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RISK OF COLORECTAL CANCER IN DEPRESSED PATIENTS, NEGATIVE LIFE EVENTS, AND THE PREVALENCE RATE OF DEPRESSIVE SYMPTOMS: A CASE-CONTROL STUDY

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Abstract – *Objective:* *This study aimed at investigating the risk of Colorectal Cancer (CRC) among depressed and Negative Life Events (NLEs) people and the prevalence of depressive symptoms.*

Materials and Methods: *A case-control study was performed from the Colonoscopy Unit of the Cancer Institute in Tabriz. A total of 207 cases with confirmed pathology findings and 207 controls, at the same time for the cases, were included. Multiple logistic regression was used to estimate the adjusted odds ratios and 95% confidence intervals.*

Results: *In the final multiple variable models, depression was associated with CRC insignificantly (OR=1.42, 95% CI: 0.92–2.21); however, NLEs were associated with CRC risk (OR=1.84, 95% CI: 1.08–3.16). Likewise, family history of CRC, diabetes, and smoking were associated with an elevated risk of CRC. Moreover, the prevalence rate (%) of depressive symptoms among cases and controls was revealed as 11-8 severe, 19-14 moderate, 27-24 mild and 43-54 minimal, respectively.*

Conclusions: *There was a significant positive association between CRC and NLEs while no evidence found that depression increases the risk of CRC.*

KEYWORDS: *Depression, Colorectal cancer, Negative life events, Case-control, Tabriz.*

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality and the third most common neoplasm in the world[1]. CRC is responsible for approximately 10% of global cancer incidence[2]. The highest rates of CRC are reported from developed countries (central and Northern Europe, USA, Canada, and Australia). In the United States CRC is the second most common cause of malignancy related mortality. The prevalence rate of CRC in Asia is lower than Europe and North America[3]. More than 65% of new CRC cases are found in developed countries, approximately half of them attributed to Americas and Europe[2]. CRC is the third most common cancer in Iran[4]. Among Iranian women and men CRC is the third and fourth most common malignancy, respectively. The incidence rate of CRC was increased significantly in the last decades in Iran and East Azerbaijan province, as a developing country[5,6].

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Several risk factors are related to CRC including lifestyle, genetic and family history, dietary pattern, smoking, history of diabetes, physical activity and other risk factors[1,7]. We then investigated whether history of depression in the past and experience of various Negative Life Events (NLEs) could be risk factors for CRC; they deserve attention since a low number of analytic studies focused on these aspects. NLEs are defined as discrete experiences that disrupt the usual activities of people, causing a substantial change requiring readjustments[8].

Depression is a common psychiatric disorder in the general population. The prevalence rate of major depression ranges from 0.9% to 9.4% in the elderly population[9]. The findings showed that depression is a risk factor for several diseases. Depressive disorders have a strong impact on the quality of life of cancer patients[10]. Epidemiological studies showed that depression is the most prevalent cancer-related symptom, and it is comorbid with other psychological and emotional problems among CRC patients. Moreover, the presence of depression produces complications in the patients' treatment and can lead to poor compliance with treatment resulting in worsening the situation[11].

Depression and NLEs are common psychological problems that affect the quality of life. Depression and NLEs could be a risk factor for either starting a disease or a disease morbidity and mortality. The impact of depression and NLEs on CRC is poorly understood.

The main objective of this study was to investigate the risk of CRC among depressed patients and individuals who experienced NLEs. Another aim was to assess the prevalence rate of depressive symptoms among CRC patients.

PATIENTS AND METHODS

Study design and sampling

A case–control study was performed from Colonoscopy Unit of the Cancer Institute in a general and referral hospital (Imam Reza) in Tabriz city (Azerbaijan province) from June 2015 to September 2016. The sample size was estimated based on Epi-info software and was 207 subjects for each case and control groups (totally 414 subjects) by considering α=0.05%, β=0.2, confidence level (CI) 95%, OR= 2, P0=0.3.

Inclusion criteria for the cases were confirmed CRC patients with positive colonoscopy and pathology findings, being a registered case in National Cancer Registry (NCR), and completing an informed consent form.

Exclusion criteria for the cases included the presence of any other neoplasms and having Intellectual Disability. Inclusion criteria for the controls included lack of any neoplasm and completing an informed consent and their exclusion criteria were involving with any neoplastic disorder, age above 75 years old, and involving with diet-related chronic diseases.

Cases and controls

Based on the inclusion criteria, 207 CRC patients were included as cases. The cases were selected by random sampling from the monthly list of patients referring to the Colonoscopy Unit and based on the estimated proportional sample size of each month of admission.

