Gastrointestinal Cancer: Research & Therapy

Open Access

Austin Publishing Group

Review Article

Perspectives on the Aetiology and Pathogenesis of Colorectal Cancer

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Received: December 08, 2023
Accepted: January 18, 2024
Published: January 25, 2024

Abstract

Detailed awareness of the relative risks of the aetiologic factors (age, diet, gut microbiota, obesity, chronic inflammation, familial) and the mechanisms of effect and evidence for the pathogenesis of Colorectal Cancer (CRC) are important. The aim of this review was to discuss the aetiology and pathogenesis of colorectal cancer. Electronic searches of the Medline (PubMed) database, Cochrane library and Science citation index were performed to identify original published studies on the aetiology and pathogenesis of colorectal cancer. Relevant articles were searched from relevant chapters in specialized texts and all included. The underlying mechanisms in colorectal cancer carcinogenesis entails the understanding of the polygenic and single gene alterations in sporadic, Familial Adenomatous Polyposis (FAP) and familial microsatellite instability/ Mismatch Repair (MSI-high/ dMMR) tumours such as Lynch/ Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndromes. The understanding of the possible sequence of genetic changes through key mutations in the development of colorectal polyps and invasive cancer (adenoma-carcinoma sequence) is crucial. While a major role for diet in the aetiology of colorectal cancer is incontrovertible, the culprit dietary component has not yet been positively identified. There is the potential for colorectal cancer microbiota serving as biomarker for CRC. Although most colorectal cancers are sporadic, genetic factors make a significant contribution. The knowledge of specific genetic events which take place in colorectal carcinogenesis may well have implications for diagnosis, prognosis and ultimately for gene and personalised biological therapy. Future research will identify the best ways to regulate the gut microbiota in reducing the burden of CRC.

Keywords: Cancer; Colorectal; Aetiology; Adenoma- carcinoma sequence; Pathogenesis

Introduction

Colorectal Cancer (CRC) is the third most common cancer worldwide, the commonest gastrointestinal malignancy and the second commonest cause of cancer death. In 2020, more than 1.9 million new cases of colorectal cancers and more than 930,000 deaths were estimated to have occurred worldwide [1]. Large geographical variation in incidence and mortality rates were observed. The incidence rates were highest in Europe and Australia and New Zealand, and the mortality rates were highest in Eastern Europe. By 2040 the burden of colorectal cancer will increase to 3.2 million new cases per year (an increase of 63%) and 1.6 million deaths per year (an increase of 73%) [2]. Despite the steadily rising incidence of CRC, the overall 5- year survival rate is currently in the region of 50% and has improved over the last 30 years from 20% in 1971-75, presumably because of early diagnosis, adequate staging and effective multimodal treatment [2-6]. Although the diseases of colon and rectal cancer appear to be distinct, there are recognised difficulties in distinguishing them in mortality statistics. 76% of all colorectal cancer patients are diagnosed between 65 and 85 years old but affecting a younger age in the developing world with the adoption of the western diet and lifestyle [1,7]. The incidence of rectal cancer is higher in men, and that of colonic cancer is higher in women. Within the colon about 50% of cancers occur in the left side and 25% in the right. In 4-5% of cases there are synchronous lesions, and 2-3% has subsequent metachronous carcinoma. Rectum (37%) and sigmoid (27%) continue to be the major sites for carcinoma with an associated higher incidence of *p*53 gene mutation probably because of the longer time rendered for carcinogenesis [8]. The CRC usually begins with the non-cancerous proliferation of mucosal epithelial cells.

Citation: Patrick WE. Perspectives on the Aetiology and Pathogenesis of Colorectal Cancer. Gastrointest Cancer Res Ther. 2024; 7(1): 1036.

These growths known as polyps grow gradually for 10-20 years before becoming cancerous (adenoma- carcinoma sequence) [9]. Only about 10% of all adenomas progress to invasive cancer, although the risk increases as the polyp grows larger. Invasive cancer arising from such polyps are adenocarcinomas and accounts for 96% of all CRCs. Almost 75% fall into a moderately differentiated (Broder's grade 2 or 3) histologic category while poorly differentiated (Broder's grade 4) represent a 5 % minority [10]. Sporadic colorectal cancer accounts for nearly 70% of the cases. Only 5% are related to hereditary conditions such as the Lynch syndrome or Familial Adenomatous Polyposis (FAP) characterised by DNA mismatch repair genes and microsatellite instability, and 20-30% of the cases have a familial disposition with no associated or known germline mutation [11]. This is corroborated by the fact that chromosomal instability which is characteristic of the sporadic cancers can be observed in about 70% of CRC cases [12]. Mutation in the Adenomatous Polyposis Coli (APC) gene instigates progression to carcinoma according to the classical adenoma to carcinoma model via chromosomal instability [13]. The serrated polyp pathway represents an alternative pathway to the evolution of CRC, and phenotypically present as heterogenous outgrowths such as hyperplastic polyps, sessile serrated adenomas or mixed hyperplastic polyps/ serrated adenoma [14]. BRAF mutations are the most frequent initial insult compounded by epigenetic CpG island methylator phenotype. Dysbiosis in gut microbiome, especially overgrowth of *Fusobacterium nucleatum* has been implicated in progression of serrated polyp to adenocarcinoma [15,16]. In the high risk group, the contribution of inheritance (genotype) is overwhelming, though environmental influences may modify disease severity (phenotype). It is this minority (accounting for < 5% of large bowel cancer) with the mostly dominant inheritance of a single gene that is traditionally described as being at risk of 'inherited bowel cancer'. In the low and moderate risk groups, genotype may still contribute to risk but less markedly, and thought to play a part in about 30% of colorectal cancers [17]. This may be due to low penetrance genes that influence dietary carcinogen metabolism. The risk for carcinoma of the colon in the general population has been defined as average risk with the lifetime risk of colorectal cancer in the UK being about 5% [9]. Knowledge of molecular genetics in this commoner sporadic colorectal cancer group has increased rapidly in recent years, but the stimuli which lead to these carcinogenic changes are still obscure. The fact that only 10-15% of CRC cases are hereditary underlines an important role of the environment as a factor that genetically and epigenetically influences the development of CRC. The elucidation of the influence of geography, race, sex, and diet on the composition of the microbiome on the pathogenesis of CRC is also important [18-20].

