Diet and Cancer

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Environmental and lifestyle factors, including diet, may be responsible for the recognised worldwide variation in the incidence of specific types of cancer. Chemical carcinogenesis is a multistage process occurring over a relatively long period of time. The mechanisms are complex as different factors are involved. Genetic damage develops following exposure to carcinogenic agents. Progression to malignancy is, at this stage, not inevitable. Specific agents are needed to ‘promote’, and induce ‘progression’ or inhibit subsequent changes to develop invasive malignancy. Understanding the roles played by different agents and mechanisms in the overall carcinogenic process for a specific cancer may form the basis for risk assessment and eventual prevention. The multistep process of carcinogenesis including initiation, promotion, and progression, are all needed for clinically invasive cancer to develop. Efforts directed to any of these phases can prevent the development of cancer.

A variety of carcinogenic and mutagenic substances are present in our diet. Some are found naturally in the food ingredients, whereas others result from pesticide residues, environmental pollution, food additives, preparation and processing procedures, and fungal contamination. The control of these factors may render some cancers potentially avoidable.

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The role of macro and micro-nutrients in the causation of cancer and eventually in its prevention is complicated by their combined distribution in food products. Intensive research into the nature of cancer prevention by nutrient components and their synthetic analogs is still in its infancy. As cancer induction, promotion and progression is a slow mechanism that could take many years, it is uncertain what time-period of dietary intake is most relevant. Currently, recommended prevention strategies include choose more/choose less approach, through emphasizing a shift away from high-fat, low-fiber foods that may increase cancer risks, toward foods low in fat and rich in fiber and nutrients.

**Key Words:** Cancer, diet, lifestyle.

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**INTRODUCTION**

Existing epidemiological studies show remarkable worldwide variation in the incidence of specific types of malignant disease. This variation is not only regional but also temporal, frequently associated with socio-economic changes. Pockets of both relatively high and low incidence of some malignancies could occur within the same country. This marked regional variation in incidence, is not exclusively due to ethnic or hereditary factors, but is most frequently associated with environmental and lifestyle factors. The term "lifestyle" refers to the national nutritional customs and factors such as cigarette smoking and other tobacco use. Doll and Peto in 1981 concluded that most common cancers in the developing world are related to environmental factors and are, thus, potentially avoidable.

Support for the influence of environmental and lifestyle effects came from studies of intercontinental migration. This has been associated with changes in incidence of different malignancies in the migrants to that of the country to which they have moved. The rate of change varies, for unrecognized reasons, in different populations and for varying malignancies. The evidence arising from migrant studies further proves that regional variations in the incidence of cancer could be due to some features of lifestyle in those regions. This hypothesis is supported by observing changes in the incidence of malignant disease in societies undergoing rapid change in their diet or lifestyle.

The worldwide difference in incidence, the temporal variations, the mortality figures for diverse cancers, and the altered risk for migrants from areas of low- to high-incidence, as well as the analysis of data obtained under controlled conditions in animal models have, in addition, confirmed the multiplicity of causative factors involved in most frequent human cancers.

The hypothesis that dietary factors can influence cancer risk, particularly in certain high-risk groups, is supported by both descriptive and analytic epidemiologic research. The results of epidemiologic and laboratory studies provide a rationale for intensive research into the nature of cancer prevention by nutrient components and their synthetic analogs.

**PRINCIPLES OF CARCINOGENESIS**

A brief understanding of the mechanism of carcinogenesis would help in unraveling the complex interaction of the different factors involved in this process. For the development of malignant disease at the cellular level, somatic mutation must occur in the DNA following exposure to carcinogenic agents. This somatic mutation involves translocation and amplification of specific genes that translate to a distinct expression of the properties of the cells bearing such altered genes. These genes are known as proto-oncogenes. Following several cell duplication-cycles, the genetic damage generally becomes irreversible.

