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Special Issues

Gene-Diet Interaction on Cancer Risk in Epidemiological Studies

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Genetic factors clearly play a role in carcinogenesis, but migrant studies provide unequivocal evidence that environmental factors are critical in defining cancer risk. Therefore, one may expect that the lower availability of substrate for biochemical reactions leads to more genetic changes in enzyme function; for example, most studies have indicated the variant *MTHFR* genotype *677TT* is related to biomarkers, such as homocysteine concentrations or global DNA methylation particularly in a low folate diet.

The modification of a phenotype related to a genotype, particularly by dietary habits, could support the notion that some of inconsistencies in findings from molecular epidemiologic studies could be due to differences in the populations studied and unaccounted underlying characteristics mediating the relationship between genetic polymorphisms and the actual phenotypes. Given the evidence that diet can modify cancer risk, gene-diet interactions in cancer etiology would be anticipated. However, much of the evidence in this area comes from observational epidemiology, which limits the causal inference. Thus, the investigation of these interactions is essential to gain a full understanding of the impact of genetic variation on health outcomes.

This report reviews current approaches to gene-diet interactions in epidemiological studies. Characteristics of gene and dietary factors are divided into four categories: one carbon metabolism-related gene polymorphisms and dietary factors including folate, vitamin B group and methionines; oxidative stress-related gene polymorphisms and antioxidant nutrients including vegetable and fruit intake; carcinogen-metabolizing gene polymorphisms and meat intake including heterocyclic amins and polycyclic aromatic hydrocarbon; and other gene-diet interactive effect on cancer.

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ONE CARBON METABOLISM-RELATED GENE POLYMORPHISMS AND DIETARY FACTORS ON CANCER RISK

The gene-environment interactions studies have focused on "low-methyl" diet and genotype. Folate deficiency contributes to chromosomal instability and may increase susceptibility to radiation-induced DNA damage [1]. Thus, folate deficiency may contribute to carcinogenesis through several biological mechanisms and these mechanisms may be differentially important to cancer etiology. Two mechanisms have been proposed by which folate deficiency could affect malignancy: 1) by causing DNA hypomethylation and proto-oncogene activation and/or 2) by inducing uracil misincorporation during DNA synthesis, leading to catastrophic DNA repair, DNA strand breakage, and chromosome damage, although human evidence in support of these mechanisms is limited [2,3].

I. Breast Cancer

Relationships between folate status and *MTHFR* genotype have been examined in respect to breast cancer risk in Chinese women [4]. Although there was no difference in the distribution of *MTHFR C677T* genotype among cases and controls, there was a significant inverse association of breast cancer risk with dietary folate intake for each of the genotypes that appeared to be stronger for those carrying the TT version of the gene. Eight recent studies reported the interactive effect between folate intake and the one-carbon metabolism-related gene on breast cancer (Table 1). There are gene-diet interactions between folate, vitamin B_2, B_6, B_{12}, and methionine as dietary factor, and *MTHFR, MTR, MTRR, SHMT1, MTHFD1, TYMS, FTHFD, CBS*, as the one-carbon metabolism-related gene. Among these gene-diet combinations, there was an interactive effect between *MTHFR* and folate, *MTRR* and folate, and *MTR* and vitamin B_2 on the breast cancer risk.

II. Colorectal Cancer

Gene encoding enzymes catalyzing one carbon transfer reactions and other folate-related transformations reviewed by Sharp and Little [5] who provided support for the notion that folate, methionine, and alcohol intake

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Table 1. Interactive effect between one-carbon metabolism-related gene polymorphisms and diet/ nutrients on breast cancer risk

