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Role Of Cytokine Gene Polymorphism and Interaction of Diet and Nutrition with Genetic Susceptibility in Colorectal Adenocarcinoma

Gagan Mittal[1*] and Ruchi Sachdeva[2]

[1*]Department of Zoology, RKSD College, Kaithal
[2]Department of Bioinformatics, Goswami Ganesh Dutta Sanatan Dharma College, Sector-32, Chandigarh

Abstract
Colorectal cancer (CRC), one of the leading causes of cancer-related deaths globally, presents a growing health challenge not only in Western countries but also in rapidly urbanizing nations like India. While traditionally associated with older adults, CRC is now increasingly being diagnosed in younger populations under the age of fifty, raising serious public health concerns. This multifactorial disease arises from a complex interplay of genetic predispositions, lifestyle factors, dietary habits, and environmental exposures. This review explores the role of cytokine gene polymorphisms, dietary methylation pathways, promoter hypermethylation of tumor-suppressor genes, and the polymorphic variants in detoxification genes like NAT1 and NAT2, in contributing to colorectal cancer susceptibility. We delve into how chronic inflammation and individual genetic makeup influence cancer risk, especially in the context of common inflammatory cytokines like IL-6, IL-10, TNF-α, and TGF-β. Additionally, we highlight how Western dietary patterns—characterized by low folate and high alcohol and red meat intake—may amplify this risk through epigenetic and metabolic disruptions. Importantly, we examine the unique landscape of CRC in India, where dietary transitions, genetic diversity, and environmental influences offer a distinct context to understand gene-environment interactions. With a growing body of evidence suggesting that certain genetic variants may alter an individual's risk based on diet and lifestyle, this paper underscores the need for more region-specific research to inform early detection strategies, preventive interventions, and personalized treatment approaches.

Keywords: cytokine gene, gene polymorphism, diet, nutrition, genetic susceptibility, colorectal adenocarcinoma

Introduction

Colorectal cancer encompasses malignant growths originating that start in the colon or rectum and is commonly referred to as bowel cancer. Colorectal cancer refers to any cancer, often presenting as a lump, tumor, or abnormal growth. The United Kingdom's National Health Service identifies it as one of the most prevalent cancers worldwide. The World Health Organization ranks colorectal cancer as the second most commonly diagnosed cancer worldwide, just after lung cancer. What is especially concerning is that recent studies in the U.S. have shown a troubling trend of the disease appearing at a younger age, especially in people under fifty.

According to Medilexicon's medical dictionary, colorectal cancer is "an autosomal dominant predisposition to early-onset colorectal cancer in the absence of adenomatosis. The disease phenotype may be limited to the colorectum (Lynch syndrome I) or coexist with extracolonic tumors such as endometrial or gastric cancer, among others (Lynch syndrome II). The genetic basis is in one of several genes responsible for DNA mismatch repair; in over 90% of cases, the mutation is one of two genes: MSH2 and MLH1." Colorectal cancer may be benign, i.e., the tumor will not spread, or it may be malignant, consisting of cells capable of damaging other body organs by spreading to them. The colon, part of the large bowel, is responsible for reabsorbing undigested food products, including

significant amounts of water and nutrients. The rectum lies at the end of the colon and stores faecal matter comprising of stools, waste material, etc., before being expelled from the body.

Only a small percentage of colorectal cancers are attributable to inherited genetic syndromes. In contrast, most cases are thought to be caused by multiple factors, including environmental exposures and mild genetic predisposition. Both cigarette smoking and consumption of red meat have been associated with an increased risk of colorectal cancer in several previous studies (Zheng, et al., 2021; Norat et al., 2002; Giovannucci, 2001). A plethora of potential carcinogens, e.g., polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and other aromatic amines, have been reported from cigarette smoke and red meat cooked at high temperatures (Zheng & Lee, 2009; Cross & Sinha, 2004; IARC Press, 2004). These procarcinogens can be activated in vivo to reactive metabolites that may easily bind to DNA and thus induce DNA damage, subsequently leading to tumor initiation.

Role of Cytokine Gene Polymorphisms

In the Western world, one of the significant causes of cancer morbidity and mortality remains colorectal cancer. As resources are increasingly directed toward disease prevention, strategies for identifying and targeting high-risk individuals are important. Regular use of nonsteroidal anti-inflammatory drugs (NSAID), such as aspirin, has been shown to reduce the incidence of colorectal cancer and mortality happening due to it by as much as 50% and has thus become an attractive option for chemoprevention (IARC-WHO, 1997, Thun et al., 2002). However, with the complications related to long-term NSAID use, it is imperative to identify those for whom the benefits outweigh the risks.

