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(Review)

A Comprehensive Guide to the Evaluation of certain interfering SNPs on a lncRNA: miRNA: protein Axis in CRC Diagnosis

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ABSTRACT

In terms of both incidence and mortality, colorectal cancer (CRC) ranks high among all cancers. Prognosis and survival rates are low for patients with advanced colorectal cancer. There have to be advancements in the diagnosis and treatment of colorectal cancer if more people are going to survive after being diagnosed with the disease. Recently, there has been enough attention paid to the role that noncoding RNAs (ncRNAs) such as long ncRNAs (lncRNAs) and microRNAs (miRNAs) play in several biological processes to warrant their inclusion. Several disorders, including cancer, have been linked to ncRNA mutations or aberrant expression. Research into the crosstalk between lncRNAs, miRNAs, and their master-controlled proteins has emerged as a new emphasis in the quest to understand the molecular mechanism that leads to cancer, specifically CRC. Colorectal cancer risk, prognosis, and therapy response may be influenced by single nucleotide polymorphisms (SNPs) in lncRNA and microRNA genes. Exploring miRNA:mRNA interactions could help shed light on the roles of previously unknown SNPs. Hence, many cutting-edge CRC diagnostic strategies and biomarkers are highlighted in the present study.

Keywords: CRC; Diagnosis; lncRNAs; miRNAs; SNPs.

Introduction

There will be an estimated 28.4 million new cases of cancer diagnosed worldwide in 2040, up 47% from the corresponding 19.3 million cases in 2020, as reported by the World Health Organization [1]**.** Rising cancer rates may have multiple causes, including increased longevity, cancer prevention initiatives, and better diagnosis. As the number of people diagnosed with cancer rises, so does the number of innovative, successful treatments for the disease. Despite these developments, medication resistance is still a major problem for cancer patients. Spreading cancerous tumors can infect neighboring tissues and metastasize to other parts of the body [2].

To put it simply, cancer is a disease in which cells in the body multiply and spread uncontrollably. Tumors caused by cancer are often known as malignant tumors. Leukemia and other blood cancers rarely manifest as physical tumors. Malignant tumors can invade nearby tissues, whereas benign ones cannot. When surgically removed, benign tumors often do not return, while malignant tumors can recur. Yet, some benign tumors, especially those in the brain, can cause serious symptoms or even be fatal [3]. To make sense of the vast complexity of cancer biology, Hanahan and Weinberg defined six key features of cancer in 2000: This includes (a) the ability to generate their growth signals, (b) the ability to avoid apoptosis, (c) the ability to sustain angiogenesis for an indefinite period, (d) the ability to replicate indefinitely, (e) the ability to ignore signals that try to slow their growth, and (f) the ability to actively invade and spread. In a study published 11 years later, the same authors expanded on the list of cancer hallmarks to include the role of the tumor microenvironment [4] **(Figure1 and 2).**

Cancer of the colon or rectum is known as colorectal cancer (CRC). The colon and rectum are the final stages of the digestive system, where waste products and byproducts of energy production are expelled [6]. Despite their physical similarities, malignancies of the colon and rectum are treated differently because they originate from different cell types and have unique characteristics. Tumors can also be seen to have anatomical position-dependent physiologic differences within the colorectum [7].

Polyps, which are benign growths that develop on the rectum (the inner lining of the colon) and enlarge gradually over 10-20 years, are the most common precursor to colorectal adenocarcinoma. Adenomatous polyps (APs), commonly called adenomas, are the most frequent type. The glandular cells that produce lubricating mucus for the bowel wall are the precursors to adenomas. Adenomas are quite common, affecting anywhere from one-third to half of the

population at some point in their life [8]. While all adenomas have the potential to become cancerous, it is estimated that less than 10% will progress to invasive cancer [9]. The risk that an adenoma will develop into cancer rises as the tumor gets bigger. Nearly all colorectal cancers (CRCs) are adenocarcinomas, which start in the colorectal mucosa [10].

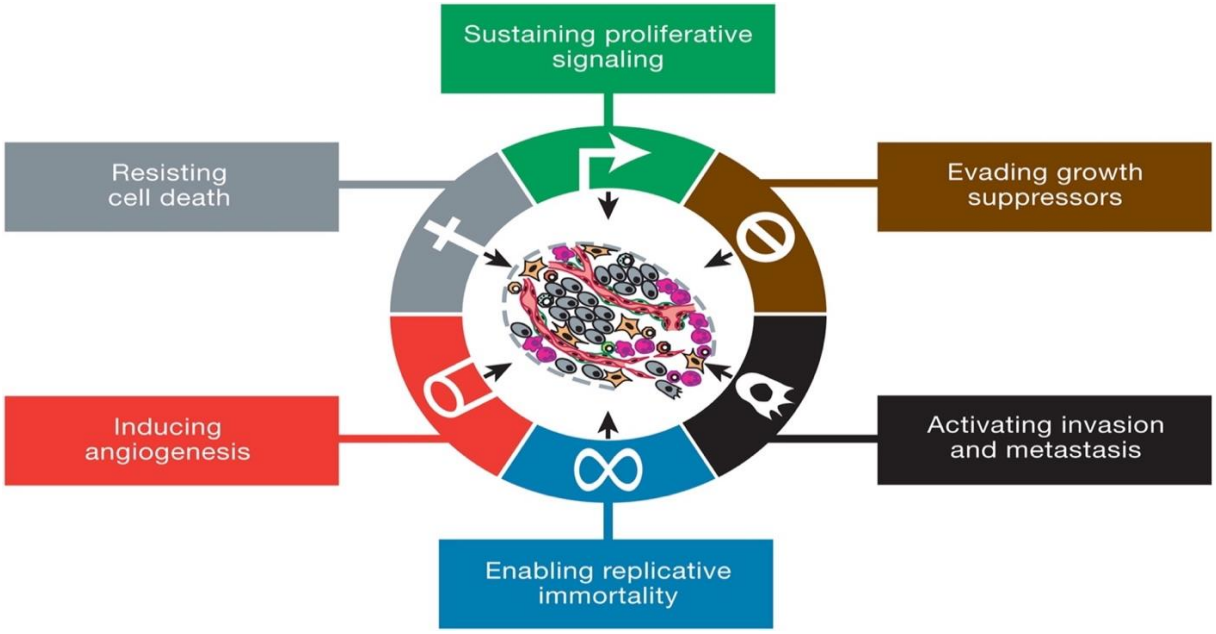

Figure 1. Hallmarks of cancer [5]**.**

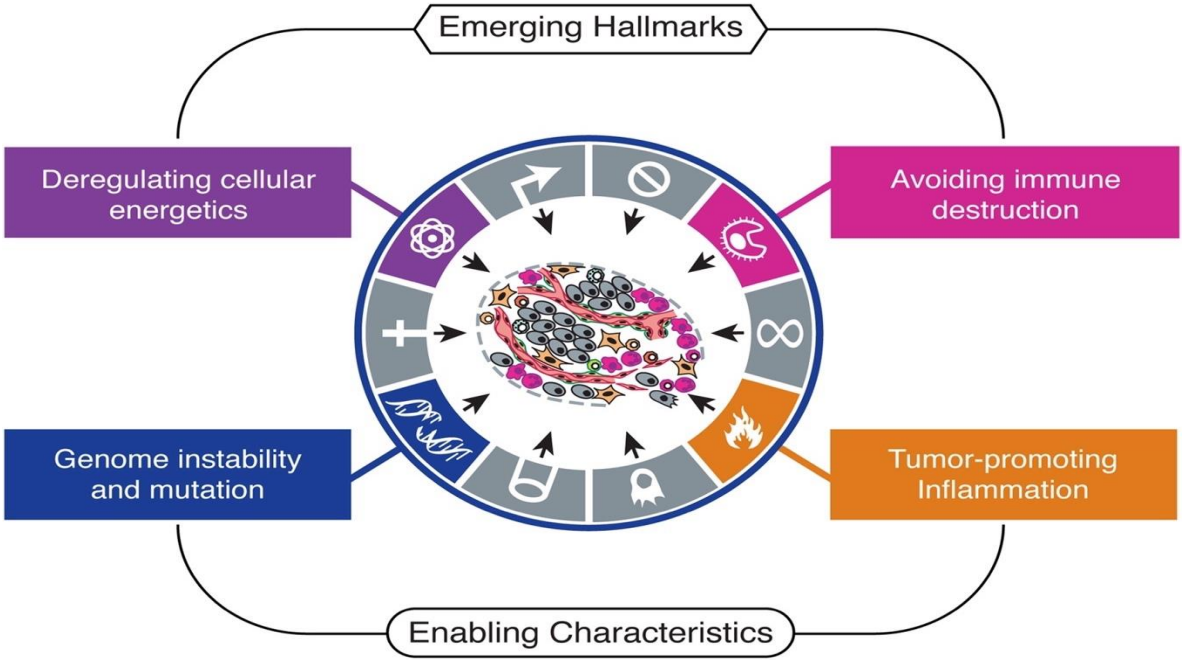

Figure 2. The next generation of the hallmarks of cancer [4]**.**

Once cancer has developed in the inner lining of the large intestine, it may spread to the colon or rectum wall **(Figure 3)**. Cancer cells normally migrate first to surrounding lymph nodes, which are bean-shaped structures that aid in the battle against infections. Lymph nodes are bean-shaped structures that contribute to the fight against infections and are typically the first target of cancer cells migrating from the primary tumor. Metastasis refers to the spread of cancer cells from their original location through the circulatory system to other locations in the body [11].

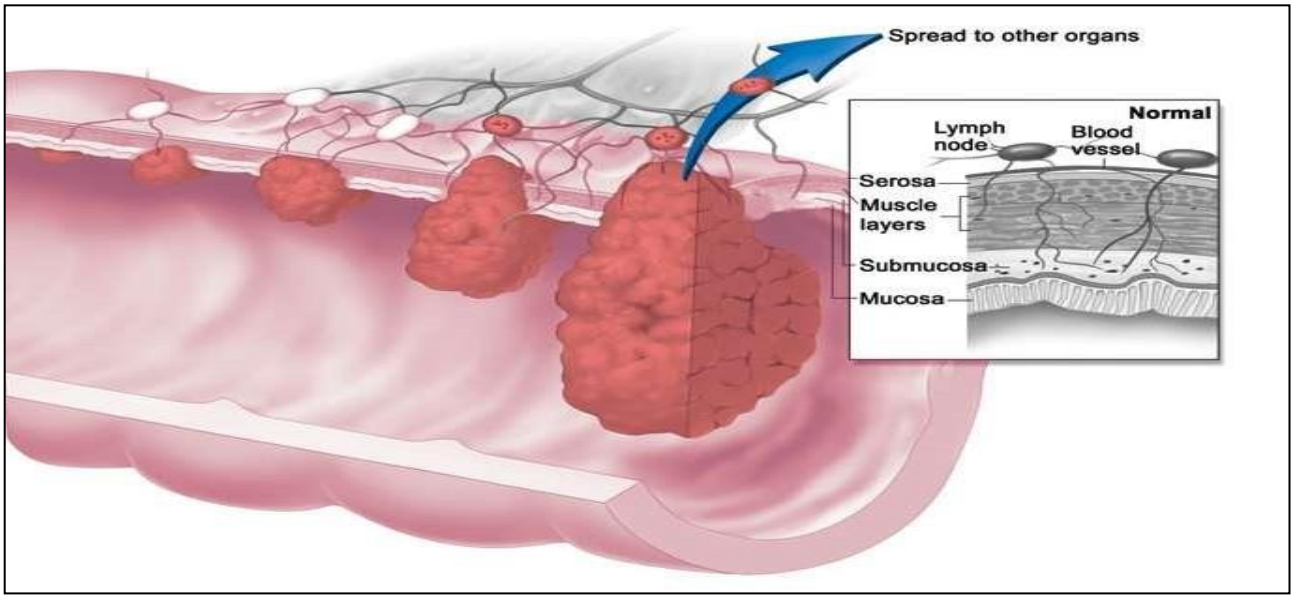

Figure 3. CRC growth [12]. Migration of cancer cells from the same organ to the rest of the organs.

1- Epidemiology of CRC

According to the World Health Organization, colorectal cancer is the third most prevalent disease in males and the second most common cancer in women worldwide. The International Agency for Research on Cancer (IARC) estimates that 1,065,960 men and 865,630 women will be diagnosed with the disease worldwide in 2020, making up 10% of all cancer cases worldwide **(Figure 4)**. Around 55% of all occurrences occur in the more industrialized nations. Death rates have dropped dramatically (935,173 deaths overall, or 9.4% of the population **(Figure 5)**. Higher mortality rates (52%) are indicative of a worse outlook in the world's less developed regions [1].

In Egypt, CRC scored the eighth cancer in incidence and accounted 3.9 % of cancer cases for both sexes (3.7% for males and 4.1% for females) **(Figure 6)**. Regarding mortality, CRC was the eighth cause of cancer death with about 3.2% of all cancer deaths in both sexes, while it was the ninth for males (2.7%) and the seventh (3.8%) for females in 2020 **(Figure 7)** [1].

