Research Article

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Oral Contraceptive Use and Colorectal Cancer in the Nurses' Health Study I and II

Brittany M. Charlton[1,2,3], Kana Wu[4], Xuehong Zhang[5], Edward L. Giovannucci[1,4,5], Charles S. Fuchs[6], Stacey A. Missmer[1,5,7], Bernard Rosner[5], Susan E. Hankinson[1,5,8], Walter C. Willett[1,4,5], and Karin B. Michels[1,5,9]

Abstract

Background: It remains unclear if oral contraceptive (OC) use is associated with the incidence of colorectal cancer. Few studies have examined this association by duration of OC use, time since last OC use, and different cancer subsites.

Methods: Among 88,691 participants of the Nurses' Health Study I (NHSI) and 93,080 participants of the Nurses' Health Study II (NHSII), we assessed OC use every 2 years between 1976 and 2010 and categorized it as ever use, duration of use, and time since last use. We included incident colorectal cancer cases through 2010 (NHSI: age at diagnosis = 36–88, N = 1,764; NHSII: age at diagnosis = 33–64, N = 206). Multivariable hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards regression models.

Results: Ever OC use was not associated with colorectal cancer in NHSI [1.01 (0.91, 1.12)] nor NHSII [1.03 (0.69, 1.53)]. In NHSII, when compared with never-users, longer durations (5+ years) of OC use were inversely associated with the risk of colon cancers ($P_{\text{trend}} = 0.02$) but the number of endpoints was limited. No other colorectal cancer subsites were associated with OC durations or times since last OC use in either cohort.

Conclusions: In two large prospective cohorts, we found little evidence that OC use may be protective for colorectal cancer, except potentially with longer durations of use among younger women.

Impact: Our results do not support the previous initial studies that reported an inverse association of recent OC use with colorectal cancer but instead support newer, larger studies demonstrating no such association. *Cancer Epidemiol Biomarkers Prev; 24(8); 1214–21. ©2015 AACR.*

Introduction

An estimated 1 in 20 people in the United States will develop colorectal cancer in their lifetime, the third leading cause of cancer-related death with over 50,000 deaths expected this year (1). Women have a lower risk of developing colorectal cancer than men (41.4 compared with 55.7 per 100,000; ref. 2), particularly before age 50, suggesting that sex hormones may play a role in colorectal carcinogenesis. A large body of literature supports that hormone therapy (HT) decreases colorectal cancer risk (3, 4) but the evidence for oral contraceptives (OC) is equivocal. Meta-analyses have estimated that OC use is associated with a 19% reduction in colorectal cancer (5, 6) but the two largest cohort studies were more recently published demonstrating no such association (7, 8).

The relationship between reproductive factors and colorectal carcinogenesis was first examined in the 1960s when excess colorectal cancer cases were identified in nuns compared with the general female population (9). This led to the hypothesis that endogenous hormones may play a role in colorectal carcinogenesis, as nuns generally differ in their hormonal exposure due to nulliparity. Soon after, researchers hypothesized that exogenous hormones may decrease colorectal cancer risk as well, including a proposed mechanism of estrogen reducing secondary bile acid production (10, 11). This was followed by further evidence from observational studies, including cohort (12–20) and case–control (21–31) studies, and randomized control trials (32), which suggested that exogenous hormone use, including OCs and HT, was inversely associated with colorectal cancer.

But this protective association was not observed in all studies of OC use (33–38), including the two largest studies (7, 8), and many were not able to examine important aspects of this relation. For example, some studies have not been able to explore precise exposure data such as duration (12, 13, 19, 22, 24–26, 30, 31) and recency of use (12, 13, 15–22, 24–26, 29–31, 33, 34, 36–38). The most recent meta-analysis (5) highlighted that the apparent protection conferred by OC use may be greater for recent use, so examining aspects of the exposure, including timing, may be especially relevant. Other studies have not been able to examine potential heterogeneity of the outcome with regard to different cancer subsites (e.g., colon or rectal); nor have they explored subsites within the colon (e.g., proximal or distal). Furthermore,

