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Role of diet and nutrition in deoxyribonucleic acid damage

Faiza Rizvi[1]*, Sohail Hassan Khan[2], Fizza Naeem[1]

[1]Institute of Home and Food Sciences, Government College University, Faisalabad, (PAKISTAN)

[2]Poultry Research Institute, Murree Road, Shamsabad, Rawalpindi, (PAKISTAN)

E-mail: f.razvi85@gmail.com; sohailhassan64@gmail.com; raowaseem@yahoo.com

ABSTRACT

Deoxyribonucleic acid (DNA) damage is an elementary root of developmental and degenerative diseases. DNA damage is accelerated by oxidative stressors such as tobacco smoke, strenuous exercise, and a high-fat diet. There is significant interest in the functions of nutrients and DNA damage in carcinogenesis. Numerous surveillances provide support for a defensive association between high dietary intakes and/or supplemental doses of vitamins with cancer risk. There are nine key nutrients that may affect genomic integrity in various ways. When feed consumption increased, six nutrients out of nine (folate, vitamin B_{12}, niacin, vitamin E, retinol, and calcium) are associated with a drop in DNA damage, whereas other three nutrients (riboflavin, pantothenic acid and biotin) are associated with an increase in DNA damage to the same extent observed with occupational exposure to genotoxic and carcinogenic chemicals. Fruits and vegetables have been shown to decrease oxidative DNA damage in numerous studies.

KEYWORDS

DNA damage;
Vitamins;
Antioxidants;
Minerals.

INTRODUCTION

Deoxyribonucleic acid damage is a primary cause of developmental and degenerative diseases[10]. Deoxyribonucleic acid damage is generated by exogenous agents such as ionizing radiation (IR), ultraviolet (UV) light exposure, genotoxic compounds including chemotherapeutic drugs such as adriamycin, and endogenous factors such as reactive oxygen species which are generated by mitochondria in the process of β-oxidation. Depending on the types and the harshness of DNA lesions, cells respond to DNA damage by undergoing cell cycle arrest or apoptosis when the damage is away from repair[76]. Genomic integrity is persistently faced by the effects of DNA-damaging agents.

Double-stranded DNA breaks (DSBs) are considered to be the most genotoxic lesions since incorrect repair can lead to chromosome breaks and other aberrations that are characteristic of and which may lead to cancer[44]. Many of the proteins involved in DNA damage response are found to promote cancer development when mutated[35]. Furthermore, it was recently reported that in many cell types, the conversion from pre-cancer to cancer is accompanied by activation of the DNA damage response, which ceases to exist once converted to cancer cells[6]. The function for this activation is to inhibit cell proliferation or to induce apoptosis. As a result, cells with mutations in proteins involved in DNA damage response are selected and become cancerous. Thus, DNA damage response acts

