

MINI REVIEW

Effect Modification of Meat Intake by Genetic Polymorphisms on Colorectal Neoplasia Susceptibility

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Abstract

Colorectal cancer incidences differ considerably between Western and non-Western countries. In recent years, a dramatic increase in colorectal cancer incidence has been reported in several Asian countries. Immigration studies have suggested that environmental rather than genetic factors are primarily responsible for the international variability and secular trends of colorectal cancer incidence rates. Therefore, not only the main effect of a gene but also the influence of gene-environment interactions on cancer risk are important from the public health perspective. This review encompasses the literature on gene-diet interactions, particularly focusing on meat intake and its association with the risk of colorectal carcinoma or adenomas. It is generally accepted that genotypes which are associated with the higher enzyme activity for metabolic activation or lower activity for detoxification would affect individual's susceptibility to meat carcinogens. The most intensively studied genes were those involved in xenobiotic metabolism, including N-acetyltransferase (NAT), cytochrome P450 (CYP) families, glutathione S-transferase (GST), and sulfotransferase (SULT). However, the associations were not consistent across studies. The role of genetic polymorphisms and their role in effect modification of environmental carcinogens should be assessed in well-designed large-scale epidemiological studies with comprehensive information for risk factors for better understanding the etiologic role of dietary factors and in developing personalized cancer prevention strategy in the genome-wide association study era.

Keywords: Gene-diet interaction - colorectal neoplasia - meat - heterocyclic aromatic amines - human

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Introduction

A systematic review of epidemiological literature has suggested that red and processed meat consumption is a convincing risk factor for colorectal cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007). Meat contains high animal fat and is energy dense-food which affect on weight gain and consequent overweight and obesity (World Cancer Research Fund/American Institute for Cancer Research, 2007). In addition, mutagens such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are produced during high-temperature cooking of meat, and these compounds induce colon tumors in laboratory animals (Vineis & McMichael, 1996). Hepatic or colonic cytochrome P450 (CYP), N-acetyltransferase (NAT), glutathione S-transferase (GST), and sulfotransferase (SULT) family enzymes are involved in metabolic activation or detoxification of HCAs (Nowell et al., 2004). Further, GSTs facilitate detoxification of PAHs via glutathione conjugation, whereas CYPs, NAT1, and NAT2 activate PAHs to produce active metabolites (Sachse et al., 2002). Therefore, effect modification of the association between meat or meat-mutagen intake and colorectal cancer risk by generic polymorphisms has been suggested.

The purpose for this review is to summarize literatures on meat intake and its association with the risk of colorectal carcinoma or adenomas, focusing on gene-environmental interaction. We hypothesized that study subjects who possessed genotypes which were associated with inducing higher biological activity for meat carcinogens, would be more susceptible to colorectal neoplasia development.

Specific Enzymes

N-acetyltransferases

Relationship between the genotypes and phenotypes of NAT1 and NAT2 polymorphisms has been well established through measurement of the catalytic activity for N-acetylation (Fretland et al., 2001). In colonic tissue, NAT1 is expressed at a higher level than NAT2; therefore, its role has been suggested in colorectal carcinogenesis (Hickman et al., 1998). In animal studies, rapid acetylator mice showed 3-fold more DNA adducts in the colon mucosa than slow acetylator mice after feeding on 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) (Nerurkar et al., 1995); further, a 2-fold higher number of aberrant crypt foci and higher 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-DNA adduct levels in rapid-acetylator rats were observed compared

Table 1. Literatures Assessed Interaction between Meat or Meat Mutagen Intakes and Genetic Polymorphisms of N-acetyltransferase (NAT) 1 and 2 on the Risk of Colorectal Neoplasia

