Review Article

The Sciences (ISSN 1608-8689) is an International Journal serving the International community of Medical Scientists

For further information about this article or if you need reprints, please contact:

Nawazish A. Khan
Department of Nutrition,
East Carolina University,
Greenville, USA

E. mail: nak0524@mail.ecu.edu

The Sciences 2 (1): 38-43
January - February, 2002

Antioxidants and Cancer

Nawazish A. Khan

Certain types of cancers are attributed to the damaging effects on free radicals or reactive oxygen species (ROS) produced as a by product during the normal oxidative metabolism. It is a commonly held belief that the long-term regular supplement of antioxidants in appropriate quantities helps to minimize the harmful effects of ROS. This article provides a consolidated review on the existence, mechanism of action at molecular level, and effectiveness of antioxidants in cancer prevention. The studies reviewed here indicated that there is a growing evidence which suggested a preventive role played by antioxidants against fatal diseases such as cancer and cardiovascular disease.

Key words: Cancer, antioxidants, ROS

ANSInet
Asian Network for Scientific Information

Department of Nutrition, East Carolina University, Greenville, USA

Introduction

Cancer is one of the major killers after cardiovascular disease and most of the cancers are incurable at the time of diagnosis. As stated by Montesano *et al.* (2001) cancer is the second most common cause of mortality after cardiovascular diseases among the 60 million deaths occurring every year worldwide. This disease is a major public health problem in developed countries and is becoming an important cause of mortality in the adult population in developing countries. Although there has been success in curing non-metastatic cancer, most forms of metastatic cancer are generally incurable with conventional treatment modalities such as surgery, radio- and chemotherapy.

Like all other incurable and chronic diseases, prevention is the best cure. When we talk about the cancer prevention, two major terms flash into our minds, that is primary and secondary prevention of cancer. Adami *et al.* (2001) have affirmed that overall; cancer is a highly preventable disease. Prevention of cancer may be accomplished through primary prevention, secondary prevention, or a combination of the two approaches. The objective of primary prevention is to prohibit effective contact of a carcinogenic agent with a susceptible target in the human body so that the sequence of events that culminates in the occurrence of clinical cancer does not begin or is aborted at the start. Secondary prevention relies on presymptomatic disease detection at an early stage, and hopefully, more treatable stage before the appearance of the symptoms or signs that usually results in the patient's receiving early medical attention. Oxidants or reactive oxygen species (ROS) are one of the carcinogenic agents, which are produced during normal metabolism of body so the contact with these carcinogenic agents is unavoidable. This is where, the antioxidants plays their role in preventing primary cancer caused by carcinogenic agents.

Reactive Oxygen Species (ROS): Despite the essential nature of oxygen for all aerobic organisms, oxidative metabolism is not without consequences. Free radicals or ROS, the normal products of oxidative metabolism, continuously arise from a variety of cellular reactions. In addition, the potential consequences of ROS production are as varied as the reactions that produce them (Hauck and Bartke, 2001). Lopaczynski and Zeisel (2001) have discussed the ROS production and existence at cellular level and stated that ROS are normal oxidant by-products of aerobic metabolism, and under normal metabolic conditions about 2-5% of O_2 consumed by mitochondria is converted to ROS. The ROS include three major radical species:

Superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), highly reactive hydroxyl radical (OH), and peroxyl radicals (ROO^-). Superoxide anion is formed as a result of the leakage of electrons from mitochondrial electron transport and the reduction of molecular oxygen (O_2); this occurs primarily at Complex I (NADH dehydrogenase) and Complex III (ubiquinone-cytochrome b-c1 complex). Hydrogen peroxide is generated spontaneously by the dismutation of superoxide anion (O_2^-), under the effects of superoxide dismutase (SOD). The intracellular levels of H_2O_2 are normally less than 100 nM, and this species can easily diffuse through cellular membranes, but H_2O_2 is much less reactive than superoxide anion. Hydroxyl radicals ($^{\cdot}OH$) are the most reactive form of ROS produced in mammalian cells, their production is catalyzed by transition metals (e.g. Fe[II] ions generated via reduction of Fe[III] by O_2^-) in the presence of H_2O_2 via the Fenton reaction. Hydroxyl radicals are highly reactive at the site of their production. In addition to mitochondria, other potential sources of superoxide anion, H_2O_2, and OH are the endoplasmic reticulum (e.g., NADH cytochrome c reductase; cytochrome P-450) and the nuclear membrane. As cancer is the abnormal growth of some specific kinds of cells as a result of insert to genetic material by carcinogenic agents, deoxyribonucleic acid (DNA) is the most important target for ROS in the carcinogenesis process. Damage to DNA can take many forms ranging from specifically oxidized purine and pyrimidine bases (more than 20 such oxidative changes have been identified) to DNA lesions such as strand breaks, sister chromatid exchanges, and the formation of micronuclei. The highly reactive OH radicals are able to react with nucleotide bases (as well as with the deoxyribose chain), forming a variety of modified bases among which 8-hydroxy guanine (8-OHdG) is the most important because it represents a premutagenic alteration. DNA strands breaks can occur when the deoxyribose chain interacts with $^{\cdot}OH$ radicals. Iron atoms that are bound to DNA can interact with highly diffusible, but relatively unreactive H_2O_2 in a metal-catalyzed Fenton-type reaction to produce OH-mediated, DNA damage and strand breaks. Specific DNA oxidation products accumulate depending on the ROS involved, its rate of production, and the cellular ability to protect or repair its DNA from the oxidative damage. High levels of ROS interact with lipids and produce harmful changes in lipids. As stated by Burton and Traber (1990) lipid peroxide is a form of oxidative damage that occurs in cell membranes when unsaturated fatty acids react with excess levels of ROS (e.g., $^{\cdot}OH$ radicals or a transition metal/oxidant complex) to form both fatty acid radicals and lipid Hydro peroxides. Lipid Hydro peroxides cause reversible alterations to membrane structure and function, and are a source of highly reactive aldehydes [e.g., 4-hydroxynonenal (HNE), malondialdehyde (MDA)] that are capable of modifying both DNA and proteins resulting in mutagenic, genotoxic, and cytotoxic events. Although these ROS are generally known for the negative role they play to produce fatal health disorders but in moderate amounts (if their level don't cross the upper limits to produce oxidative stress) they also take part in some normal body functions. According to Yermolaieva *et al.* (2000) Reactive oxygen/nitrogen species (ROS/RNS) often are considered as tissue-damaging agents in connection with oxidative stress, aging, and neurodegenerative diseases, especially in the presence of elevated cytosolic Ca^{2+}. The idea of possible involvement of ROS and free radicals in electrical and developmental neuronal plasticity has been suggested recently. For example, visual stimulation causes the consumption of glucose and oxygen to rise in the human visual cortex. This interdependence between the neuronal metabolic state and functional activity indicates a possible physiological role for ROS/RNS as potential regulators of neuronal activity. In young rat cortical brain slices and undifferentiated PC12 cells, paired application of depolarization/agonist stimulation and oxidation induces long-lasting potentiation of subsequent Ca^{2+} signaling that is reversed by hypoxia. This Ca^{2+} potentiation critically depends on NO production and involves cellular ROS utilization.

The apoptotic cell death process is a basic biological phenomenon that occurs when a genetically encoded cell death-signaling program is activated. As a result of apoptosis many cells can be deleted from tissues in relatively short time. Therefore, apoptosis results in the orderly elimination of cells while minimizing tissue damage without inducing inflammation. Apoptosis is responsible for cell death in development, normal tissue turnover, atrophy induced by endocrine and other stimuli, negative selection in the immune system, and substantial proportion of T-cell killing. Many cancer therapeutic agents exert their effects through initiation of apoptosis, and even the process of carcinogenesis itself sometimes depends on a critical failure of apoptosis that permits the survival of cells after mutagenic DNA damage. Although for long ROS was considered as simply a toxic by-product of normal cellular metabolism, there is a growing body of evidence that ROS in addition to regulating apoptotic signal transduction it may also be responsible for activating apoptotic death pathways (Lopaczynski and Zeisel, 2001).

Oxidative Stress: Oxidative stress is defined as a process in which the balance between oxidants and antioxidants is shifted toward the oxidant side. This shift can lead to the antioxidant depletion and potentially to biological damage if the body has an insufficient reserve to compensate for consumed antioxidants. Exposure to oxidants, whether endogenous or exogenous, can initiate free-radical-mediated reactions and lead to oxidative stress (Elsayed, 2001). According to Lachance *et al.* (2001) oxidizing equivalents

in excess of the cell-buffering capacity and enzymatic capabilities result in potentially cytotoxic oxidative stress (endogenous). A certain physiologic level of ROS is crucial for the proper regulation of cell functions such as intracellular signaling, transcription activation, cell proliferation, inflammation, and apoptosis.

