REVIEW ARTICLE

Effects of gene polymorphisms of metabolic enzymes on the association between red and processed meat consumption and the development of colon cancer; a literature review

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Abstract

The role of environmental factors and genetic susceptibility in the development of colon cancer (CC) has been already proven, but the role of gene polymorphisms in modifying the risk of environmental factors such as nutritional factors is still unknown. This study aimed to investigate the effect of polymorphisms of involved genes in the association between red meat consumption and the development of CC. The present review was carried out using keywords such as polymorphism and/or protein and/or red meat and/or processed meat and/or colon cancer. PubMed and Science Direct databases were used to collect all related articles published from 2001 to 2017. The presence of SNP in the coding genes of proteins involved in metabolism of nutrients could play significant roles in the extent of the effects of nutrition in the development of CC. The effect of dietary proteins greatly depends on the polymorphisms in the metabolising genes of these substances. Gene polymorphisms may have a role in colorectal cancer risk, especially in people with high meat intake, and this leads to a difference in the effects of meat consumption in different individuals. To conclude, dietary recommendations for the prevention and control of CC should be modified based on the genotype of different individuals. Increasing our knowledge on this field of nutritional genomics can lead to personalised preventive and therapeutic recommendations for CC patients.

Key words: Colon cancer; Polymorphisms; Protein; Colorectal cancer

Colon cancer (CC), also known as colorectal cancer (CRC), is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths worldwide. The prevalence of CC among Iranian people was between 7 and 8 per 100 000 people, with a significant increase over the last several years. In most cases, CC occurs in people aged 50 years or older and the risk of CC recurrence is increased with age. It has been reported that about 6 to 7% of CC cases have a genetic origin. Approximately 10 to 15% of CRC occur in patients where at least one of his/her relatives also had CC. Also, some hereditary syndromes are also effective on the risk of CC including Lynch syndrome and familial adenomatous polyposis syndrome. In addition, some environmental factors such as alcohol consumption, smoking, physical inactivity, high-fat diet and consumption of red and processed meat are
also considered as risk factors for CRC(3). Recent studies reported that change in the expression level of some genes is also a mechanism involved in the effects of these environmental factors(6–8). Moreover, some people are at higher risk for CC because of their genotype(9). In other words, the development of CRC is a complex process that involves positive and negative interactions between genes and environmental factors. In the present study, the effects of the interactions between gene polymorphisms and red and processed meat consumption on the risk of CC have been reviewed.

Red and processed meat and colon cancer

Many studies have shown that there is a significant association between a red and processed meat-rich diet and CRC(10,11). This association has been attributed to several dietary factors, including heterocyclic amines, aromatic hydrocarbons produced during high temperature heating processes, N-nitrosamines that are found in many food products after nitrite addition and processed meat that contains high levels of preservatives. The polymorphisms in some genes involved in the metabolism of these components and risk of CC are discussed below.

N-acetyltransferases

Many studies have examined the enzymes involved in the metabolism of amines and heterocyclic amines and suggested a significant relationship between polymorphisms of these enzymes and risk of CC(12,13). Heterocyclic amines are produced during cooking meat at high temperatures. N-acetyltransferases (NAT) are important enzymes in the metabolic activation of heterocyclic amines, which are found in two forms of NAT1 and NAT2. The rs1495741 polymorphism of NAT2 was strongly related to its activity and the GG, AG and AA genotypes are classified as enzymes with rapid, intermediate and slow activity, respectively. In people with the GG genotype of this polymorphism, there is a strong association between the consumption of red meat and the risk of CC in people with NAT2 gene polymorphisms(15). However, Barrett et al.(16) provide no support for the hypothesis that those with the fast phenotype of NAT2 are at increased risk of CRC.

A study was conducted on 147 CRC patients (seventy-six women and ninety men); the cancer risk in women was found to be lower in the NAT intermediate activity phenotype, but this difference was not found in men. It has also been reported that in people with the GG genotype of NAT2 G857A, meat intake more than three times per week increased CRC risk(17). However, some other studies failed to find any interaction between GG genotype, meat intake and CRC(18–20). For example, Chan et al.(20) reported that there was no interaction between the amount of meat consumed with NAT1 and NAT2 and the risk of developing CRC. Overall, it can be concluded that NAT2 gene polymorphisms may have a role in CRC risk, especially in people with high meat intake.

