Review

Colorectal Cancer: Current Updates and Future Perspectives

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Colorectal Cancer: Current Updates and Future Perspectives

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Abstract: Colorectal cancer is a frequent neoplasm in western countries, mainly due to dietary and behavioral factors. Its incidence is growing in developing countries for the westernization of foods and lifestyles. An increased incidence rate is observed in patients under 45 years of age. In last years the mortality for CRC is decreased, but this trend is slowing. The mortality rate is reducing in those countries where prevention and treatments have been implemented. The survival is increased to over 65%. This trend reflects earlier detection of CRC through routine clinical examinations and screening, more accurate staging through advances in imaging, improvements in surgical techniques and advances in chemotherapy and radiation. The most important predictor of survival is the stage at diagnosis. The screening programs are able to reduce incidence and mortality rates of CRC. The aim of this paper is to provide a comprehensive overview of incidence, mortality and survival rate for CRC

Keywords: colorectal cancer; incidence; mortality; screening; survival

Introduction

Colorectal Cancer (CRC) is the third most commonly diagnosed malignancy and the second cause of death due to cancer worldwide[1–4]. There are significant variations in CRC incidence and mortality among various countries of the world which are based on different factors: gender[5], age[6–8], and ethnicity[6]. It imposes a substantial global burden in terms of its complications, mortality, side effects of treatment, health care services utilization and medical costs[5,9]. The higher rates of incidence are registered in most developed countries, but the diffusion of Western behaviors and lifestyle is responsible for the increase of colorectal cancer cases in less developed countries[10]. The different possibilities of access to care still play a fundamental role in survival and mortality for this neoplasm[11].

In recent years, artificial intelligence has also played a key role in early diagnosis and prediction of cancers[12–18], including CRC[19, 20], as described by numerous studies in the literature. In this clinical context, knowledge of epidemiological data is of great importance to analyze the trend of incidence and prevalence of pathology and to develop new predictive oncological techniques.

Nowadays, the most commonly used CRC serum biomarker is carcinoembryonic antigen (CEA)[21–23]. CEA is a protein that is produced by the developing fetus and by some types of cancer cells. CEA levels are typically low in healthy people, but they can be elevated in patients with CRC. CEA is not a specific biomarker for CRC, as it can also be elevated in patients with other diseases[24], such as inflammation of the colon. However, it is a useful biomarker for monitoring patients with CRC for recurrence or progression of the disease[25]. Another CRC serum biomarker is carbohydrate antigen 19-9 (CA 19-9)[22, 26, 27]. CA 19-9 is a protein that is produced by the pancreas and by some types of cancer cells included cholangiocarcinoma[28–31]. CA 19-9 levels are typically low in healthy people, but they can be elevated in patients with CRC, especially those with advanced disease[22, 32]. CA 19-9 is not a specific biomarker for CRC, as it can also be elevated in patients with other diseases, such as

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pancreatitis. However, it can be a useful biomarker for monitoring patients with CRC for recurrence or progression of the disease. SEPT9[33], methylated SEPT9[33, 34], microRNAs, and circulating tumor DNA (ctDNA)[35] and urine-based biomarkers, as volatile organic compounds (VOCs)[36], microRNAs[37], and DNA methylation markers showed promising results in early-stage CRC detection.

The aim of this paper is to provide a comprehensive overview of incidence, mortality and survival rate for CRC. Furthermore, we analyze the current screening program available and the future perspectives of serological tests to early detect CRC.

Incidence

CRC is the third most commonly diagnosed malignancy after breast and lung cancer with more than 1.9 million of new cases. It's accounts for about 10% of all cancer incidence worldwide[38, 39]. The global CRC incident rate is estimated to increase by 60% in 2030[40], and the number of CRC cases is predicted to reach 3.2 million by 2040[41]. Based on the sex, it's third most common cancer in males after lung and prostate cancers, and the second most common in females after lung cancer[42]. In general, the incidence of CRC is higher in males than that in females. Moreover, the CRC develops in different site depending on sex of the patient: females have cancer in the right colon while males have it in the left colon. Additionally, males are more likely to develop metastatic colon cancer, and females are more likely to develop metastatic rectal cancer as they age[43].

The global incidence of CRC is not uniformly distributed among regions of the world but varies substantially up to 8- and 6-fold for colon and rectal cancers, respectively[38].