as a protective mechanism against cancer development[46]. The DNA damage at the base sequence, epigenome and chromosome level is the most fundamental cause of developmental and degenerative diseases[22]. Although genes are critical for determining function, nutrition modifies the extent to which different genes are expressed and thereby modulates whether individuals attain the potential established by their genetic background[59]. Genome damage impacts on all stages of life. There is good evidence to show that infertile couples exhibit a higher rate of genome damage than fertile couples[80], when their chromosomal stability is measured in lymphocytes using the micronucleus assay. The infertility may be due to a reduced production of germ cells because genome damage effectively causes programmed cell death or apoptosis, which is one of the mechanisms by which grossly mutated cells are, eliminated[40]. When the latter mechanism fails, reproductive cells with genomic abnormalities may survive leading to serious developmental defects[78]. Specific micronutrient deficiencies that cause genome damage may themselves cause developmental defects in the foetus or increased risk of cancer in the child. There are thousands of DNA alterations in each human cell daily; if not efficiently repaired, our genome would rapidly be destroyed. Diet and lifestyle are major mediating factors. For example, DNA damage is accelerated by oxidative stressors such as tobacco smoke, strenuous exercise, and a high-fat diet[84]. On the other side, diets low in fat and/or high in cruciferous vegetables have been shown to lower the oxidative DNA damage rate in humans, as indicated by reduced urinary excretion of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG). In other reports, the dietary intake of vitamin C determined the concentration of 8-oxodG in human sperm DNA, while dietary fish oil and calcium reduced oxidative DNA damage rate in colonic epithelial cells[59]. Therefore Nutrition has a critical role in DNA metabolism and repair. A large body of evidence suggests that a significant percentage of deaths resulting from cancer due to DNA damage in the United States could be avoided through greater attention to proper and adequate nutrition[37]. Numerous studies in humans, animals, and cell cultures have demonstrated that macronutrients, micronutrients and naturally occurring bioreactive chemicals (e.g., phytochemicals such as flavonoids, carotenoids, coumarins, and phytosterols; and zoochemicals such as eicosapentaenoic acid and docosahexaenoic acid) regulate gene expression in diverse ways. Many of the micronutrients and bioreactive chemicals in foods are directly involved in metabolic reactions that determine everything from hormonal balances and immune competence to detoxification processes and the utilization of macronutrients for fuel and growth. Some of the biochemicals in foods (e.g., genistein and resveratrol) are ligands for transcription factors and thus directly alter gene expression. Others (e.g., choline) alter signal transduction pathways and chromatin structure, thus indirectly affecting gene expression[59].Dietary profile differs between individuals to varying extents depending on their acquired or inherited dietary preferences and food availability; furthermore uptake of micronutrients from the digestive system and transport into cells of the body also varies depending on genetics and altered expression of transporters that occurs with age. Currently dietary reference values (e.g., recommended daily intakes, upper safety limits) and culture medium recipes and conditions do not take into consideration impact on genome integrity and yet harm to the DNA sequence and/or the epigenome is the most fundamental and critical pathology underlying cellular and organism health and disease. The DNA damage, cell death and cell growth in cultured cells are strongly affected by concentration of essential micronutrients such that both deficiency or excess within the physiological range can profoundly harm the genome and alter cell growth and survival kinetics[85]. The use of excessively high concentrations of methyl donors (e.g. folate, methionine, choline vitamin B_{12}) in culture medium theoretically may lead to an adverse DNA methylation pattern that may inappropriately silence important house-keeping genes although strong evidence for this hypothesis is currently lacking[85]. In well-nourished human volunteers, fruits and vegetables have been shown to decrease oxidative DNA damage in several studies, but data from short-term human intervention studies suggest that the protective agents are not vitamin C, vitamin E, β-carotene, or flavonoids[34]. Numerous studies have examined associations of antioxidant intakes (from diet and/or supplements) with oxidative DNA damage and cancer risk. Most intervention trials that focused on intakes of fruits and/or vegetables have shown significant reductions in oxidative DNA damage levels[70,73]. A large body of

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evidence suggests that even a moderate daily dose of supplementary vitamin C (200 mg) induces the formation of genotoxins from lipid hydroperoxides, thereby resulting in DNA damage and initiation of carcinogenesis[53]. There is overwhelming evidence that a large number of micronutrients (vitamins and minerals) are required as cofactors for enzymes or as part of the structure of proteins (metalloenzymes) involved in DNA synthesis and repair, prevention of oxidative damage to DNA as well as maintenance methylation of DNA[2]. Current RDAs for vitamins and minerals are based largely on the prevention of diseases of deficiency, such as scurvy in the case of vitamin C, anaemia in the case of folic acid and pellagra in the case of niacin. However, these deficiency diseases are rare in the developed countries but degenerative and developmental disease is very important and common. Recently, the dietary allowance for folic acid for the prevention of neural tube defects has been revised to more than double the original RDA[22]. There is a strong international awareness that it is also necessary to redefine RDAs for the prevention of degenerative disease (such as cancer, cardiovascular disease and Alzheimer's disease) and compression of the morbidity phase during old age. Since diseases of development, degenerative disease and ageing itself are partly caused by damage to DNA[3], it seems logical that we should focus better our attention on defining optimal requirements of key minerals and vitamins for preventing damage to both nuclear and mitochondrial DNA. Poor lifestyles demonstrate cumulative association with leukocyte DNA damage in Japanese hard-metal workers[87]. The aim of this review paper is to give an overview of role of vitamin, antioxidants, minerals, fatty acids and bioflavonoids in DNA damage.