Cytochrome P450 2E1 and cytochrome P450 1A2

Cytochrome P450 (CYP) enzymes are critically important for the metabolism of these carcinogens by N oxidation(25). CYP2E1 is an enzyme that plays a key role in the metabolism of nitrosamines and other carcinogens(10,21). The CYP2E1 (C2 allele) is associated with an increased risk of CRC per 25 g/d higher red meat or processed meat intake. Generally, it can be concluded that CYP2E1 gene polymorphisms may have a role in CRC risk, especially in people with higher meat intake.

Cyclo-oxygenases

Cyclo-oxygenases (COX) play a key role in converting arachidonic acid into prostaglandins. Red meat contains a substantial amount of arachidonic acid and most probably is involved in the inflammatory response and initiation of CC especially in people with a polymorphism in the COX-1 and COX-2 genes. This polymorphism occurs in the promoter region of the gene, resulting in a possible increase in gene expression with consequent elevation of levels of the COX-2 protein. Individuals who carry the polymorphisms that could affect the expressions of COX-2 are more susceptible to CC(26). There are two isoforms of the COX enzyme, COX-1 (or prostaglandin-endoperoxide synthase 1; PTGS1), that produces PG1, and COX-2 (or PTGS2), which produces PG2. The rs20417 (−765G>C) and rs5275 (8473T>C) polymorphisms of COX-2 play an important role in many cancers such as gastric cancer, prostate cancer and CRC. Some studies have also shown that the COX-2 rs1195AA genotype can also play a supportive role in the development of CRC. Makar et al.(22) showed that polymorphism rs20417 (−765G>C) in the COX-2 gene increases the risk of rectal cancer by up to two times higher than others. No significant relationship was reported between COX-1 gene polymorphisms and CRC in this study. In one meta-analysis study, there was a significant relationship between the COX-2 rs20417 polymorphism and the risk of CRC in an Asian population(23). Andersen et al.(24) suggested that the relationship between the COX-2 rs20417 polymorphism and the risk of CRC is influenced by dietary meat intake and COX-2 rs20417 risk allele carriers were at 8% increased risk of CRC per 25 g/d higher red meat or processed meat intake. Generally, it can be concluded that COX-2 gene polymorphisms may have a role in CRC risk, especially in people with higher meat intake.
### Table 1. Summary of study descriptions and outcomes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Study design</th>
<th>Sample characteristic</th>
<th>Examined components</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAT</strong></td>
<td>Wang et al. (2015)</td>
<td>Interaction between red meat intake and NAT2 genotype in increasing the risk of CRC in Japanese and African Americans</td>
<td>Meta-analyses</td>
<td>2744 cases, 8315 controls</td>
<td>NAT genotype (SNP rs1495741)</td>
</tr>
<tr>
<td></td>
<td>Ananthakrishnan et al. (2015)</td>
<td>Red meat intake, NAT2, and risk of CRC: pooled analysis of 11 studies</td>
<td>Pooled analysis</td>
<td>8290 cases, 9115 controls</td>
<td>NAT2 phenotype based on polymorphism at rs1495741</td>
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<td></td>
<td>Barrett et al. (2003)</td>
<td>Investigation of interaction between NAT2 and HA as potential risk factors for CRC</td>
<td>Case-control study</td>
<td>484 cases, 738 controls</td>
<td>NAT2 phenotype</td>
</tr>
<tr>
<td></td>
<td>Sørensen et al. (2008)</td>
<td>Prospective study of NAT1 and NAT2 genetic polymorphisms, tobacco smoking and meat consumption and risk of CRC</td>
<td>Case-control study</td>
<td>379 cases, 769 controls</td>
<td>NAT 1 and NAT2 fast and slow NAT acetylator phenotypes</td>
</tr>
<tr>
<td></td>
<td>Lilla et al. (2006)</td>
<td>Effect of NAT1 and NAT2 genetic polymorphisms on CRC risk associated with exposure to tobacco smoke and meat consumption</td>
<td>Case-control study</td>
<td>505 patients with incident CRC, 604 controls</td>
<td>NAT 1 and NAT2 fast and slow NAT acetylator phenotypes</td>
</tr>
<tr>
<td></td>
<td>Procopciuc et al. (2017)</td>
<td>NAT2/environmental factors and their association as a modulating risk factor for sporadic colon and rectal cancer</td>
<td>Case-control study</td>
<td>150 cases, 162 controls</td>
<td>NAT2 phenotypes</td>
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<tr>
<td></td>
<td>Da Silva et al. (2011)</td>
<td>NAT2 genetic polymorphisms and risk of CRC</td>
<td>Case-control study</td>
<td>147 patients with CRC, 162 controls</td>
<td>People with GG genotype (NAT2 fast acetylators)</td>
</tr>
<tr>
<td></td>
<td>Tiemersma et al. (2002)</td>
<td>Meat consumption, cigarette smoking and genetic susceptibility in the aetiology of CRC</td>
<td>Case-control study</td>
<td>102 incident CRC cases, 537 controls</td>
<td>NAT2 gene polymorphisms (NAT2 fast acetylators)</td>
</tr>
<tr>
<td></td>
<td>Chan et al. (2005)</td>
<td>Prospective study of NAT2 genotypes, meat intake, smoking and risk of CRC</td>
<td>Nested case-control study</td>
<td>183 women with CRC, 443 controls</td>
<td>NAT2 gene polymorphisms</td>
</tr>
<tr>
<td><strong>COX</strong></td>
<td>Zhu et al. (2010)</td>
<td>–2765G&gt;C and 8473T&gt;C polymorphisms of COX-2 and cancer risk: a meta-analysis based on 33 case-control studies</td>
<td>Meta-analyses</td>
<td>19 100 cases, 29 777 controls</td>
<td>COX-2 gene, –2765G&gt;C and 8473T&gt;C polymorphisms</td>
</tr>
<tr>
<td></td>
<td>Makar et al. (2013)</td>
<td>COX-1 (PTGS1) and COX-2 (PTGS2) polymorphisms, NSAID interactions, and risk of colon and rectal cancers in two independent populations</td>
<td>Case-control study</td>
<td>2053 colon and rectal cancer patients, 2648 controls</td>
<td>COX-2 gene, rs20417 (–765G&gt;C) polymorphism</td>
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Table 1. Continued