Discussion

Aetiology

Environment and nutrition: The epidemiology of colorectal cancer would suggest that colorectal cancer is primarily an environmental disease. Colorectal cancer is a major medical problem for Western developed countries. There are substantially lower rates observed in Eastern Europe and lowest rates in developing countries. Migrants from countries where the risk of large bowel cancer is low to countries where such risk is high acquire the high risk of the host country in their lifetime. Such phenomena were observed in Japanese migrants to Hawaii and Polish migrants to Australia [20]. The rising incidence of colorectal cancer with the aggressive K-ras mutations in the developing world is due to the adoption of the western diet and life-style [3]. Fat, animal protein and total caloric consumption as well as dietary fibre and micronutrients such as vitamins and minerals are all suspected of having potential roles. This can be either protective as in the case of dietary fibre or conducive which appears to be the effect of high fat, high total calories and perhaps high meat consumption. The epidemiological association between high fibre diet and decreased incidence of colorectal cancer was first pointed out by Burkitt. [21]. The mechanism for the protection against colon carcinogenesis is for the insoluble and therefore poorly fermentable fibres such as cellulose, lignin or wheat bran which by increasing bulk may reduce carcinogen concentration and speeds transit. They may also exert a protective effect by the adsorption of co-carcinogens and promoting agents. Viscous fibres such as pectin, guar, oat bran, corn bran, agar and carrageenan are subject to extensive fermentation producing short chain fatty acids that can stimulate mucosal proliferation and enhance colon carcinogenesis [22]. While beef consumption over the last five decades has more than doubled, the incidence of colon cancer over the same time period has remained stable [23]. It is difficult especially in epidemiological studies to separate the effects of highly inter-correlated factors such as dietary fat, animal protein and total calories. Some experts put forward the view that total caloric consumption rather than fat intake is the more significant determinant of increased colon cancer risk [24]. A potential protective role for vitamin D (and calcium) has been suggested [25]. Although the metabolic activities of the micro-flora are greatly influenced by dietary factors it has little effect on the actual composition of the flora. However, there is growing evidence that the gut microbiota plays a major role in the pathogenesis of CRC and its progression via modulation of the anti-cancer immune response [26].

The Role of the Gut Microbiota

Microbiome modulation is one of the most prospective new strategies in medicine. The gut microbiota influences colorectal carcinogenesis through a variety of mechanisms- inflammation, regulation of immune response and modified metabolism of dietary components which can also lead to the production of harmful microbial-derived products such as metabolites or genotoxins. Gut microbiome cause initial inflammation and modulation of different signalling pathways in the carcinogenesis. During the development of cancer, a complex interaction is established among the gut microbiome, tumour microbiome and immune system. The CRC microbiota has a different composition of strains of bacteria - *bacteroides fragilis, streptococcus gallolyticus, enterococcus gallolyticus, enterococcus faecalis, E coli, fusobacterium nucleatum, peptostreptococcus* than a healthy gut microbiome. Thus, CRC biomarkers may serve as important information for screening, early detection and prediction of the treatment outcome of CRC [27]. Gut microbiota of older people differs from that of younger adults which may influence the development of age-related disease by modulating metabolic and inflammatory processes [28]. CRC- associated microbiota also contributes to oncogenic epigenic signatures such as stress [22]. In recent years, the rise of CRC in those under 50 years known as early-onset CRC is known to be epidemiologically, pathologically, anatomically and biologically different from late-onset CRC. It is anatomically more frequent in the left colon and rectum, family and hereditary conditions are a factor in 30%, 60% are microsatellite and chromosome stable. There is a higher percentage of Kras and Tumour Protein p53 (TP53) mutations, LINE-1 hypomethylation, a lower % of BRAF and APC mutations. The metabolic difference which entails a higher BMI

and obesity caused by exposure to carcinogenic factors early in life with interaction of the gut microbiome and inflammation plus external factors such as low quality food, additive laden-food may cause dysbiosis and inflammation [8,29]. This may plausibly explain the use of the anti-inflammatory effect of low-dose aspirin in preventing CRC in younger adults (50-59 years) [30]. Certain microbiota mediate the effects of a certain diet on CRC risk by generating butyrate, folate and biotin which play a key role in the regulation of epithelial proliferation. Bile acids have been studied extensively as candidate carcinogens because of their structural similarity to the carcinogenic polycyclic aromatic hydrocarbons. High fat diets are associated with increased concentration of faecal bile acids and have been shown to act as colon tumour promoters but do not have the properties of genotoxic carcinogens [25,31]. In the experimental animal, bile acids in solution, and fatty acids can induce mucosal injury and mucosal proliferation that can be inhibited by calcium [32]. An analysis of molecular alterations in left- and right- sided colorectal carcinomas demonstrated that the specific type of *CpG* island in the human genome involved in epigenicity was incrementally methylated during tumour development in the right-sided colon, and may play a major role in the progression of right- sided colon cancers [33]. The fact that aging is associated with alterations in DNA methylation, which may affect susceptibility to cancer, may explain why CRC is commonly in the right side of the colon among older adults [34,35]. In 2007, the World Cancer Research Fund (WCRF) systematic review of the world literature showed evidence for decreased risk of colon cancer from physical exercise, dietary fibre, calcium, garlic, non-starchy vegetables and pulses. Evidence for increased risk was uncovered for obesity, red meat, processed meat, alcohol, animal fat and sugar. Being overweight and underactive stood out as major risk factors. Long-term smoking is associated with a relative risks of between 1.5 and 3.0 [36,37].

