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Multiple Associations of Clinicopathological Characteristics and Risk Factors of Colorectal Cancer in the Iranian Population

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Abstract

Background: Previous studies have demonstrated that clinicopathological features of colorectal cancer (CRC) could be diverse in different CRC patients groups. The present study aimed to analyze the association between clinicopathological characteristics and the risk factors in different CRC patients groups, which is categorized by sex, family history, age, and also primary tumor site in the Iranian CRC patients.

Method: In this cross-sectional study, we included 304 patients with CRC. The data of clinicopathological features were collected from documented pathology reports. Subsequently, we carried out multiple analyses to discover the association among these elements.

Results: Our analysis demonstrated that there was a significant difference between men and women regarding the mean age at diagnosis, tumor locations, mean size of tumors, positive family history, smoking status, and physical activity (P <0.05). Out of all the patients, 22.4% had a positive family history of cancer. The patients with a positive family history just have lower mean age, body mass index (BMI), and higher physical activity compared with patients without family history of cancer (P <0.001). 31.9% of the patients were in the age group of below 55 and 68.1% were in the age group of 55. The majority of our patients in <55 age group were male, in which the subjects had higher physical activity and lower BMI, compared with patients in ≥55 group (P<0.05). Based on our analysis, there was no significant difference between pathological features such as tumor grade, stage, size, and the risk factors including BMI and physical activity in different tumor locations (P >0.05).

Conclusion: Gaining information about the association between clinicopathological characteristics and the risk factors in CRC could provide a better understanding of disease pathogenesis and consequently, improve the management of diseases.

Keyword: Colorectal cancer (CRC), Characteristics, Clinical presentations, Risk stratification

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Introduction

Cancer is a major public health problem in Iran as well as all over the world. Colorectal cancer (CRC), in developed regions, is the third and second most prevalent cancer among men and women, respectively.[1] Statistics indicate that CRC is the fourth leading cause of cancer-related mortality worldwide and accounts for about 861,000 deaths every year.[1,2] Generally, the incidence of CRC is lower in Asia than that in western countries; however, recent studies have revealed increasing rates of CRC in Asia and particularly in Iran, as a developing country.[3] It is established that CRC is a complex disease, influenced by both genetic and environmental factors.[4-6] Environmental risk factors, for instance gender, age, body mass index (BMI), physical activity, and smoking status are some of the most effective factors in the etiology of CRC; which therefore, could contribute to the CRC risk and development.[3, 7] Understanding the risk factors for CRC could offer risk reduction strategies for asymptomatic individuals and patients younger than 50 years.[3, 8, 9] Studies have demonstrated that the clinicopathological features of CRC in younger patients and/or in patients, with family history is generally different. That is due to a strong suspicion that the genetic and epigenetic etiology of the disease is different from older-onset disease and patients without any family history of CRC.[10, 11] For instance, CRC tumors in younger patients who, are in a more advanced stage of disease at the time of diagnosis, represent more aggressive histopathologic characteristics compared with elder subjects.[12-14] Furthermore, certain studies revealed that right-sided colon cancer is clinically different from left-sided and rectal cancer. In detail, they reported that right-side tumors tend to have an advanced and larger size, which are often poorly-differentiated. They also demonstrated that tumors that exist in the left-side have polypoid morphology, while right-sided tumors have flat morphology.[15, 16] These variances lead to differences in treatment efficacy and performance of colonoscopy in the detection of tumors in early stages.[16] On the other hand, to date, the relation between risk factors and clinicopathological characteristics in CRC patients has remained unknown. According to the difference in population life-style and genetic background, the risk factors and their effect on CRC incidence and correlation with clinicopathological characteristics in different populations might be diverse.

We conducted this research to analyze the association between clinicopathological characteristics and the relevant risk factors in different CRC patients groups, which are categorized by sex, family history, younger and elderly patients, and also, primary tumor site in the Iranian CRC patients.

Methods

In our cross-sectional study, we included 304 patients with adenocarcinoma from the colonoscopy unit of Al Zahra Hospital and CRC center of Seyed Al Shohada Hospital in Isfahan city during 2015-2018. The patients were initially diagnosed with colonoscopy and then followed their pathology report for the ultimate confirmation of their colonoscopy-based CRC diagnosis. Information about pathological and clinical characteristics such as location, grade, stage, tumor size, and demographic data such as the age of diagnosis and gender were collected from documented pathology reports. Additionally, we asked all our participants to fill in a questionnaire in order to register the parameters known as CRC risk factors including BMI (weight in kilograms divided by height in meters squared), physical activity, smoking status, and family history of CRC and other cancers. This study was approved by the University Ethics Committee (approval number 392263). All the participants filled and signed written informed consent.

