RESEARCH ARTICLE

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Oral Contraceptives Use and Colorectal Cancer Risk Among Moroccan Women: A Case-Control Study

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Abstract

Objective: Colorectal cancer (CRC) encompasses both non-modifiable and modifiable risk factors. While diet remains the main factor influencing CRC risk, hormonal and reproductive factors have also demonstrated a potential impact on CRC risk. This study aims to explore the relationship between oral contraceptives (OC) use and Colorectal cancer risk among Moroccan women. **Methods:** We conducted a case-control study included 300 participants, divided into 150 cases and 150 controls matched by age (± 3 years). Through a face-to-face interview with trained investigators, we collected data on oral contraceptives use among participants. we performed conditional logistic regression to estimate Odds Ratio (OR) and 95% confidence interval (95% CI), to elaborate a basic model and adjusted model for confounding factors to assess the relationship between OC use and CRC risk. **Results:** An inverse correlation was observed between OC use and CRC risk with OR^2:0.57 (0.36-0.92), using OC at younger ages (≤24 years) for a longer period (>8 years) was also associated with a decreased risk of CRC, with OR^2: 0.52 (0.31-0.89) and OR^2: 0.43 (0.26-0.79), respectively. this association was consistent across all tumor location in the adjusted model, with OR^2: 0.54 (0.27-0.98) for colon cancer, OR^2: 0.47 (0.21-0.96) for rectal cancer, and OR^2: 0.35 (0.12-0.9) for colorectal cancer. Furthermore, combined oral contraceptives use significantly reduced CRC risk, with OR^2: 0.42 (0.21-0.75), whereas no significant reduction was observed with progestin-only pills with OR^2: 0.64 (0.32-1.17). **Conclusion:** These findings underscore the potential role of reproductive and hormone factors, such as oral contraceptive use, in reducing colorectal cancer risk, particularly for combined oral contraceptives initiated in a younger age, also the importance of incorporating reproductive and hormone factors in future research in Morocco, providing a broader understanding of colorectal cancer prevention strategies.

Keywords: Oral contraceptives- hormonal and reproductive factors- colorectal cancer- prevention- women-Morocco

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Introduction

Colorectal cancer is the third most common cancer in the world, accounting for 9.6% of the new cases in 2022, following lung cancer (12.4 %) and breast cancer (11.5%) [1]. CRC involves both non-modifiable risk factors, such as age and family history of CRC, and modifiable risk factors, including diet, obesity, and cigarettes [2]. The incidence of CRC is lower among women than men, which first suggested an influence of reproductive and hormonal factors, such as the use of exogenous hormones like OC [3]. Back in 1969, Fraumeni observed a higher incidence of CRC among nuns than the rest of the general population [4]. Some epidemiological studies have identified an inverse relationship between OC use and the risk of CRC, reporting a 20 to 40% lower risk of CRC comparing ever users of OC to never users [5].

OC or birth controls are referred as pills containing hormones such as synthetic estrogen and progesterone to prevent pregnancy. Pills that combine both progesterone and estrogen are known as Combined Oral Contraceptive (COC), while those containing only progestin are called Progestin-Only Pills (POP). COC are generally classified into 3 or 4 generations, depending on the type of progestin combined with estrogen [6]. OC may affect the carcinogenesis of CRC through various mechanisms, first sex hormones such as estrogen can modulate the concentration of bile acids in the blood, which are known to play a role in CRC development [7]. Additionally, these hormones can also modulate colonic transit, potentially influencing the exposure of the colon to carcinogens [8].

In Morocco, CRC is the fourth most common cancer and first digestif cancer with an incidence rate of 12.3/ 100 000 person for both sexes combined, with a slightly lower incidence among women compared to men (11.4 vs 13.4/ 100 000) [9]. Previous studies conducted in Morocco focused only on the common modifiable risk factors such as diet, physical activity, Body Mass Index (BMI), and monthly income. unfortunately, there is a significant lack of information regarding other potential modifiable risk factors [10–12]. The aim of this study is to investigate the relationship between oral contraceptives use and

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Colorectal cancer risk among Moroccan women stratified by tumor location and the of oral contraceptives used.

