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ORIGINAL ARTICLE

A comparative study on the prognostic impact of concurrent smoking and alcohol drinking on colon and rectal cancers: A frailty competing risks survival analysis

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ABSTRACT

Aim: This study aimed to design a model and to compare the prognostic impact of concurrent using of tobacco and alcohol in colon and rectal cancers via a competing risks approach.

Background: Many authors have confirmed both alcohol and tobacco smoking as the risk factors of CRC. The effect of concurrent using has been explored for an association with CRC and a comparison between sub-sites found in few studies.

Patients and methods: 1219 patients with CRC diagnosis according to the pathology report of Research Institute For Gastroenterology And Liver Diseases (RIGLD) cancer registry, from 1 January 2002 to 1 October 2007, were entered into the study. Separately and concurrently, tobacco smoking and alcohol drinking were analyzed using competing risk parametric survival analysis with frailty parameter adjustment utilizing STATA statistical software.

Results: In separate evaluations, tobacco smoking and alcohol use were significantly related to the survival only in patients with colon cancer (Hazard Ratio (HR) =1.61 and 95% Confidence Interval (CI) = (1.16-2.23) for tobacco and HR=1.93 and 95% CI= (1.22-3.06) for alcohol). In addition, these factors were significantly different between two sub-sites of colon and rectum (HR=1.78, (95% CI= (1.12-2.83) for tobacco and HR=4.44, 95% CI= (1.74-11.37) for alcohol). Also, results of concurrent analysis showed that only "current or past tobacco- current or past alcohol" category had significant relationship to the survival in patients with colon cancer (HR=2.17 and 95% CI= (1.27-3.71)) and this was significantly different between two sub-sites (HR(C/R) =5.16 and 95% CI= (1.65-16.12)). In total, survival probability of colonic patients was lower than that of rectum cancer patients.

Conclusion: Concurrent using of tobacco and alcohol might be a prognostic factor of survival in patients with colon cancer. These results could be beneficial for prognosis and treatment application planning screening programs and its possible modifications.

Keywords: *Tobacco, Alcohol, Colon, Rectal, Competing Risks Survival*.

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INTRODUCTION

Worldwide, colorectal cancer (CRC) is the third most common malignancy (1) and is the fifth and third most common cancer in men and women respectively, in Iran (2). CRC rates are increasing (2-9). The incidence of CRC has increased recently in Iran too (10), especially it is higher than expected in young patients (11-13) and this made the CRC an important public health problem in our country.

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Apart from genetic syndromes that markedly increase the risk of colorectal cancer, colon and rectal carcinomas are thought to have an important environmental etiology from which some can be controlled and called modifiable risk factors. Since large portion of the disease is theoretically avoidable by early diagnosis (14, 15), this assumption necessitated the assessment of the measures for reducing the risk of CRC. In this context of modifiable set risk factors, many authors confirmed both alcohol (16-22) and tobacco smoking (21, 23-25) as the risk factors of CRC separately or simultaneously. The effect of concurrent use has been explored for an association with CRC just in few studies (26) and it was evaluated by sub-sites in another study (27). However, this evaluation has been made in a case control study based on the number of patients in the combination level of alcohol and tobacco use and not in the context of patients' survival. The objective of this study was to evaluate the concurrent prognostic impact of alcohol use and tobacco smoking site-specific for colon and rectal cancers and to compare the effect between these two cancers. The outcomes of this study may help to have a more insuring decision making for the patient management.

PATIENTS and METHODS

Study Participants

Data were acquired from Cancer Registry Center of the Research Institute of Gastroenterology and Liver Disease (RIGLD), Shahid Beheshti Medical University, Tehran, Iran. The patients from ten public and private collaborative hospitals were treated and referred to the cancer registry. All patients with CRC diagnosis according to the pathology report of cancer registry were eligible for this study. Based on this criterion, 1219 patients (802 (65.8%) of subjects with colon cancer, 392 (32.2%) of subjects with rectal cancer and 25 (2.1%) with unknown cause) were entered in the study.

Follow up

The follow up time was defined as the date of diagnosis up to the 1 October 2007 as the time of the death from the disease (as the exact failure time) or survival (as the censoring time). The start time of the study was considered as 1 January 2002. Deaths were confirmed through the telephonic contact to relatives of patients. We encounter a few number of CRC patients (2.1%) wherein no information about the cause of death was obtained, but only the dates of their death were known, which were excluded from the analysis.

Prognostic Factors

For all patients and based on hospital document information, the tobacco smoking and alcohol history, separately or in a combination level of them were used in the analysis. Based on site topography of the cancer, the colon and rectal were separated to define the colon and rectal sites of the cancer.

