

## Recent advances in understanding of interactions between genes and diet in the etiology of colorectal cancer

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### Abstract

At an international level, colorectal cancer (CRC) is a major cause of morbidity and mortality. Diet plays a major etiologic role, and a range of putative dietary carcinogens have been identified. The probability with which these lead to mutations, and thereby cause cancer, is strongly impacted by variants in genes coding for xenobiotic metabolizing or DNA repair enzymes. Nutrient deficiencies also play a role, which will be exacerbated by variants in metabolic genes. However, many of the causal genes in sporadic CRC have hitherto proved elusive. The power of large international collaborations, coupled with genome-wide association studies, has implicated a major functional role of the tumour growth factor- $\beta$  pathway in CRC susceptibility. Nutrient regulation of gene expression may be especially important here. Future large collaborative studies must consider gene-gene and gene-diet interactions, coupled with high throughput genomic technologies, in order to uncover the relative roles of genetic variants, mutagenic xenobiotics, nutrient imbalance and gene expression in the etiology of CRC.

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**Key words:** Transforming growth factor  $\beta$ ; Colorectal

### INTRODUCTION

Colorectal cancer (CRC) is the fourth biggest cause of cancer mortality, with more than a million new cases, worldwide, being diagnosed each year. The disease appears to increase in parallel with economic development, and it has been suggested that a westernised lifestyle, including the Western diet, is a key risk factor<sup>[1]</sup>. We have recently summarised the evidence for an etiologic role of both dietary mutagens and also certain nutrient deficiencies in human cancer<sup>[2]</sup>. However, there is also good evidence for genetic susceptibility to CRC, and increasing reason to believe that this interacts with environment, including diet, in causing disease risk<sup>[3]</sup>.

While multiple genetic variants have been shown to be involved, many of these have only a small individual effect<sup>[4]</sup>. Genome wide association studies (GWAS) have revealed the significance of genes and pathways hitherto unsuspected of playing a role in CRC, and that nutrients may play a key role in affecting their gene expression. Transforming growth factor  $\beta$  (TGF- $\beta$ ) pathway may provide an important example of this. Approaches outside classic epidemiology will be essential to uncover the relative role of genes and diet, and the interactions between these,

in the etiology of this disease. This editorial draws attention to some of the current literature, and points to possible future directions of these studies. References are made to recent comprehensive reviews where possible.

## EXAMPLES OF KNOWN DIETARY MUTAGENS AND ANTIMUTAGENS IN CRC, AND THEIR INTERACTIONS WITH GENOTYPE

A Medline search was performed using the keywords [(single nucleotide polymorphism) SNP or polymorphism or variant or copy number or genetics], combined with (colon or rectum or colorectal) and (diet\$ or nutr\$ or phytochemical). Relevant papers published since the beginning of 2008 were scanned, and some additional articles were obtained from references within the papers. The references thus identified revealed two common themes in studies to that date (May 1, 2009).

High red meat and poultry diets were implicated in CRC risk in a considerable number of studies, as summarised by Joshi *et al*<sup>[5]</sup> and Yeh *et al*<sup>[6]</sup>. The fact that it was well cooked meats for which the evidence appears most convincing, draws attention to the possibility of a major class of chemicals, heterocyclic amines, as a major etiological factor. These had been originally identified as putative dietary carcinogens using mutagenicity testing approaches<sup>[7]</sup>. Heterocyclic amines are formed during high-temperature cooking of protein products, and are mutagenic following metabolic activation into a DNA-reactive species. They are known mutagens in a wide range of test systems, carcinogens in rodent models and primates, and probable carcinogens in humans<sup>[2]</sup>. The requirement of these compounds for metabolic activation, means that their effectiveness as carcinogens depends in part upon the activity of genes that encode xenobiotic metabolizing enzymes. There are a number of common genetic variants in genes as Cytochrome P450 1A1 and 1A2, or N-acetyl transferase, that profoundly affect individual sensitivity to heterocyclic amines<sup>[6]</sup>. The DNA adducts formed are susceptible to DNA repair processes, and again, variants in common DNA repair enzymes will modulate the risk of CRC by heterocyclic amines<sup>[5]</sup>.

