RESEARCH COMMUNICATION

Comparison of Survival between Patients with Hereditary Non Polyposis Colorectal Cancer (HNPCC) and Sporadic Colorectal Cancer

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Abstract

Background: Hereditary non polyposis colorectal cancer (HNPCC) appears to have a better prognosis than sporadic cancer. In the present study we evaluated the clinical outcomes of HNPCC patients with their sporadic colorectal cancer counterparts arising from the general population recorded in a population-based cancer registry in Iran. Patients and methods: The population studied consisted of 121 individuals including 61 patients with sporadic colorectal cancer and 60 with HNPCC who were followed-up between 2003 and 2008 in Taleghani Hospital Tehran. The subjects with HNPCC were screened according to Amsterdam criteria II and Bethesda Guidelines. Subjects with sporadic cancer had no familial history of colorectal cancer. Observed survival was estimated using the Kaplan-Meier method and compared with the log rank test. Multivariate analysis was performed using Cox' regression analysis. Results: In the HNPCC group, 85.0% showed tumors in the colon, vs. 68.9% in the sporadic cancer group. The 5-year survival was 82.5% in the HNPCC study group compared with only 56.4% in the sporadic colorectal cancer group (P=0.044). The age distribution at diagnosis of sporadic patients was significantly higher than HNPCC patients (mean 50.1 years vs 44.3 years P=0.008). The hazard ratio for sporadic cases was 2.93 (95% CI 1.06-8.11) compared with the HNPCC group (P=0.038). Conclusion: Our findings corroborate the results of previous studies which showed overall survival of colorectal cancer in patients with HNPCC is better than with sporadic CRC patients.

Key Words: Survival - HNPCC - sporadic colorectal cancer

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death, after lung cancer, in the USA. About 148,300 new cases are diagnosed each year, and 56,600 Americans die annually from this disease (Dionigi et al., 2007). The incidence of CRC is lower in Iran than in Western countries, being the fifth and third most common cancer in men and women. However, its incidence in Iran has increased recently. Thus, the importance of CRC as a public health problem is increasing in our country (Azadeh et al, ; Moghimi-Dehkordi B et al., 2008). The great majority (80%) of patients with colorectal cancer have sporadic disease with no evidence of having inherited the disorder. In the remaining 20% a potentially definable genetic component exists (Giardiello et al., 1995).

In 1996 Dr. Henry Lynch and colleagues described the familial aggregation of colorectal cancer with stomach and endometrial tumours and coined the name Cancer Family Syndrome (Nishisho et al., 1991). Later investigators termed this constellation the Lynch Syndrome. More recently, this condition has been designated HNPCC. Unlike Familial Adenoma Polyposis (FAP), in which colorectal cancer arises as a result of polyposis (4100 adenomas), colorectal cancer usually arises from a single colorectal lesion in HNPCC - hence the name (Lynch et al., 1993; Rodriquez-Bigas et al., 1997; Vasen et al.,1998). HNPCC accounts for about 1-3% (range 1-13%) of all colorectal cancers (Lynch et al., 1996; Vasen et al., 1996). This syndrome is an autosomal dominant condition caused by a mutation of one of the DNA mismatch repair genes.

It is transmitted from one generation to another in accordance with an autosomal dominant model (Vasen et al., 1991). HNPCC or Lynch syndrome is characterized by early age of cancer onset (mean age 45 years) proximal predominance of colorectal cancer (CRC) (Vasen, 1999).

HNPCC is a distinct clinicopathological entity nevertheless, examination of familial pedigrees points to an autosomal dominant pattern of inheritance, with the syndrome being distinguished from sporadic colorectal cancer by the young age at onset of malignancy. Colorectal

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cancer (CRC) in HNPCC more often have a better prognosis than in sporadic colorectal carcinoma (Aarnio et al .,1995; Watson et al.,1998; Barnetson et al., 2006; Elsakov et al., 2006; Vasen et al., 2007), but it has been unclear whether this could be due to difference in tumor location or to a more favorable prognosis of cancer in HNPCC.