A specific agent that induces mutations and DNA damage in a cell system is labeled
genotoxic. Almost all human carcinogens are genotoxic, with a potential cancer risk, if given in appropriate doses and adequate duration of exposure. Each human cancer has specific genotoxic carcinogens as causative factors. The genotoxic factors associated with human cancers include aflatoxin, and hepatitis viral infection for hepatocellular carcinoma, alcohol and tobacco smoking for carcinoma of the mouth, pharynx, esophagus and larynx, smoking, asbestos, and polycyclic hydrocarbons for cancer of the lung, and aromatic amines and smoking for bladder cancer. A genotoxic can be direct-acting, procarcinogen or an agent that can lead to DNA changes through alteration in replication. Direct-acting genotoxic chemicals are organic compounds such as ethylene imine and bis (chloromethyl) ether that interact with the nuclear DNA. Procarcinogens, on the other hand require conversion through metabolic activation into direct-acting compounds. These include chemicals such as vinyl chloride, 2-naphthylamine, 2-amino-3-methyl imidazo[4,5-f]quinoline nickel, dimethyl nitrosamine, chromium. Some inorganic carcinogens are not directly genotoxic, but can change the DNA by selective alteration in DNA replication.

Though genetic changes occur after exposure to genotoxic factors, progression to malignancy is not inevitable. These genetically-altered cells require specific agents to 'promote' and induce 'progression' to overt and invasive malignancy. Promoters do not interact with DNA, yet they enhance the process of carcinogenesis. They operate, under a variety of conditions, by promoting the mechanism of carcinogenesis or through other unknown mechanisms. A promoter is not genotoxic or carcinogenic, but it enhances the effect of the direct-acting and the procarcinogen agents. It cannot cause cancer without a preceding cell change. Its action requires their presence at high levels over a long period. Its effect is reversible, and is often tissue-specific. Recognized examples are the bile acids as promoters of colon cancer, and saccharin as promoter for cancer of the urinary bladder. Other agents acting as inhibitors of post-genetic-alteration carcinogenesis, operate in animal models and most likely in some forms of human cancer.

Delineating the role of each genotoxic carcinogen, cocarcinogen, promoter or inhibitor in the overall carcinogenic process for a specific cancer by uncovering the action mechanisms, may form the basis for risk assessment and eventual prevention.

**FOOD AND CARCINOGENESIS**

Worldwide observations suggest that lifestyle and lifestyle-related behaviour can cause and / or promote the development of cancer and may account for most neoplasms in man. The complexity of the mechanisms involved and the diverse etiologic factors have slowed progress in this area of research. Mechanisms of carcinogenesis as a basis for delineating and classifying risk factors, has just recently been disclosed, and helped in defining methods for detecting carcinogens in the broadest sense.

A variety of carcinogenic and mutagenic substances are present in our diet. Some of these substances are found naturally in the food ingredients, whereas others result from pesticide residues, environmental pollution, food additives, preparation and processing procedures, and fungal contamination.

Naturally occurring carcinogens include tannins, found in herbal teas; hydrazines, found in edible mushrooms; and safrole and related natural alkenyl benzene, found in flavorings and spices. Naturally occurring flavonoids, widespread in edible plants and fruits are mutagenic.

Fungal contamination of stored food can produce potent carcinogenic mycotoxins such as aflatoxin. In some areas of Africa, aflatoxin contamination of grain is implicated in higher than expected rates of liver cancer.

Nitrosamines constitute a significant source of carcinogens in the human diet. Nitrosamines
are produced from the interaction of nitrite with secondary or tertiary amines. Sodium nitrate and its bacterial reduction product, sodium nitrite, occur naturally in plants, meats, and dairy products. They also, are widely used as preservatives in smoked meat and salted fish. The Nitrosamines, such as dimethylnitrosamine, are potent carcinogens. Epidemiologic studies demonstrated an association between nitrate and nitrite consumption and the incidence of stomach and esophageal cancer. This finding could be of interest in Saudi Arabia, in view of the high incidence of esophageal cancer in some regions. The generation of nitrosamines in stored food or in the gut, can be reduced with ascorbic acid and other antioxidants.