Statistical Analysis

Survival time was calculated in months and was represented as mean (±Standard deviation) survival time. Finkelstein and Esaulova (2008), to address the problem of bivariate frailty competing risks models via a bivariate frailty, showed that when the components of the system conditionally on independent frailty terms, themselves are independent, then the mixture failure rate of the system can be constructed by the sum of mixture failure rate of individual components (28). Based on this idea, the Lun-McNeil (L-M) competing risk approach had been introduced for modeling the factors in the analyses by introducing a gamma frailty component to adjust the problem of independence of the competing causes of death (290. Parametric survival models were compared and the best model was chosen by Akaike Information Criterion (AIC) (30) and probability plot. Based on the best model, cause-specific Hazard Ratios (HR) (and their 95% confidence intervals (CI)), was considered as the effect size of interest (29, 31). The HR of difference and its

95% CI was also computed. Data were analyzed using STATA 10 Statistical software.

RESULTS

The mean follow up time (± SD) in months for patients with colon and rectal cancers was 26.35 (±25.27) and 23.88 (± 20.56), respectively. The mean age at diagnosis (± SD) in months was 53.56 (±14.21) in colon cancer patients and 55.03 (±37.63) in rectal cancer patients. There were 566 (74%) and 194 (26%) never and past or current tobacco smokers respectively in colonic patients and 266 (75%) and 90 (25%) never and past or current tobacco smokers respectively in patients with rectal cancer. Also, there were 684 (91%) and 71 (9%) never and past or current alcohol drinkers respectively in colonic patients and 331 (92%) and 27 (8%) never and past or current alcohol drinkers respectively in patients with rectal cancer. In colon cancer patients, 1, 2, 3, 4 and 5-year survival probability were 91.7%, 83.7%, 75.9%, 69.0% and 63.3%, respectively. The mean survival time (95% confidence interval) of these patients was 111.82 (102.25 – 121.39) months. In rectal cancer patients, 1, 2, 3, 4 and 5-year survival probability were 96.0%, 91.2%, 84.0%, 78.2% and 76.0%, respectively. The mean survival time (95% confidence interval) of these patients was 135.95 (126.20 – 145.70) months.

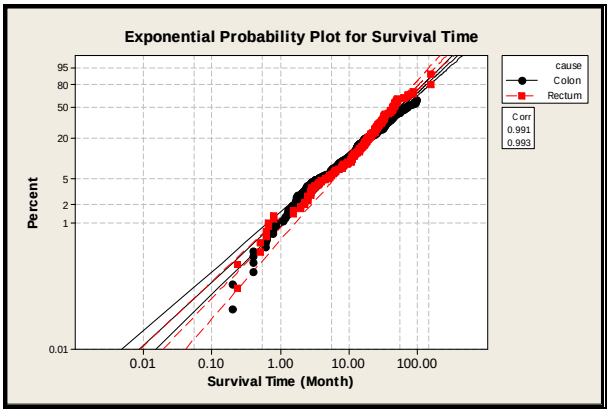

Fig 1. Probability plot of Exponential model for colon and rectal cancers.

Table 1. Results of evaluation of parametric survival regression using AIC

Model	Weibull	Exponential	Log Normal	Log Logistic	Gompertz
AIC	2310.29	2309.79	2316.55	2310.09	2310.65

Table 2. Results of L-M Exponential regression for tobacco smoking and alcohol use in colon and rectum

Characteristic	Categories	Colon Cancer			Rectal Cancer		
		HR[b]	95% CI	P-value c	HR[b]	95% CI	P-value c
Tobacco Smoking							
	never used	1 [a]	-----	-----	1 [a]	-----	-----
	current or past use	1.61	1.16-2.23	0.005	0.90	0.61-1.32	0.591
Alcohol History							
	never used	1 [a]	-----	-----	1 [a]	-----	-----
	current or past use	1.93	37	0.005	0.44	0.19-1.01	0.051

[a] Reference category
[b] Hazard Ratio
[c] Based on L-M Exponential model

Table 3. Comparison the Hazard ratios between colon and rectal sub-sites for tobacco smoking and alcohol history

Characteristic	HR [a] (C/R)[b]	95% CI (C/R)	P-value [c]
Tobacco Smoking (current or past use)	1.78	1.12-2.83	0.014
Alcohol History (current or past use)	4.44	1.74-11.37	0.002

[a] Hazard Ratio based on L-M model
[b] Colon with respect to Rectum
[c] Based on L-M Exponential model

Table 4. Results of L-M Exponential regression for concurrent using of tobacco and alcohol in colon and rectum

