RESEARCH ARTICLE

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Adherence to the Mediterranean Diet and Colorectal Cancer Risk Among Moroccan Population: Hospital-Based Case Control Study

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Abstract

Background: Colorectal cancer (CRC) is a significant public health problem, including Morocco. The Mediterranean Diet (MD) has demonstrated potential anticancerogenic effects toward CRC in Northern Mediterranean countries. Using a Modified Mediterranean Diet (MMD) score adapted to southern countries, we investigated the relationship between adherence to the MD and the risk of CRC among the Moroccan population. **Material and Methods:** During the study, we recruited 395 cases matched with 395 controls by sex and age (± 3 years). Using an adapted Food Frequency Questionnaire, we assessed the dietary intakes of participants to calculate the MMD score. We estimated the odds ratio and 95% confidence interval for both basic and adjusted models to evaluate the relationship between adherence to the MD and the risk of CRC. **Result:** We observed a significant inverse association between adherence to the MD and CRC risk. In the adjusted model, moderate adherence to the MD was associated with 52% lower risk of CRC [odds ratio (OR*): 0.48 and 95% confidence interval (95% CI): 0.37-0.69], while high adherence to the MD was associated with 61% lower risk of CRC compared to the lowest category. When stratified by sex, both moderate [OR*: 0.36 (CI95%: 0.27-0.55)] and high [OR*: 0.43 (CI95%:0.27-0.74)] adherence were inversely correlated with CRC risk for women, while for men, only high adherence was inversely correlated with the risk of CRC [OR*: 0.3 (CI95%:0.19-0.5)]. **Conclusion:** Adherence to MD is associated with a decreased risk of CRC, an association that may be influenced by tumor location, sex, and age. Despite certain differences between northern and southern countries, the MD can be an effective preventative measure against CRC for populations in the Southern Mediterranean region.

Keywords: Colorectal cancer- mediterranean diet- Morocco- prevention- case control

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Introduction

Over the past few decades, Morocco has recorded a significant increase in its urban population, reaching over 63% of the total population of approximately 34 million in 2014 [1]. This demographic transition has been accompanied by various industrial and economic transformations within the Moroccan population [2]. These changes have led the Moroccan population to greater adherence to a Western lifestyle, which has impacted the dietary habits. This shift is characterized by a higher consumption of animal products and processed foods, coupled with a reduced intake of green vegetables and micronutrients. Additionally, there has been a decrease in physical activity and an increase in sedentary behaviors due to office work and the widespread use of cars and other means of transportation [3,4]. Simultaneously, several cardiovascular diseases and cancers, such as CRC, have emerged among the Moroccan population. Globally, CRC ranks as the 3rd most frequent cancer, with nearly 1.9 million new cases reported in 2020 and almost 1 million deaths [5]. In Morocco, unfortunately we dispose only two regional cancer registers. The first is the register of the Grand Casablanca region, which reported an age-standardized incidence of 9/100 000 for both sexes combined in 2017. For the Rabat region, the age-standardized incidence was 7.02/100 000 for men and 5.86/100 000 for women in 2012 [6,7]. According to the Global Cancer Observatory (GLOBOCAN), CRC ranks as the third most frequent cancer, accounting for 8.3% of cases in 2022 for both sexes combined, with an age-standardized incidence of 13.4/100 000 for men and 11.4/100 000 for women. Projection studies suggest an exponential increase in CRC incidence over the coming years, with an estimated incidence of 26/100 000 for both sexes combined by 2030 [8]. CRC develops over a long period of time, allowing for prevention through early diagnostics or dietary interventions, which could potentially prevent up to 70% of CRC cases [9]. Before the demographic changes that led to dietary transition

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among the Moroccan population, Morocco, as one of the Mediterranean countries, traditionally adopted a MD. Which is characterized by cereal-based diet with a high consumption of fruit and vegetables, along with a reduced consumption of animal products. Olive oil is also an important component of the MD, serving as a source of monounsaturated fatty acids, with a moderate wine consumption in some countries [10,11]. The MD has demonstrated protective effects against various cardiovascular diseases and cancers, due to the effect of different components of the MD, such as vegetables, fruits, and olive oil, which exhibit some anti-inflammatory, anti-cancerogenic and anti-oxidant properties [12]. The MD score is a metric that serves to evaluate the adherence of populations to the MD based on the consumption or not of various components of the MD. Some components may differ according to some studies design, but generally includes: vegetables, fruits, olive oil, cereals, fish, red meat, and dairy products [10]. Given certain socio-cultural and religious differences between the countries in the northern and southern Mediterranean, such as the consumption of wine as mentioned previously, which is illegal in the majority of the southern countries due to religious reasons. The classic MD score is less efficient in the southern countries to assess their adherence to the MD. The Modified Mediterranean Diet (MMD) score has been developed to evaluate adherence in the populations of the Southern Mediterranean countries, adapted to their socio-cultural and religious characteristics [13]. No previous study in Morocco has evaluated the adherence to the MD with CRC using this adapted MMD score. The aim of our study is to investigate the relationship between adherence to the Mediterranean diet and CRC risk in the Moroccan population using a Modified Mediterranean Diet score, stratified by sex, tumor location and age categories.

