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REVIEW

Advances in the study of Lynch syndrome in China

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Abstract

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is an autosomal dominant genetic condition that has a high risk of colon cancer as well as other cancers due to inherited mutations in mismatch repair (MMR) genes. During the last decades, there have been great advances in research on Chinese Lynch syndrome. This review mainly focuses on the genetic basis, clinicopathologic features, diagnosis, intervention, chemoprevention, and surveillance of Lynch syndrome in China. In addition to frequently altered MMR genes, such as *MLH1*, *MSH2*, *MSH6*, and *MLH3*, other MMR-associated genes, such as those encoding human exonuclease 1, transforming growth factor β receptor 2, and alanine aminopeptidase, metastasis-associated protein 2, adenomatosis polyposis coli down-regulated 1, and hepatic and glial cell adhesion molecule have also been implicated in Chinese Lynch syndrome. Most Chinese researchers focused on the clinicopathologic features of Lynch syndrome, and it is noticeable that the most frequent extracolonic tumor in northeast China is lung cancer, which is different from other areas in China. The Chinese diagnostic criteria for Lynch syndrome have been established to identify gene mutation or methylation. With regard to chemoprevention, celecoxib may be effective to prevent polyps relapse in Lynch syndrome carriers. Additionally, a colonoscopy-based surveillance strategy for the prevention and early detection of neoplasms in Lynch-syndrome carriers has been proposed.

Key words: Clinicopathologic features; Diagnostic criteria; Genetics; Intervention; Lynch syndrome

Core tip: Lynch syndrome is an autosomal dominant inherited disorder. The estimated number of Lynch syndrome carriers in China is larger than that in any other country worldwide. This review summarized recent advances in studies of Chinese Lynch syndrome.

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INTRODUCTION

Lynch syndrome is an autosomal dominant inherited disease that is typically characterized by hereditary nonpolyposis colorectal cancer (HNPCC) and has a high risk of other tumors, such as endometrial cancer, ovarian cancer, gastric cancer, intrahepatic cholangiocarcinoma, urological cancer, and skin cancer, which is caused by germline mutation in mismatch repair (MMR) genes. Individuals with unique colon cancer, are categorized as Lynch Ⅰ. The others, suffering from Lynch syndrome-related tumors, in addition to colorectal cancer (CRC), are considered as Lynch Ⅱ. HNPCC is the main clinical pattern of Lynch syndrome, and also the most common autosomal dominant hereditary CRC. The two terms, Lynch syndrome and HNPCC, have been used interchangeably, until recent advances in the understanding of the disease led to the term HNPCC falling out of favor. In the population of CRC patients in China, the prevalence of Lynch syndrome meeting the Amsterdam Criteria (AC) Ⅰ and Ⅱ, and Japanese Criteria were 0.5%-1.2%, 2.1%-2.9% and 2.4%-2.9%, respectively[1,2]. Lynch syndrome accounts for 5.6%-6.4% of all Chinese CRC patients[3,4].

Lynch syndrome is distinctive from sporadic CRC in many aspects, including genetics, clinical features, intervention, and treatment. This article is aimed to review the current knowledge and status of the above aspects in China, by searching on PubMed, CNKI, and VIP databases for relevant studies published between 2004 and 2014.

GENETICS

It has been demonstrated that germline mutations in MMR genes are the genetic basis of Lynch syndrome, including *MLH1*, *MSH2*, *MSH6*, *MSH3*, *PMS1*, *PMS2,* and *MLH3*. Mutant *MLH1* and *MSH2* were reported to be the most common pathogenic genes in Chinese Lynch syndrome, with the frequency of mutation and loss of expression of *MLH1* higher than that of *MSH2*[5-7]. In parts of China, the rates of loss of expression of *MLH1* and *MSH2* in Lynch syndrome patients are 15%-48% and 34%-40%, respectively[8-10]. In foreign patients, the mutation rates of those genes varied from 41% to 90%[11-13], whereas the mutation rates of *MLH1* and *MSH2* in Chinese Lynch syndrome patients that met the ACI or ACII criteria were 35% and 14%, respectively[6]. A study of 76 Chinese families, who met Bethesda 1, 3, or 4, showed that the mutation rates of these two genes were only 25% and 9%, respectively[14]. Endometrial carcinoma (EC) is one of the main Lynch Syndrome-associated extracolonic tumor. An investigation of female EC patients below age 50 in South China showed that the rate of loss expression of MMR proteins was 30%, most of whom had an abnormal expression of *MLH1*[15]. For more details, please see Table 1[16-24].