Author (Population)	Study	SNPs	Diets/nutrients	Results		
				SNPs	Diet/nutrients	Interaction
Ericson et al., (Sweden) [6]	Malmo Diet and Cancer Cohort	*MTHFR*	Folate intake	rs1801133 (OR, 1.34 for women above 55 yr; OR, 1.29 for below 55 yr)	Unknown	Folate intake and *MTHFR* (rs1801131) CC genotype (p= 0.03)
Suzuki et al., (Japan) [7]	HERPACC	*MTHFR ; MTR ; MTRR ;TS* (2R)	Folate intake	*MTHFR* (p= 0.048) for postmenopausal *MTRR* (p=0.041) for premenopausal	Inverse assoc (p= 0.010)	Lowest category of folate and *MTRR* GG genotype (p=0.008)
Lissowska et al., (Poland) [8]	Population-based case control	*MTHFR ; MTR ; MTRR; CBS; SLC19A1*	Folate Vitamin B_2, B_6 B_{12}, Methionine Ethanol	*MTR* (rs1805087, p=0.013)	No assoc for all selected nutrients	Lowest category of vitamin B_2 and *MTR* GG genotype (p=0.05)
Stevens et al., (USA) [9]	CPS-II Nutrition Cohort	*MTHFR ; MTR ; MTRR ; SHMT1; MTHFD1 ; TYMS ; DHFR ; FTHFD ; CBS*	Dietary folate, total folate, alcohol and methionine	*MTHFD1* (rs1950902, p=0.048) *FTHFD* (rs2276731 and rs2002287, p=0.022 and 0.034, respectively)	Unknown	Total folate intake and *MTHFR* (p= 0.03) Mehtionine and *FRHFD* (rs2002287) genotype (p=0.035)
Xu et al., [10]	Long Island Breast Cancer Study (LIBCSP)	*DHFR*	Multivitamin use	No assoc	Unknown	19bp +/+ vs. -/-OR=1.52 for vitamin user only
Shrubsole et al., (China) [4]	Shanghai Breast Cancer Study	*MTRR* *MTR*	Folate Methionine Vitamin B_2, B_6	No assoc	Folate (p=0.02) Met(p<0.01) Vit. B6 (p=0.03)	No interactive effect
Chen et al., (USA) [11]	LIBCSP	*MTHFR*	Dietary folate Total foate Vitamin B_1, B_2, B_6 Niacin	*MTHFR* (rs1801133 and rs1801131) (p trend=0.03 and 0.03, respectively)	Vitamin B_1 (p=0.002), B_2 (p=0.05) and B_6 (p=0.03) for no supplement user	No interactive effect However, low-risk (CC genotype and high folate intake) vs. high risk group OR, 1.83. Similar associations were observed vitamin B1, B_2, B_6 and niacin (OR, 2.06, 1.88, 2.05, and 2.36, respectively)
Marchand et al., (USA) [12]	Multi-ethnic Cohort Study	*MTHFR*	Folate Ethanol	No assoc	Unknown	No interactive effect

Assoc: association.

interact with *MTHFR C677T* status to influence bowel cancer risk. Since the review, eight out of twelve studies [13-24] have supported the idea that there is a modified effect for *MTHFR* genetic polymorphisms between one carbon metabolism-related nutrients, including folate [13-18], vitamin B_2 [19] and vitamin B_6 [20], and colorectal cancer risk.

Besides the interaction between folate and *MTHFR* genetic polymorphisms, van den Donk et al. [19] suggested an inverse association between vitamin B_2 and colorectal adenomas; moreover, the inverse association between vitamin B_2 intake and colorectal adenomas seemed more pronounced among *MTHFR* TT individuals. In human studies, it was observed that the homocysteine-lowering effect of vitamin B_2 was essentially confined to subjects carrying the *MTHFR* TT genotype [25,26] and even to subjects with the *MTHFR* TT genotype and have a low folate status [27]. Theodoratou et al. [20] reported an interaction effect between *MTHFR A1298C* polymorphism and total vitamin B_6 intake among rectal cases ($p_{interaction} = 0.04$).

III. Lung Cancer

In a large non-Hispanic white population, significant gene-diet interaction was observed between the *TS3'UTR* (thymidylase synthase 30 UTR) polymorphism and alcohol consumption, and between *TSER* (thymidylate synthase [*TYMS*] promoter enhancer region) and vitamin B_{12} [28]. However, the underlying biological relevance of these *TYMS* polymorphisms and their mechanisms of gene-diet interactions warrant further study. The author also provides evidence supporting the association between the *MTR 2756A >G* and *MTRR 66A>G* polymorphisms and lung cancer [29] and evidence of gene-diet interactions between the *MTHFR C677T* polymorphism and dietary intake of vitamin B_6, vitamin B_{12}, and methionine in women [30].