Materials and Methods

Study design and population

Hospital-based case-control study was conducted at the University Hospital Center Mohamed VI in Marrakech, which is responsible for the Marrakech-Safi region, the third populous region in Morocco with a population of approximately 4.5 million persons. From November 2022 and over a period of 15 months, we recruited cases consequently following the order of admission to the hospital. Controls were recruited simultaneously as cases, matched according to sex and age (± 3 years) at a ratio of 1case per 1control. The minimum simple size needed for the study was 343 cases and 343 controls, with a power of 80% and 5% type I error, to detect an Odds Ratio (OR) of 1.6 for 25% of exposed controls. During our study, we approached 430 eligible cases and 430 controls, from which 409 cases and 409 controls were recruited (acceptance rate of 95.11%), the main reason for non-participation was the length of the interview (around 20 min). 14 cases and 14 controls were excluded from the study before all the statistical treatment and analysis due to incomplete or invalidated data, at the end 395 cases and 395 controls were analyzed. Recruitment of cases was based on several inclusion criteria: participant had to be adult with recent histopathological confirmation of CRC Within a maximum of 3 months, absence of any pathology that might influence their diet or require a specific diet, absence of any eating disorders, finally, full cognitive and medical capacity to conduct the interview. However, controls were recruited at the same hospital but from the traumatology department during the same period of time following these inclusion criteria: adult participant with no history of CRC or any other cancer, absence of any gastrointestinal pathology identified as a risk factor for CRC, absence of first-degree family related case of CRC, absence of any pathology that might influence their diet or require a specific diet, and absence of any cognitive or eating disorders. The companions of cases were accepted as controls as long they were not a family member and met inclusion criteria, considering that, in majority of time case's companions share a similar socio-economics characteristics with the cases. After explaining the aims of the study, a written informed consent was obtained from all participants, through a face-to-face interview data was collected by trained investigators. During a period of 3 weeks, the investigators underwent training session on how to properly administrate a questionnaire, assist participants without influencing them, and avoid misclassification. The investigators also had session on how to collect data uniformly to reduce the investigator bias. The protocol of our study was approved by the Research Ethics Committee of the Moroccan Association for Research and Ethics (No:12-REC-2022).

General characteristics

the general characteristics of participants were collected using a structured questionnaire. The first part of the questionnaire included: age (years), sex (male, female), educational level (illiterate, koranic, primary, secondary, university), residency (urban, rural), marital status (never married, married, widowed, divorced), monthly income was categorized into 3 groups: low (<2000 MDH), medium (2000-5000 MDH) and high (>5000MDH), family history of CRC (yes, no). the second part of the questionnaire included lifestyle habits, such as BMI calculated based on weight and height (Kg/m2). For cases, the weight prior to the first symptoms of CRC, while for controls, weight was measured during the interviews to the closed 100 g, height was also calculated during the study to the closed 0.1 cm, then categorized BMI into 4 groups according to the standard classification: underweight (<18.5 kg/m2), normal (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2) and obesity (≥30 kg/m2); physical activity categorized into 3 groups: low (< 600 MET-min/week), moderate (600–3000 MET-min/week) and high (≥ 3000 MET-min/week) using the Global Physical Activity Questionnaire (GPAQ) to calculate metabolic equivalent [14]. Smoking status was defined according the classification of the International Union against Tuberculosis and Lung Diseases Guide, categorized into 3 groups: never smoker, ex-smoker, current smoker [15]; alcohol consumption (yes, no).

Assessment of dietary intakes

To collect the dietary intakes of participants, we

used a semi-quantitative food frequency questionnaire (SQ-FFQ). Due to particularity of Moroccan cuisine we adopted during the study a validated and adapted FFQ for Moroccan adult population that include some Moroccan traditional dishes, the SQ-FFQ used included 30 foods groups of 255 food items [16]. To assess consumption frequency, the questionnaire categorizes consumption into 8 frequencies: never, one to three times per month, one time per week, two to four times per week, five to six times per week, one time per day, two to three times per day, and finally four times or more per day. For each food item we used local household servings to convert frequency of intake into an average daily intake. We then used various databases to calculate total energy and nutriments intakes (Moroccan, Tunisian, and French food composition table) due to the incomplete Moroccan table [17–19].

Modified Mediterranean Score

Based on the basic MD score, an MMD score was developed to assess countries in the southern Mediterranean region, considering their religious and socio-economic particularities [13]. The MMD score include 12 components : cereals (including all types of couscous, rice, bread, smida , assida, and dchicha), legumes (peas, lentils, chickpeas and all types of beans), potatoes (all types of potatoes), vegetables (all types of vegetables), fruits (all types of fruits), eggs (both industrial and farmer eggs) fish (white fresh fish, fat fresh fish, and seafood), dairy products (all modern dairy products as milk and cheese, all traditional dairy products as jben, raib, and lben), red meat (all types of red meat including traditional ones as quadid and Khliaa, as well as processed meat), Poultry (all types of poultry and also turkey), the ratio of MUFA/SFA (as the ratio of monounsaturated fatty acids per statured fatty acids mainly from olive oil but also other types of oils), and sweets (including both Moroccan and western confectioneries). For each component, a sex-specific median is determined. When the consumption of red meat, dairy products, potatoes, poultry and sweets is equal or more than the median, a score of 0 is attributed. When consumption is less than the median, we attribute the score of 1. Conversely, for cereals, vegetables, fruits, legumes, fish, and the ratio MUFA/SFA when the consumption is equal or more than the median, we attribute the score 1 and when the consumption is less than the median, we attribute the score 0. Each participant will have a score that varies between 0 and 12, we categorized the adherence to the MD of all participants into 3 groups: Low (from 0 to 4), moderate (from 5 to 7), and high (from 8 to 12).

