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Colorectal Cancer: An Overview

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Abstract: Colorectal cancer is a multifactorial disease. It is the third most frequently diagnosed cancer, and the second most common cause of cancer-related deaths worldwide. The etiology of colorectal cancer remains unclear. Although early diagnosis can significantly improve the prognosis, colorectal cancer patients often have no typical clinical manifestations, or display only non-specific signs in the early stage, resulting in a low early diagnosis rate. Multiple treatment modalities, depending on the stage of the tumor and patient characteristics, are available. These include surgery, chemotherapy, radiotherapy, molecular targeted therapy, immunotherapy, and other programs. This chapter provides an overview of colorectal cancer. Epidemiology, etiology, pathogenesis, clinical manifestations, diagnosis, treatment, prognosis, and prevention strategies of colorectal cancer are discussed.

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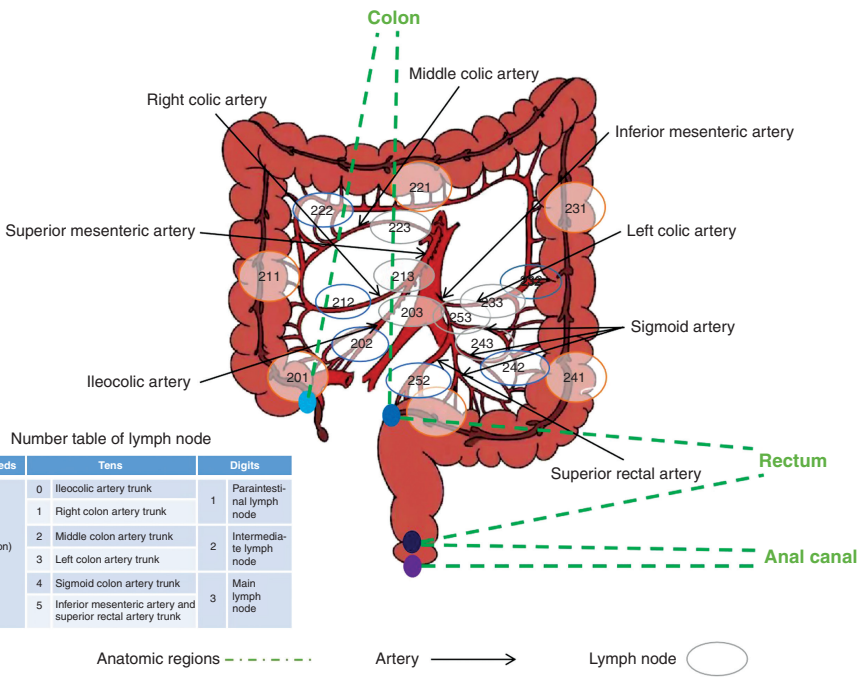
INTRODUCTION

The adult large intestine includes the colon, rectum, and anal canal. The colon can be divided into the right colon (cecum, ascending colon, and right 2/3 transverse colon) and left colon (left 1/3 transverse colon, descending colon, and sigmoid colon). The blood supply of the colon is mainly from the mesenteric artery; the veins are accompanied by the arteries of the same name, and the lymphatic network drains through the regional lymph nodes (Figure 1) (1, 2). The colon is innervated by the vagus and pelvic nerves. The function of the right



Number table of lymph node

Hundreds	Tens		Digits	
2(Colon)	0	Ileocolic artery trunk	1	Parainternal lymph node
	1	Right colon artery trunk		
	2	Middle colon artery trunk	2	Intermediate lymph node
	3	Left colon artery trunk		
	4	Sigmoid colon artery trunk	3	Main lymph node
	5	Inferior mesenteric artery and superior rectal artery trunk		

Figure 1. Anatomy, blood supply, and lymph node drainage of the large intestine. For anatomic regions, the three major parts (colon, rectum, and anal canal) relevant to colorectal cancer are labelled. For blood supply, only arterial supply is highlighted. The oval shape represents region(s) of lymph node groups or nodal stations. Usually, the lymph node stations of the large intestine are indicated with a three-digit number in the 200s. The simplest explanation for understanding the numbers, from left to right, is as follows: the first digit, 2, represents the anatomical group (in this case, the large intestine – hundreds in the table) the second middle digit represents the blood supply (in this case, the arteries—tens in the table) and the third digit represents lymph node group (oval shape—digits in the table). Concept for the figure is based on the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3rd English Edition.

colon is mainly to absorb water and some nutrients, while the main function of the left colon is to store and excrete feces. Notably, the colon secretes gastrointestinal hormones and alkaline mucus substances.