Carcinoma in High Risk Groups

Such groups include patients with a previous personal history of colorectal carcinoma and adenoma, Familial Adenomatous Polyposis Coli (FAPC), Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer (HNPCC)), and patients with chronic inflammatory bowel disease [4,38]. These groups have a relatively higher life-time risk in excess of 50% of developing bowel cancer. Studies involving these high risk groups offer important clues to the pathogenesis of colon cancer. In addition, individuals with inherited colorectal cancer syndromes are at risk of a range of extra-intestinal manifestations, including thyroid, soft tissue (e.g. desmoid), and brain tumours, which need specialised follow-up [39]. Cancer arising in chronic inflammatory bowel disease, both ulcerative colitis and Crohn's disease has many unique characteristics. The occurrence of malignant transformation in long-standing ulcerative colitis has been known for years until 1967 that dysplasia was recognised as a histopathological marker for impending or actual malignancy. Infact, ulcerative colitis should always be considered when large bowel cancer presents at an early age. The incidence of cancer depends on the duration of the disease. After 10 years of colitis the incidence of colorectal cancer increases by 1% per year. Colonoscopic surveillance relies on the identification of flat dysplasia or a Dysplasia-Associated Lesion or Mass (DALM). The presence of low- grade dysplasia is as likely as high-grade dysplasia (54% vs 67%) to be associated with an already established cancer [40]. With extensive Crohn's colitis an 8 % risk of developing colon cancer at 22 years after disease onset is similar to the cancer risk with ulcerative colitis. There is 5% risk of dysplasia in the colonic mucosa [41,42], and associated colonic strictures should always be regarded as malignant until proven otherwise [43]. Previous gastric surgery has also been implicated, and although the association is controversial, the risk may be about two-fold. Altered bile acid metabolism may play a role in this process, both after gastrectomy and after vagotomy [44]. Microbial alterations reported after Roux-en-Y gastric bypass are similar to those observed in patients with colorectal cancer. Higher serum concentrations of bile acids and lower levels of butyrate following bariatric surgery could contribute to an increased risk of CRC [45]. However, a recent meta-analysis showed that with a longer follow-up patients who underwent bariatric surgery using sleeve gastrectomy had a 37% reduction in the risk of developing colorectal cancer compared with patients with obesity who had no surgery [46]. The risk after ureterosigmoidostomy is well established, although this operation has been largely superseded by the use of an isolated ileal conduit for urinary diversion [47].

Inheritance (Genetic factors)

The genetic changes associated with colorectal cancer and the molecular background to inherited colorectal cancer has been widely studied. *Lynch syndrome* (Hereditary Non- Polyposis Colorectal Cancer (HNPCC) is inherited in an autosomal dominant fashion and responsible for about 2% of colorectal cancers. HNPCC kindreds are usually defined as those in which at least three relatives (one of whom is a first degree relative of the other two) in two generations are affected, with at least one diagnosed at less than 50 years of age [48]. It is the commonest of the inherited bowel cancer syndromes and is distinguished from the polyposis syndromes by the absence of the large numbers of colorectal adenomas found in FAP. However, scanty adenomatous polyps are a feature of Lynch syndrome. Lynch syndrome is due to germline mutations of Mismatch Repair (MMR) genes, whose role is to correct errors in base-pair matching during replication of DNA or to initiate apoptosis when DNA damage is beyond repair. The MMR genes are tumour-suppressor genes and defective MMR results in the accumulation of mutations in a host of other genes, leading to tumour formation. A hallmark of tumours with defective MMR is Microsatellite Instability (MSI) where a short DNA sequence of up to 5 nucleotides is repeated. There is early onset of colorectal tumours (average age of 45 years), predilection for proximal colon, frequently multiple, mucinous, poorly differentiated and of 'signet-ring 'appearance with marked lymphocytic infiltration. However, the prognosis is better than same tumours arising sporadically with a better response to adjuvant chemotherapy. Less common than Lynch syndrome is *Familial Adenomatous Polyposis Coli* (FAPC) inherited through an autosomal dominant gene with incomplete penetrance. The offspring of affected individuals have a 1 in 2 chance of inheriting FAP. It is due to mutation of the tumour suppressor Adenomatous Polyposis Coli (*APC*) gene on chromosome 5q, but it is responsible for only 1% of colorectal carcinomas. About 25% of cases are due to new mutations and such patients do not give a family history. The disease develops in early adult life (second or third decade) characterized primarily by hundreds of colorectal adenomatous polyps and inevitably (100% risk) undergoes malignant transformation about 10 years after onset [49]. The extracolonic manifestations including multiple osteomas, epidermoid cysts, fibrous tumours and periampullary tumours in the duodenum are most prominent in *Gardner's syndrome*, which is now considered as a phenotypic variant of FAP. The genetic condition to the development has been shown within band 5q21 associated with the APC gene.

