Nutritional Carcinogenesis

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ABSTRACT

Human beings are often being exposed to carcinogenic factors during their life, some of which are the nutritional factors. From the mechanistic view, nutritional factors are classified into genotoxic and non-genotoxic agents. Genotoxic agent begins their action at the DNA level, causing DNA damage through several mechanisms, e.g. gene point mutations, deletions and insertions, recombinations, rearrangements and amplifications, as well as chromosomal aberrations. Most genotoxic agents are micro components of nutrition, i.e. polycyclic aromatic hydrocarbon (PAH) or heterocyclic amines (HCAs), aflatoxin, and N-nitrosamine. Non-genotoxic agents are less defined in their modes of action, but they are presumed to indirectly affect the cell through tumor promoters. These agents are generally macro components, e.g. high fat. Moreover, epigenetic factors, including changes in the DNA methylation pattern, and peroxidation process resulting reactive oxygen species (ROS), are also known to cause cancer. On the other hand, it is also well recognized that diet and nutrition contain components that can reduce the risk of cancer, in some cases by decreasing the effects of food mutagens, or through carcinogen detoxification, or protection of DNA from electrophilic carcinogen. Thus nutritionally related cancer ultimately develops from an imbalance of carcinogenesis and anti-carcinogenesis process.

Key words: *nutrition, carcinogenesis, cancer.*

INTRODUCTION

Cancer is a major burden of disease worldwide not only in developed countries but also in developing countries. Each year, tens of millions of people are diagnosed with cancer around the world, and more than half of the patients eventually die from it.[1,2] Moreover cancer rates could further increase by 50% to 15 million new cases in the year 2020, according to the World Cancer Report.[3] It is known that about 5-10% of all cancers are caused by genetic defects, while the rest of 90-95% are caused by environmental factor and lifestyle, including diet (30-35%), tobacco smoking (25-30%), and alcohol (4-6%).[4] Each year, about 550,000 Americans die of cancer; fully one-third of these deaths are linked to poor diet, physical inactivity, and obesity.[5,6]

Several lines of evidence indicate that diet and nutrition can contribute to human cancer risk.[7] The heterocyclic amines produced during the cooking of meat are carcinogenesis. Other compounds in food such as aflatoxin B1, polycyclic aromatic hydrocarbons, N-nitrosamines and alcohol are suspected as mutagen.[4,7] In addition, excessive calories and fatty acid intake also raise the cancer risk. Those data are supported by the other literature mentioning that nutrition and dietary carcinogen together constitute one of the three major causes of carcinogenesis, besides the tobacco smoking, and infections-inflammations.[8-10]

When considering human diets, it should be recognized that food contains both mutagens and components that decrease cancer risk.[7,11] Dietary constituents reduce the risk, in some cases by decreasing the effects of food mutagens, or through carcinogenic detoxification, or protection of DNA from electrophilic carcinogen. Futhermore, nutritionally related cancer ultimately developed from an imbalance of carcinogenesis and anti-carcinogenesis process.[7] This knowledge could be used to suggest a diet modification and eventually the cancer incidence could be lessened.

CARCINOGENESIS PROCESS: DIET AND NUTRITIONAL FACTORS

Human beings are often being exposed to carcinogenic factors during their life, whether they realize it or not. These factors are divided into endogenous (genetics, immunologic disturbances, endocrine imbalance) and exogenous factors (environment, physical, biologic, or chemical agents, nutrition and lifestyle).[13-15]

It was long discovered that the carcinogenesis process is complex and multistep process of which several genetic and molecular defects are needed to manifest as cancer. The three stages of carcinogenic process are initiation, promotion, and progression as described in the **Figure 1**.[12,15-18] The carcinogenesis itself is the result of oncogene activation and tumor suppressor gene inactivation.[19]

