses of 40-1800 mg/day for 1 to 3 months does not produce toxic effects[12]. From mutagenicity and other studies, the protective consumption levels can be extrapolated for humans. A daily intake of 0.5 to 1.0 g can be consumed without any adverse effect[12].

Alliums

Among the vegetables, those belonging to the allium family have received increased attention in recent times. Onion and garlic are commonly consumed through the diet. They contain sulphur compounds like diallyl sulphide and diallyl disulphide.

Wistar rats fed garlic (0.1, 0.5, 1%) or onion (1 and 5%) containing diet for one month, when exposed to either B(a)P or 3MC showed reduction in the excretion of urinary mutagens[23,24].

Effect on drug metabolising enzymes

Stimulation of the activity of liver cytosolic glutathione-S-transferase was seen on garlic feeding. The activity of the antioxidant enzyme quinone reductase in the liver and lung microsomes was elevated in animals fed garlic containing diets[23]. In onion fed rats there was stimulation in the GST and GSTMu activity in the stomach and liver tissues[25].

The reduction in the excretion of carcinogen derived mutagens in garlic/onion fed rats suggested that endogenously present mutagens could be countered by protective substances. Enhancement in the levels of tissue detoxification enzymes could be another important mechanism through which these dietary agents could confer their protective effects. Garlic at 0.1 and 0.5% and onion 1 and 5% were fed through diet in these experiments. These quantities of alliums can be easily consumed through diet[24].

Mustard

Mustard is a spice used for flavouring and as a source of edible oil in India. The leaves of this plant are consumed as vegetable. Mustard belongs to cruciferous family, other members of which are cabbage, broccoli, cauliflower, *etc*. The active principle of mustard is dithiolthione. NIN studies have shown that mustard has antimutagenic property[26]. In rats fed 10% mustard powder containing diet, significant reduction in the activity of carcinogen activation enzyme, aryl hydrocarbon hydroxylase and stimulation in the activities of carcinogen detoxification enzymes namely UDPGT and glutathione-S-transferases were observed[26].

Induction of Protective Enzymes by Vegetables

Induction of hepatic microsomal and cytosolic xenobiotic metabolising enzymes by commonly consumed vegetables such as spinach, amaranth, *gogu* and cabbage was studied in rats fed at 20% level. Stimulation of the microsomal aryl hydrocarbon hydroxylase was observed only in animals fed *gogu*, while the activities of UDP glucuronyl transferase and glutathione-S-transferase were significantly elevated in the groups - fed cabbage. Benzo pyrene binding to hepatic DNA, *in vivo*, a measure of carcinogen activation, tended to decrease in the groups fed *gogu*, onion and mustard[27].

Other Evidences for Nonnutrients as Chemopreventers

Experimental

Phenolic compounds in grains, fruits and vegetables, lignans, and flavonoids have shown chemopreventive effects in experimental animals[28]. These have been shown to exert antimutagenic activity[29]. Turmeric and curcumin have been shown to inhibit tumours in skin, breast, oral cavity and forestomach in initiation and promotion models in many species including mice, rats and hamsters[12].

Diallyl sulphide (DAS) an active component present in garlic has been shown to inhibit DNA carcinogen adduct formation in rat tissue. It was foound to reduce forestomach tumour frequency in hamster buccal pouch and rat oesophagus. Garlic oil has been shown to inhibit promotion of chemically induced skin cancers[3o].

Isothiocyanates, present in cruciferrous vegetables have been shown to block tumours induced by chemical carcinogens. Tumours of the mammary gland, digestive system, and nitrosamine induced lung tumours have been shown to occur at reduced frequency in laboratory animals fed thiocyanates prior to carcinogen exposure[31].

Short term tests and experiments on animals are used to establish the antigenotoxic potential of phytochemicals and unequivocal evidence is available to demonstrate the anticancer property of these agents[33]. However epidemiological studies need to be conducted to establish the diet–cancer relationship in humans.

