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Dietary, gut microbiome and genetic factors associated with Colon cancer - A systemic review

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Abstract

Colorectal cancer (CRC) is the third most common cancer diagnosed in both genders in the world. It is also known as colorectal adenocarcinoma and its prime function is to reabsorb remaining water, minerals and nutrients from chyme and to facilitate absorption. Majority of the CRC cases are sporadic, 5-6% are due to inherited mutations in genes, while rest of the cases indicate gene-environment interactions. Being heterogenic disorder it includes copious factors for progression of tumorigenesis such as accumulation of mutations and aberrations in oncogenes, tumour suppressor genes and other pathways which leads to genomic instability. These events are due to environmental factors such as poor diet, lacking green leafy vegetables and fiber and consumption of animal products which yield metabolites that cause imbalance in microflora, resulting in modified methylation pattern and histone structure that eventually causes cancer. Although genetic and environmental factors have prominent role to play, however, gut microbiome- a candidate biomarker has been suggested to directly contribute to the development of colorectal cancer.

Keywords: CRC, Microbiome, Cancer, diet

Introduction

Cancer can be defined as group of disorders that involves abnormal cell growth and have the capacity to invade and rife to other parts of the body. Common symptoms for cancer are lump, abnormal bleeding, unexplained weight loss and many more. The risk factors for development of cancer entails obesity, lack of physical activity, imbalanced diet, smoking, drinking of alcohol, exposure to radiations, environmental pollutants and genetic factors (WHO, 2018). The most common types of cancer are lung cancer, colorectal cancer, cervical cancer, stomach cancer which affects both genders with varying degree (WHO, 2014).

Colorectal cancer (CRC) is the third most common cancer diagnosed in both genders in the world (American Cancer Society; 2020). It is also known as colorectal adenocarcinoma and arises from glandular epithelial cells of large intestine. The prime function of colon is reabsorption of remaining water, minerals and nutrients from chyme and to facilitate absorption. Gastrointestinal epithelium is structured into crypts and villi, where crypts contain stem and progenitor cells that are capable of self renewal. Progenitor cells migrate out of crypts to villus after they differentiate into specialized epithelium and undergo apoptosis and are shed and eliminated along with faeces. This process is highly regulated by signaling proteins and most common are Wnt, BMP and TGF-B (Medema and Vermeulen, 2011).

The cancer occurs when epithelium cells acquire genetic or epigenetic mutations that confer on them selective advantage (Ewing *et al*., 2014). Owing to abnormal replication and survival, these hyper-proliferative cells give rise to a benign adenoma, which may then evolve into carcinoma and metastasize over decades (Vogelstein *et al*., 1988). About 80% CRC cases are sporadic and one fourth is familial, out of which 5-6% owing to inherited mutations in CRC genes whilst rest indicates gene-environment interactions (Migliore *et al*., 2011). Approximately 70% cases of CRC are developed with unknown etiology, however, gut microbiome- a candidate biomarker has been suggested to directly contribute to the development of colorectal cancer (Zackular *et al*., 2014). This review will elucidate the role of genetics and epigenetics risk factors, dietary habits and microbiome in causing CRC amid individuals.

Incidence:

In recent decades, the incidence of CRC has been significantly increased, having 1.8 million cases with age standardized incidence rate of 23.2 per 100,000 person/year (Naghavi *et al*., 2019). The risk of developing colorectal cancer is 1 in 23 for men and 1 in 25 for women; however, number of other factors such as smoking, alcohol, obesity, sedentary lifestyle, old age, and family history can effects the risk of development of colorectal cancer (American Cancer Society; 2020). Annually, 700,000 people succumb to deaths due to CRC (Torre *et al*., 2015) and this disease has expected to cause 53,200 demises by 2020 in USA (American Cancer Society; 2020). According to geographical distribution, rise in CRC has been observed in industrialized countries with moderate and high development index (Dolatkhah *et al*., 2015). In recent years, the incidence and mortality rates of CRC in Eastern Europe, Latin America and Asia has grown higher as compared to other countries (Center *et al*., 2009a), while it has decreased steadily in the countries with the highest human development index (HDI), such as certain Western European countries and the United States, which is attributable to introduction of ameliorated screening programs and therapeutic interventions (Arnold *et al*., 2016). With respect to gender, despite the prevalence of CRC in both sexes, it was higher in men than in women (Ferlay *et al*., 2015a) which might be due to exogenous and endogenous factors pre diagnosis that results in higher incidence rates (White et al., 2018).