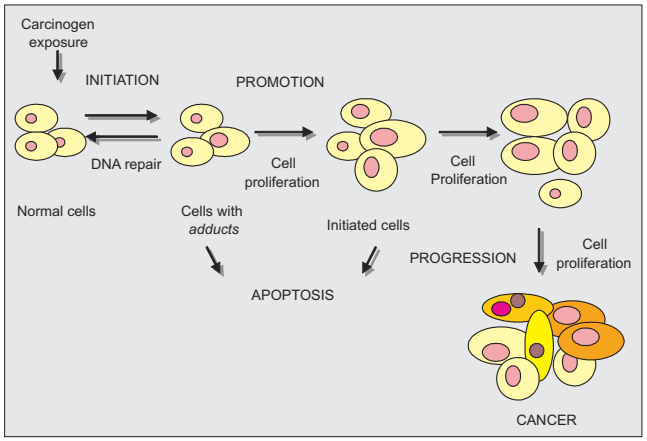

Figure 1. The stages of carcinogenesis[12]

From the mechanistic view of carcinogenesis, food mutagens are classified as genotoxic and non-genotoxic agents.[8,15] Genotoxic agents begin their action at the level of DNA, causing DNA damage through several mechanisms, e.g. gene point mutations, deletions and insertions, recombinations, rearrangements and amplifications, as well as chromosomal aberrations. Most genotoxic agents are microcomponents of nutrition, i.e policyclic aromatic hydrocarbon (PAH) or heterocyclic amines (HCAs), aflatoxin, and N-nitrosamine.[7,8,12] Non-genotoxic agents are less defined in their modes of action, but they are presumed to indirectly affect the cell through tumor promoters. These agents are generally macrocomponents, e.g. high fat. Non-genotoxic agents together with the genotoxic agents are increasing the risk of carcinogenesis, though usually a higher and longer exposure is needed.[8] The scheme of metabolic activation subsequent from carcinogen exposure and the genotoxic and non-genotoxic modes of action are shown in the **Figure 2**.

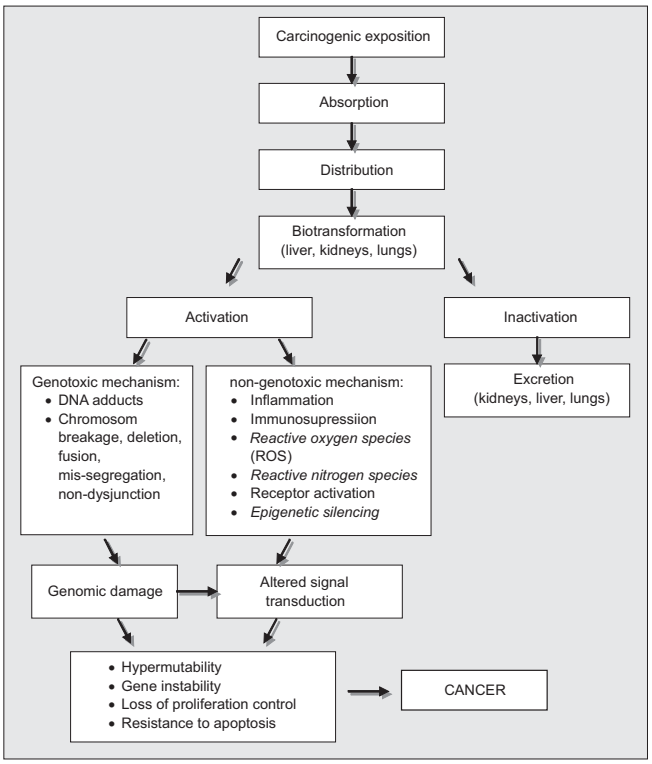

Figure 2. Metabolic activation of chemical compounds and genotoxic and non-genotoxic effects of carcinogens[12]

Food mutagens absorbed orally pass through the liver and are distributed in the body.[20,21] Those carcinogenic compounds are classified as direct act directly on DNA, but most require enzymatic conversion and are thus labeled as indirect or procarcinogens.[22-26] Metabolic activation of procarcinogen is controlled by phase I reactions, while phase II reactions protect the body through the transformation of activated compounds into inert products which are easily eliminated from the body.[7,12,27] Sometimes, the chemically modified mutagens that are more reactive (electrophilic) bind to DNA rather than the excretory carrier molecules. This binding can then cause coding errors at the time of DNA replication.[7,22,23,25] Metabolic activation occurs predominantly in the liver at the endoplasmic reticulum where the cytochrome P450 (important enzyme in phase I reactions) is more abundant. The results are powerful electrophilic product capable of establishing interaction to the nucleophilic component (DNA, RNA, and proteins), alter the structural integrity, and forming covalent bounding, called as adduct.[28,29] If the adduct being produced by metabolic activation is not able to be repaired by DNA repair before the replication process, then a mutation in

protooncogene and tumor suppressor gene will occur – a very important step in carcinogenesis initiation.[29]

