

Original Article

Hereditary nonpolyposis colorectal cancer and familial colorectal cancer in Central part of Iran, Isfahan

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Abstract

BACKGROUND: There is a lack of data on familial aggregation of colorectal cancer (CRC) in Iran. We aimed to determine the frequency of hereditary nonpolyposis colorectal cancer (HNPCC) and familial colorectal cancer (FCC) and to determine the frequency of extracolonic cancers in these families in Isfahan.

METHODS: We reviewed documents of all patients with a pathologically confirmed diagnosis of CRC admitted to Isfahan referral hospitals between 1995 and 2006. We also studied our CRC registry at Poursina Hakim Research Institute from 2003 to 2008. We found HNPCC and FCC families based on the Amsterdam II criteria and interviewed them for family history of CRC and extracolonic tumors. The family history was taken at least up to the second-degree relatives.

RESULTS: During 1996 to 2008, a total of 2580 CRC cases have been diagnosed. We found 14 HNPCC and 53 FCC families. Mean age of CRC at diagnosis was 48.0 ± 14.6 and 49.0 ± 13.9 years in the HNPCC and FCC families, respectively ($p > 0.05$). The total numbers of observed extracolonic tumors were 70 (21.6%; mean age = 53.6 ± 11.0 years) and 157 (13.8%; mean age = 54.8 ± 18.0 years) in HNPCC and FCC families, respectively ($p > 0.05$). CRC was respectively found in 52 and 76 members of the HNPCC and FCC families, revealing the frequency of HNPCC and FCC as 2.0% (52/2580) and 2.9% (76/2580), respectively.

CONCLUSIONS: We found a relative high frequency of HNPCC (2.0%) and FCC (2.9%) among CRC cases in our society and high incidence of extracolonic tumors in their families. Further studies focusing on molecular basis in this field and designing a specific screening and national cancer registry program for HNPCC and FCC families should be conducted.

KEYWORDS: Hereditary Nonpolyposis Colorectal Cancer, Familial Colorectal Cancer, Epidemiology, Iran.

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Colorectal cancer (CRC) is the second most common cause of mortality from cancer in western countries and the fourth in Iran. The incidence (age-adjusted) rate of CRC in Iran has been reported as 6 to 7.9 per 100,000 persons per year.¹ Fifteen to twenty percent of total CRC patients have a positive family history.² CRC undoubtedly has

some well-known hereditary forms among which familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) are the commonest types.³ HNPCC is more common with a frequency ranging from 1% to 6% in different populations. It includes 4.7% of CRC cases in our country.⁴ Genetic studies have shown

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HNPCC to be an autosomal dominant syndrome with a penetrance of 70% to 90% due to mutation in the mismatch repair genes. The main genes involved are MSH2, MLH1, PMS1, PMS2 and MSH6. The frequency and the types of mutations vary in different geographical areas.⁵

The diagnosis of HNPCC is predominantly based on family history of cancer according to the criteria established by the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) known as the Amsterdam criteria.⁶ CRC should be confirmed by pathological examination and FAP should be excluded. In the Amsterdam II criteria, some extracolonic tumors, such as tumors of the endometrium, urothelial and small intestine, were included. Families with CRC who do not meet all the prerequisites for classification as HNPCC are classified as familial colorectal cancer (FCC) cases.⁷

Evidence revealed that individuals with HNPCC and their relatives have higher rates of extracolonic cancers including uterine, ovarian, small bowel, hepatobiliary tract, brain, and stomach cancers. However, there are controversial results and the cancers vary in different geographical areas.^{8,9} Considering the high rate of cancers in HNPCC and FCC families, it is necessary to design specific and prompt screening programs. There is a lack of data on familial aggregation of CRC in Iran and until 2008 (the coverage of this study), there has been just one report of the spectrum of tumors related to HNPCC and FCC in our country.⁴ The aim of the present study was to find the frequency distribution of HNPCC and FCC families and extracolonic cancers in these families in central part of Iran (Isfahan).

Methods

This cross-sectional and case register study was conducted in Isfahan which is a large province in Iran, with a population of almost 4,559,256 in 2007 Census (51.2% males).¹⁰ We reviewed documents of all patients with a pathologically confirmed diagnosis of CRC who had been admitted to Isfahan referral hospit-

als, either for surgery, chemotherapy, radiotherapy, or diagnostic evaluations, between 1995 and 2006. In addition, we reviewed our CRC registry at Poursina Hakim Research Institute which has been registering CRC patients in the province of Isfahan in collaboration with Vice Chancellor of Health of Isfahan University of Medical Sciences, since 2003. The results presented in this report are related to patients' documents until the year 2008. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences and informed consents were obtained from patients or their families participating in the study.

