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• LARGE INTESTINAL CANCER •

Analysis for phenotype of HNPCC in China

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Abstract

AIM: The aims of this study were to identify the clinicopathological features of Chinese HNPCC families and to evaluate the value of criteria for suspected HNPCC (sHNPCC) in clinical diagnosis.

METHODS: According to the follow-up records, 54 HNPCC families (including 12 ICG-HNPCC families and 42 sHNPCC families) were screened out from patients with colorectal cancers (CRCs), operated upon in 2nd Affiliated Hospital of Zhejiang University from 1984 to 2001. Clinical data of probands and tumor spectrum in these families were listed and analyzed.

RESULTS: (1) Mean age, proportion of colonic cancer, poorly differentiated cancer, multiple CRCs and Dukes' A+B of the probands in ICG-HNPCC and sHNPCC kindred were 39ys and 47.5ys, 75 % and 62 %, 0 and 12.8 %, 16.7 % and 14.3 %, 58.3 % and 81 %,respectively. Compared with sporadic colorectal cancers, probands from ICG-HNPCC and sHNPCC families were obviously different at age of onset(P=0.025 and 0.031), tumor location (P=0.001 and 0.000), differentiation(P=0.002 and 0.011) and development of multiple tumors (P=0.014 and 0.002). (2) A total of 178 malignant neoplasms were found in 54 HNPCC families, including 139 colorectal cancers. Besides of colorectal cancer, extracolonic tumors occurred in stomach, endometrium, hepatobiliary system, and so on (8 gastric cancers, 6 endometrial cancers, 6 hepatobiliary system cancers and 19 others) can also be seen in Chinese ICG-HNPCC and sHNPCC families.

CONCLUSION: (1) Chinese HNPCC families have specific clinicopathological features, such as early onset, predilection for the involvement of colon, tendency of multiple CRCs, development of extracolonic tumors and well differentiation. (2) The criteria for suspected HNPCC is useful in clinical diagnosis and management of HNPCC.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant tumors. Various factors and mechanisms are involved in the development of CRC[1-5]. In recent years, much progress has been made in the studies of CRC[6-13], but its morbidity is still rising[14,15]. It has been thought that one-third of CRC have a genetic background. Hereditary nonpolyposis colorectal cancer (HNPCC) is a common autosomal dominant colorectal disorder with special clinicopathological features[16]. In clinic, it is diagnosed by Amsterdam criteria[17]: (1) three or more relatives with histologically verified colorectal cancer, one of whom is the first-degree to the other two; (2) colorectal cancer affecting at least two generations; and (3) one or more colorectal cancer cases diagnosed before the age of 50. Families fulfilling Amsterdam criteria were named as ICG-HNPCC in this study. As the criteria are too rigid for small families and it excludes extracolonic cancers associated with HNPCC, the Korean Hereditary Colorectal Cancer Registry designated the term"suspected HNPCC" [18] and designed its criteria for the families who do not fulfill Amsterdam criteria but in whom a genetic basis for colorectal cancer is strongly suspected. The criteria for suspected HNPCC are as following: (1) vertical transmission of colorectal cancer or at least two siblings affected with colorectal cancer in a family and (2) development of multiple colorectal tumors (including adenomas), or at least one colorectal cancer case diagnosed before the age 50, or development of extracolonic cancer in family member. Families fulfilling these criteria were named as sHNPCC in this paper. The criteria were accepted by the International Collaborative Group (ICG) on HNPCC for international collaborative studies. It[19] had been reported that ICG-HNPCC and suspected HNPCC have the similar molecular basis and genetic background. In China, there is still no systematic research on ICG-HNPCC or sHNPCC. Therefore, it is necessary and urgent to find out the characteristics of HNPCC in Chinese populations.

In this study we were to find out clinical phenotype of Chinese HNPCC families and to evaluate whether the criteria for suspected HNPCC is useful in clinical diagnosis and management of HNPCC.

MATERIALS AND METHODS

According to the follow-up records, 54 probands from HNPCC families (including 12 ICG-HNPCC families and 42 s HNPCC families) were screened out from patients with colorectal cancers operated upon in 2nd Affiliated Hospital of Zhejiang University from 1984 to 2001. Their clinicopathological features were compared with those of sporadic CRCs operated upon in the hospital[20]. There were 34 male and 20 female, age ranged from 19-76ys (average 45.7), 35 cases of colonic cancer and 19 cases of rectal cancer.The tumor spectrums in these families were also analyzed. All patients were diagnosed by Amsterdam criteria or criteria for suspected HNPCC.

All data were analyzed by software STATISTICA 5.0. A value of P<0.05 is considered to be statistically significant.

