Mini-Review

Hereditary Colorectal Cancer in China: Current Status and Progress

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Key Words

Clinicopathological features · Diagnostic criteria · Genetics · Hereditary colorectal cancer · Intervention

Abstract

Background: Hereditary colorectal cancer (CRC) accounts for about 5% of the total incidence of CRC. During the last decades, there have been great advances in the research of hereditary CRC in China. **Summary:** This review mainly focuses on advances of the genetic basis, clinicopathological features, diagnosis, chemoprevention and treatment of hereditary CRC in China. **Key Message:** Hereditary CRC has a higher risk to initiate the progression towards neoplasia than sporadic CRC. It can be diagnosed by clinical manifestation or the relevant genetic testing so as to guide the clinical treatment to improve the survival rate and survival quality of patients. **Practical Implications:** Hereditary CRC includes hereditary nonpolyposis CRC (Lynch syndrome), familial adenomatous polyposis and other rare types such as Peutz-Jeghers syndrome and familial juvenile polyposis. Based on the clinical manifestations and family history, highly suspected cases can be screened for in the general population and the diagnosis ruled out by genetic analysis. Then, chemoprevention, endoscopic intervention or surgery can be selected properly to improve patients' survival and quality of life.

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Introduction

The incidence of colorectal cancer (CRC) in the general population was 20.90/1,000,000 in 2012 in China [1]. The number of new cases of CRC is growing year by year. Hereditary CRC accounts for nearly 5% of all CRC cases [2, 3]. Hereditary CRC was classified as hereditary

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nonpolyposis CRC (HNPCC) and hereditary colorectal polyposis [4]. In addition, hereditary colon polyposis disease can be subdivided into adenomatous polyposis syndrome including familial adenomatous polyposis (FAP), MutY homologue-associated polyposis (MAP) and hamartoma polyposis syndrome, such as Peutz-Jeghers syndrome (PJS), familial juvenile polyposis coli (FJPC), phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS) and hereditary mixed polyposis syndrome (HMPS) [5]. The aim of this review was to summarize the current knowledge of hereditary CRC in China by searching relevant studies published between 2005 and 2015 on PubMed, China Academic Journal Network Publishing Database (CAJD) and Vip Journal Integration Platform.

Hereditary Nonpolyposis Colorectal Cancer

HNPCC, also known as Lynch syndrome, is an autosomal dominant genetic condition which has a high risk of colon cancer as well as extracolonic cancers due to inherited mutations in mismatch repair (MMR) genes. HNPCC is the most common form of hereditary CRC, accounting for 0.5–1.2, 2.1–2.9 and 2.4–2.9% of all CRC cases, respectively, according to the Amsterdam Criteria I and II and to the Japanese Criteria in China [6, 7]. The 3-, 5- and 10-year survival rates are 70.3, 49.9 and 39.7% in China, respectively. The incidence of multiple primary neoplasms in HNPCC was 20.4% [8].

Genetics

It had been confirmed that the germline mutations in MMR genes are the genetic basis of HNPCC [9]; mutations in MMR genes MLH1, MSH2, MSH6, PMS2 and EPCAM are associated with HNPCC. Besides, mutations in MSH3, PMS1 and MLH3 have been reported to be the pathogenesis of HNPCC in China [9–15]. Among the MMR gene mutations, hMLH1 accounts for about 49–57%, while hMSH2 accounts for about 45–49%, and the deletion of hMLH1 seems to be more important than MSH2 in early-onset CRC [16–19]. However, some scholars found that among CRC patients in Beijing, HNPCC has a higher morbidity (13.83%) than the average level in the world (2–5% [20]), and MSH2 mutation is very frequent (84.62%) [21]. Besides, Long et al. [22] examined MMR protein expression by using immunohistochemistry (IHC) in 173 patients with endometrial cancer and found that the loss rates of MSH6, MSH2, PMS2 and MLH1 protein was 16.18% (28/173), 12.14% (21/173), 7.51% (13/173) and 5.78% (10/173), respectively. Liu et al. [23] screened a total of 116 unrelated probands of suspected HNPCC families from the Fudan Colorectal Registry and have found that patients with hMSH2 mutation were frequently affected by synchronous and metachronous colon cancers. Certainly, more studies are needed to clarify the mutation rates of MLH1 and MSH2 in China.