A series of mutagenic heterocyclic amines that arise during the cooking of meat and in fish through pyrolysis, were recently identified by Sugimura. Pyrolysates of tryptophan, glutamic acid, and soybean are carcinogenic. Also found in charbroiled meat are polyaromatic hydrocarbons.

Other environmental contaminants in food include the growth promoter diethylstilbestrol, the pesticides DDT and chlordane, and the industrial pollutants arsenic, asbestos, heavy metals, and polychlorinated biphenyls.

Naturally occurring compounds found to have inhibitory effects on the growth of cancer include coumarins, phenols, indoles, aromatic isothiocyanates, alkyl benzenes, methylated flavones, plant sterols, selenium salts and protease inhibitors. Significant preventive antineoplastic activity also has been demonstrated with pharmacologic amounts of ascorbic acid, alpha-tocopherol (vitamin E), retinoids (vitamin A and derivatives), and beta-carotenes.

A variety of substances have been recognized as major sources of mutagens and carcinogens in the human diet. Large numbers of these substances are synthesized in edible plants, or are produced during the cooking or processing of food, or are used as food additives for preservation or flavor enhancement. Genotoxic, mutagenic, and carcinogenic derivatives, demonstrated in animal models, include dietary phenols, alkaloids and glycoalkaloids, isothiocyanates, alcohol, quinones, and cyclopropenoid fatty acids. Heterocyclic amines isolated from cooked proteins are potent carcinogens. Mycotoxins synthesized by a variety of molds contaminate human food, and several of these toxins are potent carcinogens. Aflatoxin, for example, contaminates grains, peanuts, and other stored foodstuffs and has been shown to be a human carcinogen in animal and human epidemiologic studies. Alcohol consumption has been associated with an increased risk of oral, pharyngeal, esophageal, and stomach cancer, especially in smokers. The degree of risk associated with these substances remains largely unknown.

In evaluating the risk of carcinogenesis, it is mandatory to realize that chemical carcinogenesis is a multistage process occurring over a relatively long period of time. This process can be modulated with many variables. Individual exposures to dietary carcinogens and mutagens vary in terms of dose, frequency, and duration. The necessity to define precisely the specific factors associated with each type of human cancer and determine the components that have genotoxic properties and those that have a promoting or enhancing effect is mandatory in understanding carcinogenesis and subsequently cancer prevention. The complexity of the carcinogenic risk posed to man by dietary carcinogens and mutagens, the possible modification of metabolic activation and detoxification mechanisms, the presence of other protective or inhibitory substances in the diet, as well as the impact of other lifestyle-related factors, cannot be overemphasized.

As cancer induction, promotion and progression is a slow mechanism that could take many years, it is uncertain what period of dietary intake is most relevant. Recalling the frequently changing and long term dietary information is

Diet and Cancer
usually imprecise. In addition, it is difficult to study national dietary habits by means of food groups rather than specific nutrients. As an example, foods high in beta-carotene are also high in other nutrients and may be low in fat.

The locally prevailing nutritional traditions in different regions account for the occurrence of specific types of cancer. Salted, pickled or smoked food is associated with the increased risk of cancers of the stomach in the Orient. The high-fat, low-fiber food in the West is related to risk of cancers of the colon, pancreas, breast, prostate, ovary and endometrium. The fat contents promote the risk of colon cancer while fibers reduce carcinogenesis presumably through dilution of promoters. The associated genotoxic carcinogens may be the heterocyclic amines formed during cooking of meat.

In spite of the complexity of the inter-relation of the varying food groups, a presentation of the evidence for carcinogenicity of the different groups is feasible.

**CARBOHYDRATE**

The relationship between carbohydrates and cancer is not confirmed. Studies of an increase in the incidence of liver cancer with a high intake of potatoes and gastric and esophageal cancer with a high intake of starch have been reported.