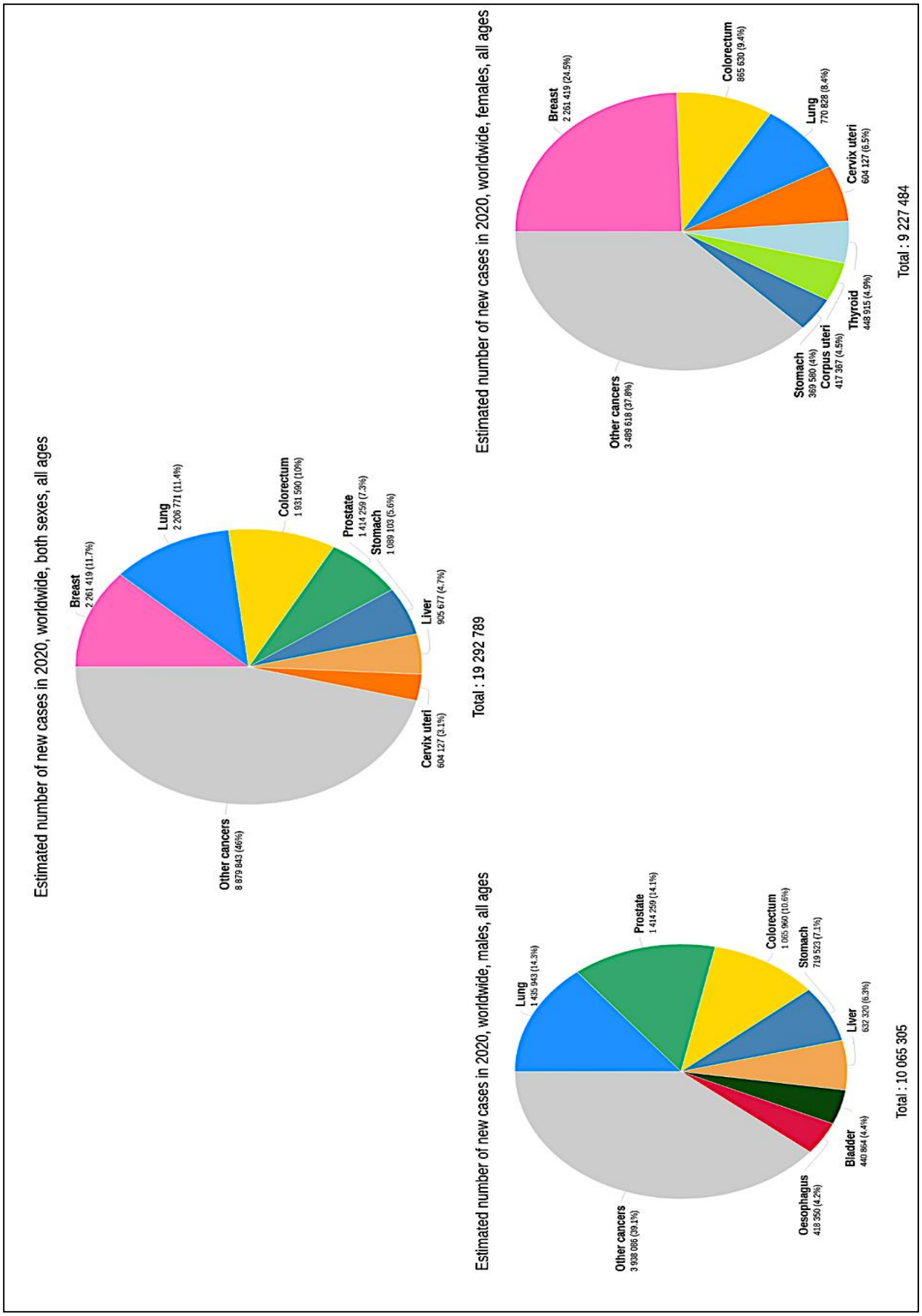

Figure 4. Incidence of CRC worldwide [1]

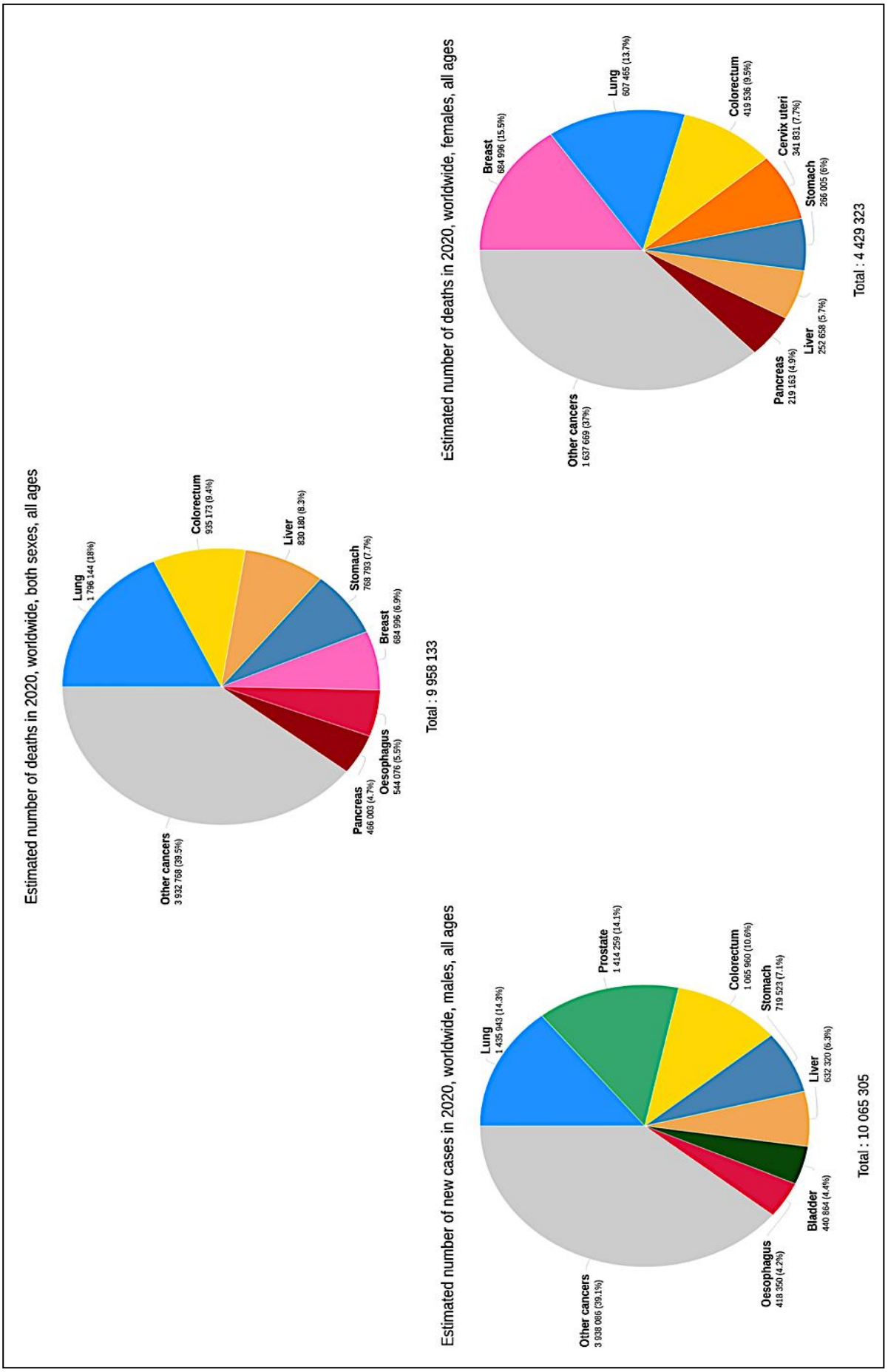

Figure 5. Mortality from CRC worldwide [1].

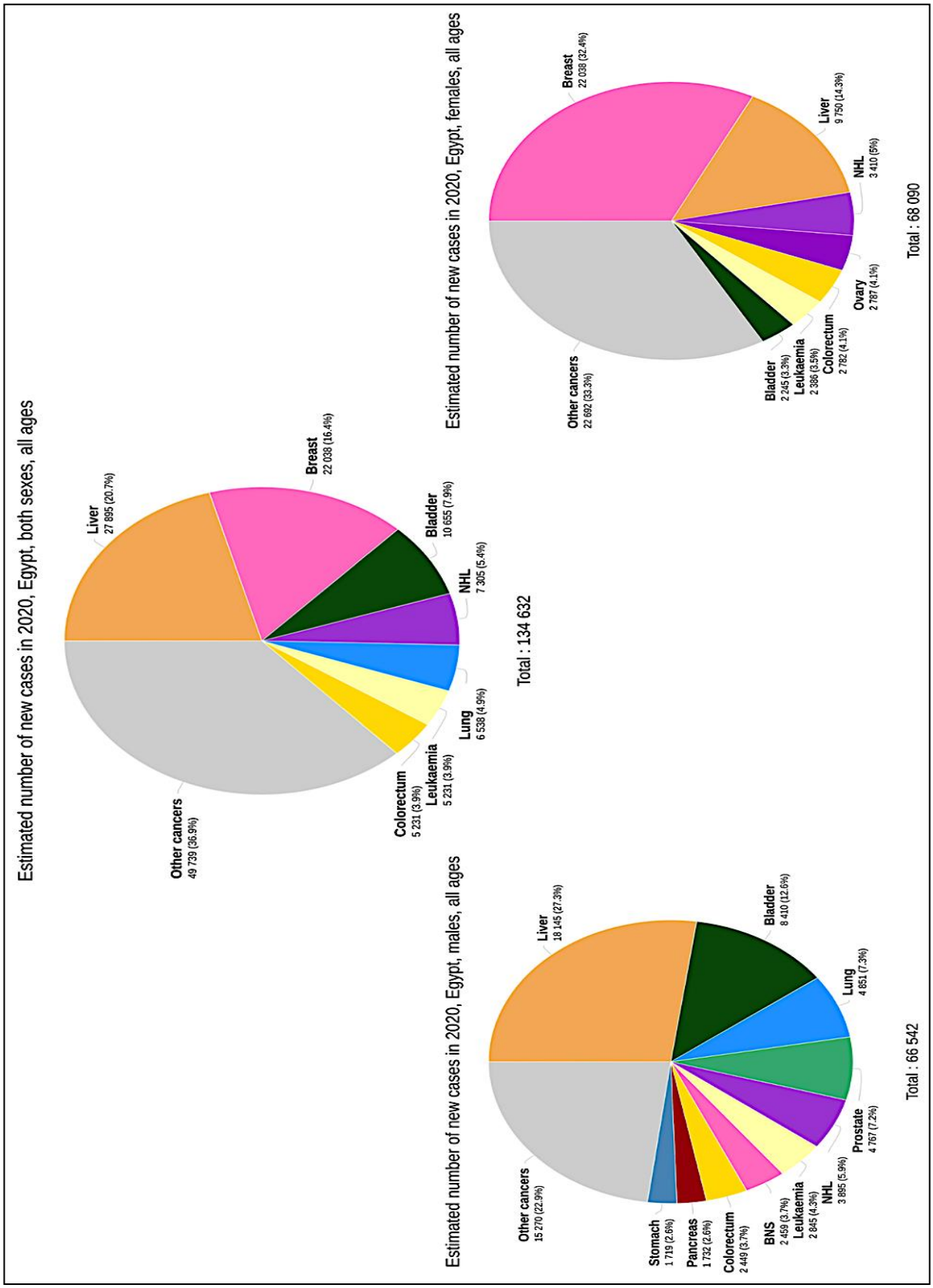

Figure 6: Incidence of CRC in Egypt [1].

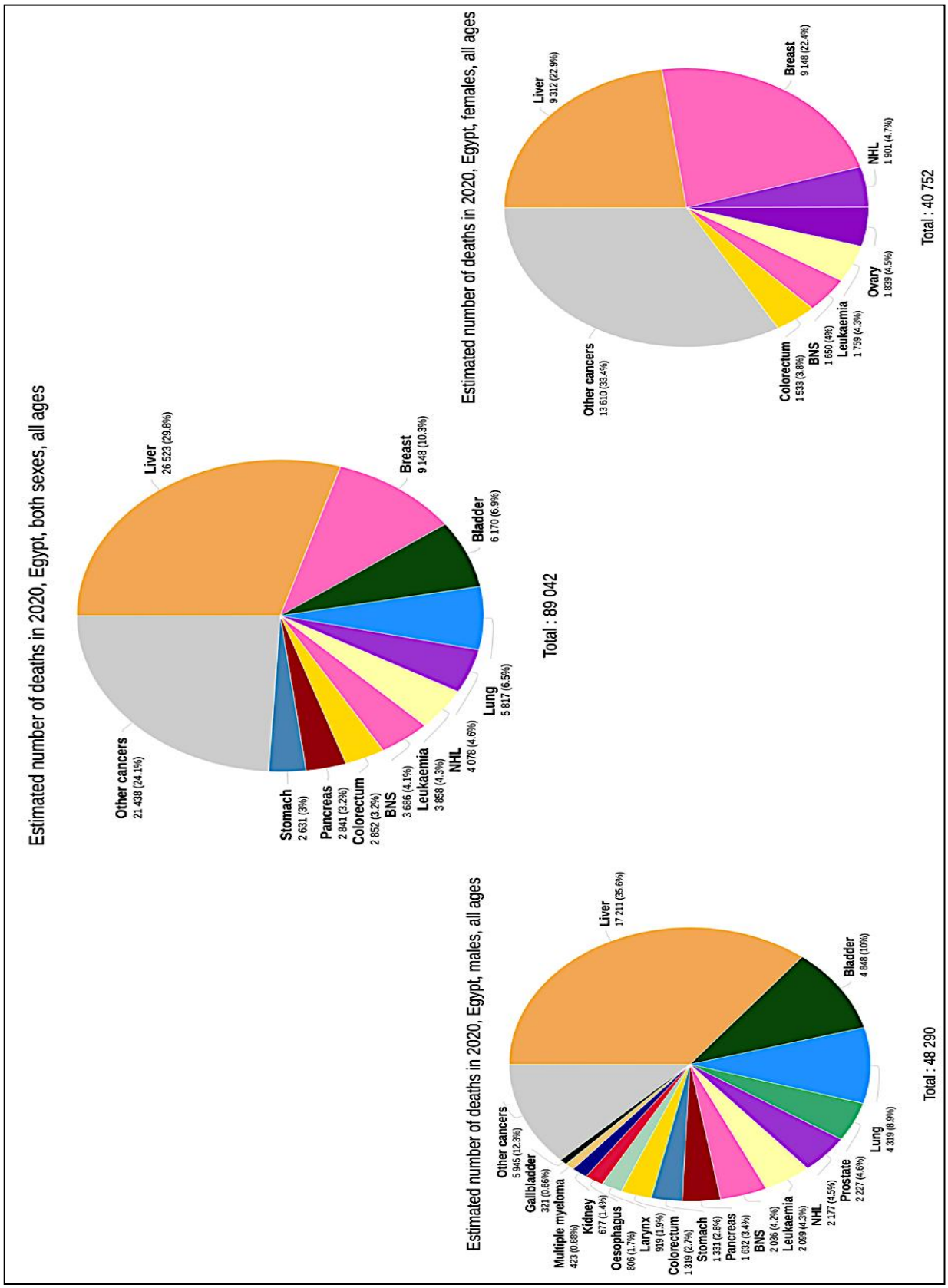

Figure 7: Mortality of CRC in Egypt [1].