Epidemiological

Epidemiological studies indicate that fruits and vegetables have health promoting factors against diseases, particularly cardiovascular and cancer. Possible plant nutrients providing this protection include micronutrient and nonnutrient components of the diet. According to National Nutrition Monitoring Bureau (NNMB) surveys in 10 states of India, there is poor consumption of green leafy vegetables and poor intake of micronutrients[33].

Oral cancer is one of the ten most common cancers in the world[34] and in India accounts for a third of all cancers[35]. A case control study was conducted by the NIN to examine the role of diet in oral and oropharyngeal cancers. Dietary intakes and nutrient estimates were obtained through diet history collected by oral questionnaire. The results suggested poor dietary intake of vegetables and fruits coupled with low estimated intake of micronutrients[36].

Cancer of the colon and rectum is the fourth most common incident cancer and cause of death from cancer, throughout the world[4]. Cross-sectional comparisons, case control studies and trends in food intake show high rates of colorectal cancer in populations consuming diets high in meat and fat and low in fibre and vegetables[37]. In prospective cohort studies an association between consumption of vegetables and fruits with reduced risk of lung, oesophagus, stomach and pancreatic cancer was observed[38].

An epidemiological study was conducted in Jiangsu province, China, where gastric cancer is low and in Yangzhong which is a high risk area for gastric cancer using a questionnaire and adjusting for ecological and life-style factors and age and sex. The study reports that allium vegetables were consumed in the low risk area more frequently, with high consumption of raw vegetables, fruits, tomatoes, kidneybeans and soyabean products. The results suggest that frequent consumption of allium vegetables, in addition to other anticancer foods may be a factor for low mortality due to gastric cancer in the low risk area[39].

From several reports it emerges that, assessment of individual nutrient intake, as opposed to fruit and vegetable consumption, does not increase the protective association of these components. However, changes in the diet that would increase consumption of fruits and vegetables would be beneficial as such a diet is unequivocally associated with cancer protection[40]. Although observational studies provide consistent data for inverse association between high intake of micronutrients and risk, randomized trials have not supported this hypothesis.

The possible explanations for these inconsistent findings are: (i) confounding by other healthy dietary and nondietary habits in observation studies; (ii) the protective role of a combination of many different nutrients and bioactive compounds present in fruits and vegetables, rather than the single nutrient or combination of a few that most trials have tested; (iii) inadequate duration of follow up in randomized trials; and (iv) heterogenecity of the populations studied[41], particularly with respect to nutrient and nonnutrient intake. Based on available information as of date, it seems prudent to advocate a diet rich in fruits and vegetables, rather than consumption of a specific nutrient or nonnutrient in order to decrease the risk of developing cancer of organs such as colon[42], stomach[43], oesophageal[43], breast[43] and prostrate[44]. Synergistic or additive effects of naturally occurring compounds in the diet cannot be compared to single or multiple nutrients, as bioavailability mechanisms of action/ interactions and biotransformations and excretion cannot be predicted.

Intervention Studies

Intervention trial is considered to be the most definitive method to evaluate the role of any nutrient/ nonnutrient. Randomized, double blind studies would be ideal for such investigations. Various intervention trials have been summarised by IARC[45].

An intervention trial supplementing micronutrients such as vitamin A, riboflavin, zinc and selenium to a group of reverse smokers indicated that the cocktail of nutrients given as a prescriptive approach could result in regression of preneoplastic lesions in the oral cavity[27]. The nutrients also prevented deterioration of lesions and appearance of new lesions in the non lesion group[27]. Similarly in tobacco chewers administration of β-carotene and vitamin A lead to disappearance of leukoplakia. Biomarkers such as carcinogen, DNA adducts and micronuclei were significantly reduced in the treated groups.

In another intervention study on tobacco chewers in Kerala, administration of spirulina for a year resulted in complete regression of leukoplakia in 45%[46]. Similar observations on chemoprevention have been noted in China where a high prevalence of oesophageal and stomach cancers exists[4].