Table 1: Incidence rates of CRC around the globe (% age)

Countries	Incidence rates per 100,000 persons	
	Males (%)	Females (%)
India	4.3	3.4
USA	34.1	25
Singapore	41.6	28.3
Japan	41.7	22.8
Israel	41.7	22.8
Korea	46.9	25.8
Australia	41.7	32.1
Southern Europe	40.4	24.1
Northern Europe	37.5	27.3
Central and Eastern Europe	37.5	23.2
Western Europe	34.5	23.7
Northern Africa	10	8.6
Eastern Africa	7.8	7.7
Middle Africa	7.8	7.3
Western Africa	6.8	6.1
Southern Africa	16.8	11.2
Russia	29	21.2
Malaysia	19.6	15.5
China	16.3	12.2
Saudi Arabia	14.3	9.8
Iran	8.7	6.4
Sri Lanka	7.5	5.8
Bangladesh	4.5	4
Pakistan	4.9	4.2
Iraq	5.2	4
Nepal	5.3	4.8
Bhutan	7.9	4.4
Afghanistan	6.9	7

Modified from http://globocan.iarc.fr./ (Colorectal cancer, globocan, 2018)

Genetics:

CRC initiation and progression entails amassing of mutations in suppressor and oncogenes providing significant information to comprehend multistep procedure of carcinogenesis. The most important event is inactivation of *APC* pathway (adenomatous polyposis coli) and mutations in *SMAD2, TP53* and *KRAS* genes (Migliore *et al*., 2011). About 75% of the patients have sporadic form of CRCs; while one-fourth have family history owing to shared genes and environment, while highly penetrating mutations in major genes account for 5-6% of CRC (Jasperson *et al*., 2010).

Tumor suppressor and oncogenes in CRC:

APC:

CRC is associated with mutation in *APC* gene, which is involved in stability of beta-catenin in the Wnt signaling pathway in normal colonic epithelial cells and regulates the expression of Wnt target genes such as c-myc oncogenes. A mutation in this gene brings about the development of multiple adenomatous polyps in the colon and rectum and extracolonic manifestations includes gastric and duodenal polyps, osteomas, epidermoid cysts and retinal lesions (Yavropoulou *et al*., 2007).

KRAS:

This gene is involved in growth, differentiation, cell proliferation and cell survival, apoptosis, inflammation and cell transformation. A mutation at codon 12 of the *KRAS* (glycine to valine) is significantly associated with apoptosis and cell survival which later results in CRC (Andreyev *et al*., 2001).

TP53:

TP53 participates in coordination of cellular responses to oxidative stress, DNA damage, cell cycle regulation and apoptosis. Mutation in TP53 occurs in core domain containing sequence specific DNA binding activity of the protein and results in lymphatic invasions in proximal tumors (Iacopetta *et al*., 2006).

Table 2: CRC genes and syndromes

Genes	Syndrome/ Defects
APC	Familial Adenomatous Polyposis/ actiavation of Wnt signaling causing loss of regulation of microtubules/mutation causes chromosomal instability
MUTYH	MUTYH Associated Polyposis/ MUTYH variants-Tyr165Cys and Gly382Asp
MLH1, MSH2, MSH6, PMS2	Lynch syndrome/ DNA single nucleotide mismatch repair defects/germ line mutation in hereditary nonpolyposis CRC/ MMR gene mutation causes microsatellite instability
SMAD4	Juvenile Polyposis syndrome/ LOH/germ line mutation/60% higher risk
STK11	Peutz-Jeghers syndrome/ mutation in gene STK encoding serine threonine kinase
PTEN	CS/promotion of activation of P13L pathway resulting in survival signaling and apoptosis suppression/chromosomal instability
TP53	Inactivating mutation causes loss of regulation of cell cycle arrest and cell death
TGFBR2	Inactivating by frame shift mutation in poly A repeat with TGFBR2 coding sequence or by mutation in kinase domain/microsatellite instability
KRAS	Activation of signaling pathways, P13K-PDK1-PKB and RAF-MEK-ERK1/2, promoting cell survival and apoptosis suppression
BRAF	Mutation in BRAF serine threonine kinase- a downstream mediator of signaling through RAF-MEK-ERK1/2 pathway, mimics consequences of KRAS mutation
GSTT1	*GSTT1* null genotype associated with CRC risk
GSTM1	Null genotype with increased risk
COX2	Promoter SNP with increased risk of CRC
MTHFR	MTHFR 677 C>T SNP
NATs	Interaction between NATs SNP and smoking status causes CRC
MTR	MTR 2756 A>G
IGF1	IGF1 promoter SNP in association with HNPCC