CONTRIBUTION OF NUTRITIONAL FACTORS TO DNA DAMAGE

Deoxyribonucleic acid damage, cell death and cell growth in cultured cells are strongly exaggerated by concentration of essential micronutrients such that both deficiency or excess within the physiological range can intensely damage the genome and vary cell growth and survival kinetics[85]. Specific micronutrient deficiencies that cause genome damage may themselves cause developmental defects in the foetus or increased risk of cancer in the child. Specific examples, include (i) increased oxidation of sperm DNA in humans with insufficient vitamin C intake[26] and the aggravating effect of vitamin C deficiency on diabetes-induced teratogenesis[66]; (ii) neural tube defects in folate-deficient human foetuses at deficiency levels that correspond with increased genome damage rate[30] and the increased risk of childhood leukaemia in children of mothers who did not take folic acid supplements during pregnancy[79]; (iii) the observation that zinc deficiency, which provokes oxidative damage to DNA and impairs DNA repair, is itself teratogenic[17]; and (iv) increasing rates of human male infertility and testicular cancer may be linked via a common mechanism, i.e. increased genome damage events in spermatogonial stem cells owing to environmental genotoxins and/or micronutrient. There is no direct and forceful evidence that oxidative DNA damage is a biomarker of subsequent cancer development, because studies to address this point have not been done. However, there is considerable circumstantial evidence, but not proof beyond reasonable doubt to support the view that it is a suitable biomarker. It follows that agents that decrease the amount of oxidative DNA damage should decrease the risk of subsequent cancer development[33]. So It is believed that antioxidants help maintain human health by decreasing oxidative damage to key biomolecules. In well-nourished human volunteers, fruits and vegetables have been shown to decrease oxidative DNA damage in several studies, but data from short-term human intervention studies recommend that the protective agents are not vitamin C, vitamin E, β carotene, or flavonoids[34].

ROLES OF VITAMINS AND ANTIOXIDANTS

Several studies have examined associations of antioxidant intakes (from diet and/or supplements) with oxidative DNA damage and cancer risk. Most intervention considerations that focused on intakes of fruits and/or vegetables have shown significant reductions in oxidative DNA damage levels[70,73]. In humans, lymphocytes are the only cell type available for estimating oxidative DNA damage in the body as a whole. That it is reasonable to regard them as a useful indicator is suggested by recent studies in rats, in which consumption of cholesterol increased oxidative DNA damage in

both lymphocytes and endothelial cells of the aorta[78]. High antioxidant intake has been shown to reduce cancer risk and may also mitigate the effects of oxidative DNA damage, which was hypothesized to be causally linked to carcinogenesis. A study examined potential racial differences in (*a)* dietary intakes and plasma concentrations of vitamin C, vitamin E, and carotenoids and oxidative DNA damage and (*b*) associations between plasma antioxidants and oxidative DNA damage. Data were from a cross-sectional study of 164 generally healthy nonsmoking African-Americans and Whites in North Carolina, ages 20 to 45 years, equally distributed by race and sex. Levels of oxidative DNA damage, measured using the alkaline comet assay, were lower in African-Americans than Whites. [83]It has been suggested that oxidative DNA damage is associated with elevated cancer risk and that antioxidants may alleviate the effects of oxidative DNA damage. In addition, diets high in fruits and vegetables, and which are also rich in antioxidants, have consistently been linked to lower risk of many cancers, including those of the breast, colon/rectum, and prostate, all of which disproportionately affect African-Americans [1].