OXIDATIVE STRESS-RELATED GENE POLYMORPHISMS AND DIETARY FACTORS ON CANCER RISK

Reactive oxygen species (ROS) cause oxidative damage to biomolecules such as DNA, proteins, and lipids, and can cause cellular alteration that may lead to tumorigenesis [31]. Oxidative stress occurs but to imbalance between antioxidant defense system and production of ROS. Fruits and vegetables are rich sources for a number of antioxidants, such as carotenoids, tocopherols, and ascorbic acid, which these compounds can decrease oxidative load [32]. ROS are also

Table 2. Interactive effect between oxidative stress-related gene polymorphisms and diet/ nutrients on breast cancer risk

Author (Population)	Study	SNPs	Diets/nutrients	Results		
				SNPs	Diet/nutrients	Interaction
Li et al., (USA) [33]	CPS-II Nutrition Cohort	*CAT* ; *MPO* ; *HO-1*; *NOS3*	Vegetable and fruit	No assoc	Unknown	Vegetable and fruit and *CAT* (p=0.04), *NOS3* (p=0.005), *MPO* (p=0.02), and total no. of low-risk alleles (p=0.006)
He et al., (USA) [34]	Nurses'Health Study Cohort	*MPO* *COMT*	Fruit and Veg Carotenoids Vitamin C Vitamin E	No assoc	Unknown	No interactive effect *MPO* CC genotype was associated with non-significant 42% reduction in risk among women with high fruit intake
Lee et al., (China) [35]	Shanghai Breast Cancer Study	*GSTP*	Cruciferous vegetable (isothicyanate)	Ile/Ile vs. Val/Val (OR, 1.50; 95% CI=1.12-1.99)	Isothicyanate (p<0.001)	No interactive effect the association of *GSTP1* and cruciferous vegetable was predominantly seen among premenopausal women (OR, 2.08)
Ahn et al., (USA) [36]	Population-based case control study	*CAT*	Fruit and Veg	% difference: -29.9 (p=0.0001)	No assoc	No interactive effect
Slanger et al., (Germany) [37]	Case-control study	*MnSOD*	Fruit and Veg β-Carotene Vitamin C	No assoc	Unknown	No interactive effect
McCullough et al., (USA) [38]	CPS II Nutrition Cohort	*VDR* (FOK1, Taq1, Apa1, Bsm1, Poly (A) tail) ; Gc protein ; *CYP24A1*	Total Ca Total Vitamin D	No assoc	Unknown	Total Ca intake and polymorphisms near the 3' end of the *VDR* (p=0.01)
Ahn et al.,(USA) [39]	LIBCSP	*GSTA1xB*	Cruciferous Yellow, Leafy Veg	No assoc	Unknown	No interactive effect
Shen et al.,(USA) [40]	LIBCSP	*XRCC1*	Fruit and Veg β-Carotene Vitamin C Vitamin E α-Carotene	No assoc	Unknown	Fruit and vegetable and *XRCC1* (*Arg194Trp* genotype (p= 0.04)
Shen et al.,(USA) [41]	LIBCSP	*MGMT*	Fruit and Veg β-Carotene Vitamin C, E α-Carotene	No assoc	Unknown	The assoc. between fruit and vegetable intake or α-Carotene and breast cancer risk was apparent a mong women with at least on variant G allele for codon 143 (OR, 0.6, in both)
Gaudet et al., (USA) [42]	LIBCSP	*MnSOD*	Fruit and Veg	No assoc	Unknown	Women carrying the Ala allele and high fruit and vegetable had a significant 37% reduction of BC risk (OR, 0.63)
Ahn et al.,(USA) [43]	LIBCSP	*CAT*	Fruit and Veg β-Carotene Vitamin C, E	TT/TC vs. CC (OR, 0.83; 95% CI=0.69-1.00)	Unknown	Interactive effect between Fruit and vitamin C (p=0.02 and 0.03, respectively) and *CAT* CC genotype
Ahn et al.,(USA) [44]	LIBCSP	*MPO*	Fruit and Veg Carotenoids Vitamin C, E	GG vs. GA/AA (OR, 0.87; 95%CI=0.73-1.04)	Unknown	Fruit and vegetable intake and *MPO* genotype (p= 0.04)
Ambrosone et al, (USA) [45]	Case-control study	*MnSOD*	Fruit and Veg Carotenoids Vitamin C, E	Val/Val +Val/Ala vs. Ala/Ala (OR, 3.5; 95% CI=1.8-6.8) among premenopausal	Unknown	The deleterious effect of the *MnSOD* polymorphisms was most pronounced among premenopusal women with low intake of fruit and veg. (OR, 6.0)
Ambrosone et al., (USA) [46]	Case-control study	*GSTM1*	Fruit and Veg Carotenoids Vitamin C, E	No assoc	Unknown	No interactive effect

Assoc: association, Veg: vegetables.

endogenously generated by enzymes including myeloperoxidase (MPO) and endothelial nitric oxide synthase (eNOS) [47,48] or neutralized by enzymes including manganese superoxide dismutase (MnSOD), catalase (CAT), and glutathione peroxidase (GPX) [49]. Variability in these enzymes and environmental exposures may determine the level of oxidative stress in the organism and play a role in cancer risk.