The highest CRC rate is documented in Asia, which accounts for 52,3% of all global CCR in 2020; China alone held 28.8% of CRC cases worldwide[43]. Considering rectal cancer, the East Asian regions have the highest incidence rate, particularly Korean males and the Macedonian females ranked first[38]. In Europe the incidence rate is 26,9% of all global cases of CCR in 2020 with the highest age-standardized incidence rate (ASIR) reported for Hungary (45.3 per 100,000). The ASIRs in most European countries exceeded 40 per 100,000 and is higher than the world average rate[44]. Norway ranking first for CRC in female while Hungary was first for CRC cases reported in males[45]. In Italy, CCR accounts for 12,7% of all cancers with 48.576 new cases diagnosed in 2020 (25,588 males and 22,988 females). The Italian incidence rate is decreasing in all regions, for both males and females[42]. The incidence of CCR in United States accounts for 25.6 per 100,000 persons. Colon and rectal cancers incidences are low in the African continent and the Southern Asian countries[38, 45].

Colorectal cancer can be considered a marker of socio-economic development, and its incidence rates tend to rise uniformly with increasing Human Development Index (HDI). Countries undergoing economic growth and westernization (medium HDI nations, such as Brazil, Russia, China, Latin America, the Philippines, and the Baltics) are experiencing increasing incidence of CRC. This trend reflects changes in lifestyle factors and diet: the economic development is responsible of increased consumption of red meal, fat, sugar, animal-source foods and energy-dense food, which is associated with reduced physical activity and rising of overweight and obesity[46–50]. Mostly high-HDI nations (such as Canada, UK, Denmark and Singapore) has seen an increase in incidence but drop-in mortality, probably due to improved treatment options. Highest HDI nations such as the US, Iceland, Japan and France has witnessed a drop in both mortality and incidence due to successes in prevention and treatment[38].

However, the decline in CRC incidence slowed from 3%–4% annually during the 2000s to 1% annually during 2011–2019, driven partly by an increase in individuals younger than 55 years of 1%–2% annually since the mid-1990s[42]. The early incidence of CCR in the United States has increased approximately to 45% in adult ages 20-49 years, from 8,6 per 100,000 in 1992 to 13,1 per 100,000 in 2016[51]. A similar pattern is observed among populations in the Netherlands, Denmark, New Zealand, Australia, the UK, Canada, Germany, Sweden and Switzerland[43], but not in Italy[52]. Incidence in individuals younger than 50 years increased by about 2% per year for rectal cancer versus 0.5% per year for tumors in the proximal colon. Early onset patients are also more often diagnosed with advanced disease, including 27% with distant metastases versus 21% of older patients[53].

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Several studies reported racial disparity in CRC incidence [38, 44, 46, 51, 52]. Siegel et al.[53] compared the CRC incidence rate between different racial groups in the US during the period 2012 - 2016; the incidence rate in African Americans was the highest (45.7 per 100,000 persons), in non-Hispanic Caucasians was 38.6 per 100,000 people and in Hispanics it was 34.1 per 100,000 persons, the lowest incidence rate was registered in Asian Americans/Pacific Islanders (30.0 per 100,000 person). Multiple studies focused on the racial difference in genetic susceptibly to CRC found no racial disparity, but the difference in incidence among the ethnic groups seems to be linked at disparity in health care access and exposure to risk factors.

Mortality

CRC is the second cause of death due to cancer with 935,173 deaths estimated worldwide in 2020[42], which accounted for about 9% of all cancer-related mortality[5]. The mortality rate for CRC seems to be decreasing in recent years, but this trend has slowed from about 4% annually during the early 2000s to about 2% from 2012 through 2020. Although mortality is decreasing in the majority of developed countries, the total deaths for colon and rectal cancer are expected to increase by 60.0% and 71.5% until 2035, respectively[54]. Nevertheless, it is important to underline the increase in surgical interventions in frailer elderly affected by concomitant chronic diseases[55, 56].

A disparity in CRC mortality rate and trend for gender has been noticed worldwide: the overall death rate is currently 43% higher in men than in women. A further difference in CRC mortality rate is related to age. The worldwide mortality rate is higher in patients of 65 years and older[57]. However, it is evident an increase in mortality rate among younger compared to older population[53]. In the US in 2020, 68% of CRC mortality was registered in patients of age 65 years and older, 25% in the age group 50-64 and 7% in patients of age less than 49[5]. In Europe, during the period 1990 and 2016, the CRC mortality rate increased by 1.1% in patients of 30-39 years old, while in patients of age group 40-49 years, the mortality rate decreased by 2.4% between 1990 and 2009, but increased by 1.1% between 2009 and 2016[5].