Clinical Features

Here we list some well-recognized HNPCC clinicopathological manifestations: (1) early onset age – the median age is about 45 years and the onset age of offspring is decreasing compared to their parents' generation; (2) appropriately 70% of tumors are located in the right-sided colon [24]; (3) there is a high risk of synchronous or metachronous primary CRCs, and 40% of HNPCC patients will develop a new CRC within 10 years after partial colon resection; (4) extracolonic cancer can co-exist, including endometrial cancer, ovarian cancer, gastric cancer, small intestine cancer, hepatobiliary cancer and urinary cancer; (5) poor differentiated adenocarcinoma, mucous carcinoma or signet ring cell carcinoma are more frequent and accompanied with lymphocyte infiltration.

Table 1. Amsterdam criteria I and II [91]

Amsterdam criteria I

At least three relatives with CRC; all of the following must be met:

- 1 One patient must be a first-degree relative of the other two
- 2 At least two successive generations affected
- 3 At least one CRC diagnosed before age 50
- 4 FAP has been excluded

Amsterdam criteria II

At least three relatives with colorectal, endometrial, small bowel, ureter, or renal pelvis cancer; all of the following must be met:

- 1 One patient must be a first-degree relative of the other two
- 2 At least two successive generations affected
- 3 At least one CRC diagnosed before age 50
- 4 FAP has been excluded

HNPCC patients have better prognosis than those with sporadic CRC [25]. Chinese HNPCC patients have some different features [26, 27]. The most frequent extracolonic cancer in China is gastric cancer, not endometrial cancer as reported in western studies [27, 28]. The median age at the onset of HNPCC is 45.3 years in Jiangxi province and 41.8 years in the city of Wuhan, which is similar to western countries [29, 30]. Jin et al. [8, 31] reported that the 3-, 5- and 10-year survival rates of HNPCC in China were 61.7, 38.11 and 25.81% in 2001 and increased to 70.3, 49.9 and 39.7% in 2005, respectively, suggesting that the prognosis of HNPCC had improved within 5 years, which was probably associated with early detection and timely treatment.

Diagnostic Criteria and Methods

The diagnosis of HNPCC mainly relies on family history and genetic linkage analysis. Patients meeting the Amsterdam criteria or Bethesda guidelines should undergo detection of microsatellite instability (MSI) and IHC analysis of hMSH2 and hMLH1 expression [32]. At present, there are some international standards on HNPCC, such as the Amsterdam criteria I and II (table 1), the Bethesda guidelines and Japanese standards. The Amsterdam criteria are widely used to screen for HNPCC. However, they are not suitable for small pedigrees, which are common in China, and some Chinese scholars think that the characteristics of HNPCC in the Chinese population are probably different from those of western countries. So the Chinese Association of Professional Committee of Colorectal Cancer has established the Chinese criteria [33]: there must be at least two relatives with CRC, two of them first-degree relatives; all of the following must be met: (1) at least one patient with multiple CRC or adenomas; (2) at least one CRC diagnosed before the age of 50 years; (3) at least one patient with extra-colonic tumors, such as gastric carcinoma, endometrial cancer, small bowel cancer, ureteral or renal pelvis carcinoma, ovarian cancer, hepatobiliary system cancer, etc.