Statistical analyses

To evaluate the general characteristics of participants, we used independent sample t-test for continuous variables, which were presented by means and standard deviation. For categorical variables, we used the chi-square test, and were presented as frequencies. Additionally, to evaluate the relationship between adherence to the MD and the risk of CRC, we used conductional logistic regression to estimate OR and 95% confidence interval (CI95%) in both crude and adjusted models. Based on the general characteristics of participants and potential confounding factors, we selected the significant confounding factors for the adjusted multivariable model. Two models were considered during the study: the basic model (OR) adjusted only sex and age (±3 years), adjusted model (OR*) additionally adjusted for educational level (illiterate, koranic, primary, secondary and university), residency (urban and rural), marital status (never married, married, widowed and divorced), BMI (underweight, normal, overweight and obesity), physical activity (low, medium and high) tabaco (never smoker, ex-smoker and smoker), total energy intake (kcal/day), red meat consumption (g/week) , fiber intake (g/day), calcium intake (mg/day) and folate intake (mcg/day). According to controls distribution, we defined sex-specific median values for adherence to each MMDS component: cereals (men: 379.12 ±17.23 ; women: 312.47 ±69.38), legumes (men: 155.79 ±93.22; women: 127.3 ±15.07), potatoes (men: 35.28 ± 11.14; women: 29.54 ± 17.86), vegetables (men: 240.95 ± 26.8; women: 226.45± 33.17), fruits (men:139.81 ±41.29; women: 104.21 ±20.71), eggs (men: 21.59 ±20.33; women: 16.26 ±13.4), fish (men: 28.83 ±19.35; women: 21.13 ±17.05), dairy products (men: 142.49 ±71.34; women: 113.21 ±57.39); red meat (men: 57.95 ±13.2; women: 43.21 ±10.79), poultry (men: 34.85 ±21.66; women: 29.15± 18.25), ratio MUFA/SFA (men: 1.49 ±0.24; women: 1.16 ±0.36) and sweets (men: 15.76 ± 16.34; women: 11.46 ±17.29) all medians value were reported as gram/day. the significant level was set at $p< 0.05$ and two-sided for all adequate statistics tests, data analysis was performed using IBM SPSS v23.

Results

Table 1 presents the general characteristics of 395 colorectal cancer cases and 395 controls. The mean age was 53.94 ±9.74 for cases and 54.72±11.51 for controls, with no significant difference (P-value: 0.304). Controls were more educated than cases, with over than 50% of cases being illtreat with a significant difference (P-value <0.001). The majority of both cases and controls resided in urban areas, with a higher proportion among controls, approximately 80% of cases versus 90% of controls (P-value< 0.001). Regarding marital status, around 76% of controls were married compared to 60% of cases (P-value< 0.001). Monthly income was similar between cases and controls, without any significant difference (P-value: 0.756). In contrast, for BMI, 48% of cases were above the normal range compared to only 25% of controls (P-value: <0.001). Similarly, concerning physical activity, 61% of cases reported low physical activity versus only 30% of controls, with a significant difference (P-value: <0.001). the prevalence of smokers was higher among cases than control, a significant difference of P-value: 0.003. However, alcohol consumption and family history of CRC were similar between cases and controls, without any significant differences P-value: 0.432 and P-value: 0.524 respectively. All fiber, calcium and folate intake were significantly higher among controls, with respectively P-value< 0.001 for fiber, P-value: 0.012 for calcium and P-value< 0.001 for folate. Conversely, both total energy

Table 1. General Characteristics of a Moroccan Case Control Study Population for Adherence to the Mediterranean Diet and the Risk of Colorectal Cancer

Characteristics	Case n(%)	Control n(%)	P-value
Sex			1.00
Male	214 (54.17)	214 (54.17)	
Female	181 (45.83)	181 (45.83)	
Educational level			<0.001
Illtreat	199 (50.37)	155 (39.24)	
Koranic	83 (21.01)	74 (18.73)	
Primary	57 (14.43)	82 (20.75)	
Secondary	47 (11.89)	59 (14.93)	
University	9 (2.27)	25 (6.32)	
Residency			<0.001
Urban	321 (81.26)	357 (90.37)	
Rural	74 (18.74)	38 (9.62)	
Marital status			<0.001
Never married	71 (19.97)	43 (10.88)	
Married	247 (62.53)	302 (76.45)	
Widowed	45 (11.39)	33 (8.35)	
Divorced	32 (8.1)	17 (4.3)	
Monthly income			0.756
Low (<2000 DHM)	90 (22.78)	87 (22.02)	
Medium (2000-5000 DHM)	171 (43.3)	164 (41.52)	
High (>5000 DHM)	134 (33.92)	144 (36.46)	
BMI			<0.001
Underweight	21 (5.31)	43 (10.88)	
Normal	184 (46.59)	252 (63.8)	
Overweight	85 (21.19)	20 (5.1)	
Obese	105 (26.91)	80 (20.22)	
Physical activity			<0.001
Low	241 (61)	119 (30.12)	
Moderate	129 (32.65)	223 (56.45)	
High	25 (6.35)	53 (13.41)	
Tobacco			0.003
Never smoker	208 (52.65)	248 (62.78)	
Ex-smoker	71 (17.97)	70 (17.72)	
Smoker	116 (29.36)	77 (19.49)	
Alcohol			0.432
No	371 (93.92)	376 (95.18)	
Yes	24 (6.08)	19 (4.82)	
Family history of CRC			0.524
No	389 (98.49)	391 (98.98)	
Yes	6 (1.51)	4 (1.02)	
	Case Mean ±SD	Control Mean ±SD	P-value
Age	53.94 ±9.74	54.72±11.51	0.304
Total Energy intake (Kcal/day)	3445.43±731.02	3281.33±607.28	<0.001
Consumption of red meat(g/week)	767.31±41.11	354.06±9.76	<0.001
Fiber intake (g/day)	31.17±24.51	47.33±7.39	<0.001
Calcium intake (mg/day)	1281.64±742.42	1411.38±719.15	0.012
Folate intake (mcg/day)	205.62±12.14	234.29±138.17	<0.001
Vitamin D intake (mcg/day)	2.3±0.13	2.4±1.01	0.051

