

# *Research Progress on Risk Factors of Digestive Tract Polyps*

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**Keywords:** Polyp; Digestive tract; Risk factors; Traditional Chinese Medicine; Western Medicine

**Abstract:** Digestive tract polyps are one of the common diseases of the digestive tract, among which gastric polyps and large intestine polyps are the most common. Due to the high risk of gastric adenoma and common intestinal adenoma, gastrointestinal polyps have attracted extensive attention from clinicians. Its pathogenesis has not yet been fully elucidated, and the etiology is considered to be related to genetics, diet and accompanying diseases, etc. Endoscopic resection is often used in treatment, while traditional Chinese medicine has increasingly obvious advantages in the prevention, treatment and postoperative rehabilitation of gastrointestinal polyps through examination of the cause and syndrome differentiation. In this paper, the etiology of digestive tract polyps was reviewed in order to be helpful for clinical diagnosis and treatment.

## 1. Introduction

Digestive tract polyps (DTP) is a neoplasm that protrudes from the mucosal surface and protrudes into the lumen, originating from the mucosal epithelium of the digestive tract. Polyps can be divided into esophageal polyps, stomach polyps, small intestine polyps and large intestine polyps according to their location, and stomach polyps and large intestine polyps are common, as shown in Figure 1. Pathological types of upper gastric polyps are divided into gastric adenoma, fundus glandular polyp, hyperplastic polyp and dysplastic polyp. Intestinal polyps can be divided into common adenoma, benign serrated lesions, inflammatory polyps and dysplastic polyps, among which gastric adenoma and intestinal common adenoma have a high risk of cancer [1]. And the development process of polyps is shown in Figure 2. The etiology and pathogenesis of DTP have not been clarified, but it is currently believed that the occurrence of polyps is related to heredity, diet and accompanying diseases [2].

There is no unified name for this disease in the field of Chinese medicine, and modern doctors roughly classify it as "fullness", "accumulation", "intestinal tumor", "intestinal abscess", "diarrhea" and other categories [3,4]. Traditional Chinese medicine is effective in reducing and eliminating DTP and preventing postoperative regeneration by examining and treating the cause and syndrome differentiation. In this paper, the etiology of DTP was reviewed in order to be helpful for clinical

diagnosis and treatment.

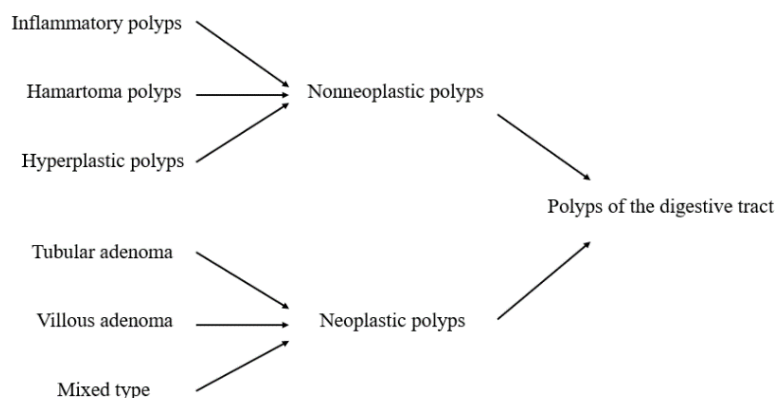


Figure 1: The classification of polyps

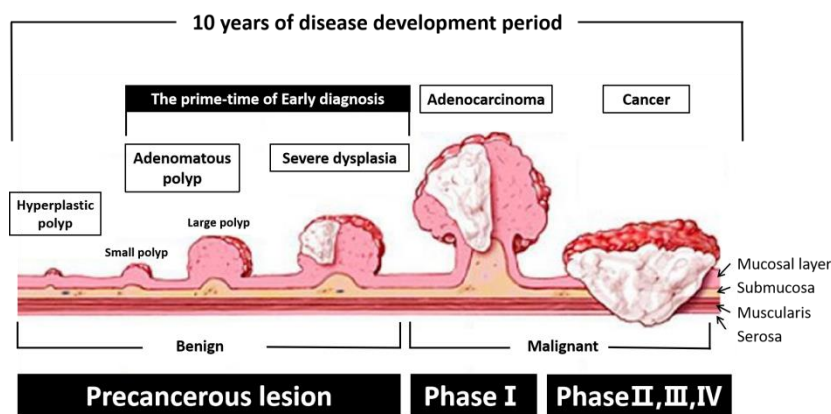


Figure 2: The development process of polyps

## 2. Etiology and pathogenesis of TCM

Chinese medicine scholars have long recognized the potential pathological factors of DTP. With the development of The Times, modern doctors have made many achievements in clinical research on the etiology of DTP.

