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MINIREVIEWS

Colorectal cancer, screening and primary care: A mini literature review

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Abstract

Colorectal cancer (CRC) is a common health problem, representing the third most commonly diagnosed cancer worldwide and causing a significant burden in terms of morbidity and mortality, with annual deaths estimated at 700000. The western way of life, that is being rapidly adopted in many regions of the world, is a well discussed risk factor for CRC and could be targeted in terms of primary prevention. Furthermore, the relatively slow development of this cancer permits drastic reduction of incidence and mortality through secondary prevention. These facts underlie primary care physicians (PCPs) being assigned a key role in health strategies that enhance prevention and prompt diagnosis. Herein, we review the main topics of CRC in the current literature, in order to better understand its pathogenesis, risk and protective factors, as well as screening techniques. Furthermore, we discuss preventive and screening policies to combat CRC and the crucial role served by PCPs in their successful implementation. Relevant articles were identified through electronic searches of MEDLINE and through manual searches of reference lists.

Key words: Colorectal cancer; Prevention; Diagnosis; Screening; Primary care

Core tip: Colorectal cancer (CRC) is a common health problem, causing a significant burden in terms of morbidity and mortality. However, if detected early, the disease is highly curable. Primary care physicians are therefore in a unique position to enhance prevention and prompt diagnosis. The purpose of this paper was to

review the main topics of CRC in the current literature to provide a more comprehensive understanding of its pathogenesis, risk and protective factors, as well as screening techniques.

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INTRODUCTION

Colorectal cancer (CRC) is a global health burden, accounting for almost 700000 deaths per year worldwide[1]. CRC is the third most commonly diagnosed cancer worldwide and second in Europe[1]. According to the World Health Organization GLOBOCAN database, in 2012, almost 1.4 million new cases of CRC were diagnosed and almost 700000 deaths occurred worldwide[1].

CRC global incidence and mortality rates appear to be substantially higher for males than for females, with 21 new cases and 10.5 deaths per 100000 population compared to 17.6 new cases and 9.2 deaths respectively. In males, CRC ranks third in incidence, following lung and prostate cancers, and in females it ranks second, following breast cancer[1,2].

There is an over 10-fold geographical variation of CRC incidence throughout the world[3]. The highest incidence rates are observed in Australia and New Zealand, with the estimated age-standardized rates being 44.8 per 100000 population in men and 32.2 in women; Europe and North America follow close behind. The lowest incidence is observed in Africa, with the rates in Western Africa being only 3.5 per 100000 in men and 3.0 in women[1,3,4].

Incidence trends reported for the past few decades have revealed very interesting findings. In the United States, overall CRC incidence has been declining since the mid-80s, right about the time that CRC screening was introduced[5-7]. In Europe, incidence trend patterns show great diversity among countries, mainly due to differences in screening policies and prevalence lifestyle risk factors between countries. The largest increase in incidence was observed in Central-Eastern Europe over the past few decades[8-12].

CRC incidence increases with age, and cases are fairly uncommon before the 4th decade of life[1,3]. This is the reason why most screening programs are targeted to people over 50 years old. Nevertheless, recent studies have revealed an alarming increase in incidence between the ages 40 to 44, prompting consideration of lowering the recommended screening age[13,14].

Mortality rates have progressively declined in most economically developed countries, in contrast with poorer regions of the world, where mortality is either stable or increasing[1,11]. This reflects the diversity in screening services accessibility, specialized care and lifestyle risk factors[11]. The highest reported mortality rates are in Central-Eastern Europe, although the highest incidence to mortality ratio is observed in Middle-Western Africa[1,15].

In this paper, we aimed to perform a narrative literature review and compile all of the up-to-date knowledge on the current CRC medical literature. Our main objective was to summarize all the available information and provide gastroenterologists and primary care physicians (PCPs) with a comprehensive background for a better understanding of the current evidence.

SEARCH STRATEGY

We conducted a literature search in the PubMed database, with publication date limited to between January 1996 and August 2016, using the following Medical Subject Heading (commonly known as MeSH) terms: "colorectal neoplasms", "diagnosis", "early detection of cancer", "primary health care". The search was limited to English language. Editorials, Letters to the Editor and Case Reports were excluded. Inclusion criteria for papers were CRC topics in prevention, screening, detection and diagnostics, as well as follow-up in primary care. The titles and abstracts of all papers identified by the electronic search were manually assessed by two researchers working independently (AH, DA). Disagreements between the two reviewers were infrequent and resolved by consensus or arbitration of a third reviewer (MK).

