RESEARCH ARTICLE

Mortality Determinants in Colorectal Cancer Patients at Different Grades: a Prospective, Cohort Study in Iran

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Abstract

Background: Colorectal cancer (CRC) is an important cause of mortality and morbidity in many communities worldwide. This population based study was conducted to assess determinants of colorectal mortality in Iranian patients. Materials and Methods: A cohort of 1,127 cases of confirmed colorectal cancer registered in a population based registry covering 10 referral hospital in Tehran, Iran, were followed for five years. Information about tumor characteristics, smoking status and family history were collected at base line and survival status were followed every six months by contacting patient or next of kin (if patients died during the follow-up). The cause of death for each case was validated by verbal autopsy and referring to patient medical records at the time of death. The data were analyzed by Stata software using univariate and multivariate analysis (Cox regression). In building the model a p value of less than 5% was considered as significant. Results: The age at diagnosis was 53.5±14 years. Sixty one percent were male. Colorectal mortality among the patients was 96.9 person-years among men and 83 person-years among women. Seventy five percent of patients lived for 2.72 years, 50% for 5.83, and 25% for 13 years after the diagnosis of colorectal cancer. The age at diagnosis was significantly different between men and women (p<0.03). Higher tumor grade predicted higher death rate; the adjusted hazard ratios were 1.79 (95%CI, 0.88-3.61), 2.16 (95%CI, 1.07-4.37), and 3.1 (95%CI, 1.51-6.34) for grades II, III, and IV respectively when they were compared with grade I as reference. Ethnicity, marital status, family history of cancer, and smoking were related to survival with different degrees of magnitude. Conclusions: Among many factors related to survival among the colorectal patients, tumor grade and smoking showed the highest magnitudes of association.

Keywords: Colorectal cancer - mortality - survival - determinant factors - Iran

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Introduction

Colon/rectum (colorectal) cancer (CRC) is a leading cause of mortality worldwide. This cancer is the third prevalent cancer leading to death in western countries (Merrill et al., 2013). The incidence varies in different communities and is declining in the United States and Europe (Jackson et al., 2006; Zheng et al., 2013) and increasing in Asian countries (Sung et al., 2005). In 2008, 608700 new cases of CRC were diagnosed and 1.2 million death was reported (Choe et al., 2005; Merrill et al., 2013). The age adjusted incidence of colorectal cancer is reported to be 9 cases per 100000 among women and 11 cases among 100000 men in Iran (Mohagheghi et al., 2009). Ethnic or racial disparity has been noted between black and white as well as native and non-natives in United States, New Zealand, and Australia (Ward et al., 2004; Jeffreys et al., 2005; Albano et al., 2007; Hill et al., 2010; Zheng et al., 2013). The survival rate of CRC is lower in developing countries than developed countries. In developing countries, diagnosis is made more in later stages of the cancer and there is a limited access to quality diagnostic and therapeutic services (Jemal et al., 2011). Although the mortalities due to CRC are decreasing in the United States, there are ethnic and racial disparities in its outcome. Ethnic minorities are less willing to screen for CRC (Perencevich et al., 2013). Socioeconomic status (SES) is inversely correlated with increased risk of CRC. The risk of CRC is higher by 30% in low SES than high SES (Doubeni et al., 2012). The CRC is rapidly rising in countries adapting western lifestyle characterized with higher meat and fat consumption and lower physical activities (Ponz de Leon et al., 2004). The incidence of CRC is more frequently observed in the individuals over 55 years. Access to diagnostic and therapeutic services play very important role in ethnic disparity seen in CRC burden (Hill et al., 2010). During the period of 1998-2001, the overall cancer age-standardized rates (ASR) were 163.0 per 100,000 males and 141.8 per 100,000 females in Iran. A study in Iran in 2008 reported that the median

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survival time after CRC diagnosis was 3.5 years. No population based data on outcome and survival among CRC patients has been reported in Iran. The aim of this study to present the survival and assess determinants of survival among CRC from a population based CRC registry in Iran.

Materials and Methods

This is a prospective cohort study. The required data were obtained from Colorectal Cancer Registry Database of the Research Center for Gastroenterology and Liver Diseases affiliated to Shahid Beheshti University of Medical Sciences. These data are relevant to the patients referring 10 public and private hospitals in Tehran, which refer the CRC patients to the Colorectal Cancer Registry. The study was initiated at September 23, 2006 and the patients were followed up till October 23, 2011. Information about tumor characteristic, smoking status, family history was collected at base line and survival status was followed every six months by contacting patient or next of kin (if patient died during the follow-up). The cause of death for each case was validated by verbal autopsy and referring to patient' medical record at the time of death. To assess the determinants of survival and eliminate confounding variables, we used the Cox proportional hazard model. The variables approximate to the level of significance ($p<0.2$) were entered into multivariate Cox regression model. In building model, Schoenfeld test with a p- vale of less than 5% was considered as statistically significant to enter into the model. Proportional hazard was assessed for the variables entered into the model using and yielded as established. A $PP<0.05$ was considered as the level of significance. The data were analyzed by Stata software Stata software (version 12). All cases of CRC had diagnosed histoptahologic confimatioin of diagnosis. Tumor grade was established by the criteria of *International Classification of Diseases* (the code C18-21), the pathology report, and the criteria of *American Commission of Cancer.*