[1]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts. [2]Division of Adolescent and Young Adult Medicine, Boston Children's Hospital, Boston, Massachusetts. [3]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts. [4]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts. [5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [6]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts. [7]Division of Reproductive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [8]Division of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Boston, Massachusetts. [9]Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Brittany M. Charlton, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115. Phone: 857-218-5463; Fax: 617-730-0004; E-mail: bcharlton@mail.harvard.edu

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most of the previous work has focused primarily on younger women, where the spectrum of cancers may be different than in older women. Elucidating these issues requires large prospective cohort data from the time that OCs debuted including precise, detailed exposure and outcome information.

We therefore examined the association of OC use and colorectal cancer using comprehensive data from two large prospective cohort studies, the Nurses' Health Study I (NHSI) and II (NHSII). Two previous analyses from NHSI exist (17, 39); the most recent was published in 1997 and examined incident cases of colorectal cancer ($N = 501$) that occurred between 1980 and 1992. Both previous analyses reported null associations except the 1997 analysis also found that women who had used OCs for 8+ years had a lower risk of developing colorectal cancer (17). With 18 additional years of follow-up (1980–2010) and four times as many cases ($N = 1,970$ in NHSI and II combined), we are now able to examine the association between OC use and colorectal cancers in detail with excellent statistical power; these data allow us to examine duration and recency of use, as well as different cancer subsites. The NHSI women are now older and we can also analyze a new cohort of younger women from NHSII who used more recent OC formulations and for whom this association has never been examined. We hypothesized that longer durations of OC use are inversely associated with colorectal cancer.

Materials and Methods

Study population

The NHSI and II are prospective cohort studies. The NHSI was established in 1976 among 121,701 U.S. female registered nurses, ages 30 to 55 years, and the NHSII was established in 1989 among 116,609 U.S. female registered nurses, ages 25 to 42 years. Information about lifestyle and medical history is collected from participants in both cohorts via mailed biennial questionnaires. Participants complete validated, semiquantitative food frequency questionnaires (FFQ) approximately every 4 years. The follow-up in both cohorts has remained more than 90% to date.

Because of the importance of several dietary risk factors for colorectal cancer risk, we started follow-up for this analysis in 1980 in NHSI and 1991 in NHSII, after the baseline dietary questionnaire, and therefore 72 cases were excluded due to being diagnosed before 1980 in NHSI though no cases met this exclusion criteria in NHSII. We also excluded women with a history of cancer [except for nonmelanoma skin cancer (NHSI: $N = 4,623$ and NHSII: $N = 1,522$)] and ulcerative colitis (NHSI: $N = 117$ and NHSII: $N = 1,078$) prior to baseline as well as those who did not complete the baseline dietary questionnaire—1980 in NHSI ($N = 27,327$) and 1991 in NHSII ($N = 21,181$). The final group comprised 181,771 women: 88,691 women followed from 1980 to 2010 in NHSI and 93,080 women followed from 1991 to 2009 in NHSII. The study was approved by the Institutional Review Board of Brigham and Women's Hospital in Boston; informed consent was implied by the return of the baseline questionnaire.

Assessment of exposure

On the baseline questionnaires for both cohorts, participants were asked whether they had ever used OCs and, if so, to list all starting and stopping dates in order to capture all time periods of use. Subsequent biennial questionnaires asked whether OCs had been used during the previous two years and the number of months of use. We classified women as never-users or ever-users, and defined ever use as a minimum of two months. Information was also collected on starting/stopping dates so we could calculate total duration of use (≤1, >1 to <2, ≥2 to <5, ≥5 to <10, 10+ years in NHSI and ≤1, >1–<5, 5+ years in NHSII due to the number of cases in each stratum), time since last use (≤4, >4 to <10, ≥10 to <15, 15+ years), and a cross product of duration-by-time since last use (e.g., ≤1-year duration and ≤4 years since last use, see Table 5). We estimated duration of use by summing OC use across questionnaire cycles. Dynamic exposures were included as time-varying variables in all regression models. No information was collected on OC formulation or brand in NHSI, though given the timeframe, these would have been exclusively first- and second-generation pills (defined by progestin type). In NHSII, participants also reported detailed information about the OC brand and formulation but this information was not used in the current analyses due to the small number of NHSII colorectal cancer cases.

