

## Naturally occurring Carcinogens (Cancer promoters) & Anticarcinogens (Cancer Inhibitors) in human diet

By Ms. U. Rangwala, & Dr.B Sesikeran, Director, NIN

'Carcinogen' refers to substances or compounds which contribute directly or indirectly to the development of cancers in humans. Human diet contains many natural substances or compounds which may contribute directly or indirectly to the development of cancers. Thus diet consumption is not an entirely risk free activity. In fact Hippocrates the Father of medicine (460-357 B.C) mentioned "He who does not know food, how can he understand the disease of man?". Understanding the different food components that can be carcinogenic or anti-carcinogenic and the steps that lead to generation of carcinogenic cells and spread of cancer is of great significance.

Cancer is a major cause of concern for most of the developing nations of the world and in India, a large segment of male population is suffering from lung and oro-pharyngeal cancer along with prostate and colon cancer whereas the female population is suffering mostly from cervical and breast cancer. Cases of breast cancer are high in urban female population while cervical cancer is more common in rural India. As we are observing a transition in Indian population from a traditional Indian to a more western culture, there is a concern that the nutritional transition to a more western diet would in future alter the occurrence of cancers. It is estimated that 80-90% of cancers are related to environmental factors (including 35% which are related to diet), which would imply that some of the human cancers may be potentially preventable. The strong influence of environmental factors is readily seen, in the studies on effect of migration from one to another culture, wherein changes in the pattern of occurrence of cancers resemble that of the newly adopted country.

Carcinogenesis is multifactorial and multistep in nature and is highly influenced by the environmental factors such as type of food consumed by a person, exposure to different pollutants and contaminants in the ecosystem, life style of an individual and the frequency of infection during the individuals lifespan. In a normal cell, there are protective mechanisms that help the cell maintain its normal healthy state. However under certain conditions, the environmental factors cause the genes in the cell to mutate by hindering either the DNA repair mechanism or the immune surveillance system of the body and initiate the cell to transform into a cancer cell. This process can be reversed if the protective mechanism is benefited by environmental and dietary factors that act as anti-carcinogens and assist in DNA repair mechanism. The candidate cells that have been initiated into carcinogenesis may become complete cancer cells, if the carcinogenic environmental factors continue to hinder the protective mechanisms or a promoter gets activated causing more mutations to take place and eventually lead to development of a fully malignant phenotype with the capacity for tissue invasion and metastasis. Although the exact mechanisms are unknown, nutrition may modify the carcinogen metabolism, cellular and host defences, cell differentiation and tumour growth and can also slow down the rate of proliferation of cancerous cells

As cancer is a multifactorial disease, it would be difficult to say that a healthy diet would suffice to prevent cancer. Knowledge of naturally occurring carcinogens helps in modifying the dietary pattern so as to minimize the risk of cancer. Some carcinogenic substances get generated by food preparation or processing or even after consumption. Foods that are processed or cooked at high temperatures may contain products of pyrolysis. Carcinogenic polycyclic aromatic hydrocarbons (PAHs) such as benzopyrene or benzo[a]anthracene form whenever organic matter is pyrolysed. Pyrolysis of protein rich foods such as meat or fish leads to the generation of heterocyclic amines such as 2-amino-3-methylimidazo [4,5-f] quinoline (IQ) and 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP), which in experimental animals have been shown to be potent mutagens. These toxic substances are also formed during charcoal broiling, frying, and smoking of meats. Several investigators have found mutagenic activity in food after frying and charcoal broiling. Epidemiological studies have indicated an increased risk of stomach and esophageal cancer with the frequent intake of smoked and fried foods. Cooking foods at lower temperature (thermolysis) may also produce oxidative or other changes in protein, fat and carbohydrate that make them carcinogenic, though mechanisms involved in these processes are not yet well understood. Some plants are found to contain natural pesticides that also act as carcinogens for humans. Carcinogenic nitrosamines such as N-nitrosodimethyl-amine and N-nitrosopyrrolidine are found in foods and more particularly those preserved by sodium nitrite, such as bacon and cured meat.