We found HNPCC families based on the Amsterdam II criteria including at least three members in a family having a cancer associated with HNPCC (colorectal, endometrial, small bowel, ureteral, renal, and pelvic cancers) in at least two consecutive generations, and one of these three members being a first-degree relative of the other two and at least one diagnosed before the age of 50 years.⁷ The FCC families were characterized by the presence of at least one individual with CRC whose diagnosis of cancer was under 50 years of age and another first/second degree relative with colonic/extracolonic tumors associated with the HNPCC. Patients with FAP or those with underlying inflammatory bowel disease (IBD) were excluded.

HNPCC and FCC families (patients or their siblings/parents in case the patient was dead or not available) were interviewed and total number of members, number of patients with CRC, number of patients with extracolonic tumors, primary sites of the extracolonic tumors, and ages at diagnosis were evaluated. The family history was taken at least up to second degree relatives. Diagnosis of extracolonic tumors was based on history taking from the family members. Data was analyzed by SPSS for Windows (version 16.0) using chi-square and t-tests.

Results

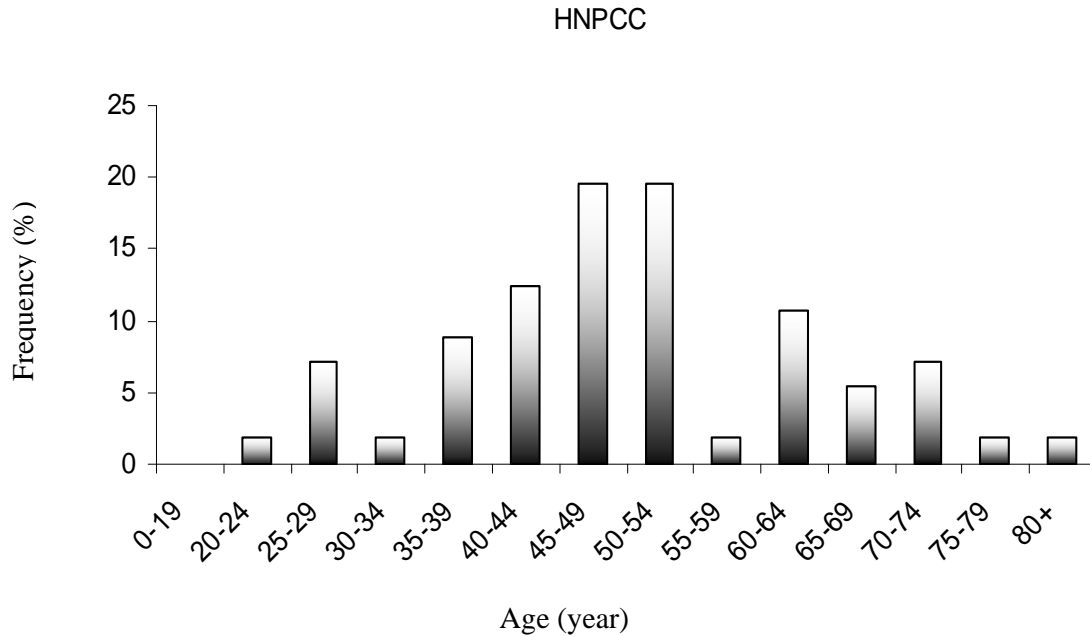
During 1996 to 2008, a total of 2580 CRC cases have been diagnosed in Isfahan. Among these

cases, there were 67 families including 14 HNPCC and 53 FCC families. The total numbers of individuals belonging to HNPCC and FCC families were 324 and 1132 members, respectively (755 males and 701 females). Figure 1 displays the percentage of diagnosed CRC in each age group. The most common age of can-

cer occurrence ranged from 40 to 55 years. In HNPCC families, the mean age of cancer occurrence with colon origin was 48.0 ± 14.6 years (range: 23-90 years) and for FCC families it was 49.0 ± 13.9 years (range 26-84 years) ($p = 0.726$).

The total numbers of observed tumors were

A.



B.