Materials and Methods

Study design and setting

The study was conducted as an epidemiological case-control study, in the period between November 2022 to March 2024. The study was carried out at the University Hospital Center Mohamed VI in Marrakech. Due to hospital authorization and ethical considerations, all the participants interactions, including recruitment and interviews, were conducted exclusively within hospital settings, no contact or approach with participant permitted outside the hospital. Prior to recruitment process, the simple size was determined using the cases-control formula for quantitative studies, for a statistical power of 80% and 5% type I error, aiming to detect an Odds Ratio (OR) of 2, assuming 30% of exposure among controls, this is resulted in a required simple size of 138 cases and 138 controls. Our study included 300 participants, divided into 150 cases and 150 controls. Investigators approached 165 eligible cases, of which 156 accepted to participate, yielding a participation rate of 94.54%, main reason for non-participation was the duration of the interview or language issues (since no investigator could speak or understand Amazigh). However, 6 cases were excluded prior to statistical analysis due to incomplete or invalidated data. For controls, 160 eligible controls were approached, with 158 agreeing to participate (a participant rate of 98.75%), of these, 5 controls were excluded from the study for incomplete or invalidated data, and 3 were excluded to maintain matching parameters with cases. For the eligibility criteria for cases included adult women aged between 25 and 70 with a confirmed histopathological diagnosis of CRC. Additionally, required the absence of any disease necessitating a specific diet, no cognitive or eating disorders, and the ability to fully participate in the interview process, who attended Oncology and Hematology Center during the recruitment period. Controls were recruited from the same hospital but from the traumatology department, to avoid any disease that could be a risk factor of CRC in the future, who attended hospital during the same period as cases. cases were enrolled consecutively based on the order of admission to the hospital and matched with cases by age (± 3 years), for cases, age was determined at the time of CRC diagnosis, while for controls, age was determined at the time of the interview, with a matching ratio of 1 case/1 control. Eligible controls were women aged between 25 and 70 years, with no prior diagnostic of any cancer, no gastrointestinal disease, have no cognitive or eating disorders, also no disease requiring a specific diet, no first-degree family history of CRC. Study was approved by the Research Ethics Committee of the Moroccan Association for Research and Ethics (No:12-REC-2022). Prior to recruitment, a written and informed consent was obtained from each participant. Data collection was based through a face-to-face interview, with an average duration of 30 min. Each participant was first approached to evaluate eligibility criteria, the investigator explains the aim and purpose of the study to participant, when the investigator obtains the written and informed consent of the participant, we procced to interview. A pilot test of the questionnaire was run for a sample of 20 participant before the study. This pilot phase allowed for the evaluation of the questionnaire and the implementation of necessary modifications to enhance its effectiveness.

Data assessment

for each participant, a variety of socio-demographic variables were assessed: age as a continuous variable, weight as a continuous variable for cases the weight recorded prior to the onset CRC symptoms and controls representing the weight measured on the day of the interview, rounded to the nearest 100 g. Height as a continuous variable, measured during the interview and rounded to the nearest 0.1 cm, BMI was calculated using height and weight formula then categorized into [13]: underweight (less than 18.5 kg/m^2), normal (from 18.5 kg/m^2 to 24.9 kg/m^2), overweight (from 25 kg/m^2 to 29.9 kg/m^2), and obesity (equal or more than 30 kg/m^2). According to the Global Physical Activity Questionnaire (GPAQ) [14], physical activity was classed into 3 groups: Low < 600 MET-min per week, Moderate between 600 to 3000 MET-min per week, and High ≥ 3000 MET-min per week. Educational level dived into 4 categorical variables: illiterate, primary, secondary, University. Residency as a categorical variable: urban, rural; family history of CRC as a categorical variable: yes, no. Monthly income of the house was in 3 categories: low (<2,000 MDH), medium (2,000-5,000 MDH) and high (>5,000MDH). Dietary intake was assessed for each participant using a Moroccan food frequency questionnaire (SQ-FFQ) [15]. This data was then converted into nutrient intake using food composition tables, enabling a detailed analysis of dietary patterns [16, 17].