The role of natural carcinogens in human cancers can be studied through or with invitro, invivo rodent assay, the later two however do not mimic human exposure.

We consume such carcinogens in very small quantities over a long period of time. 1) Therefore sensitive molecular markers of human exposure are required 2) biological markers of the compounds and databases providing concentrations of these substances in various food stuffs is needed

Studies evaluating the role of diet in the etiology of cancer tend to produce conflicting results, wherein if one major component of the diet is altered, other changes take place simultaneously, eg. Decreasing animal protein also decreases animal fat and cholesterol. This makes the interpretation of research findings difficult because the effects cannot be easily associated with a single factor. Many tumours have a long latency period, and the diet being consumed over the past 4-5 years and at the time of diagnosis may be important. Some prospective epidemiological studies attempted to circumvent this difficulty by measuring diet at one point of time and following the same subjects for several years. Diets contain both inhibitors and enhancers of carcinogenesis. Furthermore the effect of nutrients may vary depending on the type of cancer or the nutrients/ anti-nutrients balance may decide the type of cancer that would appear.

There are several methods of finding whether a substance can act as a carcinogen and one among of such methods is 'Subchronic feeding test' (ninety day toxicology study in an appropriate animal species). It is often used to define the MTD (Maximum Tolerated Dose) and, for noncarcinogens, the NOAEL (No Observable Adverse Effect Level). MTD is the highest level of a test substance that can be fed to an animal without inducing obvious signs of toxicity and the test substance is fed at its MTD as well as one or two lower doses. By one standard, a substance is of concern if a toxic effect results from ingesting 25 times the amount typically found in food. By this standard, only a tiny fraction of food constituents (which is estimated to be less than 1%) are "toxicants." There still remains the dilemma of the public perception that toxicologic risk to our food supply is much greater than scientifically derived estimates indicate. Concern over perceived risks typically focuses on synthetic contaminants, pesticide residues and food additives.

There have been few attempts to address these concerns in a systematic, scientific manner. One such approach was developed by Ames and colleagues which involves ranking carcinogenic risks according to a ratio known by the acronym HERP (Human exposure/rodent potency). A HERP can be calculated for any carcinogen so long as its human exposure level and potency in a rodent bioassay are known. To calculate HERP, the human exposure level (mg/kg body weight) and the result are then multiplied by 100. The concentration of synthetic pesticides residues and contaminants are far lower than many naturally occurring carcinogens. Ames and colleagues estimate that 99.99% of the total mass of carcinogens typically ingested is of natural origin but these conclusions must be interpreted correctly. One should not infer that the level of exposure to naturally occurring dietary carcinogens is necessarily excessive, especially in developed countries. Rather the level of exposure to synthetic pesticide residues and contaminants is ordinarily so low as to be of no health significance whatever.

One of the approaches to know the potency of the substance to promote cancer is Ames microbial mutagenesis test. In this system, the strains of bacterium *Salmonella typhimurium*, which are unable to grow in the absence of the amino acid histidine because of the defective histidine metabolic pathway, are deposited on an agar –containing petriplate. The material to be tested is placed in the centre of the dish. If the test material is mutagenic, the bacteria will revert to histidine production and once again are able to grow. This growth is seen as a ring of colonies around the area of the deposited material. Ames and his co-workers have refined the test to permit the quantification of the test material.

Many studies have evaluated the effects of minerals, vitamins, and other minor dietary components on the risk of several cancers. Some of these risk factors are potentially important, and several have already been mentioned. Cancer of the stomach, particularly in Japan has been associated with excessive salt (sodium chloride) consumption in foods such as salted fish. Salt may act as an irritant, causing degradation of the mucous lining of the stomach, leading to exposure of the epithelial cells to carcinogens in the gastric contents and to increased cell replication. Dietary selenium level may have a protective effect against a variety of cancers, particularly those of the breast and colon. Selenium may exert its protective effect via its role in the activity of glutathione peroxidase (an enzyme that protects against oxidative tissue injury). There is also limited epidemiologic evidence linking vitamin D deficiency with the risk of colorectal cancer furthermore, diets that are marginal in riboflavin and nicotinic acid have been associated with risk of esophageal cancer.

