Oral Contraceptive Use, Reproductive Factors, and Colorectal Cancer Risk: Findings from Wisconsin

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Abstract

We investigated the association of oral contraceptive (OC) use and reproductive factors with colorectal cancer risk in a large population-based case-control study. Cases were women ages 20 to 74 years, living in Wisconsin, with a new diagnosis of colon (n = 1,122) or rectal (n = 366) cancer. Control participants were randomly selected from population lists of similarly aged female Wisconsin residents (n = 4,297). Risk factor information was collected through structured telephone interviews. Compared with never users, OC users had an odds ratio (OR) of 0.89 [95% confidence interval (95% CI), 0.75-1.06] for colorectal cancer. OC use associations did not differ significantly between colon and rectal cancer sites; however, when compared with never users, recent OC users (<14 years) seemed at reduced risk of rectal cancer (OR, 0.53; 95% CI, 0.28-1.00). Women with age at first birth older than the median (23 years) had 0.83 times the risk of colon cancer compared with women with age at first birth below the median (95% CI, 0.70-0.98). We observed an inverse trend between increasing parity and rectal cancer risk (P = 0.05). Compared with nulliparous women, women with five or more births had 0.66 times the risk of rectal cancer (95% CI, 0.43-1.02). Compared with postmenopausal women, premenopausal women were at reduced risk (OR, 0.67; 95% CI, 0.47-0.97) of colorectal cancer. No significant associations were observed between colorectal cancer risk and age at menarche or age at menopause. These findings suggest differential roles of reproductive factors in colon and rectal cancer etiology.

Introduction

During the first half of the 20th century (1900-1953), white Catholic nuns living in the United States were observed to have a significant excess risk of colon cancer mortality compared with other white American women (1). This finding initiated scientific speculation regarding the role of reproductive and hormonal influences on colorectal cancer, the third most common cancer in U.S. women (2).

Fifty years later, many reproductive exposures have been examined, albeit with conflicting results. Age at menarche and age at menopause (3-17), parity (18-20), and oral contraceptive (OC) use (3-17, 19-40) have each been evaluated in relation to colorectal cancer risk with the reasoning that these factors initiate long-term changes to the hormonal milieu (18, 41). Additional evidence of an association between hormonal status and colorectal cancer risk can be observed in the Women’s Health Initiative trial, where postmenopausal hormone use has been associated with a 40% reduction of colorectal cancer incidence (42).

Other risk factors for colorectal cancer have been well established. These include age, cigarette smoking, hereditary factors, screening practices, and body composition (43). In addition, lifestyle characteristics such as nonsteroidal anti-inflammatory drug usage, physical activity, and diet have been repeatedly associated with colorectal cancer incidence (44).

The high prevalence of OC use and changing reproductive patterns in the United States bring public health importance to potential associations with colon and/or rectal cancer. We conducted a case-control study to evaluate the association of OC use and reproductive factors with colon and rectal cancer in a population-based sample of women living in Wisconsin.

Materials and Methods

This analysis was done with pooled data from two case-control studies conducted by investigators at the University of Wisconsin, Madison. Both studies were conducted according to institutionally approved protocols and used similar questionnaires. Cases and controls from both studies were combined to increase statistical power.

Identification of Cases. Cases were female Wisconsin residents, ages 20 to 74 years, with a new diagnosis of colorectal cancer during 1988 to 1991 or 1997 to 2001. Diagnostic reports, including information regarding cancer site, histology, extent of disease, and follow-up physician, were obtained from the Wisconsin Cancer Reporting System, a statewide tumor registry mandated by legal statute. The physician of record for each case received a written letter requesting permission to approach the subject. Cases with a listed telephone number and without previous colorectal cancer were eligible. Of 2,228 women identified as eligible, 129 (5.8%) were not contacted due to physician refusal, 370 (16.6%) were deceased, 211 (9.5%) refused, 26 (1.2%) could not be located, and 4 (0.2%) interviews were deemed unreliable. Overall, 67% of all women participated in the study; 80% of all living cases participated. Response rates were similar in the two study periods.

Identification of Controls. Community controls were enrolled based on random selection from population lists of Wisconsin drivers (women ages <65 years) and Medicare beneficiaries (women ages ≥65 years). Inclusion criteria required that all control subjects have a listed telephone number and be free from colorectal cancer. Of 5,044 women...
identified as potential controls, 54 (1.1%) were deceased, 598 (11.9%) refused, 93 (1.8%) could not be located, and two were unreliable interviews. Overall, 85% of population controls participated.