RESULTS

Clinicopathological features of Chinese HNPCC families

Data of 54 probands with HNPCC and sporadic CRCs were listed in Table 1. From Table 1, we found that mean age of the probands of 12 ICG-HNPCC families was 39ys, proportion of

colonic cancer, well differentiated cancer, poorly differentiated cancer, mucinous tumor, Dukes' A+B and multiple CRCs were 75 %, 54.5 %, 0 %, 8.3 %, 58.3 % and 16.7 % respectively. For the probands of 42 sHNPCC families were 47.5ys, 62 %, 30.8 %, 12.8 %, 21.4 %, 81 % and 14.3 % respectively. Compared with sporadic colorectal cancers, probands from ICG-HNPCC families were obviously different at mean age (P=0.025), tumor site (P=0.001), tumor differentiation (P=0.002) and multiple tumors (P=0.014). Similar result was obtained when compared probands of sHNPCC families to sporadic cases: there were obviously different at mean age (P=0.031), tumor site (P=0.000), tumor differentiation (P=0.011) and multiple tumors (P=0.002).

Table 1 Clinical data of 54 probands

Parameters		ICG-HNPCC	sHNPCC	Total	Sporadic CRC
Sex	male	6(50%)	14(33.3%)	20(37%)	319(43%)
	female	6(50%)	28(66.7%)	34(63.0%)	423(57%)
Mean age		39y	47.5y	45.7y	56y
tumor site	colon	9(75.0%)	26(62.0%)	35(64.8%)	226(30.5%)
	rectum	3(25.0%)	16(38.0%)	19(35.2%)	516(69.5%)
Dukes' stage	A+B	7(58.3%)	34(81.0%)	41(75.9%)	347(47.8%)
	C+D	5(41.7%)	8(19.0%)	13(24.1%)	380(52.2%)
Differentiation	high	6(54.5%)	12(30.8%)	18(36.0%)	89(15.3%)
	moderate	5(45.5%)	22(56.4%)	27(54.0%)	397(68.1%)
	poorly	0	5(12.8%)	5(10.0%)	97(16.6%)
Pathology	mucinous tumors	1(8.3%)	9(21.4%)	10(18.5%)	159(21.4%)
	Non-mucinous tumors	11(91.7%)	33(78.6%)	44(81.5%)	583(78.6%)
Multiple CRCs		2(16.7%)	6(14.3%)	8(14.8%)	25(3.4%)

Except mean age (P=0.035), there was no obvious statistical difference between probands of ICG-HNPCC and sHNPCC families, in clinicopathological features: tumor site (P=0.402), Dukes' stage (P=0.106), tumor differentiation (P=0.147), Pathology (P=0.303) and multiple tumors (P=0.838).

Tumor spectrum in HNPCC families

A total of 178 malignant neoplasms were found in 54 HNPCC families including 139 colorectal cancers, 8 gastric cancers, 6 endometrial cancers, 6 hepatobiliary cancers and 19 others. In 12 ICG-HNPCC families, there were 53 tumors, including 47 CRCs, and each family had 3.92 CRCs patients. In 42 sHNPCC families, there were 125 tumors, including 92 CRCs, and each family had 2.19 CRCs patients. Except CRCs, carcinomas of stomach, endometrium, hepatobiliary system and urologic system were the most common extracolonic malignancies in HNPCC families. Extracolonic malignancies were less in ICG-HNPCC than those in sHNPCC.

Table 2 Tumor spectrum in HNPCC families

Organs	ICG-HNPCC	sHNPCC	Total
CRCs	47	92	139
Stomach	1	7	8
Endometrium	0	6	6
Hepatobiliary system	2	4	6
Lymphatic/hemato-poieticsystem	1	1	2
Esophage	0	2	2
Breast	0	1	1
Urologic system	0	5	5
Pancreas	1	0	1
Others	1	7	8
Total	53	125	178

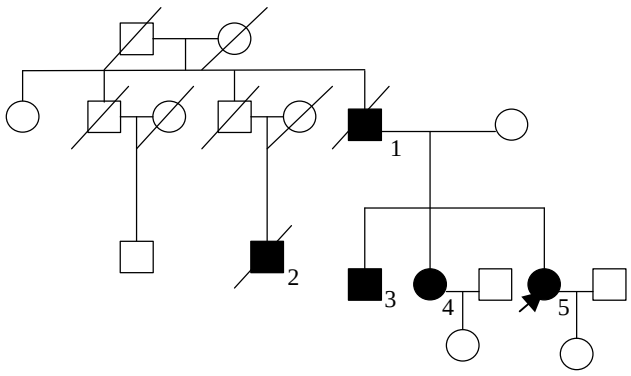

Figure 1 Pedigree of a ICG-HNPCC family.
1: father of proband, with CRC in 64ys, dead; 2: son of proband's uncle, with liver cancer, dead; 3: little brother of proband, with colonic polyps; 4: little sister of proband, with colonic cancer in 40ys, with gastric cancer 1 year later, alive; 5: arrow indicates the proband, 48ys, with colonic cancer, alive.