The reproducibility and validity of the OC data were evaluated in a study among 215 randomly selected participants from NHSII (40). The data from biennial questionnaires were contrasted with data from a subsequent telephone interview that used a structured life events calendar. Agreement for ever use versus never use was 99%, and the correlation for duration of use calculated from the two sources was 0.94.

Case ascertainment

Biennial follow-up questionnaires were used to identify newly diagnosed cases of colorectal cancer. We sought permission to obtain medical records and pathology reports for those who reported a colorectal cancer diagnosis. Cohort member deaths were identified through family members, the postal system, as well as the National Death Index, and we estimate that >98% of deaths were ascertained. For nonrespondents who after review of death certificate were determined to have died of colorectal cancer, we requested permission from next-of-kin to review medical records. Information on histopathology, anatomic location, and stage of cancer was extracted by study physicians who were blinded to exposure information. We included all incident cases of colorectal adenocarcinoma, defined according to the International Classification of Diseases, Ninth Revision, from 1980 to 2010 in NHSI and from 1991 to 2009 in NHSII. The ascertainment of colorectal cancer cases has been described in further detail elsewhere (41). Cancers were also classified by subsite (e.g., proximal, distal, or rectum).

Assessment of covariate information

Covariates were chosen based on *a priori* knowledge of risk factors, including those from a previously developed comprehensive model of colon cancer (42). Our final model adjusted for age, body mass index (BMI), height, physical activity, smoking, processed and red meat, folate, calcium, total energy, aspirin use, alcohol intake, age at first birth, parity, HT use, family history, and previous endoscopy screening.

Participant's height (inches) was reported at baseline (NHSI: 1976, NHSII: 1989) and modeled as a continuous variable. Self-reported current weight (pounds) was collected on every questionnaire, and has high validity in these cohorts. From height and weight, we calculated BMI (<18.8, 18.5–22.9, 23–24.9 25–29.9, 30+ kg/m^2). Detailed questions about physical activity were used to derive a continuous value of total metabolic (MET) hours/week. Information about smoking was modeled as a continuous variable of total pack-years. Intake of folate (mcg/day), calcium (mcg/day), processed and red meat (servings/day), and total energy (kcal/day) were accessed using the FFQs and each modeled as continuous variables from the quintile medians. Alcohol intake (<5, 5–9.9, 10–14.9, 15+ g/day), aspirin use (<4, 4–6, 7–10, 11+ times/week), age at first birth (<24, 24–25, 26–29, 30+ years), and parity (0, 1, 2, 3+ children) were modeled categorically. Use of HT was asked on every questionnaire beginning at baseline; HT use was modeled as never, premenopausal, past, or current. Family history of colon or rectal cancer in immediate family members was updated about every 4 years while information on endoscopy screening was provided biennielly. When a woman reported having an endoscopy, through sigmoidoscopy or colonoscopy, we assigned her two cycles (4 years) of screening "coverage" starting from the time at which she reported being screened (to approximately account for appropriate screening intervals). We then summed the total number of years of screening coverage for each woman. Participants could report endoscopies on every biennial questionnaire. For all regression analyses, dynamic exposure covariates were included as time-varying variables.

Statistical analyses

Person-time was calculated from the date of the return of the baseline questionnaire to the date of death, colorectal cancer diagnosis, loss to follow-up, or end of follow-up (June 2010), whichever occurred first. Cox proportional hazards regression models were used to calculate hazard ratios and 95% confidence intervals [HR (95% CI)] using age (months) and the year of questionnaire return as the time metameter. Analyses of colorectal cancer subsites were conducted using the competing risk analysis described by McNeil and Lunn (43). All analyses were done separately in each cohort and not combined due to different OC formulations (primarily first

Table 1. Age-standardized characteristics of ever and never OC users among 88,691 NHSI participants at the midpoint of follow-up (1994) between 1980 and 2010 and 93,080 NHSII participants at the midpoint of follow-up (2001) between 1991 and 2010 [means (SD) or %]