A large body of evidence suggests that even a moderate daily dose of supplementary vitamin C (200 mg) induces the formation of genotoxins from lipid hydroperoxides, thereby resulting in DNA damage and initiation of carcinogenesis[53]. Vitamin C is considered to be one of the most prevalent antioxidative components of fruit and vegetables, and it could exert chemopreventive effects without apparent toxicity at doses higher than the current recommended dietary allowance of 60 mg/d[53]. It has also been used as a dietary supplement intended to prevent oxidative stress mediated chronic diseases such as cancer, cardiovascular disease[48], hypertension[18], and stroke[52], and neurodegenerative disorder[21]. Some studies have reported higher oxidative DNA damage in men than in women, which was due to lower fruit intake in men in one study[39]. Human prostate tissues are susceptible to oxidative DNA damage. The danger of prostate cancer is lower in men reporting higher consumption of tomato products, which contain high levels of the antioxidant lycopene[33]. Prostate cancer is the second primary cause of cancer-related death among U.S. men. The frequency of prostate cancer is higher in African-American men than in Euro American men[34]. In a randomized controlled study of vitamins C and E supplemented by Huang et al.[41]. These workers reported that oxidative DNA damage (assessed by urinary 7 hydroxy-8-oxo-22 - deoxyguanosine) was lower in African-American than White participants at baseline. The authors noted that these differences were not explained by diet or lifestyle aspects and that all participants were nonsmokers. Smoking increases the threat of several chronic diseases related with elevated oxidative stress status. Almonds are a good source of antioxidant nutrients and may lessen smoking related biomarkers of oxidative stress. In smokers, after almond supplementation, the concentration of 8-hydroxy deoxyguanosine (8-OHdG) remained significantly greater than in nonsmokers by 98%. This research suggests that almond intake can boost antioxidant defenses and weaken biomarkers of oxidative stress in smokers[54]. A significant positive association for α-tocopherol and a converse association for lycopene with oxidative DNA damage were found[83]. While not significant when analyzed separately by race, the directions of these associations were consistent for both African-Americans and Whites. There appear to be differences by sex in the association between α-tocopherol and oxidative DNA damage among African-Americans, as there is a strong positive connection in men and a non-statistically significant opposite association in women. Another study comparing α-tocopherol and oxidative DNA damage have not reported a positive association in men and α- tocopherol supplementation has been associated with lower oxidative stress levels in healthy young adults[76]. Prostate cancer is the second leading cause of cancer-related death among U.S.men. According to National Cancer Institute report[63], the prevalence of prostate cancer is higher in African-American men than in Euro-American men. Human prostate tissues are vulnerable to oxidative DNA damage. The threat of prostate cancer is lower in men reporting higher consumption of tomato products, which contain high levels of the antioxidant lycopene[12]. Lycopene, a non-provitamin A carotenoid (i.e., the red pigment in tomatoes), is the most competent singlet oxygen (a reactive oxygen species) quencher among the natural carotenoids[61]. Epidemiologic studies have revealed that, among the antioxidant nutrients, only high lycopene intake or plasma concentrations are associated with a lower danger of prostate cancer. For example, consumption of four or five servings of to-

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mato products per week was associated with a 40% lower risk of prostate cancer in U.S.men[29]. The mechanism by which lycopene reduces prostate cancer risk is blurred. Lycopene has been shown to inhibit proliferation in various cancer cell lines[68], but the poor absorption of carotenoids by laboratory rodents has severely vulnerable the use of animal models in cancer prevention studies to evaluate the effectiveness and mechanism of action of lycopene. In epidemiologi studies[29], tomato sauce consumption is associated with a lower risk of prostate cancer, in part because lycopene may be better absorbed from tomato sauce than from fresh tomatoes or because lycopene is not the only antioxidant in tomato products.