Genetic Testing. When the above-mentioned criteria are met, the MSI and MMR genes should be examined to identify families with HNPCC. Many Chinese scholars detected microsatellite loci in HNPCC patients, including BAT25, BAT26, D2S123, D5S346 and D17S250, and found that MSI-H positivity was about 85.0%, the MSI rates of BAT25 and BAT26 being close to 100%. We also found that in northern Chinese patients with HNPCC, MSI-H positivity was 83.3%, and expression loss of MMR proteins accounted for about 88% of MSI-H patients, the pathogenic mutation rate of the MMR gene being 56% [34]. Because of the high incidence of MSI-H in HNPCC, MSI detection is a simple and easy way to screen for early germline mutations in MMR genes [35, 36]. Besides, IHC is a good substitutive way to evaluate the mutation of hMLH1 and hMSH2 [22]. Jin et al. [37] found that the specificity and sensitivity of IHC for

hMLH1 and hMSH2 were 91.7 and 87.5%, respectively. If both MSI and IHC results are negative, the mutation detection analysis is unnecessary. If one of them is positive, hMLH1 and hMSH2 germline mutations should be detected [34]. At present, most Chinese scholars have found that it is very effective to test the MLH1 and MSH2 gene to screen HNPCC patients [38–44]. Zhou et al. [45] reported that promoter methylation analysis in MLH1 was a promising tool for HNPCC screening.

Treatment

Chemoprevention. Nonsteroidal anti-inflammatory drugs have been proved to be a class of effective drugs in the intervention for FAP and HNPCC. We found that oral administration of celecoxib was effective. The patients treated by celecoxib 400 mg daily combined with endoscopic intervention showed protective effectiveness [46]. A report said that aspirin does not have a protective effect against CRC in the short term, but that long-term aspirin treatment has a protective effect against Lynch syndrome cancers [47].

Operative Treatment. Surgery is still the main way for the treatment of HNPCC, but there are some controversies about the optimal operative methods. Some scholars have proposed that total colectomy should be implemented to avoid the risk of multiple primary CRC and the misdiagnosis of residual colon once the diagnosis is confirmed [48]. However, some scholars have considered that extracolonic organs may suffer HNPCC-related tumors after total colectomy [49]. Presently, the National Comprehensive Cancer Network guidelines advise HNPCC patients with incipient CRC to choose total colectomy. Besides, clinical stage, prognosis, follow-up conditions and personal wishes should all be considered before choosing preventive surgery. Whether the rectum was retained or not is critical to postoperative quality of life. What is more, most HNPCC tumors are located in the proximal colon. If there is no lesion in the proximal colon, the proximal colon should be retained and the patient needs to be examined at regular intervals. When a lesion is detected, surgical treatment is recommended. In addition, endoscopic intervention has been proved to be an effective alternative way of managing HNPCC patients. We found that in MMR mutation carriers, colonoscopic surveillance can facilitate the diagnosis of more early-stage CRC than non-surveillance [50]. Moreover, Li et al. [51] reported that colonoscopic surveillance is an important way to decrease the incidence of CRC and to lower the overall mortality of HNPCC family members with MMR genes mutations.

Familial Adenomatous Polyposis

FAP is an autosomal-dominant CRC syndrome, caused by a germline mutation in the adenomatous polyposis coli (APC) gene located on chromosome 5q21 [52]. FAP is a representative form of the adenomatous polyp syndrome, and the incidence rate is about 1/7,000–22,000. It can be divided into classical FAP, attenuated FAP, MAP, Gardner syndrome and Turcot syndrome [49]. Liu et al. [53] reported that the morbidity of FAP was about 1.5/100,000 in Zhejiang province of China.

Genetics

The present study suggests that FAP is mainly caused by APC and MYH mutation; 25% of FAP cases without APC mutation are caused by MYH mutation [54]. There are one mutational allele and one normal allele of the APC gene in FAP patients. It is a classical Mendelian genetic disease. 79% of FAP patients have one mutated allele [55]. The APC gene is a housekeeping gene, and its length of open reading frame is 8,535 bp, containing 15 exons. The 15th exon is the longest one (6,577 bp), accounting for about 77% of the full-length gene (exon). The

