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Lifestyle, dietary pattern and colorectal cancer: a case-control study

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Abstract

Background In Iran, not only the incidence of colorectal cancer (CRC) is increasing but also the age of patients at diagnosis is alarmingly dropping. We need urgent actions to better understand the epidemiology of CRC and the contributing factors for such pattern in Iranian population. The aim of our study was to determine the potential contribution of lifestyle, including dietary pattern, to CRC in a large Iranian province.

Methods A hospital based case-control study was performed on 572 participants (275 cases and 297 controls). Patients in the case group were newly diagnosed with CRC in a referral hospital and patients in the control group were selected from those patients with non-malignancy diseases who were admitted to the same hospital. Control group was frequency matched to the case group for gender and age.

Results Based on the results of multivariable logistic regression analysis, direct associations were observed between usual pattern of defecation ($OR_{>3rd/every\ day}$ =4.74, 95% CI: 1.78–12.59), chicken consumption ($OR_{sometimes\ or\ always/occasionally}$ = 6.33, 95% CI:3.23–12.43), family history of CRC ($OR_{yes/no}$ =5.79, 95% CI: 2.72–12.31), and alcohol consumption ($OR_{yes/no}$ =6.03, 95% CI: 2.14–16.98) with the odds of CRC among the study population. On the other hand, taking multivitamins ($OR_{yes/no}$=0.09, 95% CI:0.04–0.20), consumption of coffee ($OR_{always/occasionally}$ =0.29, 95% CI: 0.12–0.69), taking vitamins D supplement ($OR_{yes/no}$ =0.38,95% CI:0.22–0.66), and consumption of garlic ($OR_{sometimes/occasionally}$ =0.53,95% CI: 0.30–0.95) significantly reduced the odds of CRC.

Conclusions We revealed potentially significant effects of several lifestyle related factors with CRC risk in Iranian population. More studies are required to understand the mechanism of action of the associated factors in developing CRC.

Keywords Colorectal cancer, Risk factors, Case-control study, Iran

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Introduction

Colorectal cancer is the third most common cancer and the second leading cause of disability-adjusted life years (DALYs) in the world with its incidence increasing in developing countries [1, 2]. According to the available evidence, a significant rise in the global incidence of CRC is expected from 1.93 to 3.2 million by 2040 [3]. In addition, the trend of CRC incidence varies dramatically throughout the world, with the highest in Australia and New Zealand, followed by Western Europe and North America [4]. Moreover, the incidence of this disease has doubled in young people since the 1990s and now 1 out of every 10 diagnosed patients is at the age of 50 years or younger. Based on evidence, these alterations have been attributed to changes in diet, lifestyle, and environmental exposures [5]. Some researchers suggest that the increase in the incidence of colorectal cancer especially in low- and middle-income countries may be explained by the rise in alcohol consumption, smoking, obesity, unhealthy diet, sedentary lifestyle, and increased life expectancy [2].

Colorectal cancer is also a common cancer in Iran (the third among Iranian men and fourth among Iranian women) [6]. In a recent study in Iran, the overall age-standardized incidence rate (ASR) of CRC was 114.49 [4] and the age-standardized mortality rate (ASMR) of the condition for men and women was 8.3 and 6.3 per 100,000 respectively [7]. Evidence also suggest that the incidence of CRC in Iranian younger adults is increasing worryingly [8, 9], a pattern which is mainly attributed to changing lifestyle and diet [3] (e.g. overweight, consumption of grilled meat, animal fats, and sugar) [10]. In general, it has been shown that by becoming more overweight or obese, people become more prone to several types of cancer including CRC [11]. For example, the results of a systematic review in Iran suggest that the main risk factors for CRC are high consumption of red meat, fried foods, diabetes, low consumption of fruits and vegetables, family history, and obesity [6]. Also, the results of various studies in Iran have reported the potential involvement of risk factors such as male gender, less physical activity, genetic predisposition, and alcohol consumption in development of CRC [12–14]. In addition, Safari and her colleagues showed that after adjusting for several factors, a healthy dietary pattern was significantly associated with lower risk of colorectal cancer, whereas an increased risk of colon cancer was observed with the Western dietary pattern [15]. With regard to the fact that Fars is a large province with a high incidence rate of CRC in Iran [16], this case-control study was performed to define the risk factors of colorectal cancer in Iranian population.

