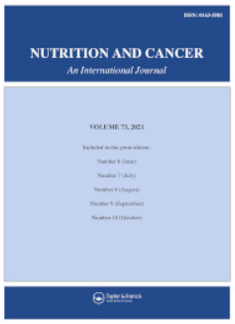

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Diet and Genetic Risk Factors of Colorectal Cancer in Palestine: A Case-Control Study

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ABSTRACT

To add evidence to the limited data available on colorectal cancer (CRC) from Palestine, we examine the risk factors associated with CRC using a matched hospital-based case-control study. A structured questionnaire was used to collect data from 105 cases and 105 controls. A multivariable conditional regression model was used to adjust for the association between study factors and CRC risk. In the model, compared with controls, cases from villages were significantly less likely to have CRC (Adjusted Odds Ratio, AOR = 0.194); taking aspirin lowered the likelihood of CRC by 24%; and having a multiple birth sibling by 33%. Also, the likelihood of CRC was lowered significantly by consuming five servings of fruits/vegetables per week or more (5–6 servings: AOR = 0.21, 7–8 servings per week: AOR = 0.04). However, cases had a significantly higher likelihood of CRC if they consumed 2–4 servings of grilled red meat per week (AOR = 4.25); smoked (AOR = 4.38); had a sedentary lifestyle (AOR = 2.53); reported parental consanguinity (AOR = 3.88); or had a family history of cancer (AOR = 6.39). Our results confirmed the association between CRC and red meat intake and smoking, and proved that parental consanguinity and family history of cancer are also risk factors for CRC.

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Introduction

Colorectal cancer (CRC) is one of the major causes of morbidity and mortality worldwide. It is the third most common cancer in the world after lung cancer and breast cancer, and the fourth in mortality (1). Several factors are associated with or protect against CRC. There is global consensus that primary prevention through lifestyle and dietary measures can prevent one-third to a half of CRC cases (2). The links between diet, weight and exercise and CRC risk are some of the strongest for any type of cancer (2). Diets that contain fatty food and red meat, abdominal adiposity and a high body mass index (BMI), physical inactivity, alcohol, and cigarette smoking are all risk factors (3–5). Conversely, protective factors include white meat and fiber consumption, intake of calcium, vitamin D, folate intake, some antioxidant vitamins and minerals intake, and a diet that includes yogurt and resistant starches (6). Also, regular physical activity has been identified as an important factor in reducing CRC risk (25–30%), with approximately 13–14% of CRC cases attributable to physical inactivity (7). Moreover, the relationship between BMI as an indicator of excess body weight and the risk of CRC is well established (5). Cigarette smoking and alcohol consumption are modestly associated with the development of CRC (8).

Prospective cohort studies and case-control studies have shown that CRC risk and the number of adenomas are associated with a family history of cancer (9, 10). Also, the risk of CRC increased among women and was higher among those who had first-degree family members diagnosed with CRC (11). Another important factor is parental consanguinity, which has been shown to increase leukemia, lymphoma, CRC, and prostate cancer risks (12).

The incidence of colorectal cancer in the Arab world is relatively low, despite ranking second to breast cancer in some countries. In Palestine, CRC ranks second in cancer mortalities with 13.9% of all cancer deaths. It ranks second to breast cancer and makes up 9.9% of all cancer cases (13). This percentage is considered high in comparison with the Arab world and surrounding countries.

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For example, colorectal cancer makes up 9.3% in males and 5.7% in females in Saudi Arabia (3), and 9.2% in Jordan (14). During recent decades, there has been a clear shift in the Palestinian population away from a Mediterranean toward a more westernized diet, characterized by increasing consumption of red and processed meat (15). Thus, the increased incidence of CRC may be related to the change in lifestyle and nutritional status. To our knowledge, no study has been carried out in Palestine to investigate dietary factors in relation to CRC risk. Therefore, the purpose of the current study was to investigate the associations of nutrition, genetic factors, and other lifestyle factors with CRC risk among patients attending the oncology department at Beit Jala Governmental Hospital in the West Bank of Palestine.