The effect of vitamin B deficiency on mitochondria was reviewed by Depeint et al.[16]. Vitamin B_{12} deficiency is common in the population that is associated with cognitive dysfunction and multiple sclerosis and induces chromosome breaks. The cognitive dysfunction associated with B_{12} deficiency improved with supplementation within the first year of onset[56]. Folate is the most often cited as critical to genomic stability among the nutrients[9]. Folate deficiency also causes chromosome breaks and is associated with several human cancers[23]. Even moderate folate deficiency within the physiological range causes as much DNA damage in cultured lymphocytes as ten times the annual allowed limit of exposure to X-rays and other forms of low linear energy transfer ionizing radiation for the general population[59]. Marginal thiamine deficiency in rats induces the formation of colonic aberrant crypt foci, a preneoplastic lesion in a model for detecting colon carcinogens[16]. Thiamine deficiency is also associated with brain dysfunction and diabetes. Niacin deficiency in cellular and animal studies appears to be genotoxic[16]. Nicotinamide, which is the dietary precursor for NAD+ (nicotinamide adenine dinucleotide), provides a substrate for PARP-1 activity. The activation of nuclear enzyme PARP-1(poly-ADP ribose polymerase) by DNA strand breaks during cellular genotoxic stress responses leads to complex signaling pathway that can enhance DNA repair, result in apoptotic cell death, or cause cellular energy loss leading to necrotic cell death[7]. Nicotinamide and niacin are readily available from plant and animal foods, and niacin can be endogenously synthesized from the amino acid tryptophan[7], which constitutes ~1% of protein in the diet. The main dietary sources of nicotinamide and niacin are various meats, liver, yeast, dairy products, legumes, beans, nuts, seeds, green leafy vegetables, fortified bread, cereals, coffee, and tea[45]. Uncooked foods mostly contain NAD+ and NADP+, which can be enzymatically hydrolysed to nicotinamide in the process of cooking[45]. Studies in adult humans in the 1950s estimated that around 60 mg of tryptophan is hepatically converted to 1 mg of niacin, which is equal to 1 niacin equivalent (NE)[45]. Vitamins B_2 (riboflavin) and B_6 (pyridoxine) in addition to iron are needed as cofactors for conversion of tryptophan to niacin[45]. The ability to convert tryptophan to niacin varies greatly between individuals and is enhanced by protein and tryptophan deficiency, and it is depressed by excessive dietary leucine[45]. Deficiency of nicotinamide and other micronutrients including riboflavin, zinc, and magnesium have been linked to the increased frequency of oesophageal cancer in certain populations in China and Italy[8]. Low dietary niacin has also been associated with an increased frequency of oral, gastric, and colon cancers, as well as oesophageal dysplasia[8]. In the Linxian trial in China, involving nearly 30,000 residents, 40 mg niacin and 3.2 mg riboflavin were supplemented in one of the treatment arms daily for over 5 years. It was shown that this combined supplementation decreased oesophageal cancer incidence and mortality by 14% and 10%, respectively[8]. The impact of niacin on human carcinogenesis is therefore confounded by the effect of other micronutrients. More direct evidence comes from studies in rats, which showed that niacin deficiency significantly increases the risk of chemotherapeutic-induced secondary leukemia[50]. Niacin and NAD+levels are important determinants of genomic responses to genotoxic insults[28].

Ultraviolet (UV) radiation in sunlight is the primary initiator of skin cancer by causing DNA damage in the skin and also by suppressing cutaneous immunity, even at exposure doses 25% to 50% of those required to cause mild sunburn[32]. Both UVB (290–320*nm*) and UVA (320–400*nm*) in sunlight are immune suppressive. UV-induced DNA damage, particularly in the form of cyclobutane pyrimidine dimers, is an important molecular trigger for UV-induced immunosuppression[4]. Agents that can modulate DNA repair and prevent UV-induced immunosuppression may thus reduce skin cancer. In mice, 200 5ØßM topical nicotinamide and 0.5%

and 1% niacin supplemented diets have both been shown to markedly protect against UV-induced immunosuppression and significantly reduce the incidence of UV-induced skin tumours[28]. In these studies, UV-induced immunosuppression was measured by passive transfer assay, whereby splenocytes from irradiated mice enhanced the growth of antigenic tumours in unirradiated, recipient mice[28]. Topical nicotinamide also slowed down the rate of skin tumour development and the effect of oral niacin on tumour inhibition was greater with increasing dose.

Many other micronutrient deficiencies are also associated with chromosome breaks and cancer in humans, cause DNA damage in rodents or human cells in culture, some studies showed that humans fed a low-choline diet develop hepatosteatosis, liver and muscle damage and lymphocyte apoptosis. The risk of developing such organ dysfunction is increased by the presence of single-nucleotide polymorphisms in genes involved in folate and choline metabolism[64]. Choline is a crucial dietary nutrient involved in a multitude of metabolic Roles[88]. It is a major source of methyl groups for methionine synthesis and is needed for the structural integrity of cell membranes, the transport of lipids from the liver and cholinergic neurotransmission[88]. In population studies, diets low in choline was associated with a greater hazard of birth defects[75] and with high homocysteine concentrations in blood. It is reported that some humans fed a diet low in choline developed hepatosteatosis, experienced liver and muscle damage, and had greater lymphocyte apoptosis[24]. Deficiency of Choline in human caused more DNA damage in lymphocytes[14]. In rats, choline deficiency has been associated with brain dysfunction[58], oxidant release and mitochondrial damage[14]. Biotin deficiency is more common than previously thought; mostly pregnant women who do not take a multivitamin show metabolic signs of deficiency[62]. Marginal biotin deficiency is teratogenic in mice[62]. Biotin is a prosthetic group in four biotin-dependent carboxylases (three of which are solely present in mitochondria) that replenish intermediates in the tricarboxylic acid cycle[62]. Biotin deficiency decreases the activity of these enzymes, leading to a decrease of two heme precursors, mitochondrial succinyl-CoA and glycine, thus resulting in heme deficiency[5]. Biotin deficiency in normal human lung fibroblasts in culture caused a 40–50% decrease in heme content, oxidant release, premature senescence, and DNA damage[5].