Table 2. Clinical features of FAP

Type	Average onset age	Number of polyps	Parenteral complications
Classical FAP	39 [92]	>100	congenital hypertrophy of the retinal pigment epithelium thyroid papillary carcinoma adrenal hyperplasia or carcinoma fundic gland polyps periampullary adenoma of the duodenum Gardner and Turcot syndrome [73]
Attenuated FAP	55 [92]	<100	fundic gland polyps duodenal periampullary adenoma
MAP	55 [93]	dozens or hundreds	not clear, but there were some reports about fundic gland polyps and duodenal periampullary adenoma [72]

product of the APC gene is a protein with 2,843 amino acids, and the molecular weight is about 310 kDa. APC gene mutations mainly include missing, insertion mutations, point mutations or frame shift mutations [56]. Besides the hot spot 1,250–1,464 bp, some Chinese scholars have reported that APC gene mutations can occur within the area 443–1,068 bp and the splicing area in intensive polyp patients. The average onset age in China is 32 years, while in western countries the onset age of intensive FAP is 10–20 years and that of middle type 20–30 years [57–59]. Another FAP-associated gene is MYH. The MYH gene is located at p34.3–p32.1 and contains 16 exons; its coding protein is a transglucosylase which participates in repairing and splicing of the bases. MYH is an autosomal recessive gene found in colorectal multiple polyp or typical adenomatous polyp patients [60, 61]. MYH gene mutation can lead to high risk of colorectal polyps and adenocarcinoma. Recently, Yang et al. [62] reported that there was a relationship between AXIN2 gene mutation and FAP.

Clinical Features

In the surgery clinic, hematochezia is the main clinical symptom of FAP, accompanied by anemia, abdominal pain, diarrhea, mucus stool, etc. Additionally, a few patients can have symptoms of intussusception or intestinal obstruction [63]. However, in the internal medicine clinic, diarrhea is the most frequent symptom of FAP, accounting for 71.0%, followed by abdominal pain (29.0%) and hematochezia (16.1%) [64]. What is more, Li et al. [65] also reported that diarrhea was the most frequent manifestation. The discrepancy in clinical manifestation may be caused by the difference in patients choosing between surgical and internal medicine departments.

The most typical characteristic of FAP patients is >100 tubular or villous adenomas in the whole colon [66]. An intensive polyp number over 1,000 is a common phenotype of FAP in China [55]. FAP patients often suffer from stomach, duodenum and ileum polyps, with an occurrence of 30–90% [67]. Duodenal carcinoma is considered to be the second most important cause of death [68, 69]. The characteristics of classical FAP, attenuated FAP and MAP are listed in table 2.

Diagnostic Criteria and Methods

The diagnostic criteria for FAP are (1) >100 colorectal adenomas, with or without a family history, and (2) >20 colorectal adenomas with a family history. An APC gene mutation test is recommended once the patients meet the above criteria [34]. A recent study suggests that MYH and AXIN2 should be detected if APC gene mutation is negative [62].

Clinical Screening

There are some major checking methods, such as endoscopic examination and genetic testing. In order to find the parenteral tumors, it is important to examine the fundus [70], the thyroid gland, the reproductive system and any other systems when the patients have been diagnosed [71].

Treatment

Chemoprevention. The nonselective and selective inhibitors of COX-2 are the major drugs for the treatment of FAP, including sulindac and celecoxib. A lot of reports say that nonsteroidal anti-inflammatory drugs can reduce the number and size of FAP adenomas [62, 65–76]. Sulindac in combination with endoscopic treatment is better than polyp resection to suppress colorectal adenoma development in the long term. Quality of life is better than with mere surgical treatment and patient compliance is lower [77, 78]. Besides, berberine inhibits colon tumor formation through inhibition of Wnt/beta-catenin signaling, indicating that berberine may be a promising drug for the prevention of colon cancer [79]. In traditional medicine, Wang et al. [80] have reported that black raspberries suppositories are effective to restrain the development of polyps in patients with FAP.

