Review article

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DNA oxidation-based analysis: A new approach to assessing the relationship between nutrition and cancer

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ABSTRACT

Background: DNA oxidation is one of the essential destructive effects of reactive oxygen species (ROS) on the cell membrane macromolecules leading to the deformation of cellular DNA. The most abundant oxidative DNA product on which most studies have focused is re-oxidized DNA, 8 oxo-deoxyguanosine (8-oxodG). This deformation of cellular DNA is associated with various cancer initiation and progression. DNA damage can be a cancer marker including 8-oxodG, thymidine glycol, 8-oxoadenine, etc. DNA oxidation is affected by environmental and non-environmental factors. Age, diet, and metabolism are at the heart of this process. This review study summarizes the types of cancer-related DNA oxidation that serve as a cancer biomarker. Also, we will look at the factors influencing their formation.

Keywords: Cancer, DNA, Oxidative damage, Mutation

INTRODUCTION:

Cancer is a complex disease in which cells undergo multiple changes in gene transcription that lead to abnormal cell growth, cell dysfunction, and invasion of other tissues [1, 2]. Several important gene mutations make fundamental changes in genes inducing cell division and preventing cell death, and making changes that balance the survival of cancer cells. These events have been well established in various cancers [3-5]. Finally, the accumulation of several fundamental mutations is necessary to transform a neoplasia to cancer [6]. ROS are considered undesirable by-products of aerobic metabolism [7]. They have been recognized as critical signaling molecules [8]. They contribute to dual effects on biological systems. They have adverse effects at physiologic levels and involve various normal cell functions, including regulation of proliferation, differentiation, epigenetic modification, and quiescence [9, 10]. Therefore, maintaining the ROS levels at normal physiologic levels is crucial for biological systems [11]. However, altered ROS hemostasis plays a significant role in protein, lipid, and DNA damage and subsequent disruption of cell functions [12, 13]. In the case of oxidative stress, considering the adverse effects of ROS are more critical because of disruption of redox balance signaling and oxidative damage to biomolecule particularlyoxidation of DNA [12, 14]. Based on solid experimental studies, cancer cells depend on an increased level of ROS to promote tumor initiation, progression, and metastasis [15]. The possible underlying mechanism by which ROS can mediate cancer development processes is DNA oxidative damage [16]. DNA oxidation products increasingly have attracted much attention in this regard. DNA oxidation products, including 8 oxo-deoxyguanosine (8-oxodG), thymidine glycol, and 8-oxoadenine, were potential cancer trigger agents [17, 18]. Understanding the DNA oxidative abortion to cancer and factors increasing ROS formation and DNA damage production can move forward knowledge. We aimed to survey the possible sources of DNA oxidation leading to cancer and their underlying mechanism

Methods:

Search strategy

In this study, published clinical practices, articles, and recommendations on the relationship between nutrition and cancer were searched manually and systematically on relevant websites such as Google Scholar, PubMed and Scopus up to June 2022.

ROS and oxidative stress:

Reactive oxygen species (ROS) are produced endogenously during normal cellular metabolic processes such as respiration and other biochemical reactions [19, 20]. These free radicals also enter the human body exogenously from the environment or diet. If the antioxidant system cannot eliminate them, they had many destructive effects on the body's cellular system [21, 22]. They attack and damage vital cellular structures and biomolecules [22]. We have several sources for ROS in the body, which mainly consist of superoxide anion (O2−), hydrogen peroxide (H2O2), and hydroxyl radicals (OH·) [23-25]. During aerobic respiration in the mitochondria, 1-5% of oxygen undergoes a single electron transfer and produces a superoxide radical anion that reaches about 2 kg per year in humans [26-28]. Superoxide has a limited function but can be converted to hydrogen peroxide, which is a potentially active free radical [23, 24]. In heavy metals such as iron and copper, hydrogen peroxide is converted to a very strong hydroxyl free radical [29, 30]. Oxygen-free radicals also enter the body through polluted air and smoke [29, 30]. The hydroxyl type of ROS is a highly reactive free radical that indiscriminately oxidizes DNA, resulting in damage or genomic instability [31]. Different kinds of carcinogens, such as benzene, aflatoxin, and benzoapyrene, partially mediated their effects via ROS formation during metabolism [32-34]. Similarly, the resumption of blood flow following ischemia in tissues leads to the production of ROS by multiple mechanisms [35, 36]. Arachidonic acid metabolism also produces reactive oxygen species. In addition, cellular respiration in leukocytes produces superoxide and hypochlorous oxide [23]. Ionizing and UV radiation are also a potential

