Chapter 31

Diet and Nutrition

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Chapter Outline

1. INTRODUCTION

While much media publicity points to exogenous causes of cancer such as cigarette smoking or occupational hazards, the evidence may be somewhat weaker as to the role of diet and nutrition. The monographs of the International Agency for Research on Cancer (IARC) provide excellent summaries, provided by international working groups, definitively showing that tobacco exposure [1], certain office working environments, and various other occupational exposures are unequivocally associated with human cancer risk [2]. DNA damage can occur through unintentional exposure to genotoxic chemicals in the diet, which may induce oxidation, DNA alkylation, cross-linking, dimerization, and strand breaks. As such, repair of this DNA damage (or protection against its formation) is essential to preserving genome stability.

Dietary factors play a well-established role in increasing cancer risk, through enhancing genomic instability. Vromman et al. ranked food components and environmental contaminants of food in terms of their potential hazard [3]. They considered arsenic and lead to be of high concern, while cadmium, methylmercury, dioxins, polychlorinated biphenyls, and toxaphene were ranked as medium priority. Although posing some risk at high levels, polybrominated biphenyls, chlordane, heptachlor, dichlorodiphenyl-trichloroethane, hexachlorocyclohexane, polychlorophenols, and their salts were classed as lower priority. Many of the reported exposures to such compounds may be inadvertent, through environmental pollutants that are accumulated by plants and animals eaten by humans [4], through mycotoxin formation on badly stored foods [5], or exposure to various cooked food mutagens/carcinogens [6,7]. However, because we eat a mixed diet, definitive human proof of many of these effects may not be as easily obtained. Furthermore, it is unethical to continue exposure to a putative mutagen/carcinogen in the expectation of providing definitive evidence of human harm. Thus, molecular evidence of genomic instability as a biomarker of cancer risk or likely cancer protection may be both more desirable and more readily obtained [8].

Dietary factors also play an essential role in protection against genomic instability, and there is increasing evidence for this [9]. In the long term, exploiting such beneficial dietary items and encouraging their increase in the diet may be the most constructive approach to protecting against human genomic instability and cancer initiation and progression.

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2. DIETARY CAUSES OF GENOMIC INSTABILITY

2.1 Dietary Excess (Obesity)

Obesity results from excess weight accumulation, generally considered to be caused by an excess of caloric energy intake in comparison with the amounts used in metabolism or consumed through exercise (Fig. 31.1). Increased oxidative stress is distinctive of obesity [10]. This condition occurs where there is an excessive production of reactive oxygen species (ROS), in comparison with the level of natural antioxidants. Enhanced ROS production is associated with a mitochondrial dysfunction in these individuals [11], and may affect the regulation of DNA methylation [12]. Global hypomethylation in repetitive sequences of the genome provides an important mechanism by which cells develop genomic instability [13]. Hypomethylation may be especially important where it occurs on the promoter of oncogenes. Delgado-Cruzata and coworkers studied the effects of weight loss on global DNA methylation in Hispanic, African-American, and Afro-Caribbean breast cancer survivors [14]. They found that DNA methylation of long interspersed nucleotide element 1 (LINE-1) was statistically significantly elevated after the intervention. Conversely, excess weight accumulation is associated with lower DNA-methylation levels.

Various posttranslational modifications alter the function of histones [15]. For example, acetylation of the lysine residues at the N-terminus of histone proteins leads to a reduction in the affinity between histones and DNA, enabling the access of RNA polymerase and transcription factors to gene-promoter regions [16]. In general, transcription is enhanced by histone acetylation and repressed by histone deacetylation. Histone ubiquitination modifies DNA-repair capacity, leading to chromatin structures conducive to the assembly of nucleotide excision repair (NER) complexes on damaged DNA [17]. Histone phosphorylation is required for efficient DNA repair. The net impact of perturbation of epigenetic mechanisms contributes significantly to genomic instability. Obesity has been found to have significant (adverse) effects on the function of histones [18,19].

