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MINIREVIEWS

Colon and rectal cancer: An emergent public health problem

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Abstract

Colorectal cancer ranks third globally, with a high mortality rate. In the United States, and different countries in Europe, organized population screenings exist and include people between 50 and 74 years of age. These screenings have allowed an early diagnosis and consequently an improvement in health indicators. Colon and rectal cancer (CRC) is a disease of particular interest due to the high global burden associated with it and the role attributed to prevention and early diagnosis in reducing morbidity and mortality. This study is a review of CRC pathology and includes the most recent scientific evidence regarding this pathology, as well as a diagnosis of the epidemiological situation of CRC. Finally, the recommendation from a public health perspective will be discussed in detail taking into account the context and the most current recommendations.

Key Words: Colon and rectal neoplasia; Colon and rectal tumor; Mortality; Morbidity

Core Tip: Colon and rectal cancers (CRC) are important public health problems. Epidemiological studies, morbidity and mortality indicators demonstrate the high burden of colorectal cancer on individuals and society. To face this issue, several measures are urgently need. Improved therapies and precision medicine for patients with CRC are required. Prevention is fundamental through dietary and lifestyle measures, along with early diagnosis.

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INTRODUCTION

Colon and rectal cancer (CRC) is one of the most incident cancer in the western world with 1.8 million cases in 2018, being more frequent after the age of 50. By 2022, it is estimated that around 2 million cases of CRC will have arisen worldwide, constituting the second most common cause of cancer mortality worldwide with 880000 fatalities[1]. Incidence rates have been increasing globally, with the highest rates being reached in high-income countries and rates lower in low-income countries. This difference in the incidence of CRC seems to result from environmental and mainly nutritional factors. The determinants associated with CRC are identified and included, age, male sex, inflammatory bowel disease, diet, and physical exercise, among others[1,2]. It is well-established that a healthy lifestyle decreased the likelihood of developing CRC[3]. This comprehensive review discussed CRC pathology, and its associated determinants, diagnosis methods, treatment, and prognosis.

CRC

CRC pathology results from the accumulation of multiple genetic and epigenetic alterations in the previously healthy colon and rectal epithelium, leading to the progression of colon and rectal adenomas to carcinoma (Figure 1)[1]. Approximately half of the patients with CRC will develop metastases in the course of the disease and the majority of metastatic CRC (mCRC) are incurable[3]. About 90% of CRC are adenocarcinomas, *i.e.*, they are malignant tumors that derive from the glandular epithelium of the colon and rectum. Despite adenocarcinoma, other types of CRC include colorectal lymphoma, squamous cell carcinoma, leiomyosarcomas, and melanomas[3]. According to the literature, about 65% of CRC cases develop sporadically, without any family history or predisposition to hereditary genetic mutations, occurring through somatic genomic and epigenetic alterations[4,5]. The remaining cases have a familial association. From these a few percentage (representing only 5% of cases) are hereditary cancer syndromes, and other unknown genomic alterations [2]. CRC is considered a heterogeneous disease from a molecular perspective. One of the main molecular pathways that are altered is chromosomal instability, occurring in 85% of cases of sporadic CRC, and characterized by changes in structure, number, loss of heterozygosity in the tumor suppressor gene, gain or loss of chromosome segments, and rearrangements, which results in variations in the number of copies of the gene[6]. These changes are often associated with mutations in specific oncogenes or tumor suppressor genes, such as tumor suppressor adenomatous polyposis coli (APC), kirsten rat sarcoma virus, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit-a, b-raf proto-oncogene (BRAF), SMAD family member 4, and p53 that regulate cell proliferation and deoxyribonucleic acid (DNA) cell cycle, playing an important role in initiation and progression pathways. Another important mechanism for the development of CRC is microsatellite instability caused by the dysfunction of DNA mismatch repair (MMR) genes during DNA recombination, DNA replication, and DNA damage. Other important pathways for the development of CRC include the CpG island methylator phenotype pathway[6]. However, in most cases, the process of CRC development begins with the transformation of previously healthy colon and rectal epithelial cells under the influence of spontaneous mutations, environmental factors, and genetic or epigenetic alterations[7,8]. These cells expand to form aberrant cells, crypt foci, and early adenomas, driven by mutations that cause hyperproliferation, such as APC mutations, or other signaling pathways with the release of cytokines and tumor microenvironment growth factors[5]. These factors lead to the growth of these adenomas and their transformation into malignant tumors in a progressively slow process that usually lasts for 10-20 years[5]. The presence of other mutations will amplify the process of CRC cells and facilitate the metastasis of these tumors to distant organs and tissues, a process called tumor progression[9].