Data Collection. Both cases and controls completed a structured telephone interview of OC use, reproductive characteristics, and colorectal cancer risk factors. Interviews were given concurrently for both case and control participants. Questions regarding personal and family histories of cancer and cancer screening were asked toward the end of the interview to maintain blinding of interviewers to the disease status of participants.

Statistical Analysis. We combined data from two case-control studies. Study I was conducted in 1988 to 1991 and study II in 1997 to 2001. Within each study, control women were generally younger than case women. In study I, the mean age was 64 years for cases and 58 years for controls. Study II was similar: the mean age was 62 for cases and 55 for controls. As expected, we observed significant changes in the prevalence of colorectal cancer screening, OC use, and body mass index (BMI) between studies (data not shown). Among cases, the proportion of women who had ever been screened for colorectal cancer was significantly higher in 1997 to 2001 than in 1988 to 1991 (31% versus 23%; P = 0.01). This relationship was reversed among controls: control women had a lower prevalence of ever screening (26.9%) in study II compared with study I (41.5%; P < 0.001). Among both case and control women, OC use increased significantly. Additionally, the proportion of women in lower BMI categories decreased, whereas the proportion in the highest BMI category increased. The proportion of women classified as smokers did not significantly change between studies for either case or control women. Due to the differences between studies described above, regression models were created conditional on age and time period of enrollment.

Only reproductive events and OC use that occurred before the reference date were included in analyses. The reference date for cases was the date of cancer diagnosis. For controls, the reference date was assigned as ~1 year before the interview based on average times between diagnosis and interview among the cases. OC use was evaluated by ever use, duration, age initiated, and recency of use. Cut points for categories of duration of use, age at first use, and recency of OC use were based on approximate quartiles among the control participants. Reproductive variables of interest included age at menarche, age at first full-term pregnancy, parity, menopausal status, and age at menopause.

After pooling data from study I and study II, several important confounders emerged. Some confounder relationships seemed to vary by cancer site, suggesting possible etiologic differences. To explore these differences, all models were produced to evaluate risk of colon and rectal cancer both combined and stratified. The following potential confounders were evaluated: family history of colorectal cancer, BMI, education, colorectal cancer screening before the reference date, cigarette smoking, postmenopausal hormone use, alcohol consumption, and physical activity. Our study population was 96% (n = 5,534) white; as such, we did not evaluate colorectal cancer risk associations by race. Those variables that obtained univariate significance, or borderline significance, in conditional logistic regression models were adjusted for in multivariate models. Age at first full-term pregnancy and parity variables were not adjusted for simultaneously when evaluating the individual effect of either variable. Body mass index was calculated as recent weight (kg)/tallest adult height (m)².

All final models for colon and rectal cancer combined were adjusted for family history of colorectal cancer (yes/no), BMI (continuous), education (five groups), colorectal cancer screening (yes/no), cigarette smoking (pack-years, continuous), age at first full-term pregnancy (continuous), and postmenopausal hormone use (never/former/current). The following covariates were adjusted for: family history (yes/no), BMI (continuous), education (five groups), colorectal cancer screening (yes/no), cigarette smoking (pack-years, continuous), and postmenopausal hormone use (never/former/current).

Odds ratios (OR) and 95% confidence intervals (95% CI) for colon and rectal cancer by OC use and reproductive factors were produced using multivariate logistic regression models adjusted for known confounders chosen using the method described above. Conditional models were stratified by age at the reference date and study of enrollment. Groups were created with ~ 50 total subjects per group after sorting by study and age (continuous) for a total of 116 groups.

To obtain Ps for trend, we included select variables as continuous linear terms in regression models. All Ps are two sided. Effect modification by OC use was evaluated by inclusion of cross-product interaction terms in logistic models and measuring the change in the log-likelihood using χ² tests. The analyses described above were done using Stata Statistical Software (45).

Polytomous logistic regression models were created to analyze colon cancer risk factor associations compared with rectal cancer. Within polytomous models, associations between cancer sites were compared with the Wald test using variables parameterized both categorically and continuously. Polytomous models were adjusted for age (continuous), study of enrollment, family history (yes/no), BMI (continuous), education (five groups), colorectal cancer screening (yes/no), cigarette smoking (pack-years, continuous), and postmenopausal hormone use (never/former/current).