Reports on *MLH3* are scarce, it was reported that mutation of *MLH3* in northern Chinese was similar to that in the Western population, but the mutation frequency seemed higher in northern China[25]. There is little evidence that *MLH3* mutation prompts the development of Lynch syndrome in northern China

Table 1 Identification of mutations in mismatch repair genes in China

Gene	Base variation	Amino acid change	Ref.
MLH1	g.677G>A	Arg226Gln	[7]
	c.107T>A	Ile36Asn	[14]
	IVS2-1G>A	(intron)	[14]
	c.488delG	(intron)	[14]
	c.497T>A	Leu166Och	[14]
	c.498A>C	Leu166Phe	[14]
	c.572G>T	Ser191Ile	[14]
	c.910T>A	Val307Glu	[14]
	c.949C>A	Leu317Met	[14]
	c.1246A>G	Lys416Glu	[14]
	c.1731G>C	-	[14]
	c.1823C>A	Ala608Asp	[14]
	c.1988A>C	Glu663Ala	[14]
	c.2038T>C	Cys680Arg	[14]
	c.2101C>A	Gln701Lys	[14,16-18]
	c.2251_2insAA	-	[14]
	c.1625A>T		[18,90]
	c.194G>A		[18,19]
	c.199G>A		[18,20,21]
	c.649C>T		[18,20,21]
	c.1646T>C		[18]
	c.1721T>C		[18]
	c.1742C>T		[18]
	c.1344insG	Glu448Glyfs*30	[27]
	c.157delGAGG	Glu54Alafs*2	[22]
	c.-64G>T	(promoter)	[22]
	c.2157dupT	Val720Cysfs*3	[22]
	c.1731+15delT	-	[23]
	c.503_4insA	(frame shift)	[49]
MSH2	g.610G>T	Gly204X	[7]
	c.1452-1455delAATG	-	[31]
	c.2108C>A	Ser703Tyr	[24]
	c.2583A>G	Q861Q	[10,49]
	c.899_890insAT	(frame shift)	[49]
	IVS7-1G>A	(splice junction)	[49]
	c.−78_−79delGT	(promoter)	[28]
	c.1216_1219dupCGAC	L407fsX417	[29]
	c.23C>T	Thr8Met	[14,66]
	c.1571G>T	Arg524Leu	[14]
	c.1917T>A	His639Gln	[14]
	c.1955C>A	Pro652His	[14]
	c.2047G>A	Gly683Arg	[14]
	c.206-?_792+?del	-	[5]
	c.1077-?_1276+?del	-	[5,83]
	c.1387-?_1510+?del	-	[5]
	c.2211-?_818+?del	-	[5]
	c.2635+?_(*3084)del	-	[5]
	c.2196T>C	-	[24]
	c.2963C>G	-	[24]
MSH6	c.2297delA	His766Leufs*8	[27]
	c.3488A>T	Glu>Val	[30]
PSM2	c.1532C>T	Thr>Met	[37]
MLH3	c.2152C>T	Pro718Scr	[25]
	c.2615C>G	Scr872Stop	[25]
	c.3488G>A	Gly1163Asp	[25]
	c.666G>A	Lys222Lys	[25]
	c.4335C>A	Gln1445Gln	[25]

or is an indicator for people at a high risk. Some novel mutation sites in *MLH1*, *MSH2,* and *MSH6* have been found by Chinese researchers during studies of MMR genes[26-30]. For example, researchers from the University of Hong Kong found a mutation site (c.1452-1455delAATG) that accounted for 36% of all the germline mutations in *MSH2*[31]. Further analysis suggested that this founder mutation may date back between 22 and 103 generations. The identification of this *MSH2* founder mutation has important implications for the design of mutation-detection strategies for the southern Chinese population.

