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Review Article

A REVIEW OF TREATMENT, RISK FACTORS, AND INCIDENCE OF COLORECTAL CANCER

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ABSTRACT

Colorectal cancer (CRC) is considered as the third most frequent cancer in the world and the incidence increases with increasing age. CRC accounts for nearly 9 % of all cancer incidence, with an estimated 1.4 million cases happening in 2012. The aim of this paper is to provide a review of incidence, risk factors, screening strategies, and treatment of colorectal cancer. We searched the studies in five English databases, including Web of Science, PubMed, Scopus, EMBASE, and Google Scholar with no limitation in publication time to find all papers regarding colorectal cancers. Papers with any language were included in the first step of search if they had an English abstract. We used the following words and terms including colorectal cancer, treatment, risk factor, diagnosis, chemotherapy, radiotherapy, surgery. Geographical variations and different time courses in the CRC incidence indicate that environmental factors and lifestyle are major factors in the development of this disease. The main preventable risk factors for CRC are nutrition, a high-fat diet, a low-fiber diet, obesity and physical inactivity, smoking and alcohol consumption, aspirin and nonsteroidal anti-inflammatory drugs, and some non-preventable risk factors such as age, gender, race, and diabetes mellitus. Colonoscopy remains the study of choice to diagnose colorectal cancer. Prior to any treatment, CT imaging of chest, abdomen and pelvis with contrast is needed for staging the patient's CRC. The preferred option for localized colorectal cancer is surgery (etc, laparoscopic surgery, colostomy for rectal cancer); whereas the adjuvant chemotherapy is generally recommended for patients with lymph node metastases. Targeted treatment of colorectal cancer by monoclonal antibodies are important bioengineered proteins that can help the body's natural immune response to detect, attack, and kill cancer cells. Monoclonal antibodies may be used alone or in combination with other treatments such as chemotherapy. CRC accounts an important health problem worldwide that is estimated to increase because of the growth and aging of the population, and because of the adoption of at-risk manners and lifestyles, particularly in economically less developed countries. Screening has been confirmed to significantly decrease mortality and can prevent the onset of the disease. More international efforts are required to situate into practice targeted prevention approaches that might reduce the burden of CRC worldwide.

Keywords: Colorectal cancer, Mortality, Surgery, Chemotherapy, Incidence, Screening

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INTRODUCTION

Cancer is among the deadliest diseases worldwide after cardiovascular diseases [1]. It is considered the second leading cause of death in developed countries and the third leading cause of death in less developed countries [2]. Colorectal cancer (CRC) is the third most commonly diagnosed malignancy worldwide and the second leading cause of cancer-related death in the United States [3]. Every year, 3800 to 4000 new cases of colorectal cancer are diagnosed in the country, which indicates the growing trend of this disease in Iran [4]. This is currently among the most common gastrointestinal cancers, which allocated the third rank among men and the fourth rank among women in Iran [4]. It was estimated that about1.2 million new cases of CRC and 608,700 deaths occurred in 2008 worldwide [5]. The highest incidence of colorectal cancer was in North America, Australia, New Zealand, Western Europe and Japan, the average incidence was in South America and the lowest was in Africa, South and Central Asia [6].

While the incidence of colorectal cancer has decreased overall, the incidence in men and women less than 50 y of age, has increased by 2% [6]. It has been projected that incidence rates for colon and rectal cancers may increase by 90.0% and 124.2%, respectively, for patients between the ages 20 to 34 y by 2030 [7]. It is thought that about 35% of these young adult colorectal cancers are associated with hereditary colorectal cancer syndromes and the reason for the increase in the incidence is currently unknown [8].

Obesity, low consumption of fruits and vegetables, inactivity, and smoking are major risk factors for CRC [9]. The CRC incidence begins to increase around the age of 40 y in both men and women and reaches its peak at the age of 50, so that most of the cases diagnosed with CRC are 50 y of age and older [10]. The aim of this paper is to provide a review of incidence, risk factors, screening strategies, and treatment of colorectal cancer. We searched the studies in five English databases, including Web of Science, PubMed, Scopus, EMBASE, and Google Scholar, with no limitation in publication time to find all papers regarding colorectal cancers. Papers with any language were included in the first step of search if they had an English abstract. We used the following words and terms including: "colorectal cancer", "treatment", "risk factor", "diagnosis", "chemotherapy", "radiotherapy", "surgery". Inclusion criteria in the present study were the studies assessing the incidence, risk factors, screening strategies, and treatment of colorectal cancer. But the papers with insufficient data, the abstract without full text, in conformity between methods and results, the inappropriate explanation of the findings were excluded from this review.