Operative Treatment. Ileal pouch anal anastomosis is the first surgical choice for FAP. However, many patients still die from Gardner or Turcot syndrome. Thus, it is important to adopt individualized treatment, depending on the patients' age, the number and distribution of colorectal polyps and intercurrent upper gastrointestinal polyp, Gardner and Turcot syndrome, and the desire of the patients and their families [81]. Surgical treatment can be applied to patients older than 15–18 years [82]. In order to improve quality of life, patients can choose subtotal colectomy to retain the rectum. Patients then need to undergo colorectal endoscopic examination every 6 months. For relapsed adenomas, it is necessary to adopt electroresection combined with nonsteroidal drugs.

Hamartomatous Polyposis Syndrome

Hamartomatous polyposis syndrome is a rare genetic polyposis including PJS, FJPC, PHTS and HMPS.

Peutz-Jeghers Syndrome

The mainly representative hamartomatous polyposis syndrome is PJS. The incidence of PJS is about 1/25,000. Skin and mucosa pigment spots, gastrointestinal hamartomatous polyps and familial transmissibility are major clinical features [83, 84].

Familial Juvenile Polyposis Coli

FJPC is characterized by multiple colorectal juvenile polyps, and the incidence is about 1/1,000,000. 'Juvenile' refers to the histology of polyps rather than the onset age [85, 86]. The clinical characteristics of PJS and FJPC are listed in table 3.

Treatment

The main clinical treatment on PJS and FJPC is surgery combined with endoscopic therapy. Small and pedicle polyps should be eliminated as soon as possible. Surgical treatment should be considered if the patient is suffering from refractory bleeding, severe anemia and malnutrition, or if the polyps cannot be removed by endoscopic excision [87].

Table 3. Clinical characteristics of PJS and FJPC

Condition	Mutation gene test	Clinical characteristics	Diagnosis
PJS	LKB1/STK11 FHIT [34, 94]	1 polyps of various sizes distributed in the digestive tract, frequently in the jejunum	multiple hamartoma polyps with mucocutaneous pigmentation
		2 acute or chronic abdominal pain, intussusception, volvulus, intestinal obstruction [87] and gastrointestinal bleeding	
		3 parenteral tumors, such as breast cancer and reproductive system tumor [83]	
FJPC	BMPRI1A/SMAD4 [95, 96]	1 infantile type: it is relatively rare; the baby manifests with mucus diarrhea, vomiting, hematochezia within a few weeks after birth	1 Jass diagnostic criteria [97]: >5 colorectal juvenile polyps
		2 colorectal type: 50–200 polyps, located in the sigmoid colon and rectum; the main symptoms are hematochezia and mucous stool	2 the whole gastrointestinal tract is affected, with a family history
		3 diffuse type: the polyps can be detected in the whole gastrointestinal tract and upper gastrointestinal hemorrhage is common [95–98]	

Challenges and Perspectives

Although there have been great advances in the research of hereditary CRC in China, there is yet no multicenter organization to study hereditary CRC, nor has there been nationwide research on epidemiological investigation. Many valuable cases of hereditary CRC are not effectively managed, which is a key problem for the research of hereditary CRC in China. In the future, there are some issues that should be considered to reveal the basic and clinical aspects of hereditary CRC. First, high-throughput sequencing, the so-called next-generation sequencing technology, makes it possible to analyze the whole genome. This revolutionary technology will be able to provide a new way to analyze the pathogenic genes of hereditary CRC. Maybe some new variants responsible for hereditary CRC can be found out by next-generation sequencing. Second, mutation in the gene intron has been reported in hereditary CRC [88], but whether it is pathogenic or not still needs to be ascertained. Third, a report from the USA demonstrated that microRNAs play an important role in the development of HNPCC and FAP [89]. MicroRNAs can specifically target MMR mRNAs involved in colon cancer progression [90], suggesting that epigenetic dysfunction may involve in the pathogenesis of hereditary CRC. However, how those factors influence the initiation and progression of hereditary CRC remains unclear. Finally, it is estimated that there are only small subpopulations of candidates joined in the program of hereditary CRC screening, thus some of the patients suffering from hereditary CRC may be missed. This may be related to the lesser number of centers and to doctors' proficiency.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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