Full texts of the articles that were considered eligible for inclusion were also scrutinized in order to offer a better approach on CRC issues related to pathogenesis, screening, diagnosis and management, as were articles related to early detection in the primary care setting.

A total of 159 studies were identified and assessed for eligibility. Among them, 7 overlapped and were excluded. Four articles were also excluded due to topical relevance to other types of cancer. Finally, 148 articles were assessed in detail for study inclusion. From these, 42 were excluded for not meeting the inclusion criteria. Figure 1 summarizes the process of identification and selection of studies.

PATHOGENESIS

The Adenoma-Carcinoma pathogenesis model is what gives endoscopic methods of screening the benefit of not only reducing mortality but also reducing incidence of CRC through early recognition and removal of adenomatous polyps from the colon[16]. The Adenoma-Carcinoma sequence applies to most CRCs and involves a sequential progression that takes, on average, a decade to occur. Many of the adenomas begin as small polyps that enlarge and become

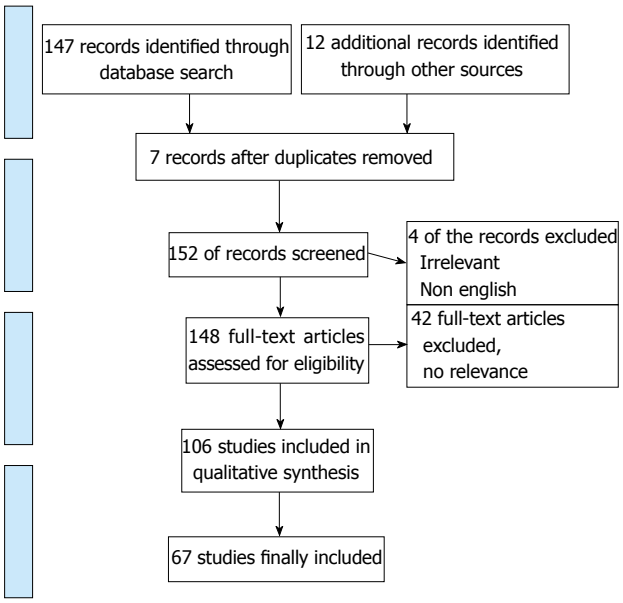

Figure 1 Study selection based on prisma diagram[112].

dysplastic and eventually cancerous[17-19]. Other CRCs may develop from non-polypoid adenomas, that are, by definition, more difficult to detect[20]. Nevertheless, there have been studies that suggest alternative developmental pathways to CRC, other than the traditional aforementioned model[21-23].

RISK FACTORS

The probability for developing CRC can be increased by both genetic and acquired/environmental factors. Although the impact of genetic susceptibility in an individual is much greater than the impact of acquired factors, the vast majority of CRC cases could be prevented through modifications in environmental factors[24-26]. A constructive way of classifying CRC risk factors is separating those that affect screening recommendations from those that do not. Hereditary syndromes, family history and inflammatory bowel diseases are the main risk factors that affect recommendations for screening[27]. In practice, risk factors that do not affect screening are the target of primary prevention strategies[24].

Hereditary colorectal syndromes comprise numerous specific genetic disorders that are associated with the development of CRC, altogether accounting for about 10% of CRC cases. The most common form is hereditary non-polyposis CRC, which reportedly accounts for only 2%-5% of CRC cases[28,29]. Family history, in addition to the genetic syndromes thus far known, constitutes a very significant risk factor for developing CRC, which appears to account for up to 25% of cases[28]. Although the mechanisms underlying this observation are not completely understood, studies have shown that individuals having first-degree family members diagnosed with CRC are at 2-3 times greater risk of developing CRC than the general population[28-31].

Although CRC, compared to other common cancers, includes a large percentage of hereditary cases, the vast majority of cases are sporadic, accounting for up to 70%[28]. The risk factors implicated in the mechanisms of sporadic disease are mainly environmental/acquired. Western lifestyle, cigarette smoking, alcohol intake, obesity and certain dietary habits are amongst the risk factors associated with increased risk for CRC[24,25,32-34].

