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Review Article

Genetic polymorphism of xenobiotic metabolising enzymes, diet and cancer susceptibility

Edyta Reszka, Wojciech Wasowicz* and Jolanta Gromadzinska

Department of Toxicology and Carcinogenesis, Nofer Institute of Occupational Medicine, 91-348 Lodz, 8 Teresy St, Poland

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There is increasing evidence identifying the crucial role of numerous dietary components in modifying the process of carcinogenesis. The varied effects exerted by nutrient and non-nutrient dietary compounds on human health and cancer risk are one of the new challenges for nutritional sciences. In the present paper, an attempt is made to review the most recent epidemiological data on interactions between dietary factors and metabolic gene variants in terms of cancer risk. The majority of case–control studies indicate the significant relationship between cancer risk and polymorphic xenobiotic metabolising enzymes in relation to dietary components. The risk of colorectal cancer is associated not only with *CYP2E1* high-activity alleles, but also *GSTA1* low-activity alleles, among consumers of red or processed meat. Genetic polymorphisms of NAT1 and NAT2 may be also a breast-cancer susceptibility factor among postmenopausal women with a high intake of well-done meat. On the other hand, phytochemicals, especially isothiocyanates, have a protective effect against colorectal and lung cancers in individuals lacking *GST* genes. Moreover, polymorphism of *GSTM1* seems to be involved in the dietary regulation of DNA damage. The European Prospective Investigation into Cancer and Nutrition study shows a significant inverse association between the polycyclic aromatic hydrocarbon–DNA adduct level and dietary antioxidants only among *GSTM1*-null individuals. However, the absence of a modulatory effect of polymorphic xenobiotic metabolising enzymes and diet on the development of cancer has been indicated by some epidemiological investigations. Studies of interactions between nutrients and genes may have great potential for exploring mechanisms, identifying susceptible populations/individuals and making practical use of study results to develop preventive strategies beneficial to human health.

Genetic polymorphism: Xenobiotic metabolism: Nutrients: Cancer

A growing incidence of cancer and other common diseases has been observed over recent decades. Therefore, extensive research has been carried out in numerous disciplines, including biochemistry, toxicology, molecular biology, genetics and epidemiology, to investigate cancer-inducing mechanisms and risk factors. It is thought that the multifactorial aetiology of cancer involves not only environmental, dietary, genetic and epigenetic modulators, but also gene–environment and gene–nutrient interactions. For a number of years, nutritional research has focused on the identification and understanding of interactions between nutrients or other dietary compounds and genes.

Increasing evidence highlights the crucial role of numerous dietary components in modifying the carcinogenic process. Diet, the major source of vitamins, micronutrients, antioxidants and phytochemicals, but also the source of carcinogens and mutagens, is found to be responsible for the majority of cancer deaths. About 35 % of cancer deaths are associated with diet, mostly with inappropriate nutritional habits, which is comparable to the tobacco-related cancer risk. However, a very wide range of confidence limits for estimating the incidence of diet-related cancer (10–70 %) has been shown (Weisburger, 1999; Kritchevsky, 2003). Epidemiological and experimental studies provide evidence that there are three dietary constituents/contaminants (alcoholic beverages, aflatoxins, salted foods) associated with the development of cancer (Montesano & Hall, 2001). Several epidemiological studies show that vegetables, fruit, dietary fibre and certain nutrients show an anticarcinogenic effect and can protect against cancer (Greenwald *et al.* 2001).

Findings that highlight the role of genetics in the aetiology of cancer reveal the occurrence of single (high-penetrance) genes, observed in fewer than 1 % of the population, and more common susceptibility (low-penetrance) genes. The group of low-penetrance genes includes genes that influence xenobiotic activation/detoxification and DNA repair (Sinha & Caporaso, 1999; Shields & Harris, 2000). The genetic predisposition to cancer may result from differences in the metabolism of genotoxic compounds and DNA-repair mechanisms. The cancer risk associated with these susceptibility genes (e.g. xenobiotic metabolising enzyme (XME) genes), is fairly moderate, whereas the impact of environmental

Abbreviations: COMT, catechol-*O*-methyltransferase; GST, glutathione S-transferase; HCA, heterocyclic amine; ITC, isothiocyanate; MnSOD, manganese superoxide dismutase; NAT, N-acetyltransferase; OR, odds ratio; PAH, polycyclic aromatic hydrocarbon; XME, xenobiotic metabolising enzymes.

* **Corresponding author:** Professor W. Wasowicz, fax +48 426568331, email wojciech@imp.lodz.pl

exposure and/or diet may be critical (Parkin *et al.* 2001; Reszka & Wasowicz, 2001).

It is well known that both nutrients and xenobiotics may influence the expression of several genes by modulating inducible sequences in promoter regions, called responsive elements. This mechanism of dietary modulation seems to be important in the biotransformation of carcinogens as several XME genes possess this inducible sequence. There is, however, an opposite mechanism in which XME genetic polymorphism may determine the effects of specific nutrients by differences in their biotransformation (Milner, 2003; Paoloni-Giacobino *et al.* 2003). Hence, the link between diet and genes has to be considered to be bidirectional.

Antioxidant responsive elements

Several known pathways include specific nutrients (antioxidants, microelements, amino acids, fatty acids, carbohydrates) that are responsible for the specific regulation of gene expression (Paoloni-Giacobino *et al.* 2003). For several years, it has been observed that some chemicals, including not only dietary antioxidants and phytochemicals, but also xenobiotics, might influence the expression of several XME. The majority of these dietary compounds (e.g. isothiocyanate (ITC), organosulphide, polyphenol and Se compounds) can protect against cancer by preventing carcinogens from modifying DNA and inducing mutations. This defence against chemicals (DNA methylation, DNA adduct formation) and oxidative stress (oxidative DNA base modification) is generally achieved by increasing the expression and/or activity of biotransformation and antioxidative enzymes.