intake and red meat consumption were significantly higher among cases than controls, with P-value< 0.001 for total energy intake and P-value< 0.001 for red meat consumption. Vitamin D intake was higher for controls but did not show any significant difference (P-value: 0.051). Table 2 presents the crude and adjusted ORs of MMD score and the risk of CRC according to tumor location. Referring to the lowest category (0-3), the ORs for CRC overall were associated with a decreased risk of CRC for both moderate and high groups, for the moderate group in the crude model OR was 0.46 (CI95%: 0.33-0.64) and OR* was 0.48 (CI95%: 0.37-0.69), concerning the highest adherence, OR was 0.33 (CI95%: 0.28-0.48) in the crude model and OR*: 0.39 (CI95%: 0.28-0.56) after adjusting for confounding factors. For colon cancer, only the high adherence group was inversely correlated with CRC risk, first in the crude model OR: 0.46 (CI95%: 0.27-0.78) then in the adjusted model OR*: 0.49 (CI95%: 0.31-0.81). While for the moderate adherence group, the risk was higher but statistically non-significant OR: 1.38 (CI95%: 0.92-2.08) and OR* was 1.39 (CI95%: 0.94-2.1) for crude and adjusted models respectively. For rectal cancer, the results were similar to colorectal cancer, showing an inverse correlation for both groups with CRC risk. In the moderate group, the OR were 0.12 (CI95%: 0.07-0.2) for the basic model and OR*: 0.17 (CI95%: 0.12-0.28) after adjusting for confounding factors. In the high adherence group the risk was slightly higher, with OR: 0.35 (CI95%: 0.23-0.54) and OR*: 0.38 (CI95%: 0.27-0.57) for the basic and adjusted models. Table 3 illustrate the ORs of each MMD score group according to the sex of participants, for men, only the high adherence group was associated with a reduction of CRC risk, with an OR of 0.28 (CI95%: 0.17-0.46) in the basic model and an OR* of 0.3 (CI95%: 0.19-0.5) in the adjusted model. For the moderate group, the ORs were OR: 0.66 (CI95%: 0.42-1.04) and OR*: 0.69 (CI95%: 0.45-1.09) for crude and adjusted models, respectively. However, for women, both moderate and high adherence groups were inversely correlated with CRC risk, with an OR* of 0.36 (CI95%: 0.27-0.55) in the moderate group and an OR* of 0.43 (CI95%: 0.27-0.74) for the high adherence group. While according by age categories, the 39 to 59-years-old group showed more adherence to the MD associated with a decreased risk of CRC in both moderate and high adherence. In contrast, both (18-38) and (60-80) were only associated with a reduced risk of CRC for the highest adherence to the MD (Table 4).

Discussion

During this present study, we report an inverse correlation between the adherence to the Mediterranean diet and a reduced risk of colorectal cancer. According to tumor location, the association remined significant for rectal cancer and the highest adherence group of colon cancer, when stratified by sex, the inverse association persisted significant for women and the highest adherence group for men. Additionally, the category of age between 39-59 adhere the most to the MD. Our results align with a previous Italian EPIC study, where adherence to the MD

Table 2. Cured and Adjusted Odds Ratio for Adherence to the Mediterranean Diet and the Risk of Colorectal Cancer According to Tumor Location in a Moroccan Case Control Study

Location	Colon		Rectal		Colorectal overall	
MMDS	OR (CI95%)	OR*(CI95%)	OR (CI95%)	OR*(CI95%)	OR (CI95%)	OR*(CI95%)
Cases/controls [0-4]	52/102		103/102		183/102	
	1.00	1.00	1.00	1.00	1.00	1.00
Cases/controls [5-7]	118/168		21/168		139/168	
	1.38 (0.92-2.08)	1.39 (0.94-2.1)	0.12 (0.07-0.2)	0.17 (0.12-0.28)	0.46 (0.33-0.64)	0.48 (0.37-0.69)
Cases/controls [8-12]	29/125		44/125		73/125	
	0.46 (0.27-0.78)	0.49 (0.31-0.81)	0.35 (0.23-0.54)	0.38 (0.27-0.57)	0.33 (0.23-0.48)	0.39 (0.28-0.56)
P-value	<0.001	0.002	<0.001	0.001	<0.001	<0.001