Risk factors of CRC

Individuals with a healthy lifestyle in countries with high wealth had a reduced CRC risk than the overall population. A study revealed that keeping a healthy weight, being physically active, limiting alcohol consumption, and eating a nutritious diet reduces the risk of colorectal cancer by 37% [13]. Frequently, the origin of colorectal cancer (CRC) is unknown; however, there are both non-modifiable and modifiable risk factors that can increase an individual's risk of developing CRC.

a. Non-modifiable risk factors

Non-modifiable CRC incidence variables are associated with genetics and medical histories, such as a long-term personal and family history of CRC or adenomatous polyps and chronic inflammatory bowel illness (IBD). Screening for colorectal cancer (CRC) should begin before age 50 for the majority of those at high risk owing to medical or family history [14].

Those with a family history of colorectal cancer are two to four times more likely to get the illness than those without a family history (parents, siblings, or descends). If a first-grade relative has been diagnosed with CRC at a young age or if many relatives have been afflicted, the risk is three to six times that of the general population [15]. Around 20% of all people with CRC had a parent with the illness. Nonetheless, CRC in the family is connected with a better prognosis, maybe due to higher awareness and earlier identification [16].

A well-defined genetic problem syndrome accounts for the disease in over 5% of CRC patients [17]. Lynch syndrome, often called hereditary nonpolyposis colon cancer, is the most frequent kind. Lynch syndrome affects about 1 in every 35 individuals with colorectal cancer [18]. The majority of the mutations that cause Lynch syndrome have been identified in the genes involved in DNA mismatch repair (MMR), including MutL Homolog 1, MutS Homolog 2, MutL Homolog 3, and MutS Homolog 6 [19].

Familial adenomatous polyposis is the second most frequent genetic propensity, however, it only accounts for about 1% of CRCs. Colorectal polyps can number in the hundreds to

thousands and often appear between the ages of 10 and 12. Without treatment, a person's lifetime risk of CRC can reach 100% by the time they reach the age of 40 [20].

Polyposis linked with the myosin heavy chain gene, an autosomal recessive polyposis syndrome produced by biallelic mutations in this gene, and polyposis syndromes of the hamartomata is further genetic disorders related to colorectal cancer (Peutz–Jeghers, juvenile polyposis, and Cowden disease). While all of these syndromes are medically significant, the majority of CRC cases are "sporadic," hence individuals do not fall within the categories of genetic risk factors or heritable syndromes [21].

Those with a personal history of chronic IBD and a colon that has been inflamed for a long period are almost twice as likely as the general population to develop CRC [22]. Ulcerative colitis and Crohn's disease are the most common types of IBD. The risk of cancer increases with the extent, duration, and severity of the disease [23]. Nevertheless, there is some evidence that the cancer risk among these people has decreased in recent years as a result of better illness (because of the use of anti-inflammatory drugs) and the increased use of screening to detect premalignant lesions [24].

For persons with type II (adult-onset) diabetes, their risk of CRC is raised [25]. This association is true even after controlling for factors including exercise, BMI, and waist circumference which are both risk factors for both type II diabetes and CRC [26]. Metformin, a common medication used to manage blood sugar in people with diabetes, has been shown to reduce CRC incidence in some trials, but this may be due to its effects on glucose control (26,27), the use of other antidiabetic drugs was not related with changes in CRC risk [27]**.**

b. Modifiable risk factors

On the other side, modifiable risk factors are connected to lifestyle-related variables such as being overweight or obese, smoking, alcohol use, eating habits, and prescription medicines. In fact, the associations between the aforementioned risk factors and CRC risk are among the strongest of all cancer types.

Regarding obesity, the connections between body weight and CRC are complicated and not entirely understood. In addition, the levels of certain hormones, such as insulin and estrogen, which can fuel cell development, or other substances that govern cell growth, such as insulin-like growth factor-1, could influence CRC risk [28]. In addition, CRC has a greater connection with colon tumors than with rectal cancers, and with males than with women. In particular, men who are overweight are at a 50% higher risk of developing colon cancer and a 20% higher risk of developing rectal cancer than people of normal weight, whereas women who are overweight get these diseases at a 20% and 10% higher risk, respectively [29]. Gaining weight early in adulthood appears to have a higher impact on CRC risk than gaining weight later in life [30,31].

Considering tobacco use, the IARC reported in November 2009 that there is adequate evidence to infer that cigarette consumption causes CRC [32]. Tobacco use has been linked to a variety of cancers, including lung, esophagus, and endometrial cancers, as well as colorectal cancer (CRC) [6]. Those who smoked 30 or more cigarettes per day had almost double the risk of developing polyps, and those with genetic defects that rendered them poor metabolizers of tobacco carcinogens had an even higher risk, according to a large case-control study of colonoscopy patients [33]. This suggested a dose-response relationship between cigarette use and CRC risk [34].

While higher cytosine-guanine islands (CpG) methylation is observed in smokers with CRC tumors, it is believed that the carcinogenic effects of tobacco are mediated by CpG methylation polymorphisms (36,37). Thus, smoking has greater carcinogenic and mutagenesis effects on colorectal cancer than on other tobacco-related malignancies [35].

There is an association between regular alcohol consumption and an elevated risk of colorectal cancer. The risk of colorectal cancer (CRC) was 20% higher in people who drank two to three alcoholic beverages per day on average across their lifetimes compared to people who drank never or rarely [36]. The link appears to be stronger among men than women, possibly because of hormonal differences in alcohol metabolism. Differences in CRC rates across regions and across time among immigrant populations are indicative of the powerful role played by dietary and lifestyle factors in the development of this disease [37]. Directly, through certain food components; and indirectly, via overnutrition and

obesity, dietary patterns likely affect risk. The risk of colorectal cancer is raised by a diet high in red and/or processed meat [38]. In 2015, the International Agency for Research on Cancer (IARC) classified processed meat as "carcinogenic to humans" and red meat as "probably carcinogenic to humans" based on information relating to colon, rectal, and bladder cancer [39]. This relationship remains unexplained, however, it may be connected to carcinogens produced when red meat is cooked at a high temperature for an extended length of time and/or nitrite additions used for food preservation [40].

Due to a combination of factors, including reduced exposure to carcinogens as a result of greater stool volume and shorter transit time, it has been found that diets high in dietary fiber, cereal fiber, and whole grains are associated with a reduced risk of colorectal cancer. There has been a lot of research, including randomized controlled studies, with conflicting results [41]. In addition, higher consumption of total dairy products, milk, and calcium decreases the risk of developing CRC. However, their precise role in CRC decreased risk remains unclear [38].

Long-term, frequent use of aspirin and other non-steroidal anti-inflammatory treatments has been shown to reduce colorectal cancer risk. [42]. Those who take aspirin but have CRC appear to have less aggressive tumors and a better prognosis than those who don't [43]. Those people in their 50s who are at high risk for cardiovascular disease should take a low-dose aspirin every day to prevent cardiovascular disease and colorectal cancer [42].

It has been shown that postmenopausal women who use hormone replacement therapy had much-reduced rates of colorectal cancer than those who do not [44]. Women who use hormones for extended periods have a lower risk, but within three years of stopping, their risk is the same as that of non-users [45]. Unfortunately, postmenopausal hormone therapy is not indicated for the prevention of CRC due to its association with an increased risk of breast and other cancers, as well as cardiovascular problems [46]. The usage of oral contraceptives has been linked to a modestly reduced incidence of colorectal cancer, according to studies [47]. The risk of colorectal cancer (CRC) may be lowered by using oral bisphosphonates, which are currently used to treat and prevent osteoporosis [48].

2- Molecular basis of CRC

Colorectal cancer is a diverse illness that manifests differently in each individual. At least three key molecular pathways have been identified as contributing to the progress of colorectal cancer (CRC): chromosomal instability, microsatellite instability (MSI), and peculiar DNA methylation. There is some overlap between the routes, and two or more pathways may occur in the same individual [49].

a. Chromosomal instability

Around 75% of all instances of CRC are caused by chromosomal instability (CIS), the most common form of genomic instability in CRC. [21]. When an entire gene is deleted due to the physical loss of an entire chromosomal section, heterozygosity is lost for that gene. What this means is that there is no longer any genetic backup for the deleted allele because there is only one copy of the gene left. The loss of a second allele renders a whole gene inactive. Missing tumor suppressor genes contribute to chromosomally unstable CRC, and examples are adenomatous polyposis coli (APC) and p53. Several genes in this system, including adeno-associated protein convertase (APC), p53, and Kirsten rat sarcoma viral oncogene homolog (KRAS), are frequently targeted for genetic alteration [49]. An overview of this pathway is given in **Figure 8**.

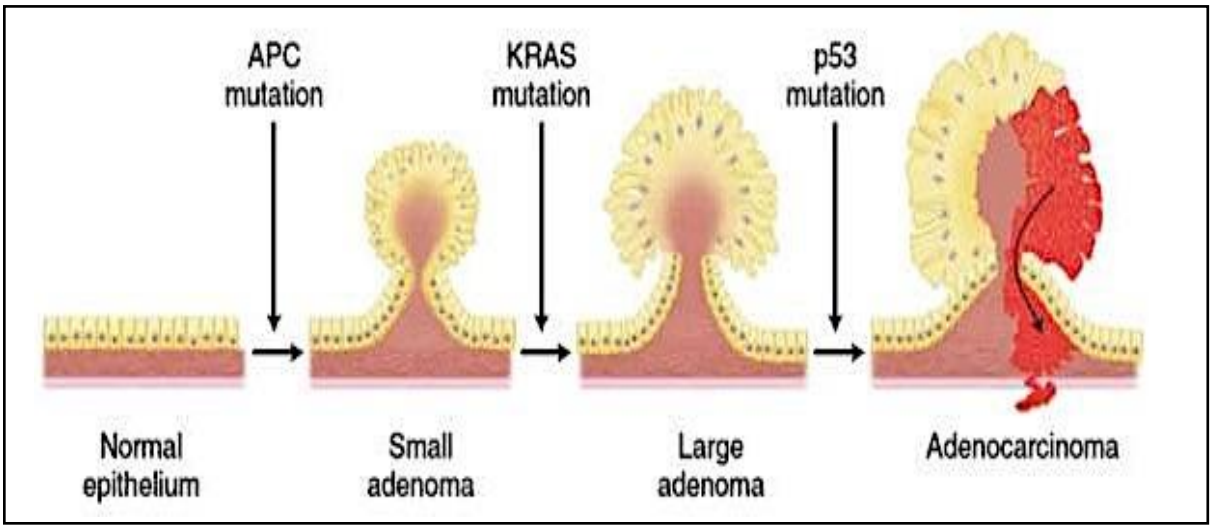

Figure 8: Typical progression from adenoma to cancer, with accompanying chromosomal instability, depicted schematically [50].

Many colorectal adenocarcinomas undergo malignant transformation through the APC gene, which has been dubbed the "gatekeeper" gene. By intracellular binding of -catenin, the APC protein controls the wingless-related integration site (Wnt)-protein signaling pathway. Mutations in APC result in the transcription of no or a nonfunctional protein. Reduced amount or function of APC protein permits intracellular buildup of -catenin and therefore greater translocation into the nucleus, where it functions as a transcription factor responsible for proteins implicated in cell signaling, proliferation, and cell-to-cell adhesion [50].

The epidermal growth factor receptor is an upstream signaling receptor for the oncogene KRAS, which is involved in the mitogen-activated protein kinase (MAPK) pathway (EGFR). During cell division, this pathway is responsible for nuclear transcription. Oncogenic mutations activate the KRAS signal and cause unchecked cell proliferation independently of upstream signaling. Almost 40% of instances of CRC are caused by KRAS mutations [51].

The gene tumor protein 53 encodes p53, which maintains the cell cycle and genetic stability. As a tumor suppressor, p53 halts the G1/S transition of the cell cycle so that mutations or replication mistakes can be fixed. If the damage is irreparable, p53 may promote cell death. It is believed that p53 is important for lesion invasiveness. It is uncommon in adenomas (5%) but prevalent in malignant polyps (50%) and in 75% of invasive CRC [52].

b. Microsatellite instability

Microsatellites are noncoding DNA regions with one to four repeating nucleotide sequences. There are hundreds of thousands of microsatellites in the human genome, and the patterns of these microsatellites offer a unique Genetic fingerprint. Regular DNA replication is related to high infidelity and error-prone microsatellites. MSI is the outcome of DNA MMR dysfunction. MMR corrects DNA replication mistakes, such as mismatches of a single base or small insertions and deletions.