The molecular basis of XME regulation was revealed at the beginning of the 1990s. It was first described as a transcriptional regulatory element for glutathione S-transferase (GST) A1 and quinone oxidoreductase 1. This sequence, termed the 'antioxidant responsive element', has been found in the promoter region of numerous XME and in several antioxidative enzymes (NAD(P)H:quinone oxidoreductase, γ-glutamylcysteine synthetase, glutathione synthetase). Molecular mechanisms of enzyme induction have not yet been well elucidated, but some findings indicate a number of proteins associated with cellular and nuclear signalling. The transcription factor NF-E2-related factor-2 and Maf small proteins play an important role in the modulation of inducible genes. Ongoing studies have revealed that monofunctional inducers can transcriptionally activate the expression of some XME genes via antioxidant responsive elements. XME genes can also be activated by bifunctional inducers that modulate the antioxidant responsive element and xenobiotic responsive element. Stimulation of the antioxidant responsive element by two groups of inducer (e.g. phytochemicals) shows their crucial role in cancer protection (Hayes & McMahon, 2001; Talalay & Fahey, 2001).

DNA damage, antioxidants and polymorphic xenobiotic metabolising enzymes

The recognition of genetic and biological variability in nutrient requirements contributed to the development of extensive studies of gene–nutrient interactions (Fairweather-Tait, 2003). It seems very useful to analyse individual genotypes with a specific focus on common genetic polymorphisms modifying the bioavailability, metabolism, affinity and activity of several dietary constituents. Various dietary compounds with potential carcinogenic activity (e.g. heterocyclic amine (HCA), polycyclic aromatic hydrocarbon (PAH), aflatoxin) can be metabolised by polymorphic XME. The process of activation by phase I enzymes and detoxification by phase II enzymes includes environmental, dietary xenobiotics as well as protective components of the diet (Sinha & Caporaso, 1999), which can influence the modulation of biotransformation enzymes (Wargovich & Cunningham, 2003). Accumulated evidence shows that fruit and vegetable intake and a genetic polymorphism of some detoxifying enzymes is associated with PAH–DNA adduct formation and cancer risk.

Well-known studies of gene–nutrient interactions show an association between nutrient level and PAH–DNA adducts in leucocytes and GST genetic polymorphism (Table 1). In 1994, Grinberg-Funes *et al.* found, in American male smokers, an inverse association between PAH–DNA adduct levels and serum cholesterol-adjusted vitamin E levels, albeit only in *GSTM1*-null subjects. Interestingly, this relationship was not observed in the group of subjects with the *GSTM1* gene, nor was the association found between β-carotene and vitamin A serum level with the GSTM1 genotype. A significantly lower level of PAH–DNA adducts in heavy smokers of both genders and Caucasian origin lacking the *GSTM1* gene was associated with a higher plasma level of another antioxidant, β-carotene (Mooney *et al.* 1997).

Two known Japanese studies, however, failed to indicate such associations. Smokers with the *CYP1A1* val/val genotype showed higher DNA adduct levels than those with *CYP1A1* ile/val and isoleucine/isoleucine genotypes, but only in the low β-carotene group ($>30{\cdot}5$ μg/dl plasma). Smokers with the *CYP1A1* ile/ile genotype and a high plasma β-carotene had a significantly higher level of DNA adducts than those with a low β-carotene concentration. It was also found in this group of individuals that high plasma β-carotene concentration and *GSTT1*-null genotype were associated with higher levels of DNA adducts than were seen in the *GSTT1*-present genotype group with a low antioxidant concentration (Wang *et al.* 1998). The study of 192 healthy Japanese individuals showed no effect of plasma β-carotene and α-tocopherol on DNA adducts, regardless of the *CYP1A1* variant and GSTM1 polymorphisms (Wang *et al.* 1997).

It is well known that GST may play an important role in cellular protection against oxidative stress. Some studies also show that a genetic polymorphism of GST may enhance defence mechanisms against oxidative stress. Antioxidants may prevent adduct formation and thereby reduce cancer risk in the case of detoxifying enzymes devoid of expression due to the variant genotype. Recent data from the European Prospective Investigation into Cancer and Nutrition study of the Italian population have revealed strong negative associations between PAH–DNA adducts and specific antioxidants for the *GSTM1*-null genotype but not the *GSTM1*-present genotype group. These inverse associations were found to be significant for plasma retinol, α-carotene and β-carotene. A borderline negative association was also found for α-tocopherol and γ-tocopherol in homozygotes lacking the *GSTM1* gene. However, this study has not shown any association between GSTM1 genotype and levels of several plasma micronutrients: β-cryptoxanthin, lutein, lycopene, zeaxanthin,

Table 1. DNA damages and dietary constituents in relation to glutathione S-transferase (GST) genetic polymorphism