Author(year)	Study design	Outcome(s)	Number of subjects	Genetic polymorphisms	Meat exposure	Main effect of gene (odds ratio (95% CI))	Main effect of meat	Interaction between meat intake and gene
Welfare et al (1997)	Case-control	Colorectal cancer	174 cancer 174 controls	NAT2*5A, *5B, *6A, *7B	Frequency of consumption of red meat, bacon, sausages, chicken, fish, brown gravy, fried, grilled or roasted meat of any kinds	0.95 (0.61-1.49) for fast vs. slow acetylators	3.0 (1.37-7.25) for the meat more than twice a week	6.04 (1.6-26) for frequent fried meat intake + fast acetylator
Chen et al (1998)	Nested case-control	Colorectal cancer	212 cancer 221 controls (men only)	NAT1 *3, *4, *10, *11; NAT2 *4, *5A, *6A, *7A	Red meat intake	NS	Proximal colon only: 3.0 (1.14-9.23) for consumption of roast meat, 2.83 (1.07-8.78) for gravy at least once a week, 3.2 (1.11-11.2) for gravy at least twice a week	3.70 (1.08-12.7) for >1 serving/day vs. ≤0.5 serving/day, <i>P</i> trend = 0.03 among 60 years old and older, NAT1 rapid acetylator; 5.82 (1.11-30.6) for >1 serving/day vs. ≤0.5 serving/day, <i>P</i> trend = 0.02 among 60 years old and older, NAT1/NAT2 rapid acetylator
Kamppan et al (1999)	Case-control	Colon cancer	1542 cancer, 1860 controls	NAT2 G191A, T341C, G590A, A803G, G857A	Serving per week for red meat, poultry, processed meat, and fish; consumption frequency for fried, broiled, baked, or barbecued red meat and white meat, doneness of red meat, use of red meat drippings, red meat mutagen index, white meat mutagen index, overall mutagen index	1.2 (1.0-1.5) for intermediate or fast acetylators only in women	1.3 (1.0-1.7) for high vs. low	NS
Le Marchand et al (2001)	Case-control	Colorectal cancer	349 cancer, 467 controls	NAT1 *10 NAT2 C481T, G590A, G857A, T341C	Intake amount of red meat and processed meat, red meat doneness preference	NS	NS	8.8 (1.7-44.9) for preference for well-done red meat + ever-smokers + NAT2 and CYP1A2 rapid phenotypes

Author(year)	Study design	Outcome(s)	Number of subjects	Genetic polymorphisms	Meat exposure	Main effect of gene (95% CI)	Main effect of meat	Interaction between meat intake and gene
Tiemersma et al (2002)	Case-control	Colorectal cancer	102 cancer 537 controls	NAT1 *4, *3, *10, *11 and NAT2 *4, *5A, *5B/C, *6, *7, *12, *14	Intake amount of total meat, red meat, white meat, and processed meat; consumption frequency for beef, pork, poultry, fish, and meat snacks	NS	2.7 (1.1-6.7) for fresh meat consumption 5+/week vs. 0-3/week	NS
Murtaught et al (2004)	Case-control	Rectal cancer	952 cancer, 1205 controls	NAT2 C481T, G590A, G857A	Serving/week for red meat, poultry, and processed meat; intake frequency of fried, broiled, baked or barbecued red meat, fried, broiled, baked, or barbecued white meat, use of red meat drippings, doneness of red meat, red meat mutagen index, white meat mutagen index, overall mutagen index	NS	1.39 (1.0-1.94) for mutagen index of >468 vs. ≤104 in men; 0.72 (0.51-1.01) for use of red meat drippings >52/year of vs. never in women	NS
Chan et al (2005)	Nested case-control	Colorectal cancer	183 cancer 443 controls (women only)	NAT2 *4, *5, *6, *7	Beef, pork, or lamb as a main dish	NS	Not mentioned	3.01 (1.10-8.18) for >0.5 serving/day vs. ≤0.5 serving/day among rapid acetylators, P _{interaction} = 0.07
Lilla et al (2006)	Case-control	Colorectal cancer	505 cancer, 604 controls	NAT1 T1088A, C1095A, G560A, T640G NAT2 C481T, G590A, A803G, G857A	Red meat consumption frequency	NS	NS	2.55 (1.07-6.07) for daily and several times a day consumption of red meat + at least one NAT fast genotype
Cotterchio et al (2008)	Case-control	Colorectal cancer	842 cancer, 1251 controls	NAT1 G459A, T1088A, NAT2 T341C, G590A, G857A	Red meat intake (servings/week), red meat doneness	1.20 (1.01-1.44) for NAT2 fast acetylators	1.67 (1.36-2.05) for >5 servings/ week of red meat vs. 0-1 servings/week; 1.57 (1.27-1.93) for >2 servings/ week of "well-done" red meat consumption vs. ≤2 "rare/regular" consumption	NS
Nothlings et al (2009)	Nested case-control	Colorectal cancer	1009 cancer, 1522 controls	NAT1 C97T, C190T, G445A, C559T, G560A, A752T, T1088A;	Intake amount of red meat, processed meat, total HCA, DiMeIQx, MeIQx, PhIP, dietary pattern(meat and fat pattern)	NS	NS	1.50 (1.08-2.10) for the highest tertile of meat and fat pattern and NAT2 rapid acetylators (P _{interaction} = 0.047)