OR, basic model adjusted only sex and age (±3 years); OR*, multivariable model additionally adjusted for educational level (illiterate, koranic, primary, secondary and university), residency (urban and rural), marital status (never married, married, widowed and divorced), BMI (underweight, normal, overweight and obesity), physical activity (low, medium and high) tabaco (never smoker, ex-smoker and smoker), total energy intake (kcal/day), red meat consumption (g/week) , fiber intake (g/day), calcium intake (mg/day) and folate intake (mcg/day); Colon and rectal cancer cases are inferior to colorectal cases overall due to unknown location cases.

Table 3. Cured and adjusted Odds Ratio for Adherence to the Mediterranean Diet and the Risk of Colorectal Cancer According to the Sex of Particpant in a Moroccan Case Control Study

Sex	Men		Women	
MMDS	OR (CI95%)	OR*(CI95%)	OR (CI95%)	OR*(CI95%)
Cases/controls [0-4]	104/64		79/38	
	1.00	1.00	1.00	1.00
Cases/controls [5-7]	72/67		67/101	
	0.66 (0.42-1.04)	0.69 (0.45-1.09)	0.32 (0.2-0.52)	0.36 (0.27-0.55)
Cases/controls [8-12]	38/83		35/42	
	0.28 (0.17-0.46)	0.3 (0.19-0.5)	0.4 (0.22-0.72)	0.43 (0.27-0.74)
P-value	<0.001	<0.001	<0.001	<0.001

OR, basic model adjusted only sex and age (±3 years). OR*, multivariable model additionally adjusted for educational level (illiterate, koranic, primary, secondary and university), residency (urban and rural), marital status (never married, married, widowed and divorced), BMI (underweight, normal, overweight and obesity), physical activity (low, medium and high) tabaco (never smoker, ex-smoker and smoker), total energy intake (kcal/day), red meat consumption (g/week) , fiber intake (g/day), calcium intake (mg/day) and folate intake (mcg/day).

was associated with a reduced risk of CRC [20]. Another European cohort study reported an 8% to 11% decreased risk of CRC when comparing the highest group (6-9) to the lowest group (0-3) [21]. In contrast with our findings, a health professional follow-up study showed no correlation between MD and CRC risk, where the hazard ratio (HR) was 0.89 (CI95%: 0.74-1.08), similarly, a Netherlands cohort study showed no correlation between adherence to MD and a decreased risk of CRC regardless of sex, with an HR of 0.97 (CI95%: 0.88-1.07) for women and an HR of 1.04 (CI95%: 0.95-1.13) for men [22,23]. However, in our study the association were more pronounced among women than men, even after adjusting for confounding factors. This difference may be attributed to sex-specified hormones, as female hormones downregulate the excretion of bile acids, leading to a lower levels in the colon where

Table 4. Cured and adjusted Odds Ratio for Adherence to the Mediterranean Diet and the Risk of Colorectal Cancer According to Age Categories in a Moroccan Case Control Study

Age	[18-38]		[39-59]		[60-80]	
MMDS	OR (CI95%)	OR*(CI95%)	OR (CI95%)	OR*(CI95%)	OR (CI95%)	OR*(CI95%)
Cases/controls	51/42		83/35		49/25	
[0-4]	1.00	1.00	1.00	1.00	1.00	1.00
Cases/controls	49/65		54/68		36/35	
[5-7]	0.62 (0.36-1.08)	0.64 (0.39-1.12)	0.33 (0.19-0.56)	0.36 (0.24-0.59)	0.52 (0.27-1.02)	0.55 (0.31-1.07)
Cases/controls	16/32		25/41		32/52	
[8-12]	0.41 (0.2-0.85)	0.42 (0.22-0.86)	0.26 (0.14-0.49)	0.29 (0.18-0.55)	0.31 (0.16-0.6)	0.31 (0.17-0.62)
P-value	0.04	0.04	<0.001	<0.001	0.001	0.002

OR, basic model adjusted only sex and age (±3 years). OR*, multivariable model additionally adjusted for educational level (illiterate, koranic, primary, secondary and university), residency (urban and rural), marital status (never married, married, widowed and divorced), BMI (underweight, normal, overweight and obesity), physical activity (low, medium and high) tabaco (never smoker, ex-smoker and smoker), total energy intake (kcal/day), red meat consumption (g/week) , fiber intake (g/day), calcium intake (mg/day) and folate intake (mcg/day).