Organization of information

The questionnaire for physical activity focused on the type of work with four options in the questionnaire, describing physical activity as follows: no activity (unemployed or retired), low activity [sedentary or standing work (for instance clerical work, taxi driving)], moderate activity [work that involved walking and standing (delivery by walking, marketing, teachers, nurses

Table 1. Characteristics of the patients and distribution in men and women

Characteristics	Total Patients (%)	Male (%)	Female (%)	*P*-value
Total patients	304(100%)	177(58.2%)	127(41.8%)	
Mean age ± SD	60.61±12.66	59.31±12.56	62.43±12.61	0.03*
Family history				
Yes	68(22.4%)	47(26.6%)	21(16.5%)	0.03*
No	236(77.6%)	130(73.4%)	106(83.5%)	
Location (1)				
Cecum	12(3.9%)	8(4.5%)	4(3.1%)	
Ascending	50(16.4%)	33(18.6%)	17(13.4%)	
Transverse	17(5.6%)	12(6.8%)	5(3.9%)	0.02*
Descending	23(7.6%)	15(8.5%)	8(6.3%)	
Sigmoid	83(27.3%)	35(19.8%)	48(37.8%)	
Rectum	119(39.1%)	74(41.8%)	45(35.4%)	
Location (2) #				
Proximal	79(26%)	53(29.9%)	26(20.5%)	0.01*
Distal	106(34.9%)	50(28.2%)	56(44.1%)	
Rectal	119(39.1%)	74(41.8%)	45(35.4%)	
Grade				
Well	105(34.5%)	41(32.3%)	64(36%)	0.10
Moderate	160(52.6%)	75(59.1%)	85(48%)	
Low	32(10.5%)	9(7.1%)	23(13%)	
Mean size ± SD	4.95±1.88	5.12±1.98	4.70±1.71	0.04*
Stage				
I	60(19.7%)	37(20.9%)	23(18.1%)	0.69
II	115(37.8%)	62(35.1%)	53(41.7%)	
III	108(35.5%)	65(36.7%)	43(33.9%)	
IV	21(6.9%)	13(7.3%)	8(6.3%)	
BMI (kg/m^2)	26.12±3.01	25.89±3.02	26.43±2.98	0.12
Smoking				
Yes	55(18.10%)	47(26.6%)	8(6.3%)	<0.001*
No	249(81.9%)	130(73.4%)	119(93.7%)	
Physical activity				
No activity	101(33.2%)	42(23.7%)	59(46.5%)	<0.001*
Low activity	139(45.7%)	81(45.8%)	58(45.7%)	
Moderate activity	49(16.1%)	40(22.6%)	9(7.1%)	
High activity	15(4.9%)	14(7.9%)	1(0.8%)	

*: $P<0.05$, BMI: Body Mass Index, #: Proximal: Ascending + Cecum + Transverse, Distal: Descending + Sigmoid, Rectal: Rectum

for instance)], and high activity [labor work (for example construction work, agricultural work, and athletes)]. Any participants who smoked at least 10 cigarettes per day for >5 years or in the past year was labeled as a smoker.[3] The frequency of the patient regarding the location of the primary tumor in pathology reports was described in six groups (location 1) including the cecum, ascending, transverse, descending, sigmoid, and rectum. Subsequently, concerning multiple analysis, we categorized the locations to three major groups (location 2): tumors in the cecum, ascending and transverse were classified as proximal, tumors in descending and sigmoid classified as distal, and tumors in rectum categorized as rectal groups. Our analysis were performed in four different CRC groups of patients, based on sex, age, family history of the disease, and location of tumors.

Statistical analysis

All the obtained data were analyzed with SPSS version 22.0 (SPSS, Inc., Chicago, IL). We assessed demographics and life-style characteristic distribution such as gender, smoking status, and family history employing Pearson Chis-quare test and compared continuous variables including

Table 2. Characteristics of patients with or without a family history of colorectal cancer