Mitochondrial (mt) DNA alterations lead to oxidative phosphorylation and the generation of adenosine triphosphate (ATP) and ROS. Not only somatic mtDNA mutations, but also changes in mtDNA copy number have been shown to lead to mitochondrial dysfunction and increased genomic instability [20,21]. Mitochondrial dysfunctions have often been related to obesity and/or lipid imbalances in the diet, since mitochondrial membranes are lipid based and their maintenance is essential to the effective functioning of the mitochondria [22,23].

2.2 Alcohol

High alcohol consumption has been associated with increased carcinogenicity of the upper gastrointestinal tract. The primary mechanism of this has been suggested as through the formation of acetaldehyde, a metabolite of ethanol which can form DNA adducts [24].

2.3 Red Meats

Red meats include beef, veal, pork, lamb, mutton, horse, or goat meat. High red meat intake has been related to an increased risk of cancer, and this appears at least partly to associate with cooking processes (Fig. 31.2). Heterocyclic amines (HCAs)

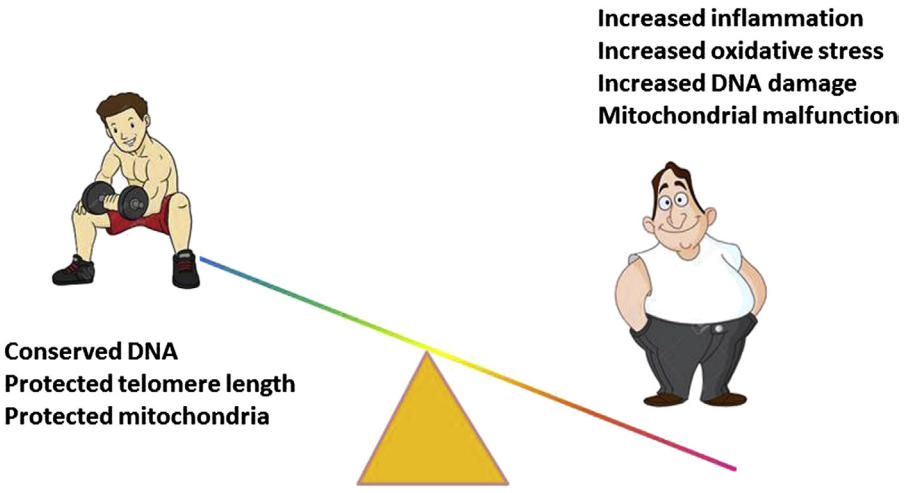

FIGURE 31.1 The significance of obesity in decreasing genomic stability, and of adequate diet and exercise in preventing this development.

formed by high-temperature cooking can generate reactive oxygen species. Carvalho and coworkers [25] correlated high temperature–cooking processes of such meats with cancer risk, and by measuring oxidative stress as malondialdehyde concentration in the plasma found suggestive evidence of a causal relationship in their Sao Paulo population. DNA-reactive polycyclic aromatic hydrocarbons (PAHs) are also formed during cooking of such meats, especially following direct heat exposure [6,26]. A 2015 IARC evaluation has concluded that well done cooked red meats enhance oxidative stress and other measures of genomic instability, at least in model systems, and are possible human carcinogens [27,28].

Advanced glycation end products such as N(E)-(carboxymethyl)lysine are present in both cooked and uncooked foods, leading to oxidative stress, aberrant cell signaling, and genomic instability, and have been associated with at least one type of cancer [29]. These reactive metabolites are produced as a byproduct of sugar metabolism [30], and appear to be related to various socioeconomic and risk factors linked to cancer susceptibility. While these are present at low levels in unprocessed red meats, they increase significantly upon cooking, but this process is reduced by previous marination of the meat [29,30].