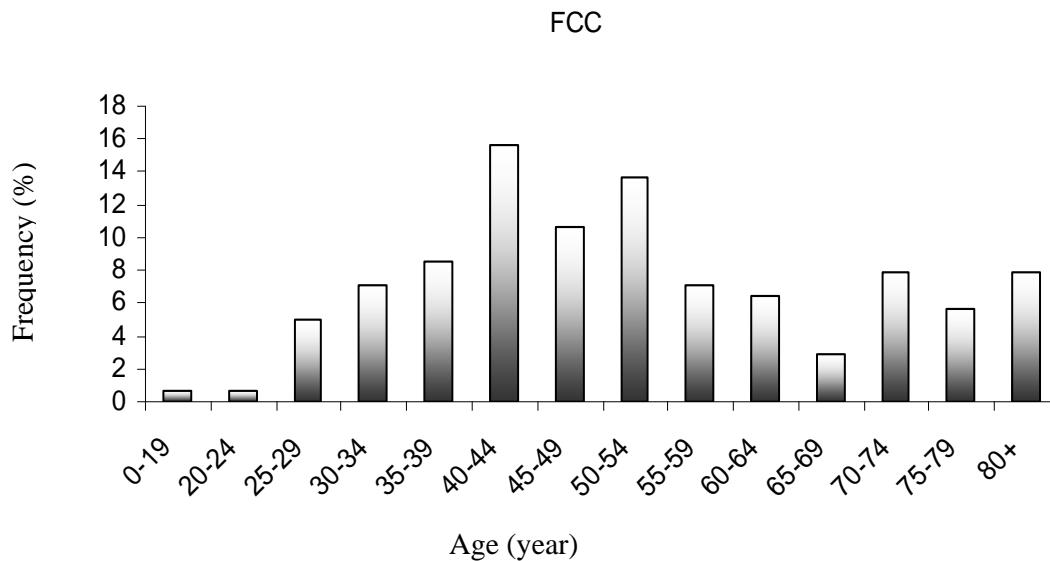


Figure 1 (A, B). Age distribution of CRC occurrence in HNPCC and FCC cases

70 (21.6%) and 157 (13.8%) in the HNPCC and FCC families, respectively. In addition, CRC was found in 52 and 76 cases of the HNPCC and FCC families, respectively. The prevalence of HNPCC and FCC was therefore calculated as 2.0% (52/2580) and 2.9% (76/2580), respectively. For extracolonic involvements, the mean age of cancer occurrence was 53.6 ± 11.0 years (range: 36-70 years) in HNPCC families and 54.8 ± 18.0 years (range: 17-97 years) for FCC families ($p = 0.801$). In both groups, cancer with colon origin was the most observed tumor. In fact, it constituted 52 (74.2%) and 76 (48.4%) patients in the HNPCC and FCC families, respectively. Among extracolonic cancers in FCC families, gastric cancer was the most frequent (12.1%) while stomach and uterine were the most frequent sites for extracolonic cancers (each one 7.1%) among HNPCC families. As Table 1 shows, multiple tumors were present in 7 patients, one patient had 3 tumors and 6 patients had 2.

Discussion

The aim of the present study was to determine the frequency of HNPCC and FCC, as well as the frequency of extracolonic cancers in the family members in central part of Iran (Isfahan). With the study of 2580 CRC cases, we found the frequency of HNPCC and FCC as 2.0% and 2.9%, respectively. Little data is available on epidemiological characteristics of patients with HNPCC in Iran. The first study in this regard has been reported by Mahdavi-nia et al. from Tehran. These investigators evaluated 449 CRC patients with pathologically confirmed CRC and found HNPCC in 21 (4.7%) probands. They suggested that family history of CRC was more frequently reported by early-onset (≤ 45 years) than by late-onset (> 45 years) patients (29.5% vs. 12.8%). They also found family history of cancer in 53.6% of early-onset and 42.7% of late-onset CRC patients with breast (9.8% and 5%), stomach (8% and 5%) and lung cancers (4.5% and 7%)

Table 1. Tumor's spectrum in HNPCC and FCC family members

Tumor site	HNPCC			FCC		
	All n = 324	Male n = 172	Female n = 152	All n = 1132	Male n = 579	Female n = 553
Colon	52 (16.0%)	24 (13.9%)	28 (18.4%)	76 (6.7%)	43 (7.4%)	33 (5.9%)
Stomach	5 (1.5%)	2 (1.1%)	3 (1.9%)	19 (1.6%)	7 (1.2%)	12 (2.1%)
Central nervous system	-	-	-	11 (0.9%)	5 (0.8%)	6 (1.0%)
Uterine	5 (1.5%)	-	5 (3.2%)	12 (1.0%)	-	12 (2.1%)
Hematopoietic	2 (0.6%)	2 (1.1%)	-	2 (0.1%)	1 (0.17%)	1 (0.18%)
Hepatobiliary	1 (0.3%)	-	1 (0.6%)	7 (0.6%)	5 (0.86%)	2 (0.36%)
Lung	-	-	-	7 (0.6%)	5 (0.86%)	2 (0.36%)
Breast	1 (0.3%)	-	1 (0.6%)	7 (0.6%)	-	7 (1.2%)
Larynx	-	-	-	3 (0.2%)	3 (0.51%)	-
Urothelial	1 (0.3%)	1 (0.5%)	-	3 (0.2%)	3 (0.51%)	-
Prostate	2 (0.6%)	2 (1.1%)	-	5 (0.4%)	5 (0.86%)	-
Renal	-	-	-	2 (0.1%)	2 (0.26%)	-
Ovarian	1 (0.3%)	-	1 (0.6%)	1 (0.08%)	-	1 (0.18%)
Esophagus	-	-	-	1 (0.08%)	-	1 (0.18%)
Small bowel	-	-	-	1 (0.08%)	1 (0.17%)	-
Total	70 (21.6%)	31 (17.3%)	39 (25.6%)	157 (13.8%)	80 (13.8%)	77 (13.9%)

