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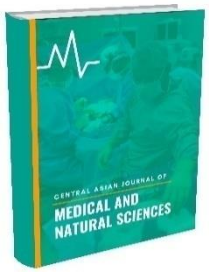

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Colon Cancer: Risk Factors and Therapeutic Approaches

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Abstract: Colorectal cancer is the third most prevalent type of cancer in both men and women, despite being the second most significant cause of cancer-related fatalities. Both colon and rectal cancers are together referred to as colorectal cancer. The first sign of colon cancer is often the formation of tiny cell groupings called polyps inside the colon. Some of these polyps could transform into cancerous tumors in five to ten years. Age raises the likelihood of developing colorectal cancer. People are frequently too ashamed to undergo early detection screening tests for this type of cancer, Despite the possibility that it may be prevented. The risk of colorectal cancer increases with age. Genetic diseases such polyposis and hereditary non-polyposis colorectal cancer, as well as a family history of colorectal cancer, as well as personal histories of inflammatory bowel illness, polyps, and malignancies, are additional risk factors.. In this review, we explain the etiology and risk factors of colorectal cancer, as well as on Therapeutic Approaches.

Colon cancer

Cancer is a wide A group of disorders distinguished by an unregulated growth of cells. Rectal cancer begins in the rectum, while colon cancer starts in the big intestine (colon). The major jobs of the large intestine are to breakdown food into excrement and absorb water and vitamins. The primary purpose of the rectum is to store excrement until the nerves in its walls provide signals to defecate. While left-sided colon and rectal tumors more frequently present with alterations in feces, right-sided colon cancers frequently present with widespread symptoms including anemia. (Röhrl, 2020; Majumdar *et al*.,1999). Symptoms of obstruction may be present with tumors. The majority of individuals with symptomatic CRC receive a diagnosis at a late stage, and 20–30% of them already have metastatic disease.(Van *et al.*, 2009; Schmoll *et al.*, 2012) About 20% of elderly persons acquire CRC, which is mostly caused by polyps called adenomas (Gondal *et al.*, 2003).Adenomas are common in people over 60, although only a tiny proportion of them progress to cancer (Gondal *et al.*, 2003).Screening programs have been widely implemented in order to find and remove precancerous polyps before they develop into cancer. (Benard *et al.*2018) .

Etiology

Although the etiology of CRC is yet unknown, the following factors may be involved: factors that are genetic: Studies have shown that first-generation relatives of colon cancer patients, who account for 20% of CRC cases, had a three-fold higher risk of developing cancer. Inherited CRC has been linked to the mismatch repair gene (MMR) and a genetic disorder termed familial adenomatous polyposis (FAP). (Maida *et al*.,2017).

Dietary factors: Currently, CRC is believed to be more common in those who eat diets high in fat, high in animal protein, and low in cellulose.,. Consuming too much fat will increase intestinal carcinogens, bile acid breakdown, bile secretion, and the activity of anaerobic bacteria in the gut (Murphy *et al.*,2019).

Non-cancerous diseases: Non-cancerous conditions can cause CRC, including colorectal polyps, colorectal adenomas, ulcerative colitis, and Crohn's disease. According to research, 3-5% of those with ulcerative colitis will later develop CRC, and 10% or more of people with ulcerative colitis who have had it for longer than 20 years will experience malignant transformation. Colonic polyps are thought to be the cause of 15–40% of colon cancers, with a precancerous period of 2–5 years. Less than 2% of adenomas with a diameter of less than 1 cm and more than 40% of adenomas with a diameter of more than 3 cm are malignant. (Sun, 2014).

Other factors: Patients receiving pelvic radiation therapy have greater rates of sigmoid and rectal cancer,and carcinogenic exposure and lifestyle variables including being overweight and inactive are risk factors for CRC. (Sun, 2014).

