FOCUS

Indeed, several nutrigenetics studies have shown diet to significantly modify the relationship between polymorphisms in genes coding antioxidant enzymes and cancer

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Nutrigenetics and Modulation of Oxidative Stress

by Laura A. Da Costa et al.

Key insights

This article highlights some of the recent nutrigenetic studies that examine interactions between diet, genetic variation in antioxidant enzymes, and oxidative stress.

Current knowledge

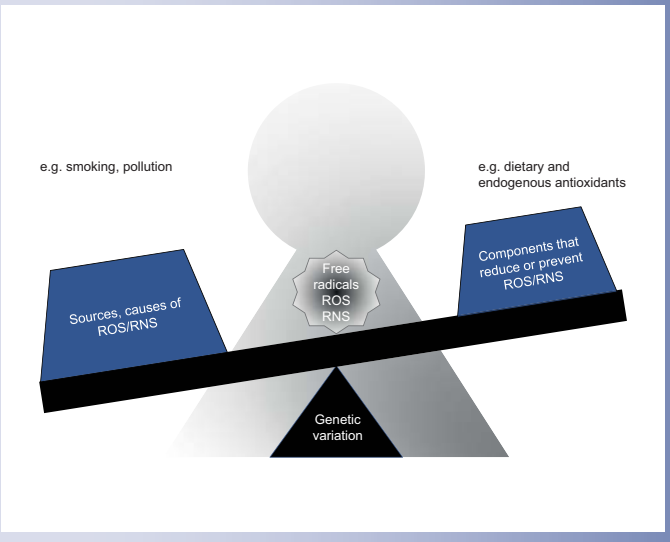
Oxidative stress develops as a result of an imbalance between the production and accumulation of reactive species and the body's ability to manage them using exogenous and endogenous antioxidants. Oxidative stress has been implicated in the development of several chronic diseases, including cardiovascular disease and cancer. Individual genetic variation in the endogenous antioxidant defense systems may affect oxidative stress and subsequent disease development. Diet modifies the relationship between genetic variation in endogenous antioxidant enzymes and oxidative stress biomarkers and related disease risk.

Practical implications

As more data emerge, our understanding of the complex relationship between genetics, diet, and disease development should improve. In addition to gaining knowledge of the role of oxidative stress in disease pathogenesis, this type of research may also have important public health implications in identifying subgroups that would benefit from dietary intervention.

Recommended reading

García-Bailo B, El-Sohemy A, Haddad P, Arora P, Benzaied F, Karmali M, Badawi A: Vitamins D, C, and E in the prevention of type 2 diabetes mellitus: modulation of inflammation and oxidative stress. Biologics 2011;5:1–13.



Genetic variation in the absorption, metabolism, distribution or elimination of exogenous dietary antioxidants can influence the level of reactive species exposure to target cells and/or tissues. ROS = Reactive oxygen species; RNS = reactive nitrogen species. When the balance is tipped to one side (i.e. accumulation of ROS/RNS), the result is altered gene expression, molecular damage, leading to oxidative sress, nitrosative stress, inflammation, and subsequent disease development. See text for details.

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Nutrigenetics and Modulation of Oxidative Stress

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Key Messages

- **Individual genetic variation in the endogenous antioxidant defense systems may affect oxidative stress and subsequent disease development.**
- **Diet modifies the relationship between genetic variation in endogenous antioxidant enzymes and biomarkers of oxidative stress and related disease risk.**
- **Genetic variation in the absorption, metabolism, distribution or elimination of exogenous antioxidants can influence exposure levels of antioxidants to target cells.**

Key Words

Antioxidants · Gene-diet interactions · Genetic variation · Nutrigenetics · Nutrigenomics · Oxidative stress

Abstract

Oxidative stress develops as a result of an imbalance between the production and accumulation of reactive species and the body's ability to manage them using exogenous and endogenous antioxidants. Exogenous antioxidants obtained from the diet, including vitamin C, vitamin E, and carotenoids, have important roles in preventing and reducing oxidative stress. Individual genetic variation affecting proteins involved in the uptake, utilization and metabolism of these antioxidants may alter their serum levels, exposure to target cells and subsequent contribution to the extent of oxidative stress. Endogenous antioxidants include the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, paraoxanase, and glutathione *S*-transferase. These enzymes metabolize reactive species and their by-products, reducing oxidative stress. Variation in the genes coding these enzymes may impact their enzymatic antioxidant activity and, thus, the levels of reactive species, oxidative stress, and risk of disease development. Oxidative stress may contribute to the development of chronic disease, including osteoporosis, type 2 diabetes, neurodegenerative diseases, cardiovascular disease, and cancer. Indeed, polymorphisms in most of the genes that code for antioxidant enzymes have been associated with several types of cancer, although inconsistent findings between studies have been reported. These inconsistencies may, in part, be explained by interactions with the environment, such as modification by diet. In this review, we highlight some of the recent studies in the field of nutrigenetics, which have examined interactions between diet, genetic variation in antioxidant enzymes, and oxidative stress.

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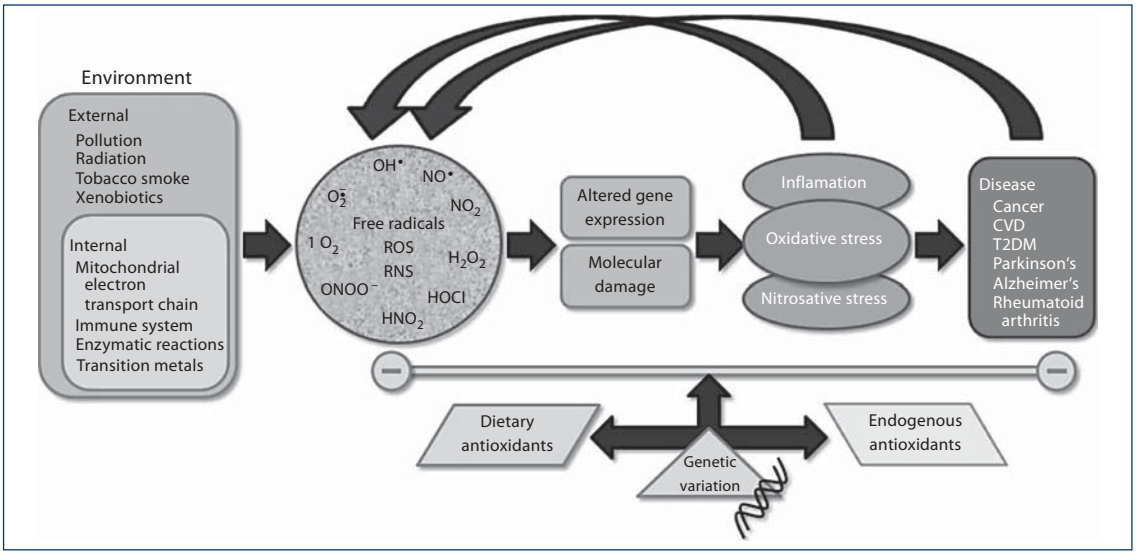