Author(year)	Study design	Outcome(s)	Number of subjects	Genetic polymorphisms	Meat exposure	Main effect of gene (odds ratio (95% CI))	Main effect of meat	Interaction between meat intake and gene
Sorensen et al (2008)	Nested case-control	Colorectal cancer	379 cancers, 769 controls	NAT2 G191A, C282T, T341C, C481T, G590A, A803G, G857A; NAT1 G445A, T1088A, C1095ANAT2 and color of meat surface after pan-frying C481T, G590A, A803G, G857A *5, *6A, *7B	Intake amount of total meat, fried meat, processed meat, red meat, and color of meat surface after pan-frying	1.31 (1.01-1.71) for fast NAT1 acetylators 1.36 (1.04-1.77) to dark color of meat surface after pan-frying	NS	NS
Goode et al (2007)	Case-control	Hyperplastic polyp, adenomatous polyp of colorectum	651 polyp cases, 556 controls	NAT1 C190T, C559T, G560A NAT2 G191A, T341C, G590A, A803G, G857A	Intake frequency of fried, broiled, barbecued meat	3.5 (1.2-10.3) for NAT2 and NAT2 intermediate /fast phenotypes + SULT1A1 1.7 (1.0-3.0) for 5/week or more vs. <5/week for concurrent hyperplastic and adenomatous polyps	NS	NS
Shin et al (2008)	Case-control	Hyperplastic polyp, adenomatous polyp of colorectum	1002 cases, 1493 controls	NAT1 C97T, C190T, G445A, C559T, G560A, A752T, T1088A, C1095A NAT2 G590A, G857A, T341C, G191A	Intake amount of total meat, red meat, MeIQx, PhIP, DiMeIQx, BaP, mutagenic activity	1.9 (1.0-3.2) for High intake amount of PhIP NAT1 rapid vs. (p _{interaction} =0.036) and slow acetylators DiMeIQx (p _{ind} =0.038) for adenomatous hyperplastic polyp	1.12 (1.02-1.22) for 10% increment of total meat + rapid or intermediate NAT1 acetylator (p _{interaction} =0.039), 1.20 (1.08-1.32) for 10% increment of red meat + rapid or intermediate NAT1 acetylator (p _{interaction} =0.014), 1.15 (1.04-1.27) for 10% increment of total meat + rapid NAT2 acetylator (p _{interaction} =0.044); all significant interactions only for concurrent adenomatous and hyperplastic polyps	1.12 (1.02-1.22) for 10% increment of total meat + rapid or intermediate NAT1 acetylator (p _{interaction} =0.039), 1.20 (1.08-1.32) for 10% increment of red meat + rapid or intermediate NAT1 acetylator (p _{interaction} =0.014), 1.15 (1.04-1.27) for 10% increment of total meat + rapid NAT2 acetylator (p _{interaction} =0.044); all significant interactions only for concurrent adenomatous and hyperplastic polyps

NS: not significant; HCA: heterocyclic amine, DiMeIQx: 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline, MeIQx: 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline, PhIP: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, BaP: benzo[a]pyrene, SULT1A1: sulfotransferase 1A1, CYP1A2: cytochrome P450 1A2

to slow-acetylators rats when they were fed PhIP, the most abundant HCA (Purewal et al., 2000). NAT1 or NAT2 polymorphisms have not been found to be directly associated with colorectal cancer risk in a meta-analysis of epidemiological studies (Brockton et al., 2000). Literatures on potential interactions between NAT1 or NAT2 polymorphisms and meat intake were summarized at Table 1. Several studies have reported that increased risk of colorectal cancer was observed with high consumption of red meat (Chen et al., 1998; Le Marchand et al., 2001; Chan et al., 2005; Lilla et al., 2006), fried meat (Welfare et al., 1997), processed meat (Kampman et al., 1999), meat and fat dietary pattern (Cotterchio et al., 2008), or high meat-mutagen index (Kampman et al., 1999) among subjects with rapid NAT1 or NAT2 acetylator genotypes. In contrast, some other studies did not report any apparent effect of interaction between NAT1 or NAT2 genotypes and meat intake on colorectal cancer risk (Sachse et al., 2002; Tiemersma et al., 2002; Murtaugh et al., 2004; Sorensen et al., 2008). In two studies on colorectal polyps, the increased risk associated with meat or meat-mutagen intake along with rapid NAT1 or NAT2 genotypes was most prominent in participants with both hyperplastic and adenomatous polyps than in those with only one type of polyps (Goode et al., 2007; Shin et al., 2008).