	NHSI		NHSII	
	Never-users ($N = 45{,}237$)	**Ever-users ($N = 43{,}454$)**	**Never-users ($N = 12{,}957$)**	**Ever-users ($N = 80{,}123$)**
Age, years	63.4 (6.5)	57.5 (6.4)	47.1 (4.5)	46.8 (4.7)
Height, inches	64.4 (2.4)	64.6 (2.4)	64.8 (2.7)	64.9 (2.6)
Physical activity, MET-hours/week	18.5 (22.5)	18.6 (22.7)	18.5 (23.0)	18.9 (23.7)
Smoking, pack-years	12.8 (19.7)	12.6 (18.6)	3.3 (8.0)	5.1 (9.6)
Processed or red meat, servings/day	0.4 (0.3)	0.4 (0.3)	0.7 (0.5)	0.7 (0.5)
Folate, mcg/day	443 (210)	443 (214)	612 (254)	606 (255)
Calcium, mcg/day	1,038 (473)	1,054 (483)	1,222 (510)	1,223 (529)
BMI[a], kg/m^2				
<18.5	5	5	17	15
18.5–22.9	18	21	24	25
23–24.9	17	18	13	15
25–29.9	31	30	22	24
30+	20	19	23	21
Aspirin use, times/week[a]				
0–3	69	70	96	95
4–6	15	15	4[b]	5[b]
7–10	8	8		
11+	8	8		
Alcohol, g/day[a]				
<5	61	58	64	60
5–9.9	8	9	7	9
10–14.9	6	7	4	6
15+	6	8	3	5
Age at first birth, years[a,c]				
<24	34	39	27	29
24–25	29	28	20	20
26–29	27	24	33	34
30+	11	9	19	17
Parity[a]				
0	7	4	37	30
1	7	6	15	19
2	25	30	28	34
3+	59	58	20	17
HT use[a]				
Premenopausal	20	22	17	14
Never	31	21	53	45
Past	19	15	15	20
Current	31	41	15	21
Endoscopy screening, last two years	21	20	10	10

[a]May not add to 100% due to missing data.
[b]Highest categories were combined in NHSII due to sparse data.
[c]Distribution among parous women.

Table 2. Colorectal cancer subsites in ever and never OC users among 88,691 NHSI and 93,080 NHSII participants

	Cases		HR (95% CI)		
				Age-adjusted	Multivariable[a]
	Never-users	Ever-users	Never-users	Ever-users	Ever-users
			NHSI		
Colorectal	1,079	685	ref.	0.97 (0.87–1.08)	1.01 (0.91–1.12)
Colon	844	541	ref.	1.01 (0.89–1.13)	1.04 (0.93–1.18)
Proximal colon	493	330	ref.	1.10 (0.94–1.27)	1.14 (0.98–1.32)
Distal colon	326	195	ref.	0.88 (0.72–1.07)	0.91 (0.75–1.11)
Rectum	235	144	ref.	0.85 (0.68–1.06)	0.89 (0.71–1.12)
			NHSII		
Colorectal	29	177	ref.	0.98 (0.66–1.46)	1.03 (0.69–1.53)
Colon	21	118	ref.	0.88 (0.55–1.39)	0.91 (0.57–1.46)
Proximal colon	14	54	ref.	0.60 (0.33–1.09)	0.63 (0.35–1.15)
Distal colon	7	62	ref.	1.37 (0.62–2.99)	1.44 (0.66–3.16)
Rectum	8	59	ref.	1.27 (0.61–2.66)	1.35 (0.64–2.85)

[a]Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate, calcium, total energy, aspirin use, alcohol, age at first birth, parity, HT use, family history, and previous endoscopy screening.

and second generation in NHSI and second, third, and fourth generation in NHSII) and usage patterns (about half of NHSI participants used OCs compared with nearly 90% of NHSII participants).