Fig. 1. Overview of the relationship between the production of reactive species, oxidative stress, disease development and the role of antioxidants and genetic variation. An accumulation of reactive species from external and internal stimuli can cause molecular damage and result in oxidative or nitrosative stress. Reactive species may also alter gene expression, leading to the release of cytokines and inflammation, which results in further production of free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Inflammation and oxidative stress may then contribute to the development of chronic disease and additional production of reactive species. Dietary and endogenous antioxidants work together to reduce oxidative stress development and damage; their functioning is further modified by individual genetic variation. CVD = Cardiovascular disease; T2DM = type 2 diabetes mellitus.

Oxidative Stress

Reactive species, including free radicals, reactive oxygen species, and reactive nitrogen species, are produced as a result of normal physiological processes and play important roles in cellular signalling, gene transcription, and the immune response [1]. In the process of aerobic metabolism, electron leakage along the electron transport chain in the mitochondria results in the production of the superoxide anion (O_2^-). Other biological reactions, including oxidative bursts produced by phagocytes and enzyme systems such as cytochrome P_{450} and xanthine oxidase, also contribute to the production of these highly reactive species [2]. Excessive production or accumulation of reactive species, however, can have detrimental effects by participating in reduction-oxidation (redox) reactions causing damage to macromolecules, cell membranes and DNA [1, 3]. This can alter biological properties of membranes, enzymes and receptors, impair cell functioning, and lead to cell death [4]. For this reason, a complex network of defense systems has developed in humans to protect against excessive production of and damage by reactive species in an effort to maintain 'redox homeostasis' [1]. When the production or accumulation of free radicals or reactive oxygen and nitrogen species surpasses the body's ability to defend them, a state of oxidative stress (or nitrosative stress) results [1, 4]. In addition to direct damage to biological molecules and tissues, oxidative stress can also activate transcription factors such as nuclear factor κB (NF-κB), which trigger signalling cascades resulting in cytokine release and inflammation [5]. Oxidative stress has been the subject of intensive research in recent years and has been linked to the pathogenesis of several chronic diseases including cancer, osteoporosis, type 2 diabetes, neurodegenerative diseases and cardiovascular disease [1]. This has been supported by many studies that have shown diets high in fruit and vegetables, and thus, rich in dietary antioxidants, are associated with a reduced risk of chronic disease. Antioxidants comprise a large group of endogenous enzymes and com-

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Table 1. Common exogenous antioxidants and examples of their dietary sources

Exogenous antioxidants	Dietary sources
Vitamin C (ascorbic acid/ascorbate)	Bell peppers, strawberries, kiwi, Brussels sprouts, broccoli
Vitamin E (tocopherols, tocotrienols)	Vegetable oil and its derivatives (margarine, salad dressing), nuts, seeds
Carotenoids (α-carotene, β-carotene, zeaxanthin, lutein, lycopene, β-cryptoxanthin, etc.)	Orange and red vegetables and fruits (carrots, tomatoes, apricots, plums) and green leafy vegetables (spinach, kale)
Polyphenols (flavonols, flavanols, anthocyanins, isoflavones, phenolic acid)	Fruits (apples, berries, grapes), vegetables (celery, kale, onions), legumes (beans, soybeans), nuts, wine, tea, coffee, cocoa
Trace elements (selenium, zinc)	Seafood, meat, whole grains

pounds as well as exogenous dietary components, which protect against oxidative stress by preventing the formation of reactive species, scavenging, neutralizing and removing reactive species, inhibiting oxidative chain reactions, chelating reactive metals, and repairing damage to biological molecules. The ability to manage and prevent oxidative stress is dependent upon the functioning of the endogenous and exogenous antioxidant defense systems, both of which may be influenced by individual genetic variation. Single nucleotide polymorphisms (SNPs) in genes that code for endogenous antioxidant enzymes or proteins involved in dietary antioxidant uptake and utilization may have a direct impact on the ability to manage oxidative stress and prevent subsequent disease development in an individual. Furthermore, the endogenous and exogenous antioxidant systems interact and complex gene-diet interactions may further impact an individual's ability to manage oxidative stress (fig. 1). The present review focuses on summarizing the relationship between polymorphisms in genes encoding endogenous antioxidant enzymes and their interaction with dietary components to modulate oxidative stress.

Dietary Antioxidants

Nutrients and phytochemicals in the diet exhibit a range of antioxidant functions and play an important role in the defense against oxidative stress (table 1). Vitamin C is an essential nutrient and the primary hydrophilic plasma antioxidant [5]. In addition to scavenging and neutralizing free radicals, vitamin C (ascorbic acid) also plays an important role in the regeneration of the α-tocopherol radical. α-Tocopherol is one of several compounds of the vitamin E family and has important chain-breaking and scavenging antioxidant functions in the lipid phase, protecting lipoproteins and cell membranes. The carotenoids make up another group of important dietary antioxidants, which like α-tocopherol, are lipid soluble and may be important in the protection against lipid peroxidation [6].