Causes and risk factors

Epidemiological studies show that the male sex and increasing age show a strong association with CRC incidence (Figure 2)[2]. Both environmental and hereditary factors also play an important role in the development of CRC[10]. The risk of developing CRC is influenced by several acquired risk factors, including environmental exposures and medical conditions where many of which have an associated genetic load (Figure 2)[2]. Data for some risk factors (*e.g.*, male sex, smoking and processed meat consumption) are well-established in the literature, other factors (supplements, drugs) are not supported by experimental studies.

The risk factors described for CRC are based almost exclusively on data from observational studies and therefore some caution is required concerning their interpretation[11]. Acquired risk factors for the development of CRC include dietary factors, lifestyle factors, side effects of medical interventions, and pre-existing medical conditions[12]. Dietary factors that potentially increase the risk of CRC include low intake of fruits, vegetables, or fiber, high consumption of red meat or saturated fat, and high exposure to caffeine or alcohol. Of these factors, the association between reduced intake of fruits, vegetables, and fiber-rich foods has been questioned due to contradictory results from large observational studies and randomized clinical trials[13]. The association of high consumption of red meat or saturated fat with increased risk of CRC is strongly supported by research, but only by observational data[14-17]. The association between CRC and smoking and physical exercise has also been supported by observational data, but these studies are also of moderate quality. Medical interventions that appear to increase the risk of CRC include pelvic irradiation, cholecystectomy, and ureter-

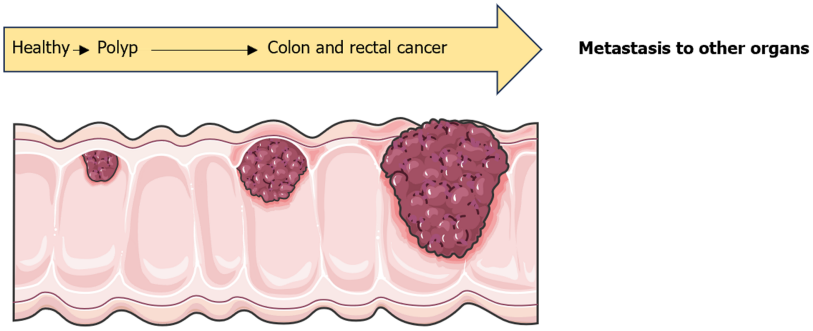

Figure 1 Progression of colon and rectal cancer pathology.

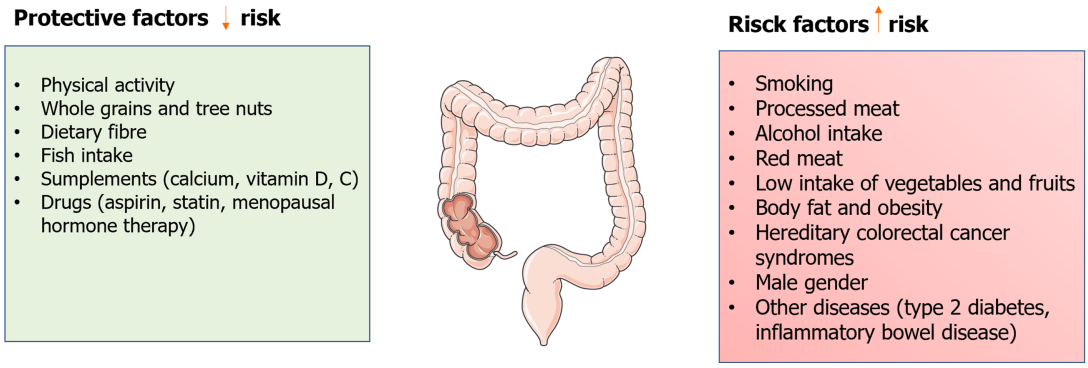

Figure 2 List of modifiable and non-modifiable determinants for colon and rectal cancer.