Gardner syndrome patients suffer from the aberration of this gene which leads to uncontrolled cell growth, and in addition there is a loss of DNA methylation, a mutation of the RAS gene on chromosome 12, a Deletion of the Colon Cancer gene (DCC) on chromosome 18, mutation of the of TP53 gene located on chromosome 17 [50]. Recent study of patients with the phenotype of FAP but no identifiable *APC* mutation has led to the discovery of *MYH-Associated Polyposis* (MAP) which has considerable clinical overlap with FAP but is genetically distinct. This condition is due to biallelic mutation of the MutY Human homologue (MYH) gene on chromosome 1p. The frequency of mutation carriage (heterozygosity) in the general population may be as high as 1 in 200 but individuals who are heterozygotes have minimally increased risk of colorectal cancer. Its autosomal recessive inheritance means that there will often be no family history of colorectal cancer or polyps [51]. *Peutz-Jeghers syndrome* is an autosomal dominant condition characterised by mucocutaneous pigmentation together with multiple gastrointestinal harmatomatous polyps. The gene responsible in some patients is STK11 (LKB!) on chromosome 19p13, although there is evidence of genetic heterogeneity as mutation at this site has been excluded in some families. Individuals with Peutz-Jeghers syndrome are at increased risk of particularly gastrointestinal malignancy, with a lifetime risk of colorectal cancer of about 20% and of gastric cancer of about 5%. Other areas of increased risk include the breasts (female), ovaries, cervix, pancreas and testes [52]. *Juvenile polyposis* is an autosomal dominant condition where multiple characteristic harmatomatous juvenile polyps occur mostly in the colon, but also in the upper gastrointestinal tract and small bowel, and associated with microcephaly and congenital heart disease. Some affected individuals have germline mutations in the SMAD4 gene or BMPR1A gene with a risk of gastrointestinal cancer in excess of 50% [53]. The PTEN gene on chromosome 10q22 is associated with *Cowden disease* which consists of gastrointestinal harmatomas and cancers [54]. *Multiple hyperplastic polyps* that have adenomatous features (mixed polyposis syndromes) are associated with a high risk for colorectal cancers [55]. A variant mutation of the APC gene on chromosome 5 q (E1317Q) particularly with the consanguineous marriages in the Ashkenazi Jewish population has been associated with an increased risk of colorectal cancer without any of the syndromes described above [56].

Pathogenesis

Oncogenes

Progress in the understanding of the molecular genetics of tumour development has emerged from the discovery of proto-oncogenes. These are a group of genes , widely conserved in nature (from yeasts to man), which encode growth factors, growth factors receptors, DNA binding and regulatory proteins, and the transmembrane signal transducing proteins mwhich participate in normal cell growth and differentiation [57]. There is good evidence that proto-oncogenes, when altered are .involved in the pathogenesis of human and animal cancers. The concept originated from the recognition that the proto-oncogenes are homologues of the transforming genes of RNA tumour viruses . About 30 retroviruses with oncogenic sequences have been identified [58]. Proto-oncogenes can exist in mutated or activated forms in non-virus infected cells which have been transformed by chemicals or isolated from human tumours. Several mechanisms of oncogene activation include gene amplification, gene rearrangement, translocation and point mutation and examples have been found in human tumours [59,60]. Amplifications of oncogenes, c-myc and c-erb-2 have recently been reported to occur at low frequencies in colon cancers [56], but alterations of the ras proto-oncogenes may have the most relevance for colon cancer [61,62]. Continued rapid progress in this field will yield a more complete understanding of these pathogenic mechanisms and elucidate alternative molecular pathways of colon cancer progression. Vogelstein and colleagues proposed this development of carcinogenesis leading eventually to an invasive malignancy as an adenoma- carcinoma sequence [63]. The APC gene truncation is usually the inciting event, followed by KRAS and TP53 mutations later in the sequence. The three major pathways involved are the Chromosomal Instability (CIN) pathway, the Microsatellite Instability (MSI) pathway and the CpG Island Methylator Phenotype (CIMP) hypermethylation. At a molecular level, the adenoma-carcinoma sequence pathway is enriched with KRAS mutations and somatic copy number alterations via CIN whereas BRAF mutations followed by gene promoter hypermethylation drive the serrated polyp pathway [64]. It is important to note that a subgroup of sporadic colorectal tumours is typified by microsatellite instability and V600 mutant BRAF . The pathogenic hallmark is the epigenetic silencing of mismatch repair proteins mediated via CpG sequence hypermethylation [65]. About 5% of metastatic CRC have HER2 transmembrane glycoprotein receptor with inherent tyrosine kinase functionality controlling epithelial cell growth [66]. HER-2 is emerging as a therapeutic target with transtuzumab- lapatinib and trastuzumab- pertuzumab combination therapies in early clinical trials [67].

Adenoma Formation

The genetic events in sporadic colorectal cancer are quite well understood. Mutations of the tumour suppressor Adenomatous Polyposis Coli (APC) gene which is central to ordered cell motility (differentiation, cellular migration, cell-cell adhesion, cytoskeletal integrity, genomic stability [68] are thought to occur early as they are found in 60% of all adenomas and 80-90% of carcinomas [69]. With the development of adenomas the proliferative compartment of the mucosa of the normal colon which is confined to the lower part of the crypt moves to the surface where it progressively expands to give rise to a polyp [70]. Germline mutations in one allele followed by loss of heterozygosity in the APC gene is the fundamental mechanism in FAP and the abnormalities of this type in histologically normal mucosa have been found in individuals with FAP [71]. Cell proliferation in the mucosa can be affected by bowel luminal factors such as deoxycholic acid, and fatty acids. There is evidence of monoclonality in both sporadic adenomas and adenomas from FAP patients. The national polyp study (US) [72] found a strong correlation between the extent of villous component and adenoma size. This favours the interpretation that as adenoma increase in size they progressively adopt a more villous growth pattern. Multiple factors including cell proliferation rate and interaction with stromal components are likely to be shown to account for the spectrum of growth patterns encountered. Alterations of the ras proto-oncogenes is relevant for colon cancer. Ras genes encode a plasma membrane-bound protein (p21) that tightly binds guanine nucleotides and exhibits weak GTP-ase activity, properties commensurate with its presumed role in growth signal transduction across the cell membrane [73]. Each mammalian cell contains 3 functional ras genes: c-Ha-ras, c-Ki-ras, c-N-ras. Gene point mutations predominantly in c-Ki-ras and at condon 12 of the gene in 40% of colon cancers induce cell growth by activating growth factor signal transduction, similarly occur in both adenomas and carcinomas [60].