2.4 Mutagens Formed During Food Processing

The 2015 IARC evaluation concluded that the evidence for carcinogenesis by processed meat was significantly stronger than for unprocessed meats, and the former should be considered as human carcinogens [27,28]. Processed meats are those which have been modified by salting, curing, fermentation, or other processes to enhance flavor or preservation. N-nitroso compounds in particular are DNA reactive, and are often formed during processing of red meats [31,32]. Smoking of salmon was shown to lead to the formation of various types of PAHs [33]. In a study from Taiyuan, China, PAHs were also shown to be formed during the cooking of vegetables, wheat flour, and fruits [8].

2.5 Mutagens Formed During Storage of Foods

Styrene has been widely used in food storage and also food preparation, as well as being released in various industrial settings. In workers exposed to this chemical, there is evidence of genotoxicity in the form of DNA adducts and strand breaks [34]. Styrene intake from various sources has also been associated with increased risk of invasive breast cancer in a population study in Texas [35]. Inappropriate storage containers of various food and drinks may themselves create a hazard. For example, an alcoholic beverage (cachaça) was found to be contaminated with PAHs when stored in a polyethylene tank, but this contamination was much less of a problem when storage was in a glass container [36]. Refrigeration has been found to be an important factor in food storage that helps to protect against the formation of various fungal toxins [37,38]. Various aflatoxins including aflatoxin B1 and aflatoxin M1, as well as ochratoxin A and fumonisin B1, are examples of important fungal secondary metabolites on badly stored nuts, grains, and other plant foods that cause DNA damage and promote genomic instability [37,39–41].

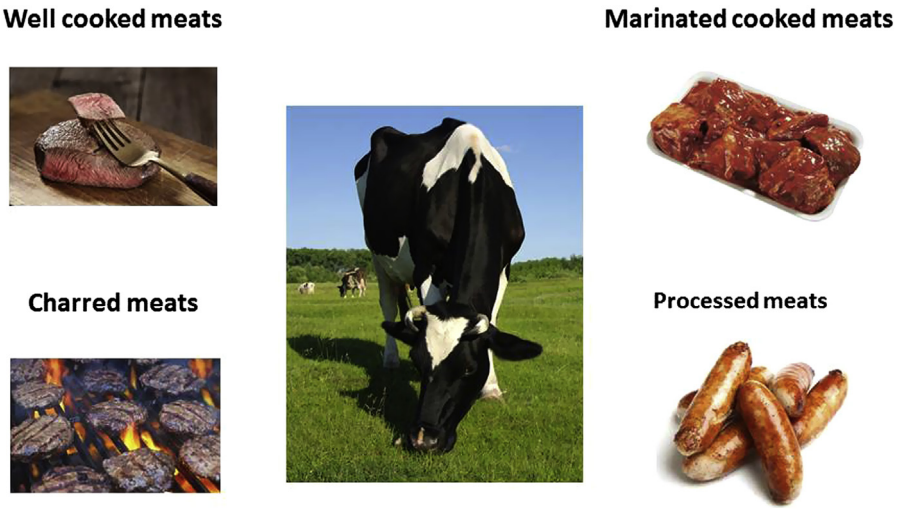

FIGURE 31.2 Some of the various ways in which red meats can enhance genomic instability. Heterocyclic amines are common in well-cooked meats, and polycyclic aromatic hydrocarbons in charred meats, both leading to DNA damage including the formation of DNA adducts. Advanced glycation end products are present in low concentrations in uncooked meats, but increase upon cooking, which process may be reduced by marinating the meats. Processing of meats to various products including sausages increases the concentration of mutagenic N-nitroso compounds.

FIGURE 31.3 The way in which certain food plants such as broccoli may function to either increase or reduce genomic instability. Glucosinolates such as 1-MIM glucosinate are innocuous unless activated by the release of myrosinase enzymes, usually contained in separate cells, when they release a DNA-reactive component. In contrast, various phytochemicals from broccoli, including sulforaphane, act to protect the integrity of DNA.