Circulating levels of dietary antioxidants have been shown to be influenced by several factors, including individual genetic variation. Ascorbic acid levels in the circulation are influenced by SNPs in the solute carrier family 23, member 1 (*SLC23A1*) gene, which codes for the vitamin C transporter type 1 (SVCT1), responsible for active transport of vitamin C from the small intestine [7, 8]. Circulating levels of α-tocopherol are also influenced by polymorphisms in genes coding for proteins involved in α-tocopherol uptake, transport, and metabolism, such as apolipoproteins, cytochrome P_{450} 4F2, and cholesterol transporter scavenger receptor class B type 1, SR-B1 [9]. Variants in similar genes have also been shown to affect circulating carotenoid levels [10]. Together these studies suggest individual genetic variation may influence dietary antioxidant status, and consequently, the body's ability to manage oxidative stress. Recently, the genetic determinants of antioxidant status have been reviewed [6]. The following sections focus on variation in genes encoding the endogenous antioxidant enzymes and their interaction with diet, including dietary antioxidants, on oxidative stress.

Recently, the genetic determinants of antioxidant status have been reviewed [6]. The present section focuses on variation in genes encoding the endogenous antioxidant enzymes and their interaction with diet, including dietary antioxidants, on oxidative stress.

Table 2. Endogenous antioxidants

Endogenous antioxidants	Examples
Enzymes	Superoxide dismutase Catalase Glutathione peroxidase Paraoxanase Glutathione S-transferase Glutathione reductase Thioredoxin reductase Heme-oxygenase Aldehyde dehydrogenase 8-Oxoguanine glycosylase
Non-enzymes	Glutathione Lipoic acid Bilirubin Melatonin Ubiquinol Uric acid
Metal-binding proteins	Ferritin Lactoferrin Metallothionein Transferrin Ceruloplasmin

Table 3. Biomarkers of oxidative stress

Lipid peroxidation
Malondialdehyde (MDA)
Thiobarbituric acid-reactive substances (TBARS)
Isoprostanes
Conjugated dienes
4-hydroxy-2-nonenal (HNE)
2-propenal (acrolein)
Protein damage
Amino acid oxidation (o,o′-dityrosine), nitration (3-nitrotyrosine), and halogenation (3-chlorotyrosine, 3-bromotyrosine)
Protein carbonyls [γ-glutamic semialdehyde (GGS), aminoadipic semialdehyde (AAS)]
DNA/RNA base oxidation
8-hydroxy-2-deoxyguanosine (8-OHdG)
8-hydroxyguanine (8-OHGua)
8-hydroxyguanosine (8-OHG)
5-hydroxymethyl-2-deoxyuridine (5-OH-mdU, HMD)
5-hydroxymethyluracil (5-OHmU)
7-hydroxy-8-oxo-20-deoxyguanosine (8-oxo-dG, 8OX)
Thymine glycol (Tg)

Endogenous Antioxidants and Measures of Oxidative Stress

The body's natural defense system against oxidative stress consists of several enzymes and non-enzymatic compounds as well as transfer proteins that sequester pro-oxidant metals inhibiting their participation in redox reactions (table 2). Components of the endogenous antioxidant defense system work together and in concert with dietary antioxidants to prevent and reduce oxidative stress. In addition, the antioxidant activity of many of these enzymes and compounds is reliant upon minerals derived from the diet such as selenium, copper, manganese, and zinc [11]. Genetic variation in the antioxidant enzymes may also impact the efficacy of the endogenous antioxidant defense system and susceptibility to oxidative stress. There are numerous measures of oxidative stress (table 3), most of which are measures of oxidized products of lipids [e.g. malondialdehyde (MDA) or isoprostanes], proteins (e.g. protein carbonyls), or DNA (e.g. 8-hydroxy-20-deoxyguanosine) [4]. A recent review examined articles published over a 6-month period in 2006 that used biomarkers of oxidative stress and noted that 71 different biomarkers were utilized [12]. This highlights the complexity and difficulty of appropriate biomarker selection and comparison of results across studies. In addition to the known analytical issues, e.g. sensitivity and stability of markers to storage, a concern with the use of oxidative stress biomarkers is that some exist in multiple forms and in multiple biological matrices [12]. While some studies have investigated the role of genetic variation in antioxidant enzymes and measures of oxidative stress, few have further examined potential modification by diet. However, numerous studies have examined interactions between diet and genetic variation in antioxidant enzymes in relation to diseases associated with oxidative stress, in particular, cancer. Oxidative stress has been implicated in the development of carcinogenesis in several ways, including direct damage to DNA by reactive species in the form of strand breaks, base oxidation, adducts, and protein crosslinks [13]. DNA damage leading to mutation may be particularly carcinogenic when affecting oncogenes and tumor suppressor genes [14]. Reactive species may also influence carcinogenesis through attack on DNA repair mechanisms, as well as additional effects on the cell cycle, gene expression, and apoptosis [15]. The following sections cover a few of the key antioxidant enzymes, genetic variation in the genes coding these enzymes, and their interaction with diet on biomarkers and diseases associated with oxidative stress.

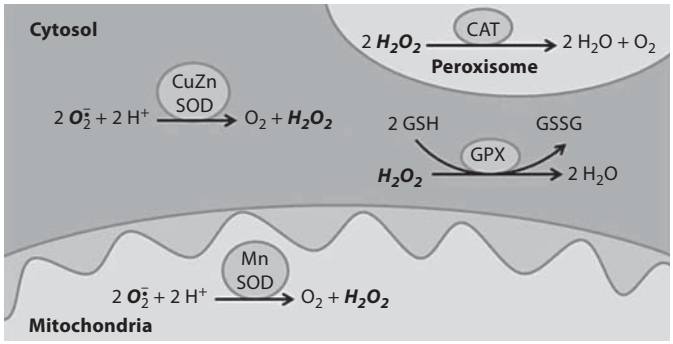

Fig. 2. Antioxidant functions of endogenous antioxidant enzymes SOD, catalase (CAT), and glutathione peroxidase (GPX). The reactive species are in bold and italicized. SODs eliminate the superoxide anion (O_2^-) in the mitochondria (MnSOD) and in the cytosol (CuZnSOD) by breakdown to H_2O_2 and oxygen. CAT and GPX [by conjugation with glutathione (GSH)] further break down H_2O_2 to water and oxygen.