Mismatch repair proteins fix polymerase mistakes by building a complex that binds to the mismatched DNA sequence, excises the error, and inserts the right sequence in its

place. Cells with incorrectly functioning MMR are unable of correcting DNA replication mistakes, resulting in the accumulation of errors. This alters the length of the microsatellite areas, creates new microsatellite pieces, and modifies the fingerprint [50].

Adenomas and cancers develop when MMR fails to prevent mutations in these genes from piling up. Since these cancers tend to be hypermutated, this molecular pathway is called the mutator phenotype. Mutations in the mismatch repair (MMR) gene of the DNA cause Lynch syndrome. Polymerase errors can be corrected thanks to a complex formed by the MMR proteins, which bind to the offending DNA sequence, removes it, and inserts the correct one in its place. Cells with incorrectly functioning MMR are unable of correcting DNA replication mistakes, resulting in the accumulation of errors. This alters the length of the microsatellite areas, creates new microsatellite pieces, and modifies the fingerprint [53].

c. Aberrant DNA methylation

Without changing the DNA sequence itself, epigenetic mechanisms like the hyper-methylation of DNA promoter regions can alter gene expression and protein translation. Cytosine methylation is a ubiquitous biological activity that takes place all over the genome and regulates a wide variety of cellular processes. Critical tumor suppressor genes often contain CpG repeat sequences that are prone to hypermethylation. As the promoter of this gene has been hypermethylated, no protein of any use is being synthesized. Regions prone to hypermethylation have several CpG islands or cytosine and guanine dinucleotide repeats. This pattern is related to abnormal methylation of the MMR gene, e.g., in around 20% of CRCs. MutL Homolog 1[54].

3- Diagnosis of CRC

Colonoscopy is the preferred procedure for diagnosing colorectal cancer (CRC). Colonoscopic detection of advanced lesions is very simple, however early CRC cancers may manifest as extremely mild mucosal abnormalities [55]. To detect these lesions, thorough mucosal examination and adequate bowel preparation are required. These and other criteria, such as adenoma identification by an endoscopist, are utilized as quality

indicators for colonoscopy because they are connected with the risk of developing CRC after colonoscopy (post colonoscopy CRC) [56].

Computed tomography colonography is a secondary imaging modality used in the evaluation of the colon for polyps and colorectal cancer (CRC) (e.g., after incomplete or inadequate colonoscopy). Despite this, imaging methods are mostly used for accurate regional and distant staging. Magnetic resonance imaging (MRI) is widely used for the locoregional staging of rectal cancer, which then directs future therapy decisions [57]. While neoadjuvant systemic treatment can reduce the size of locally advanced tumors, the significance of locoregional colon cancer staging has increased [58]. CT scans are commonly utilized for this purpose, despite their limited accuracy. CT is widely used for distant staging of the liver and lungs, with MRI playing a growing role in the diagnosis of hepatic abnormalities. Positron emission tomography imaging is gaining popularity, although its precise function for staging and assessing disease burden in advanced patients is still under question [59].

In addition to a CBC at the time of diagnosis, all standards recommend evaluating carcinoembryonic antigen (CEA) levels. Low CEA concentrations after surgery may be indicative of the presence of residual disease, while high baseline amounts are associated with a poor prognosis [60]. It is important to remember that about 10–15% of patients either do not create CEA or generate it at minute levels, as stated by the standards of the European Group on Tumor Markers (EGTM). The presence of a tumor, even at a late stage, cannot be ruled out by a normal concentration of CEA under these conditions [61]. Thus, there is an urgent need to discover new biomarkers that might detect CRC patients at an early stage.

Histopathology remains the foundation for pathological staging and treatment. In addition to [tumor size, lymph node status, and metastasis score], Beyond the traditional histological subtyping, grading, and histological assessment of lymphatic, perineural, and venous invasion, the importance of many tumor-based indicators, such as MMR testing and Immunocore, is increasingly recognized [62]. The potential to detect metastatic CRC patients who would benefit from immunotherapy has led to widespread acceptance of global MMR testing, and it is not simply being done for the diagnosis of Lynch syndrome [56].

4- Treatment of CRC

Most early cancers are only treatable locally. The incidence of these early CRC tumors has grown as a result of CRC screening efforts [63]. Malignant polyps can be removed endoscopically after diagnosis, giving the pathologist a clear view of the polyp's high-risk features including submucosal invasion depth, differentiation, lymphatic invasion, and tumor budding, as well as the polyp's deep and lateral edges. Adjuvant mesenteric lymphadenectomy surgery is a debatable topic that must be weighed against the patient's wishes and the anticipated oncological and operational risk [55].

The majority of newly diagnosed CRC patients (70-80%) have localized disease amenable to curative surgical resection. After surgical resection, current clinical practice recommends adjuvant chemotherapy with cytotoxic drugs for individuals with stage III CRC. Twenty to thirty percent of newly diagnosed patients come with metastatic disease that cannot be resected. In addition, forty to fifty percent of patients have disease recurrence or metastatic disease following surgical resection. The treatment of individuals with metastatic colorectal cancer necessitates the administration of cytotoxic medicines systemically [56].

Surgery is the foundation for therapy with the objective to cure. Importantly, the quality of CRC resection may be evaluated using objective measures. Postoperative imaging investigations have demonstrated that surgical quality might be improved, highlighting the need for physician training and expertise [64]. Certain instances require additional therapies, such as colostomies, radiofrequency ablation, or cryoablation, in addition to surgical excision.

In certain instances, if the cancer has spread to the liver or lungs, an ablation may be required. Currently used ablation techniques include radiofrequency ablation and cryoablation. Cryoablation is the opposite of radiofrequency ablation, in which the tumor is frozen. Radiofrequency ablation is conducted by transmitting radio waves to the tumor in order to heat it. These methods can be performed during surgery or non-surgically through the skin. The employment of these procedures results in minimum injury to normal tissue, although there is a chance of residual tumor. **Figure 9** shows the course of action for each stage.

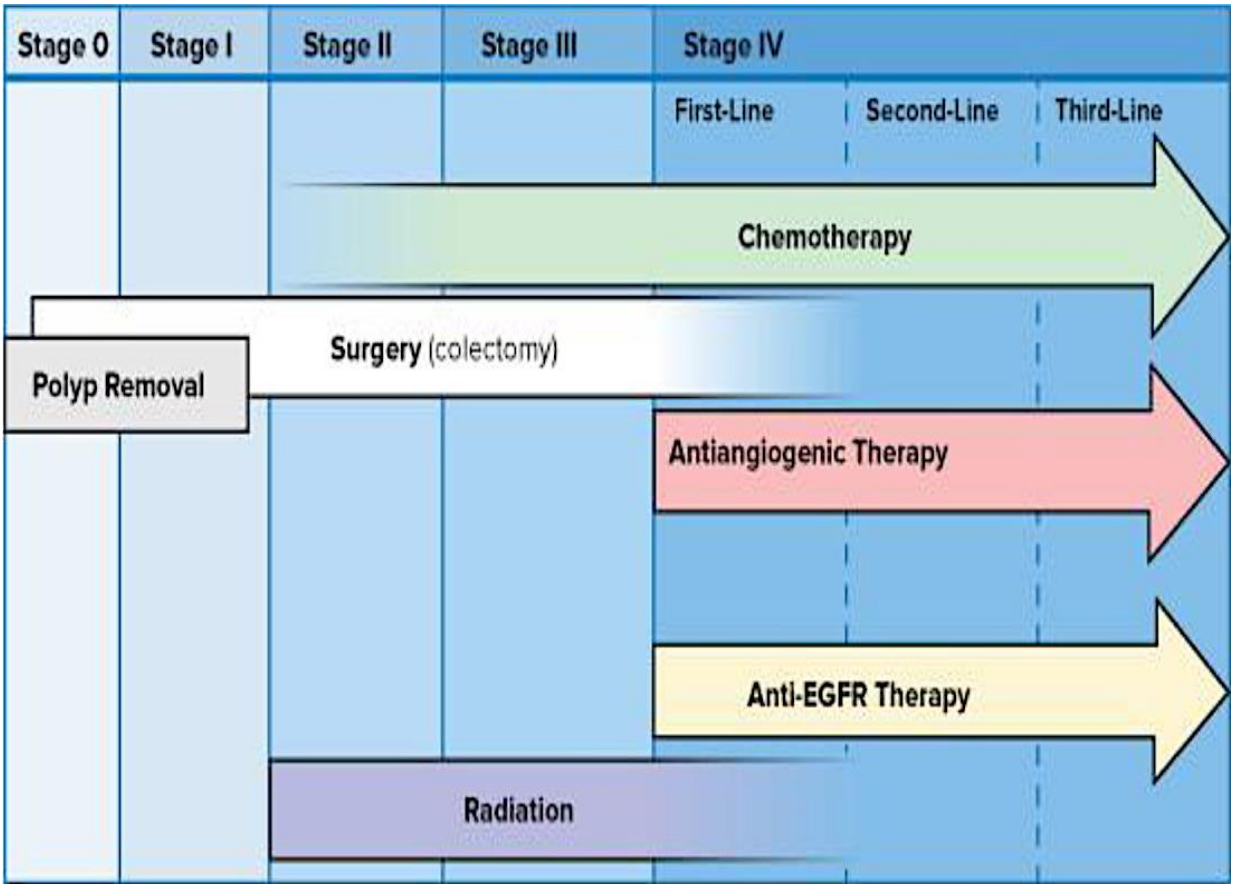

Figure 9. Treatment by CRC stage. In stages 0 and I, polyp removal is the primary line of defense. If the number of polyps is excessive, a colectomy may be considered. In phases II and III, the initial step in removing malignant polyps and/or tumors is a colectomy. Depending on the severity of the malignancy, radiation and/or chemotherapy may be offered after surgical removal. Colectomy is performed to remove any cancers at stage IV. As a first line of defense, radiation, and chemotherapy are delivered after surgery. Antiangiogenic and anti-EGFR chemotherapy are the two main kinds utilized to treat CRC in its fourth stage. Based on the biomarkers cancer exhibits, one or both of these chemotherapies will be delivered [65].

Many historical trials have demonstrated that preoperative radiation, as opposed to postoperative radiotherapy, reduces the incidence of local recurrence of CRC cancers [66]. The actual risk reduction obtained by preoperative radiation is contingent on the clinical stage and surgical quality. With a dosage of 45–50 gray in 25–28 fractions and fluoropyridine as a radiation sensitizer, chemoradiotherapy is the most common treatment

for cancer. At least 15–20% of patients have a full response, and the majority of patients see a size reduction [67].

Adjuvant fluoropyrimidine-based chemotherapy improves survival in resected stage III and some resected stage II colon cancers [68]. According to seminal studies like the multicenter international trial of oxaliplatin/fluorouracil/leucovorin, the addition of oxaliplatin to a fluoropyrimidine (fluorouracil or capecitabine) is the current standard of treatment for the adjuvant therapy of colorectal cancer [69]. The primary drawback of including oxaliplatin in chemotherapy is the development of cumulative sensory neuropathy [70].

Bevacizumab, the very first biologic therapy to be licensed for metastatic colorectal cancer (CRC), was the first anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody targeting angiogenesis, and it was found to treat all patients with this disease. The addition of bevacizumab to standard chemotherapy has been shown to increase free survival progression, although not necessarily overall survival, in later studies [71]. Aflibercept and ramucirumab are two other anti-VEGF medicines authorized for individuals with metastatic CRC [72].

The emergence of anticancer drug resistance is a serious obstacle in cancer treatment, frequently leading to recurrence and even patient death. Despite the complexity of the process underpinning chemosensitivity and chemoresistance, ncRNAs are becoming more valued for their ability to circumvent this hurdle. Noncoding RNAs

High-performance methods have demonstrated the transcription of the majority of the eukaryotic genome, which consists of around 20,000–25,000 protein-encoding genes [73], According to optimistic estimations of the quantity of ncRNA in a genome from various sources, transcription would occur from less than 2% of a genome to produce functional ncRNAs [74].

Transcriptional control, post-transcriptional regulation, organ regeneration, pathological conditions, and genetic expression are only a few of the many cellular activities recently found to be influenced by ncRNAs [75]. Many debates have been held

over these genomes, even though they play crucial biological roles [76], and further research into the roles that ncRNAs play is crucial.

Both short noncoding RNAs (sncRNAs) with fewer than 200 nucleotides and long noncoding RNAs (lncRNAs) with more than 200 nucleotides have been identified and may be systematically categorized according to size [77]. Recent attention has been drawn to the dysregulation of ncRNAs due to their strong relationship with human illnesses, particularly cancer. Noncoding RNAs (ncRNAs) have the potential to serve as oncogenes or tumor suppressors in colorectal cancer, making them useful as diagnostic or prognostic biomarkers [78].

a. Long noncoding RNAs

LncRNAs constitute >80% of all ncRNAs. Through influencing transcriptional, post-transcriptional, and epigenetic molecular processes, lncRNAs are implicated in carcinogenesis, tumor cell proliferation, invasion, migration, apoptosis, and angiogenesis, according to accumulating data. lncRNAs were also powerful modulators of precursor messenger RNA (pre-mRNA) splicing, mRNA degradation, and translation, in addition to their well-established role as regulators of transcription [79].

RNA polymerase II is responsible for the transcription of the vast majority of lncRNAs. Several have m7G caps at their 5' ends and poly (A) tails at their 3' ends, suggesting that they are transcribed and processed in a manner analogous to messenger RNAs. Yet, recent studies have shown that lncRNA fate and function are intricately linked to their transcription, processing, export, and turnover.

