scientific reports

Check for updates

OPEN

Association between prediagnostic risk factors and survival after colorectal cancer diagnosis in Golesten cohort study

Amirhossein Yadegar[1], Sahar Dalvand[2], Maryam Sharafkhah[1], Sadaf G. Sepanlou[3], Hossein Poustchi[1], Gholamreza Roshandel[4], Mahdi Sheikh[5], Alireza Sadjadi[1], Fatemeh Mohammadi[1], Sahar Masoudi[1], Reza Malekzadeh[1], Negar Rezaei[3]✉ & Alireza Delavari[1]✉

This study investigated the survival rates of colorectal cancer (CRC) and the association between several pre-diagnostic factors, including demographic, anthropometric, behavioral, nutritional, lifestyle, and medical history and CRC incidence and survival. Among 50,045 participants in the Golestan cohort study, 190 patients diagnosed with CRC during the follow-up period were included in this study. Cox regression and Kaplan–Meier were used for analysis. The CRC incidence risk was significantly higher in males (HR = 2.20; 1.54–3.14), adults aged 50–70 years (HR = 1.86, 1.36–2.55), adults aged 70 years and older (HR = 3.71; 2.13–6.44), and urban dwellers (HR = 1.74; 1.22–2.47). The 1-year, 2-year, and 5-year overall survival was 60.3%, 47.5%, and 35.2%, respectively. Higher pre-diagnostic socio-economic status (SES) was associated with a significantly decreased mortality (HR = 0.55; 0.34–0.89). While, age 70 years and older (HR = 2.79; 1.12–6.99), pre-diagnostic opium use (HR = 2.35; 1.36–4.07), and metastasis (HR = 2.97; 1.97–4.48) were associated with a significantly increased mortality. Health policies should be implemented to enhance healthcare services and screening programs in low-SES areas. The general population, especially males and adults aged 50 years and older should be informed about CRC screening, CRC symptoms, and healthy lifestyles and diets. Furthermore, there is a critical need to raise awareness about the harmful effects of opium on CRC.

Keywords Colorectal cancer, Survival, Pre-diagnostic factors, Incidence, Opium, Socioeconomic status

Abbreviations

CRC	Colorectal cancer
SES	Socio-economic status
BMI	Body mass index
MENA	Middle east and north Africa
GCS	Golestan cohort study
FFQ	Food frequency questionnaire
DGA	Dietary guidelines for Americans
MCA	Multiple correspondence analysis
ICD-10	International classification of diseases, 10th edition
PY	Person-year
HR	Hazard ratio
MACRA	Medicare access and CHIP reauthorization Act

[1]Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Epidemiology and Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran. [3]Digestive Disease Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran. [4]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran. [5]Genomic Epidemiology Branch, International Agency for Research on Cancer (IARC/WHO), Lyon, France. ✉email: n.rezaei81@yahoo.com; delavari@tums.ac.ir

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide[1]. The incidence of CRC is increasing globally[2]. Although mortality rates in developed countries show stabilizing or decreasing trends, a rapidly rising trend is observed in low- and middle-income countries[2]. Following the annual increase in CRC incidence, identifying survival rates and survival-associated variables provides an opportunity to alter the trajectory of CRC. Previous studies have reported a wide range of cancer survival rates. 5-year overall survival in patients with CRC in China, France, Iran, and Brazil has been reported as 36.4%, 43.8%, 54%, and 63.5%, respectively[3–6].

The association between CRC incidence and different parameters has been studied[2,7]. However, there are still disagreements on certain risk factors such as opium use[8]. Moreover, there are many studies on the association between various factors and CRC incidence[2,7], but the impact of associated factors on CRC survival has yet to be well-studied. Earlier studies have investigated the effects of pre-diagnostic factors on the survival of patients with CRC, focusing on anthropometric measures, physical activity, some dietary or lifestyle factors, alcohol consumption, and smoking. Some studies have shown that pre-diagnostic lack of physical activity[9], lower education[10], unhealthy diet[11,12], alcohol consumption[13], smoking[12], and red or processed meat consumption[14] were associated with poor survival. However, other studies reported no association between body mass index (BMI), physical activity, education, annual income, diabetes status, and red meat, processed meat, alcohol, or fiber intakes and CRC survival[15–17]. Specifically, reports on BMI and obesity are inconsistent[18,19]. In previous studies, opium use has been associated with pancreatic cancer[20]. Nevertheless, it is unclear whether pre-diagnostic opium use affects CRC survival.

In addition to the above-mentioned controversies, to the best of our knowledge, there is a lack of information on the survival rate and the effect of pre-diagnostic factors on the incidence and survival of patients with CRC in Middle East and North Africa (MENA) region. Furthermore, studying the pre-diagnostic factors and their association with CRC incidence and survival is valuable from a public health perspective to identify and modify reversible risk factors.

The present study aims to estimate the survival rate of patients with CRC and the effect of several pre-diagnostic risk factors on CRC incidence and survival rate, including demographic, anthropometric, behavioral, nutritional, lifestyle, and medical history, in the context of a large population-based cohort study with a median of 15 years of follow-up.

Methods

Study population

Data were obtained from the Golestan cohort study (GCS), launched in January 2004. The GCS enrolled 50,045 individuals aged 40–75 years from Gonbad City and 326 villages in Golestan province, northeastern Iran. All participants were followed up every 12 months. This cohort study is still ongoing, and the participants have been followed up for a median of 15 years. Details of the study methods and population have been described elsewhere[21].

From the entire study sample, 211 participants who were diagnosed with cancer at the time of entering the study and 51 participants who did not have detailed information about the type of cancer or other studied variables were excluded. As a result, 49,783 participants were included in the incidence analysis and 190 patients diagnosed with CRC during GCS were included in the survival analysis. All participants with CRC received routine, standard treatment. The ethics committee of the Digestive Diseases Research Institute, Tehran University of Medical Sciences, approved this study. All research was performed in accordance with the Declaration of Helsinki. All participants signed a written informed consent during the original cohort study, allowing researchers to use their anonymized data for further analysis.

Baseline data collection

A trained general physician and a trained nutritionist interviewed each participant. Two structured questionnaires were implemented: a structured questionnaire and a semi-quantitative food frequency questionnaire (FFQ). The structured questionnaire included detailed questions on demographic characteristics, residential history, indicators of socio-economic status (SES), medical history, opium use, smoking, water source, and physical activity. Because most of the participants' physical activity was related to their occupation, physical activity was defined as occupational activity and coded as yes (heavy and intense activity) or no.

Opium is obtained from the seed capsule of the *Papaver somniferum*. There are different types of opiates commonly used in the Golestan province, including Raw opium, opium dross (tarry residues formed after smoking raw opium), and refined opium or opium sap (boiled opium dross with or without raw opium), which are smoked or ingested[22]. The data on recent and past opium use was collected using self-report questionnaire[23]. Opium use was defined as using it more than once a week for at least 6 months[22]. It has been shown that self-reported opium use is highly valid in this population compared with the presence of codeine and morphine in the urine, with a sensitivity of 0.93 and a specificity of 0.89[24].

Nutritional data were collected using a 116-item FFQ specifically designed and validated for this region[25]. Responses were given for commonly used portion sizes and frequency of consumption per day, week, month, or year. This study used the Healthy Eating Index 2015 (HEI-2015), which is a valid and reliable tool for assessing diet quality[26]. This index can be used to determine whether a particular group of foods complies with the Dietary Guidelines for Americans (DGA)[27]. The HEI-2015 comprises 13 dietary components. There are nine adequacy components that are recommended to be included in a healthy diet. These components consist of total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids. Furthermore, there are four moderation components, which should be consumed sparingly, namely refined grains, sodium, sugars, and saturated fats[26].