Gene	Micronutrients/dietary constituents	Marker of DNA damage	Investigated population	Gene–nutrient interaction
GSTM1	Vitamin E (mg/mg cholesterol in serum)	PAH–DNA adducts in mononuclear cells	63 smoking males; USA	Inverse association between PAH–DNA adduct levels and serum cholesterol-adjusted vitamin E levels in *GSTM1*-null subjects (β − 0·38, $P<0·05$; *n* 31; Grinberg-Funes *et al.* 1994)
GSTM1	β-Carotene (ng/ml plasma)	PAH-DNA adducts in leucocytes	159 heavy smokers; USA Caucasians (approximately 89 %)	Inverse association between PAH–DNA adduct levels and smoking-adjusted plasma β-carotene levels in *GSTM1*-null subjects (β − 0·30, $P=0·05$; *n* 75; Mooney *et al.* 1997)
GSTT1	β-Carotene (μg/dl plasma)	PAH-DNA adducts in lymphocytes	158 Japanese males (77 smokers)	Smokers with high β-carotene level and a *GSTT1*-null genotype had higher DNA adduct levels ($P=0·07$) than subjects with a *GSTT1*-present genotype (Wang *et al.* 1998)
GSTM1	α-Carotene, β-carotene, retinol (μmol/l plasma)	PAH-DNA in leucocytes	Approximately 110 subjects; Italian volunteers in EPIC study	Inverse association between PAH–DNA adduct levels and α-carotene levels in plasma in *GSTM1*-null subjects (test for trend, $P=0·02$) Inverse association between PAH–DNA adduct levels and β-carotene levels in plasma in *GSTM1*-null subjects (test for trend, $P=0·02$) Inverse association between PAH–DNA adduct levels and retinol levels in plasma in *GSTM1*-null subjects (test for trend, $P=0·002$; Palli *et al.* 2003)
GSTM1	Leafy vegetables, white meat, vitamin C, β-carotene, vitamin E (calculated according to questionnaire data)	PAH-DNA adducts in leucocytes	634 subjects; Italian volunteers in EPIC study	Inverse association between PAH–DNA adduct levels and leafy vegetable intakes in *GSTM1*-null subjects (β − 0·52, $P=0·01$; *n* 307) Inverse association between PAH–DNA adduct levels and white meat intakes in *GSTM1*-null subjects (β − 0·44, $P=0·04$; *n* 307) Inverse association between PAH–DNA adduct levels and vitamin C intakes in *GSTM1*-null subjects (β − 0·44, $P=0·04$; *n* 307) Inverse association between PAH–DNA adduct levels and β-carotene intakes in *GSTM1*-null subjects (β − 0·51, $P=0·02$; *n* 307) Inverse association between PAH–DNA adduct levels and vitamin E intakes in *GSTM1*-null subjects (β − 0·42, $P=0·05$; *n* 307; Palli *et al.* 2004)
GSTM1	Green tea (four cups/d for 4 months)	Urinary excretion of 8-OHdG (ng/mg creatinine)	143 heavy smokers; USA, phase II randomised trial	Decrease in urinary 8-OHdG from baseline in *GSTM1*-present (t − 2·4, $P=0·006$) individuals (Hakim *et al.* 2004)
GSTT1	Green tea (four cups/d for 4 months)	Urinary excretion of 8-OHdG (ng/mg creatinine)	143 heavy smokers; USA, phase II randomised trial	Decrease in urinary 8-OHdG from baseline in *GSTT1*-present (t − 1·9, $P=0·004$) individuals (Hakim *et al.* 2004)

PAH, polycyclic aromatic hydrocarbon; 8-OHdG, 8-hydroxydeoxyguanosine; EPIC, European Prospective Investigation into Cancer.

retinol and total carotenoids (Palli *et al.* 2003). It is interesting to note that individuals with a homozygous *GSTM1* deletion showed significantly inverse associations between leucocyte PAH–DNA adducts and specific antioxidants when dietary intake of antioxidants was calculated according to questionnaire data (Palli *et al.* 2004). However, smokers with the *GSTM1* or *GSTT1* gene have a significantly lower urinary excretion of 8-deoxyhydroguanine associated with frequent green tea consumption (Hakim *et al.* 2004).

In middle-aged male smokers and non-smokers with a *GSTM1*-null genotype, the levels of glutathione and vitamin C were significantly higher than in those with a *GSTM1*-positive genotype. The level of vitamin C was also higher in individuals with the *GSTT1*-present genotype than in those with *GSTT1*-null genotype (Dusinska *et al.* 2001). The nested lung cancer case–control study conducted in Finland under the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study suggested a relationship between smoking status, *GSTM1*-null genotype and lung cancer risk. However, this relationship was not statistically significant in the study population, except for *GSTM1*-null individuals not supplemented with α-tocopherol (50 mg/d over a 5–8-year period). The odds ratio (OR) of lung cancer risk was estimated to be 21·95 (95 % CI 6·26, 72·69) in the highest smoking tertile group lacking *GSTM1* genes and without supplementation, whereas the *GSTM1*-null genotype was not significantly associated with lung cancer risk (OR 1·34, 95 % CI 0·36, 5·03) among heavy smokers supplemented with α-tocopherol. Moreover, β-carotene supplementation (20 mg/d over a 5–8-year period) did not show a modifying effect on lung cancer risk associated with polymorphic GSTM1 and smoking status (Woodson *et al.* 1999).

Only one study (Chen *et al.* 2000) has shown an association between GST genetic polymorphism and the concentrations of trace elements. In males from the Matzu population (China), the correlation between Se level and aflatoxin B_1–albumin adducts was significantly inverse among those with *GSTM1*-present and *GSTT1*-null genotypes. Another study of the interaction between microelements and genes showed a significantly higher Zn level in lung cancer patients with defective (lack or/and lower expression or/and activity) *GSTM1*/*GSTT1* and *GSTM3*/*GSTT1* genotypes and in non-cancer controls with defective *GSTP1*/*GSTT1* genotypes compared with individuals with adequate wild-type *GST* genotypes (Reszka *et al.* 2005).

Dietary carcinogens, cancer risk and polymorphic xenobiotic metabolising enzymes

Recent evidence has shown the undeniable role of susceptibility genes, which may interact with various dietary factors, and thus reveal individual susceptibility to cancer. Table 2 presents the observed statistically significant relationship between metabolic genes and specific dietary constituents.