ROLE OF MINERALS

Iron deficiency is the most common micronutrient deficiency in the world, and anemia is prevalent in underdeveloped countries[12]. In humans, iron deficiency anemia is associated with poor cognitive development in toddlers[58] suggesting that in humans during critical periods of development, iron deficiency harms the developing brain[58]. Iron deficiency also is associated with diminished immune function and neuromuscular abnormalities[82]. Dietary iron deficiency in the absence of anemia decreases aerobic capacity and physical work performance, which are improved by iron supplementation[82]. Iron deficiency in rats caused damages mitochondria and also caused oxidant release, oxidative DNA damage, and decreased mitochondrial efficiency[83].

Zinc is an essential component of numerous proteins involved in the defense against oxidative stress and DNA damage repair. Studies *in vitro* have shown that zinc depletion causes DNA damage[77]. In human cells in culture, zinc deficiency causes the release of oxidants, resulting in significant oxidative damage to DNA[38]. Zinc deficiency also causes chromosome breaks in rats and is associated with cancer in both rodents and humans[25]. Zinc deficiency in human cells also inactivates other zinc-containing proteins such as the tumor suppressor protein p53 and the DNA base excision repair enzyme, apyrimidinic/apurinic endonuclease, with a resulting synergistic effect on genetic damage[38]. Dietary deficiencies in zinc can contribute to single- and double-strand DNA breaks and oxidative modifications to DNA that increase risk for cancer development[37].

Other micronutrient deficiencies associated with chronic degenerative diseases is calcium deficiency which is very common; it has been associated with chromosome breaks[23] and diabetes[69] in humans and colon cancer in mice[55]. Rao et al.[72] reported that selenium deficiency in mice induced genes linked to DNA damage and oxidative stress and it has been suggested that selenium protects against cancer[13]. Another study showed a long-term beneficial effect on cardiovascular disease mortality and medical expenditure associated with a switch from regular salt to potassium-enriched

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salt in a group of elderly veterans. The effect was likely due to a major increase in potassium and a moderate reduction in sodium intakes[11].