Materials and Methods

Setting and Study Design

The cancer burden in Palestine is expected to increase and will pose a substantial challenge for the healthcare system. The shortage of specialized physicians and drugs, chemotherapy or radiation therapy presents a challenge to providing proper care for cancer patients (16). Limited financial and infrastructural resources, plus political uncertainty, exacerbate the problem (17). Cancer care, diagnosis, and treatment services are provided in four West Bank hospitals. However, isotope scans like PET-CT are not available and all such cases are referred to Israeli hospitals. This study was conducted at the major government hospital: Beit Jala Hospital in the southern West Bank. Beit Jala Hospital has an oncology department and day clinic that offers daycare medical services for cancer patients in the central and southern areas of the West Bank. This matched case-control study was designed to enroll 100 CRC cases and 100 CRC-free matched controls (1:1 ratio) to link most of the potential exposures (0.15 among controls) with an outcome variable with an odds ratio (OR) of 3 (3), assuming 80% study power (1-β), 5% level of significance (α), and 0.2 as a correlation coefficient for exposure(s) between cases and their matched controls.

Selection of Cases and Controls

Based on the hospital chart number, 105 cases were selected at random from those attending daycare or admitted to the oncology department or chemotherapy unit of Beit Jala Hospital. Patients with histopathologically confirmed CRC (International Classification of Disease for Oncology (ICD-O) codes: C18.0–18.9, C19, and C20), and treated by a gastroenterologist and/or oncologist were enrolled as cases. Patients with a previous diagnosis of cancer in any other site of the body, prior history of inflammatory bowel disease, familial adenomatous polyposis, and/or were severely ill were excluded.

To serve as comparable and representative controls, 105 controls of the same age and gender distribution were recruited at random. All these participants underwent a stool test for occult blood. The eligible controls had to be confirmed as free from colorectal cancer and had never been suspected of having any previous neoplastic disease or any other cancer.

Exposure Assessment

The medical records of cancer patients were used to retrieve information related to the CRC: date of diagnosis, stage at diagnosis, type of cancer, histopathological data, and therapy strategy.

A structured and pre-tested questionnaire was used to collect the data from cases and controls through face-to-face interviews by a trained interviewer. The study questionnaire was adopted from the Risk Factor Questionnaire for Colorectal Cancer Family Registry and was used for data collection (18), in addition to questions related to Palestinian social and cultural factors. In brief, the questionnaire comprised questions that were grouped into two sections: a) socio-demographic characteristics including age, gender, marital status, education, level, occupation; b) potential exposures including CRC family history, smoking, height, weight, physical activity, (assessed as metabolic equivalents – METs), dietary pattern (frequency of consumption of dietary items), and health status (having diabetes, hypertension, lipids profile, and taking medications).

The same interviewer administered the structured questionnaire for the controls and referred each participant to the hospital laboratory for a fecal occult blood stool test (FOBT). FOBT is a one-step rapid test device that is a chromatographic immunoassay for the qualitative detection of human occult blood in feces. The immunoassay method is more sensitive and specific than other methods and does not have diet restrictions before testing as the other methods do. Therefore, it is used as a screening tool for colorectal cancer or premalignant adenomas in the asymptomatic, low-risk population (19). Only participants with a negative FOBT were included

in the study. Data collection was carried out from July 2016 through May 2017.

Data Analysis

SPSS version 23 (IBM Corp., Chicago, IL, USA) was used for the data analysis. Bivariate and multivariate unconditional logistic regressions were used to assess the association of colorectal cancer with independent variables. Crude and adjusted odds ratio (AOR) and 95% confidence intervals (CIs) were calculated to determine the precision of the estimates. The level of significance used was 5%. The p-value < 0.05 indicated significance.

Ethics

This study protocol was approved by Al Quds University Ethical Review Committee. Written approval was obtained from the Ministry of Health to access patient records from the oncology department and cancer registry. Prior to the interview, written informed consent was sought from both cases and controls after explaining the study objectives. Participants were reassured of the confidentiality of the collected data.