The rectum joins the sigmoid colon, and the lower end joins the anal canal at the dentate line. The rectal blood supply mainly comes from the superior and inferior rectal arteries. Venous reflux mainly flows from the superior rectal vein to the liver. The regional lymph nodes of the rectum include pararectal lymph nodes, superior and inferior rectal artery lymph nodes, etc. The rectum is innervated by the autonomic nerves, its main physiological function is defecation. In addition, it also absorbs a small amount of water, salt, glucose, and some drugs (3).

Based on sites of onset, rectal cancer accounts for 49.66%, colon cancer accounts for 49.09%, and both sites combined account for 1.25% (4). Among colon cancers, the most common sites are the sigmoid colon (55%), followed by the ascending colon (23.3%), transverse colon (8.5%), descending colon (8.1%), cecum (8.0%), and crossing site (2.1%) (4). This chapter provides an overview of various aspects of colorectal cancer (CRC).

EPIDEMIOLOGY

CRC is the third most diagnosed cancers worldwide, of which males rank third and females rank second (5). CRC is the second most common cause of cancer-related deaths worldwide (5). In China, the incidence of CRC in the whole population ranks second among all tumors, and the age-standardized incidence is 23.7 per 100,000, among which male and female patients rank third, and the age-standardized incidence is 28.1 per 100,000 and 19.4 per 100,000 persons, respectively (6). Correlation between migration, religious factors, and the CRC suggests that the incidence of CRC is strongly related to environmental factors, lifestyle, and diet, but has no obvious relationship with ethnicity. The incidence of CRC differs by regions, with the highest incidence reported in North America, Western Europe, and Oceania, and the lowest incidence in Africa, Asia, and South America. In the mainland of China, the CRC incidence also follows an east-to-west gradient (6). The incidence of CRC is higher in the economically developed eastern coastal areas, while the incidence is relatively lower in the economically backward western areas (6).The incidence and mortality of second-generation immigrants from low-incidence areas of CRC to high-incidence areas are similar to those of residents (7).

The risk of CRC increases with age. The incidence and mortality of CRC are low until the age of 45 and increase significantly after that, peaking in the age group over 80, but a significant number of cases still occur in adolescents. CRC patients under the age of 30 account for 10–20% in China and the age of onset is 12–18 years earlier than in western countries (4, 8).

Notably, the morbidity and mortality of CRC have shifted over time. The change is different by regions. The rising rate of the original high-incidence regions slows down or decreases, while the low-incidence regions show an increasing trend, such as China. In the past 30 years, the incidence and mortality of CRC have been increasing year by year in China, especially in cities. This may be related to an aging population, changing lifestyles, and changing environments (3, 6).

In general, the epidemiological characteristics of CRC in China can be summarized as follows (3, 4): (i) higher in males than in females, and the male to female ratio is about 1.3:1; (ii) the median age of onset is 58 years; (iii) rectal cancer is more common than colon cancer; (iv) in economically developed regions, the most common site of colon cancer has changed from rectum to colon, and the proportion of right colon cancer has increased significantly.

ETIOLOGY

The etiology of CRC remains unclear, but it may be related to the following factors:

Genetic factors: About 20% of CRC cases are related to genetic factors, and investigations have shown a three-fold increased risk of cancer in the first-generation relatives of CRC patients. Familial Adenomatous Polyposis (FAP) has been identified as a genetic syndrome that predisposes to CRC, and the Mismatch Repair Gene (MMR) has also been linked to inherited CRC (9).

Dietary factors: It is currently believed that high fat, high animal protein, and low cellulose diet are related to the incidence of CRC. Excessive fat intake will promote bile secretion, bile acid decomposition, increased intestinal carcinogens, and the activity of intestinal anaerobic bacteria (10).