The oxidation-reduction (redox) state of the cell is a consequence of the balance between levels of ROS and endogenous enzymes (e.g., catalase, superoxide dismutase, glutathione peroxidase) and thiol buffers, in particular glutathione and thioredoxin. So, imbalance among ROS levels , endogenous enzymes and thiol buffers results in endogenous oxidative stress. Tobacco, ozone, and environmental pollutants are major sources for exogenous oxidative stress. In smokers, the dynamic balance between oxidation and antioxidation is seriously disrupted, and oxidative stress is clearly exacerbated, which is closely related to many disorders and diseases in smokers. Among the many substances identified in tobacco smoke, ROS are major carcinogens. Invariably, the exposure levels to carcinogens and free radicals in smoke are high compared with available body-defense mechanisms. In non-smoking subjects, even a short period of passive smoking breaks down serum antioxidant defense, with subsequent oxidation of low-density lipoprotein cholesterol. Ozone is the major oxidant in photochemical smog. Exposures to environmental pollutants such as asbestos, polychlorinated biphenyls, and mineral dust lead to the release of ROS and subsequent tissue damage.

Antioxidants and Cancer: To minimize the damaging effects of ROS, aerobic organisms have evolved both enzymatic and non-enzymatic antioxidant defense systems. Non-enzymatic systems include compounds with intrinsic antioxidant properties such as, vitamins E and C, flavonoids, -carotene, and other small molecules derived from plant sources. Enzymatic defenses include the catalases, peroxidases, superoxide dismutases, and repair enzymes (Scandalios, 1997). According to Gong *et al*. (1997) cells contain antioxidants, and antioxidant enzymes that can mitigate the deleterious effects of ROS *in vivo*. Antioxidants alleviate the oxidant load by directly quenching oxygen radicals (˙O) before they damage cellular components. Antioxidative enzymes function by catalyzing the decomposition of oxidants and free radicals. Thus we have two types of antioxidant systems that are enzymatic and non-enzymatic. It is obvious that very little support is available in the form of drugs or diet supplements to enzymatic antioxidant defense system as compared to non-enzymatic antioxidant defense system. However, certain diet modifications are considered to be supportive to enzymatic antioxidant defense system. Restriction of calorie intake (R) extends lifespan and delays the onset of many age-associated debilities. It has been hypothesized that the beneficial effects of the R diet are due to the increased activity or efficiency of cellular antioxidant defenses. Mura *et al*. (1996) stated that under physiological conditions, the free radicals are maintained at low steady state concentrations by antioxidant enzymes. Based on their research work, they concluded that R (Diet) is associated with changes in proteins and messenger RNA (RNA) levels for various antioxidant enzymes and secondary defenses. The significance of these differences vis-à-vis the life prolonging effects of 'R' remains to be determined.

The non-enzymatic antioxidants are available in our diet or as a supplements and are micro nutrients. They have strong antioxidant effects and defend the body against lethal effects of both endogenous and exogenous oxidative stresses. Their deficiency proves fatal for the body. According to Ames (2001) micronutrient deficiency can mimic radiation (or chemicals) in damaging DNA by causing single- and double-strand breaks, or oxidative lesions, or both. Chromosomal aberrations such as double strand breaks are a strong predictive factor for human cancer. Those micro nutrients whose deficiency mimics radiation are folic acid, B_{12}, B_6, niacin, C, E, iron, and zinc, with the laboratory evidence ranging from likely to compelling.

Other than protection against cancer, antioxidants also have protective effect over the proteins of lens against cataract formation, which appears due to the oxidation of its proteins. Antioxidants, such as Vitamin C and E and carotenoids, appear to protect against cataracts and macular degeneration of the eye in rodents and humans. The use of Vitamin C supplements for 10 years or more reduced lens opacities by about 80%. In a review of nutrition and pancreatic cancer, fruit and vegetable intake and Vitamin C were protective, though it is difficult to rule out that Vitamin C is a surrogate for some other compounds in fruits and vegetables. Both experimental and epidemiological data suggested that Vitamin C protects against stomach cancer, a result that is plausible because of the role of oxidative damage from inflammation by *Helicobacter pylori* infection, which is the main risk factor for stomach tedcancer. The role of Vitamin C in inhibiting oral cancer has recently been reviewed. According to Wolk *et al*. (1996) some studies suggested that Vitamin C protects against cancer, which would be plausible based on the mechanistic data, though other studies shows no effect, the variability of tissue saturation again is critical. A significant protective effect was observed for renal cancer in non-smokers, though not in smokers.