Results

The final study sample was 210 participants (105 cases and 105 controls). The majority of our cases were colon cancer, representing 92.4%, and only 7.6% were rectal cancer patients. The mean years since cancer diagnosis were 1.84 years (±SD 1.48) (first year: 51%, two-four years: 41%, more than 5 years: 6.7%). Cases diagnosed with polyps totaled 29 (27.6%), 16 cases had polyps removed more than once, of which eight cases had malignant polyps. Three of the cases were Crohn's disease positive, one study case had ulcerative colitis, and eight cases were diagnosed with irritable bowel disease. None of the cases was diagnosed with diverticular disease. Most of the cases had undergone colon or rectum removal operations ($n = 98$, 93.3%) and 76.2% ($n = 80$) had undergone complete removal of the colon or rectum.

Participants' Characteristics

Table 1 shows that the mean age of the study participants was 61.2 years (SD 12.98), mostly married. Half of the study participants had no schooling, with no difference between cases and controls, 50% were not employed and 75 women were housewives (35%). Most of the cases resided in cities (63.8%) and 77%

Table 1. Characteristics of study participants in a hospital-based matched case-control study of colorectal cancer.

		Cases $N = 105$		Controls $N = 105$		Chi-square
Variable		N	%	N	%	P value
Sex	Female	48	45.7%	47	44.8%	–
	Male	57	54.3%	58	55.2%	
Age (years)	<50	39	37.1%	37	35.2%	–
	≥50	66	62.9%	68	64.8%	
Education	No schooling	48	47.1%	56	54.4%	0.545
	School (primary and high school)	44	43.1%	37	35.9%	
	College and above	10	9.8%	10	9.7%	
Marital Status	Single	2	1.9%	4	3.8%	0.430
	Married	93	88.6%	95	90.5%	
	Divorced/Widowed/ Separated	10	9.5%	6	5.7%	
Employment status	Unemployed	51	50.0%	41	39.8%	0.142
	Employed[a]	51	50.0%	62	60.2%	
Monthly income (NIS)[b]	<2000	23	39.7%	31	33.7%	0.169
	2001–4000	13	22.4%	34	37.0%	
	>4000	22	37.9%	27	29.3%	
Residence	City	67	63.8%	33	31.4%	0.000
	Village	32	30.5%	66	62.9%	
	Camp	6	5.7%	6	5.7%	
Area of residence	Southern region[c]	81	77.1%	102	97.1%	0.000
	Middle region[d]	24	22.9%	3	2.9%	
Parental consanguinity	Not Related	66	62.9%	89	84.8%	000
	Related	39	37.1%	16	15.2%	
Being a twin, triplet, or other multiple birth sibling	Twin or other multiple	17	16.2%	30	28.6%	0.031
	No	88	83.8%	75	71.4%	

[a]Housewives were considered as unemployed.
[b]New Israeli Shekels.
[c]Southern region: Hebron, Bethlehem.
[d]Middle region: Jerusalem, Ramallah, Jericho.

were from the southern region. The control cases resided more in villages (62.9%) and 97% were from the southern region. In total, 37% of cases had parental consanguinity compared with 15.2% of the control cases ($p < 0.05$), and 16.2 cases were twins/triplets vs. 28.6% of the controls ($p < 0.05$).

Univariable Conditional Logistic Analysis

Univariable conditional logistic regression analysis was conducted to quantify the magnitude of the unadjusted associations of various demographic, dietary, and lifestyle factors with CRC status (Table 2).

Family History

Univariable conditional logistic regression (Table 2) shows that compared with controls, cases were more likely to report a positive history of CRC (uOR = 4.82; 95% CI: 1.01–22.9) and more likely to have a family history of another cancer (uOR = 4.8; 95% CI: 1.33–17.4).

