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Research Progress in Early-onset Colorectal Cancer

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Abstract: Colorectal cancer used to be a common disease among middle-aged and elderly people. In recent years, the incidence of colorectal cancer (Early-onset colorectal cancer, EOCRC) under 50 years old has increased year by year. Different from the traditional late-onset colon cancer (LOCRC), the diagnosis stage of EOCRC is mostly in the late stage, with poor cell differentiation and poor diagnosis, and there is a layer of consensus and guidance on the diagnosis, treatment or screening of EOCRC at presentation. Therefore, fully understanding the disease characteristics and risk exposure factors of EOCRC is helpful to guide early screening and treatment, which ultimately reduces the mortality of EOCRC. In this review article, we summarized the epidemiology, physiology, risk exposure factors and pathological diagnosis of EOCRC, and discussed the diagnosis and treatment prospect of EOCRC.

Keywords: Early-onset colorectal cancer; Epidemiological investigation; Phylogeny; Exposure factors; Pathological prognosis

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1. Introduction

According to the data on the prevalence of colorectal cancer in China and the world, the incidence rate and mortality of colorectal cancer (CRC) in China are on the rise. In 2020, the number of new cases ranked second among malignant tumours in China, accounting for 28.76% of global new cases, while accounts for 30.60% of global number of deaths [1]. At the same time, CRC in the Chinese population has been on the rise since the age of 40. A recent systematic review of 12 countries found that the worldwide incidence rate of EOCRC has increased by nearly 30% in the past 20 years [2].

EOCRC differs from LOCRC in epidemiology, anatomy, metabolism, and biological behavior. At present, there is a lack of international consensus and guidelines for the diagnosis, treatment, and screening of EOCRC internationally. Therefore epidemiological investigation, evaluation, and management of EOCRC are necessary. Fully understanding the disease characteristics and risk exposure factors of EOCRC will help to understand its

pathogenesis, guide early screening and treatment, and ultimately reduce the incidence rate and mortality of EOCRC.

2. Genetics of EOCRC

Pathogenic germline variation (PGV) was detected in 16% to 35% of EOCRC patients, with 34–71% being cases of Lynch syndrome and adenomatous polyposis of the colon (APC) is also more common [3]. Lynch syndrome is caused by the DNA mismatch repair (MMR) gene, *MLH1*. Germline mutations in *MSH2*, *MSH6*, or *PMS2* typically manifest as EOCRC accompanied by high-level microsatellite instability (MSI). Compared to sporadic colorectal cancer, Lynch syndrome patients have an earlier onset age, with an average diagnosis age of 40 years old. The tumor progression is faster, and there are more coexisting internal and external tumours, which are more common in the proximal colon. However, their overall prognosis is better than that of sporadic colorectal cancer. Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease, accounting for approximately 1% of all cases of colorectal cancer, and is associated with pathogenic mutations in the adenomatous polyposis (APC) gene. The characteristic is the presence of a large number of colorectal adenomas in affected individuals [4]. In a typical FAP family, the risk of EOCRC among carriers of *APC* germline pathogenic mutations at the age of 40 is close to 100%. Gene detection and preventive colectomy can effectively reduce the incidence rate of colorectal cancer in FAP family [5].

Up to 30% of all CRC cases are considered positively correlated with first-degree relatives having CRC [6]. The OR of EOCRC in first-degree relatives with a family history of colorectal cancer was 4.50, and the correlation of younger groups with siblings and sisters (OR11.68) was higher than that of parents (OR3.75). Compared to middle-aged and elderly individuals, a family history of colorectal cancer is a higher risk factor for the younger population.

Based on the above analysis, we found that EOCRC patients need to undergo strict medical history inquiries (family history and history of hereditary tumor syndrome), as well as molecular pathology and genetic screening to clarify gene mutations and molecular characteristics. At the same time, more research is needed in the future to analyze why the incidence of colorectal cancer of siblings is so closely related to the incidence of EOCRC patients and how to improve the identification and screening of this part of the population with genetic predisposing factors. These are the direct steps to curb the rise of the EOCRC incidence rate.

3. Risk exposure factors for early-onset colorectal cancer EOCRC

Although genetic predisposition is closely related to EOCRC, approximately 70% of EOCRC drivers may be associated with endogenous or exogenous exposure factors. Especially in the early stages of life, exposure factors may interact with potential genetic background factors, triggering EOCRC. In terms of analyzing exposure factors, we analyze from three overlapping areas, including the general external environment (such as social pressure, economic factors, etc.), the specific external environment (including tobacco, alcohol, drugs, diet, activities, etc.), and internal human environment (including gut microbiota, inflammation, oxidative stress, etc.).