Characteristic	Colon Cancer			Rectal Cancer		
	HR[b]	95% CI	P-value[c]	HR[b]	95% CI	P-value[c]
never tobacco- never alcohol	1[a]	-----	-----	1[a]	-----	-----
Current or past tobacco- never alcohol	1.42	0.97-2.07	0.070	1.06	0.70-1.59	0.791
never tobacco- current or past alcohol	1.60	0.64-3.97	0.316	0.51	0.12-2.20	0.367
current or past tobacco- current or past alcohol	2.17	1.27-3.71	0.005	0.42	0.15-1.17	0.100

[a] Reference category
[b] Hazard Ratio
[c] Based on L-M Exponential model

Table 5. Comparison Hazard ratios between colon and rectal sub-sites for concurrent using of tobacco and alcohol

Characteristic	HR[a] (C/R)[b]	95% CI (C/R)	P-value[c]
current or past tobacco- never alcohol	1.34	0.80-2.25	0.263
never tobacco- current or past alcohol	3.12	0.57-17.20	0.191
current or past tobacco- current or past alcohol	5.16	1.65-16.12	0.005

[a] Hazard Ratio based on L-M model

Results of Model Selection

First, the parametric model was examined compared to Cox PH regression. Probability plot of parametric distribution was evaluated and the results showed that Exponential probability plot for data in colon and rectum sub-sites revealed very well fit of this distribution to the data (see Figure 1). Therefore, in this situation, the parametric model compared to Cox PH model is more efficient. In addition, a comparison of AICs for five distributions, recommend Exponential model for this analysis (see table 1). So, Exponential model was used as the distribution of parametric survival model for the rest of analyses.

The results of separate evolution of tobacco smoking and alcohol use in colon and rectum are shown in table 2. Based on the analysis, both of factors were significantly related to the survival in patients with colon cancer ($p< 0.05$). However, they were not significant for rectal cancer ($p> 0.05$).

The results of comparison between colon and rectal sub-sites for tobacco smoking and alcohol use are included in table 3. Both factors were significantly different between two sub-sites of colon and rectum ($p<0.05$).

Results of L-M Model for Concurrent Evaluation of Tobacco Smoking and Alcohol

Frailty parameter was significant in the model ($\chi^2_{(01)} =3.66$, $p=0.03$). The results of concurrent evolution of tobacco smoking and alcohol use in colon and rectum in table 4, showed that just concurrent using of tobacco and alcohol (current or past tobacco- current or past alcohol) was significantly related to the survival in patients with colon cancer ($p< 0.05$). However, other effects weren't significant ($p > 0.05$).

Based on the results of comparison between colon and rectal sub-sites in table 5, it was observed that only the concurrent using of tobacco and alcohol (current or past tobacco- current or past alcohol) was significantly different between two sub-sites of colon and rectum ($p<0.05$).

Colon and rectal specific survival curves based on L-M Exponential model is shown in Fig. 2. As can be seen, in total the adjusted survival of patients with rectal cancer is better than those of with colon cancer.

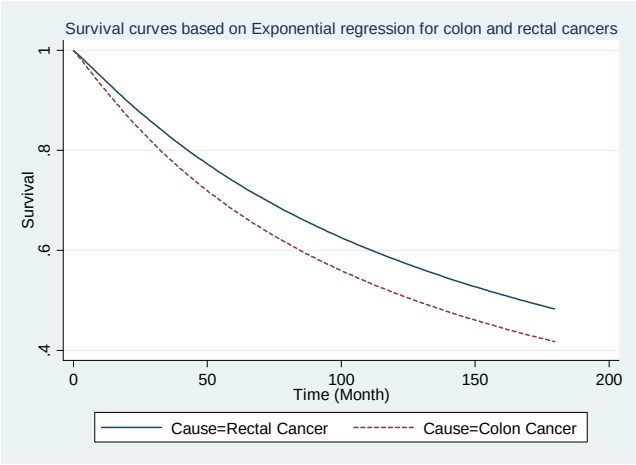

Fig 2. Adjusted survival probability based on L-M Exponential model for colon and rectal cancers

DISCUSSION

The importance of CRC as a threat of public health and its increasing rate in our country, especially in youth through three recent decades (10-13), makes it necessary to study the prognostic factors of this cancer, especially those which could be modified by changing life-style. On the other hand, due to heterogeneity of CRC by sub-sites, for further understanding of the cancers, it was necessary to estimate and to compare the risks on the sub-sites of CRC. With regard to these aims, this study was conducted on 1219 Iranian CRC patients to evaluate the effect of separate and concurrent effect of tobacco and alcohol by L-M competing risks approach considering colon and rectal cancers as competing causes of death.