Consanguinity

Of the study cases, 37.1% had parents who had a consanguinity marriage compared with 15.2% of the study controls. In the univariable conditional logistic regression, cases were three times more likely to report being from a family of a consanguinity marriage compared with controls (uOR 3.29, 95% CI: 1.63–6.38) (Table 2).

Dietary Factors

When compared with controls, cases consuming 2–4 servings of red meat weekly were two times more likely to have CRC (uOR= 2.23; 95% CI: 1.25–4.03),

Table 2. Univariable conditional logistic regression analysis of factors associated with colorectal cancer status in a hospital-based matched case-control study.

Exposure		Cases N = 105		Controls N = 105		Unadjusted	95%*		P value of chi square
		Count	N %	Count	N %	uOR	U	L	
Family colorectal cancer	Yes/No	9	8.6%	2	1.9%	4.82	1.01	22.9	0.030
Other family cancers	Yes/No	13	12.4%	3	2.9%	4.80	1.33	17.4	0.009
Consanguinity	Yes/No	39	37.1%	16	15.2%	3.29	1.63	6.38	000
Smoking status	Yes/No	10	9.5%	26	24.8%	3.13	1.42	6.78	0.003
Current smoker	Yes/No	9	8.6%	22	21.0%	2.83	1.23	6.37	0.011
Body mass index (BMI)	<30	78	74.3%	66	62.9%	1.00			0.201
	≥30	27	25.7%	39	37.1%	1.71	0.95	3.08	
Total PA METs Min/ Week	Moderate-high (600–1500)	14	13.3%	4	3.8%	1.0			0.014
	Low (<600)	91	86.7%	101	96.2%	3.88	1.23	12.2	
Sedentary time spent METs/day	≤Median (180)	38	36.2%	69	65.7%	1.00			000
	>Median (180)	67	63.8%	36	34.3%	3.38	1.92	5.95	
Number of servings of fruits and vegetables weekly (sum score)"	Less than 2	4	3.8%	13	12.4%	1.00			000
	2–4	8	7.6%	44	41.9%	1.69	.44	6.53	
	5–6	40	38.1%	29	27.6%	0.22	0.07	0.75	
	7–8	35	33.3%	13	12.4%	.114	.031	0.42	
	More than 8	18	17.1%	6	5.7%	.103	.024	0.44	
Number of servings of meat weekly (sum score)	No meat	33	31.4%	31	29.5%	1.00			0.63
	Once	40	38.1%	36	34.3%	0.96	.492	1.86	
	Twice	22	21.0%	30	28.6%	1.45	0.69	3.03	
	3–4	10	9.5%	8	7.6%	0.85	0.29	2.44	
Number of servings of red meat weekly	0–1	66	62.9%	49	46.7%	1.00			0.024
	2–4	29	27.6%	48	45.7%	2.23	1.25	4.03	
	More than 4	10	9.5%	8	7.6%	1.08	0.39	2.93	
Number of servings of grilled red meat weekly	0–1	73	69.5%	53	50.5%	1.00			000
	2–4	19	18.1%	45	42.9%	3.26	1.72	6.201	
	>4	13	12.4%	7	6.7%	0.74	0.28	1.99	
Inner appearance of red meat when cooked *by broiling, grilling, barbecuing*	I don't eat red meat	7	6.7%	6	5.7%	1.0			0.057
	Red (rare cooking)	55	52.4%	45	42.9%	0.96	0.30	3.04	
	Pink (medium cooking)	16	15.2%	9	8.6%	0.66	0.17	2.56	
	Brown (well done)	27	25.7%	45	42.9%	1.94	0.59	6.39	
Aspirin	No	88	83.8%	66	62.9%	1.00			0.001
	Yes	17	16.2%	39	37.1%	0.33	0.17	0.63	
Frequency of weekly aspirin intake (times)*	No	88	83.8%	66	62.9%	1.00			0.003
	≥7	7	6.7%	14	13.3%	0.38	0.14	0.98	
	<7	10	9.5%	25	23.8%	0.30	0.14	0.67	