Non-cancerous diseases: Non-cancerous diseases such as colorectal polyps, colorectal adenomas, ulcerative colitis and Crohn's disease, etc. can contribute to CRC. Research shows that about 3–5% of ulcerative colitis patients will develop CRC, and the incidence of malignant transformation is greater than 10% in patients with ulcerative colitis lasting more than 20 years. About 15–40% of colon cancers originate from colonic polyps, with a precancerous course of 2–5 years. Adenomas less than 1 cm in diameter have a less than 2% chance of becoming cancerous, while those larger than 3 cm have a more than 40% chance of becoming cancerous (3, 11).

Other factors: Carcinogenic exposure and lifestyle, such as sedentary and overweight, are risk factors for CRC, and the incidence of sigmoid and rectal cancer is higher in patients undergoing pelvic radiation therapy (3).

PATHOGENESIS

CRC is a multi-factorial disease. The epithelial cells of colorectal mucosa can undergo hyperplasia, atypical hyperplasia (mild, moderate, severe) and adenomas, that can eventually develop into carcinoma (12). This process is usually initiated by carcinogenic factors, causing structural changes in DNA, leading to the malignant transformation of cells into cancer. Morphology includes epithelial hyperplasia, atypical hyperplasia, adenoma formation, carcinoma in situ, and invasive carcinoma (12). In 1990, Fearon and Vogelstein proposed a molecular event model for the occurrence and development of CRC (13). With the development of research, three molecular mechanisms related to the occurrence and

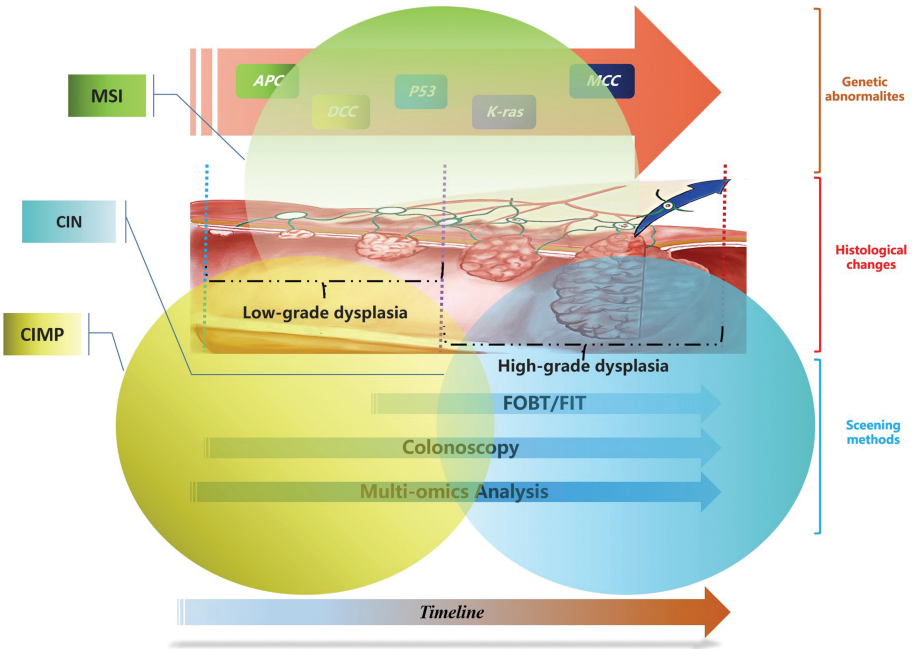


Figure 2. Genetic abnormalities, histological changes, and screening methods in the occurrence and development process of CRC. CIMP, CpG island methylator phenotype; CIN, chromosomal instability; FIT, fecal immunochemical test; FOBT, fecal occult blood test; MSI, microsatellite instability.

development of CRC have been confirmed: (i) chromosomal instability that mainly occurs in FAP (14); (ii) genetic mutations such as in Lynch syndrome and other sporadic MMR mutations (15); and (iii) hypermethylation of CPG islands in specific gene promoter regions (16). These processes are often associated with abnormal changes in multiple genes such as *APC*, *DCC*, *P53*, *K-ras*, *c-MYC*, *MCC*, and MMR-related genes (*hMLH1*, *hMLH3*, *hMSH2*, *hMSH3*, *hMSH6*, *hPMS1*, and *hPMS2*), Figure 2. It is worth noting that these abnormal molecular signaling pathways are not mutually exclusive, and multiple abnormal molecular pathways are co-existing in some CRC patients (17–19).