Characteristics	Yes (%)	No (%)	*P*-value
Mean age ± SD	47.68±9.43	64.34 ±10.89	<0.001*
Location (2) #			
Proximal	18(26.5%)	61(25.8%)	0.34
Distal	19(27.9%)	87(36.9%)	
Rectal	31(45.6%)	88(37.3%)	
Grade			
Well	23(33.8%)	82(34.7%)	0.99
Moderate	36(52.9%)	124(52.5%)	
Low	7(10.3%)	25(10.6%)	
Mean size ± SD	4.77±2.32	4.99±1.74	0.39
BMI (kg/m^2)	23.87±2.39	26.76±2.86	<0.001*
Smoking			
Yes	17(25%)	51(16.1%)	0.09
No	51(75%)	198(83.9%)	
Physical activity			
No activity	8(11.8%)	93(39.4%)	<0.001*
Low activity	27(39.7%)	112(47.5%)	
Moderate activity	24(35.3%)	25(10.6%)	
High activity	9(13.2%)	6(2.5%)	

*: *P*<0.05, BMI: Body Mass Index, #: Proximal: Ascending + Cecum + Transverse, Distal: Descending + Sigmoid, Rectal: Rectum

age, BMI, and tumor size with t-test between different groups. Mann–Whitney test was used to compare physical activity, tumor location, grade, and stages between the groups. The significance level was set at $P < 0.05$.

Results

General finding

A total of 304 patients (177 male and 127 female) with CRC were included in our study with a mean age of 60.61±12.66 (ranged from 27-87 years). Among all the patients, 68 (22.4%) had a positive family history of cancer, only 55 (18.10%) were cigarette smokers, 12 (3.9%) suffered from tumors in cecum, 50 (16.4%) in ascending, 17 (5.6%) in transverse, 23 (7.6%) in descending, 83 (27.3%) in sigmoid, and 119 (39.1%) in rectum. In the grading category, 105 (34.5%) were well-differentiated, 160 (52.6%) were moderately-differentiated and 32 (10.5%) was low-differentiated. The mean BMI and the mean size of tumors in patients were 26.12±3.01 and 4.95±1.88 centimeters, respectively. Table 1 represents other risk factors and pathological characteristics.

Considering sex

Our patients consisted of 177 (58.2%) men and 127 (41.8%) women. The analysis demonstrated that there was a significant difference between men and women regarding the primary tumor locations (*P* for location 1: 0.026 and *P* for location 2: 0.013). Based on location 2 category, concerning the male group, the primary tumor was mostly at the rectal of 74 (41.8%) patients and then, in the proximal segments of 53 (29.9%) patients, while regarding the female group, the primary tumor was mostly at the distal in 56 (44.1%) cases and then, in the rectal segments in 45 (35.4%) cases. The mean ages of diagnosis of men and women were 59.31±12.56 and 62.43±12.61, respectively, which implied a statistically significant difference (*P*=0.034). Our analysis showed that the mean size of tumors in men is slightly larger than that in women (5.12±1.98 vs. 4.70±1.71, *P*=0.02). Moreover, our results revealed a significant difference between men and women in terms of positive family history and smoking status (*P*=0.03 for family history, *P*<0.001 for smoking status). Furthermore, the patients in the male group were found to have significantly higher physical activity compared with female patients (*P*<0.001). However, in this study, we demonstrated that there was no difference between men and women

Table 3. Characteristics of the patients categorized by age

Characteristics	Patients <55	Patients ≥55	*P*-value
Total patients	97(31.9%)	207(68.1%)	<0.001
Sex			
Male	65(67%)	112(54.1%)	0.03*
Female	32(33%)	95(45.9%)	
Location (2) #			
Proximal	21(21.6%)	58(28%)	0.49
Distal	36(37.1%)	70(33.8%)	
Rectal	40(41.2%)	79(38.2%)	
Grade			
Well	32(33.0%)	73(35.3%)	
Moderate	49(50.5%)	111(53.6%)	0.90
Low	11(11.3%)	21(10.1%)	
Mean size ± SD	5.04±1.91	4.90±1.87	0.57
Stage			
I	19(19.58%)	41(19.8%)	
II	36(37.11%)	79(38.16%)	0.96
III	34(35.5%)	74(35.74%)	
IV	8(8.24%)	13(6.28%)	
BMI (kg/m^2)	25.24±2.99	26.53±2.94	<0.001*
Smoking			
Yes	19(19.6%)	36(17.4%)	0.64
No	78(80.4%)	171(82.6%)	
Physical activity			
No activity	16(16.5%)	85(41.1%)	
Low activity	34(35.1%)	105(50.7%)	<0.001*
Moderate activity	32(33%)	17(8.2%)	
High activity	15(15.5%)	0(0%)	

*: *P*<0.05, BMI: Body Mass Index, #: Proximal: Ascending + Cecum + Transverse; Distal: Descending + Sigmoid, Rectal: Rectum

regarding BMI, grade, and stage (*P*>0.05). In table 1, we summarized the distribution of patients for risk factors and clinicopathological features among all the patients and between men and women.