U, Upper; L, Lower; PA METs, World Health Organization recommended physical activity of metabolic equivalents.
*P value significance less than 0.05.

and cases consuming 2–4 servings of grilled meat were three times more likely (uOR = 3.26; 95% CI: 1.72–6.201 respectively). However, no significant association was seen between CRC and total weekly meat consumption (p value= 0.63) or higher amounts of red meat. Cases who reported consuming 5–7 servings of fruits/vegetables per week were less likely to have CRC compared with controls (uOR = 0.22; 95% CI = 0.07–0.75), and consuming 7–8 servings or more also made CRC less likely (uOR = 0.114; 95% CI: 0.031–0.42 and uOR = 0.103; 95% CI; 0.024–0.44, respectively) (Table 2).

Physical Inactivity

The univariate conditional logistic analysis showed that cases who did not engage in the required 'total physical activity' (METs), ie., WHO recommended level of physical activity, were three times more likely to have CRC (uOR =3.88; 95% CI: 1.23–11.2) compared to controls. Also, cases who were obese (BMI ≥ 30) were 1.7 times more likely to have CRC, but this association was not significant (uOR = 1.71; 95% CI: 0.95–3.08) (Table 2).

Smoking

Smoking was a positive factor for CRC when comparing cases and controls (uOR = 3.13; 95% CI: 1.42–6.78), and cases who were current smokers were two times more likely to have CRC compared with controls (uOR = 2.83; 95% CI: 1.23–6.37) (Table 2).

Taking Aspirin

Cases who reported taking aspirin were less likely to have CRC (uOR = 0.33; 95% CI: 0.17–0.63), with a similar association with frequency of use per week (>7 times a week uOR = 0.38; 95% CI: 0.14–098, <7 times a week uOR = 0.3; 95% CI: 0.14–0.67) (Table 2).

Comorbidities

When comparing cases and controls comorbidities, no significant associations were linked to CRC risk by any of the following comorbidities: diabetes, hypercholesterolemia, hypertriglycerides, Crohn's disease, familial adenomatous polyposis, ulcerative colitis, and irritable bowel syndrome (data not shown).

Multivariate Conditional Logistic Regression Model

Table 3 presents the multivariate logistic regression model of the CRC risk factors. After adjustment, cases from villages were less likely to develop CRC (AOR = 0.194; 95% CI: 0.081–0.465) compared with control and other cases living in cities or in refugee camps. Moreover, compared with controls, CRC cases who took aspirin were 24% less likely to have CRC (AOR = 0.24; 95% CI: 0.09–0.68). Those who had multiple birth siblings (twin, triplets) were 33% less likely to have CRC (AOR = 0.33; 95% CI: 0.33–0.92). The same can be said of control cases and fruit/vegetable serving intake per week. The likelihood of CRC was

Table 3. Multivariable conditional logistic regression forward model of factors associated with colorectal cancer status in a hospital-based matched case-control study.*

Variable		Sig.	AOR[a]	95% CI[b] Lower	95% CI[b] Upper
Residency	City			Ref	Ref
	Village	.000	.194	.081	.465
	Camp	.117	.276	.055	1.379
Consanguinity	Yes/No	.006	3.881	1.476	10.207
Are you a twin, triplet or other multiple birth sibling?	Yes/No	.034	.330	.119	.919
Family cancer	Yes/No	.023	6.392	1.290	31.675
Taking aspirin	Yes/No	.007	.244	.088	.678
Smoking		.007	4.377	1.494	12.820
Sedentary time spent METs/day	>Median (180)	1.00			
	≤Median (180)	.026	2.528	1.120	5.710
Grilled red meat consumption weekly	Less than 2		1.00		
	2–4	.002	4.248	1.676	10.767
	>4	.504	.621	.153	2.512
Weekly serving of fruits and vegetables (sum score)	Less than 2	1.00			
	2–4	.205	2.936	.555	15.530
	5–6	.050	.209	.044	.997
	7–8	.041	.187	.037	.935
	More than 8	.007	.068	.010	.476

