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Review

Colorectal cancer in the world: incidence, mortality and risk factors

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Abstract

A rapid literature search strategy was conducted for all English language literature published before July 2017. The search was conducted using the electronic databases PubMed, Scopus and Web of Science. The search strategy included the keywords 'colorectal cancer', 'epidemiology', 'incidence', 'mortality', 'risk factor', and 'world'. In 2012, the highest CRC incidence rates were observed in the Republic of Korea, Slovakia and Hungary while the lowest incidence rates were seen in Singapore, Serbia and Japan. The highest CRC mortality rates in both sexes were seen in Central and Eastern Europe and the lowest mortality rates were found in Middle Division of Africa. The main risk factors for CRC include nutritional factors, past medical history, smoking, socioeconomic status, and family medical history. According to the increasing trend of CRC incidence and mortality in the world, implementation of prevention programs such as screening programs, diet modification, and healthy lifestyle education is necessary.

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Keywords

Colorectal Cancer, Incidence, Mortality, Risk Factors, Worldwide

Introduction

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity in the world (Favoriti et al., 2016). It is the third most common malignancy and the fourth leading cause of cancer-related deaths worldwide, accounting for approximately 1,400,000 new cases and about 700,000 deaths worldwide (Arnold et al., 2016). In recent decades there has been a significant increase in the incidence of CRC; in particular, the number of newly diagnosed CRC cases has increased from 783,000 in 1990 to 1,361,000 in 2012 (Ferlay et al., 2015a; Rafiemanesh et al., 2016). In terms of geographical distribution, this cancer has risen in industrialized countries with moderate and high Human Development Index (HDI) (Dolatkhah et al., 2015). In recent years, the incidence and mortality rates of CRC in Eastern Europe, Latin America and Asia have grown higher than other countries (Center et al., 2009a). The incidence and mortality rates of CRC in the countries with the highest HDI, such as certain Western European countries and the United States, have steadily decreased (Arnold et al., 2016).

It seems that familiarity with preventive measures, advances in therapeutic and diagnostic procedures (such as polypectomy), improvements in quality of preoperative assessment, and treatments (such as radiotherapy and chemotherapy) have played significant roles in reducing this trend (Center et al., 2009b; Murphy et al., 2015). With respect to gender, despite the prevalence of CRC in both sexes it was higher in men than in women (Ferlay et al., 2015a). Moreover, the risk of developing colorectal cancer increases with age. Indeed, more than 90% of diagnosed patients are over 50 years old and the average age of CRC diagnosis is 64 (Amersi et al., 2005). Also, significant geographical variations in the rate of CRC incidence indicate that multiple factors can influence the increase in CRC rates. While most studies in this area have focused mainly on therapies for CRC (Alberts et al., 2005; Saltz et al., 2008), it is equally important to understand the epidemiological aspects of CRC. Indeed, comprehensive studies and analysis of the epidemiology and etiology of CRC are rare though essential. Therefore, this study aims to investigate the incidence rate, mortality rate and risk factors of CRC throughout the world.

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Methods

A rapid literature search strategy was conducted for all English language literature published before July 2017. The search was conducted using the following electronic databases: PubMed, Scopus and Web of Science. The search strategy included the following keywords: 'colorectal cancer', 'epidemiology', 'incidence', 'mortality', 'risk factor', and 'world'. The search strategy was adjusted according to different requirements for each database. The specific search was also performed in cancer-related websites for Iran-related information.

Results

Incidence rate

The incidence rate of CRC varies greatly worldwide (Arnold et al., 2016). In 2012, the highest incidence rates of CRC were found in the Republic of Korea (AGR = 45) (Jung et al., 2015), Slovakia (AGR = 42.7) (Ferlay et al., 2013), Hungary (AGR = 42.3) (Torre et al., 2015), Denmark (AGR = 40.5), and Netherlands (AGR = 40.2 per 100,000) (Ferlay et al., 2013). The lowest incidence rates were seen in Singapore (AGR = 33.7), Spain (AGR = 33.1), Coatia (AGR = 32.9), Serbia (AGR = 32.6) and Japan (AGR = 32.2 per 100,000) (Ferlay et al., 2015b). CRC incidence in developing countries has been steadily increasing (Jemal et al., 2010). The highest increase was recorded in Western Asia (including Israel and Kuwait) and in Eastern Europe (Czech Republic, Slovakia and Slovenia) (Center et al., 2009a; Center et al., 2009b; Martín et al., 2008).

