

RESEARCH COMMUNICATION

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

Mahdi Montazer Haghighi*, Mohsen Vahedi, Seyed Reza Mohebbi, Mohamad Amin Pourhoseingholi, Seyed Reza Fatemi, Mohammad Reza Zali

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 in comparison 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 patients 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. All those with sporadic cancer had no familial history of colorectal cancer. Observed survival was estimated using the Kaplan-Meier method and compared with log rank test. Multivariate analysis was performed using the 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 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 for sporadic CRC patients.

Key Words: Survival - HNPCC - sporadic colorectal cancer - comparison

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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., 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 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 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 (multiple 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. HNPCC or Lynch syndrome is characterized by early age of cancer onset (mean age 45 years) proximal predominance of 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 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. (Valle et al., 2007; Barrow et al., 2008)

In the present study we evaluated whether survival of HNPCC-affected cases differed from that 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 CRC. 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. 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 (version 13.0) software.

Results

The mean age patient at diagnosis was 47.3 ± 12.2 (range 22 - 78) years. The mean age of patients with HNPCC was 44.3 ± 10.7 years compared with 53.6 ± 14.4 years in patients with sporadic ($P = 0.008$).

In the HNPCC group 51 patients (85%) had colon tumors and 9 (15%) had rectal cancer. In comparison in

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

Prognostic factors		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)	
Cancer type	Sporadic CRC	61 (50.4)	0.044
	HNPCC	60 (49.6)	

Table 2. Variables as Prognostic Factors in the Cox Proportional Hazard Method^a

Prognostic factors	Hazard rate	P value
Grade of tumor		
Poorly Differentiated	3.04 (0.94-9.90)	0.064
Moderately Differentiated	1.46 (0.47-4.57)	0.511
Well Differentiated	1	--
Colorectal cancer		
Sporadic CRC	2.93 (1.06-8.11)	0.038
HNPCC	1	--

^aValues given in parentheses are 95% confidence intervals

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 revealed that there was difference between sporadic and HNPCC hazard ratios ($P = 0.038$) but not for grade of

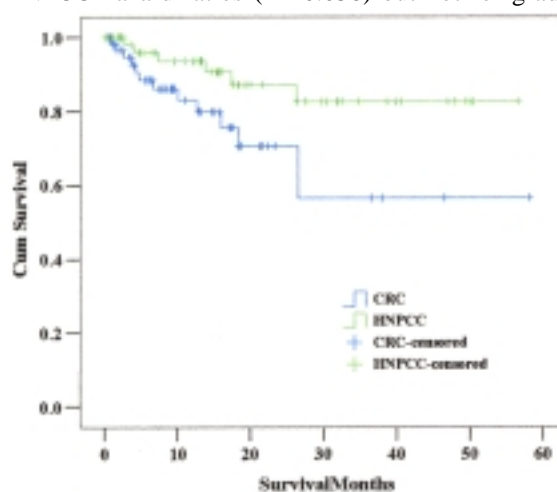


Figure 1. Overall Survival Function of Sporadic Colorectal Cancer (CRC) and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) According to the Kaplan–Meier Method

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 (Myrhoj et al., 1997; Percesepe et al., 1997; Watson et al., 1998; Barnetson et al., 2006). 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. (Young et al., 2001; Frattini et al., 2004).

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 those with HNPCC. This finding is compatible with out come from another study in Italy, showing a twofold difference (Aarnio et al., 1995).

In conclusion, although our results showed that the survival rate in HNPCC patients is higher than in sporadic cases, it is supposed that this difference arises from a concern about CRC because of their family history. So they refer to a physician sooner than the other group, and consequently their disease status may be diagnosed somewhat earlier.

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