**Epidemiology, Risk Factors, and Prevention of Colorectal Cancer-An English Version**

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**Abstract**
Colorectal cancer (CRC) is the fourth most common malignancy in Korea and has been ranked as the third leading cause of cancer deaths in 2020. Although the incidence and mortality rates of CRC have decreased in recent years in Korea, it is still a significant public health burden. From the early 1990s until the mid-2000s, the 5-year relative survival of patients with CRC in Korea continuously increased. This finding appears to be a consequence of the successful introduction of a government-led screening program; the development of improved surgical techniques, anticancer drugs, and adjuvant treatment; and the advancement of medical resources and infrastructure along with economic growth. However, the improvement in survival has stagnated since the late 2000s. The recent coronavirus disease 2019 outbreak led to a reduction in hospital visits and screenings, which is expected to cause a stage shift to advanced disease stages and a worse prognosis for patients with CRC. Exploring modifiable environmental risk factors and appropriate screening test methods in Korea is necessary to overcome these challenges. Primary prevention through risk factor mediation and secondary prevention using suitable screening programs can help reduce the incidence and mortality rates of CRC.

**Keywords**
colic neoplasms, epidemiology, risk factors, mass screening

**Introduction**
Cancer is a significant public health burden in Korea. Since surpassing cardiovascular disease for the first time in 2000, it has consistently been the first leading cause of death in the Korean national causes of death statistics[1]. According to the 2020 statistics data, 27.0% of all deaths in the country were due to cancer, and the cancer mortality rate was 160.1 per 100,000 people, which is an increase of 1.2% from the previous year. With a mortality rate of 17.4 per 100,000 people, colorectal cancer (CRC) was the third most important cause of cancer-related deaths after lung cancer (34.6 per 100,000 people) and hepatic cancer (20.6 per 100,000 people). This review aims to provide essential data for effective primary and secondary prevention of CRC by examining the epidemiology worldwide and in Korea and the domestic status of known risk factors and screening tools.

**Epidemiology**
CRC is the third most common cancer worldwide after breast and lung cancers and the second most common cause of cancer-related death after lung cancer[2]. Among men, CRC has the third highest incidence rate after lung and prostate cancers and the third highest mortality rate after
lung and hepatic cancers. Among women, it has the second highest incidence rate after breast cancer and the third highest mortality rate after breast and lung cancers. According to the GLOBOCAN 2020 estimates presented by the International Agency for Research on Cancer, which investigated the incidence and mortality rates of 36 cancer types in 185 countries worldwide, the cumulative incidence rates of CRC by the age of 75 years were 22.6% for men and 18.6% for women. CRC incidence rates vary by region, with a difference of up to 9-fold, and the incidence rate in developed countries was reported to be approximately 4-fold higher than that in developing countries. Moreover, the CRC incidence rate is closely related to economic development, and it tends to increase steadily as the Human Development Index increases in developing countries. This phenomenon may be due to the lifestyle changes that follow socioeconomic development, such as increased animal-based diet and decreased physical activity, which can act as risk factors for CRC development[3]. However, the CRC mortality rate in developed countries was found to be only approximately 2.8-fold higher than that in developing countries, which did not reflect the extent of regional disparity in CRC incidence. Despite the high incidence of CRC in developed countries, a relatively better prognosis can be expected due to early diagnosis and appropriate treatment. The fatality rate is relatively high in developing countries, where adequate treatment and medical delivery systems are lacking[4-6]. Since the early 2000s, the incidence and mortality rates of CRC have been decreasing in some developed countries, including the United States, Japan, and several Western European countries. This finding is probably a consequence of risk factor reduction due to behavior changes, such as consumption of a healthy diet and reduction of the smoking rate at the overall population level, improvement of prognosis according to the treatment development, and, above all, an increase in early diagnosis and removal of precancerous lesions after the introduction of a cancer screening program[7-9]. Although the overall incidence and mortality rates of CRC are decreasing in some high-income countries, the incidence rate of early-onset CRC in patients aged <50 years is increasing by 1%-4% annually[10]. This trend has also been observed in some Asian countries, such as Japan and Hong Kong[11]. Lifestyle factors, such as diet and obesity, and the blind spot in cancer screening, which is generally applied to the population aged >50 years, have been highlighted as factors that contribute to the increase in the incidence of early-onset CRC. However, these factors cannot explain the entire increase in the incidence of early-onset CRC. Therefore, additional research is needed to determine whether the risk factors for CRC development in the elderly population have a similar effect on early-onset CRC and whether novel risk factors that are specific to early-onset CRC exist.