PRIMARY PREVENTION

As expected, an important role in the etiology of CRC is attributed to lifestyle factors, since, as aforementioned, the majority of CRC cases are not associated with hereditary/familial factors[24,25,35]. Western lifestyle is a well-discussed risk factor for CRC, as it was readily observable by researchers that CRC incidence was consistently higher in industrialized countries[35]. This observation was further supported by the growing incidence in poorer regions as they adopted the western way of living[24,36].

Diet has been a popular subject of CRC research over the past few decades, both for its potential as a risk factor and as a protective factor. A number of researchers have argued the protective role of a diet high in fiber, with some studies showing a reduction in CRC incidence up to 50%[35,37-39]. Nevertheless, many recent reports have raised doubts about this argument, leaving the question of how protective dietary fibers really are, open for future prospective studies to answer[40,41]. Many authors have also asserted a protective role for calcium and vitamin D, as well as for other less verified dietary factors such as folate, vitamin B6, magnesium, garlic and omega 3 fatty acids[42-46]. On the other hand, frequent consumption of red meat and fat has been associated with increased risk for development of CRC[47-49].

Obesity has been consistently associated with increased risk for developing CRC, as well as with poorer outcomes following diagnosis[50-52]. In fact, a review of 29 studies reported that each 5 kg/m^2 incremental increase in body mass index is accompanied by CRC incidence increase of 24% in men and 9% in women[50]. In association with a healthy body weight, regular physical activity has been shown to reduce CRC incidence even more, with studies reporting up to 20%-30% lower risk[53,54].

Alcohol consumption as a risk factor for CRC has been a controversial subject, especially when referring to light and moderate consumption, but studies have consistently reported a higher risk for developing CRC among individuals with moderate to heavy consumption[55]. Tobacco smoking has been shown to double the risk of being diagnosed with a colon adenoma and to result to poorer outcomes following a cancer diagnosis, leading authors to recommend more intensive screening among smokers[24,56].

Although no accepted chemopreventive indications exist currently, many pharmaceutical agents have

shown preventive effects against CRC. Aspirin and COX-2 selective inhibitors are among the most investigated agents in regards to CRC prevention, and their regular use has shown ability to reduce incidence in individuals at both average and increased risk[57,58]. In the general population, the risks from their use seem to outweigh the benefits, but many advocate their use in certain individuals at increased risk for colorectal neoplasia[59].

SCREENING/SECONDARY PREVENTION

The fact that most CRCs take years to develop - following the Adenoma - Carcinoma sequence - permits the reduction of CRC mortality through screening, either by early detection and removal of the cancer or by detecting and removing the precancerous lesions[17-19].

There are roughly three categories of screening tests for CRC: stool-based, imaging, and endoscopic tests. Although stool-based tests can reduce mortality rates by early detection of asymptomatic cancerous lesions, imaging and endoscopic tests are capable of further reducing CRC incidence by detecting pre-cancerous lesions as well[16].

STOOL-BASED TESTS

Guaiac-based fecal occult blood test

Relying on the properties of alpha-guaiaconic acid, a phenolic compound extracted from Guaiacum trees, guaiac-based fecal occult blood test (gFOBT) can detect the presence of heme (of blood hemoglobin) in stool samples. Application of hydrogen peroxide onto guaiac paper causes alpha-guaiaconic acid to oxidize and turn blue. This reaction normally takes time, but heme (if present) catalyzes the reaction and within seconds a blue color change is visible[60-62]. This bioreactive method was proposed as a screening test for CRC almost half a century ago and has become the most frequently used screen for CRC worldwide[61].

While the gFOBT is cost affordable and non-invasive, it unfortunately bears many disadvantages. The interpretation of the result is subject to observer bias. Also, the reaction can be catalyzed by any peroxidase, such as heme found in meat, and false-positive results can lead to unnecessary colonoscopies; although, strict dietary restrictions that were proposed in the past seem to now be proven unnecessary[60,63]. False-negative results, on the other hand, can occur from ingestion of large doses of ascorbic acid (vitamin C)[64]. Aside from the dietary restrictions related to preparation for the gFOBT, the patient needs to provide three consecutive stool samples in order to achieve adequate sensitivity for occult blood[65]. The reported sensitivity and specificity vary between studies and different manufacturer brands, and efforts to introduce new, more sensitive guaiac-based tests resulted in lower specificity[66]. Finally, this test cannot detect polyps, since they do not bleed, and its sensitivity for advanced adenoma is relatively low[67].