On the contrary, non-genotoxic carcinogens do not need metabolic activation, do not react directly with DNA, and do not raise adducts; they act as promoters and modulate cell growth and cell death, and are potential to have the effect of genotoxic carcinogens.[23,29] One example is 12-*O*-tetradecanoilphorbol-acetate (TPA), which is a micro component, while the others are usually macrocomponents of nutrition.[8]

Mutagenesis is not the only pathway that links dietary exposures and cancers. There is growing evidence that epigenetic factors including changes in DNA methylation patterns are causing cancer and can be modified by dietary components.[7] Also there is peroxidation process that creates reactive oxygen species (ROS). ROS free radicals are causing damage to DNA, RNA, and proteins through a chain of chemical reactions, such as oxidation, nitration/nitrosation, and halogenation,[7,12] thus adding potential events of mutation and alteration to important proteins and enzymes.[30]

SEVERAL CARCINOGENIC AGENTS AND THE SOURCE FROM DIET

Several substances contained in human diets have been identified as food mutagens, some of which are described below.

Aflatoxin B1

Aflatoxin is a kind of mycotoxins produced by the mold *Aspergillus flavus*, which can be found in legumes, corns, soybeans, rice, milk, and cheese. In animal models, aflatoxins B1 (AFB1) had been proved to induce liver cancer. The mechanism of action of AFB1 begins with metabolic activation of cytochrome P450 to *exo*-8,9-*exposide*, of which then produce adducts that modified DNA. Moreover, adducts interaction with guanine will create mutational effects to p53 tumor suppressor gene, causing GC transversion into TA at specific codon 249. This transversion is almost found in liver cancer patients with high levels of aflatoxins contamination.[7,8]

Heterocyclic Amines (HCA)

Heterocyclic amines (HCA) are the carcinogenic chemicals formed within muscle meats during most types of high temperature cooking, through a pyrolisis process from amino acids, proteins, and creatines. These substrates could not be found in uncooked meats.[7,30-34]

There are about 17 different HCAs resulting from the cooking of muscle meats that may increase cancer risk. One of the most common is the 2-amino-1-methyl-6-phenylimidazole [4,5-*b*] pyridine (PhIP). PhIP induces tumors of the breast, colon, and prostate. HCA carcinogenesis mechanism begins through bioactivation of *N*-hydroxilation by cytochrome P450, especially CYP1A2, followed by esterification, resulting nytrenium ions – an ultimate carcinogen, capable of binding guanin at position C8, causing altered DNA sequences with subsequence base substitution, deletion, and insertion.[7,8]

HCA formation is influenced by four factors: type of food, cooking method, temperature, and time.[30-33] HCA are found in cooked muscle meats (beef, pork, of fish). Other sources of protein (milk, eggs, tofu, and organ meats such as liver) have very little or no HCA content naturally or when cooked. Cooking method, such as frying, broiling, and barbecuing produce the largest amounts of HCAs; *oven*, *roasting*, and *baking* produce smaller amount of HCAs, while stewing and boiling produce negligible amounts of the chemicals. Temperature is the most important factor in the formation of HCAs. The higher the temperature, the more HCAs is produced. It explains why frying, broiling, and barbecuing, which are done at above 200°C, create higher amounts of HCAs compared to stewing and boiling, which are done at or below 100°C. Foods that are cooked at longer time ("well-done" instead of "medium") will also form slightly more of the chemicals.