However, as they are more common in large adenomas than in small adenomas they are thought to represent a later event that precedes the development of invasive malignancy [74]. In addition, in many of the cancers revealing a ras mutation, the same mutation was found in adjacent residual benign adenoma which indicate that a c-ki-ras gene mutation is an early event that precedes the development of invasive malignancy (i.e. breaching the basal membrane). Further support for this view comes from the observed trend toward higher prevalence of ras gene mutation in adenomas with high grade dysplasia. Dysplasia in adenomas is classified according to the degree of cytologic atypia and architectural abnormality, but the natural history of significant dysplasia is not known from prospective observation in the colon. It is possible that some lesions regress or do not progress to invasion. However, in most it represents an intermediate stage in the evolution to invasive carcinoma [75,76]. Polyp size and extent of villous growth are determinants of risk for malignancy in colorectal adenomas [77]. Mutations of the TP53 gene is common in invasive colonic cancers but rare in adenomas and is therefore deemed to be a late event which accompanies the development of invasion [78,79]. The exception is colitis associated carcinoma where loss of TP53 is an earlier step in the pathogenesis [80]. The P53 protein has roles in the repair of DNA and the induction of programmed cell death. Kras and P53 very rarely occurs in the same tumour suggesting alternative pathways to carcinogenesis [33,81-83]. Kras mutations are not only associated with advanced stage at presentation, but also with poor prognosis in node negative disease [79,82]. Most adenomas are asymptomatic and more than 10% of the population over 45 years might have asymptomatic adenomas [6,84]. Symptoms may be bleeding, or prolapse of the polyp via the anus, or, rarely, intussusception. Diarrhoea, or discharge of mucus occurs in patients with multiple polyps or, typically in those with villous adenoma. Extreme potassium loss from a villous adenoma may result in hypokalaemia, but this is rare.

The Evidence for the Adenoma-Carcinoma Sequence

Although it is not known whether all carcinomas begin life as an adenoma, It is now widely accepted that the majority of colon cancers arise from pre-existing adenomatous polyps [9,63]. Both adenomas and carcinomas have a similar anatomical distribution in the large bowel. Patients with known carcinoma who also have polyps in their bowel are more likely to develop a subsequent carcinoma than those without polyps. The prevalence of adenomas correlates well with that of carcinomas, the average age of adenoma patients being around 5 years younger than patients with carcinomas.

Adenomatous tissue often accompanies cancer, and histologically, it is unusual to find small cancers with no contiguous adenomatous tissue. Adenomas are found in up to one-third of all surgical specimens resected for colorectal cancer Sporadic adenomas are identical histologically to the adenomas of Familial Adenomatous Polyposis (FAP), and this condition is unequivocally premalignant. Large and villous adenomas are more likely to display cellular atypia and genetic abnormalities than small lesions.

The incidence of colorectal cancer has been shown to fall with a long-term screening programme involving colonoscopy and polypectomy [9,82]. It should be recognized that although the majority of adenomas diagnosed in the West are polypoid or exophytic, the flat adenoma, defined as an adenoma where the depth of the dysplastic tissue is no more than twice that of the mucosa is now a recognised entity. There is good evidence that these lesions are pre-malignant and may have a greater tendency towards malignant transformation than polypoid adenomas. The prognosis is variable but a combination of high degree of CIMP (CIMP-H), Microsatellite Stability (MSS) and BRAF mutation carries the worse prognosis [83,85]. They are difficult to find but may account for up to 40% of all adenomas [10]. Thus, reliable diagnosis requires a skillful, experienced colonoscopist and the use of dye sprayed on to the colonic mucosa to highlight the contours of the abnormal tissue. This is also corroborated by the fact that left and right sided tumours also differs in terms of morphology and histology. LCRC are usually polypoid in appearance allowing for easy detection whereas RCRC appear as sessile serrated mucinous adenocarcinomas making them diagnosed at an advanced stage. KRAS mutation has been implicated in causing exophytic tumour growth and absence of mutant KRAS in RCRC can explain the flat morphology of these tumours [86]. Although epidemiologically, younger individuals and males are more likely to have LCRC whereas RCRC occurs predominantly in the elderly and females, LCRC still remains the most commonly diagnosed cancer site (70%) across all age groups [87] and a meta-analysis showed RCRC had poorer outcomes [88].

Conclusions

Although most colorectal cancers are sporadic, the most common pathway in the pathogenesis is the adenoma- carcinoma genetic model. This is initiated by the APC mutation, propagated by chromosomal instability causing stepwise accretion of molecular and epigenetic changes. HNPCC and FAP are the main autosomal dominant genetic syndromes involved and account for less than 5% of all colorectal cancer. It, however, corroborates the adenoma-carcinoma sequence as the pathogenic mechanism in the natural history of colorectal cancer. The Knowledge of specific genetic events which take place in colorectal carcinogenesis may well have implications for diagnosis, prognosis and ultimately for gene and personalised biological therapy. The major role for diet in the aetiology of colorectal cancer appears incontrovertible, but the culprit dietary components have not yet been positively identified. Although the colorectal cancer microbiota may serve as biomarker for CRC, future research will identify the best ways to regulate the gut microbiota with substantial short- and long-term benefits in reducing the burden of CRC.