Fecal immunochemical test

Fecal immunochemical test (FIT) detects blood in stool by using a specific antibody against human hemoglobin. As such, FIT is not affected by diet or observer bias, giving it a greater specificity than gFOBT. Besides specificity, however, its sensitivity for both cancer and adenomas has been shown to be superior to that of gFOBT[68,69]. According to a recent meta-analysis, the mean reported sensitivity and specificity for FIT detection of CRC is 79% and 94% respectively[70]. In addition, FIT requires fewer samples than gFOBT, making it more convenient for patients and thus increasing compliance[71]. Quantitative results can be provided with this method as well, facilitating the ability to determine positive cut-off points for different populations, patient characteristics, or system capabilities and resources[72].

In summary, stool-based tests are non-invasive and inexpensive methods capable of detecting occult bleeding. However, they are practically incapable of detecting polyps, since the latter do not usually bleed, and they have low sensitivity for detecting adenomas. Consequently, their role in reducing CRC incidence is close to none, but their implementation as a screening tool can reduce CRC mortality by providing early recognition of cancerous lesions. Comparing the two methods, FIT appears superior in terms of sensitivity and specificity (for both CRC and adenomas) and in terms of patient compliance. It is reasonable then to expect that, although more expensive, FIT could be more cost-effective than gFOBT since it could prompt less unnecessary colonoscopies.

IMAGING TESTS

Double-contrast barium enema

In double-contrast barium enema (DCBE), the colon is studied through X-rays obtained after coating the mucosa with barium and distending the colon with air, both of which are inserted transrectal. The DCBE is considered a safe method and has been used frequently in the past, but its use has been dramatically reduced as novel imaging methods become available. The reported sensitivity of DCBE for large polyps (> 10 mm) is only about 50%, and false positive results can occur due to inadequate bowel preparation[73,74].

Computed tomographic colonography

This method was first described more than 20 years ago, and provides 2- and 3-dimensional endoluminal images of the colon upon reconstructing of computed tomography or magnetic resonance images of the air-

distended colon[75,76]. The reported diagnostic value of computed tomographic colonography (CTC) has varied between studies, but as newer techniques of CTC are developed it is closing in on colonoscopy in terms of sensitivity and specificity for detecting CRC[77]. In a recent meta-analysis, the overall sensitivity and specificity of CTC was 66.8% and 80.3% respectively, both lower than the values for colonoscopy. For polyps > 10 mm though, the meta-analysis showed greater sensitivity and specificity (91.2% and 87.3% respectively)[78].

CTC appears to be more preferred by patients than colonoscopy; in addition, it has a very low risk of bowel perforation and requires no sedation[79,80]. On the other hand, CTC requires follow-up colonoscopy after positive results (to perform excision/biopsy), exposes the patient to radiation, and the lack of standardized methods leads to variable diagnostic performance[77,78]. The need for aggressive bowel preparation has been an issue, but newer techniques have been reported involving laxative-free CTC using "fecal tagging" with an ingested contrast agent[81]. Many authors include in CTC's advantages the potential of discovering extra-colonic pathology in asymptomatic patients, but this argument is controversial since these findings can sometimes lead to unnecessary patient anxiety, costly investigations and overdiagnosis[82-83].

Colon capsule endoscopy

The colon capsule endoscopy (CCE) method for CRC screening was initially introduced in 2006, and roughly consists of swallowing a pill-shaped device which is capable of photographing the gastrointestinal tract as it passes through it[84]. Initially, CCE did not gain significant acceptance as a screening tool for CRC, mainly because of its cost and relatively low diagnostic value compared to colonoscopy[85]. After introduction of the second-generation CCE (CCE-2) in 2009, the subject of CCE has become very popular in the medical literature[86]. The reported average sensitivity and specificity for the CCE-2 is 86% and 71% respectively, and since 2012 it has been prompted as an acceptable screening method for CRC by the European Society of Gastrointestinal Endoscopy[87]. Compared to colonoscopy, CCE might be a lot more preferable for the patient, but it is more expensive, lacks excision/biopsy ability and requires very aggressive bowel preparation[87,88].

ENDOSCOPIC TESTS

Flexible sigmoidoscopy

Flexible sigmoidoscopy (FS) enables the trained physician to visualize the distal gastrointestinal tract up to the splenic flexure, using a flexible, 60 cm long endoscope[89]. FS requires only minimal bowel preparation, no diet restrictions and no sedation, and can be performed by non-gastroenterologists (*e.g.,* PCPs) or even trained nurses[89-91]. Obviously, FS is unable to detect lesions in the proximal colon, which makes it lacking in sensitivity compared to colonoscopy[90]. In a meta-analysis, FS appeared to reduce CRC incidence and mortality among screened patients, by 32% and 50% respectively[92].