Assessment of exposure

We assessed oral contraceptives first as a categorical variable: Never-user or Ever-user, the investigators defined ever-user as participants who used OCs for a minimum duration of 6 weeks. For ever-users, detailed information was collected, including all periods and dates of use, to determinate age of first use, duration of use, and last use. Based on the distribution of controls, ever-users were categorized into two groups for each variable: age of first use ≤24 years and >24 years; duration of use ≤10 years and >10 years; last use ≤8 years and >8 years. Regarding the type of OC, ever-users were classified into 2 groups: COC and POP. Unfortunately, we were unable to assess the generation of OC used, as most participants were either unaware of the specific brand or had used multiple brands spanning different generations.

Data analysis

We used the software SPSS v23 to enter and analyze data, general characteristics of population englobed categorical variables presented by frequencies and continuous variables presented by the mean (±SD). Bivariate analyses were conducted to examine the differences between cases and controls, for categorical

variables we used the Chi-square test and for continuous variables we used student's t-test or Mann Whitney U, depending on the normality of distribution. To examinate the relationship between OC use and CRC risk we performed conditional logistic regression to estimate Odds Ratio and 95% confidence interval. During the analysis two models were elaborated, a crude model (OR^1) adjusted for age (± 3 years), a second adjusted model (OR^2) for confounding factors adjusted for: educational level, residency, marital status, BMI, physical activity, total energy intake, red meat consumption, fiber intake, calcium intake, and vitamin D intake. All OC groups were compared to never used, significant level was P-value <0.05 and two sided.

Results

Our study included 150 cases and 150 controls. Approximately 70 % of controls had at least a primary level of education, compared to only 50 % of cases (P-value: <0.001). Concerning residency, 88% of controls lived in urban areas, whereas only 52.66% of cases resided in urban settings, with a significant difference (P-value: <0.001). in this study, 78% of controls were married, 10.66% were divorced, and only 10% had never been married. In contrast, for cases 58.66% were married, 16% were divorced, and 20.66% had never been married, leading to a significant difference between cases and controls (P-value: <0.001). For household monthly income, 24.66% of cases had a low income (<2,000 DHM) versus 16.66% of controls, while almost 45% have a high house monthly income (>5,000 DHM) with no significant difference between cases and controls (P-value: 0.098). However, a significant difference (P-value: <0.001) was noted for BMI, where only 41.3% of cases had a normal BMI compared to 68% of controls, while almost 50% of cases had a BMI above the normal range, versus only 17.2% of controls. Physical activity levels also showed a significant difference (P-value <0.001), with approximately 75% of cases reporting low physical activity, while nearly half of the controls reported at least moderate physical activity. For Family history of CRC, no statistical difference was observed between cases and controls, with 148 cases and 149 controls reporting no family history of CRC (P-value: 0.561). Cases had a mean age of 48.13 ±8.32 years and 49±3.22 for controls without any significant difference (P-value: 0.233). Cases reported a significantly higher daily total energy intake (2351±74.95 Kcal) than controls (2327.43±65.11 Kcal) (P-value:0.003). Similarly, cases had a higher consumption of red mead compared to controls with respectively 236.11±21.47 g/week for cases and 223.87±39.76 g/week for controls, showing a significant difference (P-value: 0.001). Conversely, fiber intake was significantly higher among controls than cases (25.73 ± 2.66 mg/day) than cases (14.23 ± 1.16 mg/day) (P-value < 0.001). Once again, controls had a higher intake of calcium than cases, with a daily intake of 712.42±23.17 mg for controls and 703.26±12.95 mg for cases (P-value:<0.001). Folate intake was nearly identical between cases (124.37±0.43 mcg/day) and controls (124.45±0.36 mcg/day) with no significant difference (P-value:0.081). Lastly, controls had a higher intake of vitamin D compared to cases with respectively 1.8±0.3 mcg/day for controls and 1.6±0.95 mcg/day for cases (P-value:0.014) (Table 1).