they are considered cancerogenic [24]. Estrogen, the principal female hormone, can reduce the serum level of insulin-like growth factor (IGF-1), engendering a reduction of CRC risk [25]. Estrogen also shows the ability to reduce the growth of colon cancer cells in vitro, hypermethylation of the promotor region of estrogen receptor may further inhibit the colonic mucosal growth [26]. Women are also known to have healthier lifestyles than man, with better nocturnal sleep and less sedentary behavior, which contributes to the observed sex difference in the relationship between adherence to the MD and reduction of CRC risk. Many mechanisms can explain the protective effect of MD on CRC risk, the main compounds of MD are cereals, legumes and fruits, which contains numerous phytochemicals that modulate CRC signaling pathways, such as Wnt/β-catenin, signal transducer and activator of transcription (STAT), and NF-κB [27]. Firstly, the MD is rich in dietary fibers, which increase stool size and accelerate intestinal transit time, leading to the dilution of carcinogenic compounds and reducing their contact time in the intestinal lumen [28]. Moreover, dietary fibers are fermented by gut microbiota to produce short chains fatty acids (SCFAs), particularly butyrate, which have been shown to inhibit apoptosis and cell proliferation [29]. Certain compounds present in vegetables, such as indole and isothiocyanate, can stimulate apoptosis and inhibit the secretion of inflammatory signaling molecules by white blood cells [30]. Additionally, polyphenols found in fruits possess anticancer effects, such as stimulating apoptosis and inhibiting tumor promotion [31]. Resveratrol is a polyphenol found in grapes that can induce the downregulation of the anti-apoptotic protein Bcl-2 while inhibiting tumor proliferation by upregulating pro-apoptotic protein such as P53 [32]. Lycopene (LC), a natural carotenoid pigment responsible for the red color of tomatoes and other fruits [33], has the capacity to downregulate the activity of numerous inflammatory biomarkers, such as IL-6 and TNF-α, thereby inducing an anti-inflammatory effect [34]. Phytochemicals present in onion have also been found to modulate pro-inflammatory signaling pathways, such as cyclooxygenase-2 (COX- 2) and the mitogen-activated protein kinase family (MAPK), while targeting apoptotic pathways [35]. Quercetin, a key bioactive component in onion, can reduce colon cancer growth and induce apoptosis by upregulating the expression of the pro-apoptotic JNK/JUN pathway and downregulation the expression of the survival signal PI3K/Akt/mTOR [32]. Furthermore, the MD is also rich in monounsaturated fatty acids (MUFAs) and omega 3 fatty acids from fish and olive oil, MUFAs may stimulate cell differentiation and apoptosis through the COX- 2 signaling pathway, moreover, both MUFAs and omega 3 possess anti-inflammatory effects against chronic inflammation, which is known to be a risk factor for CRC [36,37]. Fish also contains n-3 polyunsaturated fatty acids (PUFA), which have the capacity to modulate lipid membranes of cancer, inducing apoptosis by blocking transduction signals [38]. Oleuropein (ORL) is a phenolic molecule contained in olive oil that has demonstrated various anti-cancer, antioxidant, and anti-inflammatory properties [39]. A recent review study indicated that ORL can suppress the development of HT-29 cells and induce apoptosis [40]. ORL can also inhibit cell proliferation by blocking the NF-κB pathway. Additionally, ORL has been found to downregulate the expression of COX-2, one of the main signaling pathways in CRC that promotes cell proliferation [41].

Our study has some limitations that must be cited, case-control studies are based on the memory of participants, despites the trained investigators to assess participants, results can be impacted by recall bias. In addition, despites efforts during the conception of the study, case-control studies can be impacted by selection bias. Misclassification can occur during data collection using the Food Frequency Questionnaire (FFQ), as participants may not accurately report their dietary intake. Retrospective studies such as case-control might be impacted by dietary changes following the health issue diagnostic, however, we selected only recent diagnosed patient and we assessing the diet of year before diagnosis. Despite these limitations, our study has several strengths, to our knowledge, no previous study has investigated the relationship between adherence to the Mediterranean Diet and the risk of CRC in Morocco using an adapted metric. We used a Modified Mediterranean Diet score adapted for south Mediterranean countries such as Morocco, data were collected using an adapted and validated Food Frequency Questionnaire for Moroccan adult population. We presented our results according to sex and tumor location, providing a better understanding on the relationship between adherence to MD and the risk of CRC, we additionally adjusted for potential confounding factors. The study was conducted at in the University Hospital Center Mohamed VI, the second-largest hospital in Morocco, covering the third most populous region in Morocco, encompassing diverse ethnicities and socio-economic levels, which may represent the general population of Morocco.

Colorectal cancer remains a public health problem in the world and Morocco. Dietary factors play a significant role in tumor prevention. During the study, results shows that adherence to the Mediterranean Diet was correlated with a reduced risk of CRC among Moroccan population, women showed a higher adherence than men. These findings can encourage Moroccan population to adhere more to the Mediterranean Diet than Occidental Diet, in addition, these findings could be generalized to all Southern Mediterranean population due to the similarities in diet and lifestyle across all the region.

Author Contribution Statement

Hamza Elbaylek and Soumia Ammor designed the study. Hamza Elbaylek and Soumia Ammor collected data. Hamza Elbaylek analyzed and interpreted the data. Hamza Elbaylek major contributor to the writing of the manuscript. Soumia Ammor revised commented on the drafts of the paper. All authors have read and approved the final manuscript.

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Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Research Ethics Committee of Moroccan Association for Research and Ethics (Date 11-08-2022/No:12-REC-22). Written informed consent was obtained from all the patients. This study is a part of an approved thesis.