Results

A total of 1127 cases of CRC with 2758 pearson years of followup contributed to this study. Out of 1127 cases, 690 (61%) were male and 530 (39%) female. The patients' age range was 14 to 94 years. Mean (SD) age at CRC diagnosis was 53.5 (14) years. Thirty point two percent of the patients were under 45 years, 45.5% were 45-65 years, and 24.3% were over 65 years. Most of patients (55.5%) were diagnosed as having CRC in the first stage of the disease. The advanced stages of disease were more prevalent in older patients ($p=0.012$). The adjusted hazard ratio (95% Confidence Interval's: CI) of mortality was 1.79(0.88-3.61), 2.16 (1.07-4.37), and 3.1(1.51-6.34) at grades of respectively II, III, and IV with reference to grade I. A curve of the patients' survival was plotted for cancer grades with confidence interval 95% (Figure 1). Cancer grades, Ethnicity, marital status, family history of cancer, and smoking were determinants of survival in the patients. Patients' characteristics for demographic variables and mortality rate due to CRC are shown in Table 1. Hazard Ratio of death yielded by univariate and multivariate Cox regression is shown in Table 2. 75%, 50%, and 25% of the patients survived respectively 2.72, 5.83, and 13 years or longer after diagnosis. Relative risk for Kurds was obtained 1.95 and significant by Cox

Table 1. Patients' Characteristics for Demographic Variables and Mortality Rate Due to CRC

Variable	percent	death	Mortality Rate	CI95% IMR
Tumor Grade				
I	8.34	9	47.5	24.7-91.3
II	36.77	67	75.5	59.4-96
III	36.56	69	93.6	73.8-117.8
IV	18.33	56	139.1	107.1-869
Ethnicity				
Fars	52	120	94.5	79-113.1
Kurd	8.2	15	103.7	62.4-171.9
Lur	7.5	16	88.7	54.3-144.8
Turk	21.5	38	70.8	51.5-97.3
Others	10.8	46	153	114.6-204.2
Gender				
Men	61.3	150	96.9	82.9-113.8
women	38.7	85	83	67.1-102.7
Marital status				
Married	93	197	85.3	74.2-98.1
Non married	7	24	161	107.9-240.3
Education				
Illitrate	26.5	56	113	86.9-146.8
Primary	32.2	49	79.8	60.3-105.5
High school	24.5	35	76.2	54.7-106.1
University	16.8	31	80	56.3-113.9
Disease Stage				
First stage	45.2	76	70.6	56.4-88.4
Advanced	54.8	124	109.8	92-131
Age groups				
< 45	30.2	73	89	70.8-112
45-65	45.5	99	83	68.6-101
> 65	24.3	63	111	87-142
Family history				
No	63.2	145	99	84-116
yes	36.8	79	78	62-97
Smoking				
No	73.5	150	86.8	64-101.9
yes	26.5	65	101.5	79.6-121.5

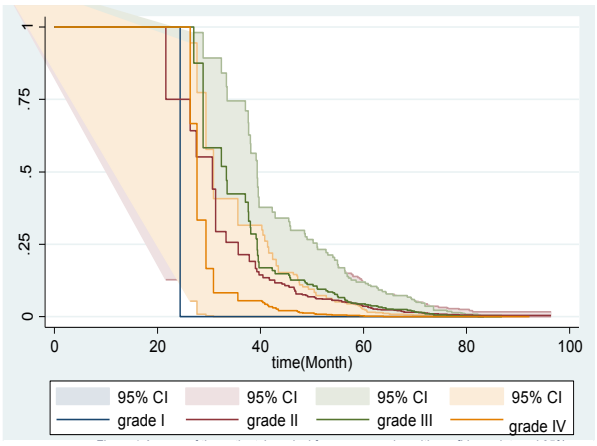

Figure 1. A Cirve of the Patient's Surval for Cancer Grades with Confidence Interval 95%