A high intake of brassicaceous vegetables has generally been associated with a decreased risk of CRC and other cancers. Epplein *et al*<sup>[8]</sup> measured a high intake of these vegetables as a function of urinary isothiocyanates, and thereby associated high intake of brassicaceous vegetables with a decrease in CRC risk (95% CI, 0.36-0.98). As previously suggested, these authors hypothesized that up-regulation of xenobiotic metabolizing enzymes, especially glutathione-S-transferases (GST), was the mechanism by which this cancer protection occurs. Such an interpretation would be consistent with non-significant associations being seen in those individuals carrying a homozygous deletion of the GSTM1 or GSIT1 polymorphism. That is, if the enzyme is not present, it cannot be up-regulated. The

authors further suggested that, for individuals with certain GSTP1 genotypes, a detectable amount of isothiocyanates further decreases the risk of CRC as compared with the wild type homozygote.

Some of the early studies in the area of gene-diet interactions required fairly primitive methods of genotyping or even phenotyping. For example Le Marchand and coworkers<sup>[9]</sup> distinguished slow and fast metabolisers using a caffeine test. The subjects were required to drink 2 cups of coffee after overnight fasting, then urine was collected and analysed for metabolites in order to consider the potential effect of the fast or slow metabolic phenotype. While far more rapid methods for genotyping now exist, these same metabolic phenotypes are still considered important in distinguishing sensitivity of different individuals to carcinogenesis through well cooked meats, and the modulation of such metabolism by dietary isothiocyanates.

## EXAMPLES OF KNOWN DIETARY DEFICIENCIES IN CRC, AND THEIR INTERACTIONS WITH GENOTYPE

Dietary deficiencies are possibly more important than dietary mutagens in the etiology of CRC. A number of studies have considered diets deficient in or supplemented with methyl donors, in subjects stratified according to metabolic genotype. For example, Figueiredo *et al*<sup>[10]</sup>, reported data from a randomized clinical trial of folic acid supplementation and the incidence of new colorectal adenomas, in 1084 Americans with a history of adenomas. They also measured dietary and circulating plasma levels of vitamins B2, B6, and B12, and alcohol consumption. Subjects were genotyped for the Methylene-tetrahydrofolate reductase-C677T polymorphism. The authors reported that those individuals with low serum folate were more likely to develop new adenomas, and this was especially true in those carrying the polymorphism.

A wealth of data is beginning to associate vitamin D levels with the development of a range of cancer types. Yin *et al*<sup>[11]</sup> performed a systematic review and meta-analysis on the association between serum 25 hydroxyvitamin D [25(OH)D] and the risk of CRC, in studies published up to September 2008. They recalculated all results in relation to an increase of serum 25(OH)D by 20 ng/mL. They were able to show highly statistically significant reductions in the risk of CRC, as well as individual measures of colon cancer or rectal cancer, with increasing serum vitamin D. Several SNPs have been identified in the vitamin D receptor, that impact the transport, metabolism, and degradation of vitamin D, and thus profoundly influence individual vitamin D status. Raimondi *et al*<sup>[12]</sup> have done a meta-analysis of the two most frequently studied SNPs, *FokI* (rs2228570) and *BsmI* (rs1544410), in relation to the risk of various types of cancer. They conclude that the evidence supports a role for these variant SNPs, per se, in the risk of several cancers, including CRC. This risk will be augmented by low circulating levels of the vitamin<sup>[12]</sup>.

## CONTRIBUTION OF GWAS TO IDENTIFYING NOVEL GENETIC VARIANTS IN CRC

Until 2006, most of the publications describing genetic variants in CRC risk used candidate gene approaches. Three important advances have moved current thinking beyond such hypothesis-driven research. The importance of collaborative approaches has been recognised, and large sample sizes incorporating pathologically-confirmed CRC cases and well matched controls have provided the necessary statistical power to detect real effects, albeit with low odds ratios, with some degree of certainty. Secondly, the development of high density array platforms has enabled large numbers of variants, usually in the form of SNPs, to be interrogated in these big population groups, at costs lower than \$US 1000, and with high accuracy. The third important advance is the identification of tagging SNPs, that may associate with functional genetic variants, and has been facilitated by the wide availability of results from the HapMap project<sup>[13]</sup>. The ability to discover genetic variants by methods that are not hypothesis-driven has thus been revolutionised by GWAS.