Additionally, epimutation of MMR genes has become to be a hot spot. *MLH1* promoter methylation was mainly found in sporadic colon cancer, so it can be used as a screening biomarker to exclude Lynch syndrome. However the detection rate of this methylation was 13%-22% in Lynch syndrome patients without confirmed germline mutations in *MLH1, MSH2,* or *MSH6*[32-34]. Carriers of the *MLH1* mutation may show loss of expression of due to the methylation of the functional allele[35,36]. Therefore, the diagnosis of Lynch syndrome should not be excluded with only the evidence of *MLH1* promoter methylation, especially for those who were diagnosed with CRC at a young age, and for those with evident family history or other risk factors.

Actually, MMR gene mutation cannot be identified in all patients who meet the diagnostic criteria. Therefore, scientists have begun to explore other genes associated with MMR to identify some novel pathogenic genes of Lynch syndrome. Using gene chips combined with immunohistochemical method, Chinese researchers found and upregulation of genes encoding alanine aminopeptidase and metastasis-associated protein 2, and downregulation of adenomatosis polyposis coli down-regulated 1 and hepatic and glial cell adhesion molecule genes in CRC patients with abnormal expression of MMR genes, compared to those who express MMR genes normally[37]. Although germline deletions in *EPCAM* is considered to inactive *MSH2* and therefore result in about 1% Lynch syndrome, there is little literature reporting its effect in Chinese Lynch syndrome.

Schmutte *et al*[38] first discovered that the human exonuclease 1 gene (*EXO1*) can interact with products of *MSH2* and participate in recognition and combination with mismatch sites. After that, some researchers agreed that *EXO1* germline mutation can result in MMR dysfunction and prompt tumor development[39-41]. However, others consider that there is no direct relationship between *EXO1* mutation and Lynch syndrome, and that the mutation exists extensively in the normal population. Despite *EXO1* mutation, MMR function can still be available through other mechanisms[42,43].

Transforming growth factor β receptor 2 (TGFβR2) is an important conversion factor in the signal transduction system. It has been found that, *TGFBR2* poly A and G repetitive sequences in microsatellite instability (MSI)-H CRC cells are likely mutated, which accounts for more than 70% in Lynch syndrome patients[44]. It is reported that *TGFBR2* expression in most MSI-H colon adenoma and carcinoma is low[45,46]. However, mutations within the TGFβ system can be easily found in many kinds of tumors, and its action in the development of Lynch syndrome and its specific value for diagnosis remain unclear.

In Lynch syndrome, the mutation of an allele of heterozygous MMR genes will lead to MMR dysfunction and then increase mistakes during DNA replication, which result in MSI. MSI is a significant feature of Lynch syndrome. It is found that the positive rate of MSI was 85% in patients with Lynch syndrome, 40% in those with ordinary hereditary CRC, and 10% in sporadic CRC cancer patients[47]. Additionally, the positive rates of MSI-H in Lynch syndrome-related adenoma and cancer are significantly higher than in sporadic colorectal adenoma and cancer (64.3% *vs* 3.1%, 71.4% *vs* 12.5%, respectively)[48,49].

CLINICOPATHOLOGIC FEATURES

Lynch syndrome is a form of MSI colon cancer with clinical manifestations that differ from familial adenomatous polyposis and sporadic colon cancer, which are chromosome instability colon cancers. Chinese Lynch syndrome patients possess the following characteristics: (1) the episode age of Lynch syndrome is 10-20 years earlier than that of sporadic colon cancer. The median episode age is 42.5-46.0 years, with a peak age of 40-49 years old, and 75% of patients are diagnosed before age 50[50] and 87% before age 60[51-54]; (2) men have a higher risk than women with a male to female ratio of 1.3-1.7:1, and the onset age of males is lower than that of females[52-55]; (3) vertical transmission: as an autosomal dominant inherited disease, if one of the parents carries pathogenic genes for HNPCC, the chance of transmission to an offspring is 50%, regardless of sex. An investigation of 69 families indicated that 94% of families had more than two generations of vertical transmission[53]; (4) proximal colon cancer is more common: international reports showed that 70% of CRC is located at the proximal colon of splenic flexure[51,56], with most studies reporting similar results[52,53,57-65]. In addition, 66% of 116 patients with CRC from 34 families had right-sided colon cancer[52], whereas an investigation of 31 Chinese families showed that CRCs were found mainly in left-sided colon and rectum rather than in right-sided colon[66]; (5) synchronous and heterochronous multiple primary carcinomas: several investigations showed that the incidence rate of synchronous and heterochronous multiple primary carcinomas in Chinese patients was 10.0%-20.4%[53,63,67,68]; and (6) high morbidity of associated extracolonic cancer: some Lynch Ⅱ patients can develop extracolonic cancer, and gastric cancer was reported as the most common type in China[61,62,69-72].