Superoxide Dismutase

Superoxide dismutase (SOD) has important antioxidant functions in the conversion of superoxide radicals into hydrogen peroxide and oxygen followed by further breakdown of hydrogen peroxide by catalase and peroxidases (fig. 2). There are 3 isoforms of SOD in humans including the copper/zinc (CuZn) SOD (SOD1), the manganese (Mn) SOD (SOD2), and the extracellular CuZn SOD (SOD3 or EC-SOD). SOD1 is a homodimer found in the cytosol of intracellular locations, whereas SOD3 is a tetramer found exclusively in extracellular domains [16]. MnSOD is the most important of the SOD isoforms being the only one essential for life [17]. A precursor of the MnSOD is synthesized in the cytosol before being transported into the mitochondria where the active homotetramer plays an essential role in neutralizing free radicals produced during aerobic metabolism [17]. The *MnSOD* gene is localized to chromosome 6q25 with the most commonly studied polymorphism being a valine to alanine amino acid change at codon 16 (Val16Ala) in the mitochondrial targeting sequence of the precursor protein (rs4880) [18, 19]. This polymorphism alters the functioning of the enzyme and the ability of the precursor enzyme to be transported into the mitochondria, and is thus believed to affect its ability to defend against oxidative stress [18, 20, 21]. In one study, levels of DNA damage differed significantly by *MnSOD* Val16Ala genotypes at baseline, although there was no difference in response to antioxidant supplementation on levels of DNA damage by genotype [22]. This polymorphism has also been extensively investigated in diseases associated with oxidative stress, such as cancer, with several studies further examining potential modulation by the diet [23]. For example, diet has been shown to modify the relationship between the *MnSOD* Val16Ala polymorphism and cervical intraepithelial neoplasia (CIN, subdivided into CIN1 and CIN2/3 based on histology) and cervical cancer [24]. In this case-control study, C allele carriers showed a 57.3% reduced risk of CIN1, but no association with CIN2/3 or cervical cancer; however, several significant interactions were noted with serum levels of dietary antioxidants on CIN1, CIN2/3, and cervical cancer risk including β-carotene, lycopene, zeaxanthin/lutein, retinol, and α- and γ-tocopherol. For example, the reduced risk of CIN1 associated with the C allele was only seen among those with above median levels of serum β-carotene [>0.205 μg/ml; odds ratio (OR): 0.286, 95% confidence interval (CI): 0.086–0.953; interaction p = 0.002] and γ-tocopherol (>0.30 μg/ml; OR: 0.272, 95% CI: 0.079–0.944; interaction p = 0.033) [24]. Two recent meta-analyses have also examined the association between the *MnSOD* Val16Ala polymorphism and breast cancer risk with modification by vitamin C, vitamin E, and carotenoid [25] and fruit and vegetable consumption [19]. While both meta-analyses showed no independent effect of genotype on breast cancer risk, intakes of antioxidants were shown to modify risk in premenopausal women [25], while fruit and vegetable consumption did not [19].

Catalase

Catalase is an antioxidant enzyme important in the body's defense against oxidative stress and is found within the peroxisomes of cells and the cytoplasm of erythrocytes. Ubiquitously expressed, catalase expression is highest in the liver, kidney, and erythrocytes [26]. The catalase enzyme consists of four identical heme-containing subunits and catalyzes the decomposition of hydrogen peroxide into water and oxygen [26] (fig. 2).

The catalase enzyme is coded by the catalase (*CAT*) gene located on chromosome 11p13 and has been found to be highly polymorphic [26]. A common SNP exists at position –262 in the 5′ untranslated region of the *CAT* gene where a C to T substitution results in lower catalase enzyme activity as reported in some [27–29] but not all studies [30]. However, the impact of this polymorphism on enzyme activity may be further influenced by ethnicity, sex, and fruit and vegetable consumption [31]. In an examination of 1,008 breast cancer cases and 1,056 controls from the Long Island Breast Cancer Study Project,

the *CAT* –262 CC genotype was associated with a 17% decreased risk of breast cancer compared to T allele carriers (OR: 0.83, 95% CI: 0.69–1.00 adjusted for age, family history, and body mass index) [27]. When non-supplement users were examined, significant gene-diet interactions were noted for the *CAT* –262 polymorphism and fruit consumption (p = 0.02) and dietary vitamin C intake (p = 0.03). A higher consumption of fruit (>10 servings/week) or dietary vitamin C (>133.7 mg/day) combined with the CC genotype showed the lowest risk of breast cancer in this study (OR 0.59: 95% CI: 0.38–0.89 for high fruit intake and 0.62, 0.40–0.95 for high dietary vitamin C intake) [27]. Additional studies on other SNPs in the *CAT* gene and oxidative stress-related outcomes continue to be investigated [32] and should improve our understanding of the impact of genetic variation in the *CAT* gene on oxidative stress and potential modulation by the diet.

Glutathione Peroxidase

The glutathione peroxidases are a family of selenium-dependent enzymes that include glutathione peroxidase 1 (GPX1), GPX2, GPX3, and phospholipid hydroperoxide GPX4. The GPX enzyme is ubiquitously expressed with cytosolic GPX1 being most abundant in erythrocytes, kidney, and liver, cytosolic GPX2 in gastrointestinal tissues, and extracellular GPX3 in plasma. Unlike the tetrameric GPX1, GPX2, and GPX3, GPX4 is monomeric and has been localized to both the cytosol and membranes [26]. The enzymes reduce hydrogen peroxide, lipid peroxide, and other hydroperoxides to their corresponding alcohol forms using glutathione or other reducing compounds [33]. Each GPX enzyme is coded by discrete genes located on different chromosomes.

The *GPX1* gene has been localized to chromosome 3p21.3 and a well-studied polymorphism at amino acid position 198 results in a proline to leucine change, which has been shown to affect GPX activity in some [34–36], although not all studies [37, 38]. Carriers of the leucine allele have also been shown to have significantly higher levels of lipoperoxides and MDA in low-density lipoproteins [36]. This polymorphism has also been associated with several types of cancer with conflicting results reported. Interactions with the environment may explain some of these discrepancies with tobacco smoking [34], selenium [35, 39], alcohol [35], and fruit and vegetable consumption [34, 40], all being shown to modify GPX activity in some studies. In one study, alcohol consumption modified the relationship between Pro198Leu genotype and erythrocyte GPX activity; however, fruit and vegetable consumption and selenium intake did not [35]. The association between the Pro198Leu polymorphism and colorectal cancer was examined in 375 colorectal cancer cases and 779 gender-matched controls from the prospective Diet, Cancer and Health Study [34]. Erythrocyte GPX activity and the Pro198Leu polymorphism were not independently associated with colorectal cancer risk in this study, yet, significant gene-diet interactions were noted such that only subjects with the Leu/Leu genotype saw higher colorectal cancer risk with alcohol consumption (interaction p = 0.02) while only subjects with the Pro/Pro genotype and higher dietary vitamin C intake saw a reduced risk of colorectal cancer (interaction p = 0.05) [34]. In other studies, consumption of fruits and vegetables [41] as well as serum antioxidants and antioxidant supplementation [42] have not been shown to significantly modify the relationship between the Pro198Leu polymorphism and lung cancer.