The beneficial association between NSAID use and a lower risk of colorectal cancer adds to the growing evidence that chronic inflammation may play a key role in the pathogenesis of sporadic colorectal cancer. In the case of chronic inflammation in the gastric mucosa, it is known that a pro-inflammatory cytokine gene profile increases the risk of malignant progression (El Omar et al., 2003). A recent study has shown that common polymorphisms in several inflammatory genes are also associated with sporadic colorectal cancer risk (Landi et al., 2003). This was the first report to suggest that genes encoding interleukin (IL)-6, IL-8, and proliferator-activated receptor-γ are important for inflammation-related risk of sporadic colorectal cancer. The risk of CRC may also be influenced by genetic variants in other genes controlling the inflammatory response, and they will modify the effects of other factors, such as NSAIDs, that act on this response.

IL-1β and tumor necrosis factor α (TNFα) are prototypical pro-inflammatory cytokines with several functional polymorphisms. The IL-1B-31 T to C single nucleotide polymorphism (SNP) and the TNF-α-308 G to A SNP are functionally significant, with the C allele of IL-1B-31 and the A allele of TNF α-308 being associated with increased production of their respective cytokines (Hwang et al., 2002; Abraham & Kroeger, 1999). In Helicobacter pylori-induced gastritis, an increased risk of gastric cancer is related to these pro-inflammatory alleles (El Omar et al., 2003).

Within the gastrointestinal tract, transforming growth factor-β (TGF-β) is an important immunoregulatory cytokine, and this is shown in TGF-B gene knockout mice, which proceed to develop uncontrolled gastrointestinal inflammation (Kulkarni et al., 1993). The −800 (G to A) and −509 (C to T) SNPs of the TGF-B1 gene are in linkage disequilibrium, and the −509 T allele has been related to a higher plasma concentration of the cytokine and a higher level of transcriptional activity than the −509 C allele (Grainger et al., 1999). A gene dose effect has been observed for the T allele so that individuals homozygous for −509 T/T were found to have higher plasma concentrations of TGF-β1 than heterozygous C/T and homozygous C/C individuals (Grainger et al., 1999). It could be postulated that having the −509 T allele is protective against colorectal cancer. There are no published reports of this SNP about colorectal cancer.

IL-10, a Th2 anti-inflammatory cytokine, is crucial in modulating gastrointestinal tract inflammation (Moore et al., 2001). The IL–10–deficient mouse develops atrophic gastritis, chronic enterocolitis, and ultimately, colorectal cancer (Kuhn et al., 1993). Promoter SNPs exist at positions −1082 (G/A), −819 (C/T), and −592 (C/A) of the IL-10 gene on chromosome one. The −819 and −592 loci are in

total linkage disequilibrium, and together, the three loci form three haplotypes (GCC, ACC, and ATA) that have been associated with more excellent or lower IL-10 production. The −1082 IL-10 A allele has been associated with the production of reduced protein levels in the cells stimulated with the ATA haplotype, leading to low IL-10 expression and the GCC haplotype with high IL-10 expression (Eskdale et al., 1998). However, the functional consequences of these haplotypes remain uncertain, as several contradictory studies have been published (Rees et al., 2002; Kilpinen et al., 2002; Eskdale et al., 1999). Gibson et al. identified additional SNPs in the IL-10 promoter in Europeans and found that distal SNP haplotypes were also associated with quantitative IL-10 production. The low ATA IL-10 haplotype is associated with an increased risk of gastric adenocarcinoma, and this may be related to the role of IL-10 as an anti-inflammatory cytokine down-regulating IL-1β, TNF-α, IFN-γ, and other pro-inflammatory cytokines (El Omar et al., 2003). It is presently unknown whether the ATA IL-10 haplotype is also a risk factor for colorectal cancer.