to be the commonest extracolonic cancers among family members of patients with early-onset and late-onset CRC, respectively.⁴ Another recent report from northern Iran which included 293 CRC cases found HNPCC in 10.9% and 2.7% of the cases based on either Amsterdam I or II criteria. HNPCC cases in that study included 25.5% of those aged < 45 years and 3.6% of those aged ≥ 45 years.¹¹ In our study, we evaluated nearly all families with HNPCC and families with dominant hereditary predisposition in the province of Isfahan. The extracolonic involvements were analyzed in two groups of HNPCC and FCC patients. The age of cancer occurrence in HNPCC and FCC families was within the range described in other studies.^{9,12,13} We found that in HNPCC families, CRC represents more than 70% of all tumors that is much higher than 16.9% reported by the other study in Iran,⁴ and 50% reported from other countries.¹⁴ Another study from Iran which included 1138 cases of CRC from 2000 to 2007 reported family history of cancer in 35.1% and CRC history in 4.3% of the CRC cases' relatives. However, it did not report data on HNPCC or FCC.¹⁵ The variation in reported frequencies of HNPCC and FAP could be due to different genetic backgrounds,¹⁶ and also to differences in the ability of diagnoses of CRC among family members.¹¹ While in other studies from Iran subjects were from a limited geographic region, our study included a large province and the largest number of CRC cases from Iran.

We also found a high frequency of uterine cancer in our population which was expected as a result of its previously demonstrated relation with HNPCC. Moreover, a high incidence of gastric cancer was revealed in our study population although there has not been a definite finding in previous studies. Despite the fact that studies in western countries did not show this incidence to be higher than normal population,¹⁴ Asian studies confirmed it.^{17,18} Another cancer which is still a controversy to consider as a part of HNPCC tumor spectrum is the breast cancer.^{8,19,20} It did not show a high

incidence in comparison to other extracolonic tumors in our study. A number of recent surveys which suggest including this type of cancer in HNPCC tumor spectrum are mainly based on molecular studies.^{19,20} However, it is important to know that the high incidence of cancer among the families is more essential than presence of MLH1 mutation because this mutation is in relation with other types of cancers which are not associated to HNPCC.²¹ Some other studies found higher incidences of breast cancer maybe due to closer screening.¹⁴ Another study on HNPCC in Iran also found family history of breast cancer in 6.9% of CRC patients.⁴ Nevertheless, we believe that there is still not enough evidence to include breast cancer as a part of HNPCC tumor spectrum. The occurrence of rare tumors (a part of the HNPCC spectrum), such as renal, pelvic and small bowel tumors, in the FCC families suggests that some members of these families have a genetic predisposition similar to HNPCC but do not meet the clinical prerequisites of HNPCC syndrome. Therefore, these families should be included in screening programs performed for HNPCC families.

There were some limitations to this study. Like every other cancer registry, our cancer registry in the province of Isfahan did not include all cases of CRC. However, to the best of our knowledge, this study included the largest number of CRC cases report from Iran. It thus accessed relatively more reliable data. Like the other study in Iran by Malekzadeh et al,¹ we used the Amsterdam II criteria to find HNPCC and FCC cases. Since Amsterdam II criteria have a relatively low sensitivity, the Bethesda guidelines were developed and later revised in 2004 to help identify a larger proportion of families with HNPCC.²² Bethesda guidelines, however, have low specificity, i.e. 80% or more of patients who meet the Bethesda guidelines will not have Lynch syndrome. Indeed both of these guidelines have limitations and the results of our study need to be confirmed by genetic studies. In addition, another limitation to this study was that history taking was used as

the basis of information regarding cancer in the family. Although family members, in our society, are usually aware of serious diseases such as cancer in their relatives, a future national cancer registry program could provide more reliable information regarding cancer history in the families.

Conclusion

Based on the results of this study, clinical diagnosis of HNPCC and FCC was respectively observed in 2.0% and 2.9% of the studied cases in central Iran (Isfahan). Along with other studies from our society, these results show that hereditary and familial forms of CRC are important types of cancer and need appropriate screening strategies to decrease the burden of the disease. High incidence of extracolonic tu-

mors in HNPCC and FCC families in our society indicates that a detailed family history is mandatory when evaluating patients with CRC. The results of this study need to be confirmed by further studies focusing on molecular basis in this field. Moreover, a specific screening program for HNPCC and FCC families and a national registry program should be designed.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

MHE generated the idea and designed the study. ZKR and AMF also participated in study designing. All authors participated in data gathering, data analysis, and writing the draft of the manuscript and finally approved the final report.

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