Early onset Colorectal Cancer: A Narrative Review

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Abstract

Colorectal cancer remains a leading cause of cancer related deaths and there has been a rise in the incidence of early onset colon cancer or colon cancer diagnosed before the age of 50 years old. Early onset CRC (colorectal cancer) has several differences in clinical presentation as well as histopathology, genetics alteration and molecular profiling. Demographic variance also exists in both the developing and developed countries. Increasing obesity and lifestyle disorder in younger population may influence this trend. Some studies have observed that early onset CRC may have worse outcomes than older populations. This narrative review aims to highlight the pathogenesis of early onset CRC, as well as its clinical presentation, treatment, prognosis and how it differs from late-onset CRC.

Introduction

CRC usually presents with nonspecific symptoms such as blood in stools, altered bowel habits, fatigue and weight loss. 1 There is an increasing concern regarding the rise of CRC in younger populations. Increasing obesity and unhealthy lifestyles such as Westernized high-fat diets may have influenced this trend. Screening colonoscopy and removal of precancerous polyps are shown to decrease mortality. 2-4

10% of newly diagnosed CRC cases are diagnosed before the age of 50 making it an emerging health problem. 5 Five year survival rate for CRC is approximately 60% for the localized stage but declines to 14% for distant metastasis. 6 Numerous studies have shown that early onset colon cancer has a lower survival rate compared to late-onset colon cancer, signifying potential molecular biology difference. 7 The characteristics and molecular pathogenesis of early onset colon cancer differ from those of late-onset, as it has a wide spectrum of diseases. 8 In this review we discuss the incidence, pathogenesis, risk factors, clinical presentation, treatment and prognosis of early onset CRC.

Incidence and Epidemiology

Recent studies have demonstrated an increased number of colon cancer cases diagnosed in population younger than 50 years of age. Despite advances in treatment and screening modalities CRC remains the third most common cancer and second most common cause of cancer related deaths worldwide. 9 There is a rising incidence of CRC in populations younger than 50 years of age in high income countries. 10 It accounts for 10% of newly diagnosed colon cancer cases and contributes to the overall mortality. 11 In western countries such as the United States 5% of all CRC diagnosed patients are <45 years of age based on the Surveillance, Epidemiology and End Results Program (SEER). 5 Eastern European countries reported an annual increase of 7.4% in colon cancer among young individuals between 2008 and 2016. 12 Rising cases of early onset colon cancer are also seen in other countries, such as Egypt and Iran. 2 It is evident that an increasing incidence of early onset CRC is observed in both developed and developing countries, and there is also decreasing mortality in developed countries such as Japan, the United States, Australia, and Western European countries which is likely due to the advancement of treatment and screening modalities. On the other hand, there is increasing mortality in countries such as Mexico, Brazil, and Eastern European countries which could be related to health inequality due to a lack of resources. 13 It is important to note that Asia accounts for half of the
colon cancer burden worldwide, especially China which has the highest deaths and disability rates from colon cancer, attributable to dietary risks, followed by the United States, India, and Japan. 14,15

Pathogenesis

Role of Genetics and Molecular Profile

Studies have shown that there is a difference in genetic variants between early and late-onset CRC. In a 2021 Spanish Ministry-funded study it was shown that approximately 13% of patients with early onset CRC carry pathogenic germline variants in known cancer predisposition genes.16 Patients with early onset colon cancer tend to have more hereditary syndromes (such as familial adenomatous polyposis, MUTYH-associated polyposis, Lynch syndrome, and certain hamartomatous polyposis conditions). 17 Histopathology features show that early onset CRC often has signet ring cell histology, lymphovascular invasion and perineural invasion compared with late-onset CRC. These features are associated with aggressive tumors and a worse prognosis. 18 Molecular profiling studies have shown that patients with early onset CRC have distinct molecular subtypes compared to older patients including increased expression of CMS1 of unclear etiology. 19 Epigenetic alterations such as changes in DNA methylation patterns are observed in early onset CRC. Hypomethylation of long interspersed nuclear elements is significantly higher in younger patients than in older patients and is associated with a lower survival rate. 20,21

Lifestyle and Modifiable Risk Factors

While genetics play an important role, lifestyle and environmental factors play an even bigger role in disease expression in early onset CRC. 22,23 Various risk factors of CRC are illustrated in figure 1.