I. Breast Caner

Ambrosone et al [45]. reported that premenopausal women who were homozygous for the *A* allele and with low intake of fruit and vegetables had increased risk of breast cancer. The MnSOD, key component of the mitochondrial antioxidant defenses, catalyzed the dismutation of the superoxide anione into oxygen. The *MnSOD* genotype that has the alanine (*A*) allele rather than the valine (V) allele appears to enhance transport of the

Table 3. Interactive effect between selected genetic polymorphisms and meat intake on breast cancer risk

Author (Population)	Study	SNPs	Diets/nutrients	Results		
				SNPs	Diet/nutrients	Interaction
Egeberg et al., (Denmark) [50]	Diet, Cancer and Health Cohort Study	*NAT1 ; NAT2*	Red meat, Fish Poultry, Processed meat	*NAT1* slow vs. fast (OR, 1.43; 95% CI=1.03-1.99)	Red and processed meat (p=0.03 and 0.02, respectively)	*NAT2* genotype and total meat (p=0.03) and red meat (p=0.04)
Brandt et al, (Germany) [51]	Population-based case-control study	*egfr gene* (CA simple sequence repeat (SSR), CA repeat)	Red meat	*CA SSR* (p=0.04) CA repeat ($\geq$ 19 vs. <19) (p=0.03)	Unknown	*CA SSR* and red meat intake (p= 0.02)
van der Hel et al., (The Netherlands) [52]	Monitoring Project on Cardiovascular Disease Risk Factors (MPCDRF)	*NAT1 ; NAT2 GSTM1 ; GSTT1*	Processed meat Fresh meat Fresh red meat Fresh white meat	*GSTM1* (present vs. absent, OR, 1.46; 95% CI=1.02-2.09)	No assoc	No interactive effect
Krajinovic et al, (Frebch-Canadian) [53]	Case-control study	*CYP1A1 CYP2D6 GSTM1; GSTT1; GSTP1 NAT1; NAT2*	Meat doneness	*CYP1A1* (C4887A, OR, 3.3; 95% CI=1.1-9.7)	No assoc	The consumption of well-done meat was associated with 4-fold increase among carriers of *NAT1**10 (OR, 4.4)
Delfino et al., (USA) [54]	Case-control study	*NAT2*	Red & White meat PhIP, MeIQx DiMeIQx	No assoc	All selected meat and HCA (p<0.01) except DiMeIQx	No interactive effect
Deitz et al., (USA) [55]	Iowa Women's Health Study	*NAT2*	Meat doneness Red meat	No assoc	Meat doneness (p=0.0033)	Meat doneness and *NAT2* (p=0.06). BC risks were elevated with increasing meat doneness, particularly among women with the rapid/intermediate *NAT2* genotype (p<0.01)
Gertig et al., (USA) [56]	Nurses' Health Study	*NAT2*	Red and white meat, processed meat considering cooking method	No assoc	Bacon (OR, 1.4; 95% CI=1.0-1.9)	No interactive effect
Ambrosone et al., (USA) [57]	Case-control study	*NAT2*	Beef, pork, processed meat, poultry, fish		Pork (p=0.05)	No interactive effect

protein into the mitochondrial matrix and may lead to greater MnSOD activity [58]. Since 2000, fourteen studies have examined the interactive effect between oxidative stress-related gene polymorphisms and diet/nutrients on breast cancer risk, and Table 2 summarizes those results. Only four studies observed an interactive effect; between *MPO* [33,44], *NOS3* [33], *CAT* [33], and *MGMT* [41] as the related genetic factor, and fruit and vegetable intake including β-carotene and vitamin C as dietary factors. Li et al. [33] observed borderline significant interactions between vegetable and fruit intake and the common *CAT* CC genotype. This genotype was inversely associated with breast cancer risk only among women with higher consumption of fruits and vegetables. Similarly, the low-risk *NOS* T allele and the *HO-1* S allele and MM genotype were also found to be protective among women with high fruit and/or vegetable intake, particularly when the total number of low-risk alleles was jointly considered.