Considering family history

Among all the patients, 68 (22.4%) had a positive family history of cancer and 18 (5.92%) had a family history of CRC. The patients with a positive family history had a lower mean age (47.68±9.43 vs. 64.34 ±10.89) and BMI (23.87±2.39 vs. 26.76±2.86) compared with the patients without a family history of cancer (*P*<0.001). Furthermore, the ones with a family history had higher physical activity compared with the ones without a family history (low physical activity) (*P*<0.001). There was not any difference between the patients with family history and without a family history in terms of primary tumor locations, grade, mean size of tumors, and smoking status of patients (*P*>0.05) (Table 2).

Considering age

Herein, our findings demonstrated that 97 (31.9) out of the 304 patients were in the age group of <55 years and 207 (68.1) was in the age group of ≥55. In <55 age group, 67% were male and 33% were female, while in ≥55 age group, 54.1% were male and 45.9% were female, (*P*= 0.033). The BMI in patients of <55 group was 25.24±2.99, which was 26.53±2.94 in patients of ≥55 group. The difference in BMI between these age groups was statistically significant (*P*<0.001). The patients of <55 group had significantly higher physical activity compared with patients of ≥55 group (*P*<0.001). Based on the age group analysis, we did not observe any differences in tumor size, location, grade, and smoking status (*P*>0.05). Table 3 depicts the characteristics of the patients categorized by age.

The distribution of tumor location in the four

Table 4. Characteristics of the patients categorized by tumor location

Characteristics	Proximal # (%)	Distal # (%)	Rectal # (%)	*P*-value
Mean age ± SD	61.38±11.60	60.92±13.86	59.82±12.26	0.66
Grade				
Well	20(25.3%)	46(43.4%)	39(32.8%)	
Moderate	43(54.4%)	50(47.2%)	67(56.3%)	0.06
Low	13(16.5%)	9(8.5%)	10(8.4%)	
Mean size ± SD	5.33±2.14	4.97±1.74	4.67±1.78	0.052
Stage				
I	8(10.1%)	21(19.8%)	31(26.1%)	
II	32(40.5%)	42(39.6%)	41(34.5%)	0.22
III	33(41.8%)	35(33.0%)	40(33.6%)	
IV	6(7.6%)	8(7.5%)	7(5.9%)	
BMI (kg/m^2)	26.05±2.98	25.96±2.98	26.29±3.07	0.69
Smoking				
No	68 (86.1%)	76(71.7%)	105(88.2%)	0.003*
Yes	11(13.9%)	30(28.3%)	14(11.8%)	
Physical activity				
No activity	23 (29.1%)	41(38.7%)	37(31.1%)	
Low activity	36(45.6%)	46(43.4%)	57(47.9%)	0.61
Moderate activity	17 (21.5%)	13(12.3%)	19(15.9%)	
High activity	3(3.8%)	6(5.6%)	6(5.1%)	

*: *P*<0.05, BMI: Body Mass Index, #: Proximal: Ascending + Cecum + Transverse; Distal: Descending + Sigmoid, Rectal: Rectum

different age groups demonstrated that tumors in the proximal segment had a higher frequency in the groups of <40 years and between 50-60 years and tumors in the distal segment had higher frequencies in the groups of 60-69 years; whereas, tumors in the rectal segment had a higher frequency in the group of ≥70.

Considering tumor location

The mean ages of our patients with tumors in proximal, distal and, rectal were 61.38±11.60, 60.92±13.86, and 59.82±12.26, respectively. Comparison of these results revealed no statistically significant difference (*P*=0.66). The mean size of tumors in the patients in different locations was 5.33±2.14 (proximal), 4.97±1.74 (distal), and 4.67±1.78 (rectal) centimeters. Even though the mean tumor size in proximal segment was larger than that in the other segments, these results were not very impressive (*P*=0.052). Based on our analysis, there was no significant differences between pathological features such as tumor grade, stage, size, and risk factors including BMI and physical activity in different tumor locations (*P*>0.05). Regarding the smoking status groups, we observed a significant difference between smoking status and tumor location (*P*=0.003). The distribution of tumors in smokers and non-smokers demonstrated that in our smoker patients, 54.5% of the tumors were in distal, 25.5% in rectal, and 20% in the proximal segment. Meanwhile, in the non-smoker patients groups, 42.2% of the tumors were in rectal, 30.5% in distal, and 27.3% in the proximal segments. Table 4 summarizes the clinicopathological characteristics and risk factors of the patients based on tumor locations.