carcinogen and a pure source of ROS, which increase urinary excretion of oxidative DNA damage biomarkers as well as their leukocyte levels [37, 38]. Smoking is another source of oxygen free radicals that increase the rate of DNA oxidative damage by 35-50% [30]. In terms of cellular instructions, mitochondria are the major source of ROS in the cell and its DNA is thought to be particularly susceptible to oxidative damage [39]. Experimental models with deletion of mitochondrial matrix superoxide dismutase (SOD) exhibit increased mitochondrial DNA damage and cancer incidence [40, 41]. DNA oxidation products such as 8-oxodG are often thought of as indicators of oxidative stress [37]. This deformation of cellular DNA is associated with cancer progression.

DNA damage and cancer:

AOur knowledge of cancer pathogenesis is required for cancer prevention and treatment. In living cells, reactive oxygen species are continuously formed following biochemical reactions and a network of external factors [21, 22]. Elimination of ROS by the antioxidant defense system is often ineffective, and this damage caused by ROS plays a vital role in carcinogenesis and many age-related degenerative diseases [42-46]. In fact, ROS is involved in several stages of carcinogenesis [45, 47]. These free radicals cause DNA damage, and cell division leads to mutations with unrepaired damage or improper repair. If this happens in vital genes such as oncogenes or tumor-suppressor genes, it is likely to trigger the onset or progression of the mutation. Tumor-suppressor genes regulate the cell growth, cell division and replication [48]. When a tumor suppressor gene is mutated in combination with other mutations, it can allow a cell to grow abnormally [49]. Loss of function of these genes may be more significant in the development of cancers [49]. Some of these tumor-suppressor genes are p53, Rb (Retinoblastoma) and VHL (Von Hippel–Lindau) [50, 51]. The main function of p53 gene is apoptosis [50]. Rb gene functions are regulating DNA replication, cell division and death [50]. Moreover, VHL gene functions are differentiation, cell division and death [51]. By contrast, oncogenes contribute to initiation [52]. In tumor cells, these oncogenes are often expressed at high levels [53]. Consequently, oncogenes convert to proto-oncogenes including RAS (Rat sarcoma virus), MYC (myelocytomatosis oncogene)and TRK (receptor tyrosine kinases) [53] RAS, MYC and TRK [54]. ROS can directly interfere with cellular messaging pathways and their growth [47, 55]. As a consequence of DNA oxidation, some specific growth factors, including epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) are over-expressed [56, 57]. They activate the intrinsic tyrosine kinase activity of their receptors (RTK)resulting in phosphorylation of specific tyrosine residues on the cytoplasmic tails of the receptor such as PI3KAKT and RAS-MEK-ERK [58]. Activation of these signaling pathways promotes cell proliferation, nutrient uptake, and cell survival [58]. Cell damage caused by these free radicals can induce mitosis. Therefore, exposure to ROS and mutagenic agents increases the risk of DNA damage and mutation [59]. Some mutations also can occur during mitosis, recombination, gene alterations, and gene binding. In addition, some transformation may occur during uncontrolled colonization and cell division that results from the activation of an oncogene or the inactivation of a tumor suppressor [59]. Data have shown an association between oxidative DNA damage and cancer risk at both the molecular level and the level of epidemiological studies. Case-control and cohort studies are commonly used to investigate the potential risk factors and protectives. However, these studies have some limitations, and the causality should be inferred cautiously. For example, the case-control design compared healthy subjects with cancer patients. Therefore it is difficult to measure the association of micronutrients with the disease. The disease process also affects the intake and metabolism of various nutrients. On the other hand, cohort studies require a lot of time and budget, limiting the implementation of such studies in cancer research. Therefore, a valid molecular index that is a predictor of long-term cancer risk and related to dietary intakes in the general population can be helpful in this regard. As

Table 1. Types of DNA damage

DNA chain failure	Telomere shortening	DNA methylation
Point mutation	Apurinic Stations	Chromosomal aberrations
Mitochondrial DNA mutation	DNA accumulation	Micronucleus
Nuclear p53 mutation	DNA oxidation	aneuploidy

this index is measured in healthy people, the disease process does not affect it.