Specific variants of XME genotypes and the impact of diet were also found to be very important in the development of cancer at particular sites. Diet like antioxidants, microelements and phytochemicals can be affected by carcinogens and mutagens (e.g. HCA, PAH, nitrosoamines). HCA, well-known dietary procarcinogens, derived from red or well-processed meat may increase the risk of colorectal cancer. The role of differences in CYP1A1 and N-acetyltransferase (NAT) 2 activity in the metabolism of HCA is also critical in susceptibility to cancer at this site (Wargovich & Cunningham, 2003). An Italian study comparing post-meal and pre-meal samples detected urinary mutagenicity in fifty individuals after a meal of pan-fried hamburger (rich in heterocyclic aromatic amines). Of interest here is that a higher activity of CYP1A2 increased the amount of post-meal urinary mutagens, especially in NAT2 slow acetylators (0·90 ± 0·54 7 h minimum mutagenic dose per intake for the first CYP1A2 tertile compared with 2·18 ± 1·33 7 h minimum mutagenic dose per intake for the third CYP1A2 tertile; Pavanello *et al.* 2002).

Epidemiological studies indicate that the consumption of red or processed meat and CYP2E1 genetic polymorphism, linked with a single or double 96 bp insertion in the regulatory region and inducing higher enzyme activity, is associated with an increased risk of rectal and colon cancer. Subjects with at least a single-insert variant are at significant risk of rectal cancer (OR 1·60, 95 % CI 1·1, 2·5). In individuals with this specific CYP2E1 genotype exposed to high dietary levels of nitrosamines, an increased rectal cancer risk was observed. Moreover, a three-fold risk of rectal cancer was found among consumers of salted/dried fish or oriental pickled vegetables who were *CYP2E1* insert carriers. However, no association was observed between CYP2E1 genetic polymorphism and colon cancer (Le Marchand *et al.* 2002*b*).

Among polymorphic enzymes engaged in the detoxification of well-done meat mutagens, GSTA1 and CYP2A6 also demand consideration. According to a case–control study conducted in the USA, the *GSTA1*B/*B* genotype associated with lower enzyme expression can be responsible for an increased risk of colorectal cancer, especially in consumers of well-done red meat (more than two servings per week; OR 3·3, 95 % CI 1·2, 8·9). Having applied the phenotyping approach to detecting metabolic effects of the CYP2A6 polymorphism, it was found that the greatest enzyme activity (third tertile) was associated with a significantly higher risk of colorectal cancer, irrespective of preserved meat consumption (OR 3·2; 95 % CI 1·4, 7·7 for low consumption; OR 2·8, 95 % CI 1·2, 6·4 for high consumption). It is therefore suggested that the *GSTA1* genotype and CYP2A6 phenotype may be further studied as markers of susceptibility to dietary carcinogens, including HCA and N-nitroso compounds (Sweeney *et al.* 2002).

Genetic polymorphism of NAT may also contribute significantly to breast cancer risk among US Caucasian women who consume a lot of red meat. Although the relationship between the *NAT1*11* allele, enzyme expression and *O*-acetylation activity towards aromatic amines remains unclear, this allele seems to be the breast cancer susceptibility factor in postmenopausal women. Women with at least one *NAT1*11* allele are at significantly higher risk of breast cancer (OR 3·9, 95 % CI 1·5, 10·5). The positive association between breast cancer and the *NAT1*11* allele was higher among heavy consumers of a high level of red meat (OR 6·1, 95 % CI 1·1, 33·2) than among those consuming less meat and possessing the same NAT1 genotype pattern. Moreover, the most evident relationship between the *NAT1*11* allele and breast cancer was found among women who smoked (OR 13·2, 95 % CI 1·5, 116·0) (Zheng *et al.* 1999).

Results from another American study of Caucasian postmenopausal women also indicated the important role of polymorphic NAT2 in the *O*-acetylation of HCA in breast

Table 2. Observed relationship between polymorphic metabolic genes and some food components in terms of cancer risk