Author Statements

Author Contributions

EPW was the sole author

Funding

This research received no external funding

Conflicts of Interest

The author declares no conflict of interest

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71: 209-49.

2. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival and risk factors. Prz Gastroenterol. 2019; 14: 89-103.

3. Hayne D, Brown RS, McCormark M, Quinn MJ, Payne HA, Babb P. Current trends in colorectal cancer: site, incidence, mortality and survival in England and Wales. Clin Oncol (R Coll Radiol). 2001; 13: 448-52.

4. Royal college of Surgeons. National Bowel cancer Audit report. Available from: http://www.hscic.gov.uk/bowel. Improved bowel cancer survival. 2015.

5. Dulskas A, Gaizauskas V, Kildusiene I, Samalavicius NE, Smailyte G. Improvement of survival over time for colorectal cancer patients: a population-based study. J Clin Med. 2020; 9: 4038.

6. Rosenberg R, Friederichs J, Schuster T, Gertler R, Maak M, Becker K, et al. Prognosis of patients with colorectal cancer is associated with lymph node ratio: a single centre analysis of 3,026 patients over a 25-year time period. Ann Surg. 2008; 248: 968-78.

7. Gullickson C, Goodman M, Joko-Fru YW, Gnangnon FHR, N'Da G, Woldegeorgis MA, et al. Colorectal cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: a population-based registry study. Int J Cancer. 2021; 149: 1553-63.

8. Pitchumoni CS, Broder A. Chapt 2. Epidemiology of colorectal cancer. In: Colorectal neoplasia and the colorectal microbiome. 2020; 5-33.

9. Leslie A, Carey FA, Pratt NR, Steele RJC. The colorectal adenoma-carcinoma sequence. Br J Surg. 2002; 89: 845-60.

10. Stewart SL, Wike JM, Kato I, Lewis DR, Michaud F. A population-based study of colorectal cancer histology in the United States, 1998-2001. Cancer. 2006; 107: 1128-41.

11. Kastrinos F, Syngal S. Inherited colorectal cancer syndromes. Cancer J. 2011; 17: 405-15.

12. Walther A, Johnstone E, Swanton C, Midgley R, Tomlinson I, Kerr D. Genetic prognostic and predictive markers in colorectal cancer. Nat Rev Cancer. 2009; 9: 489-99.

13. Ogino S, Goel A. Molecular classification and correlates in colorectal cancer. J Mol Diagn. 2008; 10: 13-27.

14. De Palma FDE, D'Argenio V, Pol J, Kroemer G, Maiuri M, Salvatore F. the molecular hallmarks of the serrated pathway in colorectal cancer. Cancers. 2019; 11.

15. Ito M, Kanno S, Nosho K, Sukawa Y, Mitsuhashi K, Kurihara H, et al. Association of Fusobacterium nucleatum with clinical and molecular features in colorectal serrated pathway. Int J Cancer. 2015; 137: 1258-68.

16. Park CH, Han DS, Oh YH, Lee AR, Lee YR, Eun CS. Role of Fusobacteria in the serrated pathway of colorectal carcinogenesis. Sci Rep. 2016; 6: 25271.

17. Hayne D, Brown RS, McCormark M, Quinn MJ, Payne HA, Babb P. Current trends in colorectal cancer: site, incidence, mortality and survival in England and Wales. Clin Oncol (R Coll Radiol). 2001; 13: 448-52.

18. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer: analyses of cohorts of twins from Sweden, Denmark and Finland. N Engl J Med. 2000; 343: 78-85.

19. Rebersek M. Gut microbiome and its role in colorectal cancer BMC Cancer. 2021; 21: 1325.

20. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries with special reference to dietary practices. Int J Cancer. 1975; 15: 617-31.

21. Burkitt DP. Epidemiology of cancer of the colon and rectum. Cancer. 1971; 28: 3-13.

22. Bauer HG, Asp NG, Oste R, Dahlqvist A, Fredlund PE. Effect of dietary fibre on the induction of colorectal tumours and rectal-glucuronidase activity in the rat. Cancer Res. 1979; 39: 3752-6.

23. Graham S, Dayal H, Swanson M, Mittelman A, Wilkinson G. Diet in the epidemiology of cancer of the colon and rectum. J Natl Cancer Inst. 1978; 61: 709-14.

24. Kritchevsky D, Weber MM, Buck CL, Klurfeld DM. Calories, fat and cancer. Lipids. 1986; 21: 272-4.

25. Veettil SK, Wong TY, Loo YS, Playdon MC, Lai NM, Giovannucci EL, et al. Role of diet in colorectal cancer incidence: Umbrella Review of Meta-analyses of Prospective Observational Studies. JAMA Netw Open. 2021; 4: e2037341.

26. Kim J, Lee HK. Potential role of the gut microbiome in colorectal cancer progression. Front Immunol. 2021; 12: 807648.

27. Hofseth LJ, Hebert JR, Chanda A, Chen H, Love BL, Pena MM, et al. Early-onset colorectal cancer: initial clues and current views. Nat Rev Gastroenterol Hepatol. 2020; 17: 352-64.

28. O'Toole PW, Jeffery IB. Gut microbiota and aging. Science. 2015; 350: 1214-5.

29. Wong SH, Yu JK. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nat Rev Gastroenterol Hepatol. 2019; 16: 690-704.