In this study, 65.3% of cases had ever used OC compared to 78.7% of controls, an inverse correlation was identified between OC use and CRC risk, with an estimated crude OR^1 of 0.51 (95% CI: 0.31-0.85), after adjusting for confounding factors, the inverse correlation remains present with an adjusted OR^2 of 0.57 (95% CI: 0.36-0.92) (P-value: 0.017). Regarding the age of first use, participants who started using OC at >24 years showed a decreased risk of CRC in both models, with OR^1: 0.49 (95% IC:0.28-0.9) for the crude model and OR^2: 0.52 (95% IC: 0.31-0.89) for the adjusted model. In contrast, no significant correlation was identified for participants who initiated OC use at ≤24 years with OR^1: 0.55 (95% IC: 0.31-1.01) and OR^2: 0.61 (95% IC: 0.38-1.12) (P-value: 0.039). However, for the time since last use, both categories (≤10 years and >10 years) were associated with a decreased CRC risk in the crude model, with OR^1: 0.52 (95% CI: 0.29–0.93) and OR^1: 0.5 (95% CI: 0.28–0.9), respectively. After adjusting for confounding factors, the association became statistically non-significant, with OR^2: 0.57 (95% IC: 0.35-1.07) for ≤10 years and OR^2: 0.62 (95% IC: 0.34-1.02). Moreover, for the duration of use a duration of more than 8 years was correlated with a decreased CRC risk OR^2: 0.43 (95% IC: 0.26-0.79) (P-value:0.016), while no association was detected for participants with a duration of use ≤8 years OR^2: 0.61 (95% IC: 0.36-1.08) (Table 2).

When accorded by tumor location, the association between OC use and reduced CRC risk persisted across all tumor locations with respectively OR^2: 0.54 (95% IC:0.27-0.98) for colon, OR^2: 0.47 (95% IC:0.21-0.96) for rectum, and OR^2: 0.35 (95% IC:0.12-0.9). For the age of first use, the category of ≤24 years was only correlated with a decreased CRC risk for colorectal location with OR^1 :0.35 (95% IC:0.12-0.99) in the basic model and OR^2: 0.34 (95% IC:0.11-0.97) in the adjusted model (P-value:0.046). While for both colon and rectum no association was detected in the crude model OR^1 : 0.52 (95% IC:0.27-1.02) for colon and OR^1 : 0.5 (95%IC:0.23-1.07) for rectum, however, after adjusting for confounding factors an association with decreased risk for colon cancer has been identified OR^2: 0.49 (95% IC:0.23-0.98) although this association was statistically non-significant (P-value:0.096). Regarding the time of last use, using OC for ≤10 years was correlated with a reduced risk of rectal cancer OR^2: 0.37 (95% IC:0.14-0.89) and colorectal OR^2: 0.3 (95% IC:0.09-0.96). Conversely, for colon cancer, a reduced risk was observed with OC use for >10 years with OR^2 : 0.45 (95% IC:0.21-0.92) and P-value:0.038. Finally, all locations were associated with a decreased risk of CRC with a duration of use for more than 8 years with respectively, OR^2: 0.41 (95% IC:0.17-0.89) for colon, OR^2: 0.35 (95% IC:0.11-0.87) for rectal, and OR^2: 0.29 (95% IC:0.08-0.95) (Table 3).