Discussion

In the current study, we carried out multiple analyses between clinicopathological differences and risk factors in different CRC patients groups, categorized by sex, family history, age, and also primary tumor location. Primarily, with sex categorization, we demonstrated that men were significantly different compared with women concerning the mean age at diagnosis, positive family history of disease, smoking status, physical activity, tumor location, and tumor size (*P*<0.05). This was predictable that based on Iranian culture, women have less physical activity and smoking compared with men. In a study by Ghanadi et al., the mean age of female patients with CRC

was 47.3±13.2 and the mean age of the male patients was 56.5±16, which represented a statistically significant difference.[17] on the other hand, a study by Safaee et al., carried out on the Iranian population, demonstrated that there were no significant differences between men and women regarding the age of diagnosis.[18] Furthermore, their study reported that 35.1% of patients had a family history of cancer (20% men and 15% women) and just 4.3% of patients had a family history of CRC.[18] However, in our study, only 22.4% of the patients had a family history of cancer (15.4% men and 9% women), yet it showed a higher frequency of family history of CRC (5.92%). Two different studies in Netherlands and Sweden populations revealed a high frequency of patients with a family history of CRC (11.2% and 11.4%, respectively).[19, 20] Concordant with our results, Safaee et al. reported significant differences between men and women concerning the mean size of tumors.[18] On the other hand, a study by Golfam et al. on the Iranian population demonstrated that there were no significant differences between men and women regarding the primary tumor locations, representing an inconsistency with our analysis.[21] This study also reported a different degree of tumor differentiation compared with ours. Therein, 61.5% of tumors were well-differentiated, 28.4% moderately-differentiated, and 10.1% poorly-differentiated.[21] Meanwhile, in our study, 34.5%, 52.6%, and 10.5% of the patients were well, moderately, and poorly-differentiated, respectively. Moreover, Ghanadi et al. reported that most tumors (45.2%) were well-differentiated, and Safaee and colleagues reported that most cases (39%) of tumors were well-differentiated, which is consistent with our results. They also suggested that there were no significant differences between men and women concerning the differentiation of tumors.[17, 18] Experiments have discovered that the patients with a family history of cancer have a lower age of onset for CRC compared with the patients without a family history.[22] In the present study, the patients with a family history of cancer had a significantly lower mean age, BMI, and also higher physical activity (P<0.05). These results demonstrated that genetic background might be of greater importance than the other risk factors such as age, activity, and BMI. In age categorization, our analysis demonstrated that 31.9% of the patients were in <55 group and 68.1% of them were in ≥55 group. However, studies reported that over 80% - 90% of patients are diagnosed after the age of 50 and 55.[23-25] Golfam et al. demonstrated that there was not any association between age and degree of tumor differentiation, which is consistent with our results (Table 3).[21] In the current study, there was a significant association between age classifications (<55 and ≥55 groups), sex, BMI, and physical activity (P<0.05). Some of these results were logical since in below the age of 55 the physical activity is higher and therefore, BMI is also lower in <55 groups. In our work, there was not a significant association between age and tumor location (Tables 3 and 4), which is in accordance with the results reported by Ghanadi et al. Furthermore, our results are concordant with those of a study by Golfam et al., which demonstrated that there was no significant difference between the mean age and tumor locations.[21] However, in a work by Savas et al. in Turkey, CRCs in young patients were mostly localized at the right colon rather than the left colon and rectum (P<0.05).[26] Additionally, several researchers, including Okamoto et al, and Cooper et al. revealed an increased proportion of right-sided colon cancers with the increase in age.[27, 28] Certain studies reported that tumors in young patients were in a more advanced stage at the time of diagnosis and had more aggressive histopathologic characteristics compared with elder subjects.[10, 26, 29-31] On the contrary, in our study, we reported that there was no significant difference between age groups and pathological characteristics including stage, grade, and tumor size (Table 3). Some studies demonstrated that tumors located in the right-side are in an advanced stage, poorly-differentiated and have a bigger size.[15, 16] Meanwhile, based on table 4, there was no significant association between pathological characteristics such as tumor grade, stage, and size with tumor locations in our analysis.

Finally, according to the difference in the population's life-style and genetic background, we could observe different risk factors and effects on CRC incidence, and different correlations with clinicopathological characteristics. Our research aimed to determine the association between these elements and understand the effects of certain risk factors on clinicopathological characteristics in the CRC sample in the Iranian population.

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Conflict of Interest

None declared.

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