(Modified from Migliore *et al*., 2011)

Lynch syndrome:

Lynch syndrome, also known as Hereditary Nonpolyposis Colorectal cancer (HNPCC) is a rare disorder, caused due to mutation in numerous DNA mismatch repair genes and germline mutations in *MSH2* and *MLH1* genes and accounts for 3% of total CRC (Lynch *et al*., 2009). People with lynch syndrome and their relatives are at risk of developing other types of cancer such as gastric, ovarian, biliary, urinary tract brain and endometrial adenocarcinoma (Jasperson *et al*., 2010). The genes that cause Lynch syndrome are *MSH2*, *MLH1*, *MSH6* and *PMS2* which code for MMR proteins and mutation in these leads to microsatellite instability (MSI). These microsatellites are repeats of 1-6 bp length and prone to accumulation of mutations due to binding inefficiency of DNA polymerase. Any insertion/deletion in these microsatellites leads to a frameshift mutation resulting in protein truncation (Weisenberger *et al*., 2006). In addition, Muir-Torre syndrome (MTS) is a variant of Lynch syndrome and identified by presence of one sebaceous gland neoplasm and one visceral malignancy. Familial Adenomatous

Polyposis (FAP), Attenuated FAP (AFAP) and Gardner syndrome:

FAP is autosomal dominant condition which arises due to multiple adenomas in colon and rectum after first decade of life and ultimately results in CRC. It also presents extraintestinal manifestations such as congenital hypertrophy of retinal pigment epithelium, dental abnormalities and extracolonic tumors while AFAP is mild variant of FAP and characterized by duodenum and thyroid tumors (Half *et al*., 2009; Jasperson *et al*., 2010). Gardner syndrome is an outcome of germline mutation in *APC* gene and specify by the occurrence of gastrointestinal polyps, dental abnormalities, tumors and epidermoid cysts (Juhn and Khachemoune, 2010).

Hyperplastic Polyposis Syndrome (HPPS): It is a condition identified by multiple or large hyperplastic polyps throughout the colon, however, diagnosis must accomplish one of the following criteria: a) atleast five polyps occurring in proximal region of sigmoid colon, b) more than 30 polyps should be there, c) at least one hyperplastic polyp in proximal sigmoid colon in an individual having one first degree relative with HPPS (Jass, 2000).

Various other syndromes include Peutz-Jeghers syndrome (PJS) which predisposes the patient to gastrointestinal, pancreatic, lung, breast, ovarian and uterine malignancies (Beggs *et al*., 2010). Juvenile polyposis syndrome (JPS) is characterized by polyps in gastrointestinal tract (Calva and Howe, 2008). Hereditary mixed polyposis syndrome (HMPS) is distinguished by polyps of mixed adenomatous/ hyperplastic/atypical juvenile histology having autosomal domin at inheritance and leads to CRC (Jaeger *et al*., 2003).

Cytogenetics of CRC:

Colorectal cancer development requires systematic series of events that involve transformation of normal colonic epithelium to adenomatous and ultimately to adenocarcinomas (Pino and Chung, 2010). The genome stability is requisite in maintaining cellular integrity and its loss leads to cancer progression due to acquisition of mutations associated with tumor phenotype (Mastalier *et al*., 2011). Multifold genetic alterations have been identified in genes that control cell maturation and growth, substantiating the role of genetics in occurrence of cancer (Petrutescu *et al*., 2010). There are three major subtypes that can be recognized in CRC: microsatellite instability (MSI), chromosomal instability (CIN) and CpG island methylator phenotype (CIMP) (Toyota *et al*., 1999). CIN is common genomic instability which accounts for 80-85% of colorectal tumors in CRC patients (Grady and Crather, 2008). CIN is characterized by chromosomal rearrangements and numerical abnormalities such as addition or deletions of chromosome arms or frequent loss of heterozygosity (Langauer *et al*., 1997). The first one called 'monosomic type' entailing losses or deletions in chromosome 1p, 4, 14, 5, 17, 18 and 21, while another one is called 'trisomic type' distinguished by gain of several chromosomes such as 5, 7, 8, 12 and X (Duesberg *et al*., 2006). Researchers observed that gains and losses of 18q and 20q, respectively, are the most frequent aberrations amid CRC patients (Feron *et al*., 1990; Korn *et al*., 1999; Angelis *et al*., 1999). Aggregation of losses in 8p21-pter, 15q11-q21, 17p12-13 and 18q12-21 and gains in 8q23-pter, 13q14-31 and 20q13 were found in association with adenoma to carcinogen progression (Harmsen *et al*., 2002).