Geographical variations

The incidence of this cancer varies in different parts of the world. The highest incidence of CRC has been reported in North America, Australia, New Zealand, Western Europe, and Japan. The average CRC incidence is related to the southern regions and the lowest incidence rate belongs to Africa and South and Central Asia. CRC is mainly found in developed countries that follow Western culture. In fact, the developed world accounts for 63% of all CRC cases [11].

Time course of CRC

Different populations have reported different incidence rates of CRC worldwide and these rates change over time. In some countries, the incidence rate has been declining, while in some other regions, such as Eastern Europe, the CRC incidence has risen in both men and women [12, 13].

The CRC incidence is rising rapidly in high-income countries that have recently transitioned from a low-income economy, such as Japan, Singapore, and Eastern European countries. Also, examining the standardized incidence rate of CRC in 2005-2009 revealed that this cancer has had an increasing trend in Iran (2.34-17.62 per 100000 people). The number of new cases diagnosed with this cancer is constantly on the rise. The main reasons for the increase in CRC in some areas such as parts of Asia and Eastern Europe are changes in dietary and lifestyle patterns and western-oriented

factors, including obesity and smoking. However, increasing screening, early diagnosis and treatment of patients, and removal of precancerous polyps have reduced this cancer in recent years [4, 6].

Survival rate and prognostic factors for CRC survival

Nearly one million new cases of CRC are diagnosed worldwide each year, about half of whom die. According to studies, the survival rate of CRC varies widely around the world, such that it has ranged from 13% to 66%. Based on the findings, the survival rate in developed regions has been estimated to be higher than that in developing regions. Studies conducted in Iran have estimated the 5-year survival rate as 47-50%. In general, the survival rate of CRC in women is slightly higher than that in men. Age, TNM (tumor, node, metastasis) staging, distant metastasis, grade, and tumor size are important prognostic factors for CRC. In recent years, the survival rate of CRC has been increasing due to screening, early diagnosis, and improved treatment methods [14, 15].

Risk factors

Like most of the cancers, CRC is a multifactorial disease. Geographical variations and different time courses in the CRC incidence indicate that environmental factors and lifestyle are major factors in the development of this disease. Environmental factors seem to play a more important role in CRC. This disease is more prevalent in urban areas and among people with higher socioeconomic classes. In general, risk factors for CRC can be divided into two groups: preventable risk factors and non-preventable risk factors [16].

The main preventable risk factors for CRC are related to nutrition (17). The relationship between nutritional factors and CRC has received great attention for many years and it is estimated that the incidence of CRC can be prevented by 30-50% if lifestyle and nutrition are improved [18]. The most important preventable risk factors for CRC are as follows:

High-fat diet

There is evidence suggesting that high consumption of fats, red meat, and fried foods increases the risk of CRC. The mortality rate of CRC is directly associated with the amount of meat protein, calories, and fats consumed in a person's diet. The case-control study conducted in Iran showed that consuming red meat and fried foods 4 or more times a week increased the chance of developing CRC by 7.4 and 17.8 times, respectively [19-21].

Low-fiber diet

The correlation between dietary fiber and CRC has been studied for three decades (22-24); However, no definitive relationship has yet been determined. Some studies have reported no correlation between these two variables, while others found a positive or negative relationship between them. Diets rich in vegetables and fruits are expected to play a protective role due to their high fiber and foods containing calcium, selenium, vitamins (A, E, C, and D), folic acid, carotenoids, and phenols [22-26].

Obesity and physical inactivity

Several lifestyle variables including obesity and physical activity have been proved to be associated with CRC. A study indicated that 1.3-1.4 of CRCs are caused by overweight and sedentary lifestyle, and the risk of CRC can be reduced by modulating regular physical activity. Obesity directly increases the risk of CRC independently of other factors [16, 47].

Smoking and alcohol consumption

Smoking often causes lung cancer, but it is also extremely harmful to the colon and rectum. Evidence suggests that 12%of CRC deaths are attributed to smoking. Carcinogens existing in tobacco increase the risk of CRC as well as the risk of being diagnosed with this cancer. There is also evidence of early incidence of CRC in smoking men and women. Alcohol increases the risk of CRC, even when the effects of smoking are eliminated in people who are smokers and alcoholics [29, 30].

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)

Studies have shown that taking aspirin and other nonsteroidal anti-inflammatory drugs can play an important role in preventing CRC. Evidence suggests that taking aspirin may reduce the risk of adenoma and CRC by 30-40%. Aspirin may also help reduce the risk of stomach and esophageal cancer [31].