ocolic anastomosis after major surgery of the urinary and intestinal systems. These risk factors are supported only by observational data from small studies, so their validity is also not well established with the necessary rigor. Finally, medical conditions that are associated with an increased risk of CRC include Barrett's esophagus, human immunodeficiency virus infection, acromegaly, and inflammatory bowel disease. The association between CRC and inflammatory bowel disease, the most prevalent being Crohn's disease and ulcerative colitis, is well established and forms the basis for colonoscopy surveillance recommendations widely adopted by national and international medical organizations at earlier ages concerning population-based screening ages. The association of CRC with other associated medical conditions is only supported by very limited and controversial observational data. Epidemiological studies and scientific research demonstrate a strong influence of diet and physical exercise not only on the risk of developing CRC but also on its impact on CRC. In this regard, the American Cancer Society has reinforced the role of diet and physical activity as important determinants in CRC prevention[17]. Regarding vitamin supplements that include calcium and vitamin D in reducing CRC[15], results have been controversial and their use did not demonstrate a significant reduction in the risk of developing CRC in healthy subjects[16]. In physically active patients, the risk of developing CRC is reduced by about 15% compared to people who do not practice any type of physical exercise. Another important aspect is that physical exercise has a highly beneficial impact (*i.e.*, tertiary prevention) even in patients already diagnosed with CRC[17]. A recent study has shown that patients with CRC who regularly engage in moderate-intensity physical exercise (60-75 min/d of moderate-intensity exercise) have a better prognosis and a lower mortality rate than people who do not exercise. The physically active group demonstrated a lower rate of disease recurrence, being the group with the highest survival compared to the inactive group. Thus, the American Cancer Society recommends physical activity to all cancer patients, however, it has not defined the intensity and duration of physical exercise to be practiced to enjoy its beneficial effects on CRC[10]. Still in this context of tertiary prevention, a clinical trial conducted in 2018 showed that having a healthy life, with a body mass index considered normal, being physically active, and eating a diversified diet rich in vegetables and fruits in physically active individuals diagnosed with CRC in stage III is associated with greater survival compared with controls (non-physically individuals) that are not physically active and with a diet with deficiencies in vegetables and fruit[17].

Prevention

The above-mentioned determinants are important to take into account at the level of primary, secondary, and tertiary prevention of CRC. Since CRC survival outcomes are closely related to the stage of cancer at diagnosis, CRC is one of the only types of cancer in which screening is considered a key preventive measure (secondary and in some cases even primary). In addition to adopting a healthy lifestyle and exercising, the most effective method of preventing CRC and reducing CRC-associated mortality in the population is screening individuals with an associated average risk. Most European countries, including Portugal, Canada, specific regions of North and South America, countries on the Asian

continent, and Oceania have started population screening programs as a strategy. Population-based screening aims to show the disease during its development period among the average-risk population, allowing interventions at an early stage with a consequent decrease in mortality. Thus, screening is particularly appropriate in CRC, as this cancer consists of a gradual development of the adenoma-carcinoma sequence[8]. Although the time taken for an early adenoma to progress to an established CRC is still unknown, current evidence suggests that it is no less than ten years, offering a window of opportunity for early diagnosis and treatment. In addition, CRC can be prevented by removing adenomas, and the earlier CRC is detected, the less likely the patient risks dying. Treatment outcomes are therefore positively impacted by interventions along the adenoma-carcinoma pathway. Other effective strategies include identifying and monitoring high-risk populations, including individuals with inflammatory bowel disease, families with inherited CRC syndrome, individuals whose family history suggests a genetic predisposition to CRC but have no detectable genetic markers, and individuals whose phenotypic appearance indicates high risk. As tertiary prevention in CRC, it is worth mentioning the practice of physical exercise that, as previously mentioned, improves the prognosis in patients with CRC.

Diagnosis

The United States Preventive Services Task Force strongly recommends the use of endoscopy in the diagnosis of CRC, in addition to fecal tests and computed tomography (CT)[18]. The recommendation of endoscopy as means of complete diagnosis and preferred therapy is based on the fact that polyps in the pre-malignant stage can thus not only be detected but also removed, which reduces the incidence of CRC[19]. New sequencing techniques have allowed a detailed characterization of tumors through the use of predictive biomarkers. However, its application in clinical practice is very difficult, and specific recommendations with guidelines are important to support therapeutic decisions[20]. The most used means in the diagnosis of CRC are fecal tests and colonoscopy, and other means are still under investigation. For staging, it is essential to perform a CT scan of the chest, abdomen, and pelvis before surgical resection of the CRC to diagnose possible metastases[21]. Performing CT allows detection and assessment of the extent of metastases, which may require a change in treatment strategy, for example, the need to perform CT instead of surgery first or simultaneous resection of the primary tumor and metastases[21].