Figure 1: Schematic representation of risk factors involved in the initiation and progression of colon cancer.

Highly processed diet with high intake of red meat and low fiber intake has been associated with increased risk of colon cancer.24,25 Deep-fried food interferes with lipid metabolism, increases oxidative stress, and increases carcinogen production. Food high in dietary trans fat is also associated with an increased risk of CRC. 26 Habitual red meat consumers have 20% higher risk of developing CRC when compared to occasional consumers. 27

Regular alcohol consumption is associated with colon cancer with an increased risk parallel to the duration of alcohol use. Moderate to heavy alcohol consumption has an 20% additional risk of developing CRC.28 Alcohol metabolism increases oxidative stress, disturbs the colon epithelial barrier and the colon microbiome, and produces carcinogens. 29 Studies have shown that the microbial environment of the colon, the concentration of bile salts, metabolites, and the level of oxygen also play a role in early onset colon cancer. 30
Cigarette smoking increases the risk of developing colon cancer,\textsuperscript{31} increases the expression of 5-LOX in colon cancer, disturbs the apoptosis mechanism and upregulates acetylcholine and noradrenaline receptors. \textsuperscript{32}

Physical activity decreases the risk CRC development.\textsuperscript{33} Sedentary lifestyle sitting for more than 14 hours per week may increase the risk of developing early onset CRC.\textsuperscript{34} Colon cancer survivors with high levels of physical activity have a lower risk of recurrence. \textsuperscript{35}

The rising trend of obesity in the young population is worrisome especially since studies have shown that it may increase the risk of developing CRC and may contribute to the increasing incidence of early onset CRC. \textsuperscript{23} Carcinogenic mechanism of obesity could stem from insulin resistance, which increases chronic inflammation, oxidative stress, DNA damage, and insulin-like growth factor-1 (IGF-1) levels further stimulating cell proliferation. \textsuperscript{36} Obese individuals with type 2 diabetes mellitus have an increased risk of developing colon cancer which is thought to be due to prolonged exposure to high levels of insulin in the colon. \textsuperscript{36} Obese individuals with type 2 diabetes mellitus has increased risk of developing colon cancer which is thought due to colon prolonged exposure to high levels of insulin. \textsuperscript{37} Weight loss seems to help lowering this risk. \textsuperscript{38}

Clinical Presentation, Diagnosis, and Staging

Most patients with colon cancer have nonspecific symptoms, such as fatigue due to anemia, or altered bowel habits. A thorough medical history and physical examination are warranted, including a routine complete blood count which may show anemia, a complete chemistry profile including a liver function test, and occasionally a fecal occult blood test or fecal immunochemical test. \textsuperscript{39,40} The gold standard of diagnostic studies is screening colonoscopy to check for polyps. Tissue diagnosis is obtained via biopsy. Further molecular testing is performed to detect gene variants such as KRAS, NRAS, and BRAF genes; as well as HER2 protein and NTRK genes. \textsuperscript{41} Microsatellite instability (MSI) testing is performed to detect high levels of gene changes as well as to detect mismatch repair (MMR) genes to discover genes such as MLH1, MSH2, MSH6, PMS2, and EPCAM, which may offer information regarding prognosis. \textsuperscript{42} Computed tomography (CT) scan may show a mass or metastasis to surrounding organs which can sometimes be the first sign especially if the patients are present in later stages. \textsuperscript{43}

The stages of cancer were determined based on the extent of tumor extension and involvement of distant organs (Figure 2). The colon cancer stages are listed below in table 1.

Table 1: Staging system of colorectal cancer from early to advanced.