**PROTEIN**

Epidemiological studies have suggested a possible correlation of high-protein diets with increased risk of cancers of the breast, colon, pancreas, and prostate. Nonetheless, the close inter-relationship between the intake of protein and fat in Western diet, renders data analysis rather difficult to interpret. In general, protein has no effect at or below the levels required for optimum growth.

**FAT CONSUMPTION**

Comparisons of the fat intake in various countries show that populations with the highest per capita fat consumption have the highest breast cancer mortality. This correlation has been confirmed in studies of 39 countries. Willet on the other hand found no relationship between dietary fat and breast cancer incidence in a study of 90,000 nurses. The limited variation in the fat intake of the population between 32% and 44% of total calories, might explain the absence of a correlation. Low fat intake of 15% seen in some societies might explain the international variation and the recognized correlation with the incidence of breast cancer.

Weaker correlations were shown for fat intake and cancer of the colon. The relationship of fat consumption and colon cancer is contradictory. Data suggest that factors other than fat, such as dietary fiber, may influence colon cancer risk. It is possible that dietary fiber modifies the promotion of the incidence of colon cancer by dietary fat.

Studies of the type of dietary fat implicated in cancer reflects the complexity of the issue. Not all fats have identical effects. The omega-6 polyunsaturated lipids, effective in lowering serum cholesterol, are more efficient promoters than saturated fats such as lard or beef fat. Monounsaturated oils such as olive oil have little promoting effect, and omega-3 polyunsaturated-rich fish oils appear protective. High-fat diets rich in linoleic acid, found in corn, safflower, sunflower, and other vegetable oils, may act as tumor promoters, while high-fat diets rich in oleic acid, from olive oil, and eicosapentaenoic acid, in fish oils, do not promote cancer in animals and may be protective. These differences may explain the low incidence of breast and colon cancer in the Eskimos, whose main fat source is fish, and in Greece and Spain, whose main fat source is olive oil. A recent Belgian study concluded that there is a relationship between dietary oligosaccharides, not fat, and the risk of colorectal cancer.

Berg is of the opinion that the cancers found in developed countries might be due to general overnutrition rather than to any specific...
nutrient. The role of caloric restriction in carcinogenesis is gaining much support. Fat-containing diets are calorically dense. Fats and oils have identical caloric content and caloric availability. The dramatic difference in promoting breast or colon cancer cannot be explained by calories alone. Dietary restriction experiments have demonstrated a lower breast and colon cancer incidence even with high-fat diets. A study of colon cancer in three socioeconomic groups in Hong Kong, revealed that the most affluent group ingested more total calories and more fiber and vitamins, yet had twice the tumor incidence of the least affluent. Reduction of energy intake may be one way in which dietary fiber influences colon cancer.

FIBER

Diet fibers made up of specific components, including cellulose, hemicellulose, pectin, gums, and lignin, are difficult to quantify accurately in foods and thus may have varying effects. With the exception of lignins, fibers are carbohydrate in nature. Fiber may be insoluble as with cellulose and wheat bran, or soluble as with pectin and guar gum. Each fiber substance has a unique chemical structure and individual physiological effects.

Though most international and national studies identified a protective association between dietary fiber and the risk of colon cancer, other studies show no association, and a few studies indicate increased risk. These inconsistent findings may be explained by the heterogeneity of the dietary fibers from different food sources. Wheat bran appears to inhibit colon cancer development in animal models more consistently than other fiber sources. More information is needed with regard to the physiologic properties of the different fiber components and their protective effects.

A possible protective role of fiber against large bowel cancer was first suggested by Burkitt. The low colon cancer rates in US Mormons and Seventh-Day Adventists and rural Scandinavians, correlate with the higher intake of fiber-rich foods than in the general population.

The mechanisms suggested for the inhibitory effect of fiber on colorectal carcinogenesis include; fecal bulk increase resulting in the reduction of fecal mutagen concentrations, the enhancement of colonic transit time and the reduction of the period of colonic mucosal exposure to fecal mutagens and possible changes in colonic pH or bacterial metabolism which reduces mutagen formation.