Also 207 controls without neoplastic conditions and diet-related diseases were identified from the same hospital and referred to that hospital at the same time for the cases.

Group matching was applied between case and control groups based on the variables of sex and age as the potential confounders. In this matching, equal subjects from each gender and age group were included in the case and control groups.

Data Collection

Baseline and demographic information were collected via a structured questionnaire by trained interviews who were not aware of patients' grouping. History of depression was assessed from at least 12 months before to the CRC diagnosis and confirmed based on the consumption of anti-depressant drugs, medical records in the community health centers (family physicians), clinics, or hospitals. We assumed that the history of depression and NLE among people may predispose and trigger the chance of CRC and based on this concept all psychological and NLE associated evidences were collected before the CRC diagnosis.

History of NLE was assessed also by Holmes and Rahe valid questionnaire (Persian version)[12]. This valid and reliable questionnaire is a 43-item of common various types of NLEs. We identified any NLEs experience at least 12 months before the cancer diagnosis and included family or marital conflicts (disputes, divorce or separation and conflicts or disagreement with first- and second-degree family members), unexpected loss of loved ones (parent, first-degree family, offspring, and partner), unemployment more than 6 months, serious financial and economic problems (crisis), occupational problems, life failures in studying or working, exposure to new conditions, migration or being refugee, emotional issues with the opposite sex and psychological distress[13].

To minimize the recall bias by respondents we asked them to think for a few days and remember any event of the past in detail. Moreover, we interviewed with the first-degree family of respondents and native community health workers to obtain valid information. The native community health workers in the health system of Iran have a face-to-face contact with large numbers of community members as a part of their routine performance.

A valid and reliable questionnaire of the Patient Health Questionnaire (PHQ9) was used for assessing the current depressive symptoms among study participants (CRC patients and controls). PHQ9 is a rapid and practical scale and it is appropriate for patients who are not in a well situation to respond. PHQ9 evaluates the passive thoughts of depressive symptoms within the last two weeks and is often used to screen depressed patients[14,15]. Response options for each item of the PHQ9 include: "not at all" (0 points), "several days" (1 point), "more than half the days" (2 points) or "nearly every day" (3 points). PHQ9 total scores range from 0 to 27. The interpretation of scores are based on : 1- 4 as minimal symptoms of depression , 5–9 mild, 10–14 moderate, and ≥15 severe[15]. A PHQ9 score >10 has been shown to have a sensitivity of 88% and a specificity of 88% for major depression[16]. Family CRC history was assessed among the first-degree relatives (parents, siblings, children, and grandchildren) via confirmed pathology findings or death by CRC.

Statistical Analysis

SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA) was used for data analysis. Kolmogorov-Smirnov test was used for checking data normality. Chi-square test was used to determine the relationship between binary variables in the case and control groups. Single logistic regression was used to estimate crude Odds Ratio (OR), and then significant variables and *p*-values with less than 0.2 were applied in multiple logistic regression to estimate the Adjusted Odds Ratio [17] with a 95% confidence interval (CI) for the risk of CRC. *p*-value ≤0.05 and 95% confidence interval were considered significant for all of the tests.

RESULTS

Table 1 shows the baseline and demographic status of the study participants. A total of 414 subjects (207 cases and 207 controls) participated

TABLE 1. Demographic and baseline characteristics of study participants.

Variables	*Cases (n=207)*	*Controls (n=207)*	*p-value*
Gender			0.921
Female 194 (46.86%)	95 (46)	99 (48)	
Male 220 (53.14%)	112 (54)	108 (52)	
Age ± (SD) 59.52 ± 13.58	60.54 ± 13.23	59.51 ± 13.73	
≤ 45	22 (10.62)	22 (10.62)	0.834
46-59	68 (32.8)	71 (34.3)	
≥ 60	117 (56.5)	114 (55)	
Occupation			
Employee	29 (14)	26 (12.56)	0.327
Farming related	24 (11.6)	24 (11.6)	
Household	91 (44)	109 (52.6)	
Others	63 (30.4)	48 (23.18)	
Educational level			
Primary school	131 (67.6)	140 (67.6)	0.723
Secondary school	57 (27.5)	36 (17.4)	
High school and Academic	19 (9.2)	31 (15)	
Residence			
Urban	144(69.5)	158(76)	0.250
Rural	63(30.5)	49(24)	
Smoking status(times/week)			0.054
Never	169 (81.6)	142 (68.5)	
Former	32 (15.45)	23 (11)	
Current < 20	16 (7.7)	13 (6.3)	
Current ≥20	2 (1)	17 (8.2)	
Smoking hookah			0.410
Yes	10 (4.8)	8 (3.8)	
No	197 (95.2)	199 (96)	
Never	88 (42.5)	70 (33.8)	

TABLE 2. Association between CRC and depression, NLEs and related factors.