Table 2 Frequency of extra colonic cancer related with hereditary nonpolyposis colorectal cancer in China *n* (%)

Ref.	Extra colonic cancer			*n*	Diagnostic criteria	Hospital location
[73]	Lung	Gastric	Endometrial		ACII	Liaoning
	56 (20.07)	48 (17.20)	32 (11.47)	279		
[52]	Gastric	Glioma	Cardiac/retinoblastoma/ovarian		ACII, JC	Beijing
	13 (41.90)	3 (9.68)	2/2/2 (6.45)	31		
[53]	Gastric	Endometrial	Esophagus		ACII, JC, BG	Beijing
	18 (28.13)	11 (17.19)	7 (10.94)	64		
[63]	Endometrial	Brest	Lung/Gastric		ACI, ACII, JC	Tianjin
	9 (19.57)	7 (15.22)	6/6 (13.04)	46		
[69]	Gastric	Endometrial/Lung/Brest/Bladder			ACI, ACII	Guangdong
	5 (31.25)	2/2/2/2 (1.63)		16		
[55]	Gastric	Liver	Endometrial		ACI, ACII, JC, BG	Shanghai
	16 (18.60)	10 (11.63)	8 (9.30)	86		
[54]	Gastric	Endometrial	Liver		ACI, ACII	Shanghai
	8 (25.00)	8 (25.00)	5 (15.63)	32		
[70]	Gastric	Endometrial	Liver		ACI	Shanghai
	25 (39.68)	11 (17.46)	6 (9.52)	63		
[72]	Gastric	Esophagus	Mouth		Chinese C	Zhejiang
	9 (37.50)	3 (12.50)	2 (8.33)	24		

ACI: Amsterdam criteria I; ACII: Amsterdam criteria Ⅱ; JC: Japanese criteria; CC: Chinese criteria; BG: Bethesda guideline.

Our group[52,53] reported that 20%-23% of all patients with Lynch syndrome experienced extracolonic cancer, of which, 42% had gastric cancer and 18% had endometrial cancer. Others reported that lung cancer was the most common in northeast China[68,73] and endometrial cancer was predominant in Tianjin[63,74] (Table 2).

DIAGNOSTIC CRITERIA AND METHODS

The International Collaborate Group on HNPCC established the first unified clinical criteria on Lynch syndrome in Amsterdam, Netherlands in 1990, known as the ACI. However, this criterion only took Lynch I into account, excluding Lynch syndrome-related cancers, and is useless for screening in small families. The ACI was later modified in 1999 as the ACII. During that time, the Japanese Criteria and the Bethesda Guideline and the modified version were issued by the Japanese Society for Cancer of the Colon and Rectum and the National Cancer Institute, respectively. Researchers from Fudan University and Shanghai Cancer Center established the Recommended Fudan Criteria, based on investigations upon the features of Chinese patients: (1) three or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of HNPCC-related cancers (including CRC, endometrial cancer, gastric cancer, liver cancer, ureter and renal pelvis cancer); (2) two successive affected generations; (3) one or more of the HNPCC-related cancers diagnosed before age 50 years; and (4) exclusion of familial adenomatous polyposis. The difference between these criteria and the ACII lies in the addition of gastric cancer and liver cancer into the category of HNPCC-related cancers. Nevertheless, these criteria are all based on retrospective data, and require several members with a confirmed diagnosis of HNPCC to determine the Lynch syndrome families. Over the past several decades, the family scale has diminished due to family planning, which makes pedigree analysis, the main method for diagnosis of inherited cancer, increasingly impractical[75]. Besides, most of the mutation carriers of MMR genes cannot be identified by these criteria. Therefore, it may be wise to take the advantage of molecular genetic characteristics to screen families with Lynch syndrome.