2.6 Accumulation of Environmental Pollutants in Animal Flesh

Various chemical toxins may accumulate in the flesh of grazing animals or fish in polluted estuarine regions [42,43]. These may include pesticides [3,44] and heavy metals such as mercury, cadmium, or lead [45,46]. The latter have been found at high levels in the flesh of slaughter-house animals, and have recognized genotoxic effects [43].

2.7 Natural Pesticides in Food Plants

While much publicity focuses around red meat and adverse effects associated with cooked or processed animal flesh, it is also important to record that many food plants contain natural pesticides, or are able to release such products under some conditions. An apparently enigmatic example is provided by broccoli (Fig. 31.3). While this contains a number of important and generally beneficial phytochemicals, as will be discussed in the next section, it is also able to release toxins in response to tissue damage caused by insect or other pests [47]. For example, 1-methoxy-3-indoylmethyl (1-MIM) glucosinate is found at high levels in cruciferous vegetables such as broccoli and cabbage. This forms DNA adducts in vitro, and is mutagenic following activation by the myrosinase enzyme [48]. It is noteworthy that these two plant components (1-MIM glucosinate and myrosinase) are typically found in separate cells. But after pest-induced cell damage, the two components can combine to form a DNA-reactive end product, in vitro and in vivo [48].

3. DIETARY PROTECTION AGAINST GENOMIC INSTABILITY

3.1 Classic Nutrients

Biomarkers relevant to genomic stability, including telomere length and mtDNA deletions, have been utilized in establishing recommended daily intakes for nutrients [49,50]. Accumulating evidence shows that genome integrity is highly sensitive to nutrient status, and that optimal levels may differ among individuals. Many investigations to date are limited by considering only the effects of single nutrients, without looking at the potential interactions among these, and of nutrients with toxicants in the diet. For example, Fenech has suggested that it is inappropriate to consider single nutrients, but we should be looking at nutrient combinations, using what he describes as a nutriome [51]. Nevertheless, it is clear that different nutrients and classes of nutrients have some important functional differences in the maintenance of genomic stability. Examples of some important nutrients and bioactives are given in Table 31.1.

3.1.1 Lipids

As described earlier, high intakes of saturated fats from animal products have been associated with obesity, and consequently detrimental effects on genomic stability [52]. Obesity and/or higher caloric intake also had a marked effect in promoting telomere shortening. While too high a fat intake overall may be detrimental, some fats may play an important

TABLE 31.1 Important Nutrients and Phytochemicals in the Maintenance of Genomic Stability

Processes Affected	Nutrients or Bioactive Substances
DNA oxidation	Vitamins (C, D, and E), Se, DHA, EPA, genistein, curcumin, RSV
DNA synthesis	Folate, vitamin B12, zinc, magnesium
DNA repair	Niacin, zinc, folate
DNA methylation	Vitamins A and D, folate
Other epigenetic effects	Vitamin D, RSV, EGCG, sulforaphane
Necrosis/apoptosis	Vitamins A, C, D, K12, niacin, zinc, DHA, EPA, curcumin
Chromosome segregation	Vitamin A, folate, magnesium
Telomere length	Vitamin D, niacin, folate, Se, DHA, EPA, curcumin, RSV

Data from references identified in the text.

protective role in the maintenance of genomic stability. Those for which the most information is available are the omega-3 and 6 (n-3 and n-6) polyunsaturated fatty acids (PUFAs). Within the n-3 PUFA family, the two long-chain PUFA eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) have been demonstrated to affect various key events that may protect against DNA oxidation and leukocyte telomere shortening, while promoting apoptosis and reduction of damaged cells [53–57]. These two PUFA also play key roles in protection against inflammation, reducing the possibility that an overreaction to immune stimulation may lead to DNA damage and genomic instability [22,58–61]. What may be almost as important as the individual PUFA here are the ratios between n-6 PUFA (which may promote inflammation) and long-chain n-3 PUFA.