Stages

The pathological stage represents the most important prognostic factor in patients with CRC[22]. The tumor-nodes-metastasis classification system, as defined by the American Joint Committee on Cancer, is the most commonly used staging system and is based on the depth of intestinal wall invasion, the extent of regional lymph node involvement, and presence of distant sites of the disease[23]. The depth of tumor invasion defines the T stage and varies from *in situ* (Tis), T1 (a tumor that invades the subserosa), T2 (a tumor that invades the muscular layer), T3 (a tumor that invades the muscularis propria up to the subserosa) and T4 (invasion of the serosa or adjacent structures). As the depth of tumor invasion increases, the risk of nodal and distant spread also increases. Pathological review of surrounding lymph nodes defines three categories: N: N0 (no lymph nodes involved), N1 (1-3 lymph nodes involved), and N2 (more than 3 lymph nodes involved). Current guidelines recommend identifying 12 or more lymph nodes in the resected sample, as testing with fewer regional lymph nodes has been associated with worse outcomes in patients with negative lymph node disease and with positive lymph nodes[24]. Examination with fewer lymph nodes may reflect a less complete operative procedure or inadequate inspection of the pathology specimen, leading to tumor "under-staging" and subsequent omission of beneficial adjuvant therapy[23]. Table 1 summarizes the staging of CRC.

Treatment

The different modalities available for the treatment of CRC include surgery, CT, and radiotherapy. Surgery is the main form of treatment for CRC, and CT is used as an adjuvant treatment. Approximately 92% of patients with colon cancer and 84% with rectal cancer undergo surgery as a first therapeutic option, the majority with curative intent. Approximately 20% of patients with CRC have advanced disease at diagnosis, while 30%-40% of patients undergoing curative surgery eventually relapse locally or at distance[25]. The metastatic pattern is influenced either by the histological subtype or primary tumor localization. Indeed, colon cancer patients develop a higher rate of abdominal metastases (*e.g.*, liver), while rectal cancer more often metastasizes to extra-abdominal sites including the lungs. The more common histology of adenocarcinoma metastasizes to the liver, while mucinous and signet-ring histology more frequently has peritoneal metastases[26]. The advancement of surgical techniques has made it possible for patients with mCRC to have a curative nature. Surgery should be performed laparoscopically whenever possible. However, certain lesions are not amenable to a minimally invasive approach due to several factors, such as a large tumor mass, or the fact that the tumor is locally advanced. The laparoscopic procedure should achieve the same goals as the open approach procedure (laparotomy) and when this is not possible, conversion to a laparotomy approach is recommended. There are several studies, including a meta-analysis that demonstrate oncologic non-inferiority and better short-term outcomes with laparoscopy compared to the open surgical approach when performed by experienced surgeons[21].

After surgical resection, patients with stage II disease may benefit from adjuvant CT in case of the presence of major risk factors for relapses, such as an inadequate lymph node sampling < 12 or pT4 stage including perforation. Other minor risk factors for stage II risk assessment are the presence of high-grade tumors, vascular, lymphatic, and perineural invasion, tumor presentation with obstruction, and high preoperative carcinoembryonic antigen (CEA) levels. The main agents used in CT are 5-fluorouracil (5-FU) or oral capecitabine (fluoropyrimidines) for 6 months. The addition of oxaliplatin to 5-FU or capecitabine (FOLFOX or XELOX) may be evaluated in presence of major risk factors for relapse and younger age. Moreover, deficient MMR (dMMR)/microsatellite instability (MSI) testing must be performed to identify a small subset of stage II patients with a very low risk of recurrence and in whom the benefits of fluorop-

Table 1 Tumor-nodes-metastasis staging classification for colon and rectal cancer

Stage	Tumor	Regional nodules	Metastases
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II	T3, T4	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1, N2	M0
Stage IIIA	T1, T2	N1	M0
	T1	N2a	M0
Stage IIIB	T3, T4a	N1	M0
	T2, T3	N2a	M0
	T1, T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3, T4a	N2b	M0
	T4b	N1, N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

yrimidines have not been demonstrated[27].

In the case of patients with CRC with lymph node involvement (stage III), they should undergo adjuvant CT, to reduce mortality. Combination CT with fluoropyrimidines and oxaliplatin is the standard of treatment. The duration of treatment is different depending on the risk of relapse. In low-risk patients (T1-3 N1) options are XELOX for 3 months or FOLFOX for 6 months. Differently, high-risk patients (T4 and/or N2) should receive 6 months of therapy either with FOLFOX or XELOX[27].