Paraoxanase

Paraoxanase 1 (PON1) is a calcium-dependent hydrolyzing enzyme with substrates including insecticides, nerve agents, lactones, and other endogenous compounds such as oxidized low-density lipoproteins. Mainly synthesized in the liver, PON1 circulates in the plasma bound to the surface of high-density lipoproteins and contributes to the antioxidant capacity of high-density lipoproteins [43]. PON1 belongs to a family of 3 enzymes coded by 3 different genes *(PON1*, *PON2*, and *PON3)* located on chromosome 7q21.22. Two common polymorphisms in the coding region of the *PON1* gene have been extensively investigated: a leucine to methionine substitution at amino acid position 55 (L55M) and a glutamine to arginine substitution at amino acid position 192 (Q192R). Both polymorphisms have been shown to impact PON activity in a direction that is dependent upon the substrate and may directly impact the enzyme's ability to defend against oxidative stress [43, 44]. Other factors that may influence PON1 activity have been recently reviewed and include age, gender, drugs, dietary antioxidants and polyphenols, dietary lipids, and alcohol [43].

Several studies have shown that the impact of these variants on PON1 activity may also be modulated by the diet, including orange and blackcurrant juice [45] and diets high in vegetables [46] and oleic acid [47]. Diet has also been shown to interact with *PON1* polymorphisms to modulate oxidative stress. Tomato juice, which is rich

in lycopene, has been shown to significantly reduce plasma MDA (measured as thiobarbituric acid-reactive substances or TBARS) in *PON1* 192R allele carriers in a study of healthy young men [48] and elderly subjects [49]. In a recent cross-sectional study of 107 women, neither the *PON1* M55L nor the Q192R polymorphisms significantly modified the relationship between serum lycopene and levels of TBARS, however, both polymorphisms showed significant interactions with serum lycopene on markers of bone turnover, which may also indicate increased oxidative stress [50]. Studies have also shown consumption of restructured walnut paste-enriched steaks to significantly interact with the *PON1* Q192R polymorphism such that the walnut-enriched meat decreased sVCAM-1 (interaction p = 0.026), a marker of inflammation and endothelial activation [51], and lipid peroxidation (interaction p = 0.04) [52] in 192R allele carriers only.

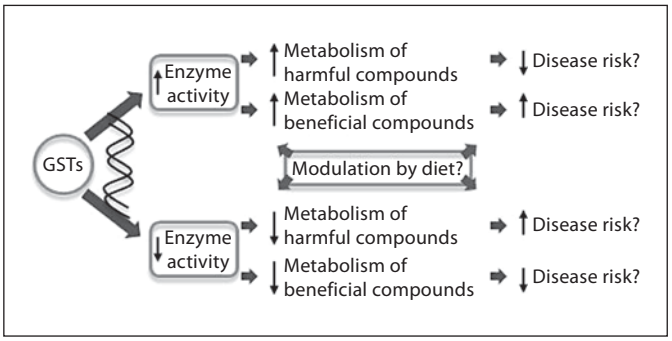

Fig. 3. Potential role of glutathione *S*-transferase (GST) polymorphisms on disease risk. Genetic variation in the GST enzymes can result in altered activity. The reduced activity may result in an increase or decrease in metabolism of both harmful compounds (including by-products of oxidative stress and carcinogens) as well as beneficial compounds (such as isothiocyanates). As such, the GST polymorphisms have been proposed to increase or decrease disease risk and this relationship may be further modified by diet.

Glutathione *S*-Transferases

Glutathione *S*-transferases (GSTs) are a large group of multifunctional proteins localized in the cytosol, mitochondria and membrane of cells [53]. They are phase II detoxification enzymes that, through the action of conjugation with glutathione, metabolize xenobiotics such as carcinogens and pollutants, and by-products of oxidative stress [54]. There are 7 classes of cytosolic GSTs including α, μ, ω, π, ς, θ, and ζ encoded by genes on chromosomes 6, 1, 10, 11, 4, 22, and 14, respectively [53, 54]. Nutrigenetics studies have focused on the GST μ1 (GSTM1), θ1 (GSTT1), and π1 (GSTP1), classes for which common genetic variants have been identified and shown to affect enzyme activity. In both the *GSTM1* and *GSTT1* genes, a deletion polymorphism exists such that those homozygous for the null allele show a loss of enzyme function [55, 56]. In the *GSTP1* gene, several polymorphisms have been identified, including a non-synonymous-coding polymorphism resulting in a isoleucine to valine amino acid change at codon 105 (Ile105Val) and an alanine to valine amino acid change at codon 114 (Ala114Val) [57]. While one study showed levels of 8-oxo-7,8-dihydro-2′-deoxyguanosine to differ by *GSTP1* but not *GSTM1* or *GSTT1* genotypes [58], another found no differences in protein carbonyl levels by any GST genotype [59].