Variable		*CRC (n=207)*	*Control (n=207)*	*OR (95% CI)*	*p-value (χ^2)*
History of depression	Yes	45	29	1.73 (1.05 – 2.91)	0.034
	No	162	176		
Duration of depression	No history	162	176	1	1
	≤ 5 years	22	17	1.40 (0.68 – 2.92)	0.317
	> 5 years	23	12	2.08 (1.02 – 4.74)	0.045
History of NLEs	Yes	88	62	1.70 (1.13 – 2.56)	0.01
	No	119	143		
Family history (first degree)	Yes	58 (28)	28 (13.5)	2.49 (1.51 – 4.10)	0.001
	No	149 (72)	179 (86.5)		
History of diabetes	Yes	48 (23.2)	21(10.14)	2.67 (1.53 – 4.65)	0.001
	No	159 (76.81)	186 (89.85)		
BMI*	<30 kg/m²	162	175	1.45 (0.95 – 2.21)	0.079
	≥30 kg/m²	44	30		

*Body Mass Index (BMI) assessed before cancer morbidity based on medical records.

in this study. Out of them, 194 (46.86%) and 220 (53.14%) were female and male, respectively. The average age of the respondents was 59.52 years standard deviation (SD): 13.58. Age (groups) and gender frequency (proportion) were almost equal among control and case groups (due to group-matched design). Regarding the other baseline characteristics, a significant association was found between smoking status and risk of CRC, whereas occupation, educational level, residence, and also smoking hookah were not associated with CRC.

We found that depression was associated with an increased risk of CRC (p=0.034). However, after categorized into two groups (< 5 and ≥ 5 years' history), depressed patients with more than 5 years history had an elevated risk of CRC (OR=2.18, 95% CI: 1.02 – 4.95) while patients with a history of <5 years did not show any increase risk of CRC. Moreover, individuals who have had a history of SLEs (p=0.01), family history (first degree) of CRC (p=0.001), and a history of diabetes (p=0.001) were significantly associated with an elevated risk of CRC (Table 2).

Table 3 shows the various types of NLEs among case and control groups. Out of these, loss of loved ones, family conflicts and financial problems increased the risk of CRC (p<0.05). Furthermore, serious occupational problems and unemployment of more than 6 months were associated with CRC but were not significant (p>0.05).

Table 4 indicates the results of multiple logistic regression after adjusting for the potential confounders and estimating the measure of associations (crude and adjusted odds ratios) and 95% confidence intervals for CRC risk and the history of depression and NLEs in the presence of other predictors. The final analysis showed that depression did not significantly increase the risk of CRC (OR=1.42, 95% CI: 0.92 – 2.21), while NLEs were significantly associated with increased risk of CRC (OR=1.84, 95% CI: 1.08 – 3.16). Moreover, we found that subjects with a history of CRC in the first degree of the family (2.91 times), history of diabetes (1.41 times), and current smoking (2.16 times) increased odds of CRC risk.

TABLE 3. History* of NLEs types among case and control groups.

Types of NLEs	*CRC (n=207)*	*Control (n=207)*	*p-value*
Loss of loved one	50 (24.16)	24 (11.6)	0.006
Financial problems	18 (9.17)	13 (6.3)	0.043
Family conflicts	22 (10.63)	12 (5.8)	0.024
Serious occupational problems	28 (13.53)	18 (8.7)	0.072
Unemployment of > 6 months	8 (3.87)	7 (3.38)	0.560
Other NLEs**	9 (4.35)	8 (3.87)	0.671

*At least 12 months prior of cancer diagnosis.
**Included life failures, psychological distress, retirement, and change in work, residence, sleeping, and eating habits.

TABLE 4. Multiple logistic regression for crude and Adjusted Odds Ratio (AOR) and 95% CI for CRC risk.