ROLE OF FATTY ACIDS

Omega-3 fatty acid deficiency is associated with melanoma and other cancers[15] as well as cognitive dysfunction[57]. A study indicated that increasing dietary levels of polyunsaturated fatty acid (PUFA) to 15% may negatively affect some indices of DNA stability. However, increasing the dietary intake of vitamin E by 80 mg/day lessens the damaging effects of PUFA[43]. Vitamin E consumption decreases the DNA damage detected after exhaustive exercise, suggesting that additional vitamin E can prevent oxidative damage to DNA[36]. Consumption of diets lacking in antioxidants such as vitamin E and selenium increases DNA damage in rats, particularly when the level of dietary PUFA is raised[31]. Numerous studies have implicated that fatty acids, dietary fat and obesity play a role in cancer development[60]. Fatty acids are the building blocks of fat and exist either in free forms or components of triacylglycerol, phospholipids, and cholesterol. The concentration of free fatty acids in serum, is >500 μM under normal conditions and >1200 μM under fasting, with palmitic acid accounting for 28%[27]. They can be obtained from the dietary fat or synthesized in the cells, especially in lipogenic tissues such as liver, adipose, and lactating breast. Fatty acids are synthesized by fatty acid synthase (FASN) using malonyl-CoA and acetyl-CoA as substrates. For people with a balanced diet, *de novo* fatty acid synthesis is insignificant and FASN protein level is very low in lipogenic as well as other tissues. Fatty acids play important roles in energy storage, membrane structure, protein acylation, signal transduction, and regulation of gene transcription[67]. However, cancer cells, especially of the breast, prostate, colon, ovary, endometrium, and thyroid origin, express very high levels of FASN[51]. Fatty acid synthase is also expressed in early stages of tumor development or precancer lesions such as colonic adenoma, dysplastic squamous epithelium, and carcinoma of the tongue, although this up-regulation is more pronounced in the late stages of tumors. Moreover, FASN can be detected in the serum of these patients and this can be used as a diagnostic marker. Studies specified that saturated fatty acids (SFAs) could compromise DNA damage-induced cell response in primary cells but not in immortalized cells. Pretreatment with palmitic acid, myristic acid, or stearic acid enhanced cell proliferation[89]. The actions of SFAs in DNA damage response might also be one of the mechanisms underlying the association between high dietary fat/obesity and tumorigenesis[47]. Cells with active fatty acids metabolism might have defect in cell cycle arrest or apoptosis in response to genotoxic stress. The major cancers associated with obesity are breast, prostate, endometrium, colon, and gallbladder cancers. Most of these cancer types express very high levels of FASN[82]. Noteworthy is that the correlation between high dietary fat and increased risk for tumorigenesis is still controversial except in ovarian cancer[71]. Inhibitors of FASN have been found to induce apoptosis in cancer cells that have high levels of FASN. These include breast, prostate, colon, and lung cancers. An increase in SFA levels compromises DNA damage response while inhibition of FAs synthesis boosts these cellular events, lowering the cellular level of FAs might reduce the risks of cancer development. In addition, lowering the cellular level of FAs might also improve the effectiveness of radiotherapy and chemotherapy with genotoxic drugs. Some chemotherapeutic drugs such as cyclophosphamide, busulfan, cisplatin, and mitomycin cause interstrand and/or intrastrand crosslinks, while some, e.g., irinotecan and dactinomycin, affect DNA unwinding and therefore DNA replication[49].

BIOFLAVONOIDS

Flavonoids comprise the most common group of plant polyphenols and provide much of the flavor and color to fruits and vegetables. More than 5000 different flavonoids have been described. The six major subclasses of flavonoids include the flavones (e.g., apigenin, luteolin), flavonols (e.g., quercetin, myricetin), flavanones (e.g., naringenin, hesperidin), catechins or flavanols (e.g., epicatechin, gallocatechin), anthocyanidins (e.g., cyanidin, pelargonidin), and isoflavones (e.g., genistein, daidzein). Flavonoids consumption has been linked to protection against heart disease and cancers[74]. Bioflavonoids, which are generally considered fairly beneficial, can cause breaks in DNA that may trigger the progress of infant leukemia. Some bioflavonoids were as vigorous in causing DNA

damage as the powerful anticancer drug etoposide, or VP16, which has been tide to secondary leukemia—bone marrow cancers that result from previous anticancer therapy[20]. Even though bioflavonoids may be beneficial in certain circumstances, but some studies suggested that high dietary intake of bioflavonoids could cause DNA breaks in myeloid-lymphoid leukemia and probably in other partner genes, infant leukemias are rare, affecting only about 37 out of every 1 million children in the United States[20]. Some researchers have disputed that the cause may be an infectious agent, but epidemiological studies have suggested that maternal consumption of foods, such as bioflavonoids, could lead to an increased risk of infant leukemia[20]. The health benefits of a diet high in foods containing bioflavonoids such as soybeans, citrus fruits and root vegetables are unquestioned. The possible benefits of bioflavonoids themselves also have been demonstrated, such as the low mortality rates from prostate cancer in Asian men compared to Western countries, which may be because of higher intake of isoflavones. The benefits of dietary supplements containing bioflavonoids, however, may not be so believable. This study suggests that pregnant women, at least, should be especially vigilant about taking such supplements or even eating a diet high in bioflavonoids[20].