To create a variable that can be used as a proxy for SES, this analysis used multiple correspondence analysis (MCA) on house ownership, house structure, house size in square meters (m^2), ownership of household appliances, including bath in the residence, personal car, motorcycle, black and white TV (B/W TV), color TV, refrigerator, freezer, vacuum cleaner, and washing machine[28]. We classified SES according to its tertiles.

Height and weight were also measured. According to the Quetelet equation, BMI was calculated by dividing weight (kg) by height squared (m^2). BMI was categorized as follows: underweight (BMI < 18.5 kg/m^2), normal (18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2), and overweight and obese (BMI ≥ 25 kg/m^2)[29]. Diabetes was defined as a self-reported diagnosis and/or the use of antidiabetic medications.

Ascertainment of mortality and incidence

ICD-10 (International Classification of Diseases, 10th Edition) codes C18 (colon cancer), C19 (recto sigmoid junction cancer), and C20 (rectal cancer), were used in the current study.

Each participant was instructed at enrollment to contact if they experienced gastrointestinal symptoms, were hospitalized, or developed a new major disease. Upon enrollment, each participant received a personal GCS identification card. They can use the card to visit Atrak Clinic if they have gastrointestinal symptoms. The Atrak Clinic is a specialized gastroenterology clinic located in Gonbad's main hospital and offers services for free[30]. All data were recorded on a computerized database. The databases of Atrak Clinic and of the Golestan Cancer Registry were reviewed monthly for cancer cases. Also, because almost all study participants or their relatives had access to telephone, all participants were actively followed up with annual telephone calls. During each call, the follow-up team completed a case review questionnaire and recorded the participant's vital status and any disease or hospital admission since the previous follow-up contact. If a participant could not be reached by phone after seven attempts over two weeks, the researchers contacted friends or local health workers. Three outcomes were evaluated in the GCS: death, the incidence of any cancer, and the incidence of gastrointestinal cancer. In the case of a death reported by telephone or through local health workers or provincial death registry monthly reports, a general practitioner who was a member of the follow-up team visited the deceased person's home and completed a validated verbal autopsy questionnaire by interviewing the closest relatives of the deceased person[31]. In addition, all available and related medical documents, including medical charts, radiographs, pathology reports, hospital discharge documents, etc., were collected from all hospitals or pathology centers in the province and neighboring provinces. Metastasis was determined according to medical documents. Two internists independently reviewed all collected documents, including verbal autopsy data and medical charts, and the cause of death was recorded using ICD-10 codes. If the results were consistent, a diagnosis was made. In the case of mismatch, a more experienced internist reviewed all the documents and the two primary diagnoses and made the final diagnosis. If a definitive diagnosis was impossible for any reason, the cause of death was coded as "unknown".

Statistical analysis

The CRC incidence and mortality rates per 100,000 person-year (PY) for all participants were calculated, along with the mortality-to-incidence ratio (MIR). The MIR is a metric calculated by dividing the mortality rate by the incidence rate in a specified population over a defined time frame. The MIR indicates the fatality associated with a specific type of cancer in relation to its incidence. Age- and sex-standardization was calculated using the 2016 population census of Iran[32].

In terms of cancer incidence, all participants in the GCS were included in the risk set, and incident CRC was the target event. The entry time (T0) was regarded as the time of entering the study, and the exit time (T1) as the time of CRC diagnosis. Individuals that had not experienced the event of interest by the last follow-up time were censored, along with those that were lost to follow-up.

In the survival section, only people diagnosed with cancer in the cohort follow-up were included in the analysis, and the target event was death from cancer. In this part of the analysis in the Cox regression model, the entry time (T0) and exit time (T1) were the times of cancer incidence and death, respectively. Censored cases included all subjects alive until the last follow-up time and subjects lost to follow-up. Kaplan–Meier was used here to determine overall and metastasis status survival curves.

The effect of risk factors on cancer incidence and survival was investigated with a Cox regression model. First, a minimally adjusted model was conducted for each variable, which was adjusted for sex, age and SES. Then all variables were entered in a full model to adjust for all potential confounding effects. The Schoenfeld residuals test was used to evaluate the proportional hazards assumption by checking for trends in the residuals over time for each covariate. The test confirmed that the assumption was valid, with no significant violations detected.

A sensitivity analysis was conducted to examine cancer incidence risk factors, excluding the first two years of follow-up. The rationale for this exclusion was to minimize the potential impact of reverse causality. In the analysis of factors affecting cancer survival, individuals diagnosed within the first two years of follow-up were excluded to ensure the associations reflected long-term effects rather than early influences from undetected disease or other risk factors. Data analysis was performed using STATA v.14 software (StataCorp LLC.) and Python (version 3.12) with the NumPy (version 1.26) and Matplotlib (version 3.8.1) libraries[33,34]. A p-value lower than 0.05 was considered statistically significant.

Results

Baseline characteristics

Data from 49,783 cohort participants were used in this study. A total of 190 patients were diagnosed with CRC during the follow-up period. The age- and sex-standardized rates of CRC incidence were 27.80 per 100,000 overall, 37.29 per 100,000 in males, and 20.26 per 100,000 in females. During the follow-up period until July 2022, 126 (66.3%) patients with CRC died. The age- and sex-standardized rates of mortality were 18.32/100,000

overall, 24.24/100,000 in males, and 13.85/100,000 in females. The MIR was 0.66 in total, 0.65 in males and 0.68 in females. Additionally, 54 (28.4%) patients had metastasis. Table 1 shows the CRC incidence and mortality rate in the study population based on demographic, anthropometric, medical history, behavioral, nutritional, and lifestyle variables. The baseline characteristics of the study population are presented in Supplementary Table S1.

CRC incidence

The hazard ratios (HRs) for cancer incidence in the minimally adjusted model were significantly higher in males than in females (HR = 1.85; 95% CI = 1.39–2.46), in the age group 50–70 years (HR = 1.92; 95% CI = 1.41–2.61) and > = 70 years (HR = 4.07; 95% CI = 2.41–6.86) than in < 50 years, in the higher than in the lower SES group (HR = 1.62; 95% CI = 1.16–2.26), in urban than in rural dwellers (HR = 1.91; 95% CI = 1.38–2.64), in overweight and obese participants (BMI ≥ 25 kg/m^2) than in individuals with normal BMI (18.5–25 kg/m^2) (HR = 1.43; 95% CI = 1.03–1.98), and in participants with a history of diabetes than in participants without a history of diabetes