<table>
<thead>
<tr>
<th>Stages</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>The early stage of cancer is also known as intramucosal carcinoma.</td>
</tr>
<tr>
<td>I</td>
<td>In this stage cancer has grown into submucosa through muscularis mucosa</td>
</tr>
<tr>
<td>IIA</td>
<td>This is the second stage of cancer where cancer has grown into the outermost layers of the colon.</td>
</tr>
<tr>
<td>IIB</td>
<td>In this second stage, cancer has grown through the wall of the colon.</td>
</tr>
<tr>
<td>IIC</td>
<td>In this stage cancer not only grown through the wall of the colon also attached to other nearby tissues or organs</td>
</tr>
<tr>
<td>IIIA</td>
<td>In this third stage of cancer, tumor grows through the mucosa into the submucosa and has spread to 4 to 6 nearby lymph nodes.</td>
</tr>
<tr>
<td>IIIB</td>
<td>The cancer has spread into the outermost layers of the colon through the visceral peritoneum.</td>
</tr>
<tr>
<td>IIIC</td>
<td>The cancer has spread into outermost layers of the colon through the visceral peritoneum and has spread to 7 or more lymph nodes.</td>
</tr>
<tr>
<td>IVA</td>
<td>In this last stage of cancer, it has grown into one distant organ or distant set of lymph nodes.</td>
</tr>
<tr>
<td>IVB</td>
<td>Cancer has spread to more than one distant organ.</td>
</tr>
<tr>
<td>IVC</td>
<td>The cancer along with distant organs has spread to distant parts of the peritoneum (the lining of the abdominal cavity).</td>
</tr>
</tbody>
</table>

Figure 2: Schematic representation of colon cancer and its various stages.
Treatment

Colorectal cancer treatment options consist of surgical and systemic treatments based on staging. Oncologic societies around the world have similar guidelines when it comes to treating both early and late-onset colon cancer, however, more publications have proposed more aggressive surgical and nonsurgical modalities for early onset CRC diagnosed in stage III and IV. Surgery is the mainstay of treatment for localized diseases. Patients who present with acute obstructive colon cancer often require a stent placement to relieve obstruction and surgery is performed with subsequent stoma creation. Laparoscopic-assisted colectomy is appropriate and curative in patients with suitable risks. Neoadjuvant chemotherapy is often recommended for locally advanced tumors, and this study showed a decrease in the number of affected lymph nodes, improved staging, and reduced post-operative morbidity compared to patients who did not receive chemotherapy while having an acceptable level of toxicity. Some observational studies have shown that adjunctive therapy such as regular low doses of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), may have protective effects against colon cancer with tolerable side effects. A Swedish cohort study showed that hormonal therapy such as estrogen alone or a combination of estrogen-progestin therapy may reduce the risk of colon cancer mortality by 26% in women older than 40 years of age. Continuous advancement in precision oncology including immunotherapy, are promising, including the clinical benefits of anti-EGFR treatments for metastatic colon cancer. Immunotherapy treatment modalities such as PD-1 inhibitors (pembrolizumab and nivolumab) and CTLA-4 inhibitors (ipilimumab) offer promising results in the metastatic stage.

Prognosis

Early onset colon cancer seems to have a poorer prognosis compared to older populations as well as faster progression allaying concern of possibly different biological processes. Early onset colon cancer patients tend to have advanced stage upon diagnosis with higher mortality as well as more likely to receive postoperative chemotherapy and multivalent regimens compared to older patients. Data suggests that the poor outcome of early onset colon cancer is most likely due to the advanced stage of the disease. Prognostication is based on the location of the tumor, depth of tumor invasion, tumor stage, tumor differentiation, surgery, pathological type, tumor size, lymph node metastasis, and distant metastasis. The tumor site may have some prognostic value but requires further validation.

Conclusion

There is an increasing incidence of colorectal cancer diagnosed at younger ages which may be associated
with an increasingly unhealthy diet and lifestyle. Early onset CRC seems to have a worse prognosis and has higher mortality than late-onset CRC. It is unclear whether early onset CRC differs from late-onset CRC at the molecular level. Treatment protocols are based on the stages of cancer, however, it is important to note that early onset CRC patients appear to be diagnosed at later stages and therefore more often need systemic therapy.

References


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Legends:

Figure 1: Schematic representation of risk factors involved in the initiation and progression of colon cancer.

Figure 2: Schematic representation of colon cancer and its various stages. Colon cancer starts as noncancerous clumps of cells (polyps). Some of these polyps progressively (stage I to IV) turn to cancer. Colon cancer stage IV causes distant metastasis to other organs.

Table 1: Colorectal cancer staging from early to advanced