PATHOLOGICAL TYPE AND METASTASIS

In early stages, CRC is confined to the intestinal mucosa and submucosa (12). Lymphatic metastasis usually does not occur in early CRC (12). When the tumor breaks through the submucosa, lymphatic metastasis occurs in about 10% of patients. The gross types of CRC mainly include uplift, ulceration, and infiltration (12). The pathological histological types mainly include papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, undifferentiated carcinoma, adenosquamous carcinoma, squamous cell carcinoma, and carcinoid carcinoma (12). Adenocarcinoma has the highest

incidence, accounting for more than 90% (colon cancer). Ji et al. analyzed the clinical data of 1092 primary CRC patients and found that adenocarcinoma accounted for 93.4%, mucinous adenocarcinoma and signet ring cell carcinoma accounted for 3.9% and 0.6% respectively, and carcinoid accounted for 0.2% (20). CRC spreads and metastasizes mainly through the following four pathways:

Local invasion: The tumor infiltrates into the local area of the primary lesion and adjacent structures.

Lymphatic metastasis: The neoplastic cells use the intramucosal lymphatic system to reach regional lymph nodes, eventually causing distant lymph node metastasis; about 60% of CRC metastasis occurs through this route (3).

Hematogenous metastasis: The cancer cells spread via the blood vessels. The most common target organs of CRC through hematogenous metastasis are liver and lung; about 30% of CRC are transferred through this route (3).

Implantation and metastasis: After the cancer cells fell off, they are implanted in the abdomen and pelvic peritoneum to form metastatic foci (3).

CLINICAL MANIFESTATIONS

Early CRC is often asymptomatic (19). With the progress of the disease, the following symptoms will generally occur.

`*Hematochezia:* In small amount of hematochezia, general stool has no visible changes, but fecal occultation test can be positive; blood stool, mucus blood stool, or jam-like stool may appear when there is a lot of blood in the stool (3).

Intestinal obstruction: It is often a characteristic of advanced CRC; abdominal pain, abdominal distention, nausea, vomiting, exhaustion, and defecation will occur when intestinal obstruction caused by the enlargement of the mass (3).

Abdominal mass: It usually occurs in the right colon cancer; this symptom is a mass enlargement to a certain extent, palpable abdominal mass.

Systemic symptoms: CRC generally has no obvious symptoms at the early stage, so the course of the disease is relatively long, leading to tumor proliferation, cachexia, anemia, emaciation, and other symptoms.

Due to the different anatomical and physiological functions of colon and rectum, the clinical manifestations of tumors in different anatomical sites are also different. Generally, abdominal mass and systemic symptoms are more common in right colon cancer, blood stool and obstruction are more common in left colon cancer, and changes in defecation habits are more common in rectal cancer (3).

DIAGNOSIS

Most CRC patients have no obvious clinical symptoms at the early stage, resulting in a low early diagnosis rate. Many patients are diagnosed at an advanced stage,

losing the opportunity for radical treatment. In general, it is clinically recommended that those over 20 years of age with the following symptoms require further investigation: (i) recent persistent abdominal discomfort, such as abdominal pain, gas, etc.; (ii) changes in defecation habits, such as diarrhea, constipation, or both, and changes in stool shape; (iii) blood in stool or mucous blood stool; (v) unexplained anemia or progressive weight loss; and (vi) abdominal mass (21) .