Tenesa and Dunlop<sup>[14]</sup> described the importance of GWAS in identifying components of TGF- $\beta$  superfamily signalling pathway as risk factors for CRC. The five genes of potential interest are Mothers against decapentaplegic drosophila homolog of 7 (SMAD7)<sup>[15,16]</sup>, Rhoophilin, Rho GTPase binding protein 2 (RHPN2)<sup>[17]</sup>, two Bone morphogenetic protein genes BMP2 and BMP4<sup>[17]</sup>, and Gremlin 1<sup>[18]</sup>. These may possibly act through effects on gene regulation. Tenesa and Dunlop (2009) primarily derive this conclusion from three GWAS in England, Scotland and Canada<sup>[16,19,20]</sup>, and a meta-analysis of the studies from the United Kingdom<sup>[17]</sup>. Although, individually, some of these genes have a relatively low effect on risk, the fact that they are in the same pathway highlights the potential importance of gene-gene interactions in the risk of this disease.

There are a number of recent reviews on the role of TGF- $\beta$  in cancer, including Glasgow and Mishra<sup>[21]</sup>. This large family of growth and differentiation factors regulates a number of cellular processes, including proliferation, adhesion, and apoptosis, through various interrelated signalling networks. The process is tightly regulated, and it appears that CRC is only one of the various cancers in which deregulation of this pathway may play a mechanistic role. For the present purposes, it is of considerable importance that several aspects of the function of these signalling pathways are regulated by nutrients.

Dietary supplementation, with compounds such as genistein or quercetin, may affect the expression and activity of TGF- $\beta$ <sup>[22,23]</sup>. Conjugated linoleic acid, reputed to have anticancer properties, stimulates the production of NAG-1 (non-steroidal anti-inflammatory drug-activated gene-1), itself a member of the TGF- $\beta$  superfamily<sup>[24]</sup>. Probiotics are known to have an effect on immune response, which may be partly mediated through TGF- $\beta$ .

For example, Taylor *et al*<sup>[25]</sup> showed that supplementation of infants with probiotics (*Lactobacillus acidophilus*) for the first 6 mo of life led to reduced production of TGF- $\beta$  in response to polyclonal (SEB) stimulation. Nguyen and co-workers<sup>[26]</sup> suggested that butyrate, a short chain fatty acid produced during the digestion and fermentation of certain dietary fibres, enhanced the activity of the TGF- $\beta$  signalling pathway in various human colon and epithelial cell lines. They extrapolated their *in vitro* results to suggest that this activity would be enhanced in the gut through dietary fibre consumption.

Malnutrition may also have profound effects on TGF- $\beta$  production. Hillyer *et al*<sup>[27]</sup> showed elevated bioactivity of TGF- $\beta$ , in the blood of acutely protein and energy malnourished weanling C57BL/6J mice. Glucose starvation may also lead to effects on signalling. For example, Suzuki *et al*<sup>[28]</sup>, showed the involvement of TGF- $\beta$  1 signalling in hypoxia-induced tolerance to glucose starvation, in the human hepatoma cell line HepG2. TGF- $\beta$  may in turn play a key role in regulating cholesterol homeostasis in macrophages, through its effects on the regulation of expression of key genes implicated in cholesterol accumulation (e.g. LPL) and efflux (e.g. ApoE)<sup>[29]</sup>.

## GENE-DIET AND GENE-GENE INTERACTIONS IN CANCER PREVENTION

The observation of TGF- $\beta$  involvement in CRC, and recognition of possible nutrient regulation of signalling in this pathway, opens up the possible range of gene-diet interactions in this disease. While much of the work in the past, and some still appearing in the published literature, considers a limited range of nutrients and a limited range of polymorphisms, it will be important to move thinking “outside the box”. This may involve new statistical approaches, or the application of other-OMICs technologies to CRC research.

Statistical approaches to gene-gene interactions have recently begun appearing in the literature. For example, Torkamani *et al*<sup>[30]</sup> developed a pathway analysis approach to characterising gene-gene interactions in seven common diseases for which GWAS were published by the Wellcome Trust Case Control Consortium<sup>[31]</sup>. They identified several likely pathways to disease predisposition that would not have been uncovered using standard statistical analysis criteria. Even without these analytical methods, the fact that five out of ten new genetic variants identified for CRC are within the TGF- $\beta$  pathway, provides a compelling reason to consider this pathway as a significant factor in CRC risk. Tenesa and Dunlop<sup>[14]</sup> estimated that the ten common variants uncovered by GWAS have an accuracy of prediction of genetic risk of approximately 26%. They suggest that the importance of recent GWAS is in emphasizing the importance of common variants in disease risk, and suggest that consideration of gene-gene interactions will be essential in disentangling the role of genes in disease risk. They acknowledge the role of environmental risk factors including age and gender

in improving the overall predictive value of disease risk. However, these calculations neglect is the pivotal role of dietary interactions and it is essential that this component is factored into subsequent analyses.

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