Relative to mRNAs, a higher proportion of lncRNAs are nucleus-localized [80,81] bringing up the fundamental question of what causes their disparate distribution. A comparison of the global properties of lncRNAs and mRNAs shows that the former are less conserved during evolutionary time, have fewer exons, and are expressed at lower levels [82]. Recent advances in RNA capture long seq have allowed for more accurate annotation of lncRNAs' whole lengths, including their 5′ ends, revealing just a small size difference between lncRNAs and mRNAs despite their fewer and longer exons. Several lncRNAs were found to be highly expressed in the human neocortex, as determined by single-cell sequencing [83].

As a result of poor splicing, polyadenylation, and exosome destruction on chromatin, LncRNAs are much more nuclear than mRNAs [84]. Nonetheless, the functional characterization of lncRNA is now under investigation. The subcellular localization of lncRNAs is critical for revealing their specific function. Localized nuclear LncRNAs frequently function as epigenetic modulators. **(Figure 10A, B)**, whereas cytoplasmic proteins frequently have post-transcriptional functions [85]. For example, spermatogenesis-associated serine-rich 2 (SPATS2) mRNA is stabilized by the small nucleolar RNA host gene 5 (SNHG5), which creates an RNA: RNA duplex that blocks access to the mRNA by the destabilizing protein **(Figure 10 F)** [86,87].

LncRNAs also stay put in the nucleus thanks to interactions with proteins that aid in their subcellular localization **(Figure 10A, C)**. For instance, heterogeneous nuclear ribonucleoprotein U (hnRNPU) governs the localization of the lncRNAs X-inactive specific transcript (XIST) and functional intergenic repeating RNA element (FIRRE) to certain chromosomal loci, and suppression of hnRNPU results in their mislocalization [88]. In general, it is believed that processed lncRNAs would be exported to the cytoplasm similarly to mRNAs, however, this is yet to be empirically confirmed [85].

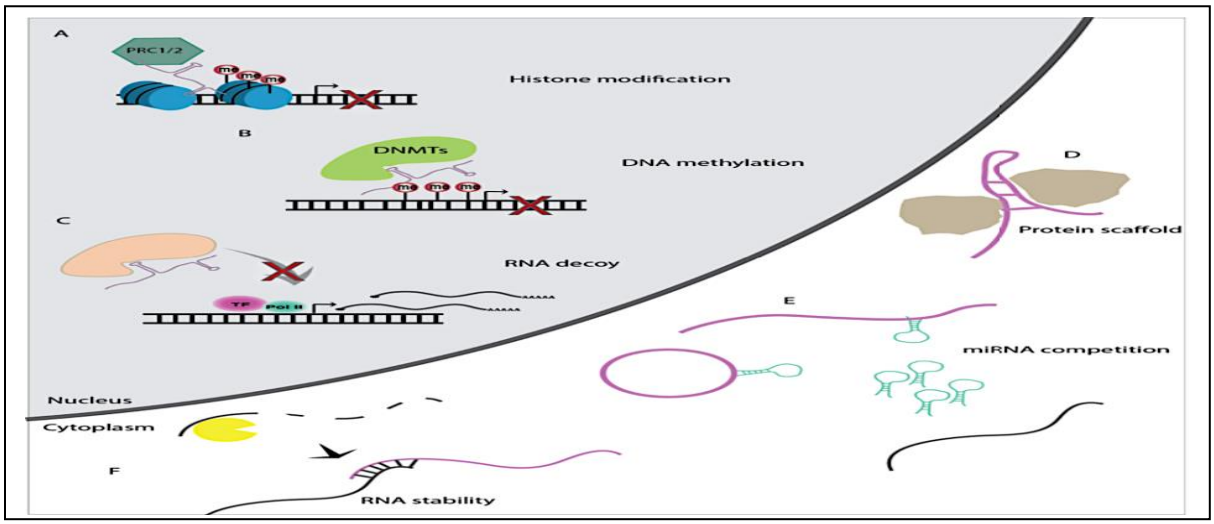

Figure 10. Roles that lncRNAs play in the body [89]. (A, B) epigenetic modifying proteins are gathered at chromatin by LncRNA (C) LncRNA can act as a decoy keeping proteins away from the DNA. (D) LncRNAs can serve as scaffolds to assemble proteins. (E) LncRNA and circular RNA (ciRNA) can act as miRNA sponges. (F) By generating RNA:mRNA duplexes, LncRNA can impede the access of RNA breakdown proteins.

Nonetheless, lncRNAs are typically categorized primarily on their chromosomal position and connection to protein-coding genes, even though a lncRNA's subcellular localization can help in predicting its function. To add to this complexity, lncRNAs can be further categorized into several distinct types **(Figure 11)**.

Included are antisense RNA (asRNA), long intergenic RNA (lincRNA), sense overlapping RNA, sense intronic RNA, processed transcripts (lacking an open reading frame and not fitting into any of the other categories), and transcribed pseudogenes. Additional RNA subgroups, such as enhancer RNA (eRNA) and ciRNA, are developing; however, they partially overlap with existing ncRNA subgroups. LincRNAs are the most prevalent form of lncRNA; their expression is tissue-specific. Nonetheless, asRNA ranked second, behind lincRNAs [90].

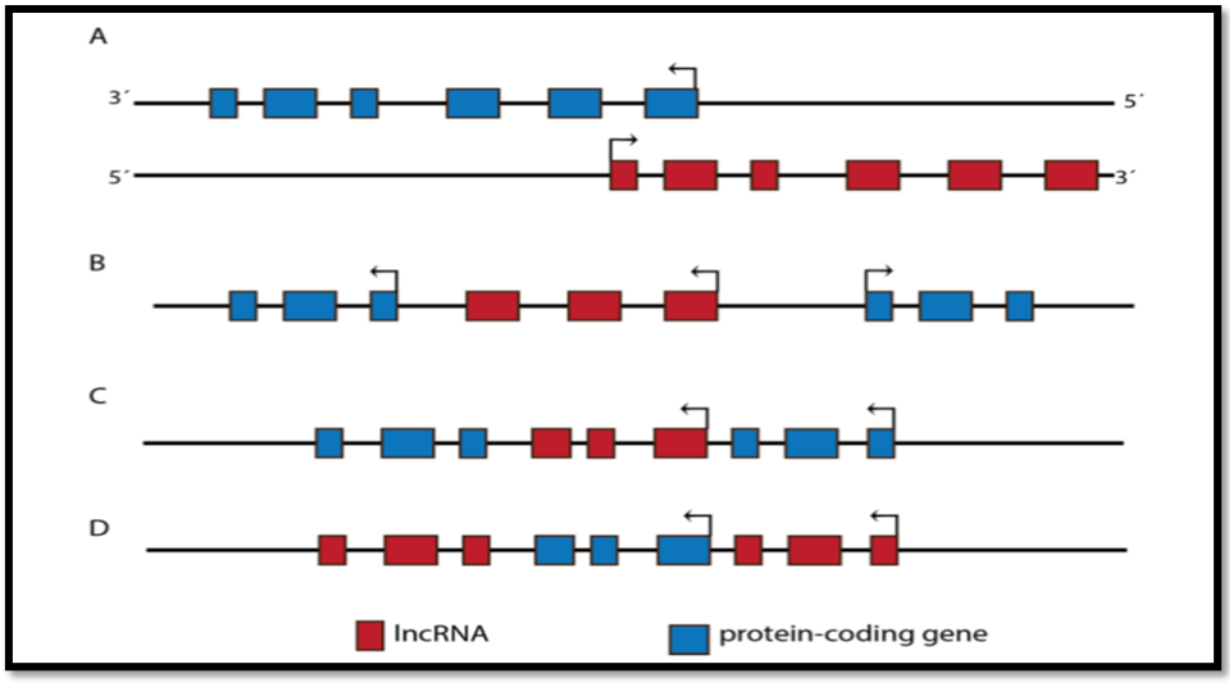

Figure 11: Schematic representation of the major categories of lncRNAs [91].
(A) Antisense RNA, (B) LincRNA, (C) Sense-intronic RNA, and (D) Sense-overlapping RNA

Furthermore, lncRNAs can regulate chromatin structure and gene expression in cis or trans, and can be classified based on their subcellular localization (nuclear, cytoplasmic, or present in both compartments) or mechanism of action on the chromatin (cis- or trans-acting depending on the target genomic locus). Gene expression can be regulated by long noncoding RNAs (lncRNAs) in two ways: in cis, by DNA looping between the lncRNA and its target

gene, and in trans, by acting as recruiters or decoys for chromatin modifiers and transcription factors to activate or mute genes, respectively [92].

Cancer arises from oncogene activation and mutations in tumor-suppressor genes, both of which result in uncontrolled cell growth and resistance to the programmed cell death pathway known as apoptosis. Microarray, RNA sequencing, and real-time polymerase chain reaction were just a few of the techniques used to examine gene expression in this study (PCR) [93], Many types of tumors and normal tissues express lncRNAs at different amounts, as has been shown in many studies [94,95]. Many reasons indicate that lncRNAs may affect carcinogenesis, despite the fact that some of these aberrant expression patterns may be subsequent outcomes of cancer transformation. The discovery that lncRNAs are often located at critical sites, regions of single nucleotide polymorphisms (SNPs), amplifications, or at common breakpoints, the presence of sequence motifs and other elements that result in specific structures, their regulation, and their functional relationships with other nucleic acids and proteins, and the presence of sequence motifs and other elements that result in specific structures, regulation, and functional relationships [96]. Previous studies have shown that specific lncRNAs with aberrant expression levels are critical regulators of tumor genesis and progression [97]. For instance, the HOX transcript antisense RNA (HOTAIR) is significantly expressed in a variety of primary somatic cancers, including hepatic cancer [98], pancreatic cancer [92], and cervical cancer [99], ln addition to some metastatic cancers, such as metastatic breast tumors [100] and melanoma [101].

In colorectal cancer, dysregulated lncRNAs have been linked to both diagnosis and prognosis, suggesting they may serve as novel biomarkers or therapeutic targets. Colorectal cancer is one type of malignancy where lncRNAs have been shown to play a role in recent studies and reviews (CRC). Recent research has shown that long noncoding RNAs (lncRNAs) play a role in colon cancer (CRC) chemoresistance through multiple mechanisms, including epigenetic modification, interaction with other miRNAs, acting as structural RNAs in scaffolding ribonuclear protein complexes, and regulating the expression of several genes involved in invasion, metastasis, apoptosis, cell proliferation, and differentiation [102].

Furthermore, lncRNAs can be categorized as competing for endogenous RNAs (ceRNAs) that obstruct miRNA targets; hence, they act as miRNA sponges to control CRC

cell motility, invasion, and proliferation [103]. lncRNAs can be found in plasma and serum, two components of the periphery of the blood [104]. It has been found that certain lncRNAs are upregulated in tumors and act as oncogenes, whereas others are downregulated and act as tumor suppressors [105]. For instance, loc285194 is a tumor suppressor, whereas HOTAIR is the first discovered lncRNA that plays a crucial oncogenic function via epigenetic regulatory mechanisms [106]. Moreover, recent studies have shown distinct and variable expression of lncRNAs in CRC, suggesting that lncRNAs may serve as novel molecular indicators in cancer diagnosis and treatment [107]. **Table 1** displays the lncRNAs implicated in the development of colorectal cancer.

Certain lncRNAs tend to be overexpressed in CRC cells and tissues, and they are related to poor CRC patient prognosis and metastasis. Many expressed lncRNAs were discovered to be related to colorectal cancer (CRC) in the era of advanced bioinformatics techniques and microarray tests. In a microarray expression investigation, 762 significantly differently expressed lncRNAs were found in matched CRC tissues [77]. In a separate study, researchers looked for lncRNAs linked to lymph node metastasis in colorectal cancer patients. They found 1133 lncRNAs that were expressed differently in metastatic lymph nodes compared to normal lymph nodes; 260 were elevated and 873 were downregulated [108].

Table 1. lncRNA aberrant expression is a hallmark of CRC.

LncRNA	Loci	Length	Purpose in Biology
CCAT1	8q24.21	2628nt	Functions as an oncogene by increasing c-MYC expression, hence facilitating tumor cell proliferation and migration [109].
CCAT2	8q24.21	340nt	Functions as an oncogene by increasing c-MYC expression, hence facilitating tumor cell proliferation and migration [110].
CCAT1-L	8q24.21	5200nt	Functions as an oncogene by increasing c-MYC expression, hence facilitating tumor cell proliferation and migration [111].
H19	11q15.5	6295nt	It acts as both an oncogene and a tumor suppressor gene [112].
HOTAIR	12q13.13	2337nt	Acts as an oncogene by binding to HOXD and luring the

			PCR2 and LSD1 complexes to it.
MALAT1	11q13.1	8708nt	Promotes cell proliferation, migration, and invasion, and acts as an oncogene by controlling alternative splicing of the endogenous target gene [113].
MEG3	14q32.2	1.6~1.8kb	Supports p53 gene expression; this in turn reduces tumor growth; p53 acts as a tumor suppressor gene [114]
OCC-1	12q23.3	1139nt	Promotes cell proliferation, and functions as an oncogene [115].
PTENP1	9P21	3917nt	Functions as a tumor suppressor gene via binding to miRNA regulatory regions and PTEN [79].
UCA1	19P13.12	1441nt	Functioning as an oncogene by influencing cell growth and development and encouraging tumor invasion [116].
HULC	6p24.3	500nt	Acts as an oncogene by binding competitively to microRNAs to control cell invasion and metastasis [117].
Loc285194	3q13.31	2105nt	p53 and miRNA expression regulation, tumor growth suppression, and tumor suppressor gene function [79].
PCAT1	8q24	725nt	Acts as an oncogene by promoting cell proliferation via interaction with PRC2 [118].
PVT1	8q24	1536nt	Exhibits oncogene function and widespread overexpression in several cancers [119].