Variables	*Crude OR (95% CI)*	*Adjusted* OR (95% CI)*
History of depression	1.73 (1.05 – 2.91)	1.42 (0.92 – 2.21)
p-value	0.034	0.116
History of NLEs	1.70 (1.13 – 2.56)	1.84 (1.08 – 3.16)
p-value	0.01	0.026
Family history (first degree)	2.49 (1.51 – 4.10)	2.91 (1.64 – 5.18)
p-value	0.001	0.001
History of diabetes	2.67 (1.53 – 4.65)	1.41 (1.43 – 4.04)
p-value	0.001	0.001
Current smoking	1.90 (1.17 – 3.09)	2.16 (1.31 – 3.61)
p-value	0.008	0.002

*Adjusted for Body Mass Index (BMI).

Figure 1 shows the prevalence rate of depressive symptoms among studied participants according to the case and control groups. The findings showed that depressive symptoms were prevalent among CRC patients compared to the controls (p-value=0.027). After assessing by PHQ9, the proportion of depressive symptoms in case and control groups reported 11% and 8% severe, 19% and 14% moderate, 27% and 24% mild, 43% and 54% minimal, respectively.

DISCUSSION

This case-control study aimed at investigating the risk of CRC in depressed patients and people who experienced NLEs (before cancer diagnosis) and the distribution of depressive symptoms among case and control groups. In this case-control study after adjusting for the potential confounders, depression increased the chance of CRC insignificantly; however, NLEs were associated with CRC risk. Moreover, we found depressive symptoms were more prevalent in CRC patients than the controls.

Depression and CRC

In agreement with our results, a review study with a sample size of 93,805 CRC patients (15 studies) reported the prevalence of depression ranged from 1.6%–57%[2]. Likewise, the same results were reported by Medeiros et al[18]. They found depression and anxiety were higher in CRC patients compared to the control group. In a study from Saudi Arabia[19], the prevalence rate of depressive disorder in CRC patients was reported by 30%. Out of them (12.9% major depression, 5.7% minor depression, and 11.4% for dysthymia) that is approximately the same as our study results. In our study, we com-

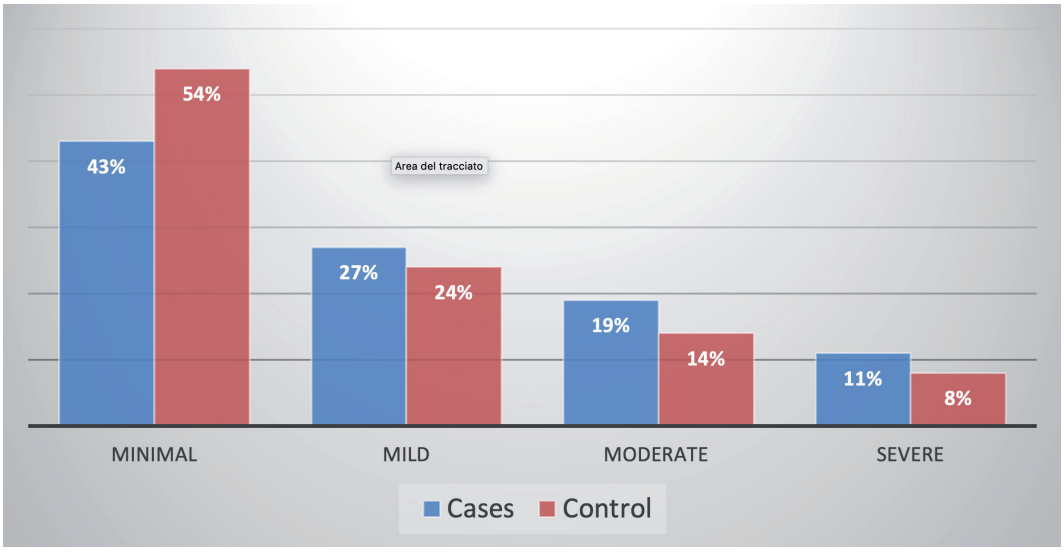

Fig. 1. Distribution of depressive symptoms* among case and control groups (p-value=0.027).
*Adjusted for Body Mass Index (BMI). Scale categorized: Minimal: 1-4, Mild: 5-9, Moderate: 10-14, Severe: ≥ 15.

pared depressive symptoms between CRC patients and controls without any neoplasms (11% and 8% severe, 19% and 14% moderate, 27% and 24% mild, 43% and 54% minimal symptoms among case and control groups, respectively).

Moreover, in a systematic review and meta-analysis with the sample size of 10,071 CRC patients and included 70 studies across 14 countries, the prevalence rates of depressive disorders were reported as major depression 16.3% (13.4–19.5%), minor depression 19.2% (9.1–31.9%), and 2.7% for dysthymia (1.7–4.0)[20]. The prevalence rate of major depression in this review study was reported marginally higher than our study (19% *vs.* 11%). The high prevalence of major depression in this large review study may be due to the review type of the study and the summary of findings of different studies from different countries and used various tools (scale) among included studies.