According to the annual report of cancer statistics from the Korea Central Cancer Registry, 29,030 patients were newly diagnosed with CRC in 2019, of which 17,119 (59.0%) were men and 11,911 (41.0%) were women. Moreover, CRC was the fourth most common cancer after thyroid, lung, and stomach cancers in the whole population. When divided by gender, it was the third most common cancer among men after lung and stomach cancers and the third most common cancer among women after breast and thyroid cancers[1]. The CRC incidence rate in Korea has continuously increased since 1999 when the National Cancer Statistics was first published. The age-standardized incidence rate in 2011 was 39.8%, which was 2-fold (21.3%) higher than that in 1999. However, this age-standardized incidence rate has been gradually decreasing in both men and women since the incidence rate in men and women peaked in 2011 and 2012, respectively (Figure 1A). When reviewed by the cancer location, the trend is similar; the incidence rates of both rectal and colon cancers peaked between 2011 and 2012, respectively, and are currently declining (Figure 1B). In the first report published in 1999, rectal cancer accounted for more than half of CRC cases in both men and women. However, the proportion of colon cancer increased, and that of rectal cancer decreased over time (Figure 2). Of the 29,030 patients with CRC diagnosed in 2019, 11,828 were diagnosed with rectal cancer, representing a total of 40.7%. The downward trend in rectal cancer rates was even more pronounced among women. Rectal cancer accounted for only 35.9% of CRC cases among women in 2019. Such changes in the proportion of colon and rectal cancer cases were similarly observed in other countries, such as the United States and Japan, but the reasons for this are unclear[12,13]. Increased early detection of proximal colon cancer due to the introduction of cancer screening programs, including colonoscopy, and changes in risk factors that have different effects depending on the cancer location have been proposed to contribute to such proportional changes. Because the right and left colons have distinct developmental origins and immunological responses, as well as functions and physiology, they are expected to respond differently when exposed to the same risk factor[14]. For example, obesity has a more substantial effect on colon cancer than on rectal cancer, and smoking is more strongly associated with rectal cancer than with colon cancer. Therefore, increasing obesity rates and decreasing smoking rates are expected to contribute to the decrease in the rectal cancer rate[15,16]. The increase in early-onset CRC reported in Western European and Asian countries with high Human Development Index, such as Taiwan, Japan, and Hong Kong, was not fully replicated in the National Cancer Statistics of Korea. However, the incidence rate, which decreased in all age groups except for the age groups ≥85 and 25-29 years starting from 2010, showed a gradual increase from 2016 in the young
Adenocarcinoma is the most common type of CRC diagnosed in Korea. However, non-adenocarcinomas in the colorectum are not extremely rare. According to the National Cancer Registry data, 5.43% of all patients with CRC were diagnosed with non-adenocarcinoma between 2007 and 2016[17]. Non-adenocarcinoma was found to be most prevalent among people in their 50s, unlike adenocarcinoma, whose incidence increases sharply after the 60s. Among non-adenocarcinomas, neuroendocrine tumors were the most common (75.3%), followed by lymphomas (10.1%), squamous cell carcinomas, nonspecific carcinomas, gastrointestinal matrix tumors, sarcomas, and melanomas. Neuroendocrine tumors were common in the rectum, as in most other Asian countries, and lymphoma appeared to originate in the proximal colon[18].

In Korea, patients with CRC have the highest survival rate worldwide. The 5-year relative survival rate for patients with CRC diagnosed during 1993-1995 was only 56.2%, whereas that for patients diagnosed during 2015-2019 was 74.3%, which indicated an improvement of nearly 20%[1]. Regarding the treatment results of Korean patients with CRC by the Surveillance Epidemiology and End Results summary stage, the 5-year relative survival rate of regional stage patients increased from 78.8% during 2006-2010 to 82.1% during 2015-2019 (Table 1)[1,19]. The 5-year relative survival rate for all patients with CRC increased steadily from the early 1990s to the mid-2000s, and it started to stagnate in the mid-70% range from the late 2000s (Table 2)[1]. Nevertheless, it was still high enough compared with the rate in the United States (64.9%), the United Kingdom (60.0%), and Japan (67.8%)[20]. This improvement in treatment results is probably due to a combination of various factors, such as the introduction of the CRC screening program into the National Cancer Screening Program in 2004 for the early detection of cancer, improvement in surgical instruments and techniques, development of anticancer...
Table 1. The 5-Year Relative Survival of Korean Patients with Colorectal Cancer by Stage at Diagnosis (2015–2019; %).