ETHANOL CONSUMPTION

Most studies on the correlation of ethanol consumption and cancer are limited by the difficulty of obtaining an accurate history of alcohol intake. In developed countries, alcohol consumption is widespread and represents a significant component of dietary intake for some individuals. Recent studies show that high alcohol intake is associated with an increased risk of several types of cancer, such as cancer of the esophagus, pharynx, larynx, and mouth. These cancers are also associated with smoking. A recent prospective study showed that colorectal cancer is associated with excessive beer drinking. An increase in breast cancer has been reported with moderate drinkers compared with nondrinkers, especially for women who drank before the age of 30 years, regardless of later consumption levels.

Based on an analysis of epidemiologic studies, the International Agency for Research on Cancer considers the evidence sufficient for categorizing alcoholic beverages as carcinogenic. The most compelling studies showed enhanced cancer risk when alcohol is present as a cocarcinogen such as in combination with cigarette smoking.

A more precise evaluation of alcohol carcinogenicity is limited by the fact that the ethanol source is variable. Beer, wine, distilled spirits, and locally prepared beverages contain
multiple constituents with potential biologic activity. Although ethanol is not a mutagen in fermented preparations, it is frequently accompanied by mutagenic constituents. Associated impaired nutritional status may also influence cancer risk. Decreased levels of some micro nutrients, especially vitamin A and carotenoids, may be linked to cancer development. The frequent hepatotoxicity associated with ethanol consumption, may interfere with the successful metabolism and excretion of potentially carcinogenic agents.

MICRO NUTRIENTS

The study of the role of micro nutrients in the causation of cancer and eventually in its prevention is complicated by their combined distribution in food products. Prevention of human cancer requires the definition of optimal levels of recommended daily allowances of micro nutrients. A brief summary of the roles of a number of micro nutrients recognised for their effectiveness is presented.

**Vitamin A:** Vitamin A (retinol) and its isomers, derivatives (retinal, retinoic acid), and synthetic analogs have been studied experimentally. It is required for the proper growth and differentiation of epithelial tissue, bone, reproduction, and vision. Retinol and its isomers directly modify the expression of a neoplastic phenotype, and arrest the dedifferentiation of a cell. The mechanism of the action of vitamin A in its numerous physiologic roles has not been fully identified. A significant increase in cancer risk at various sites was associated with diminished vitamin A intake. Risks reported for the groups with low vitamin A intake were about twice those for the high intake groups.

**Vitamin C:** Inhibition of carcinogen formation has been demonstrated with ascorbic acid in both humans and experimental animals. Epidemiologic data suggest an inverse association between ingestion of foods containing vitamin C and the development of cancer of the esophagus and stomach. It is possible that vitamin C inhibits nitrosamine formation from secondary and higher amines in combination with nitrite. The exact mechanism is difficult to prove as vitamin A, betacarotene, and vitamin C are present together in many fruits and vegetables, and the epidemiologic studies in most cases do not allow a clear distinction of the dietary factor responsible for potential benefits.

**Vitamin E:** Vitamin E is difficult to study epidemiologically because of its varying distribution. Varying observations of its impact on the incidence of cancer have been reported by Willett and Menkes.

**Calcium and vitamin D:** Both agents were reported to have an inverse, though disputed association with colorectal cancer in a 19-year prospective study in humans. The lower colon cancer risk seen in Finland may be related to the customary higher intake of calcium-rich dairy products and the effect of cereal fiber.

**DIET AND SPECIFIC CANCER SITES**

**Cancer in Endocrine Sensitive Organs**

The development of cancer in the endocrine-sensitive tissues including breast, ovary, endometrium, and prostate, is likely to be related to hormonal control and balance. An overview of the entire complex, feedback-controlled interaction of the hormones of the ovary, testes, adrenals, thyroid, liver and kidney concerned with steroid hormone metabolism is necessary. Nutritional factors, particularly fats and proteins, control endocrine metabolism and balance. The interaction between dietary elements and specific hormone levels in relation to cancer of the endocrine-related organs has not been determined.