Methods

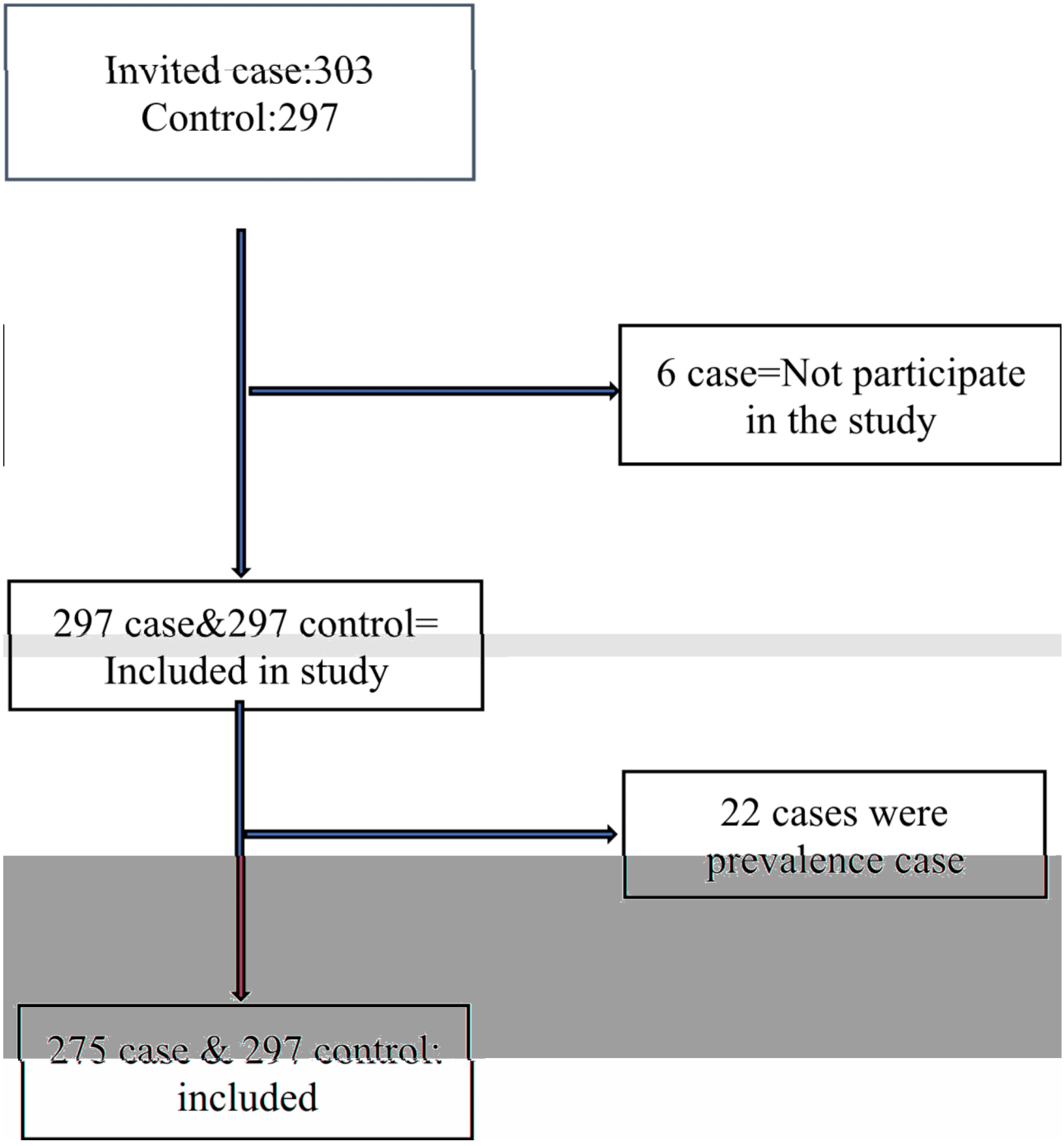
Settings All participants were patients who visited Imam Reza educational clinic in Shiraz the capital of Fars province. The clinic is a large and well-known referral center in the southern part of the country. Running under Shiraz University of Medical Sciences, the clinic provides a wide range of medical cares to patients from the surrounding provinces.

Selection of cases

From November 2017 to March 2022, all newly diagnosed cases (n=303, mean time from diagnosis to interview=8.1 months) of colorectal cancer who visited the clinic for routine follow-up were invited to participate. The diagnosis procedure of CRC was mainly started by a visit to a physician due to related symptoms and being referred to a gastroenterologist for colonoscopy and tissue sampling for pathology as the final stage of diagnosis (all patients had a positive pathology report). Among the invited patients, only 6 (2%) refused (n=4) or were not able (n=2) to participate (participation rate 98%). In addition, 22 patients were later excluded due to being diagnosed in other centers before being referred to the study center. As a result, a total number of 275 patients were included in the study (Graph 1).

Selection of controls As hospital controls, 297 patients from those visited acupuncture, orthopedics and rehabilitation wards (admitted due to fracture and its related pain and movement limitation) were selected during the same period. The control participants went under no particular CRC screening procedure. This was based on the assumption that the selected participants experience the same rate of CRC as general population (expected to have CRC in less than 1 participant among the control group). As a result, we expect no adverse effect of undiagnosed CRC among controls on the results [17]. Controls were frequency-matched with cases for age and gender.

Inclusion and exclusion criteria All new cases of colorectal cancer who were diagnosed in the study center were included in the study. Patients without a pathology report were not included. Patients who were simultaneously suffering from another type of cancer or had a history of cancer were excluded from the study. Controls were included if they reported no history of cancer at enrolment. Both case and control participants were also excluded if they were not able to take part in the interview due to their health status. all participants provided informed consent at the start of interview. The ethics committee of Shiraz University of Medical Sciences approved the protocol of this study (IR.SUMS.SCHEANUT.REC.1400.056).



Graph 1 Flow chart of enrolment in the study

Data collection To maintain temporality, except for demographic data, all participants were requested to answer the questions referring to their usual lifestyle a year before the interview. Due to the predominantly low level of education in the study population, a team of two epidemiologists, one public health nurse and an oncologist designed an interview-administered questionnaire to collect the required information (listed below). The clinical data was obtained from the patient's medical files. In order to evaluate the reliability of the questionnaire and the method of interview, a pilot study on 50 cases was conducted. Cases were decided to be included in the pilot study due to the concerns over their ability and willing to participate and response. Using the test-retest approach the questionnaire found to be adequately reliable (Cronbach's alpha = 0.79). A trained female nurse interviewed all

participants in a private place. The interviewer was rigorously trained to follow standardized approach and procedure for cases and controls. Regular monitoring of the interview process was conducted, including audio recordings (with participant consent) and periodic reviews of interview techniques. Participants (cases and controls) were asked to report their usual lifestyle, diet and health status from a year before the interview (for controls) or before experiencing the first symptom of their current condition (for cases, whichever was the first). Demographic status (i.e. age, gender, marital status, place of residency, level of education, and occupation) was obtained from the patient's medical file. In addition, patients reported their perceived economic status, height (cm), weight (kg), hospitalization history (yes, no), family history of gastrointestinal diseases (yes, no), family history of any type of cancer (yes, no), stool consistency (watery, normal, hard), defecation pattern (every day, every 2 or 3 days, more than 3 days), and regular physical activity (yes, no). Participants also reported some dietary related factors such as regular fasting (yes, no), ever smoked daily for at list 6 month (yes, no) [18], iron intake (yes, no), multivitamins intake (yes, no), and taking antibiotics (never, rarely, several times). To ease the interpretation of the results, age (frequency matched) was categorized and used in the analysis. Body mass index was calculated and categorized based on WHO's recommendation (<18.5 as underweight, 18.5–24.9 as normal, 25-29.9 as overweight, and ≥30 as obese). In addition, the participants reported their consumption of several food items that are common in Iranian diets in an ordinary base (i.e. <1 times/week as never or occasionally, 1–6 times/week as sometimes or often, and ≥1 times/day as always). These foods are namely; fruits, vegetables, sweets, pickles, milk, red meats, fish, chicken meats, beans, nuts, garlic, onion, coffee, and sausages. Moreover, usual type of oil consumed (saturated/ animal fat, and unsaturated fat) and regular use of alcohol (yes, no) were reported by the participants.