Further examination includes routine physical and other examinations. Digital rectal examination is recommended for patients suspected of rectal cancer. Other examinations include: (i) fecal occult blood test (FOBT)—positive results can be obtained with about 5 ml of bleeding in the digestive tract, so it has a certain clinical value for the screening and diagnosis of CRC (3); (ii) tumor markers—there are no specific tumor markers for CRC but currently, CEA (carcinoembryonic antigen) and CA19–9 (carbohydrate Antigen 19–9) are commonly used, and the sensitivity of combined detection of CEA and CA19–9 is higher than that of each separately, which has important clinical significance for the evaluation of therapeutic effect and monitoring of disease recurrence (3); (iii) endoscopy—colorectal endoscopy directly observes the position, size, and shape of the lesion, and the most important is feasible pathological tissue biopsy; (iv) X-ray—X-ray examination after barium enema can find signs of filling defect and mucosal destruction at the tumor site. Gas-barium double-contrast acts on the detection of colon cancer with small lesion, but it is not suitable for patients with intestinal obstruction; (v) ultrasound—ultrasonography has a certain effect on the detection of intestinal masses and abdominal lymph nodes; (vi) computed tomography (CT)—CT is of great diagnostic value for displaying the size of lesions, the relationship with adjacent tissues and organs, abdominal lymph nodes, and other conditions, which can assist in clinical staging; (vii) nuclear magnetic resonance (NMR)—similar to CT, but higher tissue resolution than CT examination, especially for pelvic lesions, such as rectal cancer, preoperative evaluation of great clinical value; and (viii) positron emission computed tomography (PET/CT)—it provides information on the anatomical site and metabolic characteristics of the tumor, and has great guidance for the diagnosis, preoperative staging, and recurrence assessment of CRC (3, 21, 22).

TREATMENT

The treatment principle of CRC is an individualized comprehensive treatment based on surgery, supplemented by chemotherapy, radiotherapy, molecular targeted therapy, immunotherapy, and other programs (21, 23). Studies have shown that the 5-year survival rate of patients with early CRC, who receive surgery-based treatment, is more than 90% (24).Therefore, surgery remains the cornerstone of CRC treatment. For initially inoperable CRC patients, and some CRC patients with metastasis, the feasibility of surgery should be evaluated after neoadjuvant therapy to strive for the opportunity of surgical treatment. The surgical methods mainly include radical surgery and palliative surgery (21) .

CRC chemotherapy mainly includes neoadjuvant chemotherapy, adjuvant chemotherapy after radical surgery, and palliative chemotherapy (25). Neoadjuvant chemotherapy is often used in combination with radiotherapy, which can reduce the clinical stage of the tumor, strive for the opportunity of surgery, improve the

quality of life of patients, and reduce postoperative recurrence. Adjuvant chemotherapy can eliminate the remaining tumor cells after radical surgery and further consolidate the effect of radical surgery. The purpose of palliative chemotherapy is to improve the quality of life and prolong the survival time of patients with advanced CRC. Commonly used chemotherapy drugs include fluorouracil, irinotecan, oxaliplatin, and raltitrexed. The above chemotherapy drugs are often used in combination, and commonly used combination chemotherapy regimens include FOLFOX, FOLFIRI, CAPEOX, FOLFOXIRI, etc. (26).

The application of molecularly targeted drugs has brought significant benefits to CRC patients. Currently, molecularly targeted drugs used in the clinical treatment of CRC mainly include two types, one is anti-angiogenesis drugs represented by bevacizumab and the other is anti-epidermal growth factor drugs represented by cetuximab. Clinically, molecular-targeted drugs are recommended to be used in combination with chemotherapeutic drugs, because they are non-cytotoxic drugs and have relatively mild adverse reactions, which generally do not significantly increase the adverse reactions of chemotherapy (23).

Radiotherapy is mainly used for rectal cancer patients, which can improve local control rate, improve quality of life, and prolong survival. The radiotherapy schemes for rectal cancer mainly include preoperative radiotherapy, preoperative concurrent chemoradiotherapy, and postoperative concurrent chemoradiotherapy combined with adjuvant chemotherapy (27).

Recent studies have shown that immunotherapy can prolong survival in CRC patients (28). Other treatments include hyperthermia combined with chemotherapy or radiotherapy, biotherapy, traditional Chinese medicine, local cryotherapy, radiofrequency therapy, and palliative care (21).

PREVENTION AND PROGNOSIS

According to the pathogenic factors of CRC, the prevention methods of CRC include: (i) diet—intake of fresh vegetables, fruits, crude fiber food, appropriate minerals and trace elements such as calcium, magnesium, and vitamin D (25); (ii) lifestyle management—quitting smoking, limiting alcohol consumption, proper exercise, and weight control; (iii) active treatment of benign colorectal diseases, such as polyps, adenomas, ulcerative colitis, and Crohn's disease; (iv) regular screening—early screening to prevent CRC is very important (29).