Intervention trials using antioxidants in various doses and combinations have yielded inconsistent results for protection against lung cancer in smokers, invasive cervical cancer, oesophageal and gastric cancers and colorectal polyps[47]. In most trials biomarkers of oxidative DNA damage, lipid peroxidation and other intermediate cytological end point markers are used to study the cause - effect relationships. A cocktail of micronutrients has been supplemented in the studies. Results of such trials are difficult to interpret and yield unexpected results[48].

Dietary Modification Studies

Women's Health Initiative (WHI) 10 year trial was started in 1993 to assess the effect of diet low in fat and high in fruits, vegetables and fibre on cancer incidence among more than 50,000 post menopausal women[49]. Women's Intervention Nutrition Study (WINS) is a 5 year clinical trial designed to test whether dietary fat reduction will reduce breast cancer recurrence and increase survival among 2000 women breast cancer patients[49]. Can dietary intervention with increased fruits and vegetables consumption provide the key answer? A recent study has demonstrated that a group of healthy individuals who consumed increased quantities of fruits and vegetables for 2 weeks had elevated plasma levels of antioxidant nutrients as compared to basal values; the levels of α tocopherol and retinol did not show elevation[50].

In another recent study, a group of subjects on normal diet, except vegetables high in carotenoids for 2 weeks, were supplemented with tomato juice (weeks 3 and 4), carrot juice (weeks 5 and 6) or spinach (weeks 7 and 8). The supplementation resulted in a significant decrease in the endogenous levels of strand breaks in lymphocytes DNA as measured by comet assay; oxidative damage was significantly reduced by carrot juice[51]. High intake of cruciferous vegetables associated with reduced risk for colorectal cancer have been shown to induce GST in human plasma and lymphocytes following consumption of brussels sprouts. This stimulation has been shown in plasma GST–α and rectal GST–α and GST–π in humans after one week of consuming brussels sprouts[52-54]. This is supported by another intervention study in fried meat consumers in whom a two-fold reduction in urinary mutagenicity was observed[55].

In a dietary intervention study, a group of subjects with non melanoma skin cancer was placed on low fat diets for 2 years. The incidence of both premalignant lesions (actinic keratoses) as well as skin cancer *per se* was reduced significanty[56,57]. An intervention study is currently underway to investigate the effect of wheat bran fibre. However, in studies of this kind a double blind regimen is not possible where the intervention comprises a diet high in fibre and low in fat[58]. Cancer as an unambiguous end point needs prolonged duration of study.

Conclusions

Prescriptive and proscriptive approaches for cancer prevention in relation to diet are important to reduce the incidence of cancer particularly that of the aerodigestive system and cervical cancer in India. The current focus is on cost-effective health care strategies of which dietary changes are one. Beside the nutrients, the nonnutrient components of diet are gaining importance in studies pertaining to diet–cancer relationship. Plant foods including vegetables, fruits and spices possess phytochemicals which have antioxidant activity. Spices such as turmeric, onion and garlic were shown to be potent antimutagens in *in vitro* and *in vivo* conditions. These were also shown to induce the drug metabolizing enzymes involved in detoxification of harmful substances in the tissues. Studies on turmeric have established its anticarcinogenic potential in animals. In humans, turmeric and curcumin reduced urinary mutagens excretion by smokers, and the precancerous lesions in reverse smokers.

Evidence from epidemiological studies indicates that diets high in fruits and vegetables with phytonutrients and low in certain types of fat, along with moderate caloric intake and fibre rich food are associated with reduced cancer risk[58]. Results from clinical trials with nutrients/ nonnutrients as supplements have not given conclusive evidence for protective effects against cancer[59]. It is important to realize that a supplement of any nutrient or nutrients against the backdrop of a poor diet can hardly be expected to produce the desired outcome. A more appropriate approach should be a food based one. Beside the protective effects of nutrients and nonnutrients their synergistic effect is also an important point to be considered. Therefore dietary preventive measures or promotion of healthy dietary habits and life styles, though demanding, are perhaps the right answer for cancer prevention.

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