| Stage at diagnosis | 2006–2010 (%) | 2011–2015 (%) | 2015–2019 (%) |
|--------------------|--------------|--------------|--------------|
| Overall            | 72.6         | 75.0         | 74.3         |
| Localized          | 33.2         | 92.8         | 35.3         |
| Regional           | 41.0         | 78.8         | 43.4         |
| Distant            | 15.3         | 19.7         | 15.9         |
| Unknown            | 10.5         | 61.3         | 5.4          |

Table 2. Trends in the 5-Year Relative Survival of Korean Patients with Colorectal Cancer (2015–2019).

| Period of diagnosis | Total (%) | Male (%) | Female (%) |
|---------------------|-----------|----------|------------|
| 1993–1995           | 56.2      | 56.6     | 55.7       |
| 1996–2000           | 58.9      | 59.8     | 57.7       |
| 2001–2005           | 66.9      | 68.8     | 64.4       |
| 2006–2010           | 73.9      | 75.8     | 71.1       |
| 2011–2015           | 76.1      | 77.8     | 73.6       |
| 2015–2019           | 74.3      | 75.5     | 72.6       |

drugs, and the advancement of medical resources and infrastructure accompanying economic development. In 2018, 77.4% of colon cancer surgeries and 81.6% of rectal cancer surgeries were performed laparoscopically in Korea, which is an unprecedentedly high rate of minimally invasive surgery. The number of surgical cases of elderly patients in their 80s and 90s who had avoided active treatment before due to the difficulty of recovery after surgery has gradually increased in recent years[21]. The long-term treatment results of elderly patients are not yet as good as those of younger patients. One reason for this observation is that elderly patients do not adequately complete the standard treatment according to their disease stage for various reasons, such as refusal of adjuvant chemotherapy after surgery. These would be the possible target to improve the treatment outcomes of elderly patients with CRC in the future[22,23].

The coronavirus disease 2019 (COVID-19) pandemic significantly changed the use of health and medical services. Colonoscopy using gas, which is indispensable for the diagnosis and treatment of CRC, general anesthesia including mechanical ventilation, and undulations of laparoscopic surgery were thought to increase the risk of virus transmission. Despite various coping strategies presented to protect medical staff and patients[24], all external activities, including hospital visits in the general population, were reduced. Consequently, the rate of colonoscopy for early CRC detection was also greatly reduced[25,26], which is expected to lead to advanced disease stages and worse survival rates for patients with CRC diagnosed in the future. A domestic study that compared patients with CRC in 2020 (during the early stages of the COVID-19 pandemic) with those in the period 2017–2019 (before the COVID-19 pandemic) failed to demonstrate a stage shift to an advanced disease stage. However, poor prognostic factors, such as the rate of unresectable stage IV disease, increased preoperative carcinoembryonic antigen levels, and peritumoral lymphatic invasion in patients with stage I–II diseases, were significantly increased in the COVID-19 epidemic population[26]. Another study reported that delayed treatment to prevent the transmission of COVID-19 infection resulted in disease progression in patients with rectal cancer during the quarantine period[27]. The COVID-19 pandemic is not yet over. Considering the history of repeated emergence of infectious diseases, such as severe acute respiratory syndrome in 2002, Middle East respiratory syndrome in 2012, and COVID-19 in 2019, follow-up epidemiological studies throughout the COVID-19 pandemic and development of appropriate coping strategies in the context of an infectious disease outbreak are essential tasks to improve CRC treatment outcomes as well as the research on direct treatment for CRC.

Risk Factors

Several international immigration cohort studies demonstrated that various environmental factors, as well as genetic factors, play a significant role in the risk of CRC development[28,29]. Therefore, the incidence of CRC can be reduced through environmental risk factor mediation. National studies estimated that approximately 10% of all CRC cases could be prevented through the mediation of alcohol consumption, obesity, smoking, and physical activity[30–32]. Furthermore, a previous study claimed that if all modifiable risk factors were removed, more than half of all CRC cases could be prevented[33].