We conducted interaction analyses to assess whether associations varied across categories of BMI (<25, 25+ kg/m^2), smoking status (never, ever), alcohol consumption (<5, 5+ g/day), physical activity [<10.2, 10.2+ (median) MET hours/week], folate [<414, 414+ (median) mcg/day], family history (yes, no), or age at diagnosis (continuous years). All analyses were conducted with SAS software version 9.2. Trend tests were performed by modeling the median values of exposure categories as a continuous variable and using the Wald statistic to test for statistical significance. All statistical analyses were two-sided, using a 5% significance level.

Results

In our population of 88,691 women from NHSI with information on OC use, 45,237 were never-users (51%) and 43,454 were ever-users (49%) at last OC report. NHSI ever-users reported a 4.2-year mean duration of use. Among 93,080 NHSII participants, 12,957 were never-users (14%) and 80,123 were ever-users (86%) at last OC report. NHSII ever-users reported a 6.0-year mean duration of use. Compared with never-users in both cohorts, ever-users were more likely to have smoked, be younger, including at first birth, have more children, and have used HT (Table 1).

After 30 years and 2.5 million person-years of follow-up in NHSI, we observed 1,764 colorectal cancer cases: 1,385 colon (including 823 proximal and 521 distal) and 379 rectal cancers. The median age at diagnosis in NHSI was 70 and ranged from 36

Table 3. Colorectal cancer subsites by OC duration among 88,691 NHSI and 93,080 NHSII participants

Duration of OC use (years)	Never	≤1	>1 to <2	≥2 to <5	≥5 to <10	10+	
	N cases HR (95% CI)[a]						P_{trend}
	NHSI						
Colorectal	1,119	195	67	155	154	74	
	ref.	1.07 (0.91–1.25)	1.09 (0.85–1.41)	0.96 (0.80–1.15)	0.99 (0.83–1.18)	0.98 (0.77–1.25)	0.69
Colon	877	159	50	119	123	57	
	ref.	1.14 (0.96–1.36)	1.07 (0.80–1.44)	0.98 (0.80–1.20)	1.02 (0.84–1.25)	0.98 (0.74–1.28)	0.79
Proximal colon	511	105	30	59	79	39	
	ref.	1.34 (1.08–1.67)	1.20 (0.82–1.74)	0.89 (0.67–1.17)	1.19 (0.93–1.52)	1.17 (0.84–1.63)	0.36
Distal colon	340	53	17	54	42	15	
	ref.	0.93 (0.69–1.25)	0.85 (0.52–1.40)	1.05 (0.78–1.42)	0.84 (0.60–1.17)	0.64 (0.38–1.09)	0.09
Rectum	242	36	17	36	31	17	
	ref.	0.84 (0.59–1.21)	1.13 (0.68–1.89)	0.89 (0.61–1.29)	0.86 (0.59–1.27)	1.01 (0.61–1.66)	0.72
	NHSII						
Duration of OC use (years)	Never	<1	>1 to <5	5+			
Colorectal	59	28	68	51			
	ref.	1.13 (0.71–1.81)	1.31 (0.90–1.91)	0.86 (0.58–1.28)			0.23
Colon	47	20	43	29			
	ref.	1.02 (0.59–1.75)	1.04 (0.67–1.62)	0.61 (0.38–0.99)			0.02
Proximal colon	26	8	21	13			
	ref.	0.75 (0.33–1.69)	0.96 (0.53–1.74)	0.51 (0.26–1.00)			0.05
Distal colon	21	12	21	15			
	ref.	1.34 (0.64–2.78)	1.11 (0.59–2.08)	0.71 (0.36–1.40)			0.15
Rectum	12	8	25	22			
	ref.	1.58 (0.64–3.94)	2.37 (1.16–4.81)	1.86 (0.91–3.82)			0.24

[a]Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate, calcium, total energy intake, aspirin use, alcohol, age at first birth, parity, HT use, family history, and previous endoscopy screening.