Variable	N of incidence/person-year at risk	Incidence rate per 100,000 PY (95% CI)	N of mortality/person-year at risk	Mortality rate per 100,000 PY (95% CI)
Sex				
Female	83/413,536.6	20.07 (16.18–24.88)	56/414,033.9	13.53 (10.4–17.6)
Male	107/288,575.17	37.07 (30.67–44.81)	70/289,104.5	24.21 (19.2–30.6)
Age (year)				
< 50	66/367,393.9	17.96 (14.11–22.86)	40/367,811.6	10.88 (8–14.8)
50–70	106/309,163.86	34.28 (28.34–41.47)	73/309,713.6	23.57 (18.7–29.6)
> = 70	18/25,539.69	70.47 (44.40–111.86)	13/25,598.8	50.78 (29.5–87.5)
SES				
First tertile	56/245,396.38	22.82 (17.56–29.65)	43/245,624.5	17.51 (13–23.6)
Second tertile	45/217,128.98	20.72 (15.47–27.75)	31/217,393.4	14.26 (10–20.3)
Third tertile	89/239,586.41	37.14 (30.17–45.72)	52/240,120.5	21.66 (16.5–28.4)
Place of residence				
Rural	123/556,624.58	22.09 (18.51–26.36)	87/557,286.6	15.61 (12.7–19.3)
Urban	67/145,487.19	46.05 (36.24–58.51)	39/145,851.9	26.74 (19.5–36.6)
BMI (kg/m^2)				
Normal	56/247,636.87	22.61 (17.40–29.38)	35/247,955.7	14.12 (10.1–19.7)
Underweight	9/30,686.43	29.32 (15.26–56.36)	6/30,737	19.52 (8.8–43.5)
Overweight and obese	124/423,714.66	29.26 (24.54–34.89)	84/424,368	19.79 (16–24.5)
Physical activity				
Inactive	106/330,420.61	32.08 (26.51–38.80)	72/331,016.6	21.75 (17.3–27.4)
Active	82/358,173.28	22.89 (18.43–28.42)	52/358,598.3	14.5 (11–19)
History of Diabetes				
No	170/658,288.97	25.82 (22.22–30.01)	111/659,232.2	16.84 (14–20.3)
Yes	20/43,822.8	45.63 (29.44–70.73)	15/43,906.2	34.16 (20.6–56.7)
HEI-2015				
First quartile	46/185,746.26	24.76 (18.54–33.06)	29/186,034.8	15.59 (10.8–22.4)
Second quartile	44/183,751.87	23.94 (17.82–32.18)	32/183,956.6	17.4 (12.3–24.6)
Third quartile	36/154,343.08	23.32 (16.82–32.33)	27/154,553.7	17.47 (12–25.5)
Fourth quartile	60/163,207.43	36.76 (28.54–47.35)	34/163,516.6	20.79 (14.9–29.1)
Cigarette ever used				
No	153/587,744.04	26.03 (22.21–30.50)	98/588,590.1	16.65 (13.7–20.3)
Yes	37/114,367.73	32.35 (23.44–44.65)	28/114,548.3	24.44 (16.9–35.4)
Opium ever used				
No	166/593,975.57	27.94 (24.00–32.53)	104/594,867.8	17.48 (14.4–21.2)
Yes	24/108,136.2	22.19 (14.87–33.11)	22/108,270.6	20.32 (13.4–30.9)
Water source				
Pipe	166/583,483.26	28.44 (24.43–33.12)	108/584,367.7	18.48 (15.3–22.3)
Other	24/118,613.51	20.23 (13.56–30.18)	18/118,755.7	15.16 (9.5–24.1)

Table 1. The colorectal cancer incidence rate and cancer death probability in the study population. The table demonstrates the CRC incidence and mortality rate in the study population based on demographic, anthropometric, medical history, behavioral, nutritional, and lifestyle variables. PY: person-year; SES: socio-economic status; BMI: body mass index; HEI-2015: Healthy Eating Index 2015.

(HR = 1.65; 95% CI = 1.03–2.64) (Table 2). There was no significant difference in the incidence risk between the different groups in other variables.

Fully adjusted analysis revealed that the HRs for cancer incidence were significantly higher in males than in females (HR = 2.20; 95% CI = 1.54–3.14), in the age group 50–70 years (HR = 1.86; 95% CI = 1.36–2.55) and the age group > = 70 years (HR = 3.71; 95% CI = 2.13–6.44) than in participants < 50 years, and in urban than in rural dwellers (HR = 1.74; 95% CI = 1.22–2.47) (Table 2) (Fig. 1). No differences were found in the results when sensitivity analysis was performed, and the significance level remained at the same level (Supplementary Table S2). This indicates that excluding early cases did not substantially affect the observed associations, confirming that the findings are robust and not influenced by potential reverse causality.

	Cancer incidence					
	Minimally adjusted			Fully Adjusted		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Sex						
Female	1			1		
Male	1.85	(1.39–2.46)	< 0.001	2.20	(1.54–3.14)	< 0.001
*Age (year)						
< 50 year	1			1		
50–70 year	1.92	(1.41–2.61)	< 0.001	1.86	(1.36–2.55)	< 0.001
> = 70 year	4.07	(2.41–6.86)	< 0.001	3.71	(2.13–6.44)	< 0.001
SES						
First tertile	1			1		
Second tertile	0.90	(0.61–1.33)	0.594	0.74	(0.49–1.11)	0.150
Third tertile	1.62	(1.16–2.26)	0.005	1.18	(0.81–1.73)	0.388
Place of residence						
Rural	1			1		
Urban	1.91	(1.38–2.64)	< 0.001	1.74	(1.22–2.47)	0.002
BMI (kg/m^2)						
Normal	1			1		
Underweight	1.34	(0.66–2.71)	0.415	1.47	(0.72–2.99)	0.288
Overweight and obese	1.43	(1.03–1.98)	0.032	1.26	(0.90–1.77)	0.174
Physical activity						
Inactive	1			1		
Active	1.09	(0.79–1.50)	0.610	1.09	(0.78–1.51)	0.618
History of Diabetes						
No	1			1		
Yes	1.65	(1.03–2.64)	0.036	1.51	(0.92–2.40)	0.101
HEI-2015						
First quartile	1			1		
Second quartile	0.94	(0.62–1.42)	0.754	0.91	(0.60–1.39)	0.670
Third quartile	0.88	(0.56–1.37)	0.574	0.82	(0.52–1.28)	0.386
Fourth quartile	1.24	(0.83–1.87)	0.292	1.01	(0.65–1.55)	0.974
Cigarette ever used						
No	1			1		
Yes	0.88	(0.59–1.30)	0.519	0.95	(0.63–1.45)	0.827
Opium ever used						
No	1			1		
Yes	0.66	(0.42–1.02)	0.065	0.72	(0.45–1.16)	0.178
Water source						
Pipe	1			1		
Other	0.76	(0.49–1.17)	0.213	0.91	(0.58–1.42)	0.681

Table 2. Hazard ratios for different variables in relation to cancer incidence in the study population. *: Age at the time of study entry for incidence. This table indicates that male sex, age 50 years and older, and being an urban dweller were associated with a significantly increased risk of CRC incidence. HR: hazard ratio; SES: socio-economic status; BMI: body mass index; HEI-2015: Healthy Eating Index 2015.