#### **Fat:**

There are large differences among countries in dietary fat intake that correlate with the incidence of cancers such as those of the breast, colon, and prostate and the international correlations can be striking (e.g.,  $\approx 0.8$  for fat and breast cancer). Many factors, other than intake of fat that are related to levels of economic development could also be involved. Many, but not all, studies described a positive association between animal fats, or more specifically, saturated fats and colon cancer incidence. One study showed an association between animal fat consumption and the development of precancerous adenomatous polyps in the colon. However, the association of colon cancer with red meat consumption rather than fat has been more consistent. A meta-analysis of 23 case control and cohort studies of dietary fat and breast cancer risk showed that the association was weak. It has been argued that there were insufficient differences between diets in most of these studies to allow detection of associations.

#### **Protein:**

Understanding the role of protein in tumour development is complicated by the fact that most diets high in protein are also high in carbohydrate and fat and low in fiber. The effect of protein on experimental carcinogenesis depends on the tissue of origin and the type of tumour, as well as the type of protein and the caloric adequacy of the diet. In general, tumorigenesis is suppressed by diets containing levels of protein below that required for optimal growth, while it is enhanced by protein levels two or three times the amount that is required. The effects may be due to specific amino acids, a general effect of proteins breakdown or in the case of low protein diet, depressed food intake. Epidemiologic data is limited and conflicting. Increased meat intake has been associated with increased risk of advanced prostate cancer.

#### **Nitrates, Nitrites, and nitrosamines:**

Nitrates and nitrites have received attention because of their relationship with the nitrosamine, and are potent carcinogens in various species. Nitrates can be readily reduced to nitrite, which in turn can interact with dietary substances such as amines and amides to produce N-Nitroso compounds, or nitrosamides. This conversion known as N-nitrosation, has been demonstrated to occur in saliva as well as in the stomach, colon and bladder. It is not known, however, whether N-nitrosation is a cause of any human cancer. Gastric cancer is not common, and incidence has decreased steadily during the past 50 years. Nitrates are present in a variety of foods, but the main dietary sources are vegetables and drinking water. Sodium and potassium nitrates are used in the processes of salting, pickling, and curing foods. Nitrosamines are present in tobacco smoke.

Epidemiologic studies implicate interplay of dietary factors in the development of cancer in gastric mucosa. Available evidence suggest that the mucosa may be damaged by a diet rich in salt, thus increasing vulnerability to a carcinogen derived from a diet rich in nitrates /nitrites. It also appears that both cancer initiation and progression may be inhibited by the consumption of fresh

vegetables, especially those that contain vitamin C and other reducing agents, which have been shown to inhibit nitrosamine formation.

#### **Alcohol:**

Cancer risk has been associated with many non-nutrients and one of them is alcohol. Alcohol consumption is a risk factor for several types of cancer, particularly those of tissues that come in direct contact with the alcohol, such as the oral cavity and the larynx, although other sites such as colorectal, breast, and liver are also at increased risk. At some sites, alcohol acts synergistically with other agents. Thus, the effects of alcohol and tobacco are almost multiplicative in the development of oral and esophageal cancer. There is also synergy between alcohol consumption and aflatoxin B1 or hepatitis B virus in the development of liver tumours. Epidemiological association between the consumption of specific alcoholic beverages and the development of specific cancer suggest that it is likely that cancer risk may be related not only to the quantity of alcohol consumed, but also to other constituents in it. Several mechanisms have been proposed for the effects of alcohol on carcinogenesis, which include DNA adduct formation, free radical generation and inhibition of DNA repair enzymes by the alcohol metabolite acetaldehyde and effects of alcohol on the enzymes of carcinogen metabolism, excretion, and recirculation of bile acids as well as on levels of estrogens. Additionally, PAHs and nitrosamines are present in some alcoholic beverages.