This increase indicates a growth in the prevalence of CRC risk factors associated with the Western lifestyle, such as unhealthy diet, obesity and tobacco consumption (Favoriti et al., 2016). In most parts of the world, the incidence rate of CRC was higher in men than in women (Torre et al., 2015). The causes of this difference may be due to the complex relationship between the exposure of men to certain risk factors and the different cancer screening tests for men and women (Brown et al., 2005; Meissner et al., 2006). The incidence rate of CRC increases with age (Boyle and Langman, 2000) and increases significantly among the age group of 40-50 years. CRC incidence rates will continue to rise in the coming decades (Ahnen and Macrae, 2010).

Mortality rate

In 2012, about 693,099 CRC deaths were recorded worldwide, accounting for 8% of all cancer deaths (Ferlay et al., 2015b; Torre et al., 2015). In 2015, CRC was recognized as the third leading cause of cancer-related deaths with 49,700 diagnosed cases (26,100 cases in men and 23,600 in women) (Siegel et al., 2015). Colorectal cancer, indeed, is the fourth leading cause of cancer-related

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deaths in men and the third leading cause among women worldwide. The mortality rates vary according to each nation's HDI. As an example, the highest mortality rate is observed in countries with high HDIs; these counties include those of Central and Eastern Europe and of Latin America (Favoriti et al., 2016). The highest mortality rates in both sexes was observed in Central and Eastern Europe (ASR = 20.3 in men and 12.1 in women, per 100,000). The lowest mortality rates were seen in the Middle Division of Africa (ASR = 3.5 and 2.7, per 100,000, in men and women, respectively) (Center et al., 2009a).

Mortality rates have shown a downward trend in most economically-developed countries (e.g. United States, Australia and New Zealand), most Western European countries (e.g. France, Germany and Spain), some Asian countries (e.g. Japan), Eastern European countries (e.g. Czech Republic, Latvia and Slovakia), and South Africa. The decrease in mortality could be due to improved diagnostic procedures, prevention and reduction of risk factors, and access to healthy diets (Bosetti et al., 2011; Edwards et al., 2010). However, the CRC mortality rate is still high in some countries with limited resources (such as Mexico, Brazil, Chile, Romania and Central America) (Center et al., 2009a; Chatenoud et al., 2014). The increase in mortality rate could be due to the lack of predictive measures and/or an increase in the incidence of CRC (Jung et al., 2015). Between 2001 and 2010, mortality rates decreased in both sexes by 3% per year (Siegel et al., 2015). With regard to gender, the mortality rate in men is 30 - 40% higher than in women. In terms of race, the mortality rate in U.S. blacks (29.4 per 100000) is approximately 50% higher than in whites (Favoriti et al., 2016). Moreover, the environmental factors and the delay in performing screening tests could be contributing factors to the observed differences (Potosky et al., 2002; Wang et al., 2012).

Risk factors

Nutritional factors

Intake of fruits, vegetables and high-fiber diet

Several epidemiological studies have shown an association between increased consumption of fruits and vegetables and reduced risk of CRC (Slattery et al., 1998; Terry et al., 2001). Fruit and vegetables appear to have a protective effect against CRC due to the richness of fiber, folic acid, antioxidants and vitamins (Negri et al., 1998; Willett et al., 1990). Several epidemiological and laboratory studies have confirmed the role of dietary fiber in the pathogenesis of CRC (Ahnen and Macrae, 2010). Several observational studies have reported a correlation between intake of a high-fiber diet and reduced risk of CRC (Bingham et al., 2003; Larsson et al., 2005a; Peters et al., 2003). The findings of a meta-analysis study also indicated that a high-fiber diet could reduce CRC incidence by up to 50% (Trock et al., 1990). A diet rich in fiber can reduce the

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risk of *CRC* by lowering the pH of the sigmoid colon, reducing the colon transit time, and increasing the uptake of folic acid and micronutrients (such as antioxidants) in vegetables (Kritchevsky, 1995; Rex et al., 2009).

High consumption of red meat and saturated fats

Increased consumption of meats, animal fats, and cholesterol-rich foods *are associated with an increased risk of CRC* (Chao et al., 2005). The findings of a longitudinal study showed that CRC risk is significantly higher in people who eat more than 160 grams of processed meat every day (Norat et al., 2005). Another study also found that people who eat red meat more than five times a week were three times more likely to develop CRC than others (Wei et al., 2004). Indeed, the risk of CRC increases after high meat consumption due to stimulation of insulin secretion, increased iron absorption (heme), and increased fat intake (Gerhardsson de Verdier et al., 1991). Moreover, longer cooking time of meats increases heterocyclic *amine production, which* can also contribute to the increase in CRC incidence (Anderson, 2011; Martínez et al., 2007). Studies have found that after controlling variables (such as intake of vegetables and fruits), the risk of CRC incidence in people receiving a cholesterol-rich diet was significantly higher in comparison to those who consumed lower cholesterol levels (Järvinen et al., 2001; Lin, 2009).