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<tr>
<td>Andersen et al. (2013)</td>
<td>Interactions between diet, lifestyle and IL-10, IL-1B and PTGS2/COX-2 gene polymorphisms in relation to risk of CRC in a prospective Danish case–cohort study</td>
<td>Case–control study</td>
<td>9070 CRC cases, 1789 controls</td>
<td>COX-2 gene, −765G&gt;C polymorphism</td>
<td>Suggested that COX-2 −765G &lt; C risk allele carriers were at 8 % increased risk of CRC per 25 g red meat or processed meat intake per d</td>
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<tr>
<td>Le Marchand et al. (2002)</td>
<td>Red meat intake, CYP2E1 genetic polymorphisms, and CRC risk</td>
<td>Case–control study</td>
<td>521 patients with CRC, 639 controls</td>
<td>Polymorphisms in CYP2E1</td>
<td>This study showed that individuals carrying a variant of the C2 allele have lower enzyme activity Homozygous individuals for the C2 allele were also more likely to develop CRC</td>
</tr>
<tr>
<td>van der Logt et al. (2006)</td>
<td>Role of epoxide hydrolase, NAD(P)H:quinone oxidoreductase, CYP2E1 or alcohol dehydrogenase genotypes in susceptibility to CRC</td>
<td>Case–control study</td>
<td>371 patients with sporadic CRC, 415 healthy controls</td>
<td>Polymorphisms in CYP2E1</td>
<td>Risk of cancer in individuals carrying CYP2E1 Rsas I C2 allele decreases in comparison with patients carrying CYP2E1 96-bp insertion</td>
</tr>
<tr>
<td>Morita et al. (2009)</td>
<td>Genetic polymorphisms of CYP2E1 and risk of CRC: the Fukuoka Colorectal Cancer Study</td>
<td>Case–control study</td>
<td>685 incident cases of CRC, 778 controls</td>
<td>Polymorphisms in CYP2E1</td>
<td>There was a significant relationship between the −154A&gt;C polymorphism of CYP1A2 and consumption of cooked meat at high temperature with the risk of CRC</td>
</tr>
<tr>
<td>Wang et al. (2012)</td>
<td>Carcinogen metabolism genes, red meat and poultry intake, and CRC risk</td>
<td>Case–control study</td>
<td>577 cases, 307 controls</td>
<td>−154A&gt;C polymorphism of CYP1A2</td>
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**Nucleotide excision repair pathway**