Diep *et al*. (2006), found that losses at 17p and 18 and gains at 8q, 13q, and 20 occur early in establishment of CRC whereas loss at 4p contributes to the aggressiveness of tumor and enable them to penetrate muscular layer. Another study reported that after numerous investigations they observed gains in 3q, 5p/5q, 7, 8q, 20q, 13, and X and losses in 8p and 18q (Knutsen *et al*., 2010). Out of these, recurrent aberration among CRC patients is in 18q21-18q21.1 region which contains tumor suppressor genes such as SMAD4/DPC4 (Thibodue *et al*., 1993).

Microbiome in Human Intestine:

Human intestine comprises of more than 100 billion bacteria (anaerobic and aerobic), playing a prominent role in modulating the host metabolism, immunity and converting dietary constituents into the active form (Wong and Yu, 2019). The normal gut microbiota is rich in anaerobic bacteria which is 100 to 1000 times more than aerobic and facultative bacteria, respectively. The colon has a reductive environment devoid of oxygen, which allows *Bacteroidetes* and *Firmicutes* to be the dominant phyla followed by *Actinobacteria* and *Verrucomicrobia* (Li and Tang, 2018; Tomezzato *et al*., 2018). Although, colonic bacteria exist in symbiotic relationship with humans, under certain situations due to imbalance, the number of harmful bacteria elevate, resulting in the

development of inflammatory and chronic diseases such as obesity, type 1 and 2 diabetes, kidney disorders, inflammatory bowel disease and colorectal cancer (Larsen *et al*., 2010; Ley *et al*., 2006). Apart from this, DNA damage owing to superoxide radicals, genotoxin formation, enhanced T-cell proliferation and activation of procarcinogenic pathway due to number of receptors that have shown to be involved in cancer development (Toprak *et al*., 2006; Cuevas-Ramos *et al*., 2010). Research demonstrated that intestinal microbiota plays significant role in conversion of latent carcinogens into bioactive forms using various enzymes such as β-glucuronidase, β-glucosidase, azoreductase, and nitroreductase (Rowland, 2009). Most common is azoxymethane (AOM) which is hydrolyzed into methylazoximethanol in liver and then conjugated to glucuronic acid before excretion into intestine where it is converted into a highly reactive methyl carbon ion by bacterial β-glucuronidase (Neufert *et al*., 2007). A report by Takada *et al*., 2008 suggested that inhibiting the activity of β-glucuronidase significantly reduces the tumor-inducing potential of AOM in rats.

Streptococcus bovis is the first bacterium linked with high prevalence of CRC due to its infection among the patients (Kuiper and Jong, 1990). Kuster and co workers in 2006, observed that *helicobacter pylori* is gram negative bacillus that has been found associated with colorectal cancer, while Arthur *et al.* (2012), found *E.coli* to be present in mucosa of tumor and normal tissue from patients having CRC. *Fusobacterium* is oral and gut residing gram negative bacteria, contributing to colorectal cancer development by invading colonic mucosa (Kostic *et al*., 2013). Other *sulfidogenic* bacteria such as *Desulfovibrio* and *Bilophila wadsworthia* have been known to cause CRC through the production of hydrogen sulfide, a toxic substance known to cause chromosomal instability in amalgamation with other mutations in DNA repair mechanism in carcinogenic process (Attene-Ramos *et al*., 2006). Zackular and co-workers 2014, discovered *porphyromanas, lachnospiraceae and enterobacteriacea* were the inhabitants of fecal matter in the patients with carcinoma rather than healthy subjects. Another common anaerobic bacteria is *Bacteroides fragilis* with enterotoxigenic strain (ETBF) cause diarrhoea in humans and effect the development of CRC by producing metalloprotease toxin (Sears *et al*., 2008).