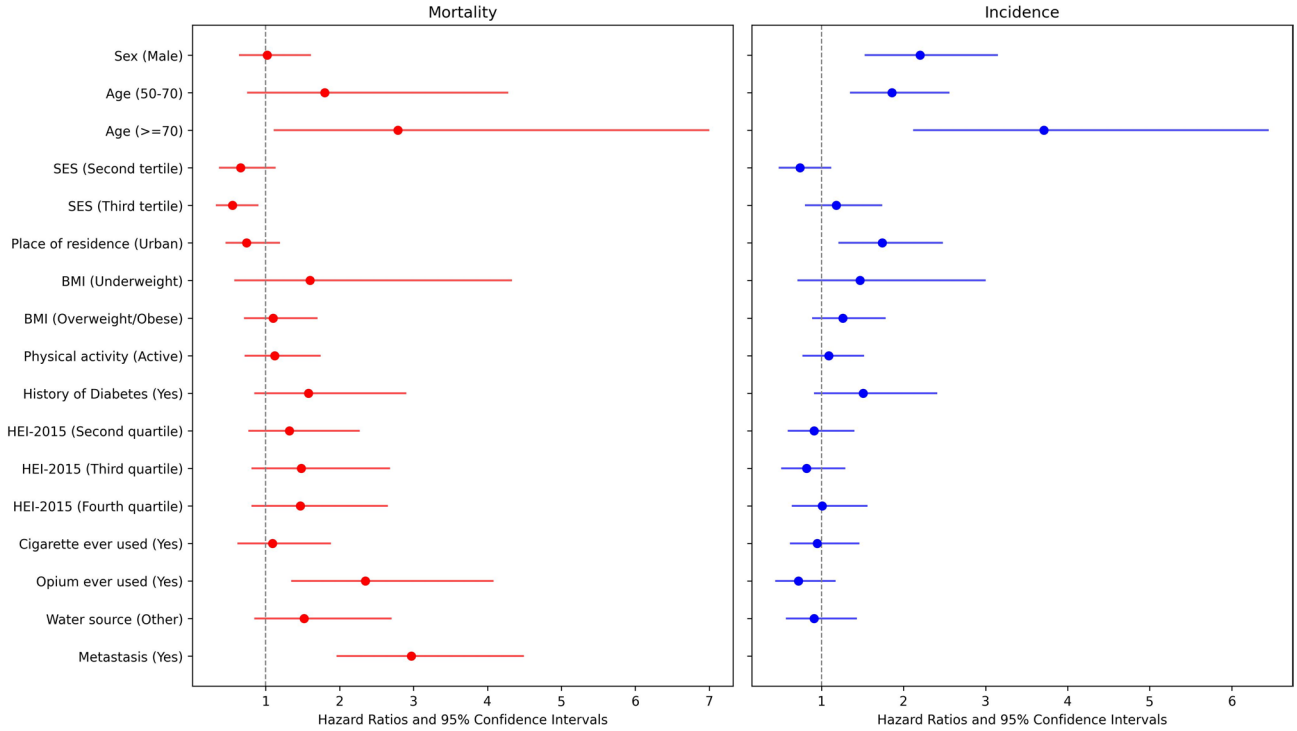

Fig. 1. Forest plots of hazard ratios for mortality and incidence across study variables. Based on the Cox regression model, the risk of mortality was substantially higher in the age group > = 70 years, those with lower SES, individuals who had ever used opium, and patients with metastasis. Additionally, being male, being 50 years or older, and being an urban dweller were linked to a significantly higher incidence of CRC. SES: socio-economic status; BMI: body mass index; HEI-2015: Healthy Eating Index 2015; CRC: colorectal cancer.

Survival analysis on CRC patients

Kaplan Meier's analysis of patients with CRC is shown in Fig. 2 and 3. Figure 2 shows that the 1-year, 2-year, and 5-year, overall survival among patients with CRC was 60.3%, 47.5%, and 35.2%, respectively. There was a statistically significant difference in the survival rate of patients with and without metastasis (p-value < 0.001). The 5-year survival rate (95% CI) for patients with CRC with and without metastasis was 0.08 (0.02–0.17) and 0.47 (0.38–0.56), respectively. (Fig. 3).

An overall significant decreased risk of mortality among incident cases was observed in the minimally adjusted model for having higher SES than lower SES (HR = 0.51; 95% CI = 0.34–0.77). In contrary, a significant increased risk of mortality was observed for patients who had ever used cigarette (HR = 1.64; 95% CI = 1.01–2.66), patients who had ever used opium (HR = 2.21; 95% CI = 1.35–3.60), and for patients who had metastasis (HR = 2.69; 95% CI = 1.85–3.92) (Table 3).

In the fully adjusted model, the HR for mortality was significantly lower in patients with higher SES than in patients with lower SES (HR = 0.55; 95% CI = 0.34–0.89). The HRs for mortality were significantly higher in the age group > = 70 years (HR = 2.79; 95% CI = 1.12–6.99) than in patients < 50 years, and in patients with metastasis than in patients without metastasis (HR = 2.97; 95% CI = 1.97–4.48) (Table 3) (Fig. 1). The risk of mortality for patients who had ever used opium was 2.35 times (95% CI = 1.36–4.07) that for patients who had never used opium. Sensitivity analysis did not reveal any differences in results, and the significance level did not change (Supplementary Table S2). This supports the robustness of the findings and indicates that excluding early cases had no meaningful impact on the identified associations.

Discussion

In this prospective cohort study, several pre-diagnostic factors were associated with CRC incidence and mortality risk. The mortality risk was significantly higher in the age group > = 70 years, patients with lower SES, patients who had ever used opium, and patients with metastasis. Also, male sex, age 50 years and older, and being an urban dweller were associated with a significantly increased risk of CRC incidence. This study demonstrated that the overall survival of 1-year, 2-year, and 5-year was 60.3%, 47.5%, and 35.2%, respectively. Patients with metastasis had lower survival than patients without metastasis.

Similar to our findings, Chen et al. reported a 5-year survival rate for CRC of 36.3%[3]. Joachim et al. showed that 1-year, 5-year, and 10-year survival for CRC was 74.6%, 43.8%, and 33.0%, respectively[4]. However, some other studies found higher survival rates. A meta-analysis of 38 studies on CRC survival reported 1- and 5-year survival rates of 84% and 54%, respectively[5]. Another study showed that 5-year survival for CRC was 63.5%[6]. The

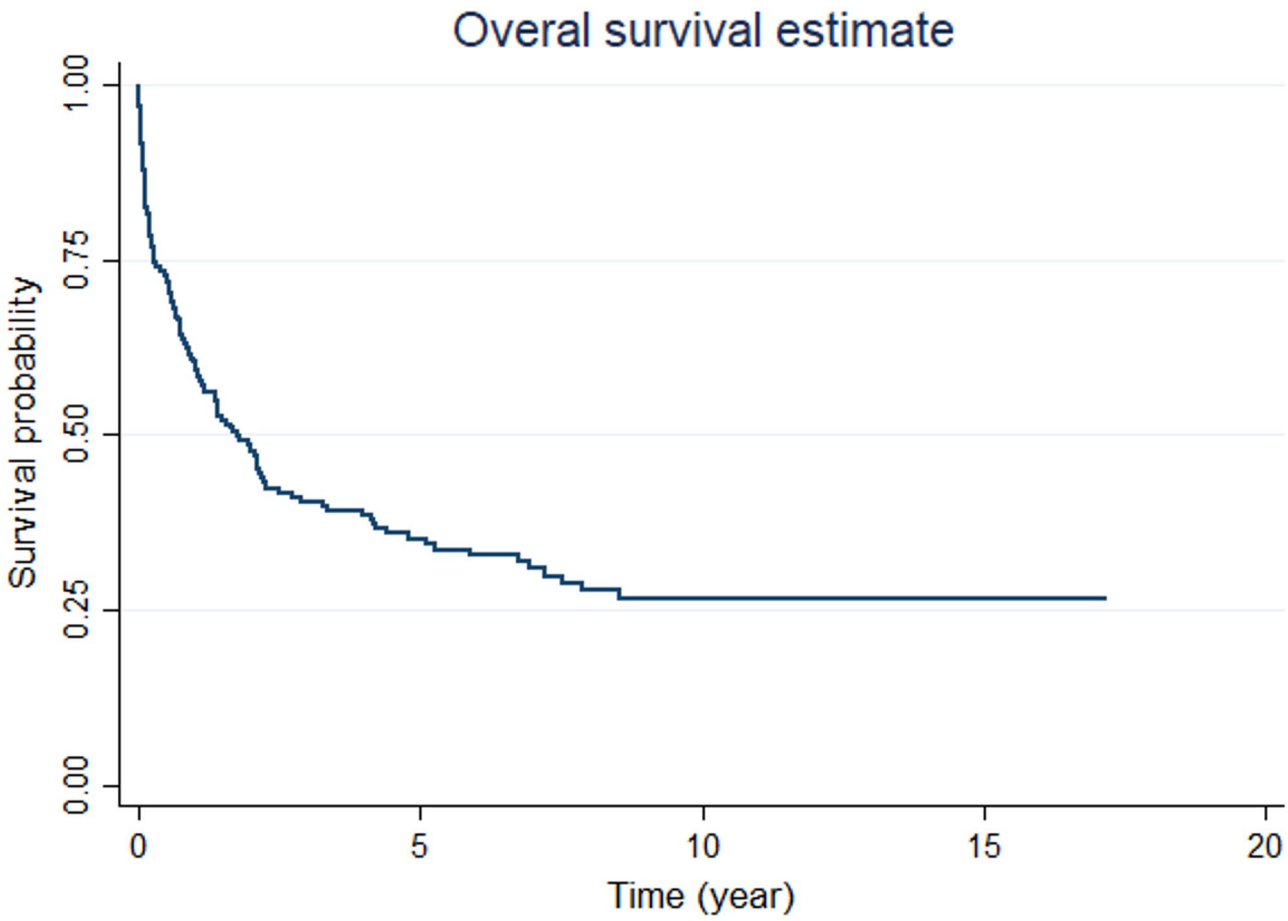

Fig. 2. Kaplan–Meier survival curve of patients with colorectal cancer (overall). The overall survival of 1-year, 2-year, and 5-year was 60.3%, 47.5%, and 35.2%, respectively.

disagreement in the results may be due to the unequal access to healthcare facilities, screening programs, health policies, stage at diagnosis, and treatment approaches in different regions.