Colonoscopy

The traditional method of colonoscopy provides visualization of the entire large bowel and the distal part of the small bowel by using a flexible, 120-cm to 160-cm long endoscope[93]. It is considered by most the 'gold standard' in CRC screening, mainly because of its high sensitivity and specificity for detecting cancerous and precancerous lesions. It also provides the ability to excise or biopsy detected lesions during the same procedure[6,13,77,90]. Unfortunately, it is also an expensive method and not free of risk; it also requires sedation and extensive bowel preparation. The reported rate of major complications, such as bleeding or bowel perforation, is approximately 0.1%-0.2%, but could become significantly higher when excisions or biopsies are performed and in elderly or comorbid patients[93].

PREVENTION: SCREENING IMPLEMENTATION AND THE ROLE OF PCPS

It is beyond doubt that the burden of CRC can be significantly reduced through primary and secondary prevention. Scientific research over the past few decades has offered, as aforementioned, a variety of options for CRC screening and a better understanding of risk and protective factors for the development of CRC. Unfortunately, underutilization of screening and a lack in preventive policies are being reported[94-98].

Some European countries still have not implemented national mass screening programs, and others that did have reported low participation rates[97,98]. In the United States, there has been a significant decrease in incidence and mortality following widespread implementation of screening, but the overall use of screening is still below national standards[94]. Additionally, it has been reported that uninsured people in the United States and people of low socioeconomic or educational status show much lower participation rates[99].

Many researchers have attempted to identify the causes of CRC screening underutilization and ways to enhance it. While the barriers and sites of potential improvement have been identified at the levels of the health care system and the patient, most of the authors have advocated for the key role of PCPs.

Patients, in many studies, have shown low awareness concerning CRC screening and its importance. In one particularly insightful study, by Aubin-Auger *et al*[97], some patients showed low interest in CRC

screening, while others expressed the belief that CRC screening concerns only high-risk individuals or individuals that do not follow a healthy lifestyle. In a systematic review by Holden *et al*[100], the authors found that most patients not being screened state their reason as "not thinking about it". Strongly indicative of how important public awareness is for CRC screening participation was the "Presidential Effect", a term given to describe the increase in CRC screening participation of United States' citizens after the nation's President, Ronald Reagan, was diagnosed with colon cancer in 1985[101]. Similar reports of the impact of public figure announcements on cancer have been made, but data show that information given occasionally and in an unorganized manner often leads to short term results and mis- or overutilization of screening services[102,103].

At the level of health care systems, barriers and possibilities for enhancing CRC screening participation are more obvious. Several studies have revealed the efficacy of organized mass screening programs, especially when using patient reminders[100,104-107]. Participation rate has also appeared to be further enhanced when PCPs are involved in the invitation process[104,105]. Findings from studies have also led to authors advocating in favor of informational campaigns that increase public awareness of screening[108]. Another interesting finding in the literature is that patients with "usual source of care" are more likely to be screened for CRC[100]. This further highlights the importance of PCPs and family physicians in modern health care systems.

Research has also indicated barriers at the level of PCPs, with troubling findings in some cases. Screening recommendation rates by PCPs seem to remain low[100,109]. Several PCPs in surveys have reported a lack of knowledge and training, and some have even reported not finding screening to be effective[97,98,109,110]. The major role of PCPs in the effort to decrease CRC incidence and enhance screening participation has become more than obvious. PCPs constitute the first level of contact in a national health system for individual patients and their families. Their role in preventive medicine, through interventions in lifestyle habits, can effectively reduce CRC incidence, as well as that for other diseases. The unique patient-physician relationship in primary health care, in terms of trust and continuity of care, can effectively contribute to patient compliance, as clearly demonstrated throughout the literature.

Interventions through health care system organization, education of PCPs on CRC screening, prevention and counseling techniques, and in public awareness will, therefore, drastically decrease the burden of CRC[111].

CONCLUSION

Despite the significant improvements in screening techniques and our understanding of risk and protective factors, CRC remains a major global health burden. PCPs face a unique challenge in their capabilities and efforts to alter this phenomenon; their role in implementing screening and preventive policies is key to reducing the burden of CRC.

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