The current study seeks to determine if Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT)1 and Plasmacytoma variant translocation 1 (PVT1) can serve as useful diagnostic and/or prognostic biomarkers in colorectal cancer. In addition, the discovery of MALAT1 and PVT1 functions facilitates comprehension of the CRC molecular process, the development of cancer, and carcinogenesis.

MALAT1

Osteosarcoma, hepatocellular carcinoma, and esophageal squamous cell carcinoma have all been linked to MALAT1, a functional lncRNA located on chromosome 11q13 [120]**.** Sequences of lncRNAs are substantially conserved across species, which suggests

that MALAT1 may have vital biological activities [121]. In 2003, MALAT1 was suggested as a predictive marker for stage I NSCLC because of its high association with metastasis in early-stage NSCLC (NSCLC) [122]. Around twenty percent of all published MALAT1 publications were cancer-related research. In addition to malignancies, MALAT1 overexpression has been linked to various non-cancerous illnesses, including myocardial infarction and hyperglycemia [121]. The importance of MALAT1 in controlling the activity of endothelial cells and artery expansion has been demonstrated in the cardiovascular vascular system, according to studies. In addition, the aberrant expression of MALAT1 in myocardial infarction patients suggested that it plays a significant role in cardiovascular disorders [123].

Importantly, MALAT1 induced inflammatory processes in hyperglycemia and was incorrectly regulated in diabetic retinopathy [124]. Moreover, MALAT1 influenced the development of proliferative vitreoretinopathy [125], Type I myotonic dystrophy is an inherited degenerative disorder [126]**,** and keratoacanthoma [127]. Moreover, MALAT1 overexpression was found in the cerebellum, hippocampus, and brain stem of human alcoholics [128] and the progression of microtia [128] reportedly correlated with MALAT1 expression. As a result, MALAT1 is involved in a wide variety of diseases and disorders.

Second research on MALAT1 in NSCLC suggested that the apparent overexpression of MALAT1 in stage I and II NSCLC original tumors enhanced the chance of metastasis [129]. Additionally, elevated MALAT1 expression promoted epithelial-mesenchymal transition (EMT) in NSCLC, which led to brain metastasis [130].

Unquestionably, the effect of MALAT1 on cancer of the digestive system merits widespread consideration. It was observed that the overexpression of MALAT1 in esophageal squamous cell carcinoma increased tumor growth and metastasis. It has been found that increased MALAT1 expression in gastric cancer promotes cancer progression and peritoneal metastasis [131]. In addition, Overexpression of MALAT1 has been linked to an increased risk of tumor recurrence following liver transplantation, which may explain why this protein is so highly expressed in hepatocellular carcinoma [132]. Aberrant MALAT1 overexpression was found to be a negative indication of the clinical development and prognosis of pancreatic cancer in a clinical study [133]. Furthermore, MALAT1

overexpression was associated with tumorigenicity maintenance and castration-resistant prostate cancer progression [134].

Metastasis Associated Lung Adenocarcinoma Transcript 1 was shown to be overexpressed in multiple myeloma patients with melanoma metastases [135]. Using the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway, MALAT1 has been found to promote osteosarcoma tumor growth and metastasis [134].

Taken together, these results suggested that MALAT1 acts as an oncogenic gene during numerous cancer types and that the putative roles of MALAT1 are linked to the hallmarks of cancer, including cell proliferation, metastasis, invasion, and apoptosis.

Recent research has focused on the role of MALAT1 in CRC, namely in the development and progression of the disease. MALAT1 expression was found to be 2.26-fold higher in male patients than in adjacent normal tissues, according to a research of 146 CRC tissue samples collected from patients at stages II and III. Nevertheless, MALAT1 was not linked to any additional clinicopathological factors. Those with higher levels of MALAT1 expression also had lower rates of both disease-free and overall survival. Based on the above data, it is likely that MALAT1 overexpression is a poor prognostic indication for patients with stage II/III CRC [136]. Concerning CRC, emphasis has been drawn to the biological activities of MALAT1 in the genesis and progression of CRC. In a study of 146 CRC tissue samples acquired from patients in stages II and III, the expression of MALAT1 was shown to be 2.26 times greater in male patients than in neighboring normal tissues. Nevertheless, no correlation was found between MALAT1 and other clinicopathological variables. In addition, patients with a greater MALAT1 expression had shorter disease-free and overall survival. The aforementioned findings suggest that the overexpression of MALAT1 may serve as a poor prognostic indicator for stage II/III CRC patients [137].

MALAT1 enhanced tumor development and lung metastasis in a mouse model and boosted colony formation and cell migration in soft agar colony formation and wound healing assays in the lab. Concerning the molecular mechanisms, MALAT1 was shown to bind competitively to the tumor suppressor gene splicing factor proline- and glutamine-rich (SFPQ), releasing the proto-oncogene polypyrimidine tract binding protein 2 (PTBP2) from the SFPQ/PTBP2 complex, and the increased SFPQ-detached PTBP2 could promote tumor

growth and migration. As a result, the 3′ terminus of MALAT1 may have crucial roles in promoting CRC cell invasion and migration [138].

The expression of MALAT1 is raised in tissues that have spread to the lymph nodes, and it is also elevated in CRC tissues overall. MALAT1 overexpression promoted CRC cell proliferation, invasion, and migration in vitro, and it facilitated tumor growth and metastasis in vivo. More investigation is needed to determine whether MALAT1 enhances these biological processes by targeting PRKA kinase anchor protein 9 (AKAP-9) [113].

Tumor growth in colon cancer cells was facilitated by MALAT1's association with transcription factor 4 (TCF4) and -catenin, but this was demonstrated to be suppressed by suppression of yes-associated protein 1 (YAP1). By acting as a sponge for miRNA-126-5p, MALAT1 enhanced the expression of VEGF and twist-related protein 1, thereby improving the biological properties of colon cancer cells (Twist1). CRC underwent EMT and angiogenesis because of MALAT1 which was triggered by YAP1 [139]. MALAT1 also served as a ceRNA to upregulate SRY-box transcription factor 9 (SOX9) expression in lung cancer by sponging miRNA-101 (81). Furthermore, substantial functions of MALAT1 in SLIAN2-associated microtubule mobility of CRC cells via sponging miRNA-106b-5p on CRC invasion and metastasis were revealed, suggesting that the combination of MALAT1/miRNA-106b-5p could serve as a precise prognostic marker for colon cancer cells [120].

PVT1

There is a one-to-one correspondence between the human and mouse plasmacytoma variant translocation-1 (PVT1) genes. Translocation variations in plasmacytomas have been linked to this locus since it was first discovered in the mouse model in the mid-1980s [140]. The PVT1 locus subsequently emerged as a site of variant translocations in human Burkitt's lymphomas [140]. Concurrent mouse and rat studies looking for retroviral integration sites in T-cell lymphomas found the PVT1 gene, suggesting its carcinogenic potential [141]. Because there are no protein-coding genes in the 8q24 region, it is considered a gene desert. PVT1 and the associated protein-coding gene MYC are just two of the many cancer-related risk alleles it carries. Further research showing widespread PVT1 amplification and

overexpression in several cancers strengthened the carcinogenic nature of this gene [142,143].

Mutations in this area, including copy number variants and SNPs, have been linked to cancer susceptibility and progression [144]. According to bioinformatics studies, PVT1 is among a small group of critically important functional lncRNAs in a variety of cancer types [145]. PVT1 consists of 1,957 bp and nine to twelve exons [146]. It is unclear where lncRNA PVT1 originates from, however, it has been studied extensively concerning a wide range of clinical outcomes and characteristics, including cell differentiation, metastasis, overall survival, and tumor stage, in a study encompassing 21 cancer types and 9972 individuals [147].

In addition, lncRNAs can adopt a variety of forms, including ciRNAs, whose tissue- and stage-specific expression has received notice [148]. ciRNAs are generated by back-splicing exons into a circular structure and are hence highly stable and resistant to degradation. PVT1 circRNA (circPVT1) has been characterized, which bodes well for the creation of biomarkers and pharmaceutical targets for cancer control [149].

PVT1 is expressed differently in different cell types, suggesting that its mechanisms of action are also cell and tissue-specific [148]. PVT1 is a gene of great interest for both cancer screening and therapeutic targeting due to its complex network of relationships, proximity to the MYC oncogene, and overexpression in cancer. Although PVT1 is linked to the differential expression of several well-known genes, including MYC, other features of its activity must also be taken into account. It was shown that PVT1 plays a crucial role in competitively suppressing miRNA, and information was provided on PVT1 evaluation of its functional processes in carcinogenesis. Furthermore, the growing frontiers of PVT1 activity and its possible role in a lncRNA-miRNA-mRNA axis were reviewed [119].

PVT1 and circPVT1 have been studied extensively for their potential role in carcinogenesis. In contrast to normal, non-tumorigenic epithelial cells, cancer cells almost always have elevated levels of PVT1. Via the microRNA-31/cyclin-dependent kinase 1 (CDK1) pathway, PVT1 promotes bladder cancer development, migration, and invasion [149]. Moreover, PVT1-derived miRNA-1207-5p enhances the development of breast cancer cells by targeting signal transducer and activator of transcription (STAT6) [149]. In

cervical cancer, it was discovered that PVT1, acting as a ceRNA or molecular sponge, modulates miRNA-424 adversely [150], during stomach cancer PVT1 serves as a competitive endogenous RNA by mopping up miRNA-186 [151].

Tumor cells can benefit from increased autophagy when PVT1 increases the expression of ULK1. Hence, PVT1 regulates autophagy through the miRNA-216b/Beclin-1/PVT1 axis. Another study shows that PVT1 acts as an endogenous sponge for microRNA-365, hence increasing the expression of autophagy-related gene 3 (ATG3) [152]. Overexpression of PVT1 has been linked to tumor development, apoptosis, invasion, metastasis, angiogenesis, and resistance to treatment in certain malignancies. Recent studies have shown that blocking PVT1 makes tumors more sensitive to radiation [153], indicating that its function as an oncogene promotes tumor development. The relationship between the role of PVT1 in tumors and many miRNAs and their downstream pathways is close.

It is hypothesized that PVT1 acted as an oncogene to promote CRC carcinogenesis by controlling the biological activity of cells [154]. Unfortunately, the particular action mechanisms of PVT1 remain unknown. The lncRNA-miRNA-mRNA network has been identified as a crucial component for comprehending the role of lncRNAs in the molecular mechanisms underlying tumor formation. Several miRNAs have been implicated directly in PVT1-mediated carcinogenesis in numerous forms of cancer [155]. Yet, there is a scarcity of research that examines PVT1 in clinical CRC trials. Overexpression of PVT1 boosted colon cancer cell line growth and lowered apoptosis, according to research [156], PVT1 knockdown decreased the proliferation, migration, invasion, and apoptosis escape of CRC cells, according to two studies [157]. Many CRC characteristics arise via a variety of pathways, such as the particular interaction between PVT1 and four-jointed box kinase 1 (FJX1) via competition for miRNA-106b-5p and endogenous sponging of miRNA-26b by PVT1 [158], and sponging of miRNA-20a-5p [159]. Another study found that apoptosis-related genes were increased by PVT1 knockdown, indicating that PVT1 knockdown boosted apoptosis in CRC cells through activating transforming growth factor- (TGF-) signaling [160]. Although attempts have been made to determine precisely how PVT1 functions in CRC, several pathways are still under research.

b. MicroRNAs

Cancer is just one of many human diseases thought to be affected by microRNAs, a family of small, noncoding RNA molecules. These RNA molecules, which range in size from around 18 to 22 nucleotides, regulate the activity of other genes [161]. In 1993, microRNAs were identified as a key regulator in the development of Caenorhabditis worms. Further research has demonstrated the role of microRNAs in virtually every physiological and pathological state [162].

The roles of microRNAs in determining cell destiny, cell proliferation, and cell death are among the most fundamental in all of biology. Beyond these fundamental roles, miRNAs participate in a wide range of biological activities, such as the immune response [163], insulin secretion [164], neurotransmitter synthesis [165], and circadian rhythm regulation [166].

Included in the family of small endogenous RNA molecules are transfer RNA, ribosomal RNA, nucleolar RNA, siRNA, and microRNA. Functionally and biochemically, microRNA and siRNA are indistinguishable. They both range in size from 18 to 22 nucleotides, have 5'-phosphate and 3'-hydroxyl termini, and work together to form the RNA-induced silencing complex (RISC) to silence certain genes. Hence, these molecules are distinguished by their respective origins. Whereas siRNA is made from long double-stranded RNA, microRNA is made from the double-stranded portion of a 60-70 nucleotide RNA hairpin precursor (dsRNA). Formerly, the term "siRNA" was used to describe any short RNA that caused post-transcriptional gene silencing via RISC. Nonetheless, distinguishing miRNA from siRNA has been the norm in recent years [79].

Biogenesis of microRNA occurs in both the nucleus and cytoplasm **(Figure 12).** Primary miRNA transcripts (pri-miRNA) are produced from microRNA genes by RNA polymerase II or RNA polymerase III; this pri-miRNA features a broad stem-loop structure with single-stranded RNA extensions at both ends. Both RNA polymerases are under independent control and recognize various promoter and terminator sequences, providing a flexible regulatory framework [167]. In RNA editing, adenosine is changed to inosine by adenosine deaminases. Adenosine into inosine editing of miRNA precursors can change

their sequence, base-pairing, structural properties, processing, and target recognition abilities since inosine has base-pairing qualities similar to guanosine's [168].

Then, the nuclear microprocessor complex produced by the RNase III enzyme Drosha and the DiGeorge critical region 8 (DGCR8) protein cleaves the pri-miRNA into precursor miRNA (pre-miRNA) (also known as Pasha) [169]. Interestingly, the Drosha-mediated transformation of pri-miRNAs into pre-miRNAs is optional. Certain intronic miRNAs, known as mirtrons, might avoid Drosha processing and create pre-miRNAs via the splicing mechanism [170].

