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Risk Factors for Colorectal Cancer and DNA Methylation Mechanisms

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Abstract: Colorectal cancer is one of the most prevalent and deadliest malignant tumors worldwide. Its development is a complex, multifactorial, and multi-stage process, influenced by both genetic factors and environmental factors such as lifestyle, diet, and epigenetic modifications. This article reviews the epidemiological status of colorectal cancer, the relationship between lifestyle factors (including sedentary lifestyle and smoking), dietary habits, and disease risk, and explores the role of DNA methylation in tumor susceptibility and its interaction with environmental factors, aiming to provide a reference for the prevention and early intervention of colorectal cancer.

Keywords: Colorectal cancer; Lifestyle; Diet; DNA methylation; Environmental factors

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1. Introduction

Colorectal cancer is a common malignant tumor of the digestive system, and its incidence rate continues to rise globally. According to the 2017 statistics on colorectal cancer, the incidence rate of colorectal cancer ranks third among malignant tumors globally, and second in developed Western countries [1]. In my country, with the improvement of living standards and changes in dietary structure, the incidence rate of colorectal cancer has shown a significant upward trend, ranking fourth among malignant tumors [2]. The occurrence of colorectal cancer is a complex process involving multiple factors and stages, involving various environmental and lifestyle factors such as diet, exercise, and smoking, and is also affected by genetic factors and epigenetic regulation. Understanding and identifying these high-risk factors and carrying out targeted screening and intervention are of great significance for reducing the incidence and mortality of colorectal cancer [3].

2. The relationship between lifestyle and colorectal cancer

The occurrence of colorectal cancer is closely related to an individual's lifestyle. In addition to genetic background,

dietary structure, exercise, smoking, and sedentary behavior can all affect the intestinal environment and the risk of tumor development through multiple mechanisms. Therefore, changing unhealthy lifestyles and screening high-risk groups can help reduce the risk of disease.

2.1. Relationship between sedentary factors and colorectal cancer

In recent years, with improved economic conditions and changes in lifestyle, sedentary behavior has become increasingly common. Studies have shown that prolonged sitting is independently positively correlated with an increased risk of colorectal cancer [4]. Compared with those who sit for less than 8 hours a day, those who sit for ≥8 hours a day have a hazard ratio (HR) of 1.14 (95% CI: 0.91–1.43) for colorectal cancer. Therefore, reducing sedentary time and increasing outdoor exercise and daily activities are of positive significance in reducing the risk of colorectal cancer [5].

2.2. Relationship between smoking factors and colorectal cancer

Smoking is one of the important risk factors for many malignant tumors. Studies have shown that smoking is significantly associated with an increased risk of colorectal cancer. A case-control study showed that smoking can alter individual susceptibility through interaction with the 14q22.3 region, thereby increasing the risk of colorectal cancer [6]. In addition, a study by Fagunwa *et al.* pointed out that there is a dose-response relationship between smoking and colorectal cancer; the longer the duration and the greater the amount of smoking, the higher the risk of developing the disease. In particular, heavy smokers who smoke ≥40 packs/year and have been smoking for ≥40 years have a significantly increased risk of colon cancer [7].

3. Relationship between dietary factors and colorectal cancer

Multiple studies have shown that a reasonable dietary structure and maintaining a healthy weight help reduce the incidence and mortality of colorectal cancer [8]. Different types of diets have significantly different effects on colorectal cancer.

High-fat diets, red meat, and processed meat intake increase the risk of colorectal cancer. It has been reported that about 60% of colorectal cancer patients come from developed countries, which is closely related to their population's preference for high-meat diets [9]. Studies have confirmed that the intake of processed meat is positively correlated with the incidence of colorectal cancer [10]. Conversely, the intake of nutrients such as whole grains, dietary fiber, folic acid, selenium, and calcium can significantly reduce the risk of colorectal cancer. Fiber-rich diets produce butyrate through fermentation by intestinal microorganisms, which not only protects intestinal epithelial cells but also plays a chemopreventive role [11].

A large-scale population screening study further showed that increased total dietary fiber intake was negatively correlated with a reduced risk of distal colon cancer, with cereal fiber and fruit fiber having the most significant protective effects [12]. Therefore, improving dietary structure, reducing the intake of red and processed meat, and increasing the intake of vegetables, fruits, and grain fiber are of great significance for the prevention of colorectal cancer [13].

4. DNA methylation and susceptibility to colorectal cancer

Epigenetics is the study of heritable changes in gene expression without altering the DNA sequence. Among these,

DNA methylation is one of the most thoroughly studied epigenetic mechanisms.

DNA methylation refers to the binding of a methyl group to the 5th carbon atom of the cytosine ring under the catalysis of DNA methyltransferase (DMT), forming 5-methylcytosine. In mammals, DNA methylation mostly occurs in the 5'-CG-3' sequence of genes [14]. The vast majority of methylation sites are located on CpG islands. This modification alters the binding affinity of transcription factors to DNA, thereby inhibiting gene expression or leading to gene silencing [15].

DNA methyltransferase-mediated DNA methylation is an important epigenetic mechanism regulating cell proliferation, differentiation, apoptosis, and the cell cycle [16]. In tumor cells, aberrant methylation of gene promoter regions can lead to the inactivation of tumor suppressor genes, thereby increasing tumor susceptibility and promoting carcinogenesis.

5. The relationship between environmental factors and DNA methylation

DNA methylation is not only genetically regulated but also significantly influenced by environmental factors. Studies have found that prenatal dietary patterns can have long-term effects on an individual's DNA methylation levels, thereby affecting adult metabolism and health. Genomic analysis of differential DNA methylation in whole blood shows that prenatal starvation can lead to differential DNA methylation expression, thus affecting long-term metabolic function [17,18]. Furthermore, excessive intake of dietary supplements containing folic acid, vitamin B12, and choline may also alter DNA methylation levels, potentially causing adverse health effects.

6. Conclusion

The development of colorectal cancer is the result of a combination of genetic, lifestyle, dietary, and epigenetic mechanisms. Sedentary lifestyle, smoking, and unhealthy diets can all increase the risk of developing the disease, while good lifestyle habits and a balanced diet have a protective effect. DNA methylation, as an important mechanism of epigenetic regulation, may be a key link in the influence of environmental factors on susceptibility to colorectal cancer. Future research should further elucidate the interaction mechanisms between environment and epigenetics to provide a theoretical basis for individualized prevention and early intervention of colorectal cancer.

Disclosure statement

The author declares no conflict of interest.

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