Familial Aspects of Colorectal Cancers in Southern littoral of Caspian Sea

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Abstract

Background: About 50,000 new cancer cases occur annually in Iran, of which gastrointestinal (GI) cancers are the most common. Colorectal cancers (CRC) account for the third and fourth most prevalent cancers amongst Iranian men and women, respectively. Since CRC has some well-known hereditary forms with differences in their prevalence according to regional heterogeneity, we designed a study to assess familial aspects of this cancer in subjects who reside in Mazandaran Province, Iran.

Methods: We interviewed all CRC patients who attended a private GI clinic during 1999 – 2007, with histologically confirmed diagnoses of colorectal adenocarcinoma, about their family histories of CRC and age at diagnosis. Pedigrees were drawn up to second-degree relatives.

Results: A total of 293 CRC cases were enrolled in the study, of which 152 were male and 141 were female. The mean age of patients was 52.6±15.2 years. Of these, 98 patients (33.5%) were under the age of 45. A total of 66 cases (22.5%) had familial histories of CRC, being significantly more prevalent in younger subjects (11.2% vs. 44.9%, P<0.0001). Thirty-two patients (10.9%) fulfilled the criteria for hereditary non-polyposis colon cancer. In addition, right-sided colon cancers were more prevalent in those with positive familial histories (P=0.05).

Conclusion: Due to the frequency of early-onset CRC and familial syndromes, a more intense screening protocol for early detection of CRC should be developed for this population.

Keywords: colorectal neoplasms, epidemiology, hereditary nonpolyposis, Iran

Introduction

Colorectal cancers (CRC) are among the most common cancers worldwide. Nevertheless the prevalence of CRC in different countries is highly variable and on occasion a greater than 25 fold difference is seen. According to reports from the International Agency of Research for Cancers (IARC), every year about 50,000 new cancer cases occur in Iran with gastrointestinal (GI) cancers being the most common, constituting almost 38% of all cancers. In Iran, CRC is the fourth most common cancer with a rate of 6 – 7.9 per 100,000 population per year. Colorectal cancer (CRC) is the third and fourth most prevalent cancer among Iranian men and women, respectively. The early-onset form of CRC (younger than 40 years of age at the time of diagnosis) accounts for almost one fifth of all CRC cases. This proportion is significantly lower in high risk countries, ranging from 2% to 8%

CRC has some well-known hereditary forms such as hereditary non-polyposis colorectal cancer (HNPCC, also known as Lynch syndrome) and familial adenomatous polyposis (FAP). HNPCC is an autosomal dominant disorder constituting 0.3% – 5% of all cases of colorectal cancer. FAP, also autosomal dominant, is a much less frequent condition, leading to less than 1% of all cancers of the large bowel.

The least well understood pattern is known as “familial” CRC, accounting for up to 25% of cases. These patients have a family history of CRC, but not consistent with HNPCC or FAP. They are assumed to be at increased risk of developing CRC, although not as high as the two previously mentioned inherited syndromes.

The genetic abnormalities underlying familial CRC are still to be determined.

A report from Iran studying the family clustering of CRC concluded that about 4.7% of cases can be classified as HNPCC. The hereditary influence on development of CRC has been shown to vary among different geographic regions and races. There has been no report on the familial aggregation of CRC in the northern part of Iran. Mazandaran is a province situated in northern Iran and the southern littoral of the Caspian Sea which is mostly populated by Guilan people. We aimed to study the pattern of familial clustering of CRC in this area.

Patients and Methods

All CRC patients who attended a private GI clinic during 1999 – 2007 were enrolled. Patients were included only if the diagnosis of adenocarcinoma was confirmed by histology. A questionnaire was completed by interviewing each subject. The questionnaire included family history of cancers, the type of cancer and age at diagnosis. Pedigrees were drawn up to second-degree relatives and confirmed by interviewing at least one other family member.

The diagnosis of HNPCC was made in those with positive familial histories according to either Amsterdam I or II criteria. FAP was also clinically diagnosed if there were more than 100 colorectal adenomatous polyps. Patients belonging to families which did not fulfill Amsterdam criteria but with at least two first- or second-degree relatives with CRC were classified as hereditary CRC (HCR). Patients with only one first-degree relative affected with CRC were referred to as “the one first-degree relatives” group.

Cases were classified as early-onset CRC if diagnosed before 45 years of age. Those diagnosed later were classified as late-onset. Chi-square and Student’s t test were used to evaluate significance. A P value of less than 0.05 was assumed to be significant. Data was analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).
Results

In this study, we enrolled 293 patients with histologically proven CRC. Of these, 152 were male and 141 female. The average number of people in each pedigree was 63. The male to female ratio was 1.07:1.00. Mean age was 52.6±15.2 years (range: 13 to 83 years).

The tumor location is listed separately for early-onset and late-onset cancers in Table 1. We observed no significant difference in tumor localization between the two groups.