Methyl-replete diets and colorectal carcinogenesis

Silverberg et al., 1990 reported that colorectal cancer is in the second position when it comes to the leading cause of cancer death in the U.S. Up to 90% of these malignancies can be attributed to environmental factors, including diet (Doll & Peto, 1981). Genes interacting with environmental or dietary exposures may play a significant role in colorectal carcinogenesis. The attributable risk for functional polymorphisms in a common nutrient- or carcinogen-metabolizing gene with a relatively modest relative risk (e.g., relative risk of 2.0) may be higher than that of rare mutations in a significant proto-oncogene or tumor-suppressor gene with much higher relative risk. In addition, studying gene-environment interactions about the risk of cancer may be valuable because positive findings would implicate the substrates with which the gene interacts as disease-causing exposures, elucidate the causes of cancer, and highlight dietary and environmental changes that can be prevented.

Direct evidence from two cohort studies, one of the men and the other of women, suggests that a methyl-deplete diet (a diet high on alcohol content and low in folate and methionine) is related to a high risk of colon carcinoma and adenoma (Giovannucci et al., 1993 and 1995). In a prospective study of 47,931 male health professionals in the U.S. (Giovannucci et al., 1995), folate and methionine intakes were each weakly inversely associated with the risk of CRC. The current intake of more than two alcoholic drinks daily doubled the risk of colon cancer; past drinkers also had twice the risk. Combinations of high alcohol and low methionine and folate intake yielded more than a threefold increase in the risk of colon cancer. A methyl-replete diet was also inversely related to the risk of colon adenomas in the same population of male health professionals as well as in another prospective study of 88,756 women (Giovannucci et al., 1993) those in the highest quintile of folate intake had a 35% reduction in risk of adenomas compared with those in the lowest quintile of intake. An intake of 30 g (2 drinks) of alcohol per day had a significant 80% elevation in risk compared with those who did not consume alcohol. Combinations of alcohol, folate, and methionine were formed to examine the joint influence on the risk of adenomas. High intake of alcohol and low methionine and folate consumption was a major risk factor for adenomas, especially adenomas 1 cm, resulting in close to a threefold increase in risk compared with individuals with high intake of folate and methionine and low or no alcohol intake. Consistent with these findings, other epidemiologic studies have reported that individuals who consume much folate are less likely to get colorectal carcinoma and adenoma (Benito et al., 1991; Ferraroni et al., 1994; Freudenheim et al., 1991). The majority of studies also indicate an association between alcohol intake and a higher risk of colorectal adenoma (Landler et al., 1993) as well as large bowel cancer (Kune & Vitetta, 1992), especially cancers in the distal colorectum (Klatsky et al., 1988). Moreover, indirect evidence implicates the benefit of a methyl-replete diet; fruits and vegetables, significant sources of folate, as well as chicken and fish, primary sources of methionine, are associated with decreased risk of colorectal cancer and adenomas (Giovannucci et al., 1992; Willett et al., 1992). In light of this evidence indicating a protective effect of methyl-replete diet against colon cancer, it is reasonable to hypothesize that functional polymorphisms in genes

associated with methyl metabolism, such as the methylenetetrahydrofolate reductase (MTHFR) gene, may confer differential susceptibility to colorectal cancer.

Promoter hypermethylation of tumor-related genes

It is well recognized that the continuous accumulation of oncogene activation and inactivation of tumor suppressor genes is associated with the progression of colorectal adenoma to cancer. Moreover, mounting evidence shows epigenetic changes. According to other epidemiologic research, those who consume much folate are less likely to get colorectal cancer, particularly gene promoter hypermethylation. According to other epidemiologic research, those who consume a lot of folate are less likely to get colorectal cancer. (Jones & Laird, 1999). Hypermethylation of CpG islands in the promoter region of tumor suppressor genes causes transcriptional silencing, with subsequent loss of protein expression. Promoter hypermethylation in the helicase-like transcription factor (HLTF) has been reported in colorectal cancers (Moinova et al., 2002). the adenomatous polyposis coli gene (APC)(Esteller et al., 2000), p16 cell cycle regulator (Herman et al., 1995), the human MutL homologue (hMLH1) gene (Kane et al., 1997), and tissue inhibitor of metalloproteinase-3 (TIMP-3) (Cameron et al., 1999), Furthermore, concurrent methylation in multiple genes, sometimes called the CpG island methylator phenotype (CIMP) when certain loci were methylated, has been reported in colorectal cancer (Toyota et al., 1999). The CIMP is more frequently observed in tumors with proximal location, microsatellite instability, and normal p53. (Shen et al., 2003) However, the role of promoter hypermethylation in the early stage of colorectal carcinogenesis, particularly in adenomas and adjacent noncancer tissues of cancer patients, is less well defined.