These polymorphisms in *GSTM1*, *GSTT1*, and *GSTP1* have been studied extensively in relation to cancer and several studies have also examined potential gene-diet interactions on cancer risks [reviewed in ref. 23, 60]. For example, a recent study examined 19 polymorphisms in 13 genes coding xenobiotic metabolizing enzymes including *GSTM1*, *GSTT1*, and *GSTP1* in 308 premalignant adenoma cases identified by colonoscopy and 296 controls [61]. Fiber, energy, total vegetable consumption and cruciferous vegetable consumption were all found to be inversely related to colorectal adenoma risk, whereas there was only a modest suggestion of an inverse relationship with fruit consumption and no relationship was found with consumption of red meat. Of the GST polymorphisms, only the *GSTM1* null genotype was significantly associated with increased risk of colorectal adenoma risk (OR: 1.43, 95% CI: 1.04–1.98). In further examination of gene-diet interactions, the authors found some evidence of an interaction between the *GSTP1* Ala114Val polymorphism and fruit consumption on colorectal adenoma risk (interaction p = 0.02). Fruit consumption was not protective among carriers of the *GSTP1* variant allele (OR: 1.28, 95% CI: 0.58–2.83), while it was shown to be protective among those homozygous for the reference allele (OR: 0.49, 95% CI: 0.34–0.71) [61]. Polymorphisms in the GST enzymes have been hypothesized and shown to have both a beneficial and adverse impact on cancer risk, possibly due to the role of GST in eliminating harmful oxidative species and carcinogens as well as beneficial dietary chemoprotective chemicals such as isothiocyanates found in cruciferous vegetables (fig. 3). Thus, GST polymorphisms may also alter the relationship between diet and other oxidative stress-related conditions, including cardiovascular disease [62].

Additional interactions involving multiple genes and multiple environmental exposures including diet may further complicate this issue.

Conclusion

Oxidative stress has been implicated in the development of several chronic diseases, including cardiovascular disease and cancer. Support for this observation comes from numerous studies that have shown genetic variation in genes coding antioxidant enzymes significantly affects risk of cancer; however, inconsistencies between studies have made drawing definitive conclusions difficult. Searching for explanations for these inconsistencies has led to the investigation of potential environmental modifiers such as diet. Indeed, several nutrigenetic studies have shown diet to significantly modify the relationship between polymorphisms in genes coding antioxidant enzymes and cancer. Although this suggests modulation of oxidative stress by diet and genetics, much fewer studies have utilized biomarkers of oxidative stress. Furthermore, many studies may be significantly underpowered to detect gene-diet interactions due to inadequate sample size [63]. Drawing conclusions from several studies is also complicated by the differences in the types of gene-diet interactions examined and the differences in calculation and interpretation of the interactions [63, 64]. Additional interactions involving multiple genes and multiple environmental exposures including diet may further complicate this issue. As more nutrigenetic research emerges, we will continue to improve our understanding of the complex relationship between genetics, diet, and disease development. In addition to gaining knowledge of the role of oxidative stress in disease pathogenesis, this type of research may also have important public health implications in identifying subgroups that would benefit from dietary intervention.

Disclosure Statement

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References

1 Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J: Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44–84.
2 Serafini M: The role of antioxidants in disease prevention. Medicine 2006;34:533–535.
3 McCord JM: The evolution of free radicals and oxidative stress. Am J Med 2000;108:652–659.
4 Dalle-Donne I, Rossi R, Colombo R, Giustarini D, Milzani A: Biomarkers of oxidative damage in human disease. Clin Chem 2006;52:601–623.
5 García-Bailo B, El-Sohemy A, Haddad P, Arora P, Benzaied F, Karmali M, Badawi A: Vitamins D, C, and E in the prevention of type 2 diabetes mellitus: modulation of inflammation and oxidative stress. Biologics 2011;5:1–13.
6 Da Costa LA, García-Bailo B, Badawi A, El-Sohemy A: Genetic determinants of dietary antioxidant status; in Bouchard C, Ordovas J (eds): Nutrigenetics and Nutrigenomics. Elsevier, 2012, in press.
7 Cahill LE, El-Sohemy A: Vitamin C transporter gene polymorphisms, dietary vitamin C and serum ascorbic acid. J Nutrigenet Nutrigenomics 2009;2:292–301.
8 Timpson NJ, Forouhi NG, Brion MJ, Harbord RM, Cook DG, Johnson P, McConnachie A, Morris RW, Rodriguez S, Luan J, Ebrahim S, Padmanabhan S, Watt G, Bruckdorfer KR, Wareham NJ, Whincup PH, Chanock S, Sattar N, Lawlor DA, Smith GD: Genetic variation at the SLC23A1 locus is associated with circulating concentrations of L-ascorbic acid (vitamin C): evidence from 5 independent studies with >15,000 participants. Am J Clin Nutr 2010;92:375–382.
9 Major JM, Yu K, Wheeler W, Zhang H, Cornelis MC, Wright ME, Yeager M, Snyder K, Weinstein SJ, Mondul A, Elaissen H, Purdue M, Hazra A, McCarthy CA, Hendrickson S, Virtamo J, Hunter D, Chanock S, Kraft P, Albanes D: Genome-wide association study identifies common variants associated with circulating vitamin E levels. Hum Mol Genet 2011;20:3876–3883.
10 Borel P, Moussa M, Reboul E, Lyan B, Defoort C, Vincent-Baudry S, Maillot M, Gastaldi M, Darmon M, Portugal H, Lairon D, Planells R: Human fasting plasma concentrations of vitamin E and carotenoids, and their association with genetic variants in apo C-III, cholesteryl ester transfer protein, hepatic lipase, intestinal fatty acid binding protein and microsomal triacylglycerol transfer protein. Br J Nutr 2009;101:680–687.
11 Klotz LO, Kröncke KD, Buchczyk DP, Sies H: Role of copper, zinc, selenium and tellurium in the cellular defense against oxidative and nitrosative stress. J Nutr 2003;133:1448S–1451S.
12 Giustarini D, Dalle-Donne I, Tsikas D, Rossi R: Oxidative stress and human diseases: origin, link, measurement, mechanisms, and biomarkers. Crit Rev Clin Lab Sci 2009;46:241–281.
13 Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C: Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer 2007;121:2381–2386.
14 Marnett LJ: Oxyradicals and DNA damage. Carcinogenesis 2000;21:361–370.
15 Halliwell B: Oxidative stress and cancer: have we moved forward? Biochem J 2007;401:1–11.
16 Zelko IN, Mariani TJ, Folz RJ: Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. Free Radic Biol Med 2002;33:337–349.
17 Macmillan-Crow LA, Cruthirds DL: Invited review: manganese superoxide dismutase in disease. Free Radic Res 2001;34:325–336.