Data Availability

The datasets used and/or analyzed during the current study are available from the first author (Hamza Elbaylek) on reasonable request.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

References

1. United Nations Department of Economic and Social Affairs. World urbanization prospects: the 2018 revision [Internet]. New York: United Nations; 2019. [Updated 2019 August; Cited at 2023 Dec 21]. Available from: https://population.un.org/wup/publications/Files/WUP2018-Report.pdf.
2. Desrues T, Moyano E. Social Change and Political Transition in Morocco. Mediterranean Politics. 2001;6(1):21-47.
3. El Rhazi K, Nejjari C, Romaguera D, Feart C, Obtel M, Zidouh A, et al. Adherence to a Mediterranean diet in Morocco and its correlates: cross-sectional analysis of a sample of the adult Moroccan population. BMC Public Health. 2012;12(1):345. https://doi.org/10.1186/1471-2458-12-345.
4. El Kinany K, Huybrechts I, Kampman E, Boudouaya HA, Hatime Z, Mint Sidi Deoula M, et al. Concordance with the World Cancer Research Fund/American Institute for Cancer Research recommendations for cancer prevention and colorectal cancer risk in Morocco: A large, population-based case–control study. Int J Cancer. 2019;145(7):1829-37. https://doi.org/10.1002/ijc.32263.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660.
6. Fondation Lalla Salma. Cancer Registry of the Grand Casablanca region for the period 2013-2017 [Internet]. Casablanca: Fondation Lalla Salma- Cancer Prevention and traitement; 2022. [Cited at 2024 Jan 03]. Available from: https://www.contrelecancer.ma/site_media/uploaded_files/Registre_des_Cancers_de_la_Region_du_Grand_Casablanca_2013-2017.pdf.
7. Tazi MA, Er-Raki A, Benjaafar N. Cancer Incidence Rate 2009-2012 [Internet]. Rabat; 2016. [Cited at 2024 12 Jan]. Available from: https://www.irc.ma/images/Registre_Cancer_Rabat_2009-2012.pdf.
8. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global cancer observatory: cancer today. Lyon: International agency for research on cancer. 2024. Available from: https://gco.iarc.who.int/today
9. Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterol Clin North Am. 2002;31(4):925-43. https://doi.org/10.1016/s0889-8553(02)00057-2.
10. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014;17(12):2769-82. https://doi.org/10.1017/S1368980013003169.
11. Allali F. Nutrition Transition in Morocco. Integrative J Med Sci. 2017;4(s):68-71. https://doi.org/10.15342/ijms.v4is.145.
12. Guasch-Ferré M, Willett WC. The Mediterranean diet and health: a comprehensive overview. J Intern Med. 2021;290(3):549-66. https://doi.org/10.1111/joim.13333.
13. El Kinany K, Mint Sidi Deoula M, Hatime Z, Boudouaya HA, Atassi M, El Asri A, et al. Modified Mediterranean diet score adapted to a southern Mediterranean population and its relation to overweight and obesity risk. Public Health Nutr. 2021;24(13):4064-70. https://doi.org/10.1017/S1368980020002062.
14. Global Physical Activity Questionnaire (GPAQ). Surveillance and population-based prevention of non-communicable diseases [Internet]. Switzerland: Department World Health Organization; 2021 [Updated 2021 Nov 13; Cited at 2023 Dec 10]. Available from: https://www.who.int/docs/default-source/ncds/ncd-surveillance/gpaq-analysis-guide.pdf
15. Jeyashree K, Kathirvel S, Shewade HD, Kaur H, Goel S. Smoking cessation interventions for pulmonary tuberculosis treatment outcomes. Cochrane Database Syst Rev. 2016;2016(1):CD011125. https://doi.org/10.1002/14651858.CD011125.pub2.
16. El Kinany K, Garcia-Larsen V, Khalis M, Deoula MMS, Benslimane A, Ibrahim A, et al. Adaptation and validation of a food frequency questionnaire (FFQ) to assess dietary intake in Moroccan adults. Nutr J. 2018;17(1):61.
17. El Kinany K, Garcia-Larsen V, Khalis M, Deoula MMS, Benslimane A, Ibrahim A, et al. Adaptation and validation of a food frequency questionnaire (FFQ) to assess dietary intake in Moroccan adults. Nutr J. 2018;17(1):61. https://doi.org/10.1186/s12937-018-0368-4.
18. El Ati JA, Béji CH, Farhat A, Haddad S, Cherif S, Trabelsi T, Danguir J, Gaigi S, Le Bihan G, Landais E, Eymard-Duvernay S. Table de composition des aliments tunisiens. Tunis: INNTA. 2007.
19. The French Agency for Food, Environmental and Occup Health Saf (ANSES). Ciqual French Food Composition Table version [Internet]. 2020 [Cited at 2023 Dec 27]. Available from: https://ciqual.anses.fr/
20. Agnoli C, Grioni S, Sieri S, Palli D, Masala G, Sacerdote C, et al. Italian mediterranean index and risk of colorectal cancer in the Italian section of the EPIC cohort. Int J Cancer. 2013;132(6):1404-11. https://doi.org/10.1002/ijc.27740.
21. Bamia C, Lagiou P, Buckland G, Grioni S, Agnoli C, Taylor AJ, et al. Mediterranean diet and colorectal cancer risk: results from a European cohort. Eur J Epidemiol. 2013;28(4):317-28. https://doi.org/10.1007/s10654-013-9795-x.
22. Petimar J, Smith-Warner SA, Fung TT, Rosner B, Chan AT, Hu FB, et al. Recommendation-based dietary indexes and risk of colorectal cancer in the Nurses' Health Study and Health Professionals Follow-up Study. Am J Clin Nutr.