Different types of DNA damage are associated with cancer risk. These injuries are summarized in Table 1. Among these injuries, oxidative DNA damage is most associated with food intake and can be measured by laboratory methods [60]. Human studies empirically point to the basic concept of oxidative DNA damage as an essential mutagenic and major carcinogen [61]. In addition, this oxidative damage plays a vital role in the aging process [62], especially in connection with mitochondrial DNA and the pathogenicity of inflammatory diseases [63].

DNA oxidation products:

Products of oxidative DNA damage range from purine and oxidized pyrimidines to alkaline instability and chain breakage, base or sugar removal, or AP (apurinic/apyrimidinic) sites formed during oxidation and repair processes [64-66]. The most abundant oxidative DNA product on which most studies have focused is re-oxidized DNA, 8-oxodG [33, 67, 68]. Open oxidation of guanine opens the ring and produces 2,6-diamino-4-hydroxy-5-formamidopyrimidine [64]. Other abundant oxidized bases of DNA include 8-oxoadenine, 2-hydroxyadenine, FapyAdenin, 5-hydroxymethyl uracil, and 5-hydroxy cytosine, cytosine glycol, and thymidine glycol (Tg). 5-methylcytosine (5-mC) is the other oxidized derivate of DNA in mammals [69]. In addition, many other changes occur in the structure of DNA sugars [64, 65]. Individual differences in DNA primarily depend on the type of reactive oxygen species involved in the reaction. Single oxygen explicitly induces the production of 8-oxide [37]. While superoxide has very little activity in generating these effects, hydroxyl radicals cause any oxidative damage [64, 70]. Apart from these factors, other factors such as oxygen pressure, chelation with metals and reductant presence, can affect the oxidation pattern and DNA change [64, 65].

Consequences of oxidative DNA damage:

Numerous animal and laboratory studies have shown that oxidative DNA damage is an important carcinogen. Despite repair systems, oxidized DNA is abundant in human tissues, especially tumors. If the oxidative DNA damage is not repaired or the repair occurs after replication, it causes mutations in the DNA bases [71]. Studies in bacteriophages and plasmids have identified the spectrum of mutations produced in DNA by free radicals. These studies show that although ionizing radiation causes oxidative damage in all four residues including adenine (A), cytosine (C), guanine (G), and thymine (T), oxidative damage is more abundant and mutagenic in the GC base pair of oncogenes and tumor-suppressor genes. In contrast mutations in the AT base pair of oncogenes and tumor-suppressor genes are rare and less mutagenic ([72]and references therein). Mutations in hot spots are clustered and mainly occur in substituting bases. While open deletion, chain deletion, and open addition occur less frequently. Hydroxyl radicals produced from ionizing radiation especially replace GC, CG, and AT bases, and depending on the DNA replication system; they return GC with AT [72]. Single oxygen and 1,2-dioxetane preferentially induce 8-oxodG production and GC substitution. Similarly, modified guanine, such as 8-oxoG, and apurinic sites

are incorrectly repaired with adenine, depending on the adjacent bases and the type of polymerase involved [73-75]. In contrast, modified adenine, such as 8-oxoA, does not mispair and does not cause mutations [76]. Therefore, most of the mutations caused by ROS in DNA are related to guanine base, especially 8-oxoG, because guanine is converted to thymine. 8-oxodG also induces activation of 12 c-Ha-ras or K-ras oncogene codons in mammalian organs [75, 77-79]. In human tumors, the conversion of guanine to thymine is abundant in the hot spot in the p53 tumor suppressor gene [80, 81]. In addition, in human fibroblasts, free radicals generated by iron and hydrogen peroxide induce GT and CA in the hot spot of 249 critical codons in p53 (tumor suppressor gene) [82]. In addition to mutations associated with improper repair in oxidized bases, ROSs may impair the proper function of β-DNA polymerase, alter cytosine methylation, and thus lack reasonable gene control [83, 84].