The Amsterdam criteria (AC) were developed by the International Collaborative Group on HNPCC in 1991 From 1993, AC was used to select patients for mutation analysis, although criticisms included the exclusion of extracolonic tumours within the criteria and the relatively low sensitivity for germline MMR mutations. These criteria were broadened in 1999 to include extracolonic cancers, the Amsterdam II criteria (AC II). In the screening procedure of the HNPCC patients we consider AC II criteria. (Barrow et al., 2008; Valle et al., 2007).

In the present study we evaluated whether survival of HNPCC-affected cases differed from the of non-HNPCC colorectal cancer patients.

Materials and Methods

We analyzed 121 patients belonging to different families, including 61 HNPCC patients with histological verified colorectal carcinoma and a consecutive series of 60 sporadic CRC patients with no familial predisposition, observed and treated at Taleghani hospital Tehran during the period 2003-2008.

The diagnosis of HNPCC is dependent upon family history and conforms to the Amsterdam criteria II and Bethesda Guidelines for hereditary non-polyposis colorectal cancer. For HNPCC patients, the follow-up procedures and adjuvant-treatment protocols were the same as for patients with sporadic colorectal cancer. Taking into consideration the increased risk of extracolonic manifestations, hereditary-colorectal cancer patients were also subjected to periodical instrumental examinations tailored to the different spectrum of the disease.

The 5-year survival curves were calculated using Kaplan-Meier methodology and log rank test was used to compare survival rates. Multivariate analysis was carried out using the Cox proportional hazard model (Kleinbaum and Kupper, 1978).Factors investigated as possible predictors of survival included sex, age at diagnosis, tumor differentiation and tumor location.

The index date for survival calculation was defined as the date of diagnostic confirmation for colorectal cancer. Clinical follow-up procedures provided information on the vital status of participants. Death certificates were obtained for all participants who died. Survival time was calculated in months. All statistical tests were two-tailed and P values of less than 0.05 were considered significant and the data were analyzed by using SPSS (version13.0) software.

Results

The mean age patient at diagnosis was 47.3 ± 12.2 (range 22 - 78) years. The mean age of patients with

Table 1. Demographic and Clinical Characteristics and Effects on Survival (Log-rank test)

Prognostic factor	Category	Number (%)	P value
Sex	Male	60 (49.6)	0.431
	Female	61 (50.4)	
Age at diagnosis	≤50	82 (67.8)	0.846
	>50	39 (32.2)	
Grade of tumor	Poorly Diff	21 (17.3)	0.164
	Moderately Diff	37 (30.6)	
	Well Diff	63 (52.1)	
Tumor site	Colon	93 (76.9)	0.845
	Rectal	28 (23.1)	
Case type	Sporadic CRC	61 (50.4)	0.044
	HNPCC	60 (49.6)	

Diff, Differentiated

Table 2. Variables as Prognostic Factors in Cox' Proportional Hazard Model[a]

Prognostic factors	Hazard rate	P value
Grade of tumor		
Poorly Differentiated	3.04 (0.94-9.90)	0.064
Moderately Differentiated	1.46 (0.469-4.57)	0.511
Well Differentiated	1	--
Case type		
Sporadic CRC	2.93 (1.06-8.11)	0.038
HNPCC	1	--

[a]Values given in parentheses are 95% confidence intervals

HNPCC was 44.3 ± 10.7 years compared with 53.6 ± 14.4 years in patients with sporadic lesions (P = 0.008).

In the HNPCC group 51 patients (85%) had colon tumors and 9 (15%) had rectal cancer. In comparison in sporadic colorectal cancer group we could detect 42 (68.9%) patients with colon tumors and 19 (31.1%) rectal cancer (P = 0.035). According to the univariate analysis, there was an interesting difference in survival between HNPCC and sporadic patients (Figure 1). The factors were considered as follow: sex, age at diagnosis more and less 50 year, grade of tumor and tumor site had no differences in subgroups survival rate (Table 1).