Variation in mortality rate was also observed between different racial groups, also. In US, the African American population being the most affected (19.0 per 100,000 persons) while the lowest rate was found in Asian Americans/Pacific Islanders (9.5 per 100,000 persons). The mortality rate in non-Hispanic whites was 13.8 per 100,000 persons and 11.1 per 100,000 persons in Hispanics[53].

CRC mortality rates change globally, with an attenuated pattern compared to that of the incidence. About 60% of all deaths occur in countries with high or very high HDI[38]. The age-standardized rate of CRC mortality per 100,000 people was 27.1 in very high HDI countries compared to 2.75 in low HDI countries, with a positive correlation between the CRC mortality rate and HDI[5]. Decreasing trends were observed in central European countries (Austria, the Czech Republic and Germany) and in the United States and Canada[5]. The mortality of CRC has been increasing in countries with low-medium HDI like countries of Eastern Europe, Asia, and South America. The lowest mortality rates were recorded from Ecuador in Latin America whilst the steepest fall in mortality was in Denmark[53]. In Italy, CCR ranks second in terms of mortality after lung cancer; if only rectal cancer is considered, it's ranks ninth in terms of mortality while colon cancer alone ranks eleventh. In 2020 were estimated 21789 deaths with a huge prevalence in males. The Southern regions show a higher mortality rate than Northern regions[42].

Survival

The 5-year relative survival rate for CRC increased from 50% in the mid-1970s to 65% during 2012–2018. This trend reflects earlier detection of CRC through routine clinical examinations and screening, more accurate staging through advances in imaging, improvements in surgical techniques and advances in chemotherapy and radiation[5, 58–62]. Stage at diagnosis is the most important predictor of survival, with 5-year relative survival ranging from 91% for localized disease to 14% for distant disease. Approximately 10% of survivors live with metastatic cancer, 44% of whom were initially diagnosed with early-stage disease. The largest survival incomes are for metastatic rectal cancer, with

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30% of patients diagnosed during 2016–2018 surviving 3 years compared with 25% only a decade earlier[63].

Liver represents the leading metastase site[3, 64–72]. Up to 25% of patients simultaneously experienced primary tumour and colorectal liver metastases (CRLM) diagnosis[73], while 20% will progress to stage IV. Although the availability of chemotherapy regimen progress in many primary tumours[15], surgical resection is considered the *gold standard* treatment for CRLM, with a 5-year survival rate from 30% to 60%[9, 39, 74–81]. However, about 80% of patients are affected by unresectable CRLM, due to bilobar multiple liver metastases and/or extrahepatic disease. Nowadays, systemic chemotherapy regimens[64, 76, 79, 82–89] are proposed to convert patients with initially unresectable CRLM to obtaining and improving long-term surgical and oncological outcomes[23, 82, 90–93]. Nevertheless, some of patients will progress during neoadjuvant chemotherapy with a debated role of liver resection in this subgroup.

Stage at diagnosis plays the largest role also in racial and ethnic survival disparities. Black individuals are most likely to be diagnosed with metastatic CRC (25% vs. 21% of White individuals), likely caused by unequal access to care compared to White patients. However, the 5-year relative survival rate for localized disease is relatively similar (89%–91%) across racial and ethnic group[63].

Men have a slightly lower 5-year relative survival rate (64%) compared with women (65%) despite a more favorable tumor subsite distribution. In particular, 35% of men versus 44% of women develop tumors in the proximal colon, which have a higher risk of death compared with left-sided cancers independent of histological and molecular characteristics. However, the largest sex disparity in 5-year survival is also for left-sided tumors at 66% in men versus 68% in women for distal colon cancer and 67% versus 70%, respectively, for rectal cancer[63]. Survival of patients with cancer located in the distal part of the colon was overall higher than that of patients with proximal colon cancer. This observation may be explained by a more favourable stage distribution of cancers located in the distal than in the proximal colon, as well by distinct molecular features between subsites[94].

Survival rates for patients with screen-detected cancer were higher than those found for patients with non-screen-detected cancer within each disease stage. This evidence is probably due to higher adherence to therapy and more healthy behaviour of patients undergoing to screening tests compared to non-screen-detected cancers, which contributes to the observed disparities in survival, particularly for patients with stage III and IV cancers.