A dietary carcinogen that has been implicated strongly in human cancer causation is aflatoxin B1. This mycotoxin contaminates certain foods consumed in South East Asia and Africa, and epidemiologic studies indicate that aflatoxin exposure together with infection with the hepatitis B virus are risk factors for liver cancer.

**Acrylamide** is a chemical used primarily for industrial purpose. It is considered a probable human carcinogen, based on data from laboratory animals. Acrylamide is used to make polyacrylamide and acrylamide copolymers, which are used in many industrial processes including production of papers, dyes, plastics and treatment of drinking water, sewage/waste. They are also present in consumer products such as food packaging and some adhesives. Acrylamide has been shown to cause cancer in laboratory rats when given in drinking water. The National Toxicology Program 'Ninth Report on Carcinogens states that acrylamide can 'reasonably be a human carcinogen'. Recent studies by research groups in Sweden, Switzerland, Norway, Britain and the United States have found acrylamide in certain foods. It has been determined that heating some foods to a temperature of 120° C (248° F) can produce acrylamide. Potato chips and French fries have been found to contain relatively high levels of acrylamide compared to other foods, with lower levels also present in bread and cereals.

#### **Anti Carcinogens**

Phytochemicals are biologically active naturally occurring chemical component in plant foods which act as a natural defence system protecting the plants from infection and microbial invasions and giving colour, aroma and flavour with more than 2000 plant pigments such as flavonoids, carotenoids and anthocyanins. Dietary source of phytochemicals include fruits, vegetables, legumes, whole grains, nuts, seeds, fungi, herbs and spices. As protection against cancer, plant based chemicals act to detoxify drug toxins, carcinogens and mutagens. These detoxification actions have overlapping and complementary mechanisms that include neutralizing free radicals and inhibiting enzymes that activate carcinogens. Phytochemicals may act as blocking or suppressing agents to reduce the risk of cancer. Blocking agents prevent the active carcinogen or tumour promoter from reaching the target tissue by several mechanisms, or a combination of mechanisms such as:

1. by inducing the activities of enzyme systems that detoxify carcinogens
2. by trapping and sequestering reactive carcinogens
3. by blocking cellular events required for tumour promotion.

Suppressing agents (whose actions are less well defined) may arrest carcinogenesis by acting on the cellular level preventing malignant expression of cells that have been exposed to cancer causing agents

#### **Limonooids:**

These are a subclass of terpenes found in citrus fruits like grapefruit and orange juice. They have been identified as chemopreventive agents that induce enzymes in the liver's phase I and phase II detoxification system. This system detoxifies carcinogens by making them more water soluble for excretion from the body.

#### **Phenols:**

These protect the plant from oxidative damage and include the subclass, flavonoids. More than 800 flavonoids are found in different plant species. Flavonoids scavenge free radical compounds, such as superoxide anion and singlet oxygen and sequester metal ions. One of the major flavonoids, quersetin is present in food such as red and yellow onions, broccoli, red grapes, apples, cereals and inhibits oxidation and cytotoxicity, by scavenging activated mutagens and carcinogens and thus may decrease the risk of cancer.

Isoflavonoids are a phenol subclass found in beans and other legumes, especially soybeans and soy foods. Some isoflavones (phytoestrogens) found in soy foods act as antioxidants, carcinogen blockers, or tumour suppressors and may exert a protective effect against hormone related cancer (e.g. Breast cancer) by reducing estrogen binding at receptor sites. Phytoestrogens may be useful in preventing or surviving prostate cancer as these compounds may act as estrogen-like agonist, preventing testosterone from accelerating tumour growth. In animal studies, soy isoflavones prolong the time of appearance of prostate cancer tumours. Epidemiologic studies have shown that, in population in which phytoestrogens intake is high, there is a decreased incidence of hormone related breast and prostate cancer.