The variables that had a P value under 0.25 in univariate method were entered into the Cox proportional hazard model (Kleinbaum and Kupper, 1978). Our finding

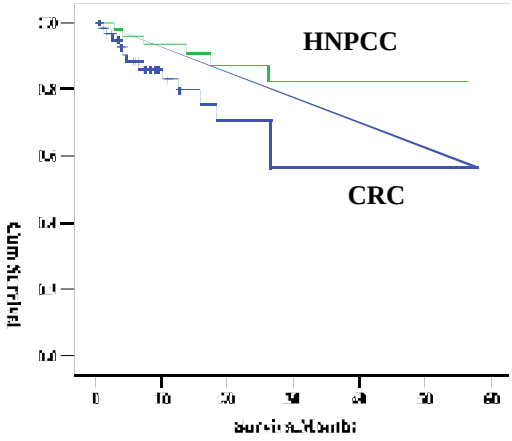

Figure 1 Overall Survival Function of Sporadic Colorectal Cancer (CRC) and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) According to the Kaplan–Meier Method

revealed that there was difference between sporadic and HNPCC hazard ratio(P = 0.038) but not for grade of tumor (Table 2).

Discussion

CRC is an important public health problem. There are nearly one million new cases of CRC diagnosed worldwide each year and half a million deaths caused by CRC. The incidence of CRC showed a remarkable increase over the three decades in Iran (Hosseini, 2004). Different survival rates of patients with colorectal cancer have been investigated in several studies (Barnetson et al., 2006; Myrhoj et al., 1997; Percesepe et al., 1997; Watson et al., 1998). The results are sometimes conflicting because of the different pathogenetic mechanism of tumorigenesis between sporadic and familiar types of colorectal syndrome (HNPCC in particular). These differences are probably due to different clinical pathological characteristics of neoplasia and genetic alterations.

Analysis of our data showed that overall 5-year survival of HNPCC patients (82.5%) was higher than sporadic cases (56.4%) (P =0.044). Our findings corroborate results of two previous studies. One Finnish study showed that (Sankila et al., 1996) the overall 5-year cumulative relative survival rate was 65% for patients with HNPCC and 44% for patients with sporadic colorectal cancer and consequentially they described a founder effect. Moreover, a recent Lithuanian study reported an improved prognosis for HNPCC patients compared to sporadic colorectal cancer patients (Elsakov et al., 2006) nevertheless, an Italian study could not confirm this result because this investigation revealed that colorectal cancer-specific 5-year survival rates were 55.2 and 42.5% for HNPCC and non HNPCC, respectively (Percesepe et al., 1997). The tumor location is considered as an important prognostic factor for survival. In our study tumor location is significantly more represented in colon. This different anatomical distribution between colon and rectal confirmed in other literatures. (Frattini et al., 2004; Young et al., 2001).

Grade of tumor, as expected, was a highly superior prognostic discriminator in both univariate and multivariate studies. Our results revealed that the grade of tumor had no influence on patient's survival. This finding is compatible with data from other studies (Díaz-Plasencia et al., 1996). In some studies, grade of tumor had influence on survival (Cusack et al., 1996; Takahashi et al., 2000). Multivariate analysis with Cox proportional hazard model showed that type was an independent prognostic factor for patients with CRC. Patients with sporadic CRC had a risk of death about threefold to those with HNPCC. This finding is compatible with out come from another study in Italy, showed twofold (Aarnio et al., 1995).

In conclusion, although our results showed that survival rate in HNPCC patients is higher than sporadic individuals, it is supposed that maybe this difference is rising from a concern about CRC in HNPCC patients regarding their family history. So they refer to a physician sooner than the other group and consequently their diseases are diagnosed earlier.

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