Polymorphic gene	Food component	Cancer risk	Investigated population	Gene–nutrient interaction
CYP2E1	Red meat, processed meat, salted/dried fish, oriental pickled vegetables; questionnaire data	Rectal cancer	US Hawaiian, Japanese Caucasians; 165 cases, 693 controls	One or two 96 bp inserts in the *CYP2E1* allele and red meat consumption greater than median (37·4 g/d) *v.* no 96 bp inserts in the *CYP2E1* allele and red meat consumption of median value or less (OR 2·1, 95 % CI 1·2, 3·7) One or two 96 bp inserts in the *CYP2E1* allele and processed meat consumption greater than median (14·8 g/d) *v.* no 96 bp inserts in the *CYP2E1* allele and processed meat consumption of median value or less (OR 3·1, 95 % CI 1·8, 5·6) One or two 96 bp inserts in the *CYP2E1* allele and salted/dried fish consumption *v.* no 96 bp inserts in the *CYP2E1* allele and no consumption of salted/dried fish (OR 3·0, 95 % CI 1·4, 6·6) One or two 96 bp inserts in the *CYP2E1* allele and oriental pickled vegetable consumption *v.* no 96 bp inserts in the *CYP2E1* allele and no consumption of oriental pickled vegetables (OR 3·2, 95 % CI 1·8, 5·7) One or two 96 bp inserts in the *CYP2E1* allele and processed meat consumption greater than median (14·8 g/d) and a low fruit and vegetable intake of median value or less (684 g/d) *v.* no 96 bp inserts in the *CYP2E1* allele and processed meat consumption of median value or less and high fruit and vegetable intake greater than median (OR 5·0, 95 % CI 2·2, 11·4; Le Marchand *et al.* 2002*b*)
CYP2E1	Processed meat; questionnaire data	Colon cancer	US Hawaiian, Japanese Caucasians; 356 cases, 693 controls	One or two 96 bp inserts in the *CYP2E1* allele and processed meat consumption greater than median (14·8 g/d) and a low fruit and vegetable intake of median value or less (684 g/d) *v.* no 96 bp inserts in the *CYP2E1* allele and processed meat consumption of median value or less and a high fruit and vegetable intake of greater than median (OR 2·1, 95 % CI 1·0, 4·0) *CYP2E1* RsaI c1/c1 genotype and processed meat consumption of greater than median (14·8 g/d) and a low fruit and vegetable intake of median value or less (684 g/d) *v. CYP2E1* RsaI c1/c1 genotype and processed meat consumption of median value or less and a high fruit and vegetable intake of greater than median (OR 2·3, 95 % CI 1·4, 3·9; Le Marchand *et al.* 2002*b*)
GSTA1	Well-done red meat; questionnaire data	Colorectal cancer	US Caucasians; 100 cases, 226 controls	*GSTA1**B/*B genotype and frequent well-done red meat consumption (>two servings/week) *v. GSTA1*A/*A* or *GSTA1*A/*B* genotype and rare well-done red meat consumption (≤two servings/week) (OR 3·3, 95 % CI 1·2, 8·9; Sweeney *et al.* 2002)
NAT1	Red meat; questionnaire data	Breast cancer (postmenopausal women)	US Caucasians; 273 cases, 657 controls	At least one *NAT1*11* allele and a high level of red meat consumption *v.* at least one *NAT1*11* allele and a low level of red meat consumption (OR 6·1, 95 % CI 1·1, 33·2; Zheng *et al.* 1999)
NAT2	Well-done red meat; questionnaire data	Breast cancer (postmenopausal women)	US Caucasians; 176 cases, 391 controls	Rapid/intermediate *NAT2* genotype and consumption of well-done red meat *v.* rapid/intermediate NAT2 genotype and rare or medium-done meat consumption (OR 7·6, 95 % CI 1·1, 50·4; Deitz *et al.* 2000)

Table 2. *Continued*

Polymorphic gene	Food component	Cancer risk	Investigated population	Gene–nutrient interaction
NAT2 and *CYP1A2* phenotype	Well-done red meat; questionnaire data	Colorectal cancer	US Hawaiian, Japanese Caucasians; 349 cases, 467 controls	Rapid NAT2 phenotype and CYP1A2 high-activity phenotype and well-done red meat consumption *v.* slow or intermediate slow/intermediate NAT2 phenotype and CYP1A2 low-activity phenotype and rare or medium-done red meat consumption (OR 3·3, 95 % CI 1·3, 8·1) Rapid NAT2 phenotype and CYP1A2 high activity phenotype and well-done red meat consumption and smoking *v.* slow or intermediate slow/intermediate NAT2 phenotype and CYP1A2 low-activity phenotype and rare or medium-done red meat consumption and smoking (OR 8·8 95 % CI 1·7, 44·9; Le Marchand *et al.* 2001)
GSTM1	Poultry, fish, questionnaire data	Colorectal cancer	The Netherlands; 102 cases, 537 controls	*GSTM1*-present and frequent poultry consumption (4 + /month) *v. GSTM1-present* and rare poultry consumption (0–1/month) (OR 0·4, 95 % CI 0·2, 0·98) *GSTM1*-present and frequent fish consumption (4 + /month) *v. GSTM1 present* and rare fish consumption (0–1/month) (OR 0·5, 95 % CI 0·2, 1·1; Tiemersma *et al.* 2002)
CYP1A1	Onions (calculated according to questionnaire data)	Lung cancer (SqCC)	US Hawaiian, Japanese Caucasians; 582 cases (136 SqCC), 582 controls	*CYP1A1* MspI *1/*1 genotype and high onion intake of greater than median (from range 7·5–20·1 g/d) *v. CYP1A1* MspI *1/*1 genotype and low onion intake of median values or less (OR 0·2, 95 % CI 0·1, 0·5; Le Marchand *et al.* 2000)
COMT	Black and green tea (calculated according to questionnaire data)	Breast cancer	Asian-American women; 589 cases, 563 controls	*COMT* HL + LL genotype and black and green tea intake *v. COMT* HL + LL genotype and no tea intake (OR 0·48, 95 % CI 0·29, 0·77; Wu *et al.* 2003)
GSTM1, GSTT1	ITC from cruciferous vegetables (calculated according to questionnaire data)	Lung cancer	USA; 503 cases, 465 controls	*GSTM1*-null and *GSTT1*-null and low ITC intake of median values or less (93·2 μg/1000 kJ) and smoking *v. GSTM1*-present and *GSTT1*-present and high ITC intake of greater than median (93·2 μg/1000 kJ) and smoking (OR 5·45, 95 % CI 1·72, 17·22; Spitz *et al.* 2000)
GSTM1, GSTT1	ITC from cruciferous vegetables (total ITC concentration in urine)	Lung cancer (men)	China; 232 cases, 710 controls	*GSTM1*-null and undetectable ITC *v. GSTM1*-null and detectable ITC (relative risk 0·36, 95 % CI 0·20, 0·36) *GSTT1*-null and undetectable ITC *v. GSTT1*-null and detectable ITC (relative risk 0·51, 95 % CI 0·30, 0·86) *GSTM1*-null and *GSTT1*-null and undetectable ITC *v. GSTM1*-null and *GSTT1*-null and detectable ITC (relative risk 0·28 95 % CI 0·13, 0·57; London *et al.* 2000)
GSTM1, GSTT1	ITC from cruciferous vegetables (measured and calculated according to questionnaire data)	Lung cancer (women)	China; 232 cases, 187 hospital controls	*GSTM1*-null and high ITC intake of greater than median (53·0 μmol/week) *v. GSTM1*-null and low ITC intake of median values or less (OR 0·55, 95 % CI 0·33, 0·93) *GSTT1*-null and high ITC intake of greater than median (53·0 μmol/week) *v. GSTT1 null* and low ITC intake of median values or less (OR 0·54, 95 % CI 0·31, 0·95) *GSTM1*-null and *GSTT1*-null and high ITC intake of greater than median (53·0 μmol/week) *v. GSTM1*-null and *GSTT1*-null and low ITC intake of median values or less (OR 0·47, 95 % CI 0·23, 0·95; Zhao *et al.* 2001)