Bioflavonoids have a relatively high antioxidant value as compared to other foods and supplements. Scientists have also showed that bioflavonoids can actually combine with vitamin C for a specific antioxidant effect: the bioflavonoids can apparently protect the vitamin C nutrient from oxidizers inside the body. It is a kind of preservative for helpful chemicals that can help the body's immune system and fight off chronic conditions. Noroozi et al.[65] assessed the antioxidant potencies of several widespread dietary flavonoids across a range of concentrations and compared with vitamin C as a positive control. Pretreatment with all flavonoids and vitamin C produced dose-dependent reductions in oxidative DNA damage. At a concentration of 279 micromol/L, they were ranked in decreasing order of potency as follows: luteolin (9% of damage from unopposed hydrogen peroxide), myricetin (10%), quercetin (22%), kaempferol (32%), quercitrin (quercetin-3-L-rhamnoside) (45%), apigenin (59%), quercetin-3-glucoside (62%), rutin (quercetin-3-beta-D-rutinoside) (82%), and vitamin C (78%). The protective effect of vitamin C against DNA damage at this concentration was significantly less than that of all the flavonoids except apigenin, quercetin-3-glucoside, and rutin. The ranking was similar with estimated ED50 (concentration to produce 50% protection) values. The protective effect of quercetin and vitamin C at a concentration of 23.2 micromol/L was found to be additive (quercetin: 71% of maximal DNA damage from unopposed hydrogen peroxide; vitamin C: 83%; both in combination: 62%). These data suggest that the free flavonoids are more protective than the conjugated flavonoids (eg, quercetin compared with its conjugate quercetin-3-glucoside, $P < 0.001$). Data are also consistent with the hypothesis that antioxidant activity of free flavonoids is related to the number and position of hydroxyl groups.

Duthie et al.[19] investigated the effects of the flavonoids quercetin, myricetin and silymarin on DNA damage and cytotoxicity in human cells. Caco-2 (colon), HepG2 (liver), HeLa (epithelial) cells and normal human lymphocytes showed different, dose-dependent susceptibilities (in terms of strand breakage) to the various flavonoids, quercetin being the most damaging. This agreed well with the ability of the flavonoids to inhibit cell growth. None of the flavonoids induced DNA base oxidation above background levels. All of the flavonoids under investigation caused depletion of reduced glutathione, which, in the case of quercetin, occurred prior to cell death. Neither cytotoxicity nor genotoxicity was associated with the antioxidant enzyme capacity (glutathione, glutathione reductase, glutathione peroxidase and catalase) of the cells.

CONCLUSIONS

Deoxyribonucleic acid damage is a primary cause of developmental and degenerative diseases. There are thousands of DNA variations in each human cell daily; if not proficiently repaired, our genome would quickly be destroyed. Diet and lifestyle are major mediating. Deoxyribonucleic acid damage is speed up by oxidative stressors such as tobacco smoke, exhausting exercise, and a high-fat diet, There are nine key nutrients that may affect genomic integrity in different ways. When consumed in increasing amounts in food, six of the nutrients (folate, vitamin B_{12}, niacin, vitamin E, retinol, and calcium) are associated with a reduction in DNA damage, whereas three others (riboflavin, pantothenic acid,

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and biotin) are associated with an increase in DNA damage to the same degree observed with occupational exposure to genotoxic and carcinogenic chemicals. It has been recommended that oxidative DNA damage is associated with elevated cancer risk and that antioxidants may lessen the effects of oxidative DNA damage. In addition, diets high in fruits and vegetables, and which are also rich in antioxidants, have consistently been linked to lower threat of many cancers, including those of the breast, colon/rectum, and prostate. As the diet gene interactions are highly multifarious and hard to calculate, thus demonstrating the need for highly controlled genotypes and environmental conditions that allow for identifying different regulatory patterns based on diet and genotype. Many micronutrients and vitamins are vital for DNA synthesis/repair and protection of DNA methylation patterns. Folate has been most widely investigated in this regard because of its distinctive function as methyl donor for nucleotide synthesis and biological methylation. Cell culture and animal and human studies showed that deficiency of folate stimulates disruption of DNA as well as variations in DNA methylation status. We should focus better our attention on defining optimal requirements of key minerals and vitamins for preventing damage to both nuclear and mitochondrial DNA. Poor lifestyles demonstrate cumulative association with leukocyte DNA damage

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