In this last part, we evaluated whether the type of the OC (COC or POP) influenced on the association between OC use and CRC risk. Table 4 presents the OR and

Table 1. General Characteristics of a Case-Control Study Population for Contraceptives Use and Colorecral Cancer Risk Among Moroccan Women

Characteristics	Case (%)	Control (%)	*P-value*
Educational level			<0.0001
Illiterate	75 (50)	46 (30.66)	
Primary	46 (30.66)	35 (23.33)	
Secondary	26 (17.33)	59 (39.33)	
University	3 (2)	10 (6.66)	
Residency			<0.0001
Urban	79 (52.66)	132 (88)	
Rural	71 (47.33)	18 (12)	
Marital status			0.0005
Never married	31 (20.66)	15 (10)	
Married	85 (58.66)	117 (78)	
Widowed	10 (4.68)	2 (1.33)	
Divorced	24 (16)	16 (10.66)	
Monthly income			0.098
Low	37 (24.66)	25 (16.66)	
Medium	62 (41.33)	58 (38.66)	
High	51 (34.01)	67 (44.66)	
BMI			<0.0001
Underweight	13 (8.6)	22 (14.6)	
Normal	62 (41.3)	102 (68)	
Overweight	65 (43.3)	19 (12.6)	
Obese	10 (6.6)	7 (4.6)	
Physical activity			<0.0001
Low	113 (75.3)	78 (52)	
Moderate	35 (23.3)	57 (38)	
High	2 (1.4)	15 (10)	
Family history of CRC			0.561
No	148 (98.66)	149 (99.33)	
Yes	2 (1.34)	1 (0.67)	
	Case Mean ±SD	Control Mean ±SD	*P-value*
Age	48.13 ±8.32	49±3.22	0.233
Total Energy intake (Kcal/day)	2351±74.95	2327.43±65.11	0.003
Consumption of red meat(g/week)	236.11±21.47	223.87±39.76	0.001
Fiber intake (g/day)	14.23±1.16	25.73±2.66	<0.0001
Calcium intake (mg/day)	703.26±12.95	712.42±23.17	0.0001
Folate intake (mcg/day)	124.37±0.43	124.45±0.36	0.081
Vitamin D intake (mcg/day)	1.6±0.95	1.8±0.3	0.014

Monthly income, Low (<2000 DHM); Medium, (2000-5000 DHM); High, (>5000 DHM); BMI, Underweight (<18.5); Normal, (18.5-24.9); Overweight, (25-29.9); Obesity, (≥ 30)

95% IC stratified by OC type, COC were the only type associated with a reduction in CRC risk OR^2: 0.42 (95% IC:0.21-0.75) and (P-value:0.001), while no correlation was detected for POP with OR^2: 0.64 (95% IC:0.32-1.17) (P-value:0.123). Concerning the age of first use, COC were correlated in both categories (≤24 and >24) with decreased risk of CRC, OR^2: 0.37 (95% IC:0.18-0.7) for ≤24 and OR^2: 0.47 (95% IC:0.21-0.96) for >24 (P-value:0.008). In contrast, no significant association was identified for POP in either age group, with OR^2: 0.64 (95% IC:0.28-1.33) for ≤24 and OR^2: 0.61 (95% IC:0.26-1.32) for >24 (P-value:0.275). For COC users, those whose last use was ≤10 years was correlated with a reduced risk of CRC with OR^2: 0.25 (95% IC:0.11-0.49) and P-value:<0.001, on the other hand, POP were associated with a decreased risk of CRC for those whose last was >10 years with OR^2: 0.31 (95% IC:0.12-0.69) and P-value: 0.003. For the duration of use, COC were once again associated with a decreased risk of CRC in both duration categories (≤8 and >8 years), with respectively OR^2: 0.5 (95% IC: 0.24-0.98) for ≤8 years and OR^2: 0.32 (95% IC:0.15-0.63) for >8 years (P-value:0.002), however, no association was observed

Table 2. The Estimated Odds Ratio and Confidence Interval for Oral Contraceptives Use with Colorectal Cancer Risk among Moroccan Women in a Case Control Study