The frequency of hereditary CRC among the two groups is given in Table 2. Ninety-eight patients (33.5%) were early-onset (diagnosed at younger than 45 years) and 195 (66.5%) were late-onset. A total of 66 patients (22.5%) had familial histories of CRC, being significantly more prevalent in the early-onset group (11.2% vs. 44.9%, P <0.0001). There were 32 patients (10.9%) classified as HNPCC (30 with Amsterdam I and 2 with Amsterdam II criteria). There were three cases of breast cancer, two gastric cancers, one endometrial cancer, one small bowel cancer, one pancreatic cancer and one case of laryngeal cancer among four of the HNPCC families (Figure 1). Twenty-six patients had positive familial histories of CRC in only one of their first-degree relatives. Eight cases of FAP were also discovered (2.7%). There were no patients classified in the HCRC group (Table 2).

Sites of tumor involvement differed significantly between those with or without familial histories of CRC (Table 3). There was a higher prevalence of right-sided colon cancers in those with positive familial histories of CRC. Those without a familial history showed a higher prevalence of rectal cancer (P<0.05). Rectal cancers were significantly less prevalent among young patients with familial histories of CRC, compared with those with no family history (11.4% vs. 52.7%, P<0.0002).

Discussion

We performed this study on CRC patients who resided in the southern littoral of the Caspian Sea. The mean age of patients was 52.5 years, being lower than reports from Western countries and similar to China.21–23 In a study that compared 690 CRC patients in Florida (USA) and 870 patients in China, the mean ages at diagnosis were 69 years and 48 years, respectively.21

In our study, 33.4% of patients developed the disease before 45 years of age, which was similar to previous reports from Iran,24 but significantly higher than some other reports. In a study performed by 21 experts from nine European countries, only 5% had early-onset CRC (<45 years).25 This higher frequency of early-onset CRC may be a reflection of the fact that Iran’s population is relatively young or could indicate recent lifestyle changes among younger subjects. A possible genetic predisposition to CRC might also be involved.26

A total of 22.5% of our patients had positive familial histories of CRC (FAP excluded). In a prospective multicenter study, Mecklin et al. reported the frequency of HNPCC to be 0.7% –
In studies from Italy, China, Denmark, southern California, and Sweden, the prevalence of HNPCC was reported to be 0.9% to 4.5%. A study from Egypt reported a relatively higher rate of 7.2%. Also in the previous report of familial CRC in Iran (Tehran), 4.7% of patients had HNPCC.

According to other studies from western countries, 1% of the colon cancers were FAP. However, in our study, 10.9% of patients had HNPCC and 2.7% FAP.

The variation in reported frequencies of HNPCC and FAP could reflect different genetic backgrounds but might also be due to differences in the ability of confirming the diagnoses of CRC among family members. In our study, subjects were from a limited geographic region and visited frequently. Thus it was more likely that any malignancies in family members were accurately reported.

Both HNPCC and FAP have high penetrance in relatives. The remaining subjects, who accounted for the majority of familial CRC, had a relatively low penetrance. In our study, 13.7% of patients with positive familial history had syndromes with high penetrance (HNPCC and FAP); only 8.9% were of low penetrance and had only one first-degree relative with CRC. There were no HCRC patients. In a Swedish study, the proportion of patients belonging to HCRC families was estimated to be 1.9%.

We observed that 25.5% of early-onset CRCs had HNPCC as compared to only 3.6% of late-onsets. This data is similar to Makela’s report about the inverse relationship between the prevalence of hereditary CRCs (including HNPCC) and age. Thus the higher prevalence of hereditary CRC syndromes (which have high penetrance) may account for the higher prevalence of CRC observed in our subjects.

The mean age at diagnosis for HNPCC patients has been reported to be between 52 and 60 years. Hampel et al. also reported the age of all Finnish Lynch syndrome families to be 55 – 60 years, while the average age of onset in sporadic CRC was about 65 years. In a Danish study, Katbaile et al. found the frequency of HNPCC to be 14.3% among patients younger than 50 years of age.

In our study, 3.5% of patients over 45 years fulfilled Amsterdam I criteria for HNPCC. Therefore, detailed family history is mandatory even in older patients.

Right-sided cancers accounted for 38.5% of cases in our study. It has been suggested that family history of CRC is related to tumor localization. In our study, right-sided colon cancers were more prevalent in subjects with positive familial histories (57% vs. 34%) with no difference between those under or above 45 years. In a study performed in China, a clinical characteristic of HNPCC was that the cancer was more likely to involve the proximal colon. Some studies also proposed a stronger familial component for proximal than distal colon cancer, while this association was not observed in other studies.

In a previous study from Iran, right-sided tumors occurred more frequently in patients with positive family histories of CRC compared to those with no history (36.9% vs. 17.7%). This pattern was almost the same in patients over and under 45 years of age. Furthermore, rectal cancer was less frequent among younger probands with positive CRC family histories.

Our study also confirms the lower prevalence of rectal cancer among those with familial histories of CRC. This is also in agreement with the previous report of Olsson and Lindblom, in which the frequency of sigmoid cancer was shown to be lower among familial cases as compared to sporadic CRC. If follows that hereditary factors are more involved in right-sided cancers and environmental factors in distal CRC.

In conclusion, due to the frequency of early-onset CRC and fa-
milial syndromes, and the high prevalence of right-sided colon cancers in this population, an intense screening protocol is required. Further research is required in order to define a protocol involving a combination of genetic and endoscopic studies for screening this and similar populations.

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References