18 Shimoda-Matsubayashi S, Matsumine H, Kobayashi T, Nakagawa-Hattori Y, Shimizu Y, Mizuno Y: Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene. A predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. Biochem Biophys Res Commun 1996;226:561–565.
19 Chen Y, Pei J: Possible risk modifications in the association between MnSOD Ala-9Val polymorphism and breast cancer risk: subgroup analysis and evidence-based sample size calculation for a future trial. Breast Cancer Res Treat 2011;125:495–504.
20 Rosenblum JS, Gilula NB, Lerner RA: On signal sequence polymorphisms and diseases of distribution. Proc Natl Acad Sci USA 1996;93:4471–4473.
21 Sutton A, Khoury H, Prip-Buus C, Cepanec C, Pessayre D, Degoul F: The Ala16Val genetic dimorphism modulates the import of human manganese superoxide dismutase into rat liver mitochondria. Pharmacogenetics 2003;13:145–157.
22 Caple F, Williams EA, Spiers A, Tyson J, Burtle B, Daly AK, Mathers JC, Hesketh JE: Inter-individual variation in DNA damage and base excision repair in young, healthy nonsmokers: effects of dietary supplementation and genotype. Br J Nutr 2010;103:1585–1593.
23 Nowell SA, Ahn J, Ambrosone CB: Gene-nutrient interactions in cancer etiology. Nutr Rev 2004;62:427–438.
24 Tong SY, Lee JM, Song ES, Lee KB, Kim MK, Lee JK, Son SK, Lee JP, Kim JH, Kwon YI: Functional polymorphism in manganese superoxide dismutase and antioxidant status: their interactions on the risk of cervical intraepithelial neoplasia and cervical cancer. Gynecol Oncol 2009;115:272–276.
25 Wang S, Wang F, Shi X, Dai J, Peng Y, Guo X, Wang X, Shen H, Hu Z: Association between manganese superoxide dismutase (MnSOD) Val-9Ala polymorphism and cancer risk – a meta-analysis. Eur J Cancer 2009;45:2874–2881.
26 Forsberg L, De Faire U, Morgenstern R: Oxidative stress, human genetic variation, and disease. Arch Biochem Biophys 2001;389:84–93.
27 Ahn J, Gammon MD, Santella RM, Gaudet MM, Britton JA, Teitelbaum SL, Terry MB, Nowell S, Davis W, Garza C, Neugut AI, Ambrosone CB: Associations between breast cancer risk and the catalase genotype, fruit and vegetable consumption, and supplement use. Am J Epidemiol 2005;162:943–952.
28 Nadif R, Mintz M, Jedlicka A, Bertrand JP, Kleeberger SR, Kauffmann F: Association of CAT polymorphisms with catalase activity and exposure to environmental oxidative stimuli. Free Radic Res 2005;39:1345–1350.
29 Bastaki M, Huen K, Manzanillo P, Chande N, Chen C, Balmes JR, Tager IB, Holland N: Genotype-activity relationship for Mn-superoxide dismutase, glutathione peroxidase 1 and catalase in humans. Pharmacogenet Genomics 2006;16:279–286.
30 Forsberg L, Lyrenás L, De Faire U, Morgenstern R: A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. Free Radic Biol Med 2001;30:500–505.
31 Ahn J, Nowell S, McCann SE, Yu J, Carter L, Lang NP, Kadlubar FF, Ratnasinghe LD, Ambrosone CB: Associations between catalase phenotype and genotype: modification by epidemiologic factors. Cancer Epidemiol Biomarkers Prev 2006;15:1217–1222.
32 Polonikov AV, Ivanov VP, Solodilova MA, Kozhuhov MA, Panfilov VI: Tobacco smoking, fruit and vegetable intake modify association between –21A>T polymorphism of catalase gene and risk of bronchial asthma. J Asthma 2009;46:217–224.
33 Masella R, Di Benedetto R, Varì R, Filesi C, Giovannini C: Novel mechanisms of natural antioxidant compounds in biological systems: involvement of glutathione and glutathione-related enzymes. J Nutr Biochem 2005;16:577–586.
34 Hansen RD, Krath BN, Frederiksen K, Tjønneland A, Overvad K, Roswall N, Loft S, Dragsted LO, Vogel U, Raaschou-Nielsen O: GPX1 Pro198Leu polymorphism, erythrocyte GPX activity, interaction with alcohol consumption and smoking, and risk of colorectal cancer. Mutat Res 2009;664:13–19.
35 Ravn-Haren G, Olsen A, Tjønneland A, Dragsted LO, Nexø BA, Wallin H, Overvad K, Raaschou-Nielsen O, Vogel U: Associations between GPX1 Pro198Leu polymorphism, erythrocyte GPX activity, alcohol consumption and breast cancer risk in a prospective cohort study. Carcinogenesis 2006;27:820–825.
36 Shuvalova YA, Kaminnyi AI, Meshkov AN, Kukharchuk VV: Pro198Leu polymorphism of *GPx-1* gene and activity of erythrocytic glutathione peroxidase and lipid peroxidation products. Bull Exp Biol Med 2010;149:743–745.
37 Arsova-Sarafinovska Z, Matevska N, Eken A, Petrovski D, Banev S, Dzikova S, Georgiev V, Sikole A, Erdem O, Sayal A, Aydin A, Dimovski AJ: Glutathione peroxidase 1 (GPX1) genetic polymorphism, erythrocyte GPX activity, and prostate cancer risk. Int Urol Nephrol 2009;41:63–70.
38 Forsberg L, De Faire U, Marklund SL, Andersson PM, Stegmayr B, Morgenstern R: Phenotype determination of a common Pro-Leu polymorphism in human glutathione peroxidase 1. Blood Cells Mol Dis 2000;26:423–426.
39 Hu YJ, Diamond AM: Role of glutathione peroxidase 1 in breast cancer: loss of heterozygosity and allelic differences in the response to selenium. Cancer Res 2003;63:3347–3351.
40 Dragsted LO, Pedersen A, Hermetter A, Basu S, Hansen M, Haren GR, Kall M, Breinholt V, Castenmiller JJM, Stagsted J, Jakobsen J, Skibsted L, Rasmussen SE, Loft S, Sandström B: The 6-a-day study: effects of fruit and vegetables on markers of oxidative stress and antioxidative defense in healthy nonsmokers. Am J Clin Nutr 2004;79:1060–1072.
41 Raaschou-Nielsen O, Sørensen M, Hansen RD, Frederiksen K, Tjønneland A, Overvad K, Vogel U: GPX1 Pro198Leu polymorphism, interactions with smoking and alcohol consumption, and risk for lung cancer. Cancer Lett 2007;247:293–300.
42 Ratnasinghe D, Tangrea JA, Andersen MR, Barrett MJ, Virtamo J, Taylor PR, Albanes D: Glutathione peroxidase codon 198 polymorphism variant increases lung cancer risk. Cancer Res 2000;60:6381–6383.
43 Costa LG, Giordano G, Furlong CE: Pharmacological and dietary modulators of paraoxonase 1 (PON1) activity and expression: the hunt goes on. Biochem Pharmacol 2011;81:337–344.
44 Mackness MI, Arrol S, Mackness B, Durrington PN: Alloenzymes of paraoxonase and effectiveness of high-density lipoproteins in protecting low-density lipoprotein against lipid peroxidation. Lancet 1997;349:851–852.
45 Dalgård C, Christiansen L, Jonung T, Mackness MI, De Maat MPM, Hørder M: No influence of increased intake of orange and blackcurrant juices and dietary amounts of vitamin E on paraoxonase-1 activity in patients with peripheral arterial disease. Eur J Nutr 2007;46:354–363.
46 Rantala M, Silaste ML, Tuominen A, Kaikkonen J, Salonen JT, Alfthan G, Aro A, Antero Kesäniemi Y: Dietary modifications and gene polymorphisms alter serum paraoxonase activity in healthy women. J Nutr 2002;132:3012–3017.
47 Tomás M, Sentí M, Elosua R, Vila J, Sala J, Masià R, Marrugat J: Interaction between the Gln-Arg 192 variants of the paraoxonase gene and oleic acid intake as a determinant of high-density lipoprotein cholesterol and paraoxonase activity. Eur J Pharmacol 2001;432:121–128.
48 Bub A, Barth SW, Watzl B, Briviba K, Rechkemmer G: Paraoxonase 1 Q192R (PON1–192) polymorphism is associated with reduced lipid peroxidation in healthy young men on a low-carotenoid diet supplemented with tomato juice. Br J Nutr 2005;93:291–297.