However, HCAs exposure can be reduced by varying methods of cooking meats, especially by stewing and boiling, and having the meats partially cooked by microwave, before frying, broiling, or barbecuing.[8]

Polycyclic Aromatic Hydrocarbons (PAH)

PAH compounds are formed during incomplete combustion of organic matter. Smoked foods, e.g. ham, sausages, and fish may contain PAH, resulting from incomplete combustion in food processing. These compounds are also commonly found in tobacco smoking. In laboratory animal studies, diets with PAH consistently induce foregut tumors and can also induce lung tumors. In humans, there is some evidences for association of dietary PAH exposure with colon cancer. Animal and human studies suggest that dietary PAH is distributed to organ besides the locally exposed tissues, so it is plausible to consider that dietary PAH may contribute to lung or breast cancer risk, for example.[7]

Benzo(a)pirene is the best-characterized PAH compound available from the diet. Carcinogenesis mechanism is conducted through BaP adduct formation, after being activated by CYP1A and CYP1B enzymes. BaP adduct is associated with site-specific hotspot mutations in the p53 tumor suppressor gene. The

mutations are observed in lung cancer of smokers.[7]

N-Nitrosamines

Both nitrate and nitrite are capable to form nitrosamines, a large group of compounds with common carcinogenic mechanism. Humans are exposed to N-nitroso compounds in diet from a variety of cured meats and fish products. Sodium nitrite has been used as food addictive for preservation and as coloring substance in meat. N-nitrosamines may also derived from nicotine of tobacco smoking.[35,36]

Cancer of the lung, liver, kidney, mammary gland, stomach, pancreas, bladder or esophagus has been observed and these sites are also considered to be the targeted organs.[37] The common carcinogenic mechanism of N-nitrosamines is associated with formation of N-nitrosodimethylamine, which undergoes enzymatic hydroxylation and subsequent hydrolysis to aldehyde and monoalkylnytrosamide that rearranges and releases a carbocation that is reactive toward DNA bases. The hydroxylation is catalyzed mainly by CYP2E1.[7]

Alcohol

Epidemiological data have identified chronic alcohol consumption as a significant risk factor for upper alimentary tract cancer, including cancer of the oropharynx, larynx, esophagus, and of the liver. The increased risk in the large intestine and in the breast is much smaller. However, although the risk is lower, carcinogenesis can be enhanced with relatively low daily doses of ethanol.[38]

The exact mechanisms by which chronic alcohol ingestion stimulates carcinogenesis are not known. Experimental studies in animals support the concept that ethanol is not carcinogen but under certain experimental conditions is a cocarcinogen and/or tumor promoter. The metabolism of ethanol leads to the generation of acetaldehyde (AA) and free radicals. Evidence has accumulated that acetaldehyde is predominantly responsible for alcohol associated carcinogenesis. Acetaldehyde is carcinogenic and mutagenic, binds to DNA and proteins, destructs folate and results in secondary hyperproliferation. It has also been shown that AA interferes with the DNA repair process, where it directly inhibits O6 methyl-guanyltransferase, an enzym important for the repair of adducts caused by alkylating agents. Moreover, individuals with polymorphism tend to accumulate acetaldehyde products, resulting in increased cancer risk. Other mechanism is through the induction of cytochrome P-4502E1 (CYP2E1) that is associated with increased free radicals generation and activation of procarcinogens compounds contained in the alcoholic beverages to their ultimate carcinogens.[38]

In heavy drinkers, the entire nutritional status is usually impaired due to primary and secondary malnutrition. Various deficiencies of vitamins and trace elements that have been shown to have protective effects, such as methyl-, folate, vitamine E, selenium and zinc, may contribute to alcohol-associated carcinogenesis.[38] Chronic alcohol consumption also induces hepatic cirrhosis, which is a major etiological risk factor for hepatocarcinogenesis. Thus, it can be concluded that all those mechanisms are working together to stimulate carcinogenic process.[38]

Various type of carcinogens, mechanism of action, and affected organs are summarized in the **Table 1**.[7,8,12,30-38]

Table 1. Various type of carcinogens, their mechanism of action, and affected organs[7,8,12,30-38]

Group	Compounds	Mechanism of action	Affected organs
Polycyclic aromatic hydrocarbon (PAH)	Benzo[a]pyrene	Form adducts with purine bases of DNA, mainly resulting on transversion	Stomach, colon, lungs, breast
Heterocyclic amines (HCA)	2-amino-1-methyl-6-phenylimidazole [4,5-*b*] piridin (PhIP)	Form adducs with DNA bases	Stomach, colon, breast, prostate
N-nitroso compounds	*N*-nitrosodimethylamine	Form *adduct* at N- and O- atom in DNA bases	Liver, lung, kidney, oral, larynx, esophagus, stomach
Natural carcinogens	Aflatoxin B1	Form *adduct* with guanine, reacts with RNA and protein	Liver
Alcohol	Acetaldehyde	Oxidative stress DNA repair inhibition Form *adduct*	Oropharynx, larynx, esophagus, liver, colon, and breast