Sample size and statistical analysis We used all available CRC cases for the analysis. A post-hoc power analysis suggested that our study can detect an odds-ratio for red meat consumption (considered the main nutritional factor) as small as 1.65 (or.60) with alpha value of 0.05 and power of 80% [19]. For categorical variables, frequencies and percentages are reported. Statistical tests (i.e. Chi-square and t-test) were conducted to measure un-adjusted associations between the study variables and colorectal cancer. In addition, as suggested by others, with regard to the unpaired matching strategy (frequency matching) unconditional logistic regression models with bonferroni correction were used to examine the crude and adjusted associations between the study variables and CRC [20]. Using all study variables (listed in Table 1) in the base model, backward and forward variable selection method was used to define the final model. However, age, gender, place of residency, education/occupation, economic status, history of diseases, BMI, and physical activity were included in the final model irrespective of the output of variable selection procedure. Reporting the odds, we used the first/lowest level of each variable as reference group. P-values<0.05 were considered significant. STATA14.0 software (STATA, College Station, TX, USA) was used for all statistical analyses.

Results

The mean age of cases and controls at the interview was 58.95±12.35 and 58.50±12.37 respectively ($P>0.953$). Case and control groups were predominantly male (57.3%) ($P>0.735$). Table 1 shows the distribution of the study variables among cases and controls.

The crude and adjusted associations between the independent factors and CRC are presented in Table 2. According to the unadjusted results, place of residency, education, occupation, smoking, fasting, family history of gastrointestinal diseases, stool consistency, family history CRC and other cancers, and defecation pattern were significantly associated with CRC. In addition, taking antibiotics, iron, vitamin D and multivitamins, consumption of fast foods, coffee, sausage, onion, garlic, fruits and vegetables, sweets, milk, pickles, red meat, fish, alcohol, and chicken were significantly associated with CRC ($p<0.05$).

The results of multivariable logistic regression analysis provided the adjusted relationships between the study variables and odds of colorectal cancer (Table 2). The usual pattern of defecation ($OR\geq_{3\ day/everyday}$ =4.74, 95% CI:1.78–12.59, $P=0.002$), chicken consumption ($OR_{sometimes\ or\ always/occasionally}$ = 6.33, 95% CI:3.23–12.43, $P<0.001$), family history of colorectal cancer ($OR_{yes/no}$ =5.79, 95%CI: 2.72–12.31, $P<0.001$), alcohol consumption ($OR_{no/yes}$ =6.03, 95% CI: 2.14–16.98, $P=0.001$), stool consistency ($OR_{too\ hard\ or\ soft\ /\ normal}$ = 3.33, 95% CI: 1.83–6.05, $P<0.001$), consumption of pickles ($OR_{always/occasionally}$ =3.66, 95%CI:1.23–10.82, $P=0.019$) or sausages ($OR_{sometimes/occasionally}$=2.85, 95%CI:1.16–7.03, $P=0.022$), smoking ($OR_{yes/\ no}$ =3.07, 95% CI: 1.61–5.85, $P=0.001$), history of other chronic diseases ($OR_{yes/\ no}$ = 3.31, 95% CI: 1.83–5.99, $P<0.001$), and taking antibiotics ($OR_{yes\ /\ no}$ =2.33, 95% CI: 1.31–4.15, $P=0.004$) were directly associated with the odds of colorectal cancer. On the other hand, taking multivitamins ($OR_{yes/no}$=0.09, 95%CI:0.04–0.20, $P<0.001$), vitamin D ($OR_{yes/no}$=0.34, 95%CI:0.19–0.62, $P=0.001$), coffee ($OR_{always/Occasionally}$ =0.31, 95%CI:0.12–0.77, $P=0.012$), fruit consumption ($OR_{sometimes/occasionally}$=0.37, 95%CI:0.18–0.73, $P=0.004$), garlic consumption ($OR_{sometimes/occationally}$=0.53, 95%CI:0.30–0.95, $P=0.033$), vegetables consumption ($OR_{somtimes/occasioonally}$=0.45,