*All significant variables ($p < 0.05$) in univariate analysis were included in a multivariate model (P value 0.05): i.e., education level, marital status, residence, consanguinity, aspirin (intake, frequency, and duration), smoking, diet, family history of CRC and cancer, being a twin/triplet, and physical activity.
[a]Adjusted odds ratio.
[b]Confidence interval.

lowered when consuming 5–6 servings per week (AOR = 0.209; 95% CI: 0.044–0.997), 7–8 servings per week (AOR = 0.041; 95% CI: 0.037–0.935), and more than eight servings per week (AOR = 0.007; 95% CI: 0.01–0.476). Cases who consumed 2–4 servings of grilled red meat were more likely to have CRC (AOR = 4.248; 95% CI: 1.676–10.767) compared with controls. For smokers, a comparison with control cases showed that smokers were four times more likely to have CRC (AOR = 4.377; 95% CI: 1.494–12.820), and this was similar for cases with a sedentary lifestyle (low physical activity) (AOR = 2.528; 95% CI: 1.12–5.71). Additionally, when compared with controls, CRC cases were three times more likely for CRC if they reported parental consanguinity in their families (AOR = 3.88; 95% CI: 1.47–10.2). A similar positive association was seen when cases had a family history of cancer, where the likelihood to have CRC increased 6 times (AOR = 6.392; 95% CI: 1.290–31.675).

Discussion

We conducted a hospital-based matched case-control study of colorectal cancer. We found an increased likelihood of CRC with greater consumption of both cooked and grilled red meat. In addition, higher odds of CRC were shown among those having parental consanguinity and/or families with a history of cancer. Smokers and those with a sedentary lifestyle also had increased odds of CRC. However, those consuming more fruits or vegetables such as oranges, mandarins, grapes, and tomatoes were less likely to have CRC.

The main strength of this study is that, to our knowledge, it is the first conducted in a country of conflict with limited resources and with a healthcare system that struggles to provide adequate services for its population. This study was conducted to investigate the potential risk factors of CRC: ie, lifestyle, diet, and genetic factors. Factors related to Arab culture such as consanguinity marriage were also included (12, 20, 21). This is a strong risk factor for several cancers in Arab countries and these findings will support other studies of this type in the region.

Regarding diet, our multiple logistic regression model showed that consumption of fruit and vegetables, and grilled red meat, are associated with CRC. Consuming five or more servings of fruit and vegetables weekly was negatively associated with the odds of CRC, meaning that it has a protective effect against CRC. This result is consistent with the literature (3, 22, 23), which concludes that consuming fruits and vegetables lowers the risk of CRC. Low intake or less frequent consumption of fruit and vegetables has consistently been shown to be a significant factor for increased CRC risk (3). Several explanations are suggested for this protective effect, including the probability that high intake of fibers in fruits and vegetables helps to increase the bulk of the stool, thereby reducing transit time through the gut and thus, attenuating carcinogens (22, 23). The antioxidants present in fruits and vegetables are also thought to play a role in decreasing cellular damage caused by reactive oxygen species which may cause cancer (24).

The logistic model showed that consumption of two or more meals of grilled meat in one week was significantly associated with a 4-fold increase in odds of CRC. This result is consistent with the findings of studies carried out in several Eastern Mediterranean countries (20), including Saudi Arabia (3), Kuwait (24), Jordan (25), and other countries worldwide (26–29), which showed a significant association between red meat consumption and CRC risk. A meta-analysis of 13 prospective studies showed an increase of 22% in CRC risk associated with high red meat consumption compared with low consumption (30). Several biological mechanism models justified this association. It is not clear whether the CRC risk is associated with the amount of red meat consumption per se or with specific meat cooking practices (31, 32). A case-control study of colorectal adenomas conducted at the National Naval Medical Center showed that red meat cooked until well done/very well done and/or by high-temperature cooking techniques such as grilling may produce carcinogens and mutants such as aromatic hydrocarbons or amines (32). Cooking meat at high temperatures results in the production and release of free radicals such as heterocyclic amines and polycyclic aromatic hydrocarbons which are believed to be carcinogenic (33). In addition, high-fat diets, especially of animal origin, and fat peroxidation process outcome in the inferential epithelium may cause intestinal inflammation that plays a role in malignancy development (34).