### 2.1. Tracing of ancient books

The knowledge of polyps in traditional Chinese medicine was first seen in "Lingshu · Water distention", saying: "cold visitors outside the intestine, Wei Qi beat, qi is not distinguished, because of the system, the habit and inside, evil is up, polyps are born [5]", the book pointed out that polyps are due to chronic illness caused by obstruction of the choroid. Li Gao put forward in his book On the Spleen and Stomach: "Wind, cold, heat, dampness, dryness, fire. . . It is caused by the weakness of the spleen and stomach, and the Zang fu organs and meridians are not affected by qi [6], suggesting that the occurrence of polyps is based on the weakness of the spleen and stomach, and is mixed with a variety of causes such as qi stagnation, phlegm, and blood stasis. In the Treatises on the Sources of Various Diseases, it's said: "All kinds of syndromes are born of cold and temperature imbalance, poor diet, and visceral qi." The disease does not move, directly named disease. If there is a lump in an illness but it can be removed, it is called "lump", indicating that the lump is an internal mass formed

by the delayed formation of qi and blood obstructions caused by external evil factors and eating disorders [7]. (Table 1)

Table 1: TCM's understanding of the pathogenesis of polyps

Book	Author	Pathogenesis
Lingshu	Physicians of the ages	Long-term illness causes obstruction of the choroids
Spleen and stomach theory	Li Gao	Based on the weakness of the spleen and stomach, as well as stagnation, phlegm, stasis, etc
Theory of the origin of diseases	ChaoYuanfang	External sensations and eating disorders lead to stagnant qi and blood

## 2.2. Modern Research

Most modern Chinese medicine scholars believe that the occurrence of polyps is related to dampness, heat, phlegm, blood stasis and other factors, and explore the etiology of polyps from the perspective of common symptoms and patients' physique, as shown in Table 2.

Wang Xinting [8] et al. believed that the disease of large intestine polyps was located in the large intestine and was closely related to humidity and heat. Professor Zhou Bin put forward DTP as "intracellular mass", and pointed out that its pathogenesis was based on weakness of the spleen and stomach, combined with phlegm turbidity, damp-heat and blood stasis, and its treatment was mainly focused on strengthening the spleen and removing dampness and eliminating phlegm and blood stasis [7]. Chinese medical master Professor Zhou Xuewen believed that recurrent gastric polyps were based on weakness of the spleen and stomach, deficiency of healthy qi, stagnation of qi, blood stasis, phlegm and toxic accumulation, and the disease was located in the stomach, closely related to the spleen, involving the liver and kidney [9]. Through research and analysis, Chen Yan [10] believed that upper digestive tract polyps were mainly caused by weakness of the spleen and stomach and disharmony between liver and stomach, and were caused by dampness, phlegm and stasis alone or in combination. Physical factors also play an important role in the pathogenesis of upper digestive tract polyps, in which Qi-deficiency and Qi-stagnation are important factors.

Table 2: Modern Chinese medicine practitioners' understanding of polyps

Author	Pathogenesis
Wang Xinting	The disease is located in the large intestine and is closely related to humidity and heat
Zhou Bin	It is based on the weakness of the spleen and stomach, and is formed by adding sputum, humid heat, and blood stasis
Zhou Xuewen	Based on the weakness of the spleen and stomach, the deficiency of healthy qi, the stagnation of qi, blood stasis, phlegm coagulation, and toxic agglomeration, the disease is located in the stomach, and the spleen is closely related, involving the liver and kidney
Chen Yan	Spleen and stomach weakness and hepatogastric discord are the basic symptoms. Under the action of wetness, phlegm and stasis, it causes disease alone or both
Chen Xun	Moist heat, qi deficiency, and sputum moisture may appear alone or intermediated in the development of DTP
Zhou Bing	The constitution is mainly yang deficiency/phlegm and depressed nature

Chen et al. [11] put forward the concept of polyposis-related constitution and believed that

dampness-heat, Qi deficiency, and phlegm-dampness may appear alone or interstitially in the occurrence and development of DTP, and people with these constitutions may be more likely to cause polyposis occurrence or recurrence. Zhou Bing et al. [12] found that the incidence of gastric polyps was higher in males than in females, and middle-aged and elderly patients were mainly characterized by Yang deficiency/phlegm-dampness and qi-stagnation. The physical types of gastric polyps patients of different genders were also different, with Yang deficiency and phlegm-dampness predominating in males, while Yang deficiency and Qi-stagnation were more common in females.