#### **Thiols:**

Thiols are sulphur containing phytonutrients found in cruciferous vegetables, such as broccoli, cauliflowers, Brussels sprouts, kale and cabbage. Cruciferous vegetables contain a subclass of thiols identified as indoles, dithiolthions and isothiocyanates. These organosulphur compounds upregulate enzymes involved in the detoxification of carcinogens and other foreign compounds. The association between increased vegetable consumption and cancer risk is most consistent for cancer of lungs, stomach, colon and rectum. Organosulphur compounds are also found in the allium or onion family, which include garlic, shallots and leeks. The phytochemical in garlicks, the allyl sulphides, the other organosulphur compounds appear to prevent carcinogen activation. Allyl sulphides have several actions, including

1. increasing the production of glutathion S transferase, a phase II enzyme of the liver's detoxification system
2. inhibiting mutagenesis
3. increasing the activity of macrophages and T- lymphocytes.

#### **Lignans:**

Phytochemicals found in flaxseed, wheat, bran, rye meal, buckwheat, oatmeal and barley are the focus of research for their anticancer property and phytoestrogen presence. The richest source of lignans is flaxseed which contains 80-800 times more lignans than any other plant food. These plant lignans are converted to mammalian lignans by gut bacteria and have biological properties that include antimutagenic and antioxidative activity. Lignans behave as phytoestrogens that may have a protective effect against hormone sensitive cancers by virtue of their interference with the sex hormones metabolism. Animal studies have revealed that sex hormone binding globulins, which enhance the clearance of estrogen and may reduce the risk of hormone driven cancer is upregulated by lignans.

#### **Dietary fibers:**

Dietary fibers appear to exert an overall preventive effect on cancer risk. Insoluble fibers bind fat-soluble carcinogens and remove them from the intestinal tract. On the other hand, some soluble fibers may actually increase cancer risk. Soluble fiber polysaccharides such as gum Arabic and carrageen, widely used as stabilizers and emulsifiers in the food industry, have been postulated to increase the cancer risk. At least three mechanisms have been proposed for their action:

1. soluble fiber reduces the ability of insoluble fibers to absorb and excrete carcinogens
2. if carcinogen bound soluble fibers are digested by colonic bacteria, the carcinogen can be deposited on the mucosal cells
3. soluble fiber polysaccharide may cross the intestinal epithelium and carry with them carcinogen in solution.

#### **Ellagic acid:**

Caneberries, along with blue berries, strawberries and apples, contain ellagic acid, a naturally occurring organic acid that, according to medical studies inhibits the initiation of cancer cells induced by certain chemicals. In its natural form in fruits, ellagic acid is bound to glucose and may possibly protect plants against microbial infections. At present time, its primary function is still unknown. However, this acid has been reported to prevent "procarcinogens" from breaking down and may act as a trapping agent for carcinogenic metabolites. The naturally occurring phytochemicals present in caneberries include catechins, monoterpenes and phenolic acids. Catechins have been linked to low rates of gastrointestinal cancer and may aid the immune system, and lower cholesterol. Monoterpenes are cancer-fighting antioxidants that inhibit cholesterol production and aid protective enzyme activity. Phenolic acids are being studied for their help in aiding the body to resist cancer by inhibiting nitrosamine formation and affecting enzyme activity

#### **Conclusion:**

30% of cancers appear to be diet related and it is possible to prevent them by modifying the diets consumed. This is perhaps the most easiest, cheapest and probably the best approach to minimize cancer incidences in such a vast and diversely cultured country like India, where people have a wide variety of healthy food choices available to choose from.

High protein and high fat from animal sources are a major risk in cancer causation and it would be advisable to consume more of vegetables and minimize diet high in n-6-PUFA (Poly Unsaturated Fatty Acids). Recent evidences indicate fat as n-3-PUFA to be a major favourable determinant in several cancers like oral, oesophageal, large intestine, breast and ovary.

\* \* \*