2018;108(5):1092-103. https://doi.org/10.1093/ajcn/nqy171.
23. Schulpen M, Van Den Brandt PA. Mediterranean diet adherence and risk of colorectal cancer: the prospective Netherlands Cohort Study. Eur J Epidemiol. 2020;35(1):25-35. https://doi.org/10.1007/s10654-019-00549-8.
24. McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. J Natl Cancer Inst. 1985;75(2):185-91.
25. Giovannucci E. Insulin, Insulin-Like Growth Factors and Colon Cancer: A Review of the Evidence. J Nutr. 2001;131(11 Suppl): 3109S-3120S. https://doi.org/10.1093/jn/131.11.3109S.
26. Issa JP, Ottaviano YL, Celano P, Hamilton SR, Davidson NE, Baylin SB. Methylation of the oestrogen receptor CpG island links ageing and neoplasia in human colon. Nat Genet. 1994;7(4):536-40. https://doi.org/10.1038/ng0894-536.
27. Afrin S, Giampieri F, Gasparrini M, Forbes-Hernández TY, Cianciosi D, Reboredo-Rodriguez P, et al. Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved. Biotechnol Adv. 2020;38:107322. https://doi.org/10.1016/j.biotechadv.2018.11.011.
28. Vernia F, Longo S, Stefanelli G, Viscido A, Latella G. Dietary Factors Modulating Colorectal Carcinogenesis. Nutrients. 2021;13(1):143. https://doi.org/10.3390/nu13010143.
29. Donohoe DR, Holley D, Collins LB, Montgomery SA, Whitmore AC, Hillhouse A, et al. A Gnotobiotic Mouse Model Demonstrates That Dietary Fiber Protects against Colorectal Tumorigenesis in a Microbiota- and Butyrate-Dependent Manner. Cancer Discov. 2014;4(12):1387-97. https://doi.org/10.1158/2159-8290.CD-14-0501.
30. Higdon J, Delage B, Williams D, Dashwood R. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. Pharmacol Res. 2007;55(3):224-36. https://doi.org/10.1016/j.phrs.2007.01.009.
31. Almanza-Aguilera E, Cano A, Gil-Lespinard M, Burguera N, Zamora-Ros R, Agudo A, et al. Mediterranean diet and olive oil, microbiota, and obesity-related cancers. From mechanisms to prevention. Semin Cancer Biol. 2023;95:103-19. https://doi.org/10.1016/j.phrs.2007.01.009.
32. Mahmod AI, Haif SK, Kamal A, Al-Ataby IA, Talib WH. Chemoprevention effect of the Mediterranean diet on colorectal cancer: Current studies and future prospects. Front Nutr. 2022;9:924192. https://doi.org/10.3389/fnut.2022.924192.
33. Arballo J, Amengual J, Erdman JW Jr. Lycopene: A Critical Review of Digestion, Absorption, Metabolism, and Excretion. Antioxidants (Basel). 2021;10(3):342. https://doi.org/10.3390/antiox10030342.
34. Sarker MT, Wan X, Yang H, Wang Z. Dietary Lycopene Supplementation Could Alleviate Aflatoxin B1 Induced Intestinal Damage through Improving Immune Function and Anti-Oxidant Capacity in Broilers. Animals (Basel). 2021;11(11):3165. https://doi.org/10.3390/ani11113165.
35. Khajah MA, Orabi KY, Hawai S, Sary HG, El-Hashim AZ. Onion bulb extract reduces colitis severity in mice via modulation of colonic inflammatory pathways and the apoptotic machinery. J Ethnopharmacol. 2019;241:112008. https://doi.org/10.1016/j.jep.2019.112008.
36. Galland L. Diet and Inflammation. Nut in Clin Prac. 2010;25(6):634-40. https://doi.org/10.1177/0884533610385703.
37. Trichopoulou A. Mediterranean Diet, Traditional Foods, and Health: Evidence from the Greek EPIC Cohort. Food Nutr Bull. 2007;28(2):236-40. https://doi.org/10.1177/156482650702800213.
38. Mukerjee S, Saeedan AS, Ansari MN, Singh M. Polyunsaturated Fatty Acids Mediated Regulation of Membrane Biochemistry and Tumor Cell Membrane Integrity. Membranes (Basel). 2021;11(7):479. https://doi.org/10.3390/membranes11070479.
39. Emma MR, Augello G, Di Stefano V, Azzolina A, Giannitrapani L, Montalto G, et al. Potential Uses of Olive Oil Secoiridoids for the Prevention and Treatment of Cancer: A Narrative Review of Preclinical Studies. Int J Mol Sci. 2021;22(3):1234. https://doi.org/10.3390/ijms22031234.
40. Nsairat H, Jaber AM, Faddah H, Ahmad S. Oleuropein impact on colorectal cancer. Future Sci OA. 2024;10(1):FSO. https://doi.org/10.2144/fsoa-2023-0131.
41. Rishmawi S, Haddad F, Dokmak G, Karaman R. A Comprehensive Review on the Anti-Cancer Effects of Oleuropein. Life (Basel). 2022;12(8):1140. https://doi.org/10.3390/life12081140.