MMR gene testing

The test of germline mutation in MMR genes is supposedly the most accurate way to identify families with HNPCC. Once a germline mutation in an MMR gene is identified, regardless of the clinical diagnostic criteria, families with HNPCC can be determined. Methods for detection of MMR gene mutation currently consist of single-strand confirmation polymorphism (SSCP), denaturing high-performance liquid chromatography (DHPLC), multiplex ligation-dependent probe amplification (MLPA), and direct sequencing.

SSCP is appropriate for detection of PCR products $\leqslant$ 500 bp. The sensitivity of SSCP is comparable to that of DNA sequencing, according to an internal report[76].

DHPLC is also known as temperature-modulated heteroduplex analysis, which is used to detect 200-500 bp PCR products. DHPLC is currently the most sensitive method for the qualitative detection of gene mutations, but its application is still limited to experimental studies[77]. Zhang *et al*[78] used DHPLC to detect germline mutations of *MLH1* and *MSH2,* which had been determined by DNA sequencing, and the result indicated that all the known mutations can be identified by DHPLC, and the sensitivity and specificity all reach 100%.

Mutation detection for large fragments of MMR genes in Chinese patients with Lynch syndrome is common[79]. We[5] investigated Chinese families with Lynch syndrome by MLPA and found that large deletions in *MLH1* and *MSH2* were responsible for approximately 19% of all mutations, and the deletions of *MSH2* were more frequent[80]. On the contrary, large deletions of MMR genes have not been identified in sporadic CRC[81].

Theoretically, the sensitivity and specificity of DNA sequencing are all 100%, through which we can figure out the location and types of MMR gene mutations. Although gene test is the most accurate method for diagnosis of Lynch syndrome, its wide application in the clinic is limited by some defects such as long testing time, high cost, and low efficiency.

Mutation tests for *BRAF* in the diagnosis of Lynch syndrome have become increasingly accepted. It has been demonstrated that *BRAF* mutations exist in 15% of CRC cases (most are sporadic). Therefore, if *BRAF* mutations are detected in patients with CRC, then the diagnosis is more likely to be sporadic CRC[35,82,83]. It should be noted that *BRAF* mutation is not common in sporadic endometrial cancer, thus, *BRAF* testing is not useful for distinguishing Lynch syndrome-related endometrial cancer from sporadic endometrial cancer[84].

Immunohistochemistry testing

MMR proteins work in dimers; MSH-2 complexes with MSH-6 or MSH-3, and MLH-1 may complex with PMS-2 or PMS-1. Monomeric MSH-6 and PMS-2 proteins are unstable, thus a germline mutation in *MSH2* typically leads to loss of expression of the proteins MSH-2/MSH-6, and a germline mutation in *MLH1* results in loss of expression of MLH-1/PMS-2. On the contrary, germline mutations in *MSH6* or *PMS2* do not cause loss of expression of MSH-2 or MLH-1[35].

Internal studies indicated that the sensitivity of immunohistochemistry (IHC) testing for MLH-1 and MSH-2 mutations was 79%-95%[85], which was 92% in an international report[86]. For most of the clinical testing laboratories, IHC testing is technically easy and convenient. Most loss of gene expression can be detected by IHC, which is cheap and consequently reduces the cost of detection. However, IHC can only determine the loss of expression of MMR proteins, but cannot detect germline mutations. And many other reasons, such as somatic mutation, promoter methylation and oxidative stress, can also lead to loss of expression of MMR proteins.