Our multivariate logistic regression showed that living in a rural area like a village is inversely associated with CRC by 27.6% in comparison to living in a city or refugee camp. However, this result is inconsistent with the results of other studies that found living in a rural area increased the risk of colorectal cancer (35, 36). Those studies justified their findings on the basis of a lack of screening behaviors and increased modifiable risk factors in those populations compared with urban areas. In our study,

lower odds in rural areas may be due to the traditional lifestyle of the people living in these villages. Smoking has been shown to be a risk factor for CRC (37). However, a cross-sectional study conducted in Jordan, Lebanon, Syria, and Palestine showed that smoking in rural areas is low compared with urban areas (38). Dietary patterns in villages are healthier and are based on more natural foods sourced primarily from local harvests or from animals raised by hand. A study of the dietary patterns of the Palestinian population in 1999 showed that villagers relied mostly on their animals and their food was more natural (15). Also, people living in villages mostly still work in farming and the greater physical activity lowers the risk of CRC, as indicated in the literature (6, 39–43). This association was confirmed in our study results which indicated that a sedentary lifestyle at least doubled the odds of CRC. Our study model produced a significant association between a sedentary lifestyle and low physical activity of 2.5 higher odds of CRC. Physical inactivity and being overweight are reported to be responsible for about one-fourth to one-third of colorectal cancer cases (40). It has been proven that higher levels of physical activity are associated with a lower risk of developing colorectal cancer. The relationship is believed to be a dose-response relationship in which the increase of frequency and intensity of the physical activity will inversely lower the risk of developing colorectal cancer (39, 43). Maintaining regular levels of physical activity, in addition to a healthy diet, will decrease the risk of colorectal cancer. The relationship between physical activity and colorectal cancer risk can be explained by the fact that physical activity raises the metabolic rate and increases oxygen uptake (43). It also increases the body's metabolic efficiency and capacity, reducing blood pressure and insulin resistance. In addition, physical activity increases gut motility, thus reducing the colorectal cancer risk (39). Similar findings were found in a case-control study in Jordan (25) where a sedentary lifestyle and a diet low in fruits and vegetables, and high in animal red meat and saturated fat, appeared to be associated with CRC.

Another important determinant of CRC is smoking. Smoking was a significant finding in our study and our logistic regression model showed that smoking increased the odds of CRC by 430%. This result is consistent with the literature and international studies. Smoking is harmful to the colon and rectum. It is estimated that about 12% of colorectal cancer deaths are attributed to smoking (44). Evidence shows that the carcinogens found in tobacco increase cancer growth in the colon and rectum, and thus, increase the risk of colorectal cancer diagnosis (45). Cigarette smoking is crucial for the formation and growth rate of adenomatous polyps, the colorectal cancer precursor lesions. Larger colon polyps were found in the colon and rectum of long-term smokers (37).