There is considerable interest in mechanisms associated with the loss of function of the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) tumor-suppressor gene in cancer [62–65]. The PTEN gene has lipid phosphatase activity and acts in the nucleus to promote genomic stability and DNA repair. Consequently, loss of this function leads to increased genomic instability [62]. In a PTEN-null mouse model, it was possible to demonstrate the importance of lipid-modifying enzymes in converting saturated fatty acids to monosaturated fatty acids, and also the negative implications of an increased ratio of long-chain omega-6 PUFA to omega-3 PUFA in genomic stability and cancer risk [65].

3.1.2 Vitamins

3.1.2.1 Carotenoids

Peto et al. [66] originally suggested a cancer-preventive role for β-carotene, based on a number of cross-sectional or case–control studies. Most such studies showed a negative correlation between blood carotenoid levels and various biomarkers of DNA damage. However, some placebo-controlled carotenoid intervention trials using disease and mortality as outcomes have suggested a significant increase rather than decrease in mortality associated with vitamin A, β-carotene, or vitamin E supplements [67]. It is possible that this depends upon the concentration used in the supplement, and also the population tested. Pro-vitamin A carotenoids include α- and β-carotene, β-cryptoxanthin, retinoic acid, retinal, and retinol, while non-vitamin A carotenoids include lycopene, lutein, astaxanthin, and zeaxanthin. A number of tissue culture studies have involved cotreatment with a DNA-damaging agent and various carotenoids [5,68–77]. While the non-vitamin A carotenoids usually decreased the DNA damage, thereby promoting genomic stability, the pro-vitamin A carotenoids had little or no effect at low concentrations but increased genomic instability at higher concentrations.

3.1.2.2 Other Vitamins

Various B vitamins have beneficial effects on the stability of both nuclear and mitochondrial genomes. These include niacin (vitamin B3), folate (vitamin B9), and vitamin B12. Folate is an essential factor in one-carbon metabolism, acting to supply the methyl units for DNA methylation. Folate deficiency, especially in the presence of suboptimal levels of vitamin B6 and vitamin B12, may have significant effects on chromosomal fragility, resulting in chromosome breaks and mtDNA deletions, as well as reduced telomere length [78,79]. Folate is a key component of a number of root vegetables, including pulses such as red kidney beans, chickpeas, and lentils [79]. The B vitamin class also includes choline, which also interacts with folate biosynthesis [80,81]. A deficiency of this nutrient can lead to DNA hypomethylation and an accumulation of strand breaks [80].

Vitamin C has been considered to be an antioxidant. In human studies, the effects of vitamin C supplementation on various markers of genome stability depend on individual responses to vitamin C levels in the diet, and on concomitant exposure to oxidative stresses [82]. Vitamin C also protects against DNA damage, DNA strand breakage, and chromosomal aberrations [69,82].

Vitamin D is also critical in the maintenance of genome stability, preventing oxidative stress, chromosomal aberrations, telomere shortening, and inhibition of telomerase activity [83–86]. There is reason to believe that a primary function of vitamin D is in preventing DNA damage, while a secondary effect is in the regulation of cellular growth [83].

Other vitamins such as biotin (or vitamin H) and the vitamin-like co-enzyme Q10 are also important in the maintenance of genomic stability [87,88]. It is important to recognize that there are considerable interindividual differences in the ability to absorb and metabolize all of these vitamins [89]. Recognizing the optimal amount is of considerable importance.

3.1.3 Minerals

While a number of minerals are typically considered as toxicants, some of these are essential micronutrients, albeit usually with a narrow window of efficacy as compared with toxicity. These include iron [90], selenium (Se) [91], and zinc [92]. Se provides a useful illustration of these complexities, since the population generally shows a "U"-shaped response curve, with both low and high selenium levels increasing genomic instability. The optimal form of Se at the optimal level may protect against DNA or chromosome breakage, chromosome gain or loss, damage to mtDNA, and detrimental effects on telomere length and function [93]. However, the optimal level of Se differs among individuals, and also with the form incorporated into the diet [91,94]. Various genetic polymorphisms may affect both the uptake and utilization of selenium among individuals [94].