Table 4. Colorectal cancer subsites by time since last OC among 88,691 NHSI and 93,080 NHSII participants

Time since last OC use (years)	Never	≤4	>4 to <10	≥10 to <15	15+	
			***N* cases** HR (95% CI)[a]			P_{trend}
			NHSI			
Colorectal	1,112	67	184	245	156	
	ref.	1.14 (0.88–1.47)	0.98 (0.83–1.15)	1.08 (0.93–1.25)	0.96 (0.81–1.15)	0.89
Colon	872	49	139	191	134	
	ref.	1.09 (0.81–1.47)	0.96 (0.80–1.16)	1.10 (0.93–1.30)	1.07 (0.89–1.29)	0.30
Proximal colon	508	31	94	109	81	
	ref.	1.28 (0.88–1.86)	1.19 (0.94–1.49)	1.14 (0.92–1.41)	1.15 (0.90–1.46)	0.13
Distal colon	338	16	44	73	50	
	ref.	0.82 (0.49–1.38)	0.72 (0.52–0.99)	1.00 (0.77–1.31)	1.00 (0.73–1.35)	0.82
Rectum	240	18	45	54	22	
	ref.	1.31 (0.79–2.17)	1.02 (0.73–1.42)	1.00 (0.73–1.37)	0.59 (0.38–0.93)	0.10
			NHSII			
Colorectal	45	13	14	18	116	
	ref.	1.00 (0.53–1.86)	0.62 (0.33–1.14)	1.04 (0.59–1.81)	0.95 (0.65–1.39)	0.86
Colon	34	9	11	11	74	
	ref.	0.92 (0.44–1.92)	0.62 (0.31–1.23)	0.82 (0.41–1.63)	0.81 (0.52–1.25)	0.56
Proximal colon	20	4	7	3	34	
	ref.	0.64 (0.22–1.90)	0.67 (0.28–1.59)	0.38 (0.11–1.29)	0.64 (0.35–1.16)	0.29
Distal colon	14	5	4	8	38	
	ref.	1.35 (0.48–3.78)	0.55 (0.18–1.69)	1.46 (0.61–3.51)	0.99 (0.52–1.89)	0.97
Rectum	11	4	3	7	42	
	ref.	1.24 (0.39–3.95)	0.59 (0.16–2.13)	1.76 (0.68–4.58)	1.42 (0.71–2.83)	0.23

[a]Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate, calcium, total energy, aspirin use, alcohol, age at first birth, parity, HT use, family history, and previous endoscopy screening.

to 88 years. After 19 years and 2.8 million person-years of follow-up in NHSII, we observed 206 colorectal cancer cases: 139 colon (including 68 proximal and 69 distal) and 67 rectal cancers. The median age at diagnosis in NHSII was 51 and ranged from 33 to 64 years.

Ever using OCs in NHSI was not associated with risk of colorectal [1.01 (0.91, 1.12)], colon [1.04 (0.93, 1.18)], proximal [1.14 (0.98, 1.32)], distal [0.91 (0.75, 1.11)], or rectal cancer [0.89 (0.71, 1.12)]. OC use in NHSII was not associated with colorectal cancer [1.03 (0.69, 1.53)] or any subsite: colon [0.91 (0.57, 1.46)], proximal 0.63 (0.35, 1.15)], distal [1.44 (0.66, 3.16)], or rectal [1.35 (0.64, 2.85)] (Table 2).

Compared with never use, longer durations of OC use (5+ years) appeared to be associated with lower risk of colon cancers in NHSII ($P_{trend} = 0.02$), but not with rectal cancers (Table 3). Time since last OC use was not associated with risk of colorectal cancers in either cohort regardless of subsite (Table 4), nor was the cross product of duration-by-time since last use (Table 5). None of these associations varied by age at diagnosis, BMI, smoking status, alcohol consumption, physical activity, folate, or family history (all *P* values for interaction terms with OC use >0.05).

Discussion

In NHSI and II, ever OC use was not associated with colorectal cancer. In NHSII alone, longer durations of OC use (5+ years) were associated with lower risk of proximal cancers but not distal or rectal cancers but statistical power was limited. Observed associations did not appear to differ by time since last OC use.