Table 1 Characteristics of the study participants

Factors		CRC patients (275)	Controls (297)	*P*-value
		N (%)	*N* (%)	
Age(year)	< 50	59(21.5)	62(20.9)	0.953
	50–60	89(32.4)	94(31.6)	
	≥ 60	127(46.2)	141(47.5)	
Gender	Male	160(58.2)	168(56.6)	0.735
	Female	115(41.8)	129(43.4)	
Place of residency	Urban	214(77.8)	251(84.5)	0.042
	Rural	61(22.2)	46(15.5)	
Education	Illiterate	39(14.2)	37(12.5)	0.622
	Other	236(85.8)	260(87.5)	
Occupation	Self-employed	113(41.1)	99(33.3)	0.099
	Employee	67(24.4)	92(31.0)	
	Housekeeper	95(34.5)	106(35.7)	
Perceived economic status	Bad	124(45.1)	133(44.8)	0.912
	Moderate	127(46.2)	135(45.5)	
	Good	24(8.7)	29(9.8)	
Marital status	Ever married	233(84.7)	249(83.8)	0.819
	Never married	42(15.3)	48(16.2)	
History of chronic diseases	Yes	161(58.5)	122(41.1)	< 0.001
	No	114(41.5)	175(58.9)	
History of hospitalization	Yes	168(61.1)	211(71.0)	0.013
	No	107(38.9)	86(29.0)	
Taking antibiotics	Rarely	74(26.9)	136(45.8)	< 0.001
	Several times	201(73.1)	161(54.2)	
Family history of gastrointestinal diseases	Yes	69(25.1)	64(21.5)	0.324
	No	206(74.9)	233(78.5)	
Family history of colorectal cancer	Yes	64(23.3)	25(8.4)	< 0.001
	No	211(76.7)	272(91.6)	
Family history of other types of cancer	Yes	133(48.4)	101(34.0)	0.001
	No	142(51.6)	196(66.0)	
Usual pattern of defecation	Every day	122(44.4)	232(78.1)	< 0.001
	Every 2 or 3 days	101(36.7)	54(18.2)	
	More than 3 days	52(18.9)	11(3.7)	
Stool consistency	Normal	117(42.5)	231(77.8)	< 0.001
	Hard/watery	158(57.5)	66(22.2)	
Sausages consumption	Rarely	211(76.7)	287(93.6)	< 0.001
	Often	64(23.3)	19 (6.4)	
Onion consumption	Occasionally	116(42.2)	80(26.9)	0.001
	Sometime	68(24.7)	97(32.7)	
	Always	91(33.1)	120(40.4)	
Garlic consumption	Rarely	187(68.0)	159(53.5)	< 0.001
	Often	88(32.0)	138(46.5)	
Nuts consumption	Occasionally	233(84.7)	240(80.8)	0.432
	Sometime	33(11.3)	44(14.8)	
	Always	11(4.0)	13(4.4)	
Beans consumption	Occasionally	94(34.2)	95(32)	0.381
	Sometime	146(53.1)	152(51.2)	
	Always	35(12.7)	50(16.8)	
Smoking	Yes	120(43.6)	70(23.6)	< 0.001
	No	155(56.4)	227(76.4)	
BMI*	Underweight &Normal	121(44.2)	119(40.2)	0.609
	Overweight	117(42.7)	133(44.9)	
	Obese	36(13.1)	44(14.9)	

Table 1 (continued)

Factors		CRC patients (275)	Controls (297)	*P*-value
		N (%)	*N* (%)	
Regular iron supplement	Yes	51(18.5)	84(28.3)	0.008
	No	224(81.5)	213(71.7)	
Regular multivitamins supplement	Yes	31(11.3)	102(34.3)	< 0.001
	No	244(88.7)	195(65.7)	
Regular vitamin D supplement	Yes	75(27.3)	157(52.9)	< 0.001
	No	200(72.7)	140(47.1)	
Regular alcohol consumption	Yes	41(14.9)	17(5.7)	< 0.001
	No	234(85.1)	280(94.3)	
Regular fasting	Yes	102(37.1)	155(52.2)	< 0.001
	No	173(62.9)	142(47.8)	
Usual type of oil consumed	Saturated/animal fat	82(29.8)	48(16.2)	< 0.001
	Unsaturated fat	193(70.2)	249(83.8)	
Vegetable consumption	Occasionally	140(50.9)	92(31.0)	< 0.001
	Sometime	85(30.9)	124(41.8)	
	Always	50(18.2)	81(27.3)	
Fruit consumption	Occasionally	142(51.6)	82(27.6)	< 0.001
	Sometime	65(23.6)	113(38.0)	
	Always	68(24.7)	102(34.3)	
Sweets consumption	Occasionally	217(78.9)	264(88.9)	0.004
	Sometimes	43(15.6)	26(8.8)	
	Always	15(5.5)	7 (2.4)	
Milk consumption	Occasionally	237(86.2)	240(80.8)	0.074
	Sometime	29(10.5)	35(11.8)	
	Always	9(3.3)	22(7.4)	
Pickles consumption	Occasionally	175(63.6)	215(72.4)	0.074
	Sometime	73(26.5)	62(20.9)	
	Always	27(9.8)	20(6.7)	
Red meat consumption	Occasionally	59(21.5)	116(39.1)	< 0.001
	Sometimes	216(78.5)	181(60.9)	
Fish consumption	Occasionally	235(85.5)	188(63.3)	< 0.001
	Sometimes	40(14.5)	109(36.7)	
Chicken consumption(P/W)	Occasionally	41(14.9)	114(38.4)	< 0.001
	Sometimes	234(85.1)	183(61.6)	
Coffee consumption	Occasionally	217(78.9)	203(68.4)	0.012
	Sometimes	29(10.5)	40(13.5)	
	Often	29(10.5)	54(18.2)	
Regular physical activity	Yes	109(39.6)	140(47.1)	0.077
	No	166(60.4)	157(52.9)	

*BMI = Body mass index

95%CI:0.24–0.85, $P=0.015$), type of oil predominantly consumed ($OR_{unsaturated\ /saturated\&animal\ fat}=0.41$, 95%CI:0.20–0.82, $P=0.012$), and fish consumption ($OR_{sometimes/occasionally}=0.36$, 95%CI:0.19–0.70, $P=0.002$) were shown to be protective (Graph 2).

Discussion

This study revealed the association of a wide range of lifestyle and dietary related factors with CRC in the Iranian population. Results of the present study suggested that the odds of CRC is larger among those who had delayed defecation, chicken meat consumption, positive family history of CRC, alcohol consumption, abnormal stool consistency, consumption of pickles or sausages, smoking, history of other chronic diseases, red meat consumption, and taking antibiotics. On the other hand, the odds are smaller in those take fasting, multivitamins or vitamin D and coffee, fruit, garlic, vegetables, fish, and unsaturated oils consumption.