Tobacco Smoking was a significant prognostic factor of colon cancer but not for rectal cancer. The hazard of dying from colon cancer in the past or current tobacco smokers was 1.61 times more than those of never smokers (HR=1.61 and 95% CI= (1.16-2.23)). Contrary to our findings, some studies suggest that long-term tobacco smoking increases the risk of both colon and rectum sub-sites (21, 23-25). It is hypothesized that smoking acts as an initiator of colorectal neoplasia (21). But, neither the International Agency for Research on Cancer nor the Surgeon General has classified smoking as a cause of CRC (32). Also the hazard of death in colonic tobacco smokers was 1.78 (95% CI= (1.12-2.83)) times more than those of rectal cancer tobacco smokers. In contrast to our findings, the results of other studies showed a slightly stronger association between cigarette smoking and rectal cancer than for colon cancer (25, 33). However, in line with our study, Giovannucci et al (1994) has previously reported a significant association with colon cancer for ≥16 pack-years vs. 0 pack-years before age 30 ((Relative Risk) RR = 1.96, 95% CI: 1.16 –3.29) and found suggestive but not statistically significant results for rectal cancer (RR = 1.62, 95% CI: 0.60–4.37) (21).

Alcohol history was significant for colon cancer (HR=1.93 and 95% CI= (1.22-3.06)), but the association was not significant for rectum. High alcohol consumption has been associated with modest elevations of CRC risk in several recent studies with an excess of colon cancer (19, 22) has been noted among persons with chronic inflammatory bowel diseases (IBD) (17). On the other hand, results of some other studies showed that alcohol was associated with tumors of the distal colon and rectum (16, 18, 34). Also our results showed that, the hazard of death in colonic alcohol drinkers was 4.44 (95% CI= (1.74-11.37)) times more than those of rectal cancer alcohol drinkers. Like our findings, a meta-analysis of cohort and case-control studies combined has reported moderately increased risks of CRC, with a dose-response relation for rising alcohol consumption (16, 35), but did not detect any differences in risk of colon cancer versus that for rectal cancer (35). However it is not in line with our findings that, Wei et al (2004), didn't observe any significant difference between these sub-sites (33). Also, a review of 27 epidemiological studies showed that cohort studies reported risk estimates of 1.0–1.7 for colon cancer and the same for rectal

cancer (20, but no comparison has been done between these two parts. Different grouping of sub-sites characterization by different patterns of exposure, for example race and genotypes may be possible reasons for the apparently inconsistent findings (16.

The results of the evaluation of concurrent use of tobacco and alcohol showed that just "current or past tobacco- current or past alcohol" category was significantly related to the survival in patients with colon cancer (HR=2.17 and 95% CI=(1.27-3.71)). In addition, only this category was significantly different between two sub-sites of colon and rectum (HR(C/R) =5.16 and 95% CI= (1.65-16.12)). Like our findings, the combination of cigarette smoking and alcohol consumption showed to increase the risk of adenomatous polyps (36). However, a review of 161,172 patients demonstrated that current alcohol and tobacco use were associated with both earlier onset of colorectal cancer and a more distal location of the lesions (27).

In their study, Acott et al (2008) observed that current alcohol consumption either alone or in conjunction with tobacco use was associated with an increased likelihood of presenting with colorectal cancer (26). These findings were also confirmed by other studies (21, 36-38).

Overall adjusted survival and 1, 2, 3, 4 and 5 year survival of patients with rectal cancer were better than those of colon cancer. This shows the better overall and year-by-year condition of patients with rectal cancer. Other studies confirm this result too (8, 39, 40). However, some investigations showed the reverse results (14, 41-44) and some others are debating this issue (3, 5, 9, 45, 46).

In the evaluation of separate and concurrent tobacco and alcohol use, some reverse relationships were observed in the site of rectum. The role of alcohol in colorectal tumor genesis is controversial (26). Some studies reported that low to moderate levels of alcohol might have a protective effect against the development of colorectal adenomas, although heavy intake would lose this effect (47, 48).

There were some limitations in our study. The information gathered about alcohol and tobacco was incomplete and it was based on only two categories of "never" and "current or past user", and in a qualitative manner; quantitative data about these two factors could lead us to more exact results. There was no information about dietary habit of the study participants where adjustment on this information would be more beneficial.

In conclusion, concurrent using of tobacco and alcohol might be a prognostic factor of survival in patients with colon cancer but not for rectal cancer. The findings might make a clue for the effect evaluation of some aspects of life style and their site-specific impact on survival in CRC patients. These results could be beneficial for prognosis and treatment application, planning screening programs and its possible modifications.

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