To our knowledge, this study was the first to evaluate the association of pre-diagnosis opium use with the mortality risk in patients with CRC. The current study found that opium use before diagnosis was associated with mortality. Molecular studies have shown that opioids affect cell proliferation, cell death, and the immune system, and their use may alter the function of cancer cells[35]. Opioids have immunosuppressant effects, allowing cancer to escape the immune system[36]. In addition, to increase the weight of opium, compounds such as lead and chromium are added to it[22]. The association between these toxic metals and CRC has been demonstrated[37]. Therefore, the general public should be aware of the negative consequences of opium use concerning CRC. Nevertheless, additional studies are required to confirm or refute the association between opium use before diagnosis and CRC survival.

In the current study, pre-diagnostic lower SES was related to a higher mortality risk. Similar to our findings, previous studies have shown that the survival rate of patients with CRC with lower SES was poorer than that of patients with higher SES[38]. Other studies found that women with low social support before CRC diagnosis had a higher mortality rate[39]. Another study showed no association between annual household income and CRC survival[17]. Nonetheless, they did not investigate other SES-associated factors. The association between lower SES and poor CRC survival may be due to a lack of medical care as a result of social, cultural, or financial barriers, reluctance to seek health care and late diagnosis in patients with lower SES[38]. This study suggests that policy-makers should enhance healthcare services in low-SES areas, such as rural areas, so that screening tests, especially colonoscopy, be widely available to rural residents. In the United States, disparities between urban and rural communities have been decreased between 2016 and 2020. The reason for this may be CRC screening awareness and the Medicare Access and CHIP Reauthorization Act (MACRA), which provides high-quality health care through financial incentives for healthcare professionals[40]. Also, people in low-SES regions should be informed about CRC symptoms, screening tests, and healthy lifestyles with interventions such as the family medicine program or new educational programs about CRC. CRC education through email and community drop boxes has been shown to be an effective method for rural areas[41].

Patients aged 70 years and over had a higher mortality risk than patients under 50 years in this study. According to previous studies, older patients have a greater mortality risk because of a complex interplay of various factors, including physiological vulnerability, disparities in treatment approaches, and the impact of age on surgical

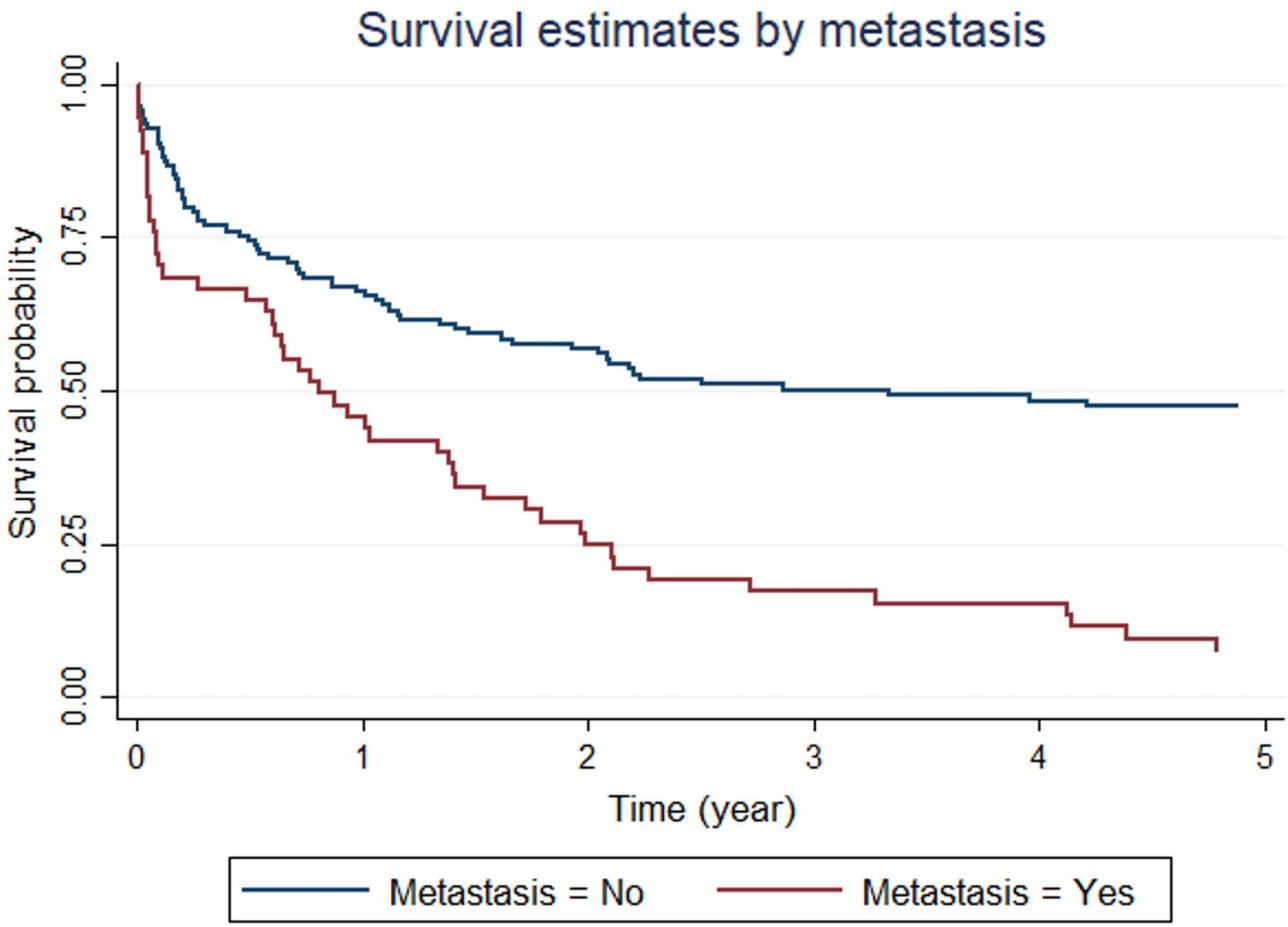

Fig. 3. Kaplan–Meier survival curve of patients with colorectal cancer based on metastasis. A significant difference in survival rates was found between patients with colorectal cancer with metastasis (5-year survival rate: 8%) and without metastasis (5-year survival rate: 47%) (p-value < 0.001).

outcomes, all of which contribute to the observed differences in survival rates in the current study[42–44]. Evidence shows that older patients have more advanced diseases at the time of diagnosis[45]. Additionally, adjuvant and palliative chemotherapy are less commonly prescribed to elderly patients due to their poor health[45]. Due to the various factors, such as side effects, the likelihood of older participants discontinuing chemotherapy is also greater[42]. In addition, the treatment of young patients is likely to be more aggressive[42]. According to studies, fewer elderly patients underwent curative major resections than younger patients, regardless of cancer stage[44]. As a result, for older patients with CRC, personalized care plans must consider age-related factors, comprehensive geriatric assessments, and appropriate treatment strategies to optimize outcomes. In contrast to our findings, in some studies, younger patients have poorer survival rates[46]. It is likely that the poor prognosis of young patients was caused by the majority of them presenting with an advanced form of the disease[46]. However, some studies have found that elderly patients do not have a shorter lifespan than young patients and only the clinical and pathological features of cancer are decisive[47]. This inconsistency calls for more research.

