Metabolic Syndrome and Risk of Colorectal Cancer: A Case-Control Study

Elham Davtalab Esmaeili [1], Khairollah Asadollahi [2], Ali Delpisheh [3], Kourosh Sayehmiri [4] and Hosein Azizi [1, 5, *]

[1]Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Social Medicine, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[3]Department of Clinical Epidemiology, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran
[4]Department of Biostatistics, Psychosocial Injuries Research Center, Ilam University of Medical Sciences, Ilam, Iran
[5]Department of Epidemiology and Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran

Corresponding author: Department of Epidemiology and Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran. Email: epid_azizi@yahoo.com

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Abstract

Background: Among Middle East countries, the prevalence of Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T2DM) dramatically increased in Iran. Very few evidence-based studies have been performed on the relationship between metabolic disorders and colorectal cancer (CRC) in developing countries at least in Iran.

Objectives: This case-control study aimed to determine the relationship between MetS and CRC risk.

Methods: A case-control study with 414 participants (207 cases and 207 controls) was conducted among referral hospitals (Imam Reza, Shahid Madani, and Sina) in Tabriz, Azerbaijan province, Iran. Cases with CRC confirmed by positive pathology and colonoscopy findings were selected and compared with the controls without neoplastic and chronic diseases at the same time and hospitals for the cases. Group matching was used based on sex and age variables for the case and control groups. MetS was defined by the International Diabetes Federation (IDF) criteria. Multiple logistic regression was used to estimate adjusted odds ratios for the association between MetS and odds of CRC.

Results: Out of 414 participants, 220 (53%) were men. Among the cases, 134 (64.73%) patients had MetS, while in the control group, 82 individuals (39.61) had MetS history. After adjusting for the confounders, MetS and DM history were significantly associated with elevated odds of CRC (OR: 2.79, %95 CI: 1.58 - 5.15, P = 0.001) and (OR: 2.57, %95 CI: 1.25 - 4.58, P = 0.006), respectively. We have observed also a dose-response relation and a trend between the components of MetS and CRC risk. So, the odds of CRC increased by rising numbers of MetS components.

Conclusions: It seems that MetS and its components are associated with an increased risk of CRC.

Keywords: Colorectal Cancer, Metabolic Syndrome, Type 2 Diabetes, Case-Control Study

1. Background

Colorectal cancer (CRC) is the third most widespread neoplasm and the second principal cause of cancer-associated deaths globally (1). Among Iranian women, CRC is the third and among men, it is the fourth most common malignancy. The incidence rate of CRC was increased significantly in the last decades in Iran, as a developing country (2). Developed countries have the highest rates of CRC, typically in western industrialized and municipal districts, including the United States, Canada, Australia, and North-Western Europe. In the United States, CRC is the second most important cause of malignancy-related fatality (3). In Asia, the prevalence of CRC is less than in North America, Europe, Australia, and New Zealand (1).

Lifestyle and metabolic disorders in particular Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T2DM) and other risk factors such as genetics, dietary pattern, smoking, obesity, stressful life events, and hormonal factors are the most important determinants of the risk of CRC in high-incidence countries (1, 4-6). MetS and T2DM are increasing dramatically in the world. Among Iranians, systematic review and meta-analysis studies indicated a high prevalence of MetS with 32% (7). MetS is a collection of metabolic factors, including high fasting blood sugar, hypertension, abdominal obesity, increased serum triglyceride level, and decreased high-density lipoprotein (HDL) cholesterol level. Several studies (8, 9) and a population-based prospective cohort study (10)

show that MetS and T2DM were associated with CRC in western and industrialized countries. T2DM and MetS have procarcinogenic effects in the gastrointestinal system, especially colon and rectum by insulin resistance (8).

The prevalence of diabetes and obesity, with an estimated total of 400 million people suffering from T2DM, have been globally increased (11). Lifestyle changes are one of the most important public health problems in Iran, located in the Middle East's diabetes belt and have one of the highest rates of T2DM with more than 4 million patients (12). In Iran, trend analysis based on systematic review studies indicated an ascending trend on both T2DM and obesity (13). Among 25 - 70-year-old persons, the T2DM incidence rate was increased by 35.1% and the total DM prevalence rate was 14.60% (14, 15).

2. Objectives

In the developing countries at least in Iran with a high prevalence of T2DM and obesity, very few analytical studies have been published on the association between CRC and metabolic disorders (7-9). Therefore, the aim of this study was to determine the relationship between CRC and MetS in Azerbaijan province, Iran.

3. Methods

3.1. Study Design

A case-control study was conducted from April 2012 through March 2014 in the general and referral hospitals (Imam Reza, Shahid Madani, and Sina) with Colonoscopy Units of the Cancer Institute, Tabriz, Azerbaijan province. The sample size was 207 subjects for each case and control groups based on Epi-info software, considering a confidence level of 95%, $\alpha = 0.05\%$, $\beta = 0.2$, OR = 2, and $P_0 = 0.3$.

3.2. Participants

The study population included all patients referring to colonoscopy units. In Iran, names, as well as demographic and pathology characteristic of all neoplasmic patients with CRC, had been registered in the National Cancer Registration (NCR) software. The list of CRC cases in colonoscopy units matched the NCR list. A total of 414 subjects aged 35 to 75 years participated in the study; 207 CRC cases were defined based on confirmed pathology and colonoscopy findings, identified no longer than 6 months previous to the interview. The cases were selected by random quota sampling from the monthly list of patients referring to colonoscopy units and based on proportional to

the size of hospital beds. Controls without neoplastic condition and chronic diseases such as psychiatry, digestive and diet-related and COPD were selected from the same hospitals and at the same period for the cases. The diagnosis of depression and psychological diseases was based on records in health centers, hospitals, and clinics, as well as self-reporting of patients. The case and control groups were matched by sex and age groups.

3.3. Matching Protocol

The group was matched for adjusting the potential confounder's sex and age. In this matching, the subjects were divided into 3 age groups, including 35 to 45, 46 to 59, and $\geq$ 60 years. In each age group, the same number of subjects (22.68, 117 in the case group and 22.71, 114 in the controls) were selected, respectively. Furthermore, almost the same number of females and males were selected in the case and control groups (95, 99 female and 112, 108 male for case and control groups, respectively).

3.4. Inclusion and Exclusion Criteria

The inclusion criteria were CRC confirmed patients with positive colonoscopy and pathology findings for the cases aged 35 to 75 years; they matched NCR, signed the informed consent, and were free of CRC. The exclusion criteria were neoplastic conditions, age above 75 years old and lower than 35 years, history of depression and psychological diseases, and diet-related chronic diseases for controls.

3.5. Data Collection

A valid questionnaire was completed by trained interviewers to assess the history of T2DM, MetS, and CRC risk factors. This questionnaire included information on socio-demographic characteristics, DM history, blood profiles, and family history of CRC, physical activity, smoking habits, and dietary intake. This questionnaire has excellent validity and reproducibility. The content validity of this questionnaire has been confirmed by the panel team, including gastroenterologist, pathologist, epidemiologist, statistician, psychiatrist, and field experts and some questions were revised. Cronbach's Alpha coefficient ($\alpha = 0.78$) was used for the reliability of the questionnaire. The information contained in the questionnaire was collected by interviewing and extracting from the existing files of patients in colonoscopy, medical records, hospital admission, and hospital surgery units. The DM history was collected at least 1 year before cancer diagnosis among cases and at the same time interval for the control group. DM status was defined on the basis of the results of the blood glucose test in the patient records and by an interview with

a patient or a medical doctor, who confirmed whether participants have diabetes and in case of a positive diagnosis, the age of diabetes diagnosis was asked. In order to confirm the diagnosis of subjects with self-reported DM, we referred to the hospital records of the patients or to the household records in the health centers. At least a 1-year interval was considered for the history of DM before the diagnosis of CRC.

MetS was defined based on the International Diabetes Federation (IDF) criteria by considering 3 or more following options: systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85, fasting blood sugar (FBS) $\geq$ 110 mg/dL, waist circumference $\geq$ 88 cm in women and $\geq$ 102 cm in men or body mass index (BMI) > 30 kg/m², serum triglycerides (TG) > 150 mg/dL, and high density lipoprotein (HDL) < 40 mg/dL in men and < 50 mg/dL in women.

Blood pressure was measured twice with mercury barometric after 10 minutes resting between measurements. The mean of two systolic and diastolic blood pressures was considered as the final blood pressure. Five mL of fasting blood specimen was taken by the trained laboratory personnel for the determination of FBS, HDL, and TG.

Physical activity was assessed based on standard metabolic energy equivalent task (MET) times/week, which was used based on different activities, which were weighted according to intensity, time and period of activity during the last 1 year before CRC diagnosis. Vegetable consumption assessed by unit and food consumption was collected by the frequency of intake of a given serving of each food item daily, weekly, monthly, and yearly.

Weight, with minimal clothes and without shoes, was measured to the nearest to 0.1 kg before admission because the weight of patients with cancer was decreased during disease period. Height was measured, using SECA body meter. Height measurement was done with a precision nearest to 0.1 cm in stand position without shoes. Then, body mass index (BMI) was calculated according to WHO standard by dividing weight (kg) by the square of height (meter). Alcohol consumption was not answered by participants due to the religious beliefs of the Islamic Republic of Iran. Therefore, it was not included in the analysis.

3.6. Statistical Analysis

SPSS software (version 16.0, Chicago, IL, USA) was used for data analysis. For checking data normality, the Kolmogorov-Smirnov test was used. The chi-square test and the Cochran-Mantel-Hansel chi-square test with adjustments for sex were used to determine the relationship between study variables in the case and control groups (16). MetS status was divided into two categories; patients with MetS and without MetS. Then, the relationship between the number of components of the MetS and CRC

with elevated components was assessed. Single logistic regression was used to estimate crude OR; then, significant variables and P values with less than 0.2 were applied in multiple logistic regression to estimate the adjusted odds ratio (AOR) with a 95% confidence interval (CI) for the risk of CRC. 95% confidence interval and P value < 0.05 was considered significant in all of the tests.

4. Results

The socioeconomic characteristics of the participants and odds of CRC were shown in Table 1. Out of the 414 subjects in the study, 220 (53%) were male. Average and standard deviation (SD) of age was 59.52 $\pm$ 13.58. Via group-matched design, age and sex were the same in controls and cases. Significant differences were found between cases and controls in the history of CRC and DM in the first-degree family, smoking, overcooked meat consumption (per week), high-fat food (per week), and physical activity.

Table 2 shows the crud and Mantel-Hansel adjusted odds ratio for CRC and history of DM and MetS status. Both the history of DM and MetS significantly increased odds of CRC by 2.71 and 2.79 times, respectively. Of 207 CRC cases, 48 (23.2%) had a history of DM at least in the last year while in the control group, 21 (10.14%) subjects had a history of DM. Also, MetS frequency was 134 (64.73%) in the case group and 82 (39.61%) in the control group. We also observed a dose-response relationship and an escalating trend between the components of MetS and CRC risk. So, the odds of CRC was increased by raising the numbers of MetS components. Patients with all MetS components had the highest odds ratio and increased the odds of CRC risk 14.47 times more than patients, who did not have any component whereas patients with only one component have the lowest odds ratio (1.52 times).

Among the components of MetS, there was a significant association between obesity, low HDL, and an increased risk of CRC (Table 3).

Final analysis by multiple logistic regression after adjusting for the confounders and estimating adjusted odds ratios and 95% confidence intervals indicated that MetS and DM history significantly increase the odds of CRC 2.71 and 2.79 times, respectively. The results showed that the odds of CRC in subjects with a history of MetS were 2.71 times higher than those without MetS. Among DM patients, the odds ratio (OR) of CRC risk was 2.79 times higher than that of the non-diabetics. Furthermore, significant differences were found between CRC and overcooked meat consumption, high-fat food, history of CRC, and DM in the first-degree family (Table 4).

Table 1. General Characteristics of Study Participants[a, b]

Variables	CRC (N = 207)	Control (N = 207)	P Value
Gender			0.921
Female	95 (46)	99 (48)	
Male	112 (54)	108 (52)	
Age (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)	
Family history of CRC in first degree			0.001
Yes	58 (28)	28 (13.5)	
No	149 (72)	179 (86.5)	
History of diabetes in first degree			0.006
Yes	78 (38)	51 (25)	
No	129 (62)	156 (75)	
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)	
Physical activity (times/week)			0.039
1 - 2 times/week	113 (45.5)	118 (57)	
≤ 3 times/week	6 (3)	19 (9.2)	
Fried	59 (28.5)	39 (18.8)	
Overcooked meat consumption (per week)			0.001
1 - 2 times ≥	54 (26.1)	89 (43)	
3 - 4 times	109 (52.6)	107 (52)	
Daily	44 (21.3)	9 (5)	
High-fat food (per week)			0.001
1 - 2 times ≥	17 (8.2)	69 (33.33)	
3 - 4 times	66 (31.8)	100 (48.3)	
Daily	124 (60)	36 (18.37)	
Fruit and vegetable intake (daily/unit)			0.011
Poorest (1 ≥)	71 (34.3)	49 (23.67)	
Sometimes (2 - 3)	113 (54.5)	125 (60.38)	
Always (4 ≤)	23 (11.2)	31 (15)	

[a]Chi-square (χ^2).
[b]Values are expressed as No. (%).

Table 2. Crude and Adjusted Odds Ratio (AORs) and 95% Cls for Colorectal Cancer Risk in Relation to the History of MetS and Its Components

Variable	CRC (n = 207)	Control (n = 207)	Crude OR (95% CI)	Adjusted OR (95% CI)
DM History[a]			2.67 (1.53 - 4.65)	2.71 (1.54 - 4.76)
Yes	48 (23.2)	21 (10.14)		
No	159 (76.81)	186 (89.85)		
P value			0.001	0.001
MetS History			2.81 (1.88 - 4.25)	2.79 (1.87 - 4.16)
Yes[b]	134 (64.73)	82 (39.61)		
No	73 (35.26)	125 (60.38)		
P value			0.001	0.001
MetS component				
0	7	28	Ref	Ref
1	27	42	2.56 (1.08 - 9.45)	1.52 (0.88 - 10.90)
2	39	55	3.16 (0.87 - 18.14)	2.42 (0.73 - 15.65)
3	52	39	6.32 (2.11 - 22.43)	7.33 (2.76 - 23.58)
4	49	28	9.20 (3.76 - 26.24)	11.17 (3.53 - 9.80)
5	33	15	11.73 (3.96 - 28.41)	14.47 (4.26 - 31.75)

[a] At least for one year.
[b] Having at least 3 components of MetS.

Table 3. Odds Ratios (ORs) and 95% Cls of Colorectal Cancer Risk Based on Each Component of MetS[a]

Components of MetS	Cases (N = 207)	Control (N = 207)	95% CI	P Value
FBS			1.17 (0.79 - 1.72)	0.428
< 110	87	95		
$\geq$ 110	120	112		
BMI			3.01 (1.99 - 4.55)	0.001
< 30 kg/m^2	99	152		
$\geq$ 30 kg/m^2	108	55		
BP			0.68 (0.45 - 1.05)	0.076
< 140/85	126	131		
$\geq$ 140/85	81	76		
HDL			2.047 (1.34 - 3.12)	0.0008
> 40 in Male and > 50 in women	51	83		
< 40 in Male and < 50 in women	156	124		
TG			1.25 (0.84 - 1.88)	0.260
< 150 mg/dL	69	80		
> 150 mg/dL	138	127		

[a] Chi-square (χ^2).

5. Discussion

In the present study, after adjustment for the potential confounders and socio-demographic variables by multiple logistic regressions, MetS and DM history were significantly associated with the increased odds of CRC. The results of this study showed that the odds of developing CRC are clearly associated with metabolic disorders. Prospective (10) and systematic review studies (8, 15) in the world have been conducted to identify the relation of the history of DM and MetS to CRC, but the present research is one of the rare studies was conducted in Iran. Our results are completely consistent with the findings of studies in other countries, including the case-control studies of Woo et al. in Korea (17), Ulaganathan (18), and Cavicchia et al. in the

Table 4. Multiple Logistic Regressions for Crude and Adjusted Odds Ratio (AOR) and 95% CI for CRC Risk and History of MetS in the Presence of Covariates

Variables	CRC (n = 207)	Control (n = 207)	Crude OR (95% CI)	Adjusted OR (95% CI)
DM history			2.67 (1.53 - 4.65)	2.57 (1.27 - 5.23)
Yes	48 (23.2)	21 (10.14)		
No	159 (76.81)	186 (89.85)		
P value			0.001	0.006
MetS status			2.81 (1.88 - 4.25)	2.86 (1.58 - 5.15)
Yes	134 (64.73)	82 (39.61)		
No	73 (35.26)	125 (60.38)		
P value			0.001	0.001
History of CRC in the first-degree family			2.48 (1.5-4.1)	1.97 (1.2-3.97)
Yes	58 (28)	28 (13.5)		
No	149 (72)	179 (86.5)		
P value			0.001	0.01
History of diabetes in the first-degree family			1.85 (1.21 - 2.82)	2.27 (1.29 - 3.97)
Yes	78 (38)	51 (25)		
No	129 (62)	156 (75)		
P value			0.006	0.004
High-fat food (per week)			3.64 (2.67 - 4.95)	3.58 (2.5 - 5.14)
1 - 2 times $\geq$	17 (8.2)	69 (33.33)		
3 - 4 times	66 (31.8)	100 (48.3)		
Daily	124 (60)	36 (18.37)		
P value			0.001	0.001
Overcooked meat consumption (per week)			2.21 (1.66 - 2.9)	1.97 (1.39 - 2.79)
1 - 2 times $\geq$	54 (26.1)	89 (43)		
3 - 4 times	109 (52.6)	107 (52)		
Daily	44 (21.3)	9 (5)		
P value			0.001	0.001
Physical activity (times/week)			0.79 (0.64 - 0.98)	0.81 (0.6 - 1.08)
1 - 2 times/week	113 (45.5)	118 (57)		
$\leq$ 3 times/week	6 (3)	19 (9.2)		
Fried	59 (28.5)	39 (18.8)		
P value			0.039	0.163
Fruit and vegetable intake (daily/unit)			0.71 (0.53 - 0.92)	0.89 (0.61 - 1.29)
Poorest (1 $\geq$)	71 (34.3)	49 (23.67)		
Sometimes (2 - 3)	113 (54.5)	125 (60.38)		
Always (4 $\leq$)	23 (11.2)	31 (15)		
P value			0.011	0.530

USA ([19]).

In a population-based prospective study of Wang et al. with the presence of 37001 patients with diabetes and 148004 controls, the incidence of CRC in diabetic patients was 2.1 times higher than that of non-diabetic patients ([10]). In a case-control study in Korea ([17]) and the present study, the odds ratio of CRC was 2 and 2.57, respectively. The same result was found in the present study and Yang et al.'s study

in the USA (20) and also a nested case-control study (21). As well, a systematic review and meta-analysis showed that the history of DM increases the risk of CRC compared with non-DM patients (8). Even, some studies have put up a step forward and have shown a positive and significant association between pre-diabetes and CRC (22).

Of course, only in the study of Dash et al. in the United States, no association was found between diabetes and CRC in African-American women (23).

There are several reasons and mechanisms to justify the relationship between metabolic disorders and DM with CRC. A theory is that hormones are involved in the incident of CRC. In patients with diabetes, there are high concentrations of insulin and insulin-like growth factor hormones. These hormones cause growth and expansion of cells and can also cause carcinogenesis (24). Another mechanism is related to insulin resistance. Insulin resistance in T2DM patients has pro-carcinogenic effects on the colon and rectum and digestive system (8).

The Islamic Republic of Iran is the second largest country in the Middle East (2). In 2000, the National Cancer Registry Program (INCRS) was launched in Iran. CRC is the third most common cancer in Iran (4). Based on the annual report of INCRS, CRC after stomach, bladder, and prostate cancer is the fourth common malignancy in men, but it the second most common malignancy after breast cancer among women (25). Although, CRC rates significantly varies in different geographical regions and provinces of Iran. Globally, CRC is the second and third most common malignancy in women and men, respectively (26). In the last decades, studies indicated a rapid increase in the incidence of CRC among Iranian (27) due to the environmental risk factors, improvement in the registry system, dietary patterns, and availability to health services. Among Iranians, the standardized rates of CRC were 8.16 and 6.17 for males and females, respectively (2).

Considering the high prevalence of DM in Iran as one of the risk factors for CRC, DM can be causative to this cancer. The health system of Iran has undergone a reform in the last decade. The National Action Plan for Prevention and Control of Non-Communicable Disease (NAP-PCND) was performed and implemented in 2015 - 2016. The National CRC Screening among the 50 - 69 age group is ongoing in Iran. Due to the preventable and screenable capability of CRC, it can reduce the incidence and burden of this cancer in the future years.

MetS is one of the most health-related problems in Iran. Evidence-based and systematic review studies show that the prevalence of MetS is 32% among Iranians (7). Our study indicates that MetS increased the risk of CRC markedly, both in univariate and multiple analyses. Most of the findings regarding the association of MetS with CRC

have been performed in developed and western societies (6, 16, and 29). Very few studies have reported the association of MetS and CRC in Iran. Most of them are cross sectional (28). The results of case-control studies are similar and in agreement with our findings (9, 29) and also a systematic review study (15). Moreover, in the present study and the study by Ulaganathan et al. (18), obesity and low HDL were the components of MetS that increased CRC risk.

According to the findings of the present study, there is a significant and affirmative relationship between high-fat diet and consumption of red meat with CRC risk. Reports from other studies also confirm our findings (29, 30), including Azizi et al.'s study in Azarbayjan province (4), a systematic review study (31), and a case-control study in Tehran (32). This observed relationship is reasonable with the delayed transmission of high-fat foods from the gastrointestinal system. This relationship also has been observed in animal clinical trials (33).

5.1. Conclusions

After adjusting for the confounders, our results indicated that MetS and DM history increase the odds of CRC risk. It is suggested that large prospective studies should be conducted with a high sample size. CRC screening should be applied among metabolic disorders especially among MetS and DM patients for the early diagnosis and treatment of CRC patients and increase the quality of life and survival of them. Moreover, health systems should apply for healthy lifestyle education programs and action plans to reduce the MetS components for CRC risk and other related chronic disease prevention.

5.2. Limitations

Although our study after adjusting for the confounders found the association between history of DM, MetS, and CRC risk, there are several limitations. We tried to reduce temporality biases between the history of DM, MetS, and CRC through including patients with DM and MetS detection 1 year before cancer diagnosis. Although another concern was selection bias, to diminish this bias, controls were study-based on cases (colonoscopy units) and case and control groups matched age and gender and logistic regression models were used to estimate adjusted ORs.

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Footnotes

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