NAT 1 and NAT 2 gene polymorphism

The phase II metabolizing enzymes N-acetyltransferases 1 and 2 (NAT1 and NAT2), both being expressed in colorectal tissue (Ilett et al., 1994; Hickman et al., 1998), catalyze N- and O-acetylation of several xenobiotics, such as heterocyclic aromatic amines and aromatic amines, which may entail detoxification or activation of the substrate (Hein et al., 1993). NAT1 and NAT2 genes exhibit several genetic polymorphisms with >25 different alleles known to date. The NAT1*10 allele is the most common variant allele among Caucasians and, although not consistently, has been linked with increased enzyme activity in vitro and in vivo (Bell et al., 1995; Hein et al., 2000). In European populations, ~60% of individuals have genotypes associated with NAT2 slow acetylation (Brockton et al., 2000). Hence, genetically determined differences in acetylation capacity may alter exposure to carcinogens and thus influence individual susceptibility to environmental exposures.

Overall, the epidemiologic evidence provides little support for the main effect of NAT1 or NAT2 genotype on colorectal cancer risk (de Jong et al., 2002; Brockton et al., 2000). Previous studies that investigated a modification of the risk of colorectal neoplasms associated with cigarette smoking by NAT2 acetylation status yielded inconsistent results (Chan et al., 2005; Tiemersma et al., 2002; Tiemersma et al., 2004; Barrett et al., 2003; van der Hel et al., 2003; Slattery et al., 2003; Slattery et al., 1998; Potter et al., 1999; Welfare et al., 1997; Probst-Hensch et al., 1995; Bell et al., 1995). However, some of the previous studies were based on a small number of cases (Chan et al., 2005; Tiemersma et al., 2002; van der Hel et al., 2003; Welfare et al., 1997; Bell et al., 1995) or used only qualitative measures for smoking (van der Hel et al., 2003; Barrett et al., 2003; Welfare et al., 1997; Probst-Hensch et al., 1995; Bell et al., 1995). Although aromatic amines and heterocyclic aromatic amines are known to be substrates for both NAT1 and NAT2 (Hein et al., 1993; Hein et al., 1994; King et al., 2000), the joint effect of NAT1 and NAT2 genotypes on colorectal cancer risk was considered only in a tiny study (Bell et al., 1995). There may be a modifying effect of NAT2 acetylation status linked to exposure to environmental tobacco smoke (ETS), which contains potentially cancer-causing arylamines, on the risk of developing colorectal cancer (IARC Press; 2004). It was only investigated in one previous study on rectal cancer (Slattery et al., 2003). Findings about correlation of colorectal cancer risk and red meat consumption point towards greater risk among

NAT2 fast acetylators than among NAT2 slow acetylators (Welfare et al., 1997; Murtaugh et al., 2004; Kampman et al., 1998; Chen et al., 1998) however, not all studies support such an effect of NAT2 acetylation status (Tiemersma et al., 2002; Tiemersma et al., 2004).

Epidemiology of CRC in India

Due to genetic, environmental, and dietary factors, CRC is becoming a major public health concern in India. Despite traditionally low incidence rates, urbanization, dietary shifts, and increased life expectancy contribute to the increasing burden of CRC. With increasing westernization of lifestyle and diet, alongside aging populations, CRC is expected to pose a significant healthcare burden in India. The disease is characterized by multiple etiological pathways involving genetic predispositions, chronic inflammation, environmental exposures, and diet. India's ethnically diverse population presents a unique opportunity to study gene-environment interactions that contribute to CRC risk.

Compared to Western countries, the overall incidence of CRC in India is low but increasing. According to estimates, the age-standardized incidence rates range from 4 to 6 per 100,000 in urban Indian men and women, whereas in the West, it ranges between 30 and 50 per 100,000. However, this apparent disparity is narrowing due to rapid urbanization, increased red and processed meat consumption, and sedentary lifestyles.

A regional study from Kashmir highlighted that CRC is the third most common gastrointestinal malignancy in the area, especially among women (Banday et al., 2016). Such findings point to the influence of localized genetic and environmental risk factors that merit further investigation.