<table>
<thead>
<tr>
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</tr>
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<tr>
<td>Khan et al. (2000)</td>
<td>A new XPC poly(AT) insertion/deletion polymorphism</td>
<td>Case–control study</td>
<td>419 cases, 219 controls</td>
<td>Four polymorphisms including A23G in XPA, Lys939Gln in XPC, and Lys751Gln and Asp312Asn in XPD</td>
<td>Significant relationship with the risk of CC</td>
</tr>
<tr>
<td>Hansen et al. (2007)</td>
<td>XPA A23G, XPC Lys939Gln, XPD Lys751Gln and XPD Asp312Asn polymorphisms, interactions with smoking, alcohol and dietary factors, and risk of CRC</td>
<td>Case–control study</td>
<td>405 CRC cases, 810 controls</td>
<td>XPC Lys939Gln, XPA A23G, XPD Lys751Gln, and XPD Asp312Asn polymorphisms</td>
<td>This study showed lower risk of cancer in women with Lys751Gln polymorphism of XPD and in homozygous individuals for XPC Lys939Gln polymorphism increased CC</td>
</tr>
<tr>
<td>Joshi et al. (2009)</td>
<td>Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and CRC risk</td>
<td>Case–control study</td>
<td>577 cases, 307 controls</td>
<td>XPD 312ASP and XPD 751Lys</td>
<td>People with high consumption of red meat and XPD 312ASP and XPD 751Lys risk alleles have a higher chance of CRC. The consumption of poultry meat in the carriers of the XPD 751Lys allele increased risk of CC</td>
</tr>
<tr>
<td>Steck et al. (2014)</td>
<td>Nucleotide excision repair gene polymorphisms, meat intake and colon cancer risk</td>
<td>Case–control study</td>
<td>331 African Americans with colon cancer, 544 controls</td>
<td>XPC (A499V and K939Q), XPD (D312N and K751Q), XPF (R415Q), XPG (D1104H) genotypes</td>
<td>This study showed the statistically significant positive association between colon cancer risk and XPC 499 AV + X PG genotype and an inverse association with XPC 939 QQ</td>
</tr>
<tr>
<td>DNA mismatch repair (MutS)</td>
<td>Mismatch repair polymorphisms and the risk of CRC</td>
<td>Case–control study</td>
<td>237 CRC cases and a subcohort of 2189 participants</td>
<td>Four SNP in three mismatch repair genes (MSH3 R940Q, MSH3 T1036A, MSH6 G39E and MLH1 I219V) were genotyped</td>
<td>Processed meat intake appeared to modify the association between MSH3 polymorphisms and CRC</td>
</tr>
</tbody>
</table>

**NAT, N-acetyltransferase; CRC, colorectal cancer; HA, heterocyclic amines; COX, cyclo-oxygenase; PTGS, prostaglandin-endoperoxide synthase; NSAID, non-steroidal anti-inflammatory drugs; CYP2E1, cytochrome P450 2E1; XP, xeroderma pigmentosum; MutS, mutator S; MSH, MutS homolog 3; MLH, Mutl, homolog 1.**
CRC\(^{29}\). Interestingly, Morita \textit{et al.}\(^{30}\) showed that there is a significant relationship between red meat consumption and an increased risk of CC in the individuals carrying the $\text{R}a$1 $\text{C}2$ allele. However, another study reported that no significant relationship was observed between the $\text{CYP2E1} \text{R}a$1 polymorphism, red meat consumption and CC\(^{31}\).

$\text{CYP1A2}$, a member of the cytochrome P450 mixed-function oxidase system, is involved in the metabolism of xenobiotics in the body\(^{32}\). Some studies have shown that individuals carrying $\text{CYP1A2}$ polymorphisms are at higher risk of developing rectal cancer but not for CC\(^{33-35}\). In a case–control study on $\text{CYP1A2}$ polymorphisms, it was found that there was a significant relationship between the consumption of cooked meat at high temperature in $-154 \text{A} > \text{C}$ polymorphism carriers of $\text{CYP1A2}$ and the risk of CRC. Overall, it is possible that $\text{CYP2E1}$ and $\text{CYP1A2}$ gene polymorphisms may have a role in CRC risk, especially in people with higher meat intake.