In 2018, the World Cancer Research Fund and the American Institute for Cancer Research in a systematic review reported red and processed meat consumption, alcohol consumption, obesity, and tall height in adulthood as risk fac-
In a study that analyzed CRC risk factors in the Korean general population, age and body mass index appeared to be significant risk factors for both men and women, and diabetes, family history of cancer, smoking, and alcohol consumption were significant risk factors for men. The risk of CRC increased as the age increased in those aged >40 years and as the body mass index increased from the 23-25 kg/m² group, which did not meet the criteria for obesity. Moreover, a history of colonoscopy was found to be a significant protective factor. This study was based on the National Health Insurance and the National Health and Nutrition Examination data. Because diet and physical activity information, which are considered important risk factors for the development of CRC, were not included in the analysis, further studies are needed to more clearly elucidate the risk factors for CRC in the Korean population.

**Screening Tests**

Because most CRC develops through the adenoma-carcinoma sequence, secondary prevention through screening to remove precursor lesions and diagnose early cancer at curable stages can concurrently reduce the incidence and mortality rates. The American College of Gastroenterology (ACG) recommends screening tests to reduce the incidence of advanced adenoma and CRC, as well as mortality from CRC. In the clinical guidelines announced in 2021, the target age for screening was expanded from 50-75 to 45-75 years. Although the level of evidence for CRC screening being useful at the age of 45-49 years is still low, this may reflect the recent and sustained increase in the incidence of early-onset CRC in people aged <50 years. The ACG also recommends fecal immunochemical test (FIT) and colonoscopy as primary screening tools. In addition, flexible sigmoidoscopy, multitarget fecal DNA test, computed tomography colonography, and capsule endoscopy, although at a low level of evidence, are accepted as tools that could be considered if the primary screening test was difficult to apply or rejected by the patient.

The FIT is an alternative to the traditional fecal occult blood test, which utilizes the oxidation of guaiac by heme peroxidase in blood cells. It is a highly sensitive test, with few false-positive reactions to foods or drugs, and does not require pretest dietary adjustments. Presently, all fecal occult blood tests in Korea’s national health screening program use the immunochemical test method instead of the traditional guaiac method. According to a domestic study of more than 30,000 test subjects published in 2018, the positivity rate of...
FIT was 1.1%, and when colonoscopy was performed in patients with positive results, the positive-predictive rates of CRC and neoplasia, including advanced adenoma, were 5.5% and 19.1%, respectively[37]. It is a noninvasive test that can be performed at a relatively low cost, and it has been the most basic screening test with a sensitivity of approximately 80% and a specificity of approximately 90%[38,39]. However, the sensitivity of the FIT, which has been proven to be useful in the diagnosis of advanced adenomas, is limited to 5%-16% in the diagnosis of sessile serrated lesions, which account for 25%-30% of sporadic CRC precursors[40,41]. Therefore, there have been attempts (e.g., multiterraced fecal DNA test) to increase the sensitivity and specificity of stool tests by targeting tumor metabolites and genes rather than blood in the feces[42-45].

Colorectal epithelial cells are naturally shed and excreted in the feces, and the tumor epithelium is also shed and mixed in the stool. Thus, CRC can be diagnosed if the DNA of the tumor epithelium in the stool can be distinguished effectively. This is the basic concept of multitarget fecal DNA testing. The technology used for DNA detection and amplification and the appropriate target gene setting are important factors that determine the efficacy of this test. Although several fecal DNA tests designed to target diverse genes failed to be commercialized owing to disappointing study results, the Cologuard (Exact Sciences), which is a combination of FIT and multitarget fecal DNA testing targeting K-ras mutations, NDGR4 and BMP3 methylation, and ACTB, showed excellent results. Moreover, it became the first multitargeted fecal DNA test to be approved by the US Food and Drug Administration (FDA) in 2014. After approval, its use has gradually increased, and it is currently specified as a second-line screening tool in accordance with the ACG guidelines[46]. Furthermore, this test is a cheaper and less expensive screening tool than colonoscopy; thus, patient compliance is expected to be higher when it is used. However, because it is a relatively new test, its long-term preventive effect on CRC has not yet been verified. The ACG medical guidelines recommend testing every 3 years, but the follow-up test interval has not yet been established. Furthermore, the possibility of overtreatment due to publicity in the market, unclear guidelines for cases in which no lesions are found in colonoscopies performed after a positive Cologuard result, and most published studies on Cologuard being conducted with the support of the manufacturing company are of concern. Thus, the long-term results of this test need to be examined.