Staging of colon cancer

Pathological stage is the key determinant of prognosis for those with colon cancer. The tumor and node metastasis (TNM) strategy, which is based on the degree of regional lymph node involvement, the depth of intestinal wall invasion, and other parameters, is the most common staging technique.(Compton and Greene 2004; Greene 2004; Greene *et al.*, 2002) . The tumor's invasion depth determines the tumor's T stage, which ranges from T1 (mucosal invasion) to T4 (invasion of the serous or nearby structures). With the depth of tumor invasion comes an increased risk of nodal and widespread metastases. Based on a pathological analysis of the surrounding lymph nodes, the three N categories are N0 (no affected lymph nodes), N1 (1-3 affected lymph nodes), and N2 (>3 impacted lymph nodes). (Swanson *et al.*,2003).

Genetic of colon cancer

A genetic predisposition accounts for roughly 5% of CRC cases, the bulk of which are sporadic. The genetic condition familial adenomatous polyposis (FAP) is characterized by many colon polyps that first emerge at a young age. The likelihood of acquiring colorectal cancer over the course of one's lifetime is roughly 100% if the colon and rectum are not removed (Kastrinos and Syngal 2011). Hereditary non-polyposis CRC, sometimes referred to as Lynch syndrome or HNPCC, accounts for 3-5% of all CRC cases. Approximately 90% of germ line mutations that cause disease are in the MLH1 and MSH2 genes. 45 years is the typical cancer diagnosis age. Lynch syndrome is also linked to other diseases such stomach cancer, ovarian cancer, endometrial cancer, and small bowel cancer. (Bonadona *et al.*, 2011; Lynch *et al.*.,2009).

Risk factors of colon cancer

Investigations have been done into the associations between various risk factors and the development of CRC. Despite the fact that two large meta-analyses have linked smoking to a number of diseases (Botteri *et al*., 2008; Huxley *et al*., 2009), CRC is frequently not the primary subject of discussion.

Recent investigations (Huxley *et al.,* 2009) have confirmed a 2004 study that found that drinking alcohol is associated with a modestly higher dose-dependent risk of developing colorectal cancer (Chan *et al.*, 2011; Vieira *et al.,* 2017). High red and processed meat diet raises the risk of CRC. As a risk factor for CRC, obesity has also been identified. (Jensen *et al.*, 2017). Both type 1 and type 2 diabetes increase the chance of developing CRC (Harding *et al.*, 2015; Yuhara *et al.*, 2011). Furthermore, sedentary habits increase the risk of colon cancer but do not increase the risk of rectal cancer (Schmid and Leitzmann 2014).

Reduced risk factors for colon cancer

According to research conducted by Larson *et al.* (2006), Aspirin, which contains acetylsalicylic acid, is frequently used to prevent both colorectal adenomas and colorectal cancer. According to Boyle et al. (2012), The risk of colon cancer (CC) is greatly reduced by regular exercise. In a randomized controlled study (RCT), oral calcium supplements were found to reduce the risk of cancer in general, but the sample size was too small for CRC specifically. (Lappe et al. 2007). Vitamin D deficiency has been linked to the growth and development of cancer in animal experiments (Tangpricha *et al*., 2005).

Consumption of dairy products and calcium has been linked to a lower risk of colon cancer among people in studies. (Slattery, 1988; Wu *et al.,* 2002). While some studies have not been able to prove a relationship, some studies have found that a high intake of dietary fiber reduces the incidence of CRC (Cummings, 1992), possibly by reducing constipation and stool transit time. Fruit and vegetable consumption may be responsible for the reduced risk associated with increased fiber intake shown in several studies (Terry *et al.*, 2001). Giovannucci, (1998) found that drinking coffee may reduce your risk of developing colorectal cancer.

Therapeutic Approaches

Radiation therapy:

Neoadjuvant therapy has been advocated for rectal cancer and has proven to be successful in reducing tumor burden in patients with intermediate and advanced stages of the disease when radiotherapy and chemotherapy are combined or used alone. The basic objectives of radiation therapy are to prolong overall survival and lessen the possibility of local recurrence. To reduce local recurrence, preoperative radiation appears to be more successful than postoperative therapy, but it does not appear to increase overall survival (van *et al.*, 2011). The superiority of short-course radiation (RT) compared to long-course RT has long been the subject of discussion. Compared to short-course RT, long-course RT is linked to greater rates of acute toxicity, but there are no discernible differences in the incidence rates of late side effects. For stage II and stage III CRC, radiation and adjuvant radiation therapy are some of the most effective treatments. Radiation treatments, however, may have certain long-term side effects on important organs. (Ngan *et al*., 2012).