The CRC survival rate varies among geographic regions. CONCORD-3 study[95] shows the survival for CRC in 71 countries. Five-year survival for colon cancer was higher than 70% in Israel, Jordan, Korea and Australia. Survival was in the range of 50–69% in 26 countries: Mauritius; Costa Rica and Puerto Rico; Canada and the US; Japan, Singapore and Taiwan; in 17 European countries (Denmark, Finland, Iceland, Ireland, Norway, Sweden, the UK; Italy, Portugal, Slovenia, Spain; Austria, Belgium, France, Germany, the Netherlands, Switzerland) and in New Zealand. As for colon, five-year net survival for rectal cancer varied widely. Survival was higher than 70% in Jordan (73%), Korea (71%), and Australia (71%). Survival was in the range 60–69% in 24 countries: in Canada and the US; in 4 Asian countries, in 17 European countries: (Denmark, Finland, Iceland, Ireland, Norway; Sweden, the UK; Italy, Portugal, Slovenia, Spain; Austria; Belgium; France, Germany, the Netherlands, Switzerland); and in New Zealand[95].

In Italy the 5-year survival for CRC is 62%, and the 10-years survival is 58% both in men and women. The southern regions have survival approximately 5-8% lower than in the Centre-North regions[52].

Screening and Preventation

A series of screening modalities for CRC are currently available: an annual or biennial fecal occult blood tests (FOBT) or fecal immunochemical test (FIT), sigmoidoscopy every 5 years, or colonoscopy every 10 years[96].

The CRC screening program is recommended for people aged between 50 and 75 years. However, in recent years, the American Cancer Society and United States Preventive Service Task Force (USPSTF) have lowered the recommended start age for screening in average-risk populations

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to 45 years old due to the early onset of CRC[5]. Among the European countries The Netherlands reported the highest participation rate of 71.3% to the screening programs, twelve countries reported participation rates of over 50%, while the participation rates in Poland (16.7%) and Belgium (4.5%) were less than 20%. In general, the participation to the screening programs is higher in Northern Europe than in South and Central Europe. In Italy, the participation rate amounts to 45,7%, with higher adherence in the northern regions than in the southern ones.

Over the last decades, screening programs have deeply influenced the incidence and mortality rates of CRC. In the US, a CRC incidence has been reduced by 20% for annual FOBT screening and by 18% for biennial regimen[44]. In Japan, a 60% risk reduction in CRC incidence was achieved among subjects who underwent FOBT screening in comparison to the non-screened population [44]. In the UK, a randomized trial with 17-year follow-up reported that flexible sigmoidoscopy screening resulted in a 26% reduction of CRC incidence[44]. With the implementation of a screening program in Italy, a decrease of cumulative incidence by 10% among the people aged between 50-69 years of age has been registered[44].

In US screening with FOBT resulted in 32% reduction in mortality by the annual screening and an 18% reduction due to the biennial screening. FOBT screening caused CRC mortality reduction by 15% in the UK, by 18% in Denmark, and by 16% in France and Sweden[5], by 30% in Japan in subjects who underwent FOBT screening, and by 31.7% in China[5]. In Italy, the effects of screening program are similar to other European countries with a reduction of 13% in CRC mortality.

Magnification endoscopy and chromoendoscopy represent useful techniques that enhance lesion demarcation improving adenoma resections. It is linked with a higher sensitivity rate when compared to classical endoscopy.

Although surgical and endoscopic innovations, many procedures have been proposed but not included in routine clinical examinations: virtual colonoscopy, serum proteomics and molecular blood tests represent promising tools for the early detection of colorectal lesions. Further studies are needed to evaluate the sensitivity and specificity of these techniques.

Several risk factors have been identified in the last decades as possible tumorigenesis causes: tobacco use, physical inactivity, obesity and alcohol.

Even though clinical trials with dietary interventions (eg, increases in fibre, fruits, and vegetables, and reductions in fat and alcohol) have shown little effect, several observational studies support a role of dietary modifications. Many drugs are being investigated for chemoprevention of this cancer[97–99]. Although a significant risk reduction for colorectal cancer or adenomas has already been recorded for several drugs (eg, aspirin, nonsteroidal anti-inflammatory drugs), the role of chemoprevention needs to be further defined.

Surgical prevention is established for FAP and ulcerative colitis, and restorative proctocolectomy with ileoanal J-pouch is recommended for most patients[100–102]. For HNPCC, the role of prophylactic surgery is less well defined, but some suggest prophylactic colectomy[100, 101]. Because prophylactic surgery is mostly on young, apparently healthy people, morbidity and mortality from surgery has to be kept to a minimum.

Conclusions

CRC is one of the cancers whose incidence and mortality are modifiable by following healthy lifestyles. However, the burden of CRC is expected to increase due to the aging of population and to the westernization of less developed countries. Screening programs are able to reduce incidence and mortality rates of CRC. More research is required to explore the reasons for the increasing burden of CRC in young adults. More efforts are needed to implement screening programs and to control risk factors of CRC to reduce its burden.

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