Inflammation plays a crucial role in the etiology of CRC as we know that the TNF-α gene has a critical promoter region polymorphism at position -308 (G>A), designated as rs1800629. This SNP has been studied extensively across different ethnicities. In the Indian context, multiple studies have assessed its role in CRC. A meta-analysis by Mandal et al. (2019) analyzed data from 15 studies comprising 3116 CRC cases and 4480 controls. The study concluded that the TNF-α -308G>A polymorphism was not linked with CRC risk in the overall population. However, subgroup analysis revealed a protective association in Asian populations (OR = 0.753; 95% CI: 0.635–0.893 for A vs. G allele). Banday et al. (2016), in a case-control study on an ethnic Kashmiri population, reported no significant association between the TNF-α -308G>A SNP and CRC risk, with no observed AA genotypes among cases or controls. These findings align with the meta-analysis and suggest that while TNF-α -308G>A may not independently confer CRC risk, it may act protectively or in conjunction with other SNPs. Nadeem et al. (2015) highlighted the potential of gene-gene and gene-environment interactions in modulating disease risk. In Indian populations, a combination of IL-6 -597 GA and TNF-α -308 GG increased the risk of type 2 diabetes mellitus up to 21 times, while a triple combination with IL-10 -592 CA increased the risk 314-fold. Though focused on T2DM, these findings have implications for CRC due to overlapping inflammatory mechanisms.

- **The Westernization of Indian Diets**

India's traditional diet, high in vegetables, fiber, and plant-based nutrients, is being replaced in urban centers by Western-style diets rich in red meat, saturated fats, and processed foods. Andersen et al. (2013) systematically reviewed diet-gene interactions in CRC. Although not India-specific, their findings emphasize how genetic polymorphisms modify the risk associated with high meat consumption and low intake of protective nutrients. In an Asian cohort, individuals with GST null genotypes who consumed high amounts of cruciferous vegetables had significantly reduced CRC risk (69%). While specific Indian data are limited, this relationship suggests that traditional Indian diets rich in vegetables could offer genetic protection. O6-Methylguanine-DNA methyltransferase (MGMT) repairs DNA damage from carcinogens. A polymorphism in MGMT (Ile143Val) was associated with increased CRC risk when vitamin intake was low, but high intake of vitamins C, E, and carotene mitigated the risk (Andersen et al., 2013). Given the prevalence of vitamin deficiencies in parts of India, public health strategies should focus on improving antioxidant intake.

- **Public Health Implications in India**

The rise in CRC in India necessitates an integrated strategy combining genetic screening, dietary modifications, and public health awareness. Most CRC cases in India are diagnosed at advanced stages due to limited access to screening and a lack of awareness. Incorporating genetic risk profiling, especially in families with a history of CRC or IBS (inflammatory bowel disease), can help in early detection. Educational campaigns promoting fiber-rich diets, reducing red and processed meat consumption, and encouraging physical activity are urgently needed. In the future, these interventions could be tailored based on genetic risk profiles. India urgently needs national level, multicentric studies incorporating genomic, dietary, and lifestyle data to build a comprehensive CRC risk model.

Conclusion

Colorectal cancer remains a pressing concern worldwide, increasingly affecting populations once considered at low risk. Our exploration of the genetic and environmental factors underlying CRC reveals the intricate balance between inherited predispositions and modifiable lifestyle choices. Genetic variations, particularly those influencing inflammatory cytokine production, methylation pathways, and carcinogen metabolism, can either heighten or reduce an individual's risk. Crucially, inflammation emerges as a central theme—both as a driver of genetic changes and as a modifiable factor influenced by diet, medication, and lifestyle. Nonsteroidal anti-inflammatory drugs like aspirin, for instance, offer significant preventive potential, but only for select groups whose genetic profile makes them more responsive to such interventions. Similarly, methyl-replete diets rich in folate and methionine may provide protection, especially in genetically susceptible individuals, while alcohol and red meat consumption appear to act as risk enhancers through their interaction with enzymes like NAT1 and NAT2. In the Indian context, the rising incidence of CRC amid changing dietary habits and increasing urbanization calls for urgent attention. The diversity of India's population provides a valuable opportunity to better understand how local environmental exposures interact with genetic makeup. While findings on specific polymorphisms such as TNF-α -308G>A are mixed, they highlight the complexity of CRC etiology and the potential role of gene-gene and gene-environment interactions. Moving forward, a more personalized approach to CRC prevention and treatment—rooted in genetic screening, dietary modifications, and targeted therapies—can significantly enhance outcomes. Public health efforts should focus on awareness, screening, and lifestyle interventions that align with both individual risk profiles and broader population trends.

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