Non-preventable risk factors

Family history and adenomatous polyps: About 20% of people with CRC have had at least one family member with this disease. Adenocarcinoma, which is caused by adenomatous polyps, accounts for 85% of all CRCs. In general, 70-90% of CRCs occur due to adenomatous polyps. Polyps larger than 2 cm in diameter are 50% more likely to become malignant. The incidence of colorectal carcinoma is higher in populations with a high prevalence of mucosal polyps, and the risk of cancer is closely correlated with the number of these polyps. By removing those preneoplastic lesions, the risk of cancer can be reduced [32, 33].

Age, gender, race, and diabetes mellitus: The CRC incidence begins to increase around the age of 40 y in both women and men and reaches its peak at the age of 50, so that 92% of CRCs have been reported in people aged 50 y and older. The CRC incidence in people aged 60-79 y old is more than 50 times higher than that in people under 40 y old [34]. CRC occurs almost equally in men and women. The incidence and mortality rates of CRC among African Americans in both men and women are higher than in whites. The risk of CRC is associated with type 2 diabetes so that women with diabetes are 1.5 times more likely to develop CRC. Many case-control studies have shown a correlation between the risk of CRC and diabetes [35-38].

Screening and diagnosis

Cancer prevention has usually received attention at primary or secondary levels of prevention. Primary prevention involves identifying and modifying genetic, biological, and environmental factors to prevent new cases [39]. Secondary prevention (screening) involves measures based on the early detection of cancer in asymptomatic individuals who are in the early stages of the disease (tables 1, 2) [40, 41]. Screening plays a key role in controlling CRC [42]. Fecal occult blood test (FOBT), flexible sigmoidoscopy (FS), colonoscopy, and virtual colonoscopy (VC) are the main screening tests for CRC. A study conducted in the United States showed that patients who were screened regularly and annually were 33% less likely to die from CRC than those who were not screened. Studies have indicated that CRC screening has recently reduced the incidence (by identifying and removing polyps) and mortality rated and increased the survival rate [42, 43].

Colonoscopy remains the study of choice to diagnose colorectal cancer. Prior to any treatment, CT imaging of the chest, abdomen and pelvis with contrast is needed for staging patient's CRC. Staging is commonly done by using Primary Tumor size (T), regional lymph Node (N) and distant Metastasis (M)-TNM classification system. Though tumor marker levels such as carcinoembryonic antigen (CEA) levels can be elevated in colorectal cancer, it is not diagnostic of CRC [44-46]. CEA levels are rather used as a tool to monitor in the post-treatment follow-up and for surveillance [46]. The most common lab parameter that is abnormal in patients with liver metastases is elevated alkaline phosphatase level. In patients with background liver disease, Magnetic Resonance Imaging (MRI) liver with contrast may add more accuracy in diagnosing liver metastases [47].

Treatment

Treatment for colorectal cancer can include treatments such as surgery, chemotherapy, immunotherapy, and other treatment options. Which treatment is right for patients depends on the stage and severity of colorectal cancer [48].

Surgery

Surgery is the most common treatment for colorectal cancer. Surgery for colorectal cancer may include removing the tumor, removing the affected areas, connecting healthy parts of the bowel, and removing nearby lymph nodes. In rare cases, the bowel may need to be completely removed. Patients may receive chemotherapy or radiotherapy before or after surgery. These adjuvant therapies are performed to target cancer cells that may remain after surgery. They may also help shrink tumors before they are surgically removed [49].

Table 1: Staging of colon cancer with various characteristics

Stage	Characteristics	References
0	This is the first stage of cancer and is found in the innermost wall of the large intestine.	[41]
I	The cancer has spread beyond the inner wall of the colon to the second and third layers and covers the inner wall of the colon, but the cancer has not yet reached the outer part of the large intestine.	[41]
II	The tumor spreads through the muscular wall of the large intestine and may also invade or attach to surrounding organs; But there is no cancer in the lymph nodes, which are small structures all over the body that make and store cells that fight infection.	[42]
III	The cancer has spread beyond the colon to one or more lymph nodes.	[41]
IV (metastatic)	The cancer has spread outside the colon to other parts of the body, such as the liver or lungs, and the tumor may be any size. The cancer may or may not have infected the lymph nodes.	[41]

Table 2: Staging of rectal cancer with various characteristics

Stage	Characteristics	References
0	The tumor is present only in the inner wall of the rectum. To treat early-stage cancer, a surgeon can remove the tumor or a small part of the bowel that is cancerous.	[42]
I	This stage is the initial form of cancer and the tumor has passed through the inner wall of the rectum but has not yet reached the muscle wall.	[42]
II	The tumor has spread to the entire intestinal wall and may now have spread to other nearby organs, such as the bladder, uterus, or prostate gland.	[42]
III	The tumor has spread to the lymph nodes, which are small structures throughout the body that make and store cells that fight infection.	[42]
IV (metastatic)	The tumor (metastasis) has spread to around parts of the body and may be of any size. The liver and lungs are the places where rectal cancer often spreads.	