Alcohol Consumption

With respect to alcohol consumption and CRC risk, a positive association between alcohol consumption and CRC incidence has been reported in several studies (Fedirko et al., 2011; Longnecker et al., 1990). Ethanol-containing beverages increase the risk of CRC incidence by producing carcinogenic substances and creating changes in bile acid compositions (Choi et al., 1999; Kune and Vitetta, 1992). The American Cancer Society has reported that an increase in alcohol consumption (more than 30 grams per day of ethanol) in men is associated with an increased risk of CRC incidence (Marmot et al., 2007). A Cohort study on 18,707 Korean adults after 11 years of follow-up showed that alcohol consumption was associated with an increased risk of CRC development among men. Also, the increase in duration and amount of alcohol consumption is directly related to the increase in CRC incidence (Shrubsole et al., 2008). The Health Professionals Follow-Up Study (HPFS) findings suggest that there is a positive relationship between alcohol consumption in men and CRC risk (Thygesen et al., 2008). The European Prospective Investigation into Cancer (EPIC) findings also showed that even after controlling for variables (such as smoking), an increase in alcohol drinking still increases the risk of CRC (Ferrari et al., 2007). The meta-analysis study also found that CRC risk was significantly increased in people who consume alcohol more frequently than twice a day (Cho et al., 2004).

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Caffeine

The relationship between caffeine consumption and CRC incidence has not been confirmed definitively (Lin, 2009). Although the findings of a meta-analysis of evidence-based studies revealed that there was a correlation between caffeine consumption and increased risk of CRC (Giovannucci et al., 1994), the NHS and HPFS findings did not prove this claim (Michels et al., 2000).

Past medical history

Diabetes mellitus (DM)

Various studies have shown that diabetes mellitus (DM) subjects are at risk for CRC compared to non-DM subjects (Hu et al., 1999; Will et al., 1998). Analysis of this cohort study, which lasted for 9 years on 484,020 individuals aged 71-50, showed that 7,598 cases were diagnosed with CRC. After controlling for non-nutritional confounders, it was found that DM was associated with an increased risk of CRC. Modifications and adaptations, in terms of dietary quality, did not affect the findings (Jarvandi et al., 2013). A meta-analysis study showed that the risk of CRC in people who have DM is 35% higher than in non-DM subjects (Luo et al., 2016). The findings of the Nurses' Health Study (NHS) study showed a direct relationship between CRC incidence and DM diagnosis (Hu et al., 1999). The increase of insulin concentration and *insulin-like growth factor* (IGF)-1 levels, increase of glucose (hyperglycemia), and prolonged exposure of the colorectal mucosa to fecal bile acids (due to constipation) all play an important role in colorectal carcinogenesis (Airley and Mobasheri, 2007; Giovannucci, 2001a; Stadler et al., 1988). Also, hyperglycemia (Jee et al., 2005; Nilsen and Vatten, 2001; Saydah et al., 2003), hyperinsulinemia (Ma et al., 2004), and *increased serum levels of* IGF-1 (Wei et al., 2005) can cause the development of colorectal tumors (Grimberg and Cohen, 2000; Tran et al., 1996). Carcinogenesis caused by insulin resistance also leads to increased cell proliferation and reduced apoptosis (Grimberg and Cohen, 2000; Gunter and Leitzmann, 2006; Sandhu et al., 2002).

Inflammatory bowel disease (IBD)

Patients with long-term inflammatory bowel disease (IBD) have an increased risk of CRC. In fact, CRC accounts for $1/6^{th}$ of ulcerative colitis (UC)-related deaths and $1/12^{th}$ of all deaths in patients with Crohn's disease (Jess et al., 2005; Jess et al., 2012). In UC, the risk of developing CRC depends on the duration and extent of disease. According to a study conducted in the United States, the highest risk was reported in patients with UC or pancolitis with a standardized incidence ratio of 2.4 (Jess et al., 2006). Findings of another study confirmed that CRC risk increases 8 - 10 years after the onset of UC-related symptoms, compared to the control group matched by other variables (Rutter et al., 2006). Generally, the cumulative incidence of CRC in patients with UC has an increasing trend. For instance, at 20, 30 and 35 years after diagnosis of UC, the percentage of UC-diagnosed patients afflicted with CRC was 5-10%,

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12-20%, and 30%, respectively (Ekbom et al., 1990; Gyde et al., 1988). There are other factors that may be associated with the risk of developing CRC in patients with IBD. For example, the risk of developing CRC increases with early onset of primary disease (before age 15) (Gupta et al., 2007). The severity of inflammation is also a key factor which increases the risk of CRC (Rubin et al., 2013).