30. Dehmer SP, Maciosek MV, Flottemesch TJ, LaFrance AB, Whitlock EP. Aspirin for the primary prevention of cardiovascular disease and Colorectal cancer: A Decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2016; 164: 777-86.

31. Reddy BS. Nutritional aspects of colon cancer. Prog Food Nutr Sci. 1985; 9: 257-82.

32. Wargovich MJ, Eng VWS, Newmark HL. Calcium inhibits the damaging and compensatory proliferative effects of fatty acids on mouse colonic epithelium. Cancer Lett. 1984; 23: 253-8.

33. Sugai T, Habano W, Jiao YF, Tsukahara M, Takeda Y, Otsuka K, et al. Analysis of molecular alterations in left- and right- sided colorectal carcinomas reveals distinct pathways of carcinogenesis. J Mol Diagn. 2006; 8: 193-201.

34. Jess P, Hansen IO, Gamborg M, Jess T, Danish Colorectal Cancer Group. A nationwide Danish cohort study challenging the categorisation into right-sided and left-sided colon cancer. BMJ Open. 2013; 3: e002608.

35. Pérez RF, Tejedor JR, Bayón GF, Fernández AF, Fraga MF. Distinct chromatin signatures of DNA hypomethylation in aging and cancer. Aging Cell. 2018; 17: e12744.

36. World Cancer Research Fund. Food, nutrition, physical activity and the prevention of cancer; a global perspective. Washington, DC: Association for International Cancer Research. 2007.

37. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2001; 10: 725-31.

38. Hull MA, Rees CJ, Sharp L, Koo S. A risk- stratified approach to colorectal cancer prevention and diagnosis. Nat Rev Gastroenterol Hepatol. 2020; 17: 773-80.

39. Waller A, Findeis S, Lee MJ. Familial adenomatous polyposis. J Pediatr Genet. 2016; 05: 78-83.

40. Thomas T, Abrams KA, Robinson RJ, Mayberry JF. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. Aliment Pharmacol Ther. 2007; 25: 657-68.

41. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. Gut. 1994; 35: 1590-2.

42. Maykel JA, Hagerman G, Mellgren AF, Li SY, Alavi K, Baxter NN, et al. Crohn's colitis: the incidence of dysplasia and adenocarcinoma in surgical patients. Dis Colon Rectum. 2006; 49: 950-7.

43. Sigel JE, Petras RE, Lashner BA, Fazio VW, Goldblum JR. Intestinal adenocarcinoma in Crohn's disease: a report of 30 cases with a focus on coexisting dysplasia. Am J Surg Pathol. 1999; 23: 651-5.

44. Caygill CPJ, Hill MJ, Hall CN, Kirkham JS, Northfield TC. Increased risk of cancer at multiple sites after gastric surgery for peptic ulcer. Gut. 1987; 28: 924-8.

45. D'Amato S, Sofia M, Agosta M, Litrico G, Sarvà I, La Greca G, et al. The impact of bariatric surgery on colorectal cancer risk. Surg Obes Relat Dis. 2023; 19: 144-57.

46. Janik MR, Clapp B, Sroczyński P, Ghanem O. The effect of bariatric surgery on reducing the risk of colorectal cancer: a meta-analysis of 3,233,044 patients. Surg Obes Relat Dis. 2023; 19: 328-34-3234.

47. Leadbetter GW Jr, Zickerman P, Pierce E. Uretersigmoidostomy and carcinoma of the colon. J Urol. 1979; 121: 732-5.

48. Peltomäki P, Nyström M, Mecklin JP, Seppälä TT. Lynch syndrome Genetics and clinical implications. Gastroenterology. 2023; 164: 783-99.

49. Waller A, Findeis S, Lee MJ. Familial adenomatous polyposis. J Pediatr Genet. 2016; 5: 78-83.

50. Gardner EJ. A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. Am J Hum Genet. 1951; 3: 167-76.

51. Morak M, Laner A, Bacher U, Keiling C, Holinski-Feder E. MUTYH-associated polyposis- variability of the clinical phenotype in patients with biallelic and monoallelic MUTYH mutations and report on novel mutations. Clin Genet. 2010; 78: 353-63.

52. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010; 59: 975-86.

53. MacFarland SP, Ebrahimzadeh JE, Zelley K, Begum L, Bass LM, Brand RE, et al. Phenotypic differences in juvenile polyposis syndrome with or without a disease-causing SMAD4/BMPR1A Variant. Cancer Prev Res (Phila). 2021; 14: 215-22.

54. Magaña M, Landeta-Sa AP, López-Flores Y. Cowden disease: a review. Am J Dermatopathol. 2022; 44: 705-17.

55. Wynter CVA, Walsh MD, Higuchi T, Leggett BA, Young J, Jass JR. Methylation patterns define two types of hyperplastic polyp associated with colorectal cancer. Gut. 2004; 53: 573-80.

56. Locker GY, Lynch HT. Genetic factors and colorectal cancer in Ashkenazi Jews. Fam Cancer. 2004; 3: 215-21.

57. Todd R, Wong DT. Oncogenes. Anticancer Res. 1999; 19: 4729-46.

58. Bishop JM. Enemies Within: the genesis of retrovirus oncogenes. Cell. 1981; 23: 5-6.

59. Weinberg RA. The action of oncogenes in the cytoplasm and nucleus. Science. 1985; 230: 770-6.

60. Guest BA. Editorial. Transforming ras oncogenes and multistage carcinogenesis. Br J Cancer. 1985; 5: 1-7.

61. Bos JL, Fearon ER, Hamilton SR, Verlaan-de Vries M, van Boom JH, van der Eb AJ, et al. Prevalence of ras gene mutations in human colorectal cancers. Nature. 1987; 327: 293-7.