49 Bub A, Barth S, Watzl B, Briviba K, Herbert BM, Lührmann PM, Neuhäuser-Berthold M, Rechkemmer G: Paraoxonase 1 Q192R (PON1–192) polymorphism is associated with reduced lipid peroxidation in R-allele-carrier but not in QQ homozygous elderly subjects on a tomato-rich diet. Eur J Nutr 2002;41:237–243.
50 MacKinnon ES, El-Sohemy A, Rao AV, Rao LG: Paraoxonase 1 polymorphisms 172T>A and 584A>G modify the association between serum concentrations of the antioxidant lycopene and bone turnover markers and oxidative stress parameters in women 25–70 years of age. J Nutrigenet Nutrigenomics 2010;3:1–8.
51 Canales A, Sánchez-Muniz FJ, Bastida S, Librelotto J, Nus M, Corella D, Guillen M, Benedi J: Effect of walnut-enriched meat on the relationship between VCAM, ICAM, and LTB4 levels and PON-1 activity in ApoA4 360 and PON-1 allele carriers at increased cardiovascular risk. Eur J Clin Nutr 2011;65:703–710.
52 Nus M, Frances F, Librelotto J, Canales A, Corella D, Sánchez-Montero JM, Sánchez-Muniz FJ: Arylesterase activity and antioxidant status depend on PON1-Q192R and PON1-L55M polymorphisms in subjects with increased risk of cardiovascular disease consuming walnut-enriched meat. J Nutr 2007;137:1783–1788.
53 Nelson EC, Rodriguez RL, Dawson K, Galvez AF, Evans CP: The interaction of genetic polymorphisms with lifestyle factors: implications for the dietary prevention of prostate cancer. Nutr Cancer 2008;60:301–312.
54 Strange RC, Spiteri MA, Ramachandran S, Fryer AA: Glutathione-*S*-transferase family of enzymes. Mutat Res 2001;482:21–26.
55 Xu SJ, Wang YP, Roe B, Pearson WR: Characterization of the human class mu glutathione *S*-transferase gene cluster and the GSTM1 deletion. J Biol Chem 1998;273:3517–3527.
56 Bruhn C, Brockmöller J, Kerb R, Roots I, Borchert HH: Concordance between enzyme activity and genotype of glutathione *S*-transferase theta (GSTT1). Biochem Pharmacol 1998;56:1189–1193.
57 Hayes JD, Flanagan JU, Jowsey IR: Glutathione transferases. Annu Rev Phamacol Toxicol 2005;45:51–88.
58 Lagadu S, Lechevrel M, Sichel F, Breton J, Pottier D, Couderc R, Moussa F, Prevost V: 8-oxo-7,8-dihydro-2′-deoxyguanosine as a biomarker of oxidative damage in oesophageal cancer patients: lack of association with antioxidant vitamins and polymorphism of hOGG1 and GST. J Exp Clin Cancer Res 2010;29:157.
59 Yeh CC, Lai CY, Hsieh LL, Tang R, Wu FY, Sung FC: Protein carbonyl levels, glutathione *S*-transferase polymorphisms and risk of colorectal cancer. Carcinogenesis 2010;31:228–233.
60 Reszka E, Wasowicz W, Gromadzinska J: Genetic polymorphism of xenobiotic metabolising enzymes, diet and cancer susceptibility. Br J Nutr 2006;96:609–619.
61 Northwood EL, Elliott F, Forman D, Barrett JH, Wilkie MJV, Carey FA, Steele RJC, Wolf R, Bishop T, Smith G: Polymorphisms in xenobiotic metabolizing enzymes and diet influence colorectal adenoma risk. Pharmacogenet Genomics 2010;20:315–326.
62 Cornelis MC, El-Sohemy A, Campos H: GSTT1 genotype modifies the association between cruciferous vegetable intake and the risk of myocardial infarction. Am J Clin Nutr 2007;86:752–758.
63 Minelli C, Gögele M: The role of antioxidant gene polymorphisms in modifying the health effects of environmental exposures causing oxidative stress: a public health perspective. Free Radic Biol Med 2011;51:925–930.
64 Thomas D: Gene-environment-wide association studies: emerging approaches. Nat Rev Genet 2010;11:259–272.