In the current study, smoking and alcohol consumption are significantly associated with the odds of CRC. Reporting similar pattern, Lee et al. reported significant associations between smoking and alcohol consumption with an increased risk of developing CRC [21]. In

Table 2 Crude and adjusted associations between the study variables and colorectal cancer^

Variables	Categories	Crude Odds Ratio (95% CI)	*P*-value	Adjusted Odds Ratio (95% CI)	*P*-value	*P*-value with Bonferroni correction
Age(year)	< 50	1	-	1	-	-
	50–60	0.99(0.62–1.57)	0.983	0.84(0.37–1.89)	0.680	0.999
	≥ 60	0.94(0.61–1.45)	0.802	0.86(0.37–2.02)	0.743	0.999
Gender	Male	1	-	1	-	-
	Female	0.93(0.67–1.30)	0.696	2.45(0.88–6.82)	0.085	0.999
Place of residency	Urban	1	-	1	-	-
	Rural	1.55(1.01–2.37)	0.041	1.01(0.48–2.12)	0.963	0.999
Education	Illiterate	1	-	1	-	-
	Other	0.86(0.53,1.39)	0.544	0.50(0.21–1.19)	0.120	0.999
Occupation	Self-employed	1	-	1	-	-
	Employee	0.63(0.42,0.96)	0.034	2.02(0.93,4.35)	0.072	0.999
	Housekeeper	0.78(0.53,1.15)	0.220	0.85(0.30,2.43)	0.774	0.999
Perceived economic status	Bad	1	-	1	-	-
	Moderate	1.06(0.75,1.48)	0.771	1.15(0.64–2.08)	0.623	0.999
	Good	0.87(0.75,1.57)	0.656	3.49(1.29–9.40)	0.013	0.513
Marital status	Ever married	1	-	1	-	-
	Never married	1.06(0.68,1.67)	0.771	NA	-	
History of chronic diseases	No	1	-	1	-	-
	Yes	2.02(1.45,2.81)	< 0.001	3.31(1.83,5.99)	< 0.001	0.003
History of hospitalization	No	1	-	1	-	-
	Yes	0.63(0.45,0.90)	0.012	NA	-	-
Taking antibiotics	Rarely	1	-	1	-	-
	Several times	2.29(1.61,3.25)	< 0.001	2.33(1.31,4.15)	0.004	0.153
Family history of gastrointestinal diseases	No	1	-	1	-	-
	Yes	1.21(0.82,1.79)	0.317	NA	-	-
Family history of colorectal cancer	No	1	-	1	-	-
	Yes	3.30(2.00,5.41)	< 0.001	5.79(2.72,12.31)	< 0.001	< 0.001
Family history of other types of cancer	No	1	-	1	-	-
	Yes	1.81(1.29,2.54)	0.001	2.82(1.59,4.99)	< 0.001	0.014
Usual pattern of defecation	Every day	1	-	1	-	-
	Every 2–3 days	3.55(2.39,5.28)	< 0.001	4.74(2.42,9.28)	< 0.001	< 0.001
	> 3 days	8.98(4.52,17.85)	< 0.001	4.74(1.78,12.59)	0.002	0.068
Stool consistency	Normal	1	-	1	-	-
	Hard/watery	4.72(3.28,6.79)	< 0.001	3.33(1.83,6.05)	< 0.001	0.003
Sausages consumption	Occasionally	1	-	1	-	-
	Sometimes/always	4.43(2.57,7.63)	< 0.001	2.85(1.16,7.03)	0.022	0.862
Onion consumption	Occasionally	1	-	1	-	-
	Sometimes	0.48(0.31,0.73)	0.001	NA	-	-
	Always	0.52(0.35,0.77)	0.001	NA	-	-
Garlic consumption	Occasionally	1	-	1	-	-
	Sometimes	0.54(0.38,0.76)	< 0.001	0.53(0.30,0.95)	0.033	0.999
Nuts consumption	Occasionally	1	-	1	-	-
	Sometimes	0.72(0.44,1.18)	0.203	NA	-	-
	Always	0.87(0.38,1.98)	0.743	NA	-	-
Beans consumption	Occasionally	1	-	1	-	-
	Sometimes	0.97(0.67,1.39)	0.873	NA	-	-
	Always	0.70(0.42,1.18)	0.190	NA	-	-
Smoking	No	1	-	1	-	-
	Yes	2.51(1.75,3.59)	< 0.001	3.07(1.61,5.85)	0.001	0.024
BMI*	Underweight &Normal	1	-	1	-	-
	Overweight	0.86(0.60,1.23)	0.423	1.54(0.84–2.82)	0.160	0.999
	Obese	0.80(0.48,1.33)	0.402	1.50(0.67–3.36)	0.314	0.999

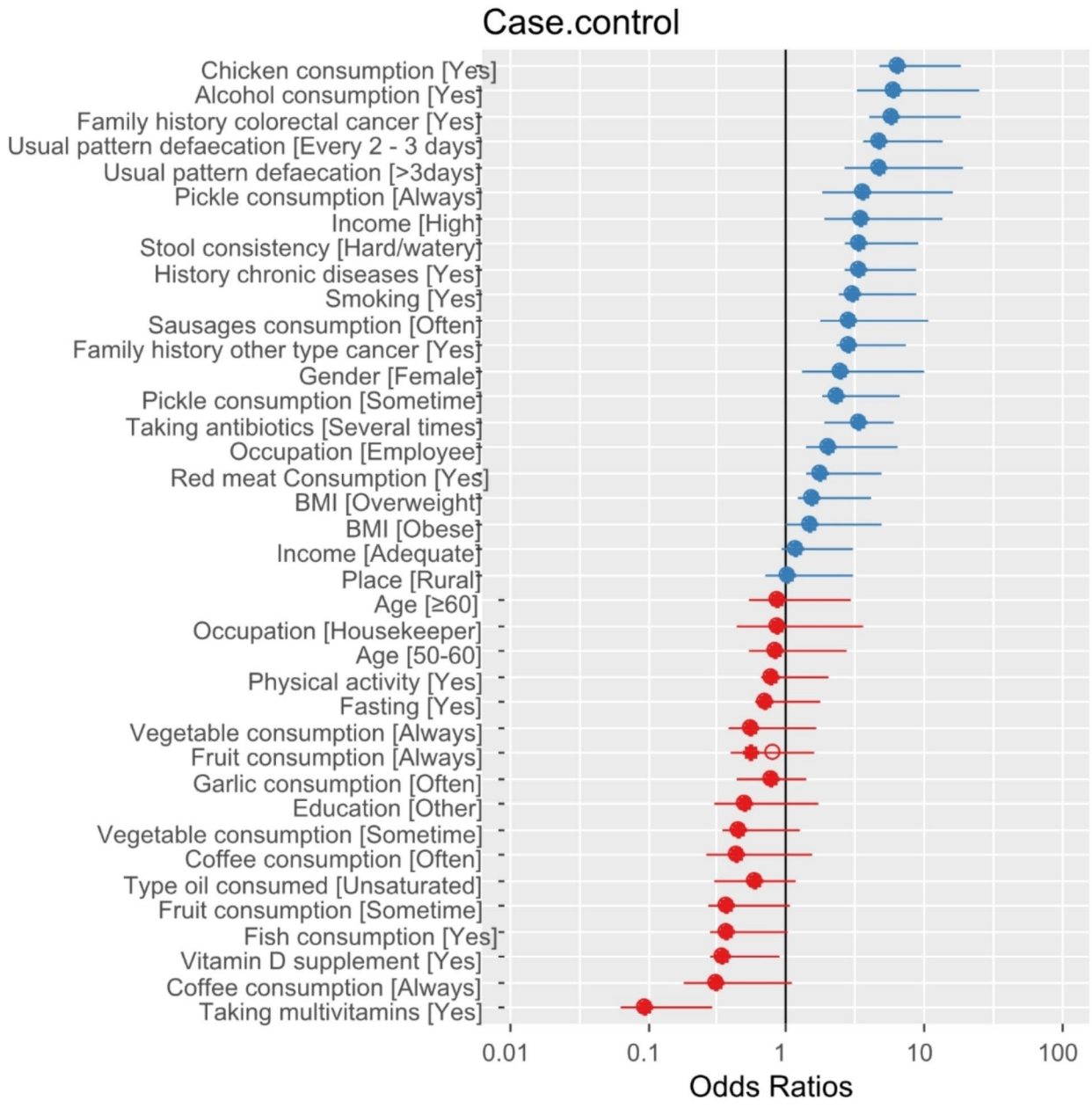
Table 2 (continued)