DNA oxidative alteration and its association with cancer are observed in many cancerous tissues. Patients with lung cancer have 25-75 bases of 8-oxodG per 105 bases of deoxyguanine in their normal tissues, which is 2-3 times higher in tumors. In addition, there are other oxidized bases of DNA [85]. Urinary excretion of 8-oxodG and related biomarkers indicate the rate of oxidative DNA change at about 104 bases per cell per day [68, 86-88]. Laboratory studies of carcinogenic oxidants, 8-oxodG, and other oxidative changes accumulate in tumor tissues [89, 90]. In rats, nickel-induced renal sarcoma, which converts GGT to GTT, has also been associated with 8-oxodG and mutations related to the 12 oncogene codons K-ras [79].

Also, laboratory reports of 8-oxodG accumulation and its correlation with mitochondrial DNA deletion in human heart muscle indicate the role of oxidative DNA change in the respiratory chain in weakly aged muscles [91]. Similarly, 8-oxodG increases with age in nuclear DNA and brain mitochondria [92].

The incidence of cancer increases with age [93]. This shows that oxygen consumption is one of the most important determinants of cancer in humans [94]. This hypothesis was reinforced when evidence of increased cancer incidence was observed in hyperthyroid women [95]. There is a strong correlation between oxygen uptake and 8-oxodG secretion in normal-weight healthy women. Observational studies such as nested case-control have shown an association between oxidative DNA damage and cancer [96]. These studies are a starting point, but there is still no finding on the causal relationship between DNA damage and cancer progression. However, a linear relationship has been observed between the two operations where DNA damage can lead to cancer. Different cancers occur in growing and increasing epithelial tissues, so it can be assumed that the stability of growing and developing cells and oxidative stress to DNA are determinants of cancer progression [44, 97].

Assessment of oxidative DNA damage and its biomarkers:

• Cellular DNA:

The presence of oxidative DNA damage in the genome and mitochondria of isolated tissues and cells has been studied by several methods. Gas chromatography / GC / MS-SIM spectroscopy is separated after acid hydrolysis of chromatin or DNA. Finally, DNA alkali derivatives degree of damage, and 20 different products of bases and DNA oxides are examined [64, 98]. For quantitative analysis, isotopes as an internal standard are suggested. However, the most commonly used method today is the enzymatic digestion of DNA isolated with different products into nucleotides. Nucleotides are usually hydrolyzed to nucleosides by alkaline phosphatase, separated by high-performance liquid chromatography (HPLC), and detected by UV and 8-oxodG electroscopy [99]. With this method, the ratio of altered DNA in nucleosides to healthy DNA can be easily measured. Immunological methods such as enzyme-linked immunosorbent assay (ELISA) can also determine 8-oxodG [100, 101].

• Urine:

Among the various oxidized DNA products, 8-oxodG, Tg, dTg, 8-oxoguanin, and 5-hydroxymethyluracil are most abundant in urine [68, 86, 102-104]. Among the mentioned factors, 8-oxodG and thymine derivatives

have been studied more.

Oxidized products from DNA repair, such as bases and oxidized nucleosides, are not suitable substrates for enzymes involved in nucleotide synthesis. Because these products are soluble in water, they are often excreted without metabolism in the same way in the urine [68, 105]. By injecting 8-oxodG, all of it is excreted in the urine within 4 hours [105]. However, urinary 8-oxodG measurements are often used to assess DNA damage [105]. DNA repair products are analyzed by the HPLC method to determine and identify 8-oxodG and 8-oxoguanine and by UV method to identify Tg, dTg, and GC / MS-SIM method is used for the sizes of all these repair products [106, 107]. But urinary 8-oxodG is not very reliable. First, it may be derived from dietary ribonucleotides, and second, it may be derived from cellular RNA [108]. It is also possible for the DNA of dead cells to undergo oxidative changes. Urinary excretion increases dramatically during rapid and extensive repair and therefore reflects the suffering of the average oxidative DNA damage in all body cells [108]. In contrast, levels of oxidized DNA bases in lymphocytes or other available cells, such as 8-oxodG, indicate equilibrium levels because they are not absorbed through the gastrointestinal tract. For example, the balance between damage and repair. But it only represents balance in the target tissue. Accordingly, the two groups of biomarkers (cellular and urinary surface) are complementary. It is better to measure both biomarkers together to estimate the exact amount of oxidative damage to DNA bases.