### **3. Etiology and mechanism of Western medicine**

The etiology of polyps is not yet clear, but studies have shown that the occurrence of polyps is related to molecular mechanisms such as H. pylori infection, bile reflux, signaling pathways, environment, smoking, and eating habits, etc. , and suggest that the occurrence of intestinal polyps is closely related to lifestyle and eating habits [13,14].

#### **3.1. Bile reflux**

Wu Lizhu et al. [15] believe that bile reflux is a high-risk factor for the occurrence of gastric polyps, and the mechanism is that bile reverting into the stomach damages gastric mucosa, thus leading to the formation of gastric polyps. Meanwhile, studies have confirmed that gastric mucosa atrophy or intestinal metaplasia are related to bile reflux, and hyperplastic polyps are easily formed on the surface of such atrophic or intestinal metaplasia gastric mucosa [16].

Domestic scholars have pointed out that the detection rate of polyps in the cardiac, stomach, duodenum and gastroduodenum of patients with bile reflux is higher than that of patients without bile reflux, and the detection rate of polyps in the fundus and stomach body is higher than that in the gastric antrum regardless of whether the patients are accompanied by bile reflux, which may be related to the long-term stimulation of mucous lake containing gastric mucosal invasion factors in the fundus and stomach body [17].

#### **3.2. Hp Infection**

Studies [18-20] have shown that the occurrence of some pathological types of gastric polyps may be related to Helicobacter pylori infection, especially proliferative polyps and fundus glandular polyps. Zhou Zheng et al. [21] confirmed that the Hp infection rate of hyperplastic polyps and inflammatory polyps was higher, which was related to Hp infection to a certain extent, and the recurrence rate of gastric polyps treated with anti-HP, EMR and ESD methods was reduced. The relationship between intestinal polyps and Hp infection was also gradually clear. Early scholars found Hp in polyp tissue through immunohistochemical methods. They tested 3483 patients with intestinal polyps and found that the Hp infection rate in the intestinal polyp group was significantly higher than that in the healthy group [22]. The most common mechanism is hypergastrinemia caused by Hp infection, which has a nutritional effect on the growth and proliferation of epithelial cells [23].

#### **3.3. Molecular mechanism**

Lv Xiaoyan et al. [24] determined the expression of Wnt1,  $\beta$ -catenin, and cyclinD1 in gastric polyps and normal gastric mucosal tissues adjacent to polyps by immunohistochemistry, and found that Wnt1 was highly expressed in the cytoplasm of hyperplastic and adenomatous gastric polyps.  $\beta$ -catenin was positively expressed in the cell membrane of gastric fundus adenomatous polyps, and was highly expressed in the cell membrane and cytoplasm of hyperplastic and adenomatous polyps.

cyclinD1 is positively expressed in the nucleus of hyperplastic polyps and highly expressed in the nucleus of adenomatous polyps, suggesting that gastric hyperplasia and the formation of adenomatous polyps are related to the initiation of Wnt/ $\beta$ -catenin signaling pathway.

Zhang Haiyun et al. [25] found that the mRNA expression levels of protein phosphatase 2A cancerous inhibitor (CIP2A) and cyclinD1 in adenomatous gastric polyps were significantly higher than those in normal gastric mucosal tissues. Liu Tianyu et al. [26] applied methylation-specific polymerase chain reaction (MSP) to find that the methylation degree of miR145 promoter in gastric polyps and gastric cancer tissues was higher than that in adjacent normal tissues, suggesting that miR145 may be involved in the carcinogenesis of gastric polyps. Chen Ji [27] et al. found that the expression of HSP70 increased in gastric polyp carcinogenesis, suggesting that it could be used for early monitoring of gastric cancer. According to the decreasing expression of Apaf-1 and ST13 in cancer transformation, monitoring the change of Apaf-1 and the reduction of the specificity of ST13 in gastric cancer can be used as diagnostic indicators for gastric cancer.

Various domestic studies have also successively confirmed the pathogenesis of intestinal polyps. Due to strong mutations in Bmpr1a, APC, SMAD4, PTEN, STK11 and other genes, various cell signaling molecules affect the growth signal regulation network composed of BMP signaling pathway, PTEN signaling pathway and Wnt signaling pathway, resulting in  $\beta$ -catenin in the intestinal excessive accumulate in cells causes dysfunction of intestinal stem cells, resulting in imbalance of self-renewal, clonal proliferation, differentiation and apoptosis [28].