Clostridium septicum, a gram positive anaerobic bacillus, present in GI tract is involved in causing myonecrosis leading to 79% mortality rate within 48 hours. Also, CRCs due to *C. septicum* are advanced malignancies that only present after significant tumor invasion, found in cecum, which is most acidic portion of large intestine with pH 5.7 rendering appropriate environment for *C. septicum* to grow (Forrester *et al*., 2016).

On the other hand, probiotic bacteria such as *Lactobacillus* and *Bifidobacterium* species shows their protective role against inflammatory bowel diseases by inactivation of microbial enzymes involved in procarcinogenic activation (Geier *et al*., 2006; Lightfoot *et al*., 2013). Lactic acid bacteria have also shown protective properties against CRC *via* different mechanisms that include strengthening the mucosal barrier and altering luminal secretions, resulting in underpinning of the host immune system (Nagpal *et al*., 2018). In 2009, Maslowski and co workers proposed the protective role of microbiota in intestine as the conversion of dietary fiber into short chain fatty acids (SCFA), such as acetate, propionate and butyrate, through microbial fermentation which are readily absorbed in colon and used as main source of energy. Further, SCFAs, encourage cell proliferation and differentiation in non-neoplastic normal colon, promote intestinal homeostasis, and the resolution of intestinal injury. *Faecalibacterium prausnitzii* and *Eubacterium rectal* are the main species producing butyrate, which is the major source of energy rendering cells with 5-15% of caloric requirement and aid in controlling proliferation, differentiation, and apoptosis in colon cells (Landi *et al*., 2011; Bishop *et al*., 2017).

Dietary habits:

Diet is the significant determinant of CRC, proposed 50 years ago, when a study was conducted on African population showed lower risk of colon cancer due to consumption of high fiber diet. The incidence of cancer escalates as the age progresses which may be the result of accumulation of structural and functional changes in cell organelles and DNA. However, the food related compounds may switch on or off the genes responsible for causing cancer and induces or protect the cellular DNA from being damaged. Many authors suggested that single nutrient is not sufficient instead combination of nutrients would be responsible for proliferation of cancer and their activity depends on the absence or presence of other compound (Tantamango *et al*., 2011; Pericleous *et al*., 2013).

Fats:

Fats are important in human diet as essential source of energy and having biological properties and health effects, however, some hypothesis suggested drawbacks of fat intake in developing colon cancer. High fat diet is rich in high caloric content which may promote cancer owing to development of overweight and obesity, directly linked to pro-tumorigenic environment, such as hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and chronic low-grade inflammation (Bruce *et al*., 2000). Existence of hyperinsulinemia/ hyperglycemia/hypertriglyceridemia and the increased secretion of interleukin-6, plasminogen activator inhibitor-1, adiponectin, leptin, tumor necrosis factor alpha, over secreation of ROS and C-reactive protein impacts the immune system function, operates in cellular cascades crucial for malignant cell transformation, promote rapid cellular multiplication and inhibit apoptosis of transformed cells leading to cancer development and progression (Brighteni *et al*., 2014; Kim *et al*., 2014).

Diet rich in fats often leads to elevated secretion of bile acid (deoxycholic acid, DOC) into GI tract, ultimately results in high concentration of bile acids in colon which is related to formation of ROS and nitrogen species (Berstein *et al*., 2011). A mouse model experiment showed that mice fed with higher levels of bile acid supplemented diet had colonic neoplasia and colon adenocarcinomas as compared to mice with standard diet (10 folds lower levels of bile acid). There were evidences which confirmed that ROS and nitrogen species cause damage to lipid and proteins in membrane, reduces the ability of DNA repair mechanism and alters the cell's antioxidant defense system, thus these events lead to initiation of carcinogenesis (Valavandis *et al*., 2012: Prasad *et al*., 2014).