Cytochrome P450

In a study of 1,023 colorectal cancer cases and 1,121 controls, combined haplotypes of 6 single-nucleotide polymorphisms (SNPs) in the CYP1A2, CYP2E1, CYP1B1, and CYP2C9 genes modified the colorectal cancer risk in subjects who consumed meat ≥ 5 times per week, compared to those who consumed meat ≤ 4 times per week (Kury et al., 2007). In a multiethnic case-control study, a remarkably elevated colorectal cancer risk was observed among ever smokers with a high intake of well-done meat and carrying both rapid NAT2 genotype and rapid CYP1A2 phenotype (Le Marchand et al., 2002). However, some other studies did not report any apparent effect modification of the association between meat intake and colorectal cancer risk by genetic polymorphisms of xenobiotic metabolism enzymes (Kampman et al., 1999; Sachse et al., 2002; Tiemersma et al., 2002; Murtaugh et al., 2004; Skjelbred et al., 2007). No interactive effect of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and CYP1A2 phenotype (Ishibe et al., 2002) or of meat or HCA intake and CYP1A2 (rs762551) polymorphism (Shin et al., 2008) has been observed on the risk of colorectal polyps.

Other xenobiotic metabolism enzymes

GSTM1, GSTP1, and GSTT1 polymorphisms are not associated with colorectal cancer risk (Sachse et al., 2002; Skjelbred et al., 2007; Cotterchio et al., 2008). No interactive effect of GSTM1 polymorphism and Western dietary pattern (Slattery et al., 2000), fresh red meat intake (Tiemersma et al., 2002), or meat-mutagen index and processed meat intake (Kampman et al., 1999) has been observed on colorectal cancer risk. However, one study reported that a combination of high white meat-mutagen index, CYP1A1*2 genotype, and

GSTM1-present genotype forms the highest risk for colon cancer (Murtaugh et al., 2005). In a study on GSTA1 polymorphism reported that subjects with GSTA1*B/*B genotype showed an increased risk for colorectal cancer among well-done meat consumers (Sweeney et al., 2002).

Two studies on SULT polymorphisms have suggested an effect modification of the association between meat intake and colorectal cancer risk by the polymorphisms. A German study reported that colorectal cancer risk increased with frequent consumption of red meat only among carriers of any SULT1A1*2 allele (Lilla et al., 2007). Similarly, a Canadian study showed that SULT1A1 G638A variant modified the association between red meat doneness and colorectal cancer risk (Cotterchio et al., 2008).

Uridine diphosphate (UDP)-glucuronosyltransferase (UGT)1A1 and UGT1A7, and aryl hydrocarbon receptor (AhR) polymorphisms have not shown any effect modification of colorectal cancer risk (Cotterchio et al., 2008). AhR regulates transcriptional expression of CYP1 family genes. Positive associations with meat, HCA, or benzo[a]pyrene intake and risk of colorectal polyps have predominantly been observed among subjects carrying the A allele of AhR Arg554Lys (rs2066853) polymorphism (Shin et al., 2008).

DNA repair genes

Joshi et al. examined the genes involved in nucleotide excision repair (ERCC1, XPD, XPC, XPA, XPF, and XPG) and mismatch repair (MLH1 and MSH2) in 577 colorectal cancer cases and 307 case-unaffected sibling controls (Joshi et al., 2009). Consumption of red meat, heavily brown on the outside or inside, increased colorectal cancer risk only among subjects with XPD codon 751 Lys/Lys or XPD codon 312 Asp/Asp genotype.

In conclusion, Most studies on the interactive effect of genetic polymorphisms and meat or meat-mutagen intake have focused on genes encoding the above mentioned xenobiotic metabolism enzymes. Although enzymes involved in metabolic activation or detoxification of meat mutagens were well identified, the results on the effect of genetic polymorphisms of these enzymes on the association between meat or meat mutagen intake and risk of colorectal neoplasia have been inconclusive. The main reasons for the inconsistency between the studies are (1) differences in the methods used for meat intake assessment and (2) relatively limited sample size used in most studies for achieving sufficient statistical power to test gene-environment interaction. Several genome-wide association studies have been identified colorectal cancer susceptibility loci in chromosomal regions 8q24.21, 18q21, 9p24, 10p14, 8q23.3 and 11q23 (Broderick et al., 2007; Tomlinson et al., 2007; Zanke et al., 2007; Tenesa et al., 2008; Tomlinson et al., 2008; Carvajal-Carmona et al., 2009; Pittman et al., 2009; Webb et al., 2009). However, only one study assessed interaction of susceptible loci rs6983267 and rs10090154 of 8q24 with environmental factors (Matsuo et al., 2009). Therefore, interaction between genetic susceptibility loci and environmental factors including meat and their mutagen intakes need to be addressed in a well-designed epidemiological

studies which considers not only gene main effect but also comprehensive environmental factors. Assessment of gene-diet interaction is essential for understanding the etiologic role of dietary factors and in developing personalized cancer prevention strategy in the post-genomic era.

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