	Cases	Controls	OR[1] (95% CI)	OR[2] (95% CI)
Used				
Never used	52	32	1.00	1.00
Ever used	98	118	0.51 (0.31-0.85)	0.57 (0.36-0.92)
P-value			0.01	0.017
First use				
≤24	56	71	0.49 (0.28-0.86)	0.52 (0.31-0.89)
>24	42	47	0.55 (0.3-1.01)	0.61 (0.38-1.12)
P-value			0.033	0.039
Last use				
≤10	50	59	0.52 (0.29-0.93)	0.57 (0.35-1.07)
>10	48	59	0.5 (0.28-0.9)	0.62 (0.34-1.02)
P-value			0.036	0.044
Duration of use				
≤8	67	69	0.6 (0.34-1.04)	0.61 (0.36-1.08)
>8	31	49	0.39 (0.21-0.73)	0.43 (0.26-0.79)
P-value			0.012	0.016

OR[1], Crude odds ratio adjusted only for age (±3 years); OR[2], adjusted for: educational level, residency, marital status, BMI, physical activity, total energy intake, red meat consumption, fiber intake, calcium intake, and vitamin D intake. First use, last use, and duration of use are in years.

Table 3. The Estimated Odds Ratio and Confidence Interval for Oral Contraceptives Use with Colorectal Cancer Risk among Moroccan Women in a Case Control Study Stratified by Tumor Location.

Location	Colon		Rectal		Colorectal	
	OR[1] (CI95%)	OR[2] (CI95%)	OR[1] (CI95%)	OR[2](CI95%)	OR[1] (CI95%)	OR[2](CI95%)
Never used	1.00	1.00	1.00	1.00	1.00	1.00
C/C	26/32		17/32		9/32	
Ever used	0.57 (0.31-1.05)	0.54 (0.27-0.98)	0.49 (0.24-1.00)	0.47 (0.21-0.96)	0.36 (0.14-0.93)	0.35 (0.12-0.9)
C/C	55/118		31/118		12/118	
P-value	0.071	0.045	0.049	0.024	0.03	0.018
First use						
≤24	0.52 (0.27-1.02)	0.49 (0.23-0.98)	0.5 (0.23-1.07)	0.48 (0.21-1.04)	0.35 (0.12-0.99)	0.34 (0.11-0.97)
C/C	30/71		19/71		7/71	
>24	0.65 (0.32-1.32)	0.64 (0.31-1.27)	0.48 (0.2-1.14)	0.45 (0.15-1.09)	0.38 (0.12-1.24)	0.38 (0.11-1.22)
C/C	25/47		12/47		5/47	
P-value	0.156	0.096	0.143	0.091	0.095	0.046
Last use						
≤10	0.69 (0.35-1.35)	0.66 (0.31-1.32)	0.38 (0.16-0.89)	0.37 (0.14-0.89)	0.3 (0.09-0.97)	0.3 (0.09-0.96)
C/C	33/59		12/59		5/59	
>10	0.46 (0.23-0.94)	0.45 (0.21-0.92)	0.61 (0.28-1.33)	0.61 (0.27-1.31)	0.42 (0.14-1.32)	0.41 (0.12-1.29)
C/C	22/59		19/59		7/59	
P-value	0.092	0.038	0.082	0.041	0.009	0.003
Duration of use						
≤8	0.68 (0.35-1.3)	0.65 (0.31-1.25)	0.57 (0.27-1.22)	0.55 (0.24-1.19)	0.41 (0.14-1.16)	0.4 (0.13-1.14)
C/C	38/69		21/69		8/69	
>8	0.43 (0.2-0.92)	0.41 (0.17-0.89)	0.38 (0.15-0.93)	0.35 (0.11-0.87)	0.29 (0.08-0.97)	0.29 (0.08-0.95)
C/C	17/49		10/49		4/49	
P-value	0.084	0.033	0.097	0.028	0.085	0.039

OR[1], Crude odds ratio adjusted only for age (±3 years); OR[2], adjusted for: educational level, residency, marital status, BMI, physical activity, total energy intake, red meat consumption, fiber intake, calcium intake, and vitamin D intake; First use, last use, and duration of use are in years.; Colorectal location refers to all cases where the cancer is located in both the colon and rectum or where the specific location is unknown; C/C: cases / controls

Table 4. The Estimated Odds Ratio and Confidence Interval for Oral Contraceptives Use with Colorectal Cancer Risk among Moroccan Women in a Case Control Study Stratified by Oral Contraceptive Type.