When evaluated separately, colon cancer risk mirrored patterns of association seen for colorectal cancer; we additionally observed a borderline significant association between alcohol consumption and decreased risk of colon cancer. Rectal cancer risk factors also reflected associations observed for colon and rectal cancer cases combined, with two exceptions. First, BMI did not seem associated with rectal cancer risk and second, participation in recreational physical...
activity at approximately age 20 was associated with decreased rectal cancer risk (borderline significance). The Wald test indicated that risk factor associations were not significantly different ($P > 0.05$) between colon and rectal cancer sites (data not shown).

**Oral Contraceptive Use.** In our study sample, 426 (43.6%) women with colon or rectal cancer reported OC use. Among women diagnosed with colon cancer, 326 (44.1%) reported ever use of OCs. Of women with rectal cancer, 100 (41.9%) reported ever use of OCs. OC use was reported by 1968 (46.6%) of control women.

Table 2 displays ORs and 95% CIs for colon and rectal cancer risk (combined and stratified) by OC use. After multivariable adjustment, OC use (compared with never use) seemed moderately protective for colorectal cancer risk (OR, 0.89; 95% CI, 0.75-1.06), conditional on age and study of enrollment. Colorectal cancer risk did not seem related to duration, the age initiated, or the recency of OC use.

After separating the two cancer sites, women who had ever used OCs (compared with never users) had 0.87 times the risk of both colon cancer (95% CI: 0.72, 1.06) and rectal cancer (95% CI: 0.65, 1.17). Duration and age of initiation of OC use did not seem related to either colon or rectal cancer risk. Recency of OC use was not strongly related to colon cancer risk; however, women in the most recent category of OC use (use within the past 14 years) seemed to have half the risk of rectal cancer compared with women who had never used OCs (OR, 0.5; 95% CI, 0.28-1.00). Formal tests revealed that OC use associations (ever use, duration, age at initiation, and recency) did not significantly differ ($P > 0.05$ by Wald test) between colon and rectal cancer sites (data not shown).

Heterogeneity of the relation between OC use and colon and rectal cancer risk was explored according to age, family history, BMI, education, screening, cigarette smoking, hormone replacement therapy, alcohol consumption, OC use, age at first birth, and menopausal status.

**Reproductive Risk Factors.** Table 3 presents ORs and 95% CIs for colon and rectal cancer (combined and stratified) by reproductive risk factors. We observed a moderate decrease in colorectal cancer risk (OR, 0.87; 95% CI, 0.75-1.01) among parous women with age at first full-term pregnancy greater than the median (22.7 years). Premenopausal women had 0.67 times the risk of colorectal cancer (95% CI: 0.47, 0.97), than the median (22.7 years). Premenopausal women had 0.67 times the risk of colorectal cancer (95% CI: 0.47, 0.97), the median (22.7 years).

Among parous women, women...
with age at first full-term pregnancy above the median (22.7 years) had 0.83 times the risk of colon cancer compared with women with age at first full-term pregnancy below the median (95% CI, 0.70-0.98). Consistent with findings for colon and rectal cancer combined, colon cancer risk was not associated with age at menarche, parity, or age at menopause.

In multivariable rectal cancer models, we observed an inverse trend between parity and rectal cancer risk (P = 0.05); this trend was associated with rectal, compared with colon, cancer sites (P = 0.06 by Wald test). Compared with nulliparous women, women with five or more births had a 34% reduction in rectal cancer risk (OR, 0.66; 95% CI, 0.43-1.02). Rectal cancer risk did not seem associated with age at menarche, age at first full-term pregnancy, or age at menopause. The association between menopausal status and rectal cancer risk did not achieve statistical significance (95% CI, 0.38-1.40); however, the direction of the association (OR, 0.73) was similar to colorectal and colon models and could not be distinguished by the Wald test (P > 0.05).

**Discussion**

The association of reproductive factors and/or OC use and colorectal cancer has been investigated in over 45 published reports. Among these, we found 25 case-control studies (3, 4, 6, 8-13, 15, 16, 19-32), nine cohort studies (5, 7, 14, 17, 33-37), three reviews (32, 38, 39), and one meta-analysis (40). Despite the wealth of literature, the relationships among OC use, reproductive factors, and colorectal cancer have remained uncertain. Within our data, we explored potential etiologic variation between colon and rectal cancer sites and found differences in known risk factor associations.