Table 5. Colorectal cancer by duration and time since last OC among 88,691 NHSI participants

			***N* cases** HR (95% CI)[a]			P_{trend}
			Time since last OC use (years)			
Duration of OC use (years)	**Never**	**≤4**	**>4 to <10**	**≥10 to <15**	**15+**	
Never	1,122					
	ref					
≤1		9	27	70	89	
		1.79 (0.92–3.47)	1.40 (0.95–2.06)	1.24 (0.97–1.59)	0.91 (0.73–1.13)	0.91
>1 to <2		4	11	28	24	
		1.35 (0.50–3.62)	0.97 (0.53–1.77)	1.06 (0.72–1.56)	1.20 (0.79–1.80)	0.87
≥2 to <5		8	32	78	34	
		1.00 (0.50–2.03)	0.85 (0.59–1.22)	0.97 (0.77–1.23)	1.02 (0.72–1.44)	0.88
≥5 to <10		17	72	59	6	
		0.98 (0.60–1.59)	0.95 (0.74–1.21)	1.05 (0.81–1.37)	1.08 (0.48–2.41)	0.91
10+		29	38	6	1	
		1.20 (0.82–1.74)	0.88 (0.63–1.21)	0.83 (0.37–1.86)	4.61 (0.63–33.71)	0.92
P_{trend}		0.67	0.67	0.68	0.70	

[a]Adjusted for age, BMI, height, physical activity, smoking, processed and red meat, folate, calcium, total energy, aspirin use, alcohol, age at first birth, parity, HT use, family history, and previous endoscopy screening.

The association between OC use and colorectal cancer in NHSI was initially examined after 8 years of follow when participants were 38 to 63 years of age (39) and then again after 12 years of follow-up when participants were 46 to 71 years of age (17). In the previous analyses, OC use was not associated with colorectal cancer except after 12 years of follow-up when OC use was inversely associated with colorectal cancer after 8+ years of use [RR = 0.60 (0.40–0.89), $P_{\text{trend}} = 0.02$]. Likewise, the present analysis found a nearly identical inverse association [(HR = 0.61 (0.38–0.99), $P_{\text{trend}} = 0.02$] among colon cancers in a similar age group, the NHSII participants (46–63 years of age).

Collectively, the previous literature has spanned from the early 1980s through the 2000s, including various OC types and age ranges. The mix of OC formulations and brands includes primarily first- and second-generation progestins with a range of estrogen doses but none of these studies have examined this information specifically. More time will need to pass before sufficient data are available from women using third- and fourth-generation pills with lower estrogen doses. In addition, few of the other studies have examined differences across age or even reported the median ages at diagnosis. It appears the majority of previous evidence weighs heavily on younger women, where the spectrum of cancers may be etiologically different than in older women. The NHSI has some of the longest follow-up time and therefore includes more cases, including among older women, than other studies.

Previous studies have produced mixed results. Two meta-analyses (5, 6) consisting of primarily case–control and small cohort studies with limited statistical power, reported a 19% reduction in colorectal cancer risk with ever OC use. The most recent meta-analysis (5) included 11 case–control studies, with the largest study containing 1,488 cases, and seven cohort studies. However, this inverse association has not been observed in all studies (7, 8, 38, 44). For example, the authors of a case–control study including 675 cases and 720 controls reported a reduced risk for other reproductive factors such as parity but found no association with OC use (44). In a similar case–control study, neither contraceptive estrogen use nor noncontraceptive estrogen use was related to the risk of colon cancer (38). In addition, the two largest cohort studies, including the National Institutes of Health–American Association of Retired Persons Diet and Health Study with 2,014 cases and the European Prospective Investigation into Cancer and Nutrition with 1,878 cases, were published after these meta-analyses with null findings (7, 8).

Previous results appear similar for colon as well as rectal cancer but, to the best of our knowledge, no study has examined associations by subsites within the colon (i.e., proximal versus distal) primarily because of limited sample size. Combining data from 10 case–control studies and five cohort studies in a meta-analysis, the relative risk for colon cancer was 0.85 (95% CI, 0.79–0.93) and 0.80 (95% CI, 0.70–0.92) for rectal cancer (5). Other reproductive factors, such as parity (18), have had heterogeneity in their association with colorectal cancer by subsites.