II. Prostate Cancer

The interactive effect of gene-diet interaction was observed to be quite consistent for prostate cancer. A large nested case-control study within the Physicians Health Study with an average of 8 years prior to cancer diagnosis found that men with high antioxidant scores had a 40% lower risk of all prostate cancer and a 60% lower risk of aggressive prostate cancer than those with low antioxidant status [59]. However, for men carrying one or more *MnSOD* V alleles, there was no significant relationship between antioxidant status and prostate cancer risk, men homozygous for the *A* allele showed a five and ten-fold reduction in total and aggressive prostate cancer risk, respectively, between those with lowest and highest quartiles of antioxidant status. Mikhak et al. [60] studied the interaction of *MnSOD* gene polymorphism and carotenoid levels on prostate cancer risk. No statistically significant interaction was found between the *MnSOD* genotype and any specific plasma carotenoid or total plasma carotenoids in relation to the risk of total prostate cancer overall or aggressive prostate cancer. However, a suggestive but not statistically significant interaction (p=0.10) was seen for plasma lycopene and aggressive prostate cancer. Among men with lycopene levels above the median, no association was observed for *MnSOD* genotype, but among men with low plasma lycopene, those with the Ala/Ala genotype had approximately a 2-fold elevated risk compared with those with the Val/Val genotype.

Another nested case-control study within the ATBC Trial provides evidence that common polymorphisms in two vitamin E transport genes, *TTPA* and *SEC14L2*, may modify the association of supplemental and dietary vitamin E intake with prostate cancer and also modestly affect circulating concentrations of vitamin E, although none of the selected polymorphisms was associated with prostate

Table 4. Interactive effect between selected genetic polymorphisms and meat intake on colorectal cancer cancer risk

Author (Population)	Study	SNPs	Diets/nutrients	Results		
				SNPs	Diet/nutrients	Interaction
Cotterchio et al., (Canada) [61]	Population-based case-control study	*CYP1A1, 1A2, 1B1, 2C9, 2E1 ; NAT1, NAT2 ; SULT1A1 ; GSTM1, GSTM3, GST1 ; UGT1A1, 1A7 ; AHR*	Red meat intake/doneness	*CYP1A1* (TT vs.CC) OR, 0.40 *NAT2* combined slow vs. fast OR, 1.20	Red meat intake 0-2 vs. >5 serv/ wk OR, 1.67 Doneness ≤2 rare vs. > 2 well-done OR, 1.57	Doneness and *CYP1B1* combined variants (p=0.04) Doneness and *SULT1*A1-638 (p=0.03)
Butler et al.,(USA) [62]	Population-based case-control study	*NAT1* *NAT2*	PhIP HCAs (MeIQx, PhIP and DiMeIQx)	*NAT2* "rapid/intermediate" vs. "slow" OR, 1.4 (1.0-1.8)	Unknown	Among African Americans, PhIP and *NAT1**10 genotype (p=0.02) Among Whites, *MeIQx* and *NAT1*-non*10 genotype (p=0.03)
Kury et al., (France) [63]	Population-based case-control study	*CYP1A2 ; CYP2E1; CYP1B1; CYP2C9*	Red meat	No assoc	< 5 vs. ≥5/wk OR, 2.81 (1.52-5.21)	Interactive effect between three allelic variant combinations and excessive red meat consumption
Berndt et al., (USA) [64]	Community-based cohort (CLUE II)	*ERCC6*	Red meat	*Arg1213Gly* (rs2228527) RR vs. RG (RR=1.36) RR vs. GG (RR=2.64) p trend=0.0006	Unknown	No interactive effect
Murtaugh et al., (USA) [65]	Population-based case-control study	*PPARc*	Dietary lipids	No assoc	No assoc	No interactive effect PA or AA genotype and low intake of MUFA (p=0.14).
Tranah et al., (USA) [66]	Nested case-control within the NHS	*APC variants*	Total calories, folate, and red meat intake	No assoc	No assoc	No interactive effect
Tiemersma et al., (Germany) [67]	Case-control study	*NAT1, NAT2* *SULT1A1* *GSTM1, GST1*	Total meat, Red meat, Poultry Gravy	*NAT1* slow vs. fast OR, 2.36 (1.11-5.00)	No assoc	No specific combination clearly increased risk of adenomatous polyps.
Sweeney et al., (USA) [68]	Case-control study	*GSTA1* *CYP2A6*	Well-done meat Preserved meat	Unknown	Unknown	CYP2A6 activity and consumption of preserved meat, (p=0.02)
Le Marchand et al., (USA) [69]	Case-control study	*CYP2E1 (the G1259C RsaI substitution and a 5' 96-bp insertion variant)*	Red meat Processed meat	No assoc	Unknown	No interactive effect; although subjects with the insert variant and a RM consumption over the median was 2.1, For PMs, this effect was more marked, with a rectal cancer OR of 3.1
Tiemersma et al., (The Netherlands) [70]	Dutch prospective study	*GSTM1 and GSTT1* *NAT1 and NAT2*	Red meat	No assoc	Highest vs. Lowest intake OR, 2.7 (1.1-6.7)	No interactive effect

cancer risk [71].