Surgical Treatment

The first line of defense against tumors has traditionally been surgery; however, Surgery is frequently demoted to the third or second line of defense with the rising use of new adjuvant medicines, changing how cancer is managed as a result of advancements in tumor immunology , molecular biology, and genetics (Sabel *et al.*, 2014; Manzini *et al.*, 2017). When hepatocellular carcinoma transplantation is not a possibility, all standards recommend resection (surgical therapy) as the preferable form of treatment in healthy livers. Thus, if liver transplantation is not feasible or is inappropriate, Zamora-Valdes *et al.* (2017) showed that patients with multi-nodular HCC may be offered liver resection as long as the underlying liver disease has not decompensated.

Immunotherapy for Colorectal Cancer

In immunotherapy, the immune system is often stimulated in a way that alerts it to begin destroying cancer cells. Tumor cells frequently express certain surface proteins that give them the ability to deceive the immune system into ignoring them. The immunotherapies advised for colorectal cancer function by inhibiting either the CTLA-4 receptor or the PD-1/PD-L1 binding interaction (PD-1/PD-L1). T-cells of the immune system can target tumors thanks to both methods. (American Cancer Society,2023.)

Since they have been demonstrated to respond better to these treatments, people with defective mismatch repair (dMMR) genes are largely advised to employ approved immunotherapies for colorectal malignancies (National Cancer Institute, 2022). Typically, the patient receives immunotherapy through intravenous infusion. The following immunotherapies for colorectal cancer have FDA approval:

Pembrolizumab ,Nivolumab, and Ipilimumab

Hormonal Therapy

According to Fairchild *et al.* (2015), hormones are chemical messengers that are produced by certain endocrine system organs or cells all over the body and act on targets that are far from their site of origin. Exogenous hormones are administered to cancer patients with hormone-dependent tumors in an effort to alter their endocrine systems by preventing either hormone production or receptor activation. Additionally, some hormones, like corticosteroids, can down-regulate genes and cause apoptosis, which has a general anti-proliferative effect (Schmidt *et al.*, 2004).

In addition, according to Fairchild *et al.* (2015) Hormone therapy used to treat cancer can be divided into three categories: Two examples of such drugs are aromatase inhibitors and their hormonal analogues, which are naturally occurring hormones or their byproducts that directly inhibit tumor growth. Cancers that are hormone-dependent are responsive to suppressing the manufacture of hormones like gonadotropins and are sensitive to circulating hormone levels.. For example, researchers have provided evidence that estrogen protects against HCC by inhibiting tumor-associated macrophages, reducing interleukin 6, and STAT3(a). A critical regulator of macrophage function) (shi *et al.*, 2014).

Virotherapy

Oncolytic viruses have received a lot of interest recently for the treatment of cancer due to the inefficiency and unfavorable side effects of traditional cancer treatments for advanced disease. According to Fukuhara *et al.* (2016), oncolytic viruses are referred to as naturally occurring or genetically altered viruses that only spread via cancer cells and kill those cells without harming healthy cells. Additionally, Jebar *et al.* (2015) demonstrated that the origin of oncolytic viral therapy rests in the expression of their proteins, selective genomic replication, and successful infection of cancer cells.

Adenovirus, echovirus, and herpes simplex virus type 1 are three oncolytic viruses. —were the focus of Russell and Peng's (2018) research, and they underline the advantages of each platform. There are more than 3,000 different viral species, however not all of them are effective against cancer. When used in conjunction with immune modulatory agents, viral therapy has showed promise in the treatment of HCCs (Yoo *et al.*, 2017).