OC type	Combined OC			Progestin-only pills		
	C/C	OR[1] (CI95%)	OR[2] (CI95%)	C/C	OR[1] (CI95%)	OR[2](CI95%)
Used						
Never used	52/32	1.00	1.00	52/32	1.00	1.00
Ever used	52/75	0.43 (0.24-0.76)	0.42 (0.21-0.75)	46/43	0.66 (0.36-1.21)	0.64 (0.32-1.17)
P-value		0.002	0.001		0.175	0.123
First use						
≤24	31/48	0.4 (0.21-0.75)	0.37 (0.18-0.7)	25/23	0.67 (0.33-1.37)	0.64 (0.28-1.33)
>24	21/27	0.48 (0.23-0.99)	0.47 (0.21-0.96)	21/20	0.65 (0.31-1.38)	0.61 (0.26-1.32)
P-value		0.01	0.008		0.397	0.275
Last use						
≤10	18/42	0.26 (0.13-0.53)	0.25 (0.11-0.49)	32/17	1.16 (0.56-2.42)	1.13 (0.51-2.37)
>10	34/33	0.63 (0.33-1.21)	0.63 (0.32-1.19)	14/26	0.33 (0.15-0.72)	0.31 (0.12-0.69)
P-value		<0.001	<0.001		0.006	0.003
Duration of use						
≤8	33/39	0.52 (0.27-0.99)	0.5 (0.24-0.98)	34/30	0.7 (0.36-1.35)	0.68 (0.32 -1.32)
>8	19/36	0.32 (0.16-0.65)	0.32 (0.15-0.63)	12/13	0.57 (0.23-1.4)	0.54 (0.21-1.38)
P-value		0.005	0.002		0.362	0.281

OR[1], Crude odds ratio adjusted only for age (±3 years); OR[2], adjusted for: educational level, residency, marital status, BMI, physical activity, total energy intake, red meat consumption, fiber intake, calcium intake, and vitamin D intake; First use, last use, and duration of use are in years; Combined OC is referred to pills containing progestin and estrogen; Progestin-only pills is referred to pills containing only progestin; C/C: cases / controls

for POP in either duration category, with OR[2] :0.68 (95% IC:0.32 -1.32) for ≤8 and OR[2] :0.54 (95% IC:0.21-1.38) for >8 (P-value:0.281) (Table 4).

Discussion

The results of our study highlight a significant correlation between oral contraceptives use and a decreased risk of CRC across all locations (colon, rectal, and colorectal), this correlation appears to be influenced by the age of use and duration of use. Furthermore, the type of the OC may also interfere in the association between OC use and CRC risk. Our results concord with a meta-analysis indicating that OC users have a 21% lower risk of CRC compared to non-users [18]. Similarly, a pooled relative risk (RR) of 4 cohort studies and 8 case-control studies demonstrated an RR of 0.82 and 95% CI was 0.72-0.92, although no association was detected for the duration of use RR: 0.85 (95% CI:0.63-1.14), when accorded by tumor location, the association persisted for both locations (colon and rectal) with respectively, RR of 0.85 (95% CI:0.79-0.93) for colon cancer and RR of 0.80 (95% CI:0.70-0.92) for rectal cancer [19]. In a Canadian case control study, ever users were found to have a reduced risk of CRC with OR:0.77 and 95% CI:0.65-0.91, when stratified by OC type, COC remained associated with reduced CRC risk (OR:0.70; 95% CI:0.52-0.95), this result is consistent with our findings where, COC were also associated with decreased risk of CRC with OR[2]:0.42 (95% CI:0.21-0.75). In the same Canadian case control study, ever-users who used OC at younger ages (<22) had a lower risk of CRC with OR:0.60 and 95% CI: 0.47-0.77 compared to those who started OC at older ages (>30) OR: 0.92; 95%CI: 0.68-1.24, similarly to our study where the age of first use was significantly correlated with CRC risk for ever-users who used OC at 24 or less with OR[2]:0.52 (95% CI:0.31-0.89) [20]. These findings align with our results, where the correlation between OC use and reduced CRC risk remained significant across all tumor locations. On the other hand, a pooled analysis of 2 American case-controls study showed no correlation between the use of OC with risk of CRC across all tumor locations, with respectively OR: 0.89 (95% IC:0.75-1.06) for colorectal cancer overall, OR:0.87 (95% CI:0.72-1.06) for colon cancer, and OR:0.87 (95% CI:0.65-1.17), furthermore, no correlation was identified with either the age of first use or the duration of OC use in these studies, which contrasts with our findings [21]. The majority of previously published studies highlights a protective effect of OC use against CRC risk, some studies also demonstrate a correlation with the duration of use, while others find no correlation with either the duration of use or the age of first use.