Based on contradictory findings and modest effects reported in the literature, it is difficult to reach a consensus on the relationship of OC use and colorectal cancer risk. Studies have reported inverse (4, 8, 14, 19, 24, 28, 37, 46) or null associations (3, 5, 6, 9, 15, 35) with two studies noting a possible increase in colorectal cancer risk associated with OC use (21, 26). Our findings indicated that ever use of OCs modestly decreased colorectal cancer risk. With colon and rectal cases combined, and colon cases alone, this decrease was not significantly related to duration of use, age at initiation of use, or recency of use. However, compared with women who had never used OCs, women who had used them within the past 14 years had the lowest risk of rectal cancer (OR, 0.53; 95% CI, 0.28, 1.00).

Many studies have looked at duration of OC use and colon and/or rectal cancer risk (3, 5, 9, 14, 15, 19, 21, 28, 37, 40, 46). Two studies reported null findings for risk of either colon or rectal cancer (15, 37), whereas others observed a protective effect towards colon cancer (OR, 0.20; 95% CI, 0.04-1.00 for >2 years of use compared with never use; ref. 19), or colon and rectal cancers combined (relative risk, 0.6; 95% CI, 0.40-0.89 for ≥8 years of use compared with never use; P > 0.05; ref. 16). Fernandez et al. also reported a decreased risk for colorectal cancer associated with >2 years of OC use compared with never use; their results did not initially achieve statistical significance (OR, 0.52; 95% CI, 0.27-1.02; ref. 28) but were significant in a later pooled analysis (OR, 0.64; 95% CI, 0.43-0.94; ref. 46). When examined separately in the pooled analysis, the inverse association for >2 years of OC use (compared with never use) was statistically significant for colon (OR, 0.52; 95% CI, 0.32-0.85), but not for rectal (OR, 0.86; 95% CI, 0.50-1.48), cancer risk (46).

Among studies that evaluated duration, only a few have additionally looked at recency of OC use (15, 28, 37, 40, 46). These studies have reported either no association for recency and risk of colon and/or rectal cancer (28, 37) or a negative association for colon (OR, 0.36; 95% CI, 0.45-0.87), but not rectal, cancer risk (46). In a meta-analysis, the summary relative risk calculated was 0.46 (95% CI, 0.30-0.71) for risk of colorectal cancer among recent (<10 years) OC users (40).

**Table 2. ORs and 95% CIs for colon and rectal cancer, combined and stratified, according to OC use**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls</th>
<th>Colorectal cancer</th>
<th>Colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 4,297* (%)</td>
<td>n = 1,488* (%)</td>
<td>n = 1,122* (%)</td>
<td>n = 366* (%)</td>
</tr>
<tr>
<td>OC use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2,257 (53.4)</td>
<td>1,032 (56.4)</td>
<td>778 (55.9)</td>
<td>254 (58.1)</td>
</tr>
<tr>
<td>Ever</td>
<td>1,968 (46.6)</td>
<td>426 (43.6)</td>
<td>326 (44.1)</td>
<td>100 (41.9)</td>
</tr>
<tr>
<td>Duration of OC use (mos)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-23</td>
<td>472 (24.0)</td>
<td>101 (22.1)</td>
<td>78 (21.1)</td>
<td>23 (24.3)</td>
</tr>
<tr>
<td>24-53</td>
<td>507 (25.8)</td>
<td>112 (28.9)</td>
<td>82 (27.8)</td>
<td>30 (31.9)</td>
</tr>
<tr>
<td>54-107</td>
<td>477 (24.2)</td>
<td>103 (24.7)</td>
<td>82 (26.1)</td>
<td>21 (21.4)</td>
</tr>
<tr>
<td>&gt;108</td>
<td>512 (26.0)</td>
<td>110 (24.3)</td>
<td>84 (24.9)</td>
<td>26 (23.4)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.1</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Age started OC use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 or younger</td>
<td>356 (18.4)</td>
<td>41 (16.5)</td>
<td>29 (15.8)</td>
<td>12 (18.0)</td>
</tr>
<tr>
<td>20-23</td>
<td>621 (32.0)</td>
<td>96 (34.0)</td>
<td>73 (34.1)</td>
<td>23 (32.9)</td>
</tr>
<tr>
<td>24-28</td>
<td>442 (22.8)</td>
<td>97 (23.4)</td>
<td>74 (23.8)</td>
<td>23 (22.8)</td>
</tr>
<tr>
<td>&gt;29</td>
<td>519 (26.8)</td>
<td>171 (26.2)</td>
<td>132 (26.3)</td>
<td>39 (26.4)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.9</td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Recency of OC use (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;14</td>
<td>518 (26.5)</td>
<td>69 (24.9)</td>
<td>53 (26.2)</td>
<td>16 (21.7)</td>
</tr>
<tr>
<td>14-18</td>
<td>392 (20.1)</td>
<td>68 (19.7)</td>
<td>49 (18.7)</td>
<td>19 (22.3)</td>
</tr>
<tr>
<td>19-23</td>
<td>478 (24.5)</td>
<td>108 (26.1)</td>
<td>83 (25.9)</td>
<td>25 (26.2)</td>
</tr>
<tr>
<td>&gt;24</td>
<td>566 (29.0)</td>
<td>175 (29.3)</td>
<td>136 (29.2)</td>
<td>39 (29.8)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.3</td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Variable sums that do not equal the total n are due to missing data.