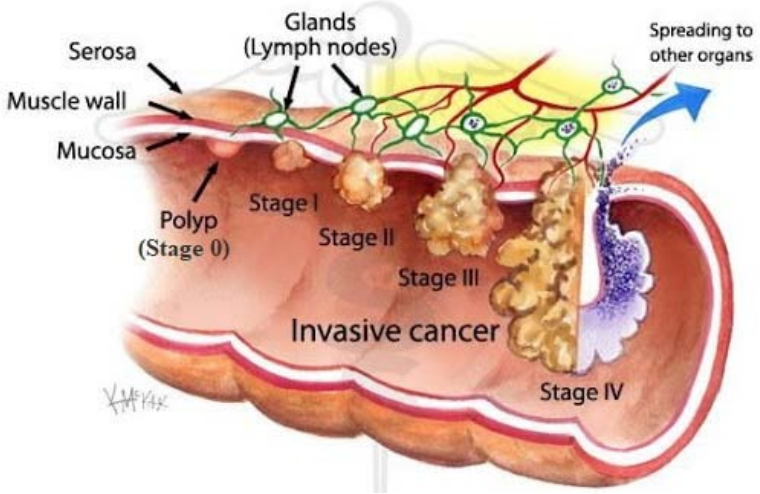

Fig. 1: Various stages of colorectal cancer [41, 42]

Laparoscopic surgery

Some patients may be able to have laparoscopic surgery to treat colorectal cancer. In this technique, several incisions are made in the abdomen of a patient under anesthesia. The incisions are small and the recovery time is shorter than standard colorectal surgery. Laparoscopic colorectal surgery can be as effective in removing cancer as conventional bowel surgery [50].

Colostomy for rectal cancer

This procedure is an open surgery or ostomy by which the intestine is attached to the surface of the abdomen to allow the lesions to leave the body. Sometimes, a colostomy is temporary to heal the bowel, but it can be permanent at times. With modern surgical techniques and the use of chemotherapy and preoperative radiation therapy, people usually do not need a permanent colostomy [51].

Radiofrequency ablation (RFA)

Some patients may use liver or lung surgery to remove tumors that have spread to these organs. Other methods include using radiofrequency energy called RFA to warm tumors or cryoablation to freeze tumors [52].

Complications of surgery

Side effects of surgery include pain and tenderness in the area of surgery. It can also cause constipation and diarrhea, which go away after a while. People who have had a colostomy may experience burning around the stoma [53].

Immunotherapy

Immunotherapy, also called biological therapy, is designed to boost the body's natural defenses against cancer. In this method, materials made in the body or in the laboratory are used to improve, target or restore the immune system (fig. 2). Drugs known as checkpoint inhibitors may be used to treat advanced colorectal cancer that has specific genetic characteristics [54].

Pemprolizumab

Pemprolizumab under the brand name Trudeau. PD-1 targets the receptor or tumor cells and prevents the tumor cells from hiding from the immune system. Pemprolizumab is used to treat metastatic bowel cancers that have the molecular property of MSI-H or dMMR [54-56].

Newlamb

It is used to treat people 12 y of age or older or with metastatic colorectal cancer (MSI-H or dMMR) [54].

Combination of Newlamp and Epiliumab

It is a combination of checkpoint inhibitors that is suitable for the treatment of patients 12 y of age and older with dMMR or MSI-H metastatic colorectal cancer. The US Food and Drug Administration (FDA) has approved specific checkpoint inhibitors for patients with non-surgical metastatic tumors in the MSI-H and dMMR status, regardless of tumor location. MSI-H is often found in colorectal tumors, especially in patients with Lynch syndrome. Checkpoint inhibitors work by blocking specific checkpoint receivers. In fact, it is the immune cells that differentiate good cells from bad cells. Immunotherapy is not recommended for all patients and the response to treatment varies from person to person. Immunotherapy may be used in combination with other treatments such as surgery or chemotherapy [54-56].