Chai Ningli et al. [29] found that the expression rate of CD44 was 95.65% in colon cancer tissues, 55.26% in tubular adenomatous polyps, and 75.76% in villous polyps. The expression of Lgr5 in tubular adenoma and villous adenoma was 86.84% and 93.94%, respectively, suggesting that the expression of Lgr5 is strongly correlated with polyp canceration. The combined detection of Lgr5 and CD44 is of great significance in the early diagnosis of intestinal lesions, especially in the prediction of intestinal polyp canceration.

### 3.4. Eating Habits

Smoking, drinking, high fat and high protein are risk factors in dietary habits [30]. Studies suggest that [31] smoking is closely related to polyps, and daily smoking intensity is related to colorectal polyps, and there is a dose-response relationship between smoking time and colorectal polyps, and smoking time over 20 years is closely related to distal polyps, polyp size and nature. Alcohol and its metabolite acetaldehyde can interfere with the absorption of potential anticancer nutrients such as folic acid and calcium by inducing DNA methylation, and increase the incidence of polyps. Studies have shown that alcohol consumption is more closely related to conventional adenoma [31]. In a 2018 report, the World Cancer Research Institute highlighted that high consumption of red meat or processed meat can significantly increase the risk of colorectal cancer, possibly because heme iron in red meat increases the risk of colorectal cancer [32].

### 3.5. Genetic factors

Genetic factors are the primary cause of familial aggregation of intestinal polyps. If the parents have a medical history of intestinal polyps, or if they are a high-risk group of intestinal polyps, the probability of their children developing intestinal polyps will increase significantly. This heritability is approximately 30%, and other family members also have an increased risk of developing intestinal polyps, as shown in Figure 3. Except for inflammatory intestinal polyps, almost all other intestinal polyps have a medical history of intestinal polyps, such as pigmentation polyp syndrome, which is an autosomal dominant genetic disease. Familial polyposis is also an autosomal dominant genetic disease.

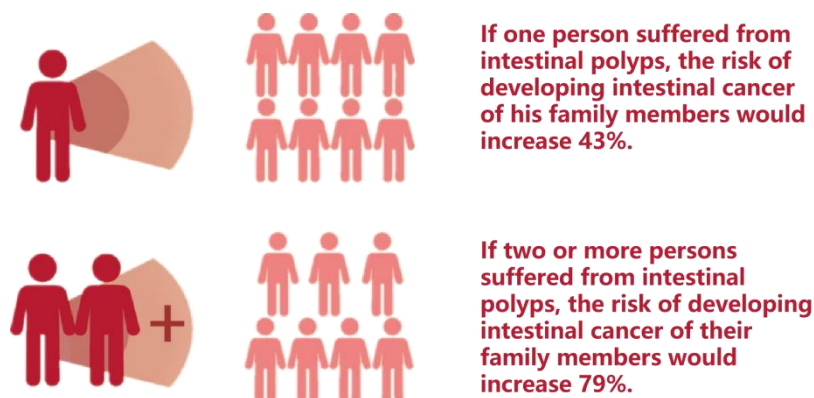


Figure 3: The heritability of intestinal polyps

In addition, gender and age of patients are important factors in the occurrence and development of gastric polyps. Liu Jing et al. [33] found that gastric polyps tend to occur in women, and patient age is positively correlated with polyp diameter, and middle-aged and elderly women are the main group of gastric polyps.

#### 4. Summary

As a common lesion of digestive system, polyps are common, young, easy to relapse and difficult to prevent. Diagnosis, treatment and prevention all rely on endoscopy, which is generally unacceptable to the public, and the preventive effect of Western drugs such as proton pump inhibitors has not been recognized by the guidelines and clinical certification. In recent years, the search for causes and active and effective preventive means have become a research hotspot of polyp disease

Traditional Chinese medicine has achieved remarkable curative effect in the treatment of polyps through the diagnosis and treatment mode of "body discrimination-disease discrimination-syndrome differentiation". However, at present, there are still few studies on the correlation between traditional Chinese medicine constitution, syndrome type and pathological type of polyps, and the sample size is uneven, which affects the reference value of statistical results, and there is a lack of comparability among relevant research literatures.

At present, the etiology of digestive tract polyps is not clear at home and abroad, and various factors affect each other, it is difficult to evaluate the mechanism of action of a single factor, and more in-depth and rigorous tests are still needed to verify.

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