Previous studies have also examined duration and recency of OC use. The latest meta-analysis found no difference according to duration of OC use for either colon or rectal cancer, although there was suggestion that the protection was stronger for more recent use (5). Based on duration information from 12 studies, the pooled relative risk was 0.88 (95% CI, 0.77–1.01) for short-term use (defined as <5 years), and 0.86 (95% CI, 0.74–1.00) for long-term use (defined as $\geq$5 years). Only four studies contributed information on recency of OC use, resulting in an overall relative risk of 0.70 (95% CI, 0.53–0.90) for <10 years of use and 0.87 (95% CI, 0.77–0.99) for $\geq$10 years of use (5). These findings are consistent with those from epidemiologic studies examining HT use and colorectal cancer, which have reported stronger effects with current use and no evidence of a dose–response relation with duration (3).

Numerous mechanisms have been hypothesized for how OC use might impact colorectal cancer (45). Slattery and colleagues suggested that estrogen and high BMI interact by modulating the insulin-like growth factor pathway (46). Estrogen may also have direct anticarcinogenic effects, as demonstrated in colon cancer cell lines (47) and estrogen receptor expression in colonic cells (48), which may regulate numerous cellular functions related to colon carcinogenesis (49, 50). Issa and colleagues proposed that estrogen may protect the estrogen receptor gene from methylation (51). In addition, McMichael and Potter used epidemiological and animal data to suggest that endogenous and exogenous hormones could affect colorectal cancer risk by reducing secondary bile acid production (10). Although understanding of the genetic model of colorectal carcinogenesis has evolved, further investigation is needed to clarify such mechanisms and point toward possible interventions.

We were limited in exploring different types of OC use. For example, we lacked detailed formulation information in NHSI and could not use the information collected in NHSII because there were too few colorectal cancer cases to stratify by OC type. We also had limited statistical power among younger women. The generalizability of our findings may be limited by the homogeneity of our population with regard to race, education, and profession. However, these cohorts offer numerous advantages, including high follow-up rates, reliable information, and medically knowledgeable and cooperative participants. Our results pertain not only to the effects of the first- and second-generation OCs in NHSI, which had estrogen doses between 50 and 150 mcg, but also to current OC generations used in NHSII, which contain lower estrogen doses (20–35 mcg). Compared with other cohort studies in which this association has been considered, our analysis drew from two of the largest cohorts with the longest follow-up time. Because of the longitudinal nature of NHSI and II, we were also able to control for potential confounders and other hormonal exposures such as HT use that may be associated with colorectal cancer. Previous studies have not always been able to examine OC and HT use simultaneously.

In conclusion, we found little evidence that OC use may be protective for colorectal cancer, except potentially with longer durations of use among younger women. Our results do not support the previous studies that have observed stronger inverse associations with more recent use than with use in the more distant past. Further research should focus on examining different types of OCs, older ages at diagnosis, and all of the subsites of colorectal cancer, specifically subsites within the colon and molecular subtypes. Overall, a better understanding of the association between hormone use, including OCs, with the risk of colorectal cancer could impact how such drugs are used in clinical settings and potentially highlight new methods of prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B.M. Charlton, K. Wu, X. Zhang, C.S. Fuchs, S.A. Missmer, W.C. Willett, K.B. Michels
Development of methodology: B.M. Charlton, K. Wu, S.A. Missmer, W.C. Willett
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.L. Giovannucci, C.S. Fuchs, S.A. Missmer, W.C. Willett
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.M. Charlton, K. Wu, X. Zhang, E.L. Giovannucci, S.A. Missmer, B. Rosner, S.E. Hankinson, W.C. Willett, K.B. Michels
Writing, review, and/or revision of the manuscript: B.M. Charlton, K. Wu, X. Zhang, E.L. Giovannucci, C.S. Fuchs, S.A. Missmer, S.E. Hankinson, W.C. Willett, K.B. Michels
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.S. Fuchs
Study supervision: K. Wu, W.C. Willett, K.B. Michels

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