In terms of nuclear export of the pre-miRNA, after nuclear processing, the pre-miRNA is exported into the cytoplasm by Exportin-5 in cooperation with Ran-GTP [171]. No matter the pre-sequence miRNA's or loop structure, exportin-5 can recognize it. To ensure that only properly processed pre-miRNAs are exported, Exportin-5 binding requires a certain length of the double-stranded stem and 3' overhangs [171].

The miRNA pathway's cytoplasmic effector machine, RISC, is guided to its target mRNAs by a single-stranded miRNA it carries. Assembly of the RISC and processing of miRNAs both occur in the cytoplasm, and both processes are controlled by the RISC loading complex (RLC). Core component Argonaute-2 (Ago2), which also mediates RISC effects on mRNA targets, is a part of RLC together with the RNase Dicer and the double-stranded trans-activation response RNA-binding protein "Tar RNA" binding protein (TRBP) [172].

RNase III Dicer cuts the pre-miRNA in half, creating a 22-nucleotide duplex with two overhanging 3'-terminal nucleotides [168]. Following Dicer-mediated cleavage, both Dicer and its TRBP interactors dissociate from the miRNA duplex. The functional guide strand, which is complementary to the target, and the passenger strand, which is subsequently destroyed, must be isolated from the double-stranded duplex to form the active RISC that induces gene silencing [167]. As a result, the miRNA duplex may give rise to two mature miRNAs. In most cases, however, only one strand is integrated into RISC, directing the complex to target mRNAs, while the other strand is degraded. Its functional asymmetry is determined by the thermodynamic stability of the base pairs on either end of the duplex, with the miRNA strand with the less stable base pair at its 5' end being loaded into RISC [173].

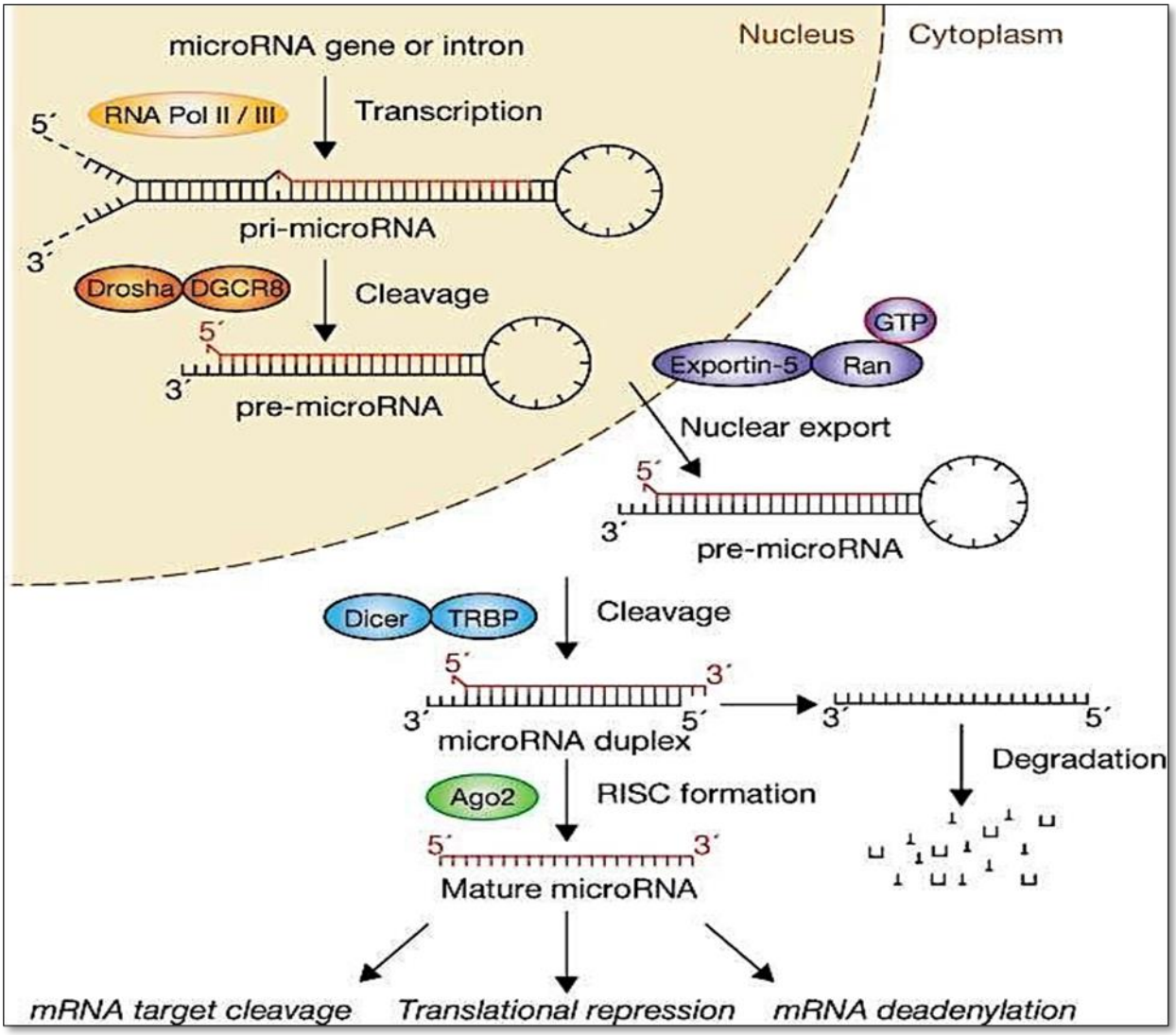

Figure 12: Pathway of miRNA processing [168]**.** Drosha: class 2 ribonuclease III enzymes that in humans are encoded by the DROSHA gene. DGCR8: RNA-binding protein DiGeorge Critical Region 8. TRBP: trans-activation response RNA-binding protein. Ago2: argonaute-2 RISC catalytic component.

The "seed" region, consisting of 6–8 nucleotides at the 5′ end of the miRNA, is the major determinant of miRNA binding to its target mRNA [78]. The expression levels of the targeted mRNA are lowered whenever the sequence of the loaded miRNA is complementary to the seed region. Even while seed matches are more common in the 3′ untranslated region (3′ UTR) of the mRNA, they can occur anywhere in the mRNA [167]. MiRNAs can cause either translational repression (in the case of insufficient complementarity with the 3′ UTR target region) or mRNA destruction (in case of perfect complementarity) **(Figure 13)**. As miRNAs

can regulate the expression of multiple genes, they can exert their effects on multiple signaling pathways in a cell all at once [174].

It has been speculated that miRNAs may function via mechanisms other than the aforementioned "conventional" manner of action. It is thought that miRNAs can increase target mRNA levels in one of two ways: either directly, by interacting with and modifying protein complexes that bind to the AU-rich region of the target mRNA, or indirectly, by interacting with and modifying repressor proteins that inhibit translation of the target mRNA [175]. Additional research shows that may stimulate ribosome biogenesis, so affecting protein synthesis, or may circumvent cell cycle arrest, thereby unleashing target gene repression [65].

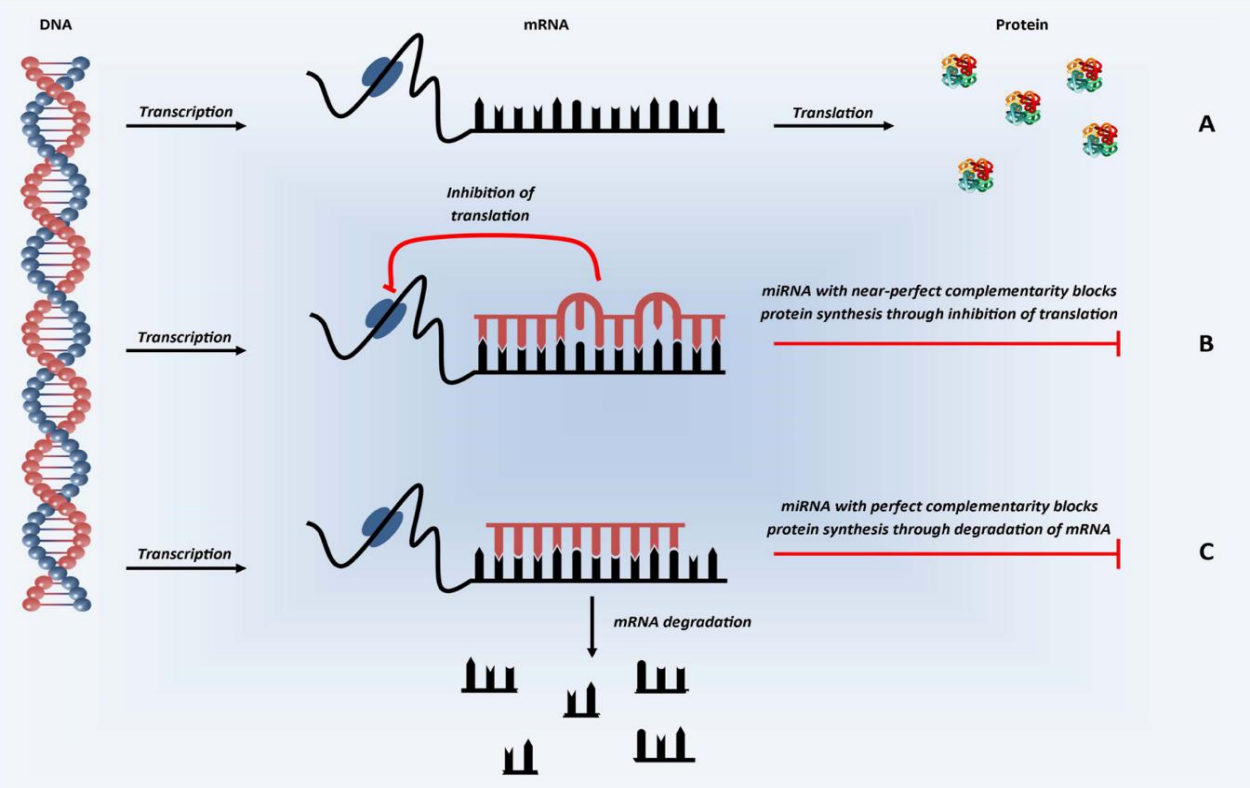

Figure 13: Schematic representation of miRNA mechanism of action [174]

Over-proliferation, loss of apoptotic regulation, acquisition of an invasive phenotype, enhanced angiogenesis, and maintenance of cancer stem cells are the most important CRC growth processes (CSCs) [176] **(Figure 14)**. Many oncogenes are activated, and crucial tumor suppressor genes are repressed, in this process. In the first study linking microRNAs with CRC,

Michael et al. discovered lower levels of miRNA-143 and miRNA-145 in CRC tissue relative to healthy tissue [177]. MicroRNAs may have an oncogenic or tumor-suppressive role in the regulation of cancer-causing pathways. Oncogenic microRNAs sometimes referred to as oncomiRs, typically target and downregulate endogenous tumor suppressor genes.

In the control of cancer-causing pathways, microRNAs may have either an oncogenic or tumor-suppressive role. Oncogenic microRNAs (or oncomiRs) are known to target and repress the expression of endogenous tumor suppressor genes. In contrast, tumor-suppressive miRNAs are essential in suppressing growth and metastasis-related gene expression. Therefore, oncomiR overexpression and tumor suppressive miRNA downregulation significantly affect cancer progression. [178].

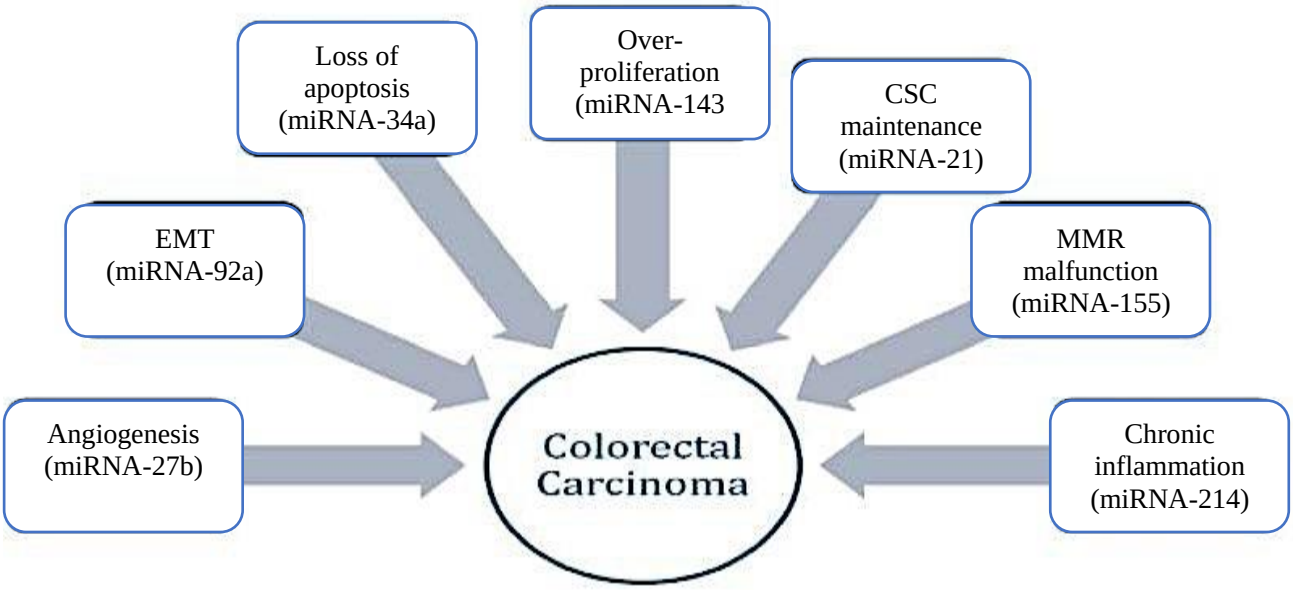

Figure 14: Pathways associated with CRC progression and examples of associated miRNAs [178]**.**

Primary tumor development is characterized by uncontrolled growth and proliferation. The protein-based MAPK pathway is a major mechanism implicated in uncontrolled proliferation in CRC. Several microRNAs have been identified as influencing the proteins in this pathway. In colorectal cancer, for instance, miRNA-7, miRNA-143, miRNA-18a, and miRNA-145 inhibit KRAS and function as tumor-suppressing miRNAs [179,180]. In addition, miRNA-101 reduced lung cancer tumor development by directly regulating many target genes by reducing the expression of enhancer zeste homolog 2 (EZH2) [181] and embryonal rhabdomyosarcoma [182]. Moreover, miRNA-186 influences cell proliferation and

apoptosis in various cancers [182]. In the control of cancer-causing pathways, microRNAs may have either an oncogenic or tumor-suppressive role. Oncogenic microRNAs (or oncomiRs) are known to target and repress the expression of endogenous tumor suppressor genes. The anti-proliferative action of miRNA-186 in multiple myeloma is due to the downregulation of Jagged1 [183]. In glioma stem cells, the highly-expressed p21-activated kinase 7 (PAK7) promotes cell proliferation and inhibits apoptosis [182].