Cholecystectomy

Several studies have been reported the association between cholecystectomy and right-sided colon cancer (Vernick and Kuller, 1982; Vernick et al., 1980). The results of a study showed that patients undergoing cholecystectomy experienced a slight increase in right-sided colon cancer (with a standardized incidence ratio of 1.16) but no left-sided colon cancer was observed among them (Lagergren et al., 2001). The cohort study also found that the risk of CRC occurrence is increased by cholecystectomy (Schernhammer et al., 2003). Findings of another study also indicate that cholecystectomy is associated with an increased risk for colon cancer (Shao and Yang, 2005). Abnormal bile duct metabolism increases the gallstone formation, leading to an increased risk of CRC. Moreover, the fecal fat level increases after cholecystectomy (Goldacre et al., 2005). Constant colon exposure to high levels of metabolic products such as bile acids, non-digestible fat, and other end-products of colonic micro flora (like methylindole and zuccato) can lead to an increased risk of CRC (Ono et al., 2013).

Ureterocolic Anastomosis

A few studies have clearly reported an increase in the risk of colorectal neoplasia near the site of ureterocolic anastomosis after extensive urethral or intestinal tract surgery (Planning; Tollefson et al., 2010). The mechanism of this risk factor (which can lead to CRC) is the exposure of colonic mucosa to urinary-bladder carcinogens (Lin, 2009).

Pelvic radiotherapy

In patients with a history of pelvic radiotherapy, the risk of CRC occurrence is very high at 5 to 10 years after radiotherapy (Felder and Rogge, 1983; Sandler and Sandler, 1983). The findings of a retrospective study showed that the risk of developing CRC in patients with a history of radiation therapy for prostate cancer is higher than others (Baxter et al., 2005).

Other Factors

Physical Activity and Obesity

Reduced physical activity has been associated with an increased risk of CRC (Lee et al., 2012; Meyerhardt et al., 2006). The findings of a case-control study in North California indicated that decreased physical activity and increased body

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mass index (BMI) can significantly increase the risk of CRC (Slattery et al., 1997). The Cancer Prevention Study (CPS-II) findings also showed that there is a significant inverse association between physical activity and the risk of CRC (Thun et al., 1992). Findings of another study indicated that CRC risk is significantly higher in idle workers compared to workers who had light or heavy physical activity (Colbert et al., 2001). Daily inactivity can increase the incidence of obesity, which is another risk factor for CRC (Bardou et al., 2013). The precise mechanism of the protective effect of physical activity is still unclear, but it seems that physical activity lowers the risk of CRC by reducing BMI, reducing the colonic transit time, and lowering insulin levels (Gribovskaja-Rupp et al., 2011; Mao et al., 2003). Obesity increases serum leptin levels (Frezza et al., 2006); leptin leads to CRC development (Sierra-Honigmann et al., 1998). Indeed, leptin enhances the growth and proliferation of colon cancer cells (Liu et al., 2001). It also increases the spread of adenomatous lesions in mouse studies (Hirose et al., 2004). Findings from a study showed that men with the highest serum leptin levels are twice more likely to develop CRC than men with the lowest serum leptin levels (Stattin et al., 2003). Obesity is one of the main risk factors for type 2 diabetes, which incidentally is one of the independent risk factors for CRC (Larsson et al., 2005b). This association is stronger in men than in women (Inoue et al., 2006). Obesity also increases insulin resistance and hyper-insulinemia (Frezza et al., 2006). The impact of diabetes on CRC will be discussed separately.

Tobacco consumption

Tobacco consumption and cigarette smoking, particularly, are common risk factors for CRC in both genders (Giovannucci, 2004). Findings from a cohort study in Korea indicated that "Former Smokers" carried a higher CRC risk than "Never" smokers (Kim et al., 2006). Another study found that CRC risk is increased in people who have smoked over 45 years, while there was no relationship between the number of cigarette packs and the risk of CRC (Cho et al., 2015). Smoking accounts for 20% of all types of CRC in the United States (Giovannucci, 2001b). Several studies have also found that smoking increases the risk of CRC by up to 30% in smokers (Giovannucci et al., 1994; Newcomb et al., 1995; Paskett et al., 2007).