MACROCOMPONENTS

Total Calorie Intake

Excess calorie intake has been known to contribute to increase risk of several cancers, e.g. breast, colon, and prostate cancer. Digestion, absorption, metabolism, and excretion of fat deposits require oxidative metabolism, which create free radicals capable of causing DNA damage.[8]

Obesity is a well-established risk factor for several cancers. Estimation from American Cancer Society study, suggests 14% of all cancer deaths in men and 20% of all cancer deaths in women from a range of cancer types are attributable to excess body weight. Significant positive associations were found between obesity and higher death rates for the following cancers: esophagus, colon and rectum, liver, gallbladder, pancreas, kidney, stomach, prostate, breast, uterus, cervix, and ovary. Based on the cohort study, it was estimated that over 90.000 cancer deaths per year could be avoided if all the adult population maintained a normal weight (BMI<25.0). A recent meta-analysis of 14 experimental studies found that energy restriction resulted in a 55% reduction in spontaneous tumors in laboratory mice. The recommended calorie restriction is to eat a reduced amount of food (about 70-80% of the amount required to maintain "normal" body weight) while still consuming all of the necessary amounts of vitamins, minerals, and other necessary nutrients. The only restriction is the total amount of energy (calories) that is consumed.[39]

The positive correlation between obesity and cancer suggested to be driven by white adipose tissue that accompanies obesity, possibly through excess secretion of adipokines, such as leptin and adiponectin. Recent studies in fatless mice, which have undetected adipokines level but display accelerated tumor formation, suggest that adipokines are not required for the enhanced tumor development. This study also indicates that some other factors have roles in obesity-link cancer. Those factors are IGF-I and proinflammatory cytokines.[40]

The involvement of insulin-like growth factor I (IGF-I) in cancer was first documented when *in vitro* studies showed that IGF-I enhances the growth of cancer cell lines. IGF-I acts directly on cells via the IGF-I receptor (IGF-IR), which is over expressed in many tumors, or indirectly by cooperation with other cancer-targeted molecules, such as the p53 tumor suppressors. Diet-induced obesity in the mouse leads to enhanced tumor growth as well as insulin resistance, increased IGF-I, and decreased IGF binding protein-1, resulting in enhanced IGF-I signaling.[40]

Fatty Acids

Animal fat rich in saturated fatty acids and plant-derived oils, like corn oil, sun-flower seed oil, which are rich in linoleic acid, one of the n-6 polyunsaturated fatty acids (PUFA)/ arachydonic acid are suggested to enhance cancer development. Increased levels of linoleic acid in the erythrocytes of premenopausal women are related to increase risk of breast cancer. In contrast, n-3 PUFA (linolenic acid), which derives from fish oils, especially EPA and DHA, and n-9 monounsaturated fatty acids (MUFA) / oleic acid, like olive oils are known to have protective effects against carcinogenesis.[41] Higher ratio of n-3 and n-6 has been observed in several studies to decrease risk of breast cancer.[42]

It has been hypothesized that cancer is the result of a failure of immune surveillance to recognize and to eliminate cells that have undergone neoplastic transformation. Although mechanism by which dietary fatty acids affect tumorigenesis are likely multifactorial, evidence suggests that modulation of host immune functions by different eicosanoid metabolites that are regulated by dietary fatty acids may be an important factor. Evidence also suggests that dietary fatty acids may influence tumor metastatic cascade by eicosanoid metabolites via specific regulation of the process involved in metastatic cascade such as tumor-endothelial cell adhesion, proteolytic enzyme activity, and gap junctional intercellular communication.[41]

Cancer Prevention

Based on data from the American Institute for Cancer Research and World Cancer Research Fund, it is estimated that around 30-40 percent of all cancers could be prevented by healthy life styles and a good diet pattern.[42]

Steinmetz and Potter reviewed the relationship between fruits, vegetables, and cancer in 206 human epidemiologic studies and 22 animal studies. They found that greater vegetable and fruit consumption are consistent to have a protective effect for cancers of the stomach, esophagus, lung, oral cavity and pharynx, endometrium, pancreas, and colon.[43] Several levels of evidence for decreased risk of various types of cancer with consumption of fruits and vegetables are shown in **Table 2**.