Radiotherapy is not considered effective in the treatment of colon cancer. In the case of rectal cancer, radiotherapy and CT are indicated for T3 and T4 tumors with lymph node involvement. In the case of locally advanced rectal cancer, the use of radiotherapy as a neoadjuvant therapy has been shown to decrease local recurrence rates by approximately 50%-60% compared to surgical treatment performed alone. In terms of CT for the localized and locally-advanced stages, the most used in the treatment of rectal carcinoma are 5-FU, leucovorin, capecitabine, and oxaliplatin[26]. The usual treatment regimen for stage II and III rectal cancer is based on total neoadjuvant CT (based on oxaliplatin and capecitabine or 5-FU) followed by concomitant 5-FU or capecitabine-based chemoradiotherapy, followed by surgical resection[28].

In stage IV both colon and rectal carcinoma, the main objective of therapy is usually to improve quality of life, with treatment being directed at symptoms, such as pain. Palliative surgery is performed to avoid complications such as intestinal obstruction or perforation and bleed and is often preceded by CT to control metastases. Palliative radiotherapy is indicated only for rectal cancer, while CT is the main treatment for mCRC. The use of more targeted therapies has drastically modified the treatment of mCRC, having changed the natural history of the disease. For nearly a decade, patients with mCRC have been among the cancer patients most benefited from targeted therapies such as monoclonal antibodies against vascular endothelial growth factor (VEGF) (*e.g.*, bevacizumab, aflibercept, and ramucirumab) and epidermal growth factor receptors (EGFR) (*e.g.*, cetuximab and panitumumab). In general, the first and second-line treatment in mCRC is made by a CT backbone, for example, FOLFOX (5-fluorouracil and oxaliplatin), FOLFIRI (5-fluorouracil and irinotecan) or FOLFOXIRI (5-fluorouracil, oxaliplatin, and irinotecan). Together with either an anti-VEGF agent or anti-EGFR antibody, which have been demonstrated to improve clinical outcomes when combined with CT. Many factors contribute to the choice of the treatment strategy. First of all, the patient's comorbidities, age, and general clinical conditions have to be considered. Secondly, the determination of the RAS and BRAF status on tumor biopsy is mandatory to guide the best treatment decision. Moreover, dMMR/MSI testing must be performed as part of the initial molecular work-up as well to select patients for immune checkpoint inhibition. In addition, sidedness (left or right primary tumor) drives the choice of the most suitable monoclonal antibody[29] (Figure 3). Some of the difficulties in the development of these drugs have been the resistance mechanisms developed by the cells, which are often only possible to be identified in clinical trials[30].

Prognosis

The stage at diagnosis is a determining factor in patient survival. Since most relapses occur within the first four years