Our model also showed that a family history of any cancer type increased the odds of CRC by 639% compared with people without a history of cancer in their families. It is known that family history is a strong risk factor for CRC (11, 29, 46). About 20% of people who develop colorectal cancer have other family members who have been diagnosed or affected by cancer (11). People who have one or more first-degree relatives with a history of colorectal cancer or other cancers are at increased risk. This association was even stronger where parental consanguinity was present. Consanguinity is a marriage between relatives and has various degrees (47). There is a historically high prevalence of consanguineous marriages in many communities throughout the world, especially in countries of the Middle East, Northern Africa, and South Asia (48). In Palestine, it has been reported that 40% of all marriages are consanguineous and about 20% are between first-degree relatives (47). Our study results showed that being born to a consanguineous parent increased the odds of developing CRC around 4-fold. Very few studies worldwide have addressed this issue. A case-control study in Qatar aimed to examine whether parental consanguinity affects the risk of cancer in a local Arab, highly inbred population. The study concluded that consanguinity had an increased effect on the overall incidence of cancer, but found an increased risk for colorectal cancer and other types of cancers (48). In a similar matched case-control study in Qatar, family history and parental consanguinity were strongly associated with the development of colorectal cancer (49). Evidence has proven that in a population with a high rate of consanguinity, there is a significant increase in the prevalence of common adult diseases like cancer, mental disorders, heart diseases, gastrointestinal disorders, hypertension, and hearing deficit (12). Our study's findings can be attributed to the high rate of consanguinity marriage in Palestine, which accounts for 44% of total registered marriages (50).

Using aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) was shown to protect against the development of colonic adenomas, and CRC and its recurrence (51). In our multivariate model, aspirin and its frequency of use were significantly inversely associated with the odds of CRC by 24%. Several observational and large randomized

clinical trials have suggested that aspirin may be a good choice of chemoprevention agent among high-risk individuals. However, the underlying process of NSAIDs in inhibiting carcinogenesis remains inconclusive and the minimum dose of aspirin required to achieve the protective effect is still uncertain. Therefore, recommendation of the use of aspirin as a chemoprevention agent should be done with caution in the absence of consensus about the balance of risks and benefits associated with long-term aspirin use (52).

This study has several strengths and also limitations that may affect some of the study outcomes. The main study limitation may be recall bias, which is a major bias in retrospective study designs. The length of the recall period varies among the participants. Those with a recent diagnosis may be able to remember their diet pattern prior to the diagnosis better than others. Some participants may have already made modifications to their dietary habits, and might over-or under-estimate their reported consumption of certain foods associated with a higher or lower CRC risk prior to their CRC diagnosis. This could be a consequence of exposure to information related to prevention and control of the disease as advised by a health care professional or via self-education, or possibly by the intervention of families in the patient's lifestyle. This information bias is not possible to control for in such a type of retrospective study design. Also, we collected detailed information on cooking practices and degrees of doneness for specific types of commonly consumed meats. We could not quantify portion size but we obtained weekly frequency consumption. Measurement errors may be associated with the food frequency dietary questionnaire. We trained the data collector on how to ask questions to minimize this type of error. Moreover, CRC cases were histopathologically confirmed. We used a stool occult blood test to include the controls, in addition to the participants confirming that they had never had any cancer diagnosis. The variations in confirmation of cases and controls could also be a type of information bias in this study. Finally, we conducted this study on survived cases; critical and end-stage cases are usually transferred to special institutions and were not included in this study.

In conclusion, colorectal cancer research is very limited in Palestine. These study findings will help in promoting cancer research and prevention in Palestine. Identified risk factors allow the establishment of evidence-based preventive actions regarding nutrition and other lifestyle habits adapted to the Palestinian context.

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Ethics Approval and Consent to Participate

This study was approved by Al Quds University Ethical Research Committee, which is based on the Helsinki declarations. Therefore, all study methods were performed following the Helsinki guidelines and regulations. Al Quds University ethical research regulations adhere to Helsinki regulations. Written approval was obtained from the Ministry of Health to access patient records from the oncology department and cancer registry. All particiapnts provided written informed consent.

Disclosure Statement

The authors declare that they have no competing interests. The authors are alone responsible for the content and writing of the paper.

Author Contributions

Nuha El Sharif was responsible for the Conceptualization, Methodology, Visualization, Writing - Original draft preparation. Nuha El Sharif and Issa Ghrouz designed the survey and developed the study tool. Issa Ghrouz was responsible for data collection, data entry, and primary analysis. Nuha El Sharif and Issa Ghrouz participated in the study of advanced analysis and the development of study tables. Issa Ghrouz and Nuha El Sharif were responsible for writing the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials

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

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