This study showed that the male sex was associated with a higher risk of CRC incidence. Earlier studies reported similar results[48]. The explanation for this sex difference could be the protective role of estrogen and X-linked genes[48]. In spite of this, sex is not considered in the current recommendations for CRC screening[49]. Further studies are still needed to clarify this association and determine whether screening should start earlier for males.

In the current study, age 50 years and older was associated with an increased risk of CRC. Our findings are consistent with current evidence[50]. The results emphasize that screening in individuals over 50 years old should not be postponed. In addition, it has been shown that increasing the participation rate of unscreened older adults is likely to be cost-effective[51]. Therefore, health policy-makers must facilitate CRC screening programs.

This analysis found that being an urban dweller was related to a higher risk of CRC incidence. Our results are in agreement with previous studies[52]. The explanation for this difference could be that urban dwellers are probably more exposed to some risk factors, such as lack of physical activity, low fiber consumption, and high red meat and processed meat consumption, which are well-known risk factors for CRC[2,7]. In addition, people in urban areas have more access to healthcare services and diagnostic tests, and as a result, urban residents are more likely to be diagnosed with cancer than rural residents. However, a policy should be implemented to inform the

Variable	Mortality					
	Minimally Adjusted			Fully Adjusted		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Sex						
Female	1			1		
Male	1.05	(0.74–1.50)	0.768	1.02	(0.65–1.60)	0.942
*Age (year)						
< 50 year	1			1		
50–70 year	1.59	(0.73–3.45)	0.238	1.80	(0.76–4.27)	0.181
> = 70 year	2.08	(0.93–4.67)	0.076	2.79	(1.12–6.99)	0.028
SES						
First tertile	1			1		
Second tertile	0.72	(0.45–1.15)	0.168	0.66	(0.38–1.12)	0.126
Third tertile	0.51	(0.34–0.77)	0.001	0.55	(0.34–0.89)	0.016
Place of residence						
Rural	1			1		
Urban	0.73	(0.47–1.13)	0.155	0.74	(0.47–1.18)	0.207
BMI (kg/m^2)						
Normal	1			1		
Underweight	1.23	(0.50–3.03)	0.649	1.60	(0.59–4.32)	0.351
Overweight and obese	1.10	(0.72–1.67)	0.653	1.10	(0.72–1.69)	0.651
Physical activity						
Inactive	1			1		
Active	0.88	(0.59–1.30)	0.516	1.12	(0.73–1.73)	0.595
History of Diabetes						
No	1			1		
Yes	1.49	(0.86–2.60)	0.156	1.58	(0.86–2.89)	0.140
HEI-2015						
First quartile	1			1		
Second quartile	1.46	(0.88–2.42)	0.144	1.32	(0.78–2.26)	0.300
Third quartile	1.52	(0.88–2.63)	0.133	1.48	(0.82–2.67)	0.197
Fourth quartile	1.22	(0.72–2.07)	0.469	1.47	(0.82–2.64)	0.193
Cigarette ever used						
No	1			1		
Yes	1.64	(1.01–2.66)	0.045	1.09	(0.63–1.87)	0.767
Opium ever used						
No	1			1		
Yes	2.21	(1.35–3.60)	0.001	2.35	(1.36–4.07)	0.002
Water source						
Pipe	1			1		
Other	1.48	(0.88–2.47)	0.140	1.52	(0.86–2.69)	0.146
Metastasis						
No	1			1		
Yes	2.69	(1.85–3.92)	< 0.001	2.97	(1.97–4.48)	< 0.001

Table 3. Hazard ratios for different variables in relation to mortality in the study population. *: Age at which cancer was diagnosed. This table shows that the mortality risk was significantly higher in the age group > = 70 years, patients with lower SES, patients who had ever used opium, and patients with metastasis. HR: hazard ratio; SES: socio-economic status; BMI: body mass index; HEI-2015: Healthy Eating Index 2015.

public about the CRC screening initiation, healthy lifestyle, and healthy eating habits, especially in males, older individuals, and urban dwellers.

There was no significant association between pre-diagnostic BMI and mortality risk in this study. Previous research on this topic has yielded inconsistent findings. Several studies have reported a significant association between pre-diagnostic BMI and CRC morality[53]. In contrast, others have identified a U-shaped relationship, with both underweight and obesity linked to higher mortality rates[15]. Some studies have found no significant association between pre-diagnostic BMI and CRC mortality risk[54]. Additionally, some evidence suggests that overweight or obesity may be associated with improved survival, potentially due to a protective nutritional reserve or better tolerance to cancer treatments[55,56]. The differences in study findings may arise from variations in

study design, population characteristics, measurement biases, or the timing of BMI measurements. For instance, weight loss before a cancer diagnosis can confound the association between BMI and outcomes, particularly if unintentional weight loss has not been considered[19,57]. Moreover, body composition or fat distribution may influence survival outcomes more significantly than BMI alone[58]. Individuals with similar BMI values can have different levels of insulin resistance or inflammation, which may impact cancer progression and treatment responses[15,59]. Additionally, the stage at which CRC is diagnosed may influence the relationship between BMI and survival. Kocarnik et al. found that obesity was associated with increased mortality in Stages I-II but decreased mortality in Stages III-IV[58], while Parkin et al. reported no difference in the relationship between BMI and survival rates across different stages of cancer[60]. These aspects underscore the complexity of the association between BMI and CRC mortality, highlighting the need for further research on this association.

The current analysis found no significant association between pre-diagnostic diabetes and CRC morality risk. The existing research in this field has yielded mixed results. A meta-analysis by Zhu et al. suggested that diabetes is associated with shorter survival in patients with CRC[61]. Walker et al. reported that diabetes was associated with poorer survival outcomes in patients with colon cancer but not rectal cancer[62]. In contrast, van de Poll-Franse et al. found that diabetes was linked to increased mortality in patients with rectal cancer but not those with colon cancer[63]. Other studies reported that diabetes did not significantly affect either short-term survival or cancer-specific survival in CRC[64]. Furthermore, Cui et al. demonstrated that while high blood glucose levels in CRC were associated with increased local tumor malignancy, they did not correlate with distant metastasis or overall survival[65]. The differences may result from variations in study populations, dataset limitations, diabetes definitions, glycemic control, cancer stage at diagnosis, comorbidities, and different regional treatments[61,62]. In addition, the higher mortality risk and poorer survival in patients with CRC and diabetes may potentially due to higher non-cancer mortality, such as cardiovascular disease (CVD), which is more prevalent in patients with diabetes[62]. Nevertheless, diabetes may impact CRC survival through a complex interaction of metabolic dysregulation, chronic inflammation, and increased CVD risk, which emphasizes the necessity for additional research to clarify these connections[61–63,65].

The current study had some strengths. Although the number of patients with CRC was relatively small, it was in the context of a population-based cohort with more than 15 years of follow-up that enrolled a large number of participants with the possibility to calculate incidence and survival rate at population-based setting. Furthermore, several pre-diagnostic factors, including anthropometric, demographic, lifestyle, nutritional, and medical history, were included in the analysis. Nevertheless, there were some limitations. First, pre-diagnosis data were collected only once before diagnosis, which may not fully reflect changes that occur over time. Second, this study lacked detailed cancer staging data, metastatic sites, and treatment information. While medical records were collected from hospitals and pathology centers, staging data, metastatic sites, and treatment information were not systematically recorded. Therefore, we put the patients into two groups: metastasis (stage 4) and no metastasis. Third, although the HEI-2015 is a validated and widely used tool for assessing diet quality, it may not accurately represent dietary patterns specific to the Golestan region. However, it has been previously used in the Iranian population[66]. The findings of this study, while specific to the population of northern Iran, may provide valuable insights into CRC risk factors and survival in other parts of the MENA region, where similar lifestyle, dietary, and socioeconomic factors may influence outcomes. However, the generalizability to other regions should be interpreted with caution due to regional differences in risk factor prevalence and healthcare systems. Further longitudinal studies are needed to investigate the effects of pre-diagnostic opium use and its intensity, as well as lower SES on CRC survival, to explore potential causal relationships, and to determine whether earlier screening for CRC in males may be warranted. Additionally, future studies should include repeated measurements of pre-diagnostic factors, detailed cancer staging and metastatic sites data, and treatment information to enable more comprehensive analyses.