There are two types of fatty acids- saturated fatty acids (SFAs) and unsaturated fatty acids (UFAs) and further unsaturated are of two types- monounsaturated (MUFAs, having one double bond) and poly unsaturated (PUFAs, having more than one double bond). Moreover, PUFAs are further differentiated into two categories-omega 3 fatty acids and omega 6 fatty acids, which regulate nervous system, blood pressure, brain function, immune regulation and inflammation processes (Calder *et al*., 2009; Patterson *et al*., 2012). Imbalance in omega 3 and omega 6 levels is directly related to pathological levels of C-reactive protein, interleukin-6, tumor necrosis factor-α and other factors identified with CRC carcinogenesis (Tyagi *et al*., 2012: Lachance *et al*., 2013). The protective effect of omega 3 was seen in the Polish-case-control study in which moderate intake of 1–2 serving of fish weekly significantly decreased the risk for CRC (Jedrychowsi *et al*., 2008) and omega 6, prevents the risk of microsatellite instability (MSI) and inactivation of anti-apoptotic genes, i.e. Bcl-2 family of genes (Song *et al*., 2015).

Dairy products:

The relationship between consumption of dairy products, red and white meat is still conflicting. Evidences showed that dairy products specially milk contains insulin like growth factor-1 (IGF-1) which increases resistance to insulin, encourage oxidative stress and inflammation, which ultimately results in development, proliferation and spread of cancer cells (Bartke, 2005). However, Kumari and her co-workers, 2016, hypothesized that ingredients present in dairy products such as calcium, vitamin D, linoleic acid give rise to probiotic bacteria that aid in reducing the risk of CRC. In an animal model, calcium has been found to be associated with decreased number of K-ras mutations in CRC (Llor *et al*., 1991). Another protective effect of calcium, it binds to bile and free fatty acids, resulting in drop in the toxic concentration of bile acids, therefore, limiting the exposure of colonic epithelial cells to these carcinogens and effects of bile acids in intestinal mucosa cells (Larsen *et al*., 2006). Hence, long term intake of calcium supplementation helps reducing the growth of tumors and also lessens the colonic content of harmful metabolites produced by microbiota (American Institute of Cancer Research, 2007).

Red and white meat:

Several surveys revealed that consumption of red meat is firmly associated with CRC while eating white meat (Fish) did not elevate the risk (English *et al*., 2004; Chao *et al*., 2005; Hu *et al*., 2008). In 2015, the World Health Organization (WHO) experts indicated the meat processing method is an important mediator of carcinogenesis in the colon. The risk of colon cancer is strongly and positively associated with the frequent eating of high temperature processed meat products, i.e. smoked, fried or grilled meat (Santarelli *et al*., 2008; Mehta et al., 2020). Nitrites and nitrates are used during processing of meat products to deter the bacterial growth and development of botulinum toxins

(Binkerd *et al*., 1975). Heterocyclic amines and polycyclic hydrocarbons are formed in processing of meat using high temperature methods (Diggs *et al*., 2011). These compounds are not carcinogenic in nature but are metabolized by a family of cytochrome P450 enzymes to genotoxic and carcinogenic substances which impact the colon mucosa in a negative way (Wogan *et al*., 2004). At high temperature, some additives are also released in to colon which perturbs the natural cellular environment and causes enhancement of cell proliferation (Kang *et al*., 2016). Studies suggested that incorporating sources of digestible protein such as fish, legumes, eggs and so on with red meat might reduce the risk for CRC (Maragoni *et al*., 2015; Joshi *et al*., 2015).

Other dietary products:

Higher intake of fiber such as green leafy vegetables, whole grains, beans and fruits are known to lowers the risk upto 50%. Also, vitamin rich diet including vitamin D, E, C, selenium, magnesium, potassium and sufficient amount of daily water have the potential to combat with the risk of CRC (Pietrzyk, 2017).

Moreover, salt play significant role in neural conduction, cardiac output, renal function and homeostasis (Dotsch *et al*., 2009), however, NaCl toxicity is related to gastric and rectal cancer (Murata *et al*., 2010). NaCl is associated with S-phase cell division, thus, higher concentration leads to 'molecular switch' turning permanently on, facilitating uncurbed cell division and progression of carcinogenesis (Omberg *et al*., 2009).

Relationship between gut microbiome and CRC:

Microbiota-mediated carcinogenesis is a complex process that takes place through changing host cell proliferation, affecting the immune system of host cell and metabolizing dietary factors (Cani and Jordan, 2018). The colon is the niche for approximately 1 million fold higher levels of microbiota as compared to small intestine (Proctor, 2011) and species like *Fusobacterium nucleatum, Bacteroides fragilis, Escherichia coli* and *Clostridium* are copious in CRC microflora and the host diet triggers these microbiota to be involved in development of CRC (Culpepper *et al*., 2014; Wirbel *et al*., 2019). Metabolization of saturated fatty acids and high glycemic index diet by gut microbiota generate noxious procarcinogenic products such as deoxycholic acid (DCA), lithocholic acid (LCA) and reactive oxygen species (ROS) which induce chronic inflammation and thus prone the cells to develop CRC (Yang *et al*., 2018).