3.2 Bioactive Food Components

Bioactives, sometimes called phytochemicals, have been defined as "constituents in foods or dietary supplements, other than those needed to meet human nutritional needs, which are responsible for changes in health status" [95]. This group includes various polyphenols, defined as having several hydroxyl groups on one or more aromatic rings, and divided into various groups according to chemical structure [96]. There is compelling evidence that a considerable range of polyphenols may stabilize genomic DNA, through various processes, including effects on DNA methylation [96].

Both genistein and dadzein are soy-derived phytoestrogens that bind to estrogen receptors and have both weak estrogenic and weak antiestrogenic effects [75,97,98]. Genistein has been shown to have antioxidant effects and may act in concert with other nutrients such as β-carotene in beneficially affecting genomic stability [75]. Genistein also showed beneficial effects in combination with the DNA-damaging agent, bisphenol A [99]. However, in common with other such compounds, genistein has been found to have adverse effects in combination with such compounds as diethylstilbestrol [100].

Curcumin is a polyphenol that is also the active ingredient in the spice, turmeric. In a rodent model of colorectal cancer, curcumin treatment led to downregulation of telomerase activity, and this effect was associated with cell-cycle arrest and induction of apoptosis [101]. Protection against genomic instability has also been shown by curcumin in combination with certain genotoxic agents. For example, in human hepatocyte LO2 cells, curcumin was able to protect against the genotoxicity of quinocetone (QCT), a controversial compound which has been used as an antimicrobial feed additive in China. Curcumin pretreatment significantly attenuated the formation of ROS, DNA fragmentation, and micronucleus formation [102]. However, in a different tissue culture model using Raji cells, curcumin increased ROS and cell-cycle arrest, leading to structural chromosome abnormalities [103].

Resveratrol (RSV) is another polyphenol which is considered to be the beneficial component in red wine. High intakes of RSV have usually been considered beneficial to human health, including cancer-protective and antiaging effects. For example, it is generally considered to be an antioxidant, and has shown a chemopreventive effect in different mouse cancer models [97,104,105]. In HeLa S3 mammalian cells, RSV has effects on gene expression leading to the induction of telomere-maintenance factors, without effects on cell proliferation. That is, it can protect against changes in telomere length [106]. However, in the HeLa colon cancer cell model, RSV has also induced DNA damage through pro-oxidant effects, leading to apoptosis [105].

Indole-3-carbinol and epigallocatechin–3-gallate (EGCG) from green tea are both examples of polyphenols that show strong evidence of modulating genomic stability through various epigenetic mechanisms [9,95].

Some phytochemicals may have complementary activities in protection against genomic stability. For example, in broccoli (Fig. 31.3), the isothiocyanate, sulforaphane, and the polyphenol, quercetin, may complement one another in their epigenetic actions [107]. Duthie [108] suggested that the evidence is particularly strong for berry phytochemicals,

specifically anthocyanins (a class of flavonoids), which modulate various biomarkers of DNA damage and carcinogenesis, in both in vitro and in vivo animal studies. However, evidence for cancer-preventive effects of any of these phytochemicals in human studies is currently weak.

Tumor-promoting inflammation is inhibited by all of the compounds except vitamin B [79,93,109–121], while only vitamin D, carotenoids, and RSV prevent tumor cells from evading the immune system [122–124].