Variables	Categories	Crude Odds Ratio (95% CI)	*P*-value	Adjusted Odds Ratio (95% CI)	*P*-value	*P*-value with Bonferroni correction
Regular iron supplement	No	1	-	1	-	-
	Yes	0.57(0.38,0.85)	0.006	NA	-	-
Regular multivitamins supplement	No	1	-	1	-	-
	Yes	0.24(0.15,0.37)	< 0.001	0.09(0.04,0.20)	< 0.001	< 0.001
Regular alcohol consumption	No	1	-	1	-	-
	Yes	2.88(1.59,5.21)	< 0.001	6.03(2.14, 16.98)	0.001	0.026
Regular fasting	No	1	-	1	-	-
	Yes	0.54(0.38,0.75)	< 0.001	0.71(0.41,1.23)	0.223	0.999
Usual type of oil consumed	Saturated/animal fat	1	-	1	-	-
	Unsaturated fat	0.43(0.30,0.67)	< 0.001	0.41(0.20,0.82)	0.012	0.458
Vegetable consumption	Occasionally	1	-	1	-	-
	Sometimes	0.45(0.30,0.65)	< 0.001	0.45(0.24,0.85)	0.015	0.582
	Always	0.40(0.26,0.62)	< 0.001	0.55(0.26,1.15)	0.115	0.999
Fruit consumption	Occasionally	1	-	1	-	-
	Sometime	0.33(0.22,0.49)	< 0.001	0.37(0.18,0.73)	0.004	0.169
	Always	0.38(0.25,0.58)	< 0.001	0.54(0.27,1.09)	0.089	0.999
Sweet consumption	Occasionally	1	-	1	-	-
	Sometimes	2.01(1.19–3.38)	0.008	NA	-	-
	Always	2.60(1.04,6.50)	0.004	NA	-	-
Milk consumption	Occasionally	1	-	1	-	-
	Sometimes	0.83(0.49,1.41)	0.511	NA	-	-
	Always	0.41(0.18–0.91)	0.030	NA	-	-
Pickles consumption	Occasionally	1	-	1	-	-
	Sometimes	1.44(0.97,2.14)	0.065	2.35(1.24,4.46)	0.009	0.332
	Always	1.65(0.89,3.05)	0.105	3.66(1.23,10.82)	0.019	0.735
Red meat consumption	Occasionally	1	-	1	-	-
	Sometimes/always	2.34(1.61,3.39)	< 0.001	1.79(0.96,3.32)	0.064	0.999
Fish consumption	Occasionally	1	-	1	-	-
	Sometimes/always	0.29(0.19,0.44)	< 0.001	0.36(0.19,0.70)	0.002	0.091
Chicken consumption	Occasionally	1	-	1	-	-
	Sometimes/always	3.55(2.36,5.33)	< 0.001	6.33(3.23,12.43)	< 0.001	< 0.001
Coffee consumption	Occasionally	1	-	1	-	-
	Sometimes	0.67(0.40,1.13)	0.139	0.44(0.18,1.05)	0.067	0.999
	Always	0.50(0.30,0.82)	0.006	0.31(0.12,0.77)	0.012	0.463
Regular physical activity	No	1	-	1	-	-
	Yes	0.73(0.52,1.02)	0.071	0.79(0.45–1.38)	0.410	0.999
Regular vitamin D supplement	No	1	-	1	-	
	Yes	0.33(0.23,0.47)	< 0.001	0.34 (0.19,0.62)	< 0.001	0.014

^ all variables listed under crude associations are used to define the final model ; *BMI=Body mass index;

America, men and women smokers were at an increased risk of colon cancer [22]. Evidence shows that smoking can trigger pathogenic reactions including severe chronic inflammation and subsequent cancer in the gastrointestinal tract. Cigarette smoke and its active compounds disrupt the basic structure of the digestive system through the induction of cellular apoptosis and the inhibition of mucosal cell renewal. Cigarette smoke also interferes with the protective mechanisms of the digestive system by reducing blood flow in the mucosa and modulating the mucosal immune system [23]. Regarding alcohol use, the conversion of ethanol into its metabolites can have carcinogenic effects in the colon. Production of acetaldehyde of other alcohol metabolites can lead to cancer-inducing factors such as DNA-adduct formation, oxidative stress and lipid peroxidation, epigenetic alterations, epithelial barrier dysfunction, and immune modulatory effects [24].