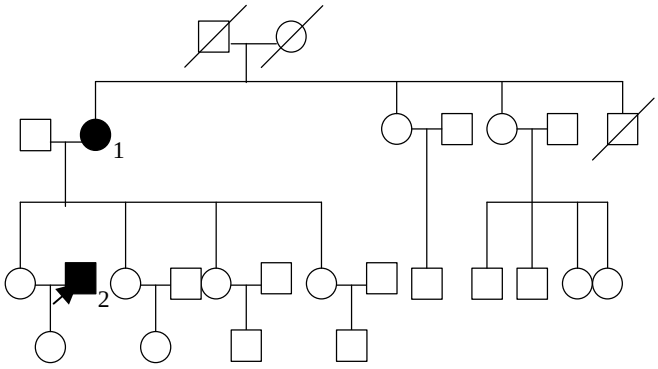

Figure 2 Pedigree of a sHNPCC family. 1: mother of proband, with CRC in 55ys, alive(80ys); 2: arrow indicates the proband, 38ys, with rectal cancer,alive.

DISCUSSION

In 1913, Warthin first described some families with an excess of colorectal, uterine and gastric cancers. It took more than half a century before Lynch undertook the task of collecting data that led to accurate description of these cancer-prone families[21]. According to the absence or presence of extracolonic malignancies, these families were divided into Lynch Ⅰ syndrome and Lynch Ⅱ syndrome[22]. Later, the syndrome was specifically called HNPCC. So HNPCC is also called Lynch syndrome.

HNPCC is an autosomal dominant disorder with special clinicopathological features[23-27], early onset (average <45ys), high frequency of cancers in proximal colon (60-70 %), excess of synchronous (18.1 %) and metachronous (24.2 %) tumors, development of extracolonic malignancies, excess of mucinous (30-40 %) and poorly differentiated tumors (23-39 %). It is often diagnosed by Amsterdam criteria, but the criteria is too strict for little families with strong genetic basis for CRCs, then sHNPCC criteria will be useful.

Mo[28] had described 10 Chinese HNPCC kindred. Among 10 kindred, patients had a mean age of 44.8ys and showed an excess of multiple CRCs (20.2%), a high frequency of cancers in colon (82.3 %). Zhao[29] got the similar results. In our study, compared with sporadic CRCs, 12 probands of ICG-HNPCC kindred showed special features, such as early onset (P<0.05),

predilection for involvement of colon (P<0.05) and tendency of multiple CRCs (P<0.05). They also had well but not poorly differentiated appearance (proportion of well differentiated cancer, poorly differentiated cancer, mucinous tumors and Dukes' A+B were 54.5 %, 0, 8.3 % and 58.3 % respectively). Perhaps it was due to the small sample of our study or the racial difference.

For the families who do not fulfill Amsterdam criteria but in whom a genetic basis for colorectal cancer is strongly suspected, sHNPCC criteria were used. It was proved that sHNPCC had the similar genetic background with ICG-HNPCC[19]. In our study, 42 probands of sHNPCC kindred had the similar clinicopathological features with ICG-HNPCC, early onset (mean age 47.5ys), predilection for involvement of colon (62 %), tendency of multiple CRCs (14.3 %) and well differentiation appearance.

No obvious difference was found between ICG-HNPCC and sHNPCC in their clinicopathological features (P>0.05), except the mean age (P<0.05). This difference might be due to the limited cases studied. According to phenotype of Chinese ICG-HNPCC and sHNPCC, it indicated that they might have similar genetic background. The criteria for sHNPCC will be helpful for clinical diagnosis and treatment of HNPCC.

Except CRCs, extracolonic tumors were often seen in HNPCC kindred[30-41], such as cancers of ovary, brain, small bowel, urologic system, breast, larynx, stomach, pancreas and biliary system as well as leukemia, lymphoma, soft tissue sarcoma, desoid tumor and cutaneous tumors. Gastric cancer, endometrial cancer, carcinomas of hepatobiliary system were the most common extracolonic malignancies. In our study, gastric cancer, endometrial cancer, carcinomas of hepatobiliary system and urologic system were the four common extracolonic malignancies. Cancers of esophagus, breast, pancreas, leukemia and lymphoma were also seen in Chinese HNPCC kindreds. We also found that extracolonic malignancies were less seen in ICG-HNPCC than those in sHNPCC, perhaps it was due to the limited cases studied.

Our results suggest that both ICG-HNPCC and sHNPCC families in China had the clinicopathological features, early onset, predilection for involvement of colon, tendency of multiple CRCs, extracolonic tumors and well differentiated appearance. They might have the similar genetic background. In recent years, Chinese families are becoming smaller and smaller due to the practising of family planning[42]. So criteria for sHNPCC will become more and more useful in clinical diagnosis of HNPCC. Now in China, establishment of HNPCC registry, genetic counseling and surveillance of high-risk asymptomatic family members are important and necessary. Endoscopic surveillance is recommended if any tumor found in some cases, and prophylactic operation is suggested[43-49].

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