In the literature, primary prevention has been reported to play a 35% role in reducing CRC mortality, secondary prevention through early screening for CRC has been reported to play a 53% role, and prescriptive treatment of patients diagnosed with CRC has been reported to play a 12% role (29–31).

The disease stage at initial diagnosis is the most important prognostic indicator of CRC. It has been reported that the 5-year survival rate of patients with localized CRC, who can be surgically resected, is about 90%, while the 5-year survival rate of advanced CRC patients who lose the opportunity of surgical treatment is reduced to about 10% (32).The natural course of progression from normal colorectal epithelial cells to benign lesions such as adenomas and eventually to cancer is generally 5–10 years (24).This process often involves abnormal changes of multiple genes, such as *APC*, *DCC*, *P53*, *K-RAS*, *C-MYC*, *BRAF*, *MCC*, and MMR-related genes. Early screening to detect limited-stage lesions in this time

window and clinical intervention is crucial to improve the prognosis of CRC patients (24, 33).

Currently, common screening and diagnosis methods for CRC include FOBT, fecal immunohistochemistry (FIT), tumor markers, and colonoscopy. FOBT is an economical and non-invasive screening method, but its sensitivity to the diagnosis of CRC is less than 50%. Although the sensitivity and specificity of FIT are higher than FOBT (78% and 96%, respectively) (34), and diet restriction is not required, the detection results of the FIT are susceptible to non-hemorrhagic tumors and hemorrhagic non-tumor diseases (35, 36). On the other hand, patients, and their family members' aversion to handling stool specimens restrict the development of this examination. Data from the UK study showed that only 50% of patients undergoing FOBT had a specimen sent in (37). Although more user-friendly DNA-based stool tests have been introduced in the UK, the delivery of fecal samples remains a major challenge. Blood samples can dynamically reflect the physiological and pathological state of the body in real-time, and it is easy to obtain. CRC markers in blood samples mainly include CEA and CA19–9, which are currently clinically used to evaluate the efficacy of anti-tumor therapy and monitor the recurrence of the disease with low sensitivity and specificity (40–70% and 73–90%, respectively) (37, 38). It has been reported that CEA fluctuates greatly in healthy individuals, and its variation in the same individual can reach 30%, leading to controversy over its value in screening asymptomatic people and diagnosing CRC (39). Therefore, CEA and CA19–9 are not suitable as screening and diagnostic markers for CRC. Colonoscopy can visually observe the shape, size, and location of colorectal lesions. Most importantly, it can obtain pathological biopsy specimens, which is an important means for CRC screening and diagnosis (32, 40). In the light of large proportion of CRC cases and that deaths could be prevented by screening and early detection and removal of colorectal adenomas or early stage CRC, colonoscopy screening could reduce mortality from colon cancer (41). However, colonoscopy is an invasive examination method that requires intestinal preparation, leading to poor patient compliance and potential examination-related risks, such as intestinal perforation (32). The accuracy of colonoscopy varies greatly due to technology-related factors (such as operator experience, bowel preparation, and examination duration) and disease-related factors (such as lesion size, number, and anatomical site) (19). Histology, genetic abnormalities, and screening methods in the occurrence and development of CRC are shown in Figure 2.

CONCLUSION

In conclusion, the incidence and mortality of CRC is high and increasing year by year. Although early diagnosis can significantly improve the prognosis, CRC patients often have no typical clinical manifestations or exhibit only non-specific signs in the early stage, and there are shortcomings in the currently used clinical screening and diagnosis methods, resulting in a low rate of early diagnosis of CRC. Therefore, it is of great value for the diagnosis and treatment of CRC to find CRC screening and diagnosis methods with safety, compliance, high sensitivity and specificity, and a good economic benefit ratio (22, 38).