### Nucleotide excision repair pathway

The nucleotide excision repair (NER) pathway plays an important role in repairing damaged DNA. The NER pathway is a particularly important excision mechanism that removes DNA damage induced by UV light and environmental carcinogens\(^{36}\). Xeroderma pigmentosum (XP) complementation group A (XPA), XP complementation group C (XPC) and XP complementation group D (XPD) are important enzymes in the NER pathway. There is a significant relationship between polymorphisms in XPA, XPC and XPD and a lower capacity of DNA repair. Numerous polymorphisms of NER genes have been identified and these changes individually or in combination may adversely affect NER fidelity, which could contribute to the risk of CRC. Four polymorphisms of these genes including A23G in XPA, Lys939Gln in XPC and Lys751Gln and Asp312Asn in XPD have been identified that may have a significant relationship with the risk of CC\(^{37}\). For example, in a study conducted by Hansen \textit{et al.}\(^{38}\), a lower risk of cancer was reported in women with the Lys751Gln polymorphism of XPD. In homozygous individuals with the XPC Lys939Gln polymorphism, the risk of CC was increased by 3–7 times per 100 g/d increased intake of red meat. In the individuals carrying the wild-type allele, meat has no effect on CRC. No significant relationship was observed between other polymorphisms and CC.

Moreover, it was shown that people with a high consumption of red meat and $\text{XPD} \text{312Asp}$ and $\text{XPD} \text{751Lys}$ risk alleles have a higher chance of developing CRC than those with $\text{XPD} \text{312Asn}$ and $\text{XPD} \text{751Gln}$ alleles\(^{39}\). There is also a statistically significant interaction between Lys939Gln of XPC and A23G of XPA with red meat and processed meat intake and the risk of CC\(^{38,40}\). Overall, it can be concluding that higher meat intake may have a role in CRC risk, especially in people with polymorphisms in genes involved in the NER pathway.

### DNA mismatch repair (mutator S)

A DNA mismatch repair protein, also known as mutator S (MutS), participates in the DNA mismatch repair system. In a study conducted on the polymorphisms of this gene, it was found that some gene polymorphisms were associated with an increased risk of CC. Processed meat intake could increase CC risk in people with the $\text{MutS}$ polymorphism\(^{41}\). In another study, a significant relationship was observed between processed meat intake, the – polymorphism of the $\text{MutS}$ gene and the risk of CC\(^{42}\). In general, it can be concluded that $\text{MutS}$ polymorphisms may have a role in CRC risk, especially in people with higher processed meat intake.

### Discussion

The presence of SNP associated with the metabolism and function of proteins could play an important role in the effects of red meat consumption on the risk of CC.

Several individual SNP have been associated with CC risk. It is plausible that a set of SNP derived from genetic pathways that are critical in colon carcinogenesis could contribute to the cancer risk. We investigated the role of polymorphisms involved in five metabolic pathways that are relevant for the activation or detoxification of carcinogens formed during red meat processing. The polymorphisms investigated in the present study were mostly functional polymorphisms that alter the expression of genes participating in metabolic pathways associated with carcinogenesis\(^{43}\).

Recent studies demonstrated the modifier role of $\text{NAT2}$ G857A, COX-2 rs20417, $\text{CYP2E1} \text{R}a$1, $\text{CYP1A2}$ 154A>C, XPC Lys939Gln, XPA A23G and MutS T1036A on the effect of red meat consumption on CRC risk. However, some studies failed to identify an association between red meat consumption and the effect of these polymorphisms on CRC risk. Possible explanations for the discrepancy might include differences in meat variable definitions, and lack of stratification by tumour subsite in these studies. Moreover, other factors including frequency of turning the meat over during the cooking process, meat thickness, cut of meat, use of marinade or thawing meat in the microwave were not considered and may have contributed to these contradictory results\(^{44}\).

### Conclusion

In conclusion, some gene polymorphisms may have a significant role in CRC risk, especially in people with higher processed meat intake. Increasing the knowledge on nutritional genomics can lead to the finding of new methods to prevent, treat and control of CC. A summary of descriptions of studies is presented in Table 1.

### Acknowledgements

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References