Table 2. Levels of evidence for decreased risk of various types of cancer with consumption of fruit and vegetables[44]

Cancer types	Level of evidence
Stomach, esophagus, oral and pharynx, colon, rectum, lung	I
Larynx, pancreas, breast, bladder	II
Ovarium, endometrium, cervix, thyroid, prostate, kidney, liver	III

There are many substances that are protective in fruits and vegetables, so that the entire effect is not very likely to be due to any single nutrient or phytochemical. Several substances known to have protective elements are: isothiocyanates, allium compounds (garlic), isoflavon, phytosterole, vitamin C, D, folate acid, beta carotene (and other carotenoids) lycopene, selenium, vitamin E, flavonoids, and dietary fiber.[44-45]

I*sothiocyanates* and *diallyl sulfide* are known to be one of anticarcinogenic compounds due to its action on suppressing carcinogenesis activity and detoxing carcinogenic compounds. Detoxication is conducted through increased level of GST and UDP-glucuronic transferase enzyme, which metabolizes the carcinogenic compounds and help those excreted from the body. The primary sources of isothiocyanates are cruciferous vegetables, like cauliflowers, cabbages, and broccoli. Diallyl sulfide, an organosulphur compound in garlic, works as inhibitor in mutation of cytochrome p450 2E1, which metabolizes ethanol, acetone, and other carcinogen compounds, such as HCA, *N*-nitrosamine, and dimethylhydrazine.[8,45]

Folic acid is the dark green leafy vegetable vitamin. It has an integral role in DNA methylation and DNA synthesis. Folic acid works in conjunction with vitamin B-6 and vitamin B-12 in the single carbon methyl cycle. If sufficient folic acid is not available, uracil is substituted for thymidine in DNA, which leads to DNA strand breakage.[42]

Many studies have found a significant reduction in colon, rectal, and breast cancer with higher intakes of folic acid and their related nutrients (vitamin B-6 and B-12). However, folate may be more important for rapidly dividing tissue, like the colonic mucosa. Therefore, the cancer risk associated with low folate intake is higher for colon cancer than for breast cancer. Most breast cancer studies only found a protective effect of folate among women who consumed alcohol. It is probably because alcohol is an antagonist of folate, so that drinking alcoholic beverages greatly magnifies the cancer risk of a low-folate diet.[41,46]

Lycopene, a predominant carotenoid in tomato products, is a potent antioxidant in chemical reactions. The mechanism of action of lycopene is known to have a protective role in carcinogenesis, especially in prostate cancer. Lycopene is usually found in red color fruits, such as tomatoes, with higher bioavailability found in cooked tomatoes than that in too raw tomatoes.[47]

Some of recommendations for a healthful pattern of nutrition and maximum lifetime benefit from the American Cancer Society, are mentioned as follows:[48]

1. Maintain a desirable body weight
2. Eat a varied diet
3. Include variety of both vegetables and fruits in daily diet
4. Eat more high fiber foods, such as whole grain cereal, legumes, vegetables and fruits
5. Cut down on total fat intake
6. Limit consumption of alcoholic beverages
7. Limit consumption of salt-cured, smoked, or nitrite-preserved foods

CONCLUSION

Diet and nutritional factors are one of several major causes of carcinogenesis. Carcinogenic processes themselves are known to involve multi steps process (initiation, promotion, progression) and influenced by various factors. Food mutagen is working through genotoxic and non-genotoxic pathway in carcinogenesis. Genotoxic pathway works on the level of DNA causing DNA damage. Moreover, non-genotoxic pathway pathway affects the cell through tumor promoters such as inflammation, immunosupression, free radical and so on. More exposure to both pathways, more risks of carcinogenesis. On the other side, diet and nutrition also have protective roles against cancer. Hence, a good knowledge of diet, nutritions, and lifestlyes are important to reduce cancer risk in the society.