A Korean company also developed a stool DNA test called EarlyTect (Genomictree, Republic of Korea). Cologuard concurrently targets multiple genes involved in CRC, whereas EarlyTect targets only syndecan-2 gene methylation. The latter test was approved by the Korean Ministry of Food and Drug Safety in 2018, and a study of domestic health screening program participants showed excellent sensitivities of 90.2% and 66.7% for CRC and advanced adenoma, respectively, using this test[47]. From 2020, a prospective multicenter study targeting the asymptomatic general population aged ≥60 years or those belonging to the high-risk group is underway, and the results are awaited.

The circulating tumor DNA test is also gaining acceptance. This test is based on the concept that tumor-derived DNA, which is released from tumor cells and circulates in the blood, reflects tumor presence and burden. It can be used not only for diagnosis but also for prediction of prognosis and monitoring of response and recurrence after treatment. Similar to stool DNA testing, the selection of the appropriate target gene is a determinant of the test performance. Although multiple gene targets are under investigation, test products for methylated septin 9 received FDA approval in 2016 and are currently in use. However, the product, which showed excellent results in preliminary studies, was disappointing in clinical practice with a low sensitivity of 50%-70%[45,48,49]. Thus, further research is required before circulating tumor DNA testing can be used in clinical practice.

The debate about whether colonoscopy can be used as a primary screening test for CRC is ongoing. Colonoscopy has the advantage of being able concurrently to detect and remove precancerous lesions and early CRC. Thus, diagnosis and treatment can be performed concurrently. Moreover, it is effective in reducing the incidence of CRC by 70% and mortality by 50%-70%[50,51]. However, it is invasive, reduces patient compliance, and has the potential for complications, such as bleeding and perforation. Colonoscopy being costlier than other screening tools and its variable adenoma detection rate, which depends on the skill of the operator, are also concerns when considering this technique as a primary screening tool[52]. At the time of the 2015 revision of the Korean CRC screening recommendations, whether colonoscopy should be adopted as a primary screening test tool was greatly debated. Although the FIT is recommended as the primary CRC screening test, colonoscopy remains to be performed selectively, considering the clinical judgment of individual risk and patient preferences[53]. Presently, colonoscopy is not included in the preliminary tests of the National Cancer Screening Program in Korea. However, a trial project to verify the effectiveness of colonoscopy as a primary screening test has been smoothly implemented since 2019. According to the results of this ongoing trial, colonoscopy appears to be included in the Korean National Cancer Screening Program in the future.

In the case of no high-risk adenoma, the United States and Korea guidelines recommend a colonoscopy follow-up interval of 10 and 5 years, respectively. Previously, colonoscopies for screening purposes for those aged ≥75 years were not recommended. However, recent studies have dem-
onstrated that colonoscopies are sufficiently effective for prevention even for those aged 275 years if they are healthy and have a sufficient life expectancy. Research on colonoscopy is providing new insights, and the target of this technique is expected to widen in the future.

**Conclusion**

Although the incidence and mortality rates of CRC have recently decreased, it remains as one of the major causative diseases threatening public health in Korea. Owing to the National Cancer Screening Program and advanced medical technology, the 5-year relative survival rate of patients with CRC in Korea is extremely high compared with the rates worldwide. However, it has remained stagnant at approximately 70% since the late 2000s. CRC is effectively preventable through primary and secondary prevention. Environmental risk factor mediation by the provision of information and encouragement of healthy behaviors, while striving for early diagnosis through appropriate screening tests, can lead to a reduction in the stagnant incidence and mortality rates.

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Conflicts of Interest

There are no conflicts of interest.

Author Contribution

Kyung Uk Jung: conception and design of the study, drafting and revising the study, and final approval of the version to be submitted.

Hyung Ook Kim, Heungdai Kim: conception of the study and final approval of the manuscript.

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