The absence of appropriate apoptotic regulation is a critical characteristic of uncontrolled cell growth. Several miRNAs have been identified as being involved in the dysregulation of apoptotic regulation in CRC. CRC is frequently associated with mutations in p53, a tumor suppressor gene that governs cell cycle and death. The activity of this protein is susceptible to both positive and negative regulation by microRNAs. For instance, it has been revealed that miRNA-96 is increased in CRC and inhibits p53 activity [184]. Yet, recent research indicates that miRNA-34a can boost p53 activation [185]. High levels of miRNA-135a/b have been associated with APC inactivation in colon cancer cells [186]. In addition, it was determined that miRNA-101 directly induced apoptosis in breast cancer cells by reducing the expression of Janus Kinase 2 (Jak2), eyes absent homolog1 (EYA1), and SRY-box transcription factor 2 (SOX2. In addition, miRNA-101 boosted NSCLC cell death directly by boosting caspase 3 activation. [187]

Subpar DNA repair; MMR enzyme deficiency has also been linked to the development of certain forms of CRC. These enzymes correct mutations in the DNA sequence that occurred during replication. Instability in microsatellites, which are repeating portions of DNA, and mutations in protein-coding genes can both result from errors in this process and contribute to disease. Inherited nonpolyposis colorectal cancer (CRC) is the most common kind of hereditary CRC, and it is caused by mutations in the MMR enzyme. in addition, about 15% of patients with extremely uncommon CRC had faulty MMR pathways [188]. In colorectal cancer, miRNAs have been shown to regulate MMR-related genes. Crucial genes in this process such as MutL Homolog 1, MutS Homolog 2, and MutS Homolog 6 are targeted by miRNA-155, for example [189].

By EMT, cancer cells can acquire invasive and metastatic properties. In osteosarcoma cells, microRNA-186 increases E-cadherin expression and lowers vimentin expression. In a

similar fashion, in CRC, miRNA-186 decreases N-cadherin expression while promoting E-cadherin transcription, reversing EMT. The reduction of zinc finger e-box binding homeobox 1 accounts for the effect of miRNA-186 on EMT in CRC cells (ZEB1). Similarly, miRNA-101 has demonstrated tremendous promise in limiting tumor cell invasion and metastasis in a range of malignancies. MicroRNA-101 was shown to inhibit osteosarcoma cell metastasis by directly suppressing Fos proto-oncogene expression (FOS) [190]. MicroRNA-21, which has been identified as one of the most significantly elevated miRNAs in CRC, inhibits a large number of genes involved in invasion and migratory control [191]. EMT is a critical step in the development of an invasive phenotype, and miRNA-92a has been demonstrated to promote it [161].

Angiogenesis is a significant step in the progression of cancer. If there is no new development in the vascular network, tumors cannot acquire adequate nutrition and oxygen supplies and invade other organs through systemic circulation. VEGF promotes the prostaglandin E synthase-1 (PGES-1)/prostaglandin E-2 (PGE-2) pathway in prostate cancer tumor angiogenesis. By targeting VEGF, overexpression of miRNA-186 inhibits PGES-1/PGE-2-mediated neovascularization, hence inhibiting prostate cancer development. In addition, the suppression of angiogenesis by miRNA-101 in CRC was explained by its downregulation of sphingosine kinase 1, which exerted its anti-CRC actions [192]. In addition, miRNA-27b has been found to have anti-angiogenic effects via targeting of VEGF-C [92]**.**

5- Gene polymorphism

Single nucleotide polymorphism is a variant in a DNA sequence that is prevalent in a population (e.g., >1%) and consists of a single nucleotide difference between individuals of the same biological species or paired chromosomes. AAGCCTA and AAGCTTA, two sequenced DNA segments from separate individuals, exhibit a single nucleotide variation. Virtually all common SNPs have only two alleles. SNPs occur in noncoding areas more frequently than coding sections or, in general, when natural selection is working and 'fixing' (eliminating other variations) the allele (eliminating other variants) of the SNP that comprises the most advantageous genetic adaptation [193].

The human genome has around 1030 million SNPs, with one SNP occurring on average for every 100300 nucleotides. More than 5 million human SNPs have been identified. An SNP in a protein's coding sequence can result in amino acid alterations that alter the protein's function. Certain SNPs in a promoter area can alter transcriptional regulation, but an SNP in an intron region can affect splicing or gene expression [194]. The majority of SNPs do not influence health or development. Yet, some SNPs are crucial to the research of human health. Researchers have identified SNPs that may aid in predicting an individual's reaction to specific medications, vulnerability to environmental variables such as pollutants, and illness risk. SNPs can also be used to monitor the transmission of disease-causing genes within families [195].

There is a clear correlation between the susceptibility variations carried by an individual and the prevalence of sporadic tumors. Numerous candidate gene and genome-wide association studies have evaluated common genetic risk factors for colorectal cancer (CRC); however, identification of SNPs that are associated with CRC susceptibility is crucial for understanding disease biology and identifying diagnostic and prognostic parameters of CRC [188]. In **Table 2**, we saw some documented SNPs that have been linked to an increased risk of developing CRC. SNPs were categorized according to their location on chromosomes and the genes they are associated with.

According to reports, ncRNAs play crucial roles in a variety of biological processes, and SNPs may contribute to illnesses or characteristics by affecting ncRNA expression. Nevertheless, the relationships between SNPs and ncRNA expression are not well understood [103].

Although it is evident that ncRNAs, particularly miRNAs, and lncRNAs, play a role in carcinogenesis through regulating EMT, research has pointed to the significance of EMT in tumor cells weakening E-cadherin-dependent cell-cell junctions and enhancing motility. While the loss of epithelial indicators such as E-cadherin has been found to be related to a poor prognosis in various forms of cancer, this finding is significant [204]. Hence, EMT is a key factor in carcinogenesis [205].

Table 2: Examples of SNPs that associated with susceptibility for the development of CRC

Example of SNPs	Type variation gene(s) near locus	Position on chromosome	OR	Risk	Reference
rs2736100	TERT, a variation with 3 primary UTRs	5p15.33	1.07	A	[196]
rs1665650	A variant intron of HSPA12A	10.q25.3	0.95	T	[197]
rs6691170	Intergenic Variant in DUSP10 (LOCI) 05372950	1q41	1.01	T	[198]
rs10911251	A LAMC1 intron variation	1q25.3	1.11	A	[198]
rs11903757	Intergenic variation at NABPI/SDPR (NABPI/SDPR)	2q.32.3	1.14	C	[198]
rs10936599	MYNN, variation in the upstream gene	3q26.2	1.07	A	[198]
rs2736100	TERT, a variation with 3 primary UTRs	5p15.33	1.07	A	[196]
rs12080929	Variant intron of TRABD2B	1p33	0.87	C	[199]
rs6983267	CCAT2 variants include an intron variant, an exon variant, and a non-coding transcript variant.	8q24.21	1.15	C	[200]
rs11987193	Intergenic Variant of DUSP4	8p12	0.79	T	[199]
rs7014346	Caspase-8 intron variant, non-coding transcript variant, POU5F1B intron variant	8q24.21	1.20	A	[201]
rs10795668	LOC105376400, upstream gene variant	10p14	1.32	A	[202]
rs1035209	Differential expression of ABCC2/MRP2 within an intergenic region	10q24.2	1.13	T	[199]
rs11196172	Intron variant of TCF7L2	10q25.2	1.14	C	[199]
rs1665650	HSPA12A, intron variant	10.q25.3	0.95	T	[202]
rs6687758	DUSP10, regulatory region variant	1q41	1.04	C	[203]
rs59336	TBX3, intron variant	12q24.21	1.15	T	[203]
rs1800469	TGFB1, a variation in an upstream gene	19q13.2	1.09	C	[203]
rs4813802	Variant in the regulatory area of BMP2/HAO1/FERMT1	20p12.3	1.10	C	[203]

6- Cadherins

An example of a transmembrane protein, a cadherin, is composed of three subunits: (1) an extracellular cadherin domain that mediates homotypic cadherin-cadherin interaction; (2) a single-pass transmembrane domain (which is absent in seven-pass transmembrane cadherins); and (3) a cytoplasmic domain that connects the cell surface to the cytoskeleton [206]. There are several different forms of cadherins, with type I classical cadherins including E-cadherin, N-cadherin, and P-cadherin, and type II classical cadherins including VE-cadherin and OB-cadherin [204]; protocadherins; cadherins of the FAT/dachsous group; cadherins of the desmosomes [207]; and cadherins of the seven-pass transmembrane family [208].

The maintenance of cellular and tissue morphogenesis in multicellular animals is primarily dependent on cell-cell adhesion [204], the adhesion connections start and keep going. Gene regulation is involved in maintaining healthy tissue homeostasis, and this is mediated in part by adhesion between cells and the extracellular matrix [204]. Defects in adhesion between cells and between cells and the extracellular matrix, as well as abnormalities in adhesion-mediated signaling pathways, may lead to malignant phenotypes in normal cells [205].

Due to its role in epithelial cell adhesion, cadherin expression has been related to cancer. It has been shown that the loss of normal membrane polarization and cell-cell adhesion are necessary steps in the progression of a well-differentiated benign adenoma with apicobasal polarisation, a feature of normal epithelial cells, into an invasive carcinoma [209].

Both E-cadherin and N-cadherin, two of the original members of the cadherin superfamily, have pivotal functions in the progression of tumors. In order to maintain polarity between epithelial cell layers and prevent tissue disruption, E-cadherin is required [210]. Loss of E-cadherin-mediated cell-cell adhesion occurs in cancer but can be restored with treatment [211].

Changes in adhesion-mediated signaling pathways occur when cell-cell adhesion is broken. Cell motility, a feature of invasive metastatic cancer, may also be impacted [204]. Cadherins have been linked to carcinogenesis, and more research into their functions in tumor growth is needed. EMT is distinguished by the downregulation of E-cadherin and the simultaneous overexpression of other cadherins, such as N-cadherin, which plays an

important role in early invasion and metastasis [212]. It is commonly established that epithelial cell EMT results in increased cell-cell adhesion as well as motility and invasiveness [213].

E-cadherin expression is often reduced in advanced malignancies, according to a number of studies, and this may be connected, at least in some cases, to increased metastasis and recurrence [107]. In vitro, studies have linked E-cadherin downregulation to the acquisition of a mesenchymal phenotype and invasive behavior [214]. Furthermore, when E-cadherin is produced constitutively, this process is partially or completely reversed [215].

The E-cadherin-catenin complex was the first candidate for a signaling pathway to be investigated. Reduction, inactivation, or relocation of E-cadherin, mutation or reduced transcription of related genes, and many other factors all contribute to decreased cell adhesion, which is crucial during tumor spread [216]. Hepatocyte growth factor, epithelial growth factor, and transforming growth factor- are just a few examples of the many stimuli that have been postulated to promote EMT by downregulating E-cadherin-mediated cell adhesion and upregulating EMT-related transcriptional factors including Snail and Twist1 [213,217,218]. Hence, the canonical Wnt signaling pathway and TCF-regulated genes are strengthened by this downregulation, which also decreases cell-cell adhesion and provides an oncogenic stimulus via catenin. Wnt5a overexpression is linked to increased cell migration and treatment resistance, suggesting that the non-canonical Wnt pathway may play a role in cancer metastasis [219].

Conclusion

As a result of the critical evaluation of the work included in the review, it is predicted that PVT1 acts as a sponge for miRNA-186 that promotes the expression of Twist1 leading to E-cadherin down-regulation, indicating the promotion of the EMT process thus enhancing invasion, migration and metastasis. Although, there is a paucity of literature on the correlation between PVT1 with miR-186 as important diagnostic and prognostic parameters in other cancer types. The identification of this correlation would be useful in understanding the disease biology and predicting important diagnostic and prognostic parameters in CRC. It is also predicted that MALAT1 acts as a sequester for miRNA-101 that will promote the expression of TGF-β leading to a decrease of E-cadherin expression, indicating the promotion

of the EMT process thus enhancing invasion, migration, and metastasis. However, An obvious inverse correlation between MALAT1 and miR-101 was observed in many types of cancer, the clinical relevance of this correlation in CRC remains to be investigated.

Conflict of Interest

The Authors declare no conflict of interest.

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