There was a modification to the relationships between the consumption of fruits and vegetables, and CAT. The CAT activity decreased with increasing intake of fruits and vegetables or those with the CT or TT genotypes, supporting that CT and TT genotypes are associated with lower CAT activity and provide a biological basis for epidemiological studies showing associations between *CAT* genotype and risk of diseases related to oxidative stress [72].

III. Lung Cancer

Dietary antioxidants and genetic differences in DNA repair genes may in part explain why only a small portion of smokers actually develop lung cancer. One abundant type of DNA damage resulting from ROS exposure produces 8-OHdG, which has been shown to be highly mutagenic, yielding G:C to T:A transversions [73].

A study of *OGG1* and vegetable intake interactions in relation to lung cancer [74] showed a tendency for vegetables to have a protective effect among carriers of the Ser wild-type allele and not among the Cys/Cys carriers. Recently, a short communication [74] reported that there was no apparent protection from vegetables among subjects with the Cys/Cys genotype without any statistically significant interactions, but among subjects with the Ser/Ser or Ser/Cys genotype, the risk of lung cancer was cut in half with high vegetable consumption. On the other hand, Sorensen et al. [75] observed a protective effect from high vegetables consumption on lung cancer among carriers of the Cys/Cys genotype rather than among carriers of the Ser/Ser and Ser/Cys genotype. After adjusting for the confounder smoking and fruit intake, the protective effect of vegetables was only evident among Cys/Cys carriers. The same tendency was seen in relation to intake of fruits.

ITCs have been shown to inhibit carcinogen activating phase I enzymes (e.g., cytochrome P450 [CYP450]) and to induce phase II detoxification enzymes (e.g., glutathione s-transferases [GSTs]), that promote excretion of carcinogens [76]. Epidemiological studies have observed that GSTM1 and GSTT1 may

interact with isothiocyanates (ITC) to modify lung cancer risk [77-79] . London et al. [77] showed that, in Shanghai, individuals with detectable urinary ITCs had a significantly reduced risk of lung cancer, and that this effect was primarily confined to individuals with *GSTM1*- or *-T1*- (or both) null genotypes among Chinese men. A similar finding for the *GSTM1* and *GSTT1* genotypes were observed among primarily non-smoking Singaporean women [79]. Among all subjects, high ITC intake conferred a 40-50% reduction in risk that was statistically significant among those with the null genotype for *GSTT1*, *-M1*, or both combined. A European multi-center study of non-smokers reported a protective association with cruciferous vegetable consumption in both *GSTM1* positive and null individuals [78]. Recently, a large hospital based case-control study (716 case, 939 controls) [80] reported the association between dietary intake of cruciferous vegetables and lung cancer risk among *GST* present and null genotypes separately. Higher cruciferous vegetable intake reduced lung cancer risk only among individuals with the *GSTM1* genotype present.

IV. Other Cancer

For gastric cancer risk, Takezaki et al. [81] reported that the ORs of habitual drinkers and frequent consumers of pickled vegetables and meat tended to be higher in *hOGG1* Cys/Cys than in Ser/Ser or Ser/Cys carriers among Chinese subjects, but the interaction was not statistically significant. In addition, Tsukino et al. [82] reported that significantly decreased gastric cancer risks were particularly evident among frequent cruciferous vegetable consumers with Ser/Ser genotype, whereas no inverse association was found between cruciferous vegetable intake and gastric cancer among those who had the Cys allele. However, still no significant interaction was found between *hOGG1* genotype and these dietary or nutrient intakes. On the other hand, risk modifications of selected DNA repair polymorphisms on the association between vegetable intake and gastric cancer risk. Increased gastric cancer risks associated with low fruit and vegetable intake were somewhat stronger for carriers of *XRCC1 -399 ArgArg, XPD-751 GlnGln/LysGln*, and *MGMT-143 ValVal/IleVal* genotypes [83].

For colorectal cancer risk, Hansen et al. [84] found no interaction between *OGG1 Ser326Cys* polymorphism and the various lifestyle factors in relation to the risk of colorectal cancer, but among homozygous carriers of the wild type *GPX1 Pro198Leu* allele did dietary vitamin C have a positive effect against colorectal cancer.