In terms of specific external environmental exposure factors, the Chinese Lifestyle Index (including smoking, drinking, diet, waist-to-hip ratio, exercise, etc.) shows that a high Lifestyle Index score (i.e. regular diet, exercise, etc.) is associated with a reduced risk of male rectal cancer. Evidence suggests that poor dietary habits are associated with the risk of developing colorectal cancer, such as smoking, consuming large amounts of "unhealthy" foods (rich in processed meat and processed foods), or consuming less "healthy" diets (containing fruits or vegetables, dietary fibre, and dietary calcium). Among them, drinking alcohol (≥ 14 times a week) and

consuming a large amount of processed meat have been proven to be positively correlated with the risk of EOCRC. The intake of beta carotene, vitamin C, vitamin E, and folic acid is negatively correlated with the risk of EOCRC. From 1961 to 2017, the energy intake of Chinese residents per capita doubled. At the same time, food consumption has shifted from grains to meat products, especially red meat. In the obesity study closely related to specific external environmental exposure factors, researchers found that obesity in youth was associated with an increase in the incidence rate and related mortality of EOCRC. Individuals with high BMI aged 17–19 have an increased risk of dying from colon cancer. Liu PH *et al.* (2019) investigated 85,256 young women and recorded 114 cases of EOCRC (with a median age of 45 years at diagnosis) [7]. Young women with normal BMI values have a significantly lower risk of developing EOCRC compared to overweight or obese young women. Therefore, the demand for processed food and supplementary food among young people in China is increasing, which may lead to a double increase in the incidence rate and mortality of early-onset colorectal cancer.

The Western dietary pattern is associated with tumours with KRAS wild-type (KRAS+/+), BRAF wild-type (BRAF+/+), no CpG to methylation phenotype, or low CpG island methylation phenotype (CIMP) and microsatellite stable (MSS) [8]. Therefore, future research linking dietary patterns with the molecular characteristics of EOCRC gene subsets will broaden our understanding of young patients.

There is a clear relationship between internal exposure factors, abnormal gut microbiota, and CRC. General external exposure factors (such as stress), specific exposure factors (such as dietary emulsifiers or intake of large amounts of processed red meat), or internal exposure factors (such as inflammation) can all affect the gut microbiota, leading to colitis and metabolic syndrome, both of which are associated with EOCRC [9]. Therefore, the regulation of gut microbiota is located at the intersection of multiple exposure factors and EOCRC, and in the future, it is necessary to systematically integrate the relationship between related exposure factors and microbial abnormalities.

In terms of general external exposure, an increase in an individual's perception of psychosocial stress can increase the risk of rectal cancer. Statistics have found that reduced sleep can lead to stress, obesity, and CRC while psychosocial pressure also increases the risk of diabetes, and diabetes is also related to EOCRC [10]. Under high-pressure environments, immune cell function and gut microbiota are both impaired, thereby promoting the occurrence of CRC. Young female CRC patients, due to fear of disease progression and factors such as postoperative stomas, further exacerbate social distancing and trigger further high stress [11].

We believe that when studying which exposure factors are associated with EOCRC, it is necessary to consider the time correlation between exposure factors and EOCRC. Exposure factors and inflammatory factors, microorganisms, etc. may have an impact on the pathological changes of the distal colon or rectum in young patients. Exposure factors exist in the process of an individual from conception to adulthood. Therefore, although alcohol and smoking are closely related to colorectal cancer, they have been mainly confirmed in elderly patients. Based on this logical framework, the future requires big data to identify the exposure factors driving EOCRC and more experiments to determine the underlying causal relationships.

4. Clinical manifestations and pathological characteristics of EOCRC

The average diagnosis age of EOCRC is 40 years old, and the incidence is comparable between males and females. Clinical staging is more common in stages III–IV [12]. EOCRC has low tissue differentiation and is mainly classified into mucinous adenocarcinoma, signet ring cell carcinoma, poorly differentiated carcinoma, and undifferentiated carcinoma. It often presents as highly unstable microsatellites (MSI H, accounting for 10% to 30%). In the early stage, tumours are prone to form concave ulcers, invading submucosal blood vessels, penetrating the intestinal wall and infiltrating the serosa and surrounding areas. The rapid growth of tumours

can easily compress and invade local nerves and can also lead to intestinal stenosis and obstruction. The initial symptoms associated with pathological changes are usually abdominal pain and discomfort, bloody stools, intestinal obstruction, and changes in stool shape or habits. Unexplained weight loss and iron deficiency anaemia can serve as warning indicators, and the possibility of EOCRC should be considered when they occur [13]. The most common site of the lesion is in the rectum, with over 70% of EOCRC patients diagnosed in the left colon. The first symptom of EOCRC left colon cancer patients is often bloody stool, mainly accompanied by cholecystitis and splenomegaly. On the other hand, patients with right colon cancer mainly experience abdominal pain and discomfort, mainly accompanied by chronic appendicitis [14].

EOCRC is prone to misdiagnosis in clinical diagnosis, and the diagnosis is often in the late stage of cancer. A team from the Zhejiang Hangzhou Key Laboratory of Cancer Prevention analyzed 1,335 colorectal patients and found that young patients had a worse prognosis, with stage III–IV patients receiving surgical resection being the most severe. The reason for their prognosis was that their condition was in the advanced stage at the time of treatment [15]. On the one hand, EOCRC often exhibits insidious growth and lacks distinctive early symptoms, often confused with other intestinal diseases. On the other hand, EOCRC patients have strong tolerance and irregular physical examinations, and when obvious intolerance symptoms appear, they are already in the late stage. In addition, young people under the age of 40 often neglect digital rectal examination and colonoscopy, and the average course of the disease from symptom onset to diagnosis is more than 4 months and even more than 6 months. Therefore, early diagnosis can greatly reduce mortality.

5. Conclusion

In the future, targeted large-scale epidemiological studies will be carried out in conjunction with disease pathogenesis studies, systematically combing the time and dose effects of pathogenic exposure factors and the correlation with EOCRC-related genotype pathogenesis driving mechanism. This will help to reduce the incidence rate and death rate of EOCRC effectively.

Disclosure statement

The authors declare no conflict of interest.

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