Depression is a strong risk factor for disease morbidity. Patients, especially those with cancers as well as depressive disorders, have a double mortality rates compared to non-depressed patients[21]. Depression is a common psychological comorbidity in CRC patients particularly in those who had received neo-adjuvant radiotherapy[11]. Patients with CRC are at specific risk of depression. Depressive disorders were associated with social and cognitive functioning, physical impairments, difficulties with personal care and constipation[11].

Moreover, depression has been associated with increased risks of diabetes, hypertension, and cardiovascular diseases[22]. A meta-analysis and systematic review study reported that depression could increase the risk of stroke morbidity and mortality [10].

To our knowledge, this study is one of the rare studies that has been examining the risk of CRC in depressed patients. Despite this, depression was frequent in CRC patients compared to controls, but no evidence found that depression increases the risk of CRC. Few studies have investigated the association between depression or depressive disorders and CRC risk. In agreement with our results, Kroenke et al[23] found a weak association between depressive symptoms and CRC. Nonetheless, most studies did not find a significant association between depression and CRC[24,25]. However, few studies recommended screening and adequate assessment of depressive symptoms and disorders as a necessary issue for cancer patients[26].

NLEs and CRC

We found NLEs associated with increased risk of CRC significantly. In the final analysis of the present study, cases had 1.84 times the odds of CRC risk than controls. Loss of loved, family conflicts, and financial problem were found significant types of NLEs for increased risk of CRC. In agreement with our results, several case-control studies that examined the associations between CRC and life events found a significant positive association between CRC risk and stressor life events[3,27]. The same results were observed in the present study and in a cohort study in Melbourne[28]. However, few studies found a weak association between CRC and NLEs[29]. On the other hand, a review study and a study from Iran showed NLEs evaluated the likelihood of depressive symptoms[30,31].

Secondary findings

Our findings showed that family history (first degree) of CRC, diabetes, and current smoking have increased the risk of CRC. In agreement with our study, many studies found family history and smoking associated with CRC risk[32,33]. In the final multiple variable model, we found diabetic patients had 1.41 times higher risk of CRC than the non-diabetic patients. The same results were found in cohort and case-control studies about diabetes[34,35] and metabolic syndrome[1]. These results provide strong evidence for family history of CRC, diabetes and smoking that are risk factors for CRC.

Strengthens and Limitations

Although in this study a significant relationship between CRC and NLEs as well as a non-significant association with depression after adjusting for the potential confounders was found, there are some potential limitations. The main concern is recall bias. We tried to reduce recall biases by including those who were not diagnosed as CRC patients more than the last 6 months of cancer diagnosis. Moreover, we used trained interviews who were not aware of the case and control groupings. Furthermore, we used native community health workers to obtain valid information about exposures and events of the long past of respondents. The native community health workers had a face-to-face contact with large numbers of community members as part of their usual routine performance.

Another concern was to obtain an accurate awareness about the required minimum time of exposure (long and persistent) to induce a causal relationship between exposures (depression and NLEs) and CRC incident. On the other hand, some depressed patients reported recurrent relapses and recurrent recovery in their interviews. To solve these problems, we have considered the

total number of times they suffered from depression in the lifetime period. Another solution was assessing the history of depression and NLEs one year before the CRC diagnosis.

Recommendation for future studies

More well-designed longitudinal studies are needed for assessing the associations between CRC and depression, and also, we recommend that the effect of acute (short-term) and chronic (long-term) types of NLEs to be assessed separately. Screening assessment is also beneficial either among CRC patients for depressive disorders or among depressed patients for possible CRC.

CONCLUSIONS

This study revealed a significant positive association between CRC and NLEs. However, there was no strong evidence that depression increases the risk of CRC. Furthermore, CRC was increasingly associated with the family history of CRC, diabetes and current smoking. Moreover, depressive symptoms were significantly frequent in CRC patients.

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All authors read and approved the final manuscript. We also thank "Clinical Research Development Unit, Razi Psychiatric Hospital, Tabriz University of Medical Sciences", Tabriz, Iran

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Informed Consent:
Written informed consent was obtained from participants before interviews.

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Data availability statement:
The datasets generated and/or analyzed during the current study are available by the corresponding author on reasonable request.

Conflict of interest:
The authors declare that there is no conflict of interests.

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