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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REFERENCES

1. Sakorafas GH, Zouros E, Peros G. Applied vascular anatomy of the colon and rectum: clinical implications for the surgical oncologist. Surg Oncol. 2006;15(4):243–55. https://doi.org/10.1016/j.suronc.2007.03.002
2. Houston SA, Cerovic V, Thomson C, Brewer J, Mowat AM, Milling S. The lymph nodes draining the small intestine and colon are anatomically separate and immunologically distinct. Mucosal Immunol. 2016;9(2):468–78. https://doi.org/10.1038/mi.2015.77
3. Sun Y. Advanced course in clinical oncology.1. Beijing:People's Military Medical Press,2014:889.
4. Wang X. Epidemiological characteristics and prevention and control strategies of colorectal cancer in China and American. Chin J Colorectal Dis, 2019,8(01) :1–5.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660
6. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32. https://doi.org/10.3322/caac.21338
7. Zheng RS, Sun KX, Zhang SW, Zeng HM, Zou XN, Chen R, et al. [Report of cancer epidemiology in China, 2015]. Zhonghua Zhong Liu Za Zhi. 2019;41(1):19–28.
8. Ye D, Liu C, Zhang Y. Epidemiology and research status of colorectal cancer. World Latest Medicine Information, 2016,16(A2) :34–35.
9. Maida M, Macaluso FS, Ianiro G, Mangiola F, Sinagra E, Hold G, et al. Screening of colorectal cancer: present and future. Expert Rev Anticancer Ther. 2017;17(12):1131–46. https://doi.org/10.1080/14737140.2017.1392243
10. Murphy N, Moreno V, Hughes DJ, Vodicka L, Vodicka P, Aglago EK, et al. Lifestyle and dietary environmental factors in colorectal cancer susceptibility. Mol Aspects Med. 2019;69:2–9. https://doi.org/10.1016/j.mam.2019.06.005
11. Roncucci L, Mariani F. Prevention of colorectal cancer: How many tools do we have in our basket? Eur J Intern Med. 2015;26(10):752–6. https://doi.org/10.1016/j.ejim.2015.08.019
12. Bu H, Li Y. Pathology (9th). People's Medical Publishing House. 2018.
13. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–67. https://doi.org/10.1016/0092-8674(90)90186-I
14. Ogino S, Goel A. Molecular classification and correlates in colorectal cancer. J Mol Diagn. 2008;10(1):13–27. https://doi.org/10.2353/jmoldx.2008.070082
15. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044–58. https://doi.org/10.1053/j.gastro.2010.01.054
16. Weisenberger DJ, Siegmund KD, Campan M, Young J, Long TI, Faasse MA, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet. 2006;38(7):787–93. https://doi.org/10.1038/ng1834
17. Mlkva I. [Genetics of Colorectal Tumorigenesis (Possibilities of Testing and Screening Prediction of Hereditary Form of Colorectal Cancer--Lynch Syndrome)]. Klin Onkol. 2016;29 Suppl 1:S55–61. https://doi.org/10.14735/amko2016S55
18. Al-Sohaily S, Biankin A, Leong R, Kohonen-Corish M, Warusavitarne J. Molecular pathways in colorectal cancer. J Gastroenterol Hepatol. 2012;27(9):1423–31. https://doi.org/10.1111/j.1440-1746.2012.07200.x