Determinants of oxidative DNA damage:

Most studies have consistently focused on 8-oxodG as the measurement criterion among all oxidized DNA products. Although there is good agreement on urinary excretion and tissue levels of oxidized products from DNA repair, it usually depends on the laboratory method being measured. For example, GS / MS reports 100-10 times higher than high performance liquid chromatography with electrochemical detection (HPLC-EC) values. One of the most critical determinants of oxidative DNA damage is metabolism and diet [109].

Metabolism and diet:

A close association has been shown between the urinary excretion of 8-oxodG and 24-hour oxygen consumption or changes in resting metabolism after human energy restriction [110, 111]. A similar correlation, including dTg excretion, has been reported across spices [87, 112, 113]. The apparent link between DNA oxidative damage and oxygen consumption is due to the conversion of 1-5% of individual electrons to free radicals during the mitochondrial respiration process [114]. The formation of hydrogen peroxide per mg of mitochondrial protein and mitochondrial level correlates with basal metabolic rate [115, 116]. Accordingly, 8-oxodG is 10-5 times more abundant in mitochondrial DNA than cell nucleus DNA [89, 117, 118]. In rats, the accumulation of 8-oxodG in liver tissue and the progression of perineoplastic injuries, and regression of Ethinyl estradiol-induced hepatocellular cells were reduced by injection of antioxidants, vitamins A, E, and β-carotene [90]. In rodents, energy restriction continuously increases life expectancy and reduces carcinogens' spontaneous induction of tumors. This effect is likely associated with decreased basal metabolic rate, improved electron coupling in the mitochondrial respiratory chain, and decreased ROS production [119, 120]. In addition, it can increase the activity or gene expression of antioxidant enzymes and DNA translators [119, 121]. Accordingly, in rodents, energy restriction is associated with decreased levels of oxidative change in nuclear DNA and mitochondria in the liver and mammary glands [122, 123] and reduced lipid peroxidation and protein oxidation [119, 120, 124, 125]. Similarly, in a human, an energy limit of 40-50% for ten days reduces urinary excretion of 8-oxodG and dTg by 50-80% [107]. In a controlled study, 16 patients who were on an 80% calorie weight maintenance diet for ten weeks had a slight increase in 8-oxodG urinary excretion and Showed no change in 8-oxodG levels in lymphocytes DNA compared with the control group (100% calorie for weight maintenance) [110, 126]. Reduce fat intake by up to 15% energy for 3-24 months, had decreased 68% of 5-hydroxy uracil levels in circulating lymphocyte DNA in 9 of 21 women at risk for breast cancer compared with 12 wom-

en on a high-fat diet (more than 30% of energy) [127]. Due to the effect of metabolism and diet on the rate of oxidative DNA damage, there is a clear relationship between oxygen uptake and increased damage.

At the epidemiological level, there are many studies on the relationship between the consumption of fruits and vegetables and some specific dietary antioxidants such as vitamin C, carotenoids, and vitamin E and the relatively low prevalence of some cancers [128]. There are several mechanisms for this, but various studies have shown that the administration and consumption of fruits and vegetables reduce oxidative DNA damage as a biomarker of DNA damage [109]. Dietary antioxidants play a vital role in the overall protection against cancer by eliminating reactive oxygen species before they can damage biological molecules [129]. In cross-sectional studies, Brussels sprout-rich diets reduce DNA damage by estimating 8-oxodG urinary excretion [130, 131]. Vitamin C intake is a determining factor in the amount of 8-oxodG in sperm DNA [132].