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)

Studies have shown that the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can play a role in CRC prevention (Chan et al., 2005; Cuzick et al., 2009; Dubé et al., 2007). Evidence suggest that a 30-40% reduction in risk of adenoma and CRC may be attributable to aspirin (Din et al., 2010).

Socioeconomic Status (SES)

The low socioeconomic status has a direct relation with the increased risk of CRC. According to one study of 506,488 participants, 7,676 developed CRC. In

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the study, it was found that CRC rates were higher in people with lower education or of lower socioeconomic status than those living in affluent areas, even after adjusting for other risk factors (Doubeni et al., 2012a). This difference can be due to higher incidence of moderating risk factors in those areas (such as immobility, unhealthy diet, smoking and obesity) as well as low screening rates in the areas (Doubeni et al., 2012b; Klabunde et al., 2011).

Family history and adenomatous polyps

In 20% of CRC cases, at least one family member typically has been afflicted with CRC (Butterworth et al., 2006). In fact, 85% of the CRCs originate from adenocinoma, which accounts for adenomatous polyps (Dove-Edwin et al., 2005). Generally 70-90% colorectal cancers arise from adenomatous polyps. Polyps larger than 2 cm in diameter have a 50 % chance of malignancy (Levin et al., 2008). The occurrence of colorectal carcinomas in populations with a prevalence of mucosal polyps is higher than others and the risk of cancer is closely related to the number of these polyps. The risk of cancer can be reduced by removing the preneoplastic lesions (Oberg et al., 2011).

Gender and Race

The role of gender in CRC development has not been determined definitively (Haggar and Boushey, 2009). Although in most studies it has been reported that CRC risk is higher in men than in women- due to the progression of colorectal neoplasia- the overall life-threatening risk of CRC in both sexes is numerically identical (Lin, 2009; Zisman et al., 2006). CRC occurrence has a 5-year delay in women, compared to men. For example, a woman's CRC risk at age 55 is equivalent to a man's CRC risk at age 50 (Lieberman, 2005). The findings of a meta-analysis study showed that the risk of CRC and advanced adenoma in men was twice that for women (Nguyen et al., 2009). However, the results from the Bressler et al. study suggest that women are more likely to be exposed to CRC than men after colonoscopy (Bressler et al., 2007). The right-sided colon cancer has been observed more in women; inversely, the left-sided colon cancer is mostly observed in men (Brenner et al., 2007). In general, more studies are needed to confirm the role of gender in the occurrence of CRC. The incidence and mortality rate of CRC for African Americans is higher (for both genders) than in whites (Shavers, 2007). It seems that the cause of this difference is related to the etiological factors, such as smoking, diabetes mellitus, and the use of screening and diagnostic tests in African Americans (Wong, 2010).

Conclusion

This study evaluates the incidence rate, mortality and risk factors for CRC, based on a review of studies conducted throughout the world. The results of our analysis indicate that most CRC risk factors are related to dietary and lifestyle

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factors and can be prevented. Due to the fact that prophylactic risk factors (such as high-fat diet, low fiber, obesity, inactivity and smoking) are major contributors to the incidence of CRC, a comprehensive planning- especially in high-risk groups- is needed to prevent these factors. Healthy lifestyle education programs and sports/recreational facilities are necessary to enhance physical activities and implement this comprehensive planning. Also, the risk factors investigated in this study are often extracted from descriptive cross-sectional, prospective, retrospective and retrospective case studies. Therefore, due to the effect of confounding variables it is necessary to carry out further studies, especially interventional studies and trials, in order to confirm these risk factors.

Abbreviations

BMI: Body Mass Index
CRC: Colorectal Cancer
DM: Diabetes Mellitus
EPIC: The European Prospective Investigation into Cancer
HDI: Human Development Index
HPFS: Health Professionals Follow-Up Study
IBD: Inflammatory Bowel Disease
IGF: Insulin-like growth factor
NHS: Nurses' Health Study
NSAIDs: Nonsteroidal Anti-inflammatory Drugs
SES: Socioeconomic Status
UC: Ulcerative Colitis

Author Contributions

All authors contributed to the design of the research. HSG, SMY, MA, AMH, AAT and AP extracted the data and summarized it. All authors drafted the first version. HSG, AMH and HS edited the first draft. All authors reviewed, commented and approved the final draft.

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