4. THE SIGNIFICANCE OF GENETIC POLYMORPHISMS

There is no question but that genetic polymorphisms in various genes such as breast cancer 1 early onset (BRCA1) and breast cancer 2 early onset (BRCA2) affect cancer susceptibility, independent of nutrition [125]. However, it is also increasingly clear that the risk of developing cancer depends upon a complex interplay among genetic susceptibility, lifestyle, and diet, and that a number of the important genes are associated with nutrient uptake, transport, metabolism, and excretion [9]. While general population recommendations for nutrients are clearly of benefit, these do not necessarily indicate the optimal diet for an individual [50,51,89,126]. Folate provides an excellent example of a vitamin for which there is strong influence of the interplay between the nutrient intake, and also certain genetic polymorphisms [51]. There is also considerable interest in vitamin D, where there have been several hundred genes reported, which may affect uptake and function of the nutrient in various ways [84]. The minerals Se, zinc, and iron are also required at different concentrations according to genotype [90,92,94].

5. CONCLUSIONS

Genomic instability plays a critical role in cancer initiation and progression. The fidelity of the genome is protected at every stage of the cell cycle. In cancer, the presence of aneuploid or tetraploid cells indicates the failure of one or many of these safety nets. The resultant genomic heterogeneity may offer the cancer cells a selection advantage against the selective nature of emerging therapies. Understanding these protective mechanisms, and how they are bypassed in cancer cells, may highlight new and more specific mechanisms for therapeutic attack and/or cancer prevention.

While much work has focused on the development of new cancer drugs, this review makes it clear that focusing on nutrition, both in terms of preventing cancer development and also its progression, may be more fruitful. Vitamins (such as B, C, and D), minerals (such as Se), and phytochemicals (such as RSV, sulforaphane, and EGCG) have shown remarkable potential for diminishing tumor risk and tumor progression. In addition to their protective properties against genomic instability, these compounds are known to inhibit proliferative signaling [119,127,128], attenuate oncogenic metabolism [126,129–134], and block inflammation [79,93,109–121].

Despite progress in antitumor therapies, the death rates from cancer remain alarming [135,136]. However, diet and lifestyle are increasingly being shown for their potential in reducing cancer risks and/or slowing tumor progression. In particular, antioxidants are critical for the prevention of DNA damage that enables cancer initiation and growth. Growing evidence shows that vitamins, minerals, and other dietary factors have profound and protective effects against cancer cells, whether they are grown in the laboratory, in animals, or studied in human populations. A better understanding of the effects and synergy of these dietary factors in the prevention and treatment of genomic instability is critical to the future reduction of mortality associated with cancer.

GLOSSARY

Anthocyanins Water-soluble vacuolar pigments that may appear red, purple, or blue depending on the pH, belonging to a parent class of molecules called flavonoids.

Bioactives Constituents in foods or dietary substances, other than those required to meet nutritional needs, which are responsible for health status.

Nutriome The combination of nutrients and their doses that optimizes genomic stability for an individual.

Polyphenols A structural class of mainly natural, but also synthetic or semisynthetic, organic chemicals characterized by the presence of large multiples of phenol structural units.

Phytoestrogen Plant-derived xenoestrogens not generated within the endocrine system but consumed by eating phytoestrogenic plants.

LIST OF ABBREVIATIONS

1-MIM 1-Methoxy-3-indoylmethyl

ATP Adenosine triphosphate

BRCA1 Breast cancer 1 early onset

BRCA2 Breast cancer 2 early onset
DHA Docosahexaenoic acid
EGCGE Pigallocatechin gallate
EPA Eicosapentaenoic acid
HCA Heterocyclic amine
IARC International Agency for Research on Cancer
LINE-1 Long interspersed nucleotide element 1
mtDNA Mitochondrial DNA
n-3 Omega-3
n-6 Omega-6
NER Nucleotide excision repair
PAH Polycyclic aromatic hydrocarbon
PTEN Phosphatase and tensin homolog
PUFA Polyunsaturated fatty acid
QCT Quinocetone
ROS Reactive oxygen species
RSV Resveratrol
Se Selenium

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