62. Meltzer SJ, Ahnen DJ, Battifora H, Yokota J, Cline MJ. Proto-oncogene abnormalities in colon cancers and adenomatous polyps. Gastroenterology. 1987; 92: 1174-80.

63. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; 61: 759-67.

64. Kasi A, Handa S, Bhatti S, Umar S, Bansal A, Sun W. Molecular pathogenesis and classification of colorectal carcinoma. Curr Colorectal Cancer Rep. 2020; 16: 97-106.

65. Jones JC, Renfro LA, Al-Shamsi HO, Schrock AB, Rankin A, Zhang BY, et al. Non-V600 BRAF mutations define a clinically distinct molecular subtype of metastatic colorectal cancer. J Clin Oncol. 2017; 35: 2624-30.

66. Greally M, Kelly CM, Cercek A. HER2: An emerging target in colorectal cancer. Curr Probl Cancer. 2018; 42: 560-71.

67. Meric-bernstam F, Hurwitz H, Raghav KPS, McWilliams RR, Fakih M, VanderWalde A, et al. Pertuzumab plus trastuzumab for HER2- amplified metastatic colorectal cancer (My Pathway): an updated report from a multicentre, open- label, phase 2a, multiple basket study. Lancet Oncol. 2019; 20: 518-30.

68. Nelson S, Näthke IS. Interactions and functions of the adenomatous polyposis coli (APC) protein at a glance. J Cell Sci. 2013; 126: 873-77.

69. Powell SM, Zilz N, Beazer-Barclay Y, Bryan TM, Hamilton SR, Thibodeau SN, et al. APC mutations occur early during colorectal tumorigenesis. Nature. 1992; 359: 235-7.

70. Maskens AP. Histogenesis of adenomatous polyps in the human large intestine. Gastroenterology. 1979; 77: 1245-51.

71. Iwama T, Utzunomiya J, Sasaki J. Epithelial cell kinetics in the crypts of familial polyposis of the colon. Jpn J Surg. 1977; 7: 230-34.

72. Winawer SJ, Zauber AG, O'Brien MJ, Geenen J, Waye JD. The National polyp study at 40: challenges then and now. Gastrointest Endosc. 2021; 93: 720-6.

73. Lowy DR, Willumsen BM. The ras gene family. Cancer Surv. 1986; 5: 275-89.

74. Scott N, Bell SM, Sagar P, Blair GE, Dixon MF, Quirke P. p53 expression and K-ras mutation in colorectal adenomas. Gut. 1993; 34: 621-4.

75. O'Brien MJ, Winawer SJ, Zauber AG, Gottlieb LS, Sternberg SS, Diaz B, et al. The National polyp study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology. 1990; 98: 371-9.

76. Berge T, Ekelund G, Mellner C, Pihl B, Wenckert A. Carcinoma. of the colon and rectum in a defined population. Acta Chir Scand. 1973; 438: 1-86.

77. Fung CHK, Goldman H. The incidence and significance of villous change in adenomatous polyps. Am J Clin Pathol. 1970; 53: 21-5.

78. Kikuchi-Yanoshita R, Konishi M, Ito S, Seki M, Tanaka K, Maeda Y, et al. Genetic changes in both p53 alleles associated with the conversion from colorectal adenoma to early adenocarcinoma in familial adenomatous polyposis and nonfamilial adenomatous polyposis patients. Cancer Res. 1992; 52: 3965-71.

79. Kastan MB, Onyekwere O, Sidransky D, Vogelstein B, Craig RW. Participation of P53 protein in the cellular response to DNA damage. Cancer Res. 1991; 51: 6304-11.

80. Schwitalla S, Ziegler PK, Horst D, Becker V, Kerle I, Begus-Nahrmann Y, et al. Loss of p53 in enterocytes generates an inflammatory microenvironment enabling invasion and lymph node metastasis of carcinogen- induced colorectal tumors. Cancer Cell. 2013; 23: 93-106.

81. Smith G, Carey FA, Beattie J, Wilkie MJ, Lightfoot TJ, Coxhead J, et al. Mutations in APC, Kirsten-ras, and P53- alternative genetic pathways to colorectal cancer. Proc Natl Acad Sci USA. 2002; 99: 9433-8.

82. Conlin A, Smith G, Carey FA, Wolf CR, Steele RJ. The prognostic significance of K-ras, p53, and APC mutations in colorectal cancer. Gut. 2005; 10: 725-31.

83. Nikolaev SI, Sotiriou SK, Pateras IS, Santoni F, Sougioultzis S, Edgren H, et al. A single- nucleotide substitution mutator phenotype revealed by exome sequencing of human colon adenomas. Cancer Res. 2012; 72: 6279-89.

84. Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet. 2000; 355: 1211-4.

85. Murcia O, Juárez M, Hernández-Illán E, Egoavil C, Giner-Calabuig M, Rodríguez-Soler M, et al. Serrated colorectal cancer: molecular classification, prognosis, and response to chemotherapy. World J Gastroenterol. 2016; 22: 3516-30.

86. Yashiro M, Carethers JM, Laghi L, Saito K, Slezak P, Jaramillo E, et al. Genetic pathways in the evolution of morphologically distinct colorectal neoplasms. Cancer Res. 2001; 61: 2676-83.

87. Jess P, Hansen IO, Gamborg M, Jess T, Danish Colorectal Cancer Group. A nationwide Danish cohort study challenging the categorisation into right-sided and left-sided colon cancer. BMJ Open. 2013; 3: e002608.

88. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. VThe relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. Eur J Cancer. 2017; 70: 87-98.