Ames (2001) have stated that people taking Vitamin E supplements (200 IU day^{-1}) appear to lower their risk for colon cancer and evidence suggests a marked protective effect of a supplement (50 IU day^{-1}) on prostate cancer. According to Kinningham (1999) epidemiological studies have also supported a role for dietary antioxidant vitamins, most notably α-tocopherol (Vitamin E), ascorbic acid (vit. C), and β-carotene, in disease prevention. Multiple studies have reported decreased rates of cancer and cardiac disease in populations with high consumption of fruits and vegetables. Factor *et al*. (2000) conducted a research to determine the effect of Vitamin E over chromosomal damage and hepatic tumor formation in a mouse model. They concluded that the results of recent studies provided *in vivo* evidence that long term dietary administration of Vitamin E at dose of 2,000 units kg^{-1} confers significant protection against both initiation and progression stages of hepatocarcinogenesis. The experimental model used in this study establishes that overproduction of ROS generated by endogenous metabolic processes has a direct impact on genomic stability and susceptibility to liver tumor development. Although considerably more work is needed to elucidate the precise mechanism(s) by which Vitamin E suppresses tumorigenesis, the promising results obtained with Vitamin E treatment in this potentially clinically relevant system suggests that dietary supplementation of Vitamin E and possibly other antioxidant agents might contribute to delaying/prevention of human liver cancer. According to Sandhu *et al*. (2000), Vitamin E is the most important lipophilic antioxidant in the prevention of cellular injury associated with oxidative stress. They concluded that Vitamin E might protect against the development of cancers associated with inflammatory conditions by scavenging these reactive species. However, an additional mechanism by which Vitamin E may be protective is: once tumors become established, Vitamin E may reduce mutations by affecting the infiltration of neutrophils or other inflammatory cells.

Elsayed (2001) has discussed the mobilization of antioxidants in the body in response to oxidative stress. According to him, lung cancer is one of the most common causes of death. Two areas of the aerobic mammalian body are continuously exposed to oxidants and thus undergo repeated oxidative stress, namely the skin and lungs. Through the process of evolution, the lungs have

developed elaborate biological defense systems that include very efficient antioxidant protective mechanisms against oxidative stress. It is only when the balance between oxidant and antioxidant is altered that the lung-defense systems cannot cope with the continuous oxidant attacks. In the lungs, the "oxygen paradox" shows the importance of maintaining a sufficient level of antioxidants and the role they play. Thus, whereas humans, as aerobic species, cannot survive without breathing O_2 from the air, O_2 is one of the most powerful oxidants in nature and can cause significant oxidative damage. The lungs have adapted to its aerobic environment and the O_2 paradox by developing efficient antioxidant-defense mechanisms against O_2 toxicity.

One of the most recognized and studied lipid-soluble antioxidants is vitamin E. Radio labeled dose of Vitamin E was incorporated into rat tissue (administered 1 h before exposure) after exposure to 0.5 ppm of O_3 continuously for 5 days. Lung tissue responded to oxidative stress with Vitamin E as:

a) Vitamin E content increased in the lung after oxidant exposure, which was described as a mobilization of the vitamin under oxidative stress.
b) Although vitamin E increased in deficient and supplemented rats, the increase was significant only in supplemented animals.
C) There was an inverse correlation between incorporation of the Radio labeled vitamin and the dietary vitamin E status, suggesting a greater demand for the vitamin with deficiency and indicating that body stores should be supplemented sufficiently to better cope with stress.

Further, the reported increase in lung vitamin E content after oxidant inhalation is not limited to the lung or the inhalation route alone, suggesting that mobilization constitutes a general response to oxidative stress. How does vitamin E increase in the lung and other organs in response to oxidative stress? One possible mechanism suggests that an event causing oxidative stress such as exposure to oxidant air pollutants, smoking, burn, or exercise can initiate chain reactions, cause lipid per oxidation and protein oxidation-generating bioactive molecules, and deplete the antioxidants at the target sites. These events would activate signal transduction pathways that in turn might cause antioxidant mobilization if the body's antioxidant stores are high. In this case, tolerance, repair, and recovery may occur. However, if antioxidants are deficient and the antioxidant capacity is limited, injury will progress and direct or indirect damage and organ dysfunction will occur. Most probably, vitamin E is supplied to the cells from other body stores through the plasma via a transport mechanism involving very low-density lipoproteins.