Table 5. Research priorities for gene-diet interaction approach suggested by Sharp and Little [5]

1. Further documentation of genotype frequencies: large, population-based studies of the polymorphisms reported in this paper and the additional, but less well studied, polymorphisms in these genes, including prevalence of combinations of polymorphisms and prevalence in different age groups; particularly needed in non-White populations and less-investigated ethnic groups in the United States and Europe
2. Clarification of functional effects of the polymorphisms: including exploration of 1) consequences of carrying combinations of polymorphisms in both in vivo and in vitro systems and 2) in vivo functional effects of particular genotypes in persons with different levels of intake of dietary factors
3. Further investigation of hypothesized mechanisms: examination of whether the polymorphisms are associated, in humans, with genomic DNA methylation, uracil incorporation, or DNA strand breaks, including exploration of whether relations differ according to levels of dietary factors
4. Studies of gene-disease associations and gene-environment and gene-gene interactions: further large population-based studies of polymorphisms and cancer and adenomas, incorporating collection of high-quality dietary data and, ideally, blood biomarkers; these studies should be large enough to have sufficient power to investigate gene-environment and gene-gene interactions and to undertake subgroup analysis by age and ethnic group, of colon and rectal tumors, proximal and distal tumors, and tumors with microsatellite instability or loss of heterozygosity
5. Pooled analyses of studies of gene-disease associations and gene-environment and gene-gene interactions to facilitate subgroup analyses and investigation of interactions
6. Further investigation of genotype and quality of life and the effectiveness of treatment in patients with colorectal cancers: large studies of representative groups of patients; analysis should include adjustment for known prognostic factors
7. Development of methodology for specifying hypotheses and statistical analysis in the context of interactions between multiple genes and multiple environmental factors

CARCINOGEN-METABOLIZING GENE POLYMORPHISMS AND MEAT INTAKE ON CANCER RISK

Metabolism of HCAs formed as a result of cooking meat for long duration by regular high temperature, varies among individuals depending, in part, on polymorphisms in genes involved in xenobiotic metabolism such as N-acetyltransferases NAT1 and NAT2 and cytochrome P4501A2 (CYP1A2) [85]. PAHs are activated by cytochrome P-450 1A1 (CYP1A1), and the resulting reactive intermediates are detoxified by glutathione-S-transferases (GSTs). Aromatic amines and HCAs are either directly detoxified or transformed to more potent carcinogens by N-acetyl-transferases 1 (NAT1) and 2 (NAT2) [86]. Depending on the substrate, fast or slow acetylation of aromatic amines might result in prolonged exposure to potential carcinogens and increased formation of DNA adducts [87]. Therefore, the level of procarcinogens activated by an individual depends on genetic background, which determines the degree of susceptibility to procarcinogen exposure and, consequently, to cancer.

I. Breast Cancer

If meat consumption does play a role in breast cancer etiology, it is possible that it may be due to meat intake being a source of mutagens and/or carcinogens such as HCAs, which are potent mammary mutagens and carcinogens in rodent models [88]. Disparate cooking methods in different populations or survey instruments inadequate to assess concentrated sources of HCAs may be related to the inconsistencies in results across various studies.

Table 3 summarizes the studies of gene-diet interaction between carcinogen-metabolizing gene polymorphisms and meat intake. Evidence for the interaction between meat consumption and both *NAT1* and *NAT2* polymorphism for the risk of breast cancer in

epidemiological studies is sparse and conflicting as shown in Table 3. It is hypothesized that an association between meat intake and breast cancer risk may be more pronounced in fast *NAT* acetylators. Recently, Egeberg et al. [50] reported that interaction analyses revealed that the positive associations between total meat intake including red meat intake and breast cancer risk were confined to intermediate/fast *NAT 2* acetylators (p interaction = 0.03 and 0.04), supporting the gene-diet interactive effect on breast cancer risk. A simultaneous evaluation of the individual and the combined effect of these enzymes with the NATs, and their interactions with meat consumption would have been valuable in understanding fully the role of the HCAs in breast cancer aetiology.