Fusobacterium nucleatum is rarely present in healthy individuals, rather resides in patients with adenomas and adenocarcinomas and potentially leads to tumorigenesis by modulating the tumor immune environment (Kostic *et al*., 2013). *F. nucleatum* is competent to bind and invade colonic epithelium through FadA adhesion protein as the latter forms complex with E-cadherin and Annexin A1 which results in increased activation of β-catenin signaling and over expression of transcription factors, Wnt genes, oncogenes and inflammatory genes (Rubinstein *et al*., 2013). It also suppresses immune cell activity by binding to TIGIF and CEACAM1 inhibitory receptors (Gur *et al*., 2019). Enterotoxigenic strain (ETBF) of *B. fragilis* produces the toxin that binds and cleaves E-catenin, therefore, disturbing epithelial cell permeability and barrier function and it also triggers β-catenin nuclear localization, elevating the expression of c-Myc gene and cellular proliferation (Wu *et al*., 2003). Moreover, *B. fragilis* has also been identified as an activation factor for colitis and tumorigenesis by promoting an aberrant immune response through IL-8 and IL-17 production (Chung *et al*., 2018).

Another strain of gut microbiome such as *Enterococcus faecalis* was observed to induce COX-2 that give rise to pro-proliferative signals through prostaglandins E2 which leads to inhibition of apoptosis and increased cell prolefiration (PGE2) (Floch *et al*., 2016).

It is a well established fact that folate is the main source of SAM (S-adenosyl-methionine) which is required for DNA synthesis and it could be produced by probiotic bacteria, *Bifidobacterium* and *Lactobacillus* (Zhou *et al*., 2013). In a study, *Bifidobacterium* was administered voluntarily (four men and three women) and fecal matter showed high concentration of folate indicating bacteria were capable of generating folate, thus, affecting DNA methylation pattern (Pompei *et al*., 2007). This also specifies that folate deficiency adds to DNA hypomethylation which is an established phenomenon in occurrence of CRC (Wasson *et al*., 2006). A population-based study reported that *Fusobacterium nucleatum* was associated with genomic hypermutation independent of *CIMP* and *BRAF* mutations (Koi *et al*., 2018). Another study observed that *Fusobacterium* was correlated with the *CIMP* phenotype, wild-type *TP53, hMLH1* methylation,

genomic hypermutation, and *CHD7/8* mutation. Further, butyrate, a byproduct of fermentation of undigested carbohydrates and proteins carried out by *Firmicutes*, regulates 4000 genes entailing apoptosis and cell cycle regulation. They are also known to inhibit histone deacetylase and induce hyperacetylase of histones, changing expression of cell cycle regulatory genes such as *CCND3* and *CDKN1A* in intestinal cells (Inamura *et al*., 2018).

Conclusion

CRC is a heterogenic disease which involves numerous factors for progression of tumorigenesis such as aggregation of mutations and aberrations in oncogenes, tumour suppressor genes and other pathways which result in genomic instability. These events owe to environmental factors such as poor diet, lacking green leafy vegetables and fiber and consumption of animal products which yield metabolites that cause dysbiosis in microflora, resulting in modified methylation pattern and histone structure that eventually causes cancer. Although genetic and environmental factors have prominent role to play, however, gut microbiome also shares a significant part in causing CRC.

Numerous studies contribute towards the understanding of colorectal cancer at molecular level and new pathways have been identified, also link between diet and microbiome has been established. However, identification of bacteria that are robust to a specific population along with which microorganism in microflora is disease causing and which is protective could open the gateway towards potential involvement of microbiota in causing colorectal tumorigenesis. Further studies on understanding pathways are required which provide mandatory information to develop drugs through clinical trials. Moreover, the immediate need is to plan preventive strategies and utilization of biomarkers for early diagnosis of CRC and stratify the patients to the appropriate treatment. Comprehending cellular and molecular mechanism along with behavior pattern of gut microbiome may bestow with primary development of effective therapies.

Conflict of Interest: None

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