Carotenoids are yellow, orange, and red pigments present in many commonly eaten fruits and vegetables. Of the more than 600 carotenoids identified in nature, approximately 40 are commonly consumed in the U. S. diet and approximately 20 are present in quantifiable amounts in human serum and tissues. In addition to serving as a source of vitamin A, dietary carotenoids have been hypothesized to play a role in the prevention of common chronic diseases. The most popular and widely recognized hypothesis to date proposes that α-carotene reduces the risk of lung cancer. Other hypotheses propose that carotenoids protect against other cancers, cardiovascular disease, and age-related muscular degeneration. Although observational epidemiological studies confirmed that carotenoids, particularly carotene and lutein, were associated with reduced risk of lung cancer but taken together, the available data do not provide convincing evidence that carotenoids contribute significantly to reduction of lung cancer risk. Specifically, there is no direct evidence that carotenoids themselves are responsible for the decreased risks of lung cancer noted in observational epidemiology studies. This lack of evidence remains the most significant gap in carotenoid research (Cooper *et al.*, 1999).

According to McKeown (1999) breast cancer is second only to lung cancer, the most common cause of cancer mortality in U.S. women. In 1999, it was predicted that 175,000 new cases of breast cancer will be diagnosed in women and that an estimated 43,300 deaths will result from this disease. The cause of breast cancer is unknown but presumably represents a complex interplay of genetic susceptibility and environmental factors. The environmental factors, which could include differences in dietary patterns, plays an important role in the etiology of breast cancer. Several dietary antioxidants such as vitamins C and E and pro-vitamin A have been suggested as protective agents against the development of several cancers, including breast cancer. A proposed mechanism by which these antioxidants protect cells from oxidative stress is by scavenging free radicals and quenching lipid per oxidation chain reactions, which could cause DNA damage. The exact biologic mechanism by which β-carotene and other carotenoids may protect against cancer remains unclear. It is biologically plausible that β-carotene functions in breast cancer prevention because of its antioxidant properties or, alternatively, through its conversion to preformed vitamin A. Animal studies have demonstrated that supplemental retinyl acetate reduces the incidence of mammary tumors, whereas *in vitro* studies have shown that retinol inhibits the growth of human breast carcinoma cells.

According to Ripple and Henry (1999) the oxidative stress hypothesis of aging postulates that oxidative damage to critical molecules accumulates over the life span and eventually impairs function. Studies of dietary antioxidants provide encouraging data regarding prostate cancer prevention. The long-term ez-tocopherol supplementation reduces prostate cancer incidence by 32% and prostate cancer mortality by 41% in cigarette smokers. Joshi *et al.* (2001) stated that epidemiological studies have shown that folate supplements can significantly reduce the risk of pancreatic cancer and breast cancer. Several biochemically plausible mechanisms for this cancer prevention activity may be proposed besides the sole known biochemical role. One such mechanism can be free radical scavenging and antioxidant activity, as it is now recognized that free radicals play an important role in the oxidative stress leading to many diseases. On the basis of their work, they demonstrated that folic acid is an effective free radical scavenger, If present in physiology, folic acid can protect bioconstituents from free radical damage at least by competition, which otherwise can lead to oxidative stress. In spite of being water-soluble molecule, folic acid can inhibit lipid per oxidation also. The scavenging and repair of thiyl radicals (Thiyl radicals are generated in the living systems, these radicals can be considered as reactive oxidants as they are able to initiate lipid per oxidation) by folic acid making it a potential vitamin to be called as an antioxidant.

Phytochemicals have antioxidant properties and have received recent attention for their possible ability to prevent cancer and heart disease. Phenolic phytochemicals are the largest category of phytochemicals and the most widely distributed in the plant kingdom. The three most important groups of dietary phenolics are flavonoids, phenolic acids, and polyphenols. Flavonoids are the largest and the most studied group of plant phenols. Flavonoids are compounds of low molecular weight that usually occur bound to sugar molecules. The dietary flavanols catechin and epicatechin occur in combined form as with gallic acid in tea; as epigallocatechin gallate and epicatechin gallate; or as condensed tannin polymers in fruits, legumes, and grains. Flavonol concentrations are higher in immature fruits, and fruits stored over the winter may have only half their original flavonol compounds. Catechins are frequently more abundant in external

tissues. Thirty percent of the dry matter from tea solutions is flavonoids. In black tea the catechins are oxidized to the flavins and the arubigens. Phenolic acids include hydroxy benzoic and hydroxycinnamic acids.