Table 2. *Continued*

Polymorphic gene	Food component	Cancer risk	Investigated population	Gene–nutrient interaction
GSTM1, *GSTT1*	ITC from cruciferous vegetables (calculated according to questionnaire data)	Colorectal cancer	China; 213 cases, 1194 controls	*GSTM1*-null and *GSTT1*-null and high ITC intake greater than median (1·23 μmol/1000 kJ) *v.* *GSTM1*-null and *GSTT1*-null and low ITC intake of median values or less (OR 0·43, 95 % CI: 0·20, 0·96; Seow *et al.* 2002)
GSTT1	Vegetables, cruciferous vegetables; questionnaire data	Colorectal cancer	UK Caucasians; 500 cases, 783 controls	*GSTT1*-null and high vegetable consumption *v.* *GSTT1*-null and low vegetable consumption (OR 0·3, 95 % CI 0·1, 0·6) *GSTT1*-null and high cruciferous vegetable consumption *v.* *GSTT1*-null and low cruciferous vegetable consumption (OR 0·4, 95 % CI 0·2, 0·8; Turner *et al.* 2004)

ITC, isothiocyanate; SqCC, squamous cell cancer; OR, odds ratio.

cancer development. An elevated risk of breast cancer was found in individuals with the NAT2 rapid/intermediate genotype and consumers of well-done red meat (OR 7·6, 95 % CI 1·1, 50·4) compared with those consuming rare or medium-cooked red meat (Deitz *et al.* 2000). It is suggested that, in order to produce carcinogen–DNA adducts as a result of the metabolic activation of HCA, *N*-oxidation involving CYP1A2 and *O*-acetylation involving NAT1 or NAT2 is required.

A case–control study of the Hawaii population, composed of Japanese, Hawaiian and Caucasian individuals, did not show a statistically significant relationship between colorectal cancer risk and red meat intake, NAT2 rapid genotype, the *NAT1*10* high-activity allele and CYP1A2 rapid phenotype. However, in individuals with NAT2 and CYP1A2 rapid phenotypes, who smoked and preferred well-done red meat, the risk of colorectal cancer was higher (OR 8·8, 95 % CI 1·7, 44·9) than it was in individuals with low NAT2 and CYP1A2 activity, a smoking habit and a preference for rare or medium red meat. The authors indicate that a higher exposure to HCA due to an intake of well-done meat elevates the risk of colorectal cancer in rapid CYP1A2 and NAT1 high-activity carriers. They also suggested that smoking, because of an induction of CYP1A2, might also contribute to this increase (Le Marchand *et al.* 2001).

According to other authors, the consumption of specific food components, including meat and pickled vegetables, and the *CYP2E1* RsaI genetic polymorphism were not associated with oesophageal and stomach cancers, as indicated in a study among Chinese individuals (Gao *et al.* 2002).

Dietary phytochemicals, cancer risk and polymorphic xenobiotic metabolising enzymes

Several epidemiological studies show the modulatory effect of fruit, vegetable and tea consumption on the development of cancer at different sites, but this effect is very often related only to individuals with particular XME genotypes. Interestingly, low fruit and vegetable consumption was found to significantly increase the risk of rectal cancer in consumers of processed meat. Carriers of at least single inserts in the *CYP2E1* allele who consumed high levels of processed meat but low levels of fruit and vegetables showed a significantly increased risk of rectal cancer (OR 5·0, 95 % CI 2·2, 11·4) compared with individuals without inserts in the *CYP2E1* allele who consumed low levels of processed meat and high amounts of fruit and vegetables (Le Marchand *et al.* 2002*b*).

For example, in the Chinese population, raw vegetable consumption and the common *CYP2E1* RsaI c1/c1 genotype, associated with high enzyme activity, may prevent the development of oesophageal cancer, and the consumption of soyabean, tomato and garlic, calculated according to questionnaire data, along with the *CYP2E1* RsaI genetic polymorphism, was not associated with the development of oesophageal and stomach cancer. One of the limitations of this study was too small a number of study individuals with oesophageal (*n* 93) and stomach (*n* 98) cancers relative to controls (*n* 196), which might have the reduced statistical power of this case–control study (Gao *et al.* 2002).

The activity of glucosinolates derived from cruciferous vegetables and ITC derived from glucosinolate hydrolysis may

serve as an example of effective protection against cancer. The protective action of ITC is generally based on their modulation of XME expression: inhibition of I phase enzymes and activation of II phase enzymes (International Agency for Research on Cancer, 2004). It is well known that ITC are metabolised by GST isoenzymes. Evidence of a relationship between GST genetic polymorphism and dietary intake of ITC allows the formulation of the hypothesis that genetic polymorphism caused by a lack of GST or its reduced activity/expression may be associated with the effective protective activity of cruciferous vegetables (Lampe *et al.* 2000; Fowke *et al.* 2003).