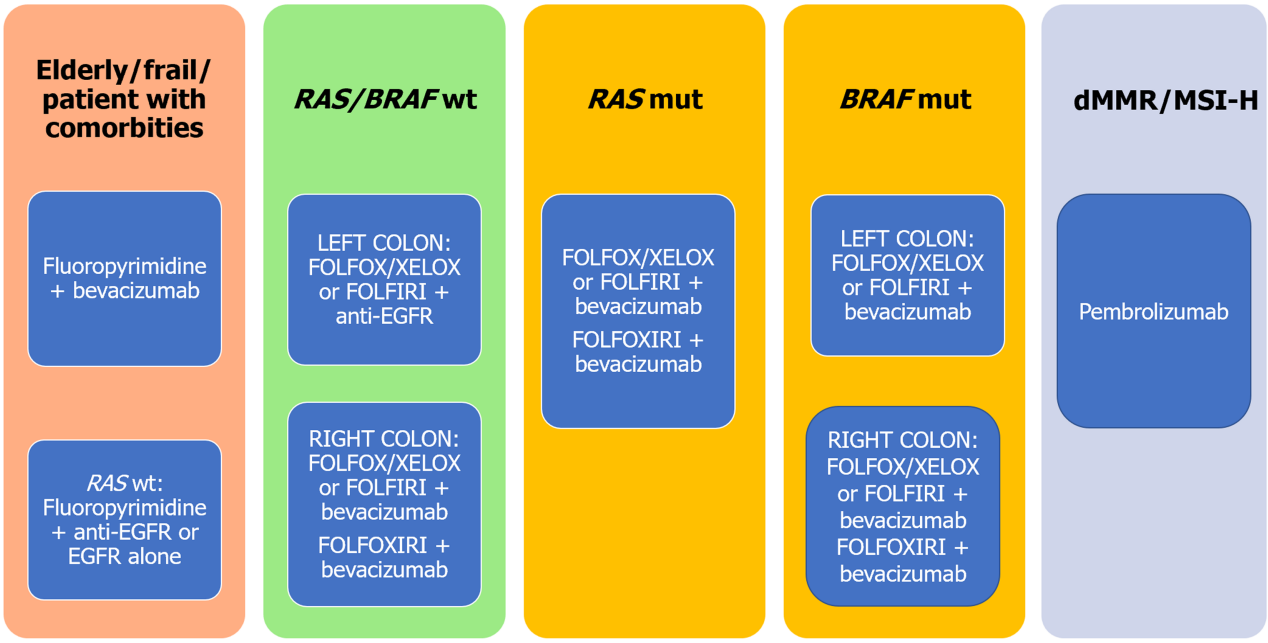

Figure 3 First-line treatment for metastatic colon and rectal cancer patients. anti-EGFR: Anti-epidermal growth factor receptor agent; dMMR/MSI-H: Deficient mismatch repair/microsatellite instability; FOLFOX: 5-fluorouracil + oxaliplatin; FOLFOXIRI: 5-fluorouracil + oxaliplatin + irinotecan; FOLFIRI: 5-fluorouracil + irinotecan; mut: Mutant; XELOX: Capecitabine + oxaliplatin; wt: Wild-type; BRAF: B-raf proto-oncogene.

after initial diagnosis, five-year survival is a commonly used indicator of cure. For stage I the 5-year survival rate is greater than 90%, decreasing to 70%-85% in stage II, to 25%-80% in stage III, and to less than 10% in IV[29]. In resettable tumors, factors that increase the risk of recurrence after surgery are poorly differentiated histology, lymphatic and venous invasion, tumor invasion through the intestinal wall with pericolic fat reaching, intestinal perforation or obstruction, as well as levels of elevated CAE[31]. Thus, the preoperative measurement of CEA is extremely relevant, as its high levels are associated with a higher risk of cancer recurrence[31]. The two molecular markers most implicated in the prognosis of patients with colorectal cancer rank are microsatellite instability and specific chromosomal deletions, such as allelic loss on chromosome 18q of tumor cells. Microsatellite instability is associated with a better prognosis than microsatellite stability. Deletion of chromosome 18q is associated with a worse prognosis[32].

CONCLUSION

CRC is an emerging public health problem with an increasing trend in its incidence and mortality worldwide[33]. Globally, CRC accounts for approximately 10% of all diagnosed cancers and associated deaths annually[34]. The determinants of CRC are older age, male sex, family history of CRC, tobacco, overweight, alcohol, processed meats, and physical inactivity, among others[2,10]. Most cancers arise from the polyps that give rise to CRC after about 10-15 years. The diagnosis can be made in several ways, including clinical presentation, endoscopy, CT, and fecal test[2]. The fecal test is a non-invasive means of diagnosis, some studies demonstrate that its use contributes not only to the reduction of CRC mortality but also to the reduction of the incidence[35]. Surgical treatment is intended to be curative and constitutes the gold standard of treatment. Prevention is fundamental and can be done at several levels, especially primary, secondary, and tertiary. From a public health perspective, primary prevention plays a key role in the management of this scourge, and measures such as smoking cessation, a healthy diet, and regular physical exercise can prevent the onset of CRC cancer[10]. The recommendations are based on the practice of daily physical exercise, for at least 30 min, the consumption of healthy foods, and a diversified diet (milk, fresh fruits, nuts, vegetables, foods with calcium, and foods rich in fiber) [10]. As secondary prevention, screening is recommended. Ideally, in the future, it may be possible to perform a colonoscopy in population-based screening, but more studies are needed to prove its superiority compared to fecal tests [36]. Clinical trials comparing the fecal blood test *vs* colonoscopy strategies are fundamental to compare the incidence and mortality associated with the two strategies in population-based screening diagnosis. Program logistics should be simplified and we should recognize a visit to the primary health care of the target population as a unique opportunity to carry out screening if it is lacking. It is also necessary to reinforce the invitations made for screening to users who do not adhere to remind them of the importance of screening.

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FOOTNOTES

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