Table 2. Hazard Ratio of Death by Univariate and Multivariate Cox Regression

Variable		Univariate HR: 95%CI	Multivariate HR: 95%CI		p value
Tumor Grade	I	Reference	-	-	-
	II	1.58:0.78-3.19	1.79	0.88-3.61	0.105
	III	2:0.99-4.03	2.11	1.19-3.75	0.032
	IV	2.81:1.31-5.71	3.1	1.51-6.34	0.002
Ethnicity	Fars	Reference	-	-	-
	Kurd	1.1:0.6-1.8	1.95	1.01-3.76	0.046
	Lur	0.9: 0.5-1.6	0.44	0.18-1.07	0.071
	Turk	0.7: 0.5-1.1	0.59	0.33-1.04	0.071
	Others	1.6: 1.1 -2.3	1.44	0.78-2.67	0.45
Marital status	Married	Reference	-	-	-
	Non married	1.8: 1.2-2.8	2.14	1.19-3.84	0.01
Education	Illitrate	1.4:0.9-2.1	1.54	0.89-2.68	0.12
	Primary	0.9:0.6-1.5	0.93	0.53-1.63	0.806
	High school	0.9:0.5-1.5	0.94	0.51-1.72	0.849
	University	Reference	-	-	-
Age at diagnosis		1.2:0.9-1.7	1.01	0.98-1.01	0.611
Family history	No	Reference	-	-	-
	Yes	0.7:0.6 -1.1	0.58	0.38 -0.89	0.014
Smoking	No	Reference	-	-	-
	Yes	1.1:0.8-1.5	1.55	1.03-2.34	0.036

regression model (p=0.046) as other variables were present in model and the confounding variables were controlled. Relative risk was lowest (0.44) in Lurs. Median survival time was 5.8, 4.8, 5.4, 8.5, 3.7, and 5.8 years in Fars, Kurds, Lurs, Turks, others, and all patients respectively.

Discussion

In our study, the crude median survival time for CRC patients was 5.83 years and tumore grade, family history, age were the major determinant of mortality. Difrent ethnicity Disparity in relative risk of CRC was seen among different ethnicity in Iranian population. Our findings are consistent with a study in the United States that reported disparities in incidence rate of cancer between Hispanic whites and non Hispanic populations. In this study, CRC and its associated mortalities were strongly and inversely correlated with the level of education and literacy. CRC survival in illiterate patients was lower compared to rate in literate people, which is in agreement with earlier studies in other countries (Albano et al., 2007; Doubeni et al., 2012).

The grade of CRC at diagnosis was an important and significant variable in the model, which is consistent with other studies (Jeffreys et al., 2005). CRC-associated mortalities were higher in above 65-year-old patients compared to the other age groups. By log-rank test, there was no significant difference in survival between men and women. The age at diagnosis was two years lower for women than men. This finding is probably in agreement with other studies reporting that women follow healthcare more seriously and have higher rate of participation in screening plans compared to men (Krieger et al., 1999; Pahlavan et al., 2006; van Jaarsveld et al., 2006; Safaee et al., 2012; Mobasheri and Ahmadi, 2014).

In the present study, smoking increased the risk of death in the patients, which is consistent with a study in the United States that reported smoking increased mortality risk after CRC diagnosis (Phipps et al., 2011). In our study, 36.8% of the patients had family history of CRC, which is higher than a study in Sari, northern Iran reporting family history of CRC 24%. In this study, risk of death was lower in the patients with family history of CRC than those without such history. Willingness to do screening, early diagnosis, and/or more prophylatic practices in the patients with family history of cancer could explain decreased risk of death. However, a study in Germany reported that smoking and being male were more effective on CRC compared to family history (Hoffmeister et al., 2010). The median of survival time after CRC treatment was 4-13 months in the present study and 15.4 months in a study in the United States (Yuste et al., 2003).

In our study, survival of the married individuals was higher than the non married, which is in agreement with similar studies (Johansen et al., 1998; Goldzweig et al., 2009). The demographic determinants of the patients' survival in the present study are similar to and consistent with other studies. Risk ratio for the mortality due to CRC has been reported in view of ethnicity. Therefore, through determining the above-mentioned variables, policy makers and planners of health system could pay more attention to access to and quality of the diagnostic and therapeutic services in Iranian ethnics, attempt to promote access to these services in ethnics with shorter survival, and hence decrease disparity in survival time in different ethnics.

This study recommends further investigations be conducted to determine genetic or environmental reasons for the disease including the diet and cultural and behavioral habits in different ethnicities to identify the causes of the difference in CRC survival among the ethnicities. Although some patients from other Iranian ethnics are likely to refer the hospitals in Tehran, one of the limitations of this study was that it was conducted only in Tehran and therefore the findings should be cautiously generalized to other Iranian ethnics. Also, conduction of a population-based work with enrollment of a satisfactory sample size including all Iranian ethnics in subsequent studies is recommended.

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