Conclusion

In the current study, overall survival rates of patients with CRC at 1 year, 2 years, and 5 years were 60.3%, 47.5%, and 35.2%, respectively. Health policy-makers should enhance healthcare services and screening programs for individuals, especially in low-SES areas. Also, the general population, especially males and adults aged 50 years and older should be informed about CRC screening, CRC symptoms, healthy lifestyles and diets, and the adverse effects of opium on CRC. More research is needed to investigate the effects of pre-diagnostic risk factors, especially opium, on CRC survival.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 22 October 2024; Accepted: 15 May 2025
Published online: 21 May 2025

References

1. Sung, H. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71**(3), 209–249 (2021).
2. Arnold, M. et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* **66**(4), 683–691 (2017).
3. Chen, J.-G. et al. Cancer survival in patients from a hospital-based cancer registry, China. *J. Cancer* **9**(5), 851 (2018).
4. Joachim, C. et al. Overall survival of colorectal cancer by stage at diagnosis: Data from the Martinique Cancer Registry. *Medicine* **98**(35), e16941 (2019).

5. Maajani, K. et al. Survival rate of colorectal cancer in Iran: A systematic review and meta-analysis. *Asian Pac. J. Cancer Prevent. APJCP* **20**(1), 13 (2019).
6. Aguiar Junior, S. et al. Survival of patients with colorectal cancer in a cancer center. *Arq. Gastroenterol.* **57**(2), 172–177 (2020).
7. Macrae, F.A., Goldberg, R.M. & Seres, D. Colorectal cancer: Epidemiology, risk factors, and protective factors 2016 [Available from: https://www.uptodate.com/contents/epidemiology-and-risk-factors-for-colorectal-cancer.
8. Sheikh, M. et al. Opium use and subsequent incidence of cancer: Results from the Golestan Cohort Study. *Lancet Glob Health.* **8**(5), e649–e660 (2020).
9. Walter, V. et al. Physical activity and survival of colorectal cancer patients: Population-based study from Germany. *Int. J. Cancer.* **140**(9), 1985–1997 (2017).
10. Kuo, W. Y., Hsu, H. S., Kung, P. T. & Tsai, W. C. Impact of socioeconomic status on cancer incidence risk, cancer staging, and survival of patients with colorectal cancer under universal health insurance coverage in Taiwan. *Int. J. Environ. Res. Public Health* **18**(22), 12164 (2021).
11. Romaguera, D. et al. Pre-diagnostic concordance with the WCRF/AICR guidelines and survival in European colorectal cancer patients: a cohort study. *BMC Med.* **13**(1), 1–12 (2015).
12. Pelser, C. et al. Prediagnostic lifestyle factors and survival after colon and rectal cancer diagnosis in the National Institutes of Health (NIH)-AARP Diet and Health Study. *Cancer* **120**(10), 1540–1547 (2014).
13. Walter, V. et al. Alcohol consumption and survival of colorectal cancer patients: a population-based study from Germany. *Am. J. Clin. Nutr.* **103**(6), 1497–1506 (2016).
14. McCullough, M. L., Gapstur, S. M., Shah, R., Jacobs, E. J. & Campbell, P. T. Association between red and processed meat intake and mortality among colorectal cancer survivors. *J. Clin. Oncol.* **31**(22), 2773 (2013).
15. Wang, N. et al. Prediagnosis body mass index and waist–hip circumference ratio in association with colorectal cancer survival. *Int. J. Cancer* **140**(2), 292–301 (2017).
16. Ward, H. A. et al. Pre-diagnostic meat and fibre intakes in relation to colorectal cancer survival in the European Prospective Investigation into Cancer and Nutrition. *Br. J. Nutr.* **116**(2), 316–325 (2016).
17. Oyeyemi, S. O., Braaten, T., Skeie, G. & Borch, K. B. Competing mortality risks analysis of prediagnostic lifestyle and dietary factors in colorectal cancer survival: The Norwegian women and cancer study. *BMJ Open Gastroenterol.* **6**(1), e000338 (2019).
18. Fedirko, V. et al. Pre-diagnostic anthropometry and survival after colorectal cancer diagnosis in Western European populations. *Int. J. Cancer* **135**(8), 1949–1960 (2014).
19. Walter, V. et al. Prognostic relevance of prediagnostic weight loss and overweight at diagnosis in patients with colorectal cancer. *Am. J. Clin. Nutr.* **104**(4), 1110–1120 (2016).
20. Sheikh, M. et al. Survival features, prognostic factors, and determinants of diagnosis and treatment among Iranian patients with pancreatic cancer, a prospective study. *PLoS ONE* **15**(12), e0243511 (2020).
21. Pourshams, A. et al. Cohort profile: The Golestan Cohort Study—a prospective study of oesophageal cancer in northern Iran. *Int. J. Epidemiol.* **39**(1), 52–59 (2010).
22. Humans IWGotIoCHt. IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Opium Consumption. Lyon (FR): International Agency for Research on Cancer© International Agency for Research on Cancer, 2021. For more information contact publications@iarc.fr.; 2021.
23. Khademi, H. et al. Opium use and mortality in Golestan Cohort Study: Prospective cohort study of 50 000 adults in Iran. *BMJ Br. Med. J.* **344**, e2502 (2012).
24. Abnet, C. C. et al. Reliability and validity of opiate use self-report in a population at high risk for esophageal cancer in Golestan, Iran. *Cancer Epidemiol. Biomark. Prev.* **13**(6), 1068–1070 (2004).
25. Malekshah, A. et al. Validity and reliability of a new food frequency questionnaire compared to 24 h recalls and biochemical measurements: pilot phase of Golestan cohort study of esophageal cancer. *Eur. J. Clin. Nutr.* **60**(8), 971–977 (2006).
26. Reedy, J. et al. Evaluation of the healthy eating index-2015. *J. Acad. Nutr. Diet.* **118**(9), 1622–1633 (2018).
27. Rosner, B. Dietary Guidelines for Americans: US Department of Health and Human Services and US Department of Agriculture; 2015. (2020).
28. Islami, F. et al. Socio-economic status and oesophageal cancer: results from a population-based case–control study in a high-risk area. *Int. J. Epidemiol.* **38**(4), 978–988 (2009).
29. Weir, C., Jan, A. StatPearls: BMI Classification Percentile And Cut Off Points. Treasure Island (FL). 2022.
30. Islami, F. et al. Epidemiologic features of upper gastrointestinal tract cancers in Northeastern Iran. *Br. J. Cancer* **90**(7), 1402–1406 (2004).
31. Khademi, H. et al. Verbal autopsy: Reliability and validity estimates for causes of death in the Golestan Cohort Study in Iran. *PLoS ONE* **5**(6), e11183 (2010).
32. Statistical Centre of Iran. Iran Population and Housing Census 2016. [Available from: https://amar.org.ir/.
33. Harris, C. R. et al. Array programming with NumPy. *Nature* **585**(7825), 357–362 (2020).
34. Hunter, J. D. Matplotlib: A 2D graphics environment. *Comput. Sci. Eng.* **9**(03), 90–95 (2007).
35. Szczepaniak, A., Fichna, J. & Zielińska, M. Opioids in cancer development, progression and metastasis: Focus on colorectal cancer. *Curr. Treat. Options Oncol.* **21**(1), 6 (2020).
36. Liang, X., Liu, R., Chen, C., Ji, F. & Li, T. Opioid system modulates the immune function: A review. *Transl. Perioper. Pain Med.* **1**(1), 5 (2016).
37. Bonfiglio, R. et al. The impact of toxic metal bioaccumulation on colorectal cancer: Unravelling the unexplored connection. *Sci. Total Environ.* **906**, 167667 (2024).
38. Kish, J. K., Yu, M., Percy-Laurry, A. & Altekruse, S. F. Racial and ethnic disparities in cancer survival by neighborhood socioeconomic status in surveillance, epidemiology, and end results (SEER) registries. *J. Natl. Cancer Inst. Monogr.* **2014**(49), 236–243 (2014).
39. Kroenke, C. H. et al. Prediagnosis social support, social integration, living status, and colorectal cancer mortality in postmenopausal women from the women's health initiative. *Cancer* **126**(8), 1766–1775 (2020).
40. Borders, T. F., Morgan, Z. J. & Peterson, L. E. Colorectal cancer screening in rural and urban primary care practices amid implementation of the medicare access and CHIP reauthorization act. *J Prim Care Community Health.* **14**, 21501319231177550 (2023).
41. Sutton, A. L. et al. Reaching rural residents to identify colorectal cancer education and intervention targets. *J. Cancer Educ.* **36**(2), 338–344 (2021).
42. McKay, A. et al. Does young age influence the prognosis of colorectal cancer: A population-based analysis. *World J. Surg. Oncol.* **12**(1), 370 (2014).
43. van Eeghen, E. E., Bakker, S. D., van Bochove, A. & Loffeld, R. J. Impact of age and comorbidity on survival in colorectal cancer. *J. Gastrointest. Oncol.* **6**(6), 605–612 (2015).
44. Høydahl, Ø., Edna, T.-H., Xanthoulis, A., Lydersen, S. & Endreseth, B. H. The impact of age on rectal cancer treatment, complications and survival. *BMC Cancer* **22**(1), 975 (2022).
45. Doat, S. et al. Elderly patients with colorectal cancer: Treatment modalities and survival in France. National data from the ThInDiT cohort study. *Eur. J. Cancer* **50**(7), 1276–1283 (2014).
46. Marble, K., Banerjee, S. & Greenwald, L. Colorectal carcinoma in young patients. *J. Surg. Oncol.* **51**(3), 179–182 (1992).