Chemotherapy

The medications oxaliplatin (OX), irinotecan (IRI), and capecitabine (CAP, XELODA, or XEL), as well as fluoropyrimidine (5-FU)-based monotherapy, are examples of multiagent chemotherapy

regimens that involve one or more agents. When additional drugs are taken, effectiveness appears to be equal, with only adverse effects possibly differing between regimens. (Tournegand *et al.*, 2014). The multiagent FOLOXIRI regimen (5-FU+OX+IRI), which is rarely used due to its potential for increased toxicity, is not supported by emerging evidence that it has increased efficacy (Vera *et al.*, 2015; Falcone *et al.*, 2007), but According to recent research findings, chemotherapy has improved the MS time of colorectal cancer patients, especially those with metastases, to approximately 20 months, making chemotherapy the backbone of colorectal cancer treatment. (Goldberg *et al.*, 2004; Cassidy *et al.*, 2004; Souglakos *et al*., 2006).

Chemotherapy for Colorectal Cancer

Chemotherapeutic drugs target rapidly proliferating cells by destroying their DNA and causing them to undergo programmed cell death, or apoptosis. Chemotherapy for colon and rectal cancer can be administered intravenously or as a systemic tablet.

The following chemotherapy medications for colorectal malignancies have been authorized by the US Food and Drug Administration (FDA):

Fluorouracil, Oxaliplatin, Capecitabine, Irinotecan hydrochloride ,tipiracil hydrochloride; Trifluridine

The Evolution Of Colorectal Cancer Chemotherapeutics

Since 1957, when 5-FU (C4H3FN2O2) was first used in the clinical therapy of CRC, there has been very minimal advancement in the management of advanced CRC.

1. Leucovorin and 5-fluorouracil

By inhibiting thymidylate synthase, the folinic acid derivative leucovorin (LV) (C20H23N7O7) enhances 5-FU's cytotoxic effects (Longley *et al* 2003). By reductively methylating reduced folate 5, 10-methylenetetrahydrofolate (CH2THF), According to Diasio and Harris (1989), thymidylate synthase catalyzes the transformation of deoxyuridine monophosphate (dUMP) into deoxythymidine monophosphate (dTMP). There is only one de novo generator of the chemical thymidylate, which is needed for DNA replication and repair, in this process. (Longley *et al*., 2003).

These active compounds inhibit RNA synthesis by inhibiting thymidylate synthase and causing incorrect incorporation of fluorine nucleotides into RNA and DNA (Longley *et al.*, 2003).

Thymidylate, a crucial chemical required for DNA replication and repair, can only be produced through processes that are catalyzed by thymidylate synthase (Longley *et al.*, 2003). Since more than 50 years ago, 5-FU has been utilized to treat CRC. In a number of early randomized studies utilizing 5-FU as an adjuvant, patient survival was not significantly improved (Panettiere *et al.*, 1988; Higgins *et al.*, 1984). According to estimates by O'Connell (1989), the total response rate to a single medication in advanced CRC ranged from 10% to 15%.

2. Capecitabine

Thymidine phosphorylase catalyzes the enzyme conversion of the oral prodrug capecitabine (C15H22FN3O6) to 5-FU. Capecitabine, which is derived from the 5-FU precursor medication doxifluridine, undergoes three activation processes before becoming FU: After being absorbed by the gut, capecitabine is first converted by carboxylesterase to 5'-deoxy-Sfluorocytidine (5'-DFCR), then by cytidine deaminase in the liver to 5'-deoxy-S-fluorouridine (5'-DFUR), and lastly to the active drug, capecitabine. FU, by thymidine phosphorylase. However, thymidine phosphorylase is selectively activated by the medication and has a lower systemic toxicity since it is more prevalent in tumor cells than in healthy tissues(Wong and Giandomenico, 1999; Miwa *et al.*, 1998).

3. Cisplatin

Cisplatin (Cl2H6N2Pt), (Cis-diamminedichloro-platinum (II)) is one of the most effective chemotherapeutic medications for the treatment of various malignancies. It was the first anti-cancer drug in its class to reach phase I clinical trials in 1971 after being given in vivo to mice with sarcoma in the late 1960s. It exhibits therapeutic efficacy in the treatment of lung, bladder, ovarian, head & neck, cervical, and testicular malignancies, with response rates exceeding 90% (Brown *et al.*, 2019). One of the strongest chemotherapy medications frequently used to treat cancer is cisplatin , because of better prognoses, these cancers now have a lower risk of being fatal. (Desoize and Madoulet, 2002). Due to the clinical success of CDDP and its derivatives, much effort was put into creating more potent metal-based anti-cancer drugs (Frezza *et al.*, 2010). However, because of side effects in healthy tissues, its use is restricted.