19. Simon K. Colorectal cancer development and advances in screening. Clin Interv Aging. 2016;11:967–76. https://doi.org/10.2147/CIA.S109285
20. Ji M, Zhao X, Hu H, Jian F. Primary colorectal cancer in 1092 cases: A five-year retrospective analysis[J]. Academic Journal of Guangzhou Medical University. 2017,45(03) :40–44.
21. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. Colorectal cancer. Nat Rev Dis Primers. 2015;1:15065. https://doi.org/10.1038/nrdp.2015.65
22. Benard F, Barkun AN, Martel M, von Renteln D. Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations. World J Gastroenterol. 2018;24(1):124–38. https://doi.org/10.3748/wjg.v24.i1.124
23. Sandhu J, Lavingia V, Fakih M. Systemic treatment for metastatic colorectal cancer in the era of precision medicine. J Surg Oncol. 2019;119(5):564–82. https://doi.org/10.1002/jso.25421
24. Zhang J, Raju GS, Chang DW, Lin SH, Chen Z, Wu X. Global and targeted circulating microRNA profiling of colorectal adenoma and colorectal cancer. Cancer. 2018;124(4):785–96. https://doi.org/10.1002/cncr.31062
25. Recio-Boiles A, Cagir B. Colon Cancer. StatPearls. Treasure Island (FL) 2022.
26. Kim JH. Chemotherapy for colorectal cancer in the elderly. World J Gastroenterol. 2015;21(17):5158–66. https://doi.org/10.3748/wjg.v21.i17.5158
27. Tam SY, Wu VWC. A Review on the Special Radiotherapy Techniques of Colorectal Cancer. Front Oncol. 2019;9:208. https://doi.org/10.3389/fonc.2019.00208
28. Sun X, Suo J, Yan J. Immunotherapy in human colorectal cancer: Challenges and prospective. World J Gastroenterol. 2016;22(28):6362–72. https://doi.org/10.3748/wjg.v22.i28.6362
29. Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. BMC Med. 2014;12:168. https://doi.org/10.1186/s12916-014-0168-4
30. Song M, Giovannucci E. Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States. JAMA Oncol. 2016;2(9):1154–61. https://doi.org/10.1001/jamaoncol.2016.0843
31. Kabat GC, Matthews CE, Kamensky V, Hollenbeck AR, Rohan TE. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. Am J Clin Nutr. 2015;101(3):558–69. https://doi.org/10.3945/ajcn.114.094854
32. Heiss JA, Brenner H. Epigenome-wide discovery and evaluation of leukocyte DNA methylation markers for the detection of colorectal cancer in a screening setting. Clin Epigenetics. 2017;9:24. https://doi.org/10.1186/s13148-017-0322-x
33. Lin J, Chuang CC, Zuo L. Potential roles of microRNAs and ROS in colorectal cancer: diagnostic biomarkers and therapeutic targets. Oncotarget. 2017;8(10):17328–46. https://doi.org/10.18632/oncotarget.14461
34. Werner S, Krause F, Rolny V, Strobl M, Morgenstern D, Datz C, et al. Evaluation of a 5-Marker Blood Test for Colorectal Cancer Early Detection in a Colorectal Cancer Screening Setting. Clin Cancer Res. 2016;22(7):1725–33. https://doi.org/10.1158/1078-0432.CCR-15-1268
35. Schreuders EH, Grobbee EJ, Spaander MC, Kuipers EJ. Advances in Fecal Tests for Colorectal Cancer Screening. Curr Treat Options Gastroenterol. 2016;14(1):152–62. https://doi.org/10.1007/s11938-016-0076-0
36. Symonds EL, Pedersen SK, Baker RT, Murray DH, Gaur S, Cole SR, et al. A Blood Test for Methylated BCAT1 and IKZF1 vs. a Fecal Immunochemical Test for Detection of Colorectal Neoplasia. Clin Transl Gastroenterol. 2016;7:e137. https://doi.org/10.1038/ctg.2015.67
37. Wise J. New bowel cancer screening test is recommended for England. BMJ. 2016;352:i273. https://doi.org/10.1136/bmj.i273
38. Young GP, Pedersen SK, Mansfield S, Murray DH, Baker RT, Rabbitt P, et al. A cross-sectional study comparing a blood test for methylated BCAT1 and IKZF1 tumor-derived DNA with CEA for detection of recurrent colorectal cancer. Cancer Med. 2016;5(10):2763–72. https://doi.org/10.1002/cam4.868
39. Saito G, Sadahiro S, Kamata H, Miyakita H, Okada K, Tanaka A, et al. Monitoring of Serum Carcinoembryonic Antigen Levels after Curative Resection of Colon Cancer: Cutoff Values Determined according to Preoperative Levels Enhance the Diagnostic Accuracy for Recurrence. Oncology. 2017;92(5):276–82. https://doi.org/10.1159/000456075

40. Vatandoost N, Ghanbari J, Mojaver M, Avan A, Ghayour-Mobarhan M, Nedaeinia R, et al. Early detection of colorectal cancer: from conventional methods to novel biomarkers. J Cancer Res Clin Oncol. 2016;142(2):341–51. https://doi.org/10.1007/s00432-015-1928-z
41. Brenner H, Stock C, Hoffmeister M. Colorectal cancer screening: the time to act is now. BMC Med. 2015;13:262. https://doi.org/10.1186/s12916-015-0498-x