REFERENCES

1. Ma X, Yu H. Global burden of cancer. Yale J Biol Med. 2006;79(3-4):85–94.
2. Farrakh A. The global burden of cancer [serial online]. 2007 [cited 2 Jun 2009]. Available online on URL:http://www.cancer.gov/newscenter/benchmarks-vol7-issue2.
3. WHO. Global cancer rates could increase by 50% to 15 million by 2020 [serial online]. 2003 [cited 2 Jun 2009]. Available online on URL:http://www.who.int/mediacentre/news/releases/2003/pr27/en/.
4. Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res. 2008;25(9):2007-116.
5. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statics. CA Cancer J Clin. 2002;55:74-108.
6. Anon. Diet and physical activity: What's the cancer connection? [serial online]. Oct 2009 [cited 25 Jan 2009]. Available online on URL: http://www.cancer.org/docroot/PED/content/PED_3_1x_Link_Between_Lifestyle_and_CancerMarch03.asp.
7. Goldman R, Shields PG. Food mutagens. J Nutr. 2003;133:965S–3S.
8. Sugimura T. Nutrition and dietary carcinogens. Carcinogenesis. 2000;21(3):387-95.
9. Doll R, Peto R. The causes of cancer: quantitative estimate of avoidable risks of cancer in United States today. J Natl Cancer Inst. 1991;66:1191-308.

10. Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. New York: Oxford University Press; 1996, p. 438-61.
11. World Cancer Research Fund and American Institute for Cancer Research. Food, nutrition and the prevention of cancer: A global perspective. Washington DC: American Institute for Cancer Research; 1997.
12. Oliveira PA, Colaço A, Chaves R, Guedes-Pinto H, De-La-Cruz L, Lopes C. Chemical carcinogenesis. Anais da Academia Brasiliera de Ciências. 2007;79(4):593-616. (Annals of the Brazilian Academy of Sciences).
13. Camargo JLV, Salvador DMF, Rocha NS, Baebisan LF, Ribeiro LR. The detection of chemical carcinogens in an alternative medium-term bioassay. J Braz Ass Advan Science. 1999;51:22-6.
14. Pitot HC, Dragan YP. Facts and theories concerning the mechanism of carcinogenesis. FASEB J. 1991;5:2280-6.
15. Poirier LA. Stages in carcinogenesis: Alteration by diet. Am J Clin Nutr. 1987;45:185-91.
16. Berenblum I. A reevaluation of the concept of carcinogenesis. Prog Exp Tumor Res. 1999;11:21-30.
17. Farber E, Cameron R. Sequential analysis of cancer development. Adv Cancer Res. 1980;31:125-226.
18. Slaga TJ, Fischer SM, Weeks CE, Klein-Szanto AJP. Multistage carcinogenesis. In: Seijei M, Bernstein IA, eds. Biochemistry of normal and abnormal epidernal differentiation. Tokyo: University of Tokyo Press; 1990. p. 19-38.
19. Hursting SD, Wei Q, Sturgis EM, Clinton SK. The cancer related genes: Oncogenes, tumor suppressor genes, and the DNA damage-responsive genes. In: Heber D, Blackburn GL, Go VLW, eds. Nutritional oncology. California: Academic Press; 1999: p. 11-27.
20. King C, Wang C, Gorelick N, Frederick C. Genotoxicity in the rodent urinary bladder. Food Chem Toxicol. 1995;33:757-69.
21. Van Leeuwen IM, Zonneveld C. From exposure to effect: A comparison of modeling approaches to chemical carcinogenesis. Mutat Res. 2001;489:17-45.
22. Hayes RB. Genetic susceptibility and occupational cancer. Med Lav. 1995;86:206-13.
23. Klaunig JE, Kamendulis LM, Xu Y. Epigenetic mechanisms of chemical carcinogenesis. Hum Exp Toxicol. 2000;19:543-55.
24. Oesch F, Herrero ME, Hengstler JG, Lohmann M, Arand M. Metabolic detoxification: implications for thresholds. Toxicol Pathol. 2000;28:382-7.
25. Poirier MC, Santella RM, Weston A. Carcinogen macromolecular adducts and their measurement. Carcinogenesis. 2000;21:353-9.
26. Luch A. Nature and nurture – lessons from chemical carcinogenesis. Nat Rev Cancer. 2005;5:113-25.
27. Harris CC. Interindividual variation among humans in carcinogen metabolism, DNA adduct formation and DNA repair. Carcinogenesis. 1999;10:1563-6.
28. Cohen SM, Garland EM, Ellwein LB. Cancer enhancement by cell proliferation. Prog Clin Biol Res. 1999;374:213-29.
29. Williams GM. Mechanism of chemical carcinogenesis and application to human cancer risk assessment. Toxicol. 2001;161:3-10.
30. Park BK, Kitteringham NR, Maggs JL, Pirmohamed M, Williams DP. The role of metabolic activation in drug-induced hepatotoxicity. Annu Rev Pharmacol Toxicol. 2005;45:177-202.
31. Skog KI, Johansson MA, Jagestad MI. Carcinogenic heterocyclic amines in model systems and cooked foods: A reviews on formation, occurrence, and intake. Food Chem Toxicol. 1998;36:879-96.
32. Keating GA, Layton DW, Felton JS. Factors determining dietary intakes of heterocyclic amines in cooked foods. Mutat Res. 1999;443:149-56.
33. Knize MG, Salmon CP, Pais P, Felton JS. Food heating and the formation of heterocyclic aromatic amine and polycylic aromatic hydrocarbon mutagens/carcinogens. Adv Exp Med Biol. 2000;459:179-93.
34. Schut HAJ, Snyderwine EG. DNA adducts of heterocyclic amine food mutagens: implication for mutagenesis and carcinogenesis. Carcinogenesis. 1999;20(3):353-68.
35. Fiddler W. The occurrence and determination of N-nitroso compounds. Toxicol Appl Pharmacol. 1995;31:352-60.
36. Tannenbaum SR. Endogenous formation of N-nitroso compounds: A current perspec-tive. The relevance of N-nitroso compounds to human cancer exposures and mechanisms. In: Bartsch H, O'Neill I and Schulte-Hermann R, eds. IARC scientific publications no. 84. Lyon, France: International Agency for Research on Cancer; 1997. p. 292-5.
37. Lijinsky W. In vivo testing for carcinogenicity. In: Cooper CS, Grover PL, eds. Chemical carcinogenesis and mutagenesis I. Berlin: Springer-Verlag;1999. p. 179-209.
38. Poschl G, Seitz HK. Review. Alcohol and cancer. Alcohol & Alcoholism. 2004;39(3):155-65.
39. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. N Engl J Med. 2003;348:1625-38.
40. Hursting SD, Nunez NP, Varicovski L, Vinson C. The obesity-cancer link: lessons learned from a fatless mouse. Cancer Res. 2007;67(6);2391-3.
41. Zhou J, Blackburn G. Dietary lipid modulation of immune response in tumorigenesis. In: Heber D, Blackburn GL, Go VLW, eds. Nutritional oncology. California:Academic Press; 1999. p. 195-213.
42. Donaldson MS. Review. Nutrition and cancer: A review of the evidence for an anti-cancer diet. Nutr J. 2004;3:19.
43. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: A review. J Am Diet Assoc. 1996;96:1027-39.
44. Béliveau R, Gingras D. Role of nutrition in preventing cancer. Can Fam Physician. 2007;53:1905-11.
45. Pinto JT, Rivlin RS. Garlic and other allium vegetables in cancer prevention. In: Heber D, Blackburn GL, Go VLW, eds. California: Nutritional Oncology Academic Press; 1999. p. 393-403.
46. Choi W, Mason JB. Folate and carcinogenesis: An integrated scheme. American Society for Nutritional Sciences. J Nutr. 2000;130:129-32.
47. Clinton SK. Tomatoes or lycopene: a role in prostate carcinogenesis? American Society for Nutritional Sciences. J Nutr. 2005;135:2057S-59S.
48. Mettlin GR, Newell R, Rivlin L, Wattenberg, et al. American Cancer Society guidelines on diet, nutrition, and cancer. CA Cancer J Clin. 1991;1:334-8.