Complications of immunotherapy

Different types of immunotherapy can cause various side effects. The most common side effects of immunotherapy may include fatigue, diarrhea, nausea, fever, muscle aches, bone pain, joint pain, abdominal pain, itching, vomiting, cough, loss of appetite, and shortness of breath. Talk to your doctor about the side effects of immunotherapy and get the necessary guidance [54-56].

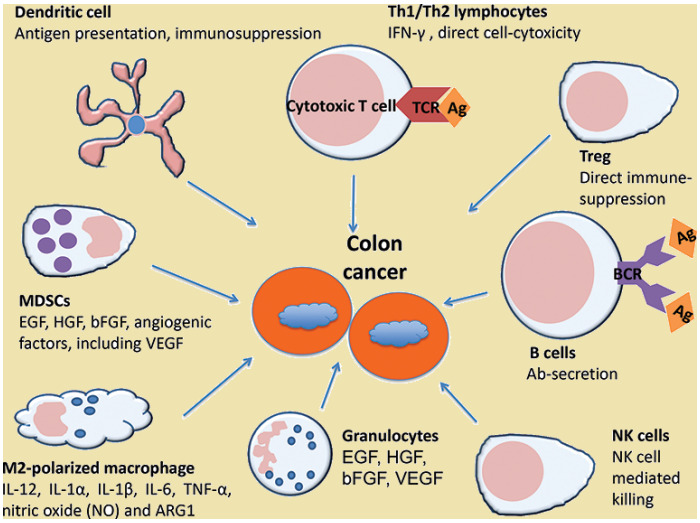

Fig. 2: Colorectal cancer progression through the evasion and suppression of the host immune system [57]

Chemotherapy

Chemotherapy drugs are used to treat colorectal cancer to kill cancer cells or stop them from growing and spreading. Chemotherapy may not be necessary for patients with stage I or II bowel cancer, but it is a common treatment option for patients with stage III or IV [58].

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is given before bowel cancer surgery. A cancer specialist may recommend a combination of chemotherapy and radiotherapy to help reduce the size of the tumor before surgery. This treatment is more common for rectal cancer [59].

Adjuvant chemotherapy

Adjuvant chemotherapy is used after surgery. This treatment may help kill the intestinal cancer cells that remain in the body after cancer removal surgery and reduce the risk of cancer coming back. Adjuvant chemotherapy may help prevent bowel cancer from spreading to other parts of the body [60].

Side effects of chemotherapy

Chemotherapy may cause vomiting, nausea, diarrhea, nerve damage, or mouth ulcers. However, medications are available to prevent these side effects. Due to the change in the way the drug is given to the patient, the side effects of chemotherapy are less severe than in the past. In addition, patients may experience fatigue and an increased risk of infection. Neuropathy that causes tingling or numbness in the hands and feet may occur with some medications. Significant hair loss is one of the most common side effects of many medications used to treat bowel cancer other than erotinotan [58].

Radiotherapy

Radiotherapy can be an option for treating colorectal cancer for the following reasons: (i) preoperative radiation therapy may help shrink tumors; whereas, the tumors disappear more easily; (ii) postoperative radiation therapy may help kill cancer cells that remain in the body; (iii) this treatment may be an option for patients who are unable to have surgery; (iv) radiation therapy may be used as a palliative procedure to shrink tumors that may cause intestinal obstruction; (v) radiation therapy may be given in combination with chemotherapy [61].

Side effects of radiation therapy

Side effects of radiation therapy may include fatigue, mild skin reactions, upset stomach, and loose bowel movements. It may also cause bloody stools. Most side effects go away after treatment. Sexual problems, as well as infertility in both men and women, may occur after pelvic radiation therapy [61].

Targeted treatment of colorectal cancer

Monoclonal antibodies are a targeted treatment used to treat colorectal cancer. Monoclonal antibodies are important bioengineered proteins that can help the body's natural immune response to detect, attack, and kill cancer cells. Monoclonal antibodies may be used alone or in combination with other treatments such as chemotherapy. Side effects of targeted treatment may include rashes on the face and upper body, which can be reduced with various treatments [62].

CONCLUSION

CRC accounts an important health problem worldwide that is estimated to increase because of the growth and aging of the population, and because of the adoption of at-risk manners and lifestyles, particularly in economically less developed countries. Screening has been confirmed to significantly decrease mortality and can prevent the onset of the disease. More international efforts are required to situate into practice targeted prevention approaches that might reduce the burden of CRC worldwide

AVAILABILITY OF DATA AND MATERIALS

Authors can confirm all relevant data are included in the article and materials are available on request from the authors.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no financial or non-financial interests with other people or organizations that could inappropriately influence this.

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