There is strong evidence that the drug's cytotoxicity is caused by its interaction with DNA, which causes DNA lesions that may hinder both DNA transcription and DNA replication. In several cancer cells, the mechanisms by which cisplatin produces its anticancer effect have been thoroughly investigated (Todd, 2010). There is substantial evidence that the drug's interaction with DNA results in DNA lesions that may impede DNA transcription and DNA replication (Kelland, 2007; Wang and Lippard .2005).

4. Oxaliplatin

Third-generation platinum-based drug oxaliplatin (C8H14N2O4Pt) is currently utilized as the first line of therapy for metastatic colon cancer (Petrioli *et al*., 2008). According to Graham *et al.* ,(2000), it causes dividing cells to undergo apoptosis and causes the mitotic cell cycle to become immobile. This is how it exerts its cytotoxic effects. When taken at medically recommended doses, According to Raymond and colleagues (1998), it is purportedly less toxic to the auditory, hematologic, and renal systems than precursor medications like cisplatin and carboplatin. But unlike other platinum-based chemotherapeutics, oxyliplatin appears to have a unique set of adverse effects. Peripheral sensory neuropathy, gastrointestinal toxicity, and hematologic toxicity were oxaliplatin's most frequently reported side effects during clinical testing. (Cassidy, and Misset, 2002).

5. Irinotecan

Camptothecin is a quinoline alkaloid, and irinotecan (C33H38N4O6) is a semi-synthetic equivalent that inhibits topoisomerase I (Top I) to produce cytotoxicity (Rougier *et al.*, 1997). To cut, relax, and reanneal DNA strands, Top I performs a critical function for DNA transcription. Irinotecan's active metabolite, SN-38, interacts with Top I and its DNA complex to form a stable ternary structure that promotes DNA damage and death while inhibiting DNA re-ligation. When irinotecan is administered, single-strand breaks in cells turn into double-strand breaks predominantly as a result of the replication fork colliding with cleavage complexes made of DNA and SN-38 during the S phase of the cell cycle (Pommier and others 1994). In the late 1990s, phase II studies examining irinotecan's overall benefits showed that it was effective as a second-line treatment for patients with advanced CRC who were intolerant to 5-FU(Grothy *et al.* (2004).

Personalized Medicine for Colorectal Cancer

According to American Cancer Society ,(2023) targeted therapy targets particular genetic and molecular pathways in order to kill cancer cells. The following targeted treatments for colorectal cancer have FDA approva:

Bevacizumab, Cetuximab, Panitumumab, Ramucirumab, Regorafenib, Tucatinib, and Ziv-aflibercept are some examples of medications.

Bevacizumab, ramucirumab, and ziv-aflibercept are examples of authorized targeted treatments that function by preventing the interaction between VEGF ligands and receptors. Tumors need this binding interaction to spread. Epidermal growth factor receptor (EGFR) ligand-binding interaction is blocked by cetuximab and panitumumab. This pathway may possibly contribute to the development of cancer. For those who have mutations in the KRAS, NRAF, or BRAF genes, the therapy is ineffective. Last but not least, regorafenib and tucatinib target the HER2 pathway, which is expressed by some cancer cells and stimulates uncontrollable proliferation.

Combination Therapy for Colorectal Cancer

Many of the pharmacotherapeutic best practices for colon and rectal malignancies involve combining therapies. Combination therapies frequently incorporate a treatment plan that combines immunotherapies or targeted medicines with chemotherapeutic medications (Seymour *et al.*, 2007). The following combination therapy for colorectal cancer have FDA approval:

- FOLFIRI: leucovorin calcium, fluorouracil, and irinotecan hydrochloride; CAPOX: capecitabine and oxaliplatin
- FU-LV: Leucovorin calcium and fluorouracil; FOLFIRI-bevacizumab; FOLFIRI-cetuximab; FOLFOX; capecitabine and irinotecan hydrochloride; and XELIRI.

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