Several investigations have demonstrated the protective effect of the consumption of cruciferous vegetables on cancer development. Based on the Shanghai population study, London *et al.* (2000) revealed that men with a homozygous deletion of the *GSTM1* and/or *GSTT1* gene and detectable ITC metabolites in the urine showed a reduced risk of lung cancer. Another Chinese study showed a reduced risk of lung cancer among women with the *GSTM1*-null and/or *GSTT1*-null genotype and high ITC intake, calculated according to questionnaire data (Zhao *et al.* 2001).

A US study also revealed a significant relationship between ITC intake and lung cancer risk relative to GST genetic polymorphism. A low consumption of cruciferous vegetables was associated with a risk of lung cancer among current smokers, regardless of the *GSTM1* and *GSTT1* genotype. However, a homozygous deletion of both *GSTM1* and *GSTT1* genes and a low dietary intake of ITC were associated with an elevated risk of lung cancer (OR 5·45, 95 % CI 1·72, 17·22; Spitz *et al.* 2000). Seow *et al.* (2002) found a protective effect of a high intake of ITC on colorectal cancer compared with a low ITC intake (OR 0·43, 95 % CI 0·20, 0·96) among Chinese carriers of the *GSTM1*-null and *GSTT1*-null genotypes.

An extensive case–control study (500 cases, 783 controls) of the UK Caucasian population was carried out to investigate the modifying effect of six polymorphic genes (*CYP1A1*, *GSTM1*, *GSTP1*, *GSTT1*, *EPHX1*, *NQO1*) on the potential relationship between diet and cancer risk. A high vegetable consumption, including cruciferous vegetables, was suggested to be the only protective effect on colorectal cancer among individuals lacking *GSTT1* alleles (Turner *et al.* 2004). However, this hypothesis needs to be further independently confirmed.

It is interesting to note that Ambrosone *et al.* (1999*a*), investigating the effect of GSTM1 genetic polymorphism and fruit and vegetable consumption on breast cancer risk, found no relationship between this polymorphism and breast cancer regardless of antioxidant defence. Moreover, no statistically significant effect of genetic polymorphisms of *GSTM1* and *GSTT1* on breast cancer risk among US women was observed, regardless of their intake of cruciferous vegetables (Ambrosone *et al.* 2004).

There is also evidence that other phytochemicals can also prevent the development of cancer. Significantly inverse associations between onions, apples, white grapefruit and lung cancer risk was found in a US population. The protective effect of onions was particularly demonstrated in squamous cell carcinoma. However, its effect was even stronger for the low-activity wild-type *CYP1A1* MspI *1/*1 genotype, when the *CYP1A1* MspI genetic polymorphism was also analysed (LeMarchand *et al.* 2000). Tea polyphenols, other protective dietary constituents, are *O*-methylated by catechol-*O*-methyltransferase (COMT). A study among Asian-American women indicated that tea catechins significantly reduced the risk of breast cancer. Moreover, a genetic polymorphism of *COMT* was also found to modify the tea-related breast cancer relationship. Women with at least one low-activity *COMT* allele (*COMT* L) who drank a lot of tea showed a significantly reduced risk of breast cancer (OR 0·48, 95 % CI 0·29, 0·77). Interestingly, the protective effect of both green and black tea was comparable in *COMT* HL and *COMT* LL genotype carriers (Wu *et al.* 2003). Moreover, the *GSTM1*-present genotype, but not the homozygous *GSTM1* deletion, and frequent poultry and fish consumption was also found to be protective against colorectal cancer (OR 0·4, 95 % CI 0·2, 0·98) in a population from the Netherlands (Tiemersma *et al.* 2002).

Diet, cancer risk and other polymorphic enzymes

A potential effect of genetic polymorphism of DNA repair systems on cancer risk associated with dietary antioxidants has been also shown. These systems play a very important role in preventing DNA oxidative damage induced by an overproduction of reactive oxygen species and insufficient antioxidant defence. Genetic polymorphism of the base excision repair *XRCC1* gene and the intake of several antioxidants was investigated in US prostate cancer patients. In human subjects, three common polymorphisms of the *XRCC1* gene at codons 194, 280 and 399, with unknown functional significance, can be observed. In a population of men, a lack of significant prostate cancer risk modulation was observed regardless of *XRCC1* genetic polymorphism. However, men homozygous for the common allele at codon 399 (*XRCC1* Arg399Arg) with a low intake of vitamin E or lycopene showed the highest risk of prostate cancer (OR 2·4, 95 % CI 1·0, 5·6 and OR 2·0, 95 % CI 0·8, 4·9, respectively), whereas a low concentration of these antioxidants and at least one copy of the variant allele was not significantly associated with cancer risk. According to Van Gils *et al.* (2002), an *XRCC1* genetic polymorphism does not influence the development of prostate cancer associated with a low intake of vitamin A or C, or β-carotene.

Another study showed, however, that a genetic polymorphism of *XRCC1* at codon 194 and low serum antioxidant concentration might be associated with lung cancer risk. Individuals with the variant *XRCC1* Arg194Trp allele tended to be at lower risk of lung cancer (OR 0·7, 95 % CI 0·4, 1·2), but those in this group who showed a high serum α-tocopherol or retinol level were at significantly lower risk of this disease (OR 0·4, 95 % CI 0·2, 0·9 and OR 0·4, 95 % CI 0·2, 0·9, respectively). It should be noted that the protective effect of a low antioxidant concentration was not observed among *XRCC1* wild-type individuals (Ratnasinghe *et al.* 2003). It was also found that a genetic polymorphism of a major excision repair enzyme 8-oxoguanine DNA glycosylase 1 (*hOGG1* Cys326Cys), associated with reduced enzyme activity, significantly increased the risk of lung cancer in a US population (OR 2·1, 95 % CI 1·2, 3·7). In this study, however, vegetable intake did not have a protective effect against lung cancer among individuals with an *hOGG1* Cys326Cys genotype (Le Marchand *et al.* 2002*a*).