The relationship between reproductive factors and CRC risk was first described after observing the high incidence of colorectal cancer among nuns in the United States [4]. To explain the influence of OC on colorectal cancer, numerous biological mechanisms and pathways have been suggested. First, it has been reported that oral contraceptives use influence the synthesis and excretion of bile acids, resulting in low levels of bile acids in the colon, where they are considered carcinogenic [7]. Moreover, estrogen and progesterone reduce the number of ovulations during women's lifetime thereby

a decreasing exposure of probable cancerogenic sex hormones [18]. Another mechanism involves the estrogen receptor gene, which may reduce and deregule the colonic mucosal growth, through hypermethylation of the promoter region [22]. Estrogen can lead to a reduction in serum levels of insulin-like growth factor (IGF-1), which has been identified to increase the risk of CRC and play a role in the physiopathology of CRC [23–25]. In vitro studies have shown that estrogen inhibits the growth of colon cancer cells, and estrogen receptors have been identified in both normal and neoplastic colon epithelial cells [26, 27]. Furthermore, the synergy between estrogen and progestogen has been found to reduce microsatellite instability [28]. Although the exact mechanisms remain unclear, these findings collectively suggest a protective effect of OC use on CRC risk.

During this study we encountered some limitations that must be acknowledged, first we were unable to assess the specific generation for combined oral contraceptives as the concentration of estrogen and progesterone vary across different generations. As with all the case-control studies relaying on participant' memory, results may be influenced by recall bias. Moreover, due to the age of some participants who stopped the use of OC, misclassification in the type of OC may have occurred. However, regardless those limitations our study has notable strengths, the use of hospital controls provided high reliability in terms of menstrual and reproductive conditions [29]. The investigators underwent rigorous training sessions to enhance quality of generated data, and minimize recall bias. To ensure that controls were not affected by diseases potentially related to colorectal cancer, we selected participants from the traumatology department of CHU Mohammed VI, which serves the Marrakech-Safi region, one of the biggest regions in Morocco, reflects significant socio-economic diversity. Moreover, to date, no study in Morocco have evaluated the influence of OC on CRC risk, our study stands out as the first to address this topic in the North-African region. Additionally, we stratified our results by tumor subtypes (colon and rectal) and OC types, adjusting for various socio-demographic and dietary confounding factors. This approach provided a comprehensive and nuanced understanding of the relationship between oral contraceptives use and colorectal cancer risk.

In conclusion, while diet remains the primary factor influencing the risk of colorectal cancer, numerous other modifiable factors interfere at different level with the risk of CRC. Results from our study, supported be the existing literature, indicate that reproductive and hormone factors, such as oral contraceptives use may play a role in reducing colorectal cancer risk, particularly for combined oral contraceptives initiated in a younger age. These results highlight the importance of considering reproductive and hormone factors in future research in Morocco, providing a broader understanding of colorectal cancer prevention strategies.

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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General

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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.

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