**Table 2. ORs and 95% CIs for colon and rectal cancer, combined and stratified, according to OC use**

*Percentages are age-adjusted to the distribution of controls.

*Conditional on age and study of enrollment; adjusted for family history of colorectal cancer, BMI, education, screening, smoking, hormone replacement therapy, and age at first birth.

*Conditional on age and study of enrollment; adjusted for family history of colorectal cancer, BMI, education, screening, smoking, hormone replacement therapy, alcohol consumption, age at first birth, and menopausal status.

*Conditional on age and study of enrollment; adjusted for family history of colorectal cancer, physical activity, education, screening, smoking, and hormone replacement therapy.

*Comparison of never-users of OCs.
Recrency of exogenous hormone use is likely an important factor to consider in addressing disease risk, as evidenced by previous investigations of postmenopausal hormone use. For example, the magnitude of the protective effect associated with postmenopausal hormone use and colon cancer risk is greater with decreasing time since last use (47).

Adding complexity to the debate, reproductive and menstrual characteristic associations with colorectal cancer risk are inconsistent. Our null findings of age at menarche and age at menopause were in agreement with several previous studies (3-10). Other investigators, however, have reported a negative association between late age of menarche and colorectal cancer risk (11-14). Additionally, published findings have reported both positive (4, 13, 15, 16, 31) and negative (6, 17) associations between late age at menopause and colorectal cancer risk (14-16, 19, 21).

After conditioning on age at study of enrollment, premenopausal women remained at reduced risk of colorectal cancer (OR, 0.67; 95% CI, 0.47-0.97) compared with postmenopausal women. This finding is in agreement with other reports of a decrease in risk of colon and/or rectal cancer combined, which is less pronounced (8, 14, 16, 19, 21, 23, 34, 36, 43). Only one study has shown multiparous women at increased risk of rectal cancer (5).

Adding complexity to the debate, reproductive and menstrual characteristic associations with colorectal cancer risk are inconsistent. Our null findings of age at menarche and age at menopause were in agreement with several previous studies (3-10). Other investigators, however, have reported a negative association between late age of menarche and colorectal cancer risk (11-14). Additionally, published findings have reported both positive (4, 13, 15, 16, 31) and negative (6, 17) associations between late age at menopause and colorectal cancer risk.

### Table 3. ORs and 95% CIs for colon cancer, combined and stratified, according to reproductive factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls</th>
<th>Colorectal cancer</th>
<th>Colon cancer</th>
<th>Rectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>768 (18.2)</td>
<td>238 (19.4)</td>
<td>179 (19.2)</td>
<td>59 (19.7)</td>
</tr>
<tr>
<td>12</td>
<td>954 (22.1)</td>
<td>326 (23.4)</td>
<td>231 (22.2)</td>
<td>95 (26.8)</td>
</tr>
<tr>
<td>13</td>
<td>1,200 (28.4)</td>
<td>411 (26.4)</td>
<td>326 (27.2%)</td>
<td>85 (24.0)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>1,317 (31.2)</td>
<td>468 (30.8)</td>
<td>355 (31.4)</td>
<td>113 (29.5)</td>
</tr>
<tr>
<td>( \ell_{\text{trend}} )</td>
<td></td>
<td></td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Age at first birth (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21</td>
<td>1,896 (50.1)</td