The two major dietary hydroxy benzoic acids are ellagic and gallic acid, which usually occur as hydrolyzable tannins and are found mainly in berries and nuts (King and Young, 1999). Ahmad and Mukhtar (1999) stated that several animal studies have demonstrated an anticarcinogenic effect of polyphenols. Some of the polyphenols studied for their anticarcinogenic potential are flavones, flavonols, isoflavones, and catechins. Tannins, found in many plant foods, have also been shown to possess anticarcinogenic and antimutagenic potentials. The chemical composition of green tea, with regard to its major components, is similar to that of the fresh leaves of the plant. It contains many polyphenolic compounds, which accounts for up to 30% of the dry weight of green tea leaves. Most of the polyphenols in green tea are flavanols, commonly known as catechins. Polyphenols in food and beverages, such as green tea, have been shown to have anticarcinogenic properties. Ahmad and Mukhtar (1999) concluded that the limitation of the human epidemiologic studies conducted so far is that these are mainly case-control studies and rely heavily on questionnaires, interviews, and subject responses. Comprehensive, in-depth cohort studies are needed to thoroughly evaluate the association between green tea consumption and cancer risk.

According to Marchand *et al.* (2000) intake of vegetables and fruits has consistently been associated with a reduced risk of lung cancer. Quercetin and other related flavonoids inhibit carcinogen-induced tumors in rodents. One of the possible mechanisms for this protective effect is the well-documented ability of some flavonoids, such as quercetin and naringenin (the aglycone derived from naringin), to inhibit certain cytochrome P450 enzymes (CYP1A1 and CYP3A4, respectively) involved in the bioactivation of chemical carcinogens. Results of their case control study on 582 patients of lung cancer showed an inverse associations between lung cancer and main food sources of quercetin (onions and apples) and naringin (white grapefruit).

Conclusion

From this review, summarized that worldwide, sixty million deaths are caused by cancer every year, Like all other incurable and chronic diseases, prevention of cancer may be accomplished through primary preventive measures. The objective of primary prevention is to prohibit the effective contact of a carcinogenic agent with a susceptible target in the human body. Oxidants or reactive oxygen species (ROS) or free radicals are one of the carcinogenic agents that are produced during normal oxidative metabolism of body. Thus, the contact with these carcinogenic agents is unavoidable. Deoxyribonucleic acid (DNA) is the most important target for ROS in the carcinogenesis process. DNA strand breaks can occur when the deoxyribose chain interacts with OH radicals. These lesions in DNA result into mutations and carcinogenesis.

While moderate amounts of ROS take part in some normal body functions such as Ca^{+2} signaling in neuronal activity and in the apoptosis, the excessive amounts of ROS are likely to cause oxidative stress by shifting the balance towards the oxidant side. This shift can lead to antioxidant depletion and potentially to biological damage if the body has an insufficient reserve to compensate for consumed antioxidants.

In order to minimize the damaging effects of ROS, aerobic organisms have evolved both enzymatic and non-enzymatic antioxidant defense systems. Non-enzymatic systems include compounds with intrinsic antioxidant properties such as vitamins E and C. Antioxidants, such as Vitamin C and E and carotenoids, appear to prevent different types of cancers. Studies shows that while Vitamin C protects against pancreatic, lungs, renal, stomach, and oral cancer, Vitamin E supplements helps lower the risk of colon and prostate cancer. Much has been studied about the relationship between carotenoids and lung cancer. Nevertheless, the available data do not provide convincing evidence that carotenoids contribute significantly towards the preventing lung cancer. In addition, different epidemiological studies have shown that folate supplements can significantly reduce the risk of pancreatic and breast cancer.

In conclusion, the literature reviewed indicates that there is growing suggestive evidence that antioxidants do have a preventive effect against fatal diseases such as cancer and cardiovascular disease. However, in case of some antioxidants such as β-carotenoids, the correlation between cancer prevention and antioxidants is not fully clear.