Yet it is clear that low-risk situation for these cancers is where the total fat intake is relatively low, the main fat component of the diet being monounsaturated fat such as olive oil, with the diet rich in omega-3 polysaturated fatty acids as
in fish oils, or a combination of all these factors. These factors are particularly significant during the development of the endocrine system at puberty. In addition, the effect of dietary change from high risk to low risk can occur at any age because of the reversibility and flexibility associated with endocrine systems. The recent decline in fertility rates and the continued Westernization of diets in developing countries, with the increased consumption of protein and animal fats might be causing breast cancer to become proportionately more important.

**Colon cancer**

The incidence of cancer of the ascending colon and cecum is uniform around the world. It does not seem to be associated with any dietary factors. On the other hand, cancer of the descending colon and the sigmoid junction seem to be associated with the type and amount of fat consumed. This could be due to cholesterol biosynthesis and total bile acid flow acting as a promoter in this site. As promoters are highly dose dependent, reducing the concentration of bile acids by lowering fat intake could lower colon cancer risk. The use of high fiber diet results in an increase in stool bulk and thereby dilutes the concentration of bile acids in the gut, and finally reduces the promoting potential. Some vegetables and fruits provide different types of fiber that do not necessarily increase stool bulk as does cereal. Fecapentaenes, direct-acting mutagens, have been observed in the stools of 10-20% of people consuming a typical Western high-fat, and low-fiber diet. Bile acids and anaerobic storage stimulate the formation of fecapentaenes. For this purpose, the frequent consumption of different kinds of vegetables and fruits is desirable.

**Gastric Cancer**

High risk population for gastric cancer usually have diets of dried salted fish, pickled vegetables, and smoked fish and low quantities of seasonal fresh fruits and vegetables. This diet is usually associated with lower intake of vitamins C, E, and A. The active carcinogens may be nitroso indoles or diazonium compounds formed from nitrite and specific substrates. Vitamins C and E may block the formation of such agents. Salt may act as a cocarcinogen.

**CONCLUSIONS AND RECOMMENDATIONS**

Carcinogenesis is a long term process that follows specific successive steps of initiation, promotion, and progression. These steps are all needed for clinically invasive cancer to develop. Prevention, henceforth would be directed towards any of these 3 phases.

Lifestyle is a factor for preventing the disease and for patient survival. Lifestyle adjustment minimizes the risk of chronic disease. Dietary restriction reduces cell cycling in major organs and depresses cancer development. The frequency of cell cycle controls the sensitivity of cells to genotoxic carcinogens. This finding links many previously unrelated phenomena.

To reduce the overall incidence of some specific cancers, simple strategies are suggested. One of these is a choose more/choose less approach, developed by NCI. This approach does not preclude the use of any food, rather, it emphasizes a shift away from high-fat, low-fiber foods that may increase cancer risk toward foods that are low in fat and rich in fiber and nutrients. The current recommendations are that: Tobacco in any form should not be used; smoking, chewing, or snuff dipping be stopped. The total fat intake be adjusted to about 20% of calories, mostly of monounsaturated oils. These lipids reduce the risk for heart disease and cancer. Fish be consumed several times a week. The intake of salted, pickled or smoked foods be reduced. Intake of cereal bran fiber foods be increased. Intake of calcium with low-fat dairy products such as skim milk, or low-fat yogurt be increased. More vegetables and fruits, as sources of vitamins, minerals, and fibers be eaten. Obesity should be avoided and an adjustment of the overall energy intake energy needs to be made. Weight control is an important health-promoting disease-prevention action. The role
of certain lipids in increasing cancer risks is undeniable, confirming the benefit of limiting fat intake to 20% of calories. Regular exercise, but only after a health check-up certifying normal blood pressure and serum cholesterol levels, to ensure cardiovascular patency. There should be no consumption of ethanol beverages.

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