Disease:

In patients at risk for cancer progressions, such as Fanconi anemia, chronic hepatitis, cystic fibrosis, and multiple autoimmune diseases, studies on biomarkers showed increased levels of oxidative DNA damage or significant defects in the repair system [97, 133-136]. Epidemiological evidence from cross-sectional, longitudinal (cohort), and case-control studies suggests a reduced risk of cancer, particularly gastrointestinal and airway cancer, in association with antioxidant-rich diets or high plasma antioxidant content [137, 138]. Antioxidants such as vitamin E, β-carotene, and selenium have been shown to reduce the risk of gastric cancer in high-risk, micronutrient-deficient populations [139]. However, in several interventional studies, the effect of these antioxidants in preventing the risk of lung and colon cancer has not been successful [140]. Therefore, it is necessary to define and explain the oxidative damage of DNA in carcinogenesis. In addition, it may improve the possibility of using interventional studies to determine the primary endpoint for cancer before a clinical trial. In this regard, S. Loft conducted a survey of oxidative DNA damage estimation and risk factors in humans, especially 8-oxodG [132]. At the laboratory level, assessments such as cytokinesis-block micronucleus (CBMN) can determine the effect of diet on DNA damage at baseline. Still, such studies are not limited to dietary recommendations [141]. They are essential, but they are also crucial in interpreting biomarker data (DNA damage) used to determine the biological dose of exposure to genotoxins or predict cancer.

Numerous studies have shown that dietary folate and B12 deficiency are essential determinants of DNA damage. Higher recommended dietary allowance (RDA) intakes of these vitamins may be necessary for subgroups to minimize DNA damage [142]. These findings indicate that to determine the values of RDA, determining the amount required for genome stability is a practical and accurate method [143, 144]. The importance of this method is further emphasized by the fact that several micronutrients such as zinc, magnesium, folate, and B12 are cofactors of DNA metabolism, and the deficiency of each cofactor may eventually lead to significant mutations and increase the risk of cancer [145, 146]. (For example, p53 activity depends on the amount of zinc received, and p53 is essential for genome stability and normal cell function) [147]. Because cancer takes several years to decades to develop, it is always impossible to conduct prospective epidemiological studies (cohorts) for such long periods [42]. On the other hand, because the degree of DNA damage is subject to the disease process, the damage is always significant in sick people. For example, cancer, rheumatoid arthritis, and diabetes are always associated with oxidative damage [109]. The disease process also affects food intake, so case-control studies are limited and should be evaluated in healthy individuals. An alternative study is a molecular epidemiological study that does not have the above limitations. But its success rate depends on the reliability of the biomarker examined. So we can imagine the possibility of using biomarkers of oxidative DNA damage to predict cancer risk. Because they provide a better understanding of how dietary factors can modulate genome stability.

Conclusion:

The most abundant oxidative DNA modification, 8oxodG, is also the most mutagenic, resulting in GT transversions frequently found in tumor-relevant genes. Many other oxidative changes of base and sugar residues often occur in DNA, but they are less well studied and their biological significance less apparent. DNA oxidation is affected by age, diet, metabolism, disease, etc. The data from human studies support the experimentally based notion of oxidative DNA damage as an essential mutagenic and carcinogenic factor. However, proof of causal relationships in humans is still lacking. The use of the biomarkers may provide this evidence and allow further investigation of the qualitative and quantitative importance of oxidative DNA modification and carcinogenesis in humans and elucidate possible preventive measures.

Abbreviation:

5-methylcytosine (5-mC)8 oxo-deoxyguanosine (8-oxodG)
Apurinic/apyrimidinic (AP)
Cytokinesis-block micronucleus (CBMN)
Enzyme-linked immunosorbent assay (ELISA)
Epidermal growth factor (EGF)
High-performance liquid chromatography (HPLC)
High performance liquid chromatography with electrochemical detection (HPLC-EC)
yelocytomatosis oncogene (MYC)
Platelet-derived growth factor (PDGF)
Rat sarcoma virus (RAS)
Reactive oxygen species (ROS)
Receptor tyrosine kinases (RTK)
Recommended dietary allowance (RDA)
Superoxide dismutase (SOD)
Thymidine glycol (Tg)
(TRK) receptor tyrosine kinases
Von Hippel–Lindau (VHL)

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