References

Adami, H. O., N. E. Day, D. Trichopoulosc and W. C. Willett, 2001. Primary and secondary prevention in the reduction of cancer morbidity and mortality. Eur. J. Cancer, 37: 118-127.

Ahmad, N. and H. Mukhtar, 1999. Green tea polyphenols and cancer: Biologic mechanisms and practical implications. Nutr. Rev., 57: 78-83.

Ames, B. N., 2001. DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 475: 7-20.

Burton, G. W. and M. G. Traber, 1990. Vitamin E: Antioxidant activity, biokinetics, and bioavailability. Annu. Rev. Nutr., 10: 357-382.

Cooper, D. A., A. L. Eldridge and J. C. Peters, 1999. Dietary carotenoids and lung cancer: A review of recent research. Nutrition Reviews, 57: 133.

Elsayed, N. M., 2001. Antioxidant mobilization in response to oxidative stress: a dynamic environmental-nutritional interaction. Nutrition, 17: 828-834.

Factor, V., M. D. Laskowska, M. R. Jensen, J. T. Woitach, N. C. Popescu, and S. S. Thorgeirsson, 2000. Vitamin E reduces chromosomal damage and inhibits hepatic tumor formation in a transgenic mouse model. Proc. Natl. Acad. Sci., USA, 97: 2196-2201.

Gong, X., F. Shang, M. Obin, H. Palmer, M. M. Scrofano, J. Jahngen-Hodge, D. E. Smith and A. Taylor, 1997. Antioxidant enzyme activities in lens, liver and kidney of calorie restricted Emory mice. Mechan. Ageing and Develop., 99: 181-192.

Hauck, S. J and A. Bartke, 2001. Free radical defenses in the liver and kidney of human growth hormone transgenic mice: Possible mechanisms of early mortality. The J. Gerontol, 56A: B153-B162.

Joshi, R., S. Adhikari, B. S. Patro, S. Chattopadhyay and T. Mukherjee, 2001. Free radical scavenging behavior of folic acid: evidence for possible antioxidant activity. Free Radical Biol. and Med., 30: 1390-1399.

King, A. and G. Young, 1999. Characteristics and occurrence of phenolic phytochemicals. J. of the Am. Dietetic Assoc., 99: 213-218.

Kinningham, R., 1999. The value of antioxidant vitamin supplements. American Family Physician, 60: 742.

Lachance, P. A., Z. Nakat and W. Jeong, 2001. Antioxidants: an integrative approach. Nutrition, 17: 835-838.

Lopaczynski, W and S. H. Zeisel, 2001. Antioxidants, programmed cell death, and Cancer. Nutr. Res., 21: 295-307.

Marchand, L. L., S. P. Murphy, J. H. Hankin, L. R. Wilkens, L. N. Kolonel, 2000. Intake of flavonoids and lung cancer. J. of the Nat Can. Instit., 92: 154-160.

McKeown, N., 1999. Antioxidants and breast cancer. Nut Rev., 57: 321-324.

Montesano, R., 2001. Introduction. Eur J. Cancer, 37: 1-2.

Mura, C. V., X. Gong, R. Villalobos-Molina, A. Taylor and M. M. Scrofano, 1996. Effects of calorie restriction and aging on the expression of antioxidant enzymes and ubiquitin in the liver of Emory mice. Mechan. Ageing and Develop., 91: 115-129.

Ripple, M. O. and W. F. Henry, 1999. Effect of Antioxidants on Androgen-Induced AP-1 and NF-kB DNA-Binding Activity in Prostate Carcinoma cells. J. the Nat Can. Instit., 91: 1227-1232.

Sandhu, J. K., A. S. H. Haqqani and C. Brinboim, 2000. Effect of vitamin E on spontaneous or nitric oxide donor-induced mutations in a mouse tumor model. J. the Nat. Can. Instit., 92: 1429-1433.

Scandalios, J. G., 1997. Introduction. Free Radical Biol. and Medic., 23: 471-472.

Wolk, A., P. Lindblad and H. O. Adami, 1996. Nutrition and renal cell cancer. Cancer Causes Control, 7: 5-18.

Yermolaieva, O., N. Brot, H. Weissbach, S. H. Heinemann and T. Hoshi, 2000. Reactive oxygen species and nitric oxide mediate plasticity of neuronal calcium signaling. Proc. Natl. Acad. Sci., USA, 97: 448-453.

MS received 14th December, 2001; accepted 31st December, 2001