MSI assessment

The stability of microsatellites can be evaluated by assessing the stability of microsatellite markers in tumor tissues. In 1997, the National Cancer Institute recommended five microsatellite markers, including BAT25, BAT26, D2S123, D5S346 and D17S250, among which, the frequency of BAT26 mutation is 95%. CAT25 and BAT26 seemed to be equally effective for screening Lynch syndrome in Chinese population. And the length distribution of CAT25 alleles was more intensive than BAT26, suggesting that CAT25 testing may be more sensitive in large-scale studies[87]. We[88] found that the positive rates of MSI-H in Lynch syndrome patients who met ACII and Bethesda Guideline 3 criteria in northern China were 85% and 81%, respectively. Xu *et al*[89] reported that the positive rates of MSI-H in patients who met ACI criteria and individuals with highly suspected diagnosis of Lynch syndrome were 94% and 93%, respectively. The sensitivity of MSI testing for the diagnosis of Lynch syndrome was reported as 91%[90]. A study from Southern Medical University showed that, MSI (-H and -L) carriers accounted for 85% of CRC patients aged below 40 years in southern China[91]. MSI testing can be used in preliminary screening for Lynch syndrome, and can be used in combination with ACII to reduce diagnostic errors[92]. However, it is hard to implement MSI testing in every clinical laboratory due to high cost and conditions. MSI cannot be detected in mucinous tumors because of technical challenges such as lack of DNA. Some Lynch syndrome-related cancers resulting from germline mutations in *MSH6* tended to have MSI-L, which may lead to a false-negative result. Additionally, approximately 15% of sporadic CRC patients exhibit MSI[93].

A combination of the above methods could enhance the sensitivity and specificity of diagnosis. It is reported that the sensitivity and specificity of IHC testing for the loss of MLH-1 and MSH-2 expression in Lynch syndrome are 91% and 87%, respectively, and those of MSI assessment of five markers are 100% and 75%, respectively; the sensitivity and specificity are 91% and 93%, respectively, when those two methods are used in combination[94].

Proteomic analysis

Chinese researchers have used surface enhanced laser desorption/ionization-time of flight-mass spectrometry combined with protein chip to analyze protein components of preoperative serum derived from 20 patients with Lynch syndrome and 25 patients with sporadic CRC[95]. Protein profiles were analyzed with Biomarker Wizard and Biomarker Pattern programs (Ciphergen Biosystems, Inc., Fremont, CA, United States). The authors concluded that, under a blind authentication mode, the diagnostic accuracy, sensitivity, total specificity, and positive predictive value were 75.6%, 69.8%, 99.2%, and 100% respectively.

INTERVENTION OF LYNCH SYNDROME

Nowadays in China, partial colectomy or local resection is usually performed prior to the confirmation of Lynch syndrome, as there are no prospective or retrospective

trials supporting that extended resection provides a survival advantage compared to partial colectomy. Zhou *et al*[96] and Li *et al*[97] reported that after conventional surgical treatment for the first CRC, the five- and ten-year accumulated risks for metachronous primary CRC were estimated at 50% and 52%, respectively. Extended resection could reduce the times of operation for metachronous CRC, but also reduced colonic function and increased the risk for old-age patients at the same time. Therefore, Lynch syndrome patients should be preoperatively identified and carefully considered for correct staging, receive more individualized colonic resection, specific follow-up, and familial screening[97-99]. For female Lynch syndrome carriers, resection of the uterus and ovaries could be considered in order to prevent Lynch syndrome-related cancers following a careful discussion of the risks, benefits, and limitations of this procedure[100].

Prophylactic colectomy did not show any survival benefit compared with surveillance for MMR gene mutation carriers without CRC, who should receive genetic counseling and should actively participate in decisions concerning the prophylactic strategies[101].

CHEMOPREVENTION

It was demonstrated in a clinical study on 1071 patients with Lynch syndrome that four-year administration of aspirin and/or resistant starch has no effect on the incidence of CRC[102,103]. However, the extended study also conducted by Burn *et al*[104] showed a trend towards protection with aspirin, but not starch. Researchers found that those who took aspirin for $\geqslant$ 2 years had an incidence rate of 0.06 per 100 person-years compared with 0.13 per 100 person-years among those who took aspirin < 2 years. Analysis within the placebo group found no significant difference in CRC incidence between those who took aspirin for $\geqslant$ 2 years (0.14 per 100 person-years) compared with those took aspirin for < 2 years (0.10 per 100 person-years). The authors implied that compliance might play a role on outcomes. Our group[105] reported that in 5/6 patients with Lynch syndrome, the polyps completely vanished after nine-month treatment with celecoxib at 400 mg/d, but side effects, such as arrhythmia, stenocardia, and nervous headache, were also observed. When the dose was adjusted to 200 mg/d, polyp recurrence was only observed in two patients two years later, suggesting that celecoxib is a promising drug for the prevention of polyp relapse in Lynch syndrome patients.