II. Colorectal Cancer

Although several epidemiologic studies have evaluated whether genetic susceptibility at the *NAT* loci modify the association between surrogates of HCA exposure (e.g. the extent to which the meat doneness or method of cooking) on risk of colon cancer [89-91], few data are available that measure individual HCA compounds in a multiethnic population-based sample (Table 4). On the other hand, Butler et al. [62] reported that NAT1 acetylation of HCAs differs by race, where PhIP increase the risk of colon cancer among African Americans with "fast" acetylation, and MeIQx increased risk among Caucasian with "slow" acetylation. They also observed that *NAT1* genotype differentially modified the association between dietary sources of HCA exposure and colon cancer by race where positive associations were present among African Americans with the *NAT1 x 10* genotype and among whites with the *NAT1*-non *10 genotype.

Besides *NAT1* and *NAT2*, several carcinogen metabolizing genes were examined the interactive effect of meat intake on colorectal cancer (Table 4). Murtaugh et al. [92] found modest interaction between *VDR FokI* polymorphisms and modifiable dietary behaviors on colorectal cancer risk. In addition, the nucleotide excision repair (NER) enzymes respond to a wide range of DNA damage but are particularly important for the removal of bulky adducts caused by environmental carcinogens, such as HCAs and PAH, which are found in tobacco smoke and meats cooked at high temperature. Berndt et al. [64] studied the gene-diet interaction between *ERCC6* and red meat intake on colorectal cancer, but did not find any significant association.

OTHER GENE POLYMORPHISMS AND DIETARY FACTORS ON CANCER RISK

Besides the above gene-diet interaction studies, several other reports studied the modified effect of genetic polymorphisms on the association between diet and breast, colorectal or prostate cancer risks.

The interaction between hormone-related gene and isoflavone intake was reported. For breast cancer risk, a multicenter hospital-based case-control study in Nagano, Japan, and from cancer-free patients in São Paulo, Brazil tested the hypothesis that polymorphisms in estrogen receptor genes may modify the association between isoflavone intake and breast cancer risk. Finally, they suggest that polymorphisms in the estrogen receptor beta gene may modify the association between isoflavone intake and breast cancer risk [93]. For prostate cancer, Hedelin et al. [94] reported a significant interaction between phytoestrogen intake and a promoter SNP in the *ESR2* gene (rs2987983) in the risk of prostate cancer in a population-based case-control study in Sweden. Another study reported by Low et al. [95] used a combination of food intake assessment and biomarkers (five SNPs in *CYP19, ESR1, SHBG*, and *COMT* genes) to assess the risk of developing prostate cancer in a nested case-control design among men in the Norfolk arm of the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Kotsopoulos et al. [96] reported the *CYP1A2* genotype modifies the association between coffee consumption and breast cancer risk among *BRCA1* mutation carriers. This study suggests that caffeine protects against breast cancer in women with a *BRCA1* mutation and illustrates the importance of integrating individual genetic variability when assessing diet-disease associations.

Some epidemiological studies have reported associations between *VDR* polymorphism genotype and risk of both colorectal adenoma and cancer. The associations were modified by dietary vitamin D and calcium intakes. Although not a universal finding, carriers of the variant *FokI* alleles have been reported to have an increased risk of colorectal cancer [97] and advanced colorectal adenoma [98], which is enhanced in individuals with low calcium intake. Recently, Hubner et al. [99] reported *VDR* polymorphism genotypes and haplotypes did not directly alter recurrence risk. The reduction in risk associated with high dairy product intake was confined to individuals with *ApaI* aA/AA genotype ($p_{interaction}$=0.02) in the United Kingdom Colorectal Adenoma Prevention trial. However, a large colonoscopy-based case-control study [100] found that persons who carried ≥ 1482Ile allele were at greater risk of adenoma or hyperplastic polyps, particularly if they consumed diets with a high Ca:Mg intake. Among persons who carried ≥ 1482Ile allele, the inverse association with magnesium intake was further reduced; whereas, high calcium intake tended to be related to a greater risk of adenoma.

RESEARCH PRIORITIES FOR GENE-DIET INTERACTION APPROACH

Methodologies are currently lacking for specification of hypotheses, clarification of functional effects, and statistical analysis relating to such complex gene-environment pathways. This area of research must be a

priority if advancements in understanding of disease etiology are to be achieved. Finally, Table 5 lists other areas for further research which are suggested by Sharp and Little [5].

In the context of breast cancer prevention, research on gene-environment interactions seems promising. Future research on gene-environment interactions should be performed in large prospective design settings to exclude recall bias and gain enough statistical power. The significance level was either barely achieved or attenuated when other risk factors were taken into account in multivariate analysis. Assessment of gene-environment interactions only included small population of individuals and generated wide confidence intervals, and testing of multiple hypotheses increased the possibility that some results arose purely by chance.

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