47. Heys, S. D. et al. Prognostic factors and survival of patients aged less than 45 years with colorectal cancer. *Br. J. Surg.* **81**(5), 685–688 (2005).
48. Abancens, M., Bustos, V., Harvey, H., McBryan, J. & Harvey, B. J. Sexual dimorphism in colon cancer. *Front. Oncol.* https://doi.org/10.3389/fonc.2020.607909 (2020).
49. Keswani, R. N., Crockett, S. D. & Calderwood, A. H. AGA clinical practice update on strategies to improve quality of screening and surveillance colonoscopy: Expert review. *Gastroenterology* **161**(2), 701–711 (2021).
50. Low, E. E. et al. Risk factors for early-onset colorectal cancer. *Gastroenterology* **159**(2), 492–501 (2020).
51. Ladabaum, U., Mannalithara, A., Meester, R. G. S., Gupta, S. & Schoen, R. E. Cost-effectiveness and national effects of initiating colorectal cancer screening for average-risk persons at age 45 years instead of 50 years. *Gastroenterology* **157**(1), 137–148 (2019).
52. Yuan, S. & Xie, S.-H. Urban–rural disparity in cancer incidence in China, 2008–2012: A cross-sectional analysis of data from 36 cancer registers. *BMJ Open* **11**(4), e042762 (2021).
53. Laake, I., Larsen, I. K., Selmer, R., Thune, I. & Veierød, M. B. Pre-diagnostic body mass index and weight change in relation to colorectal cancer survival among incident cases from a population-based cohort study. *BMC Cancer* **16**(1), 402 (2016).
54. Kuiper, J. G. et al. Recreational physical activity, body mass index, and survival in women with colorectal cancer. *Cancer Causes Control* **23**(12), 1939–1948 (2012).
55. Walter, V. et al. Prognostic relevance of prediagnostic weight loss and overweight at diagnosis in patients with colorectal cancer12. *Am. J. Clin. Nutr.* **104**(4), 1110–1120 (2016).
56. Strulov Shachar, S. & Williams, G. R. The obesity paradox in cancer-moving beyond BMI. *Cancer Epidemiol. Biomark. Prev.* **26**(1), 13–16 (2017).
57. Campbell, P. T. et al. Impact of body mass index on survival after colorectal cancer diagnosis: The cancer prevention study-II nutrition cohort. *J. Clin. Oncol.* **30**(1), 42–52 (2012).
58. Kocarnik, J. M. et al. Relationship of prediagnostic body mass index with survival after colorectal cancer: Stage-specific associations. *Int. J. Cancer.* **139**(5), 1065–1072 (2016).
59. Kahn, S. E. et al. Obesity, body fat distribution, insulin sensitivity and islet β-cell function as explanations for metabolic diversity. *J. Nutr.* **131**(2), 354S-S360 (2001).
60. Parkin, E., O'Reilly, D. A., Sherlock, D. J., Manoharan, P. & Renehan, A. G. Excess adiposity and survival in patients with colorectal cancer: A systematic review. *Obes. Rev.* **15**(5), 434–451 (2014).
61. Zhu, B. et al. The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies. *PLoS ONE* **12**(4), e0176068 (2017).
62. Walker, J. J. et al. Cause-specific mortality in Scottish patients with colorectal cancer with and without type 2 diabetes (2000–2007). *Diabetologia* **56**(7), 1531–1541 (2013).
63. van de Poll-Franse, L. V., Haak, H. R., Coebergh, J. W., Janssen-Heijnen, M. L. & Lemmens, V. E. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. *Diabetologia* **55**(8), 2163–2172 (2012).
64. Jullumstrø, E., Kollind, M., Lydersen, S. & Edna, T. H. Diabetes mellitus and outcomes of colorectal cancer. *Acta Oncol.* **48**(3), 361–367 (2009).
65. Cui, G. et al. High blood glucose levels correlate with tumor malignancy in colorectal cancer patients. *Med Sci Monit.* **21**, 3825–3833 (2015).
66. Pasdar, Y. et al. Healthy eating index 2015 and major dietary patterns in relation to incident hypertension; a prospective cohort study. *BMC Public Health* **22**(1), 734 (2022).

Acknowledgements

The authors wish to thank the participants for their kind cooperation

Author contributions

Conceptualization: N.R., S.G.S., R.M., A.D.; Methodology: M.S., N.R., S.G.S., S.D., M.S.; Formal analysis: S.D., M.S., S.M., A.Y.; Investigation: A.Y., F.M., G.R., A.S.; Validation: N.R., S.G.S., H.P.; Visualization: H.P., R.M., A.D.; Writing–original draft: A.Y., F.M.; Writing–review and editing: A.Y., S.G.S., N.R., M.S.; Project administration: S.G.S., N.R., A.D.; Supervision: R.M. All authors reviewed the manuscript.

Funding

The authors have no relevant financial or non-financial interests to disclose. The Golestan Cohort Study was supported by Tehran University of Medical Sciences (Grant No: 81/15), Cancer Research UK (Grant No: C20/A5860), the Intramural Research Program of the National Cancer Institute, National Institutes of Health, and various collaborative research agreements with the International Agency for Research on Cancer. No funding was received to assist with the preparation of this manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-02674-9.

Correspondence and requests for materials should be addressed to N.R. or A.D.