COLONOSCOPY SURVEILLANCE

A study of 140 patients with Lynch syndrome and 2350 patients from suspected Lynch syndrome families and their first-degree relatives indicated that routine colonoscopy and intervention reduced the incidence of CRC and improved the survival of patients[106]. For young patients, suspected patients, and gene mutation carriers, routine colonoscopy and intervention reduced the incidence of colon cancer and advanced adenoma[106,107].

A prospective study suggested that annual colonoscopy can lower the morbidity and mortality of patients with Lynch syndrome to the same levels as mutation-negative relatives[108]. For that reason, in 2011, Chinese experts in gastroenterology established a consensus statement upon surveillance and prevention of colon cancers.

CRC

Colonoscopy repeated at one-to two-year intervals, beginning at age 20-25 years (for *MSH6* and *PMS2* heterozygotes carriers, the risk for colon cancer is lower, colonoscopy screening may be delayed until age 30-35 years[109,110]) or at the age ten years lower than the onset age of the youngest colon cancer patient within a family[108,111]. Additionally, CT colonography has undergone major advances recent years, and it may exert a significant effect on CRC screening, when colonoscopy is not available[112,113]. But this procedure is not sufficiently widespread to become a screening method in China.

Gastric and duodenal cancers

(1) National Comprehensive Cancer Network guidelines in 2011 suggest that upper gastrointestinal endoscopy should be repeated at two- to three-year intervals, beginning at age 30-35 years, depending on the patient's condition. For individuals with chronic gastritis, atrophic gastritis, and/or intestinal metaplasia, shorter screening intervals are recommended. Of note, it is necessary to evaluate *Helicobacter pylori* infection in the biopsies, and to give appropriate treatments; (2) given that 87% of gastric and duodenal cancers occur after age 45 years, endoscopy beginning at this age may be necessary[114]; and (3) a cohort study found that more than 50% of small intestinal tumors of patients with Lynch syndrome were located in duodenum, so screening with upper gastrointestinal endoscopy may be beneficial[115], however, there is currently no evidence to support this.

Ileal tumors

For ileal tumors, patients should consider undergoing capsule endoscopy once every two to three years, beginning at age 30-35 years. In 2008, a case control study showed that there was no difference in the number of polyps detected between staining endoscopy and carefully repeated colonoscopy[116].

CONCLUSION

CRC is the third most common malignancy in men and the second in women, with over 1.2 million new cases

and 608700 deaths estimated in 2008[117]. Ten to thirty percent of patients with CRC have an obvious genetic predisposition. HNPCC is the main clinical type of Lynch syndrome. China has nearly 20% of the world's total population and is comprised of 56 populations, which is a great advantage for studies of genetic diseases. However, a unified cooperative research organization for Lynch syndrome has not yet been formed. For that reason, nationwide multi-center collaborations are rare and precious. Chinese researchers have been using advanced technologies in the detection, diagnosis, and treatment of Lynch syndrome, and carrying out long-term, large-scale follow-up studies. Our group has been engaged in clinical follow-up for years, and found that estrogen may take part in the regulation of MMR genes[118-124], providing a novel molecular mechanism for Lynch syndrome. However, except for a few in-depth studies, most Chinese researchers are still focusing on the clinicopathologic features and MMR gene mutations. We expect that a unified cooperative research organization for Lynch syndrome will soon be established in order to promote the continuous development of technologies and methods to deepen our understanding of the pathogenesis of Lynch syndrome, to figure out more accurate and convenient diagnostic criteria, to design the best therapy and surveillance protocol, and finally, to reduce the morbidity of Lynch syndrome and increase the life quality of patients.

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