Functional polymorphisms in antioxidant enzymes also provide evidence for cancer susceptibility associated with some variant alleles. A structural mutation, a T → C (val → ala) substitution in the manganese superoxide dismutase (MnSOD) gene, causing changes in secondary structure of the coding enzyme, seems to alter its transport to the mitochondrion. A case–control study, conducted in New York, revealed that women homozygous for the alanine allele had a significantly elevated risk of breast cancer (OR 4·3, 95 % CI 1·7, 10·8) compared with those with at least one wild-type *MnSOD* allele. However, a variant *MnSOD* ala/val genotype effect was observed only for premenopausal women. Moreover, mainly in this group, an association was found between dietary fruit and vegetable intake and *MnSOD* genetic polymorphism. A high total fruit and vegetable consumption, calculated according to data from a questionnaire (>764 g/d and >797 g/d, respectively) and *MnSOD* ala/val genotype exerted a weaker but still elevated effect on breast cancer risk (OR 3·2, 95 % CI 1·2, 8·2), whereas this variant genotype and a low fruit and vegetable intake were associated with a high risk (OR 6·0, 95 % CI 2·0, 18·2). Similar trends were also observed for calculated units of ascorbic acid and α-tocopherol.

The elevated risk of breast cancer was also noted among premenopausal women who were carriers of the *MnSOD* ala/val genotype and supplemented with vitamins. Women not supplemented with vitamin C and α-tocopherol showed a significantly increased risk of this disease (OR 4·8, 95 % CI 2·1, 11·0 and OR 3·8, 95 % CI 1·8, 8·2, respectively). The variant *MnSOD* allele did not influence breast cancer risk in those who took vitamin supplementation (Ambrosone *et al.* 1999*b*). Among male participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study, the *MnSOD* genetic polymorphism did not modify the risk of prostate cancer, regardless of α-tocopherol supplementation (50 mg/d over a 5–8-year period). These data, however, support the hypothesis concerning the negative effect of the *MnSOD* ala/val genotype on prostate cancer, but only for high-grade tumours (OR 2·72, 95 % CI 1·15, 6·40; Woodson *et al.* 2003).

Discussion

Genetic polymorphism of the battery of protective enzymes may increase susceptibility to oxidative stress, meaning that a higher intake of micronutrients is required. Ongoing studies have already identified micronutrients in fruit and vegetables, their function and the molecular basis of their action. It has been found that, along with defence against oxidative stress, antioxidants and microelements may play a crucial role in signal transduction owing to the modulation of several transcription factors (NF-κB, activator protein-1, mitogen-activated protein kinase; Van den Berg *et al.* 2001). The genetic polymorphism found in some selenoproteins may also specifically clarify the gene–microelement relationship (Moscow *et al.* 1994; Hu *et al.* 2001). Moreover, it is supposed that common genetic polymorphisms may modify the bioavailability, metabolism, affinity and activity of several micronutrients and antioxidants, and thus influence oxidative stress (Dusinska *et al.* 2001; Reszka *et al.* 2005).

The question of how individual genetic polymorphisms, related to the final activity of metabolising, antioxidant and DNA-repair enzymes, influence the effects of dietary antioxidants *in vivo* and cancer is still under consideration. It is thought that a diet incorporating protective micronutrients as well as carcinogens and mutagens may modulate the risk of cancer development, particularly in individuals who are, according to variant genotypes, genetically susceptible.

The body of case–control studies presented in this paper demonstrates the existence of susceptible genotypes in XME, antioxidant and DNA-repair enzymes, which can interact with dietary constituents (mutagens and/or antioxidants) and thus influence cancer risk. It has been indicated that colorectal cancer risk may be associated with *CYP2E1* high-activity (Le Marchand *et al.* 2002*b*) and *GSTA1* low-activity (Sweeney *et al.* 2002) alleles in consumers of red or processed meat. It has been found that the *NAT1*11* (Zheng *et al.* 1999) and NAT2 rapid/intermediate (Deitz *et al.* 2000) genotypes and a high intake of red meat or well-done red meat significantly increase breast cancer risk in postmenopausal women. On the other hand, a diet rich in vegetables, especially cruciferous ones, has a protective effect against colorectal (Seow *et al.* 2002; Turner *et al.* 2004) and lung (London *et al.* 2000; Zhao *et al.* 2001) cancers among individuals lacking *GST* genes. These metabolic susceptibility genes, which can influence cancer development in individuals with specific nutritional habits, show varied prevalences in human subjects. The *CYP2E1* allele frequency for 5′ inserts is estimated to be 22·7 % among Japanese individuals and only 2 % among Caucasians (Le Marchand *et al.* 2002*b*). The *GSTM1*-null or NAT2 rapid/intermediate genotype occurs in 50 % of the Caucasian population (Deitz *et al.* 2000; Spitz *et al.* 2000). An absence of a modulatory effect of polymorphic XME and dietary constituents on cancer development has, however, been indicated by some epidemiological investigations.

Our current knowledge of diet-related carcinogenesis is still limited, so individual variability in the potential relationship between dietary constituents and cancer risk or risk biomarkers merits further investigations. Epidemiological studies should also continue to clarify the role of gene–nutrient interactions in the aetiology of certain cancers. Bearing this in mind, studies of the interactions between nutrients and genes have great potential for investigating relevant mechanisms, identifying susceptible populations/individuals and making practical use of their results to develop preventive strategies beneficial to human health.

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