We revealed that the odds of fasting is lower in CRC patients. The results of an animal study showed that fasting for two weeks prevented the growth of mice tumors. Fasting suppressed M2 polarization of tumor-associated



Graph 2 Factors associated with CRC

macrophages to inhibit tumor growth by decreasing the adenosine level in the tumor microenvironment both in vivo and in vitro [25]. As a result, calorie restriction via fasting is a useful way to modulate autophagy and increase the effectiveness of anti-cancer treatments [26]. In an animal model, fasting/fasting mimicking diet (FMD) cycles may prevent cancer through reductions in glucose, visceral fat, insulin, and leptin [27].

The present study revealed a positive association between antibiotic use and odds of CRC. McDowell et al. believe that there is a strong link between antibiotic use and CRC, particularly colon cancer [28]. Antibiotics lead to the production of many chemicals and disrupting the balance of the intestinal microbiome, which can cause different types of cancers, including CRC. Although the exact mechanism of antibiotic effect on the incidence of CRC has not yet been determined, evidence suggests that even short-term treatment with antibiotics can shift gut micro biota to a long-term dysbiosis and thus cause several diseases such as CRC [29].

Our study suggested that taking multivitamins especially vitamin D supplement may significantly reduce the odds of CRC. Through multiple pathways, especially Wnt/β-catenin, apoptosis and inflammation, vitamin D

is associated with a lower risk of CRC incidence and its slower progression [30]. Vitamin D acts as a carcinogenesis inhibitor with many physiological functions, such as anti-inflammatory, immunomodulatory, enhancing DNA repair, antioxidant protection, and antiangiogenic effects [31]. Our study also supported the results from Massa et al. suggesting that taking multivitamins, even in a short period, is associated with a lower risk of developing colorectal cancer [32]. Giovannucci et al. also believe that long-term use of multivitamins reduces the risk of colon cancer due to the higher intake of folic acid [33]. Also, it has been shown that intake of folate, vitamin B2, vitamin B6, and vitamin B12 is associated with a reduced risk of colon cancer [34]. Evidence suggests that these nutrients may play a positive role in DNA methylation, thereby reducing the risk of CRC [35].

Our study showed that having bowel movement every day reduces the odds of CRC whereas having constipation act as a strong risk factor for CRC. The results of a study in Japan showed that infrequent bowel movements could increase the risk of CRC in men and women [36]. In addition, Malcolm and et al. showed that constipation almost doubles the risk of colon cancer [37]. The findings of another study encouraged physicians to consider colorectal cancer as a differential diagnosis in young patients with altered bowel habits [38]. However, a study in the Netherlands showed that frequent bowel movement is associated with an increased risk, and constipation is associated with a decreased risk of CRC [39]. According to the evidence, constipation affects the intestinal microbiota, and as a result, rises the susceptibility to intestinal diseases, including CRC [40].The explanation of the observed contradiction needs further in-depth investigations.

As suggested by Ma et al., the results of our study showed that chronic diseases (e.g. type 2 diabetes and high blood pressure) increase the odds of developing colorectal cancer [41]. Type 2 diabetes may increase the risk of CRC via hyperinsulinemia and insulin-like growth factor (IGF) axis, hyperglycemia, adipose tissue dysfunction-induced inflammation, gastrointestinal motility disorder, and impaired immunological function [42]. Also, a meta-analysis showed a positive association between high blood pressure and CRC [43] Studies show that metformin consumption reduces the growth and proliferation of colon cancerous cells by changing the levels of microRNAs [44, 45]. It is possible that the above conditions act directly or indirectly in rising the odds of CRC or through their medications respectively. Further studies are needed to reveal the actual mechanisms underneath the observed associations.

The results of the current study showed that having a family history of colorectal or other types of cancer significantly increase the odds of CRC. L. Beebe-Dimmer et al. showed that the risk of developing colorectal cancer is higher among those reporting a history of colon and prostate cancer in their first-degree family members [46]. In a study applying the novel approach of measuring risks in families, melanoma, thyroid and eye cancers are also related to CRC. The evidence even supports the priority of initiation of CRC screening among those with positive family history of cancer [47]. Evidence suggested the role of common or similar gene sequences among family members that can accelerate the occurrence of CRC [48].

The results of the present study suggested that the use of processed meats such as sausages increase the odds of CRC in the study population. Similarly, the results of a meta-analysis showed that higher consumption of processed meat is associated with an increased risk of colorectal cancer [49]. Processed meats contains nitrites, which is highly associated with an increased risk of many types of cancer including CRC. Nitrite leads to the formation of N-nitroso compounds (NOC), chemicals that are proved to be carcinogenic [50]. In another study, consumption of fast foods, including falafel and potato and corn chips was significantly associated with an increased risk of CRC in Jordan [51]. The results of a review study showed that several mechanisms such as the presence of carcinogenic N-nitroso-compounds and heme-induced promoters cause cancer through nitrite binds to the heme iron and creation of nitrosylheme [52].

We have shown that coffee may reduce the odds of developing colorectal cancer. Supporting our results, a study showed that coffee consumption is associated with a reduction in the risk of CRC progression and mortality in patients with advanced or metastatic colorectal cancer [53]. Kim et al. showed that high coffee consumption might be associated with a reduced risk of colon cancer in a Korean population [54]. It is believed that caffeine prevents the proliferation of colon cancer cells [53]. Also, it is suggested that caffeine and caffeic acid slows down the growth of colorectal cancer mainly by cell phase arrest and apoptosis boost [55]. In general, caffeine can reduce the incidence of colorectal cancer by changing the gut microbiome [56]. Also, coffee polyphenols, such as chlorogenic acids (CGAs) and specific diterpenes of coffee such as kahweol, promote anti-inflammatory, antiproliferative, antioxidant and pro-apoptotic effects [57].

The results of the present study showed that garlic consumption has a role in preventing CRC. Similarly, the results of a meta-analysis suggested that the four main organic sulfides in garlic, diallyl disulfide (DADS), diallyl trisulfide (DATS), S-allylmercaptocysteine (SAMC) and allicin, may play a positive role in the regulation of tumor cell apoptosis, migration and the cell cycle in intestinal cells [58]. In addition, Sarvizadeh et al. showed that allicin present in garlic exerts its anti-cancer activity in

gastrointestinal tract by inhibiting cell growth and apoptosis-induced cell death [59].

The inverse association between fruit and vegetable consumption and colorectal cancer has been shown by previously published epidemiological studies [60, 61]. However, Bradbury et al. found no association between fruit and vegetable consumption and CRC [62]. On the other hand, Lee et al. showed that green vegetables and fruits were strongly associated with a reduced risk of colon cancer in men and women [63]. It seems that, by increasing the speed of food transfer from the colon, the production of stool mass, and increasing bacterial fermentation, the fiber in fruits and vegetables give the intestinal bacteria less opportunity to produce carcinogenic substances [64]. Evidence shows that Naringenin, a naturally occurring flavonoid in citrus fruits, prevents the proliferation of HT-29 colon cancer cells [65].

We supported the few previously published studies that pickle consumption increases the odds of developing colon and gastric cancer [66, 67]. A possible explanation could be that pickles contain nitrite that can cause gastrointestinal cancer, e.g. rectal cancer [68, 69]. Also, high concentration of salt in pickles may partly explain the observed association [70].

We have shown that consuming unsaturated oil has a protective role in CRC when compared to saturated oils. Evidence shows that saturated fats are associated with an increased risk of thyroid cancer [71]. In South Korea, the risk of colorectal adenoma increased with higher consumption of saturated fatty acids (SFA) intake [72]. The evidence shows that reducing the consumption of saturated fats and n-6 polyunsaturated fatty acids (PUFAs) and increasing the consumption of n-3 PUFAs, particularly eicosapentaenoic acid and docosahexaenoic acid, can prevent CRC [73].

The results of the present study showed that the consumption of red and chicken meats increase the odds of developing CRC. On the other hand, consuming fish largely reduces the odds of CRC. Similarly, in their research, Dallas et al. showed that red meat consumption raises the risk of CRC [74]. The harmful role of red meat in the formation of CRC has been reported in several studies [74, 75]. However, epidemiological studies have shown that the preventive effect of fish meat on the risk of CRC is partly explained by people's lifestyle. Accordingly, people who use fish instead of meat have a healthier lifestyle including habits beneficial in preventing cancer such as reduced consumption of red meat, less smoking and more physical activity [76, 77]. Fish meat may also act as preventing factor through exposing body to long-chain n-3 polyunsaturated fatty acids (n-3 LC-PUFAs) [78]. A possible explanation for the association between CRC risk and red meat consumption is the presence of heterocyclic amines (HCAs), heme iron, PUFAs, N-nitroso compounds (NOCs) in red meat, and bile acids [79].

Strengths and limitations

The current study is conducted on all incident cases of CRC in a large population and a wide range of data on different aspects of social and health status with a large number of behavioral factors is collected and analyzed simultaneously. In addition, the study is designed avoid temporality problem via collecting information about the participant's usual life as we collected data from the time before their condition were diagnosed. However, as a common issue in case-control studies (especially when we are interested in the nutritional status before interview) recall bias and reverse causation is to be considered when interpreting the results. To address these issues the respondents were well informed that we are interested in their usual lifestyle (including diet) before they were affected by their current condition. Even otherwise, with the exception of weight and BMI which are pottentially affected by the participants conditions (with no significant effect on the model fitness), most studied parameters are not expected to be noticeably altered due to symptoms before diagnosis. Also, we used hospital controls and categorical or ordered answer questions to reduce recall bias in our study [80]. Using ordered or categorical questions can potentially reduce recall bias by providing participants with predefined response options [80, 81]. This approach helps respondents to structure their responses and reduces reliance on memory alone [82]. Inevitably, due to the essential differences in the diagnosis procedures between the outcome of interest (CRC) and conditions selected for including controls, a systematic difference in the contribution of cases and controls my existed. We did not include many potentially important dietary or behavioral parameters (such as consuming probiotic products or products quality (e.g. organic or inorganic) to our study. This was partly due to keeping the limited timeframe for conducting interview and also the low general and health literacy of the respondents causing difficulties in understanding such questions.

Conclusion

Our study suggested that some chronic diseases, family history of CRC or other types of cancer, smoking, taking antibiotics and consumption of alcohol, fast food, sausage, red and chicken meat have significant effects on a higher odds of CRC. On the other hand, taking multivitamins (vitamin D in particular), fasting, consuming fish, coffee, garlic, fruit and vegetable seems to decrease the risk of CRC. Change in our dietary habits is beneficial in reducing the risk of CRC. In addition, given the observed results, educating the community and conducting a

routine screening program for CRC in families with a history of cancer (especially CRC) can reduce diagnosis delay and mortality among patients. Further, especially designed studies are needed to enhance our knowledge about the etiology of this type of cancer.

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Author contributions
Z.R. and S.A. researched and wrote the manuscript.M.M. and H.GH. and MP.Z. critically reviewed the manuscript. M.F. critically reviewed and edited the manuscript. All authors reviewed the manuscript.

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Data availability
"The datasets generated and/or analyzed during the current study are not publicly available due to its being the intellectual property of Shiraz University of Medical Sciences but are available from the corresponding author on reasonable request".

Declarations

Ethics approval and consent to participate
The protocol of this study is approved by the ethics committee of Shiraz University of Medical Sciences and executed in accordance with the Declaration of Helsinki. (IR.SUMS.SCHEANUT.REC.1400.056). Informed consent has been obtained from all participants. All methods were performed following the declaration of Helsinki and Iranian national guidelines.

Competing interests
The authors declare no competing interests.

Conflict of interest
Authors declare no conflict of interest.

Patient and public involvement
The subject was highlighted by the public health experts in the Fars provinces health center based on the annual report on causes of death in Fars province. Patients corrected the design and questionnaire of this research during the pilot phase of the study. The feasibility, outcome and independent variables, and methods of recruitment were defined and revised during discussion with patients through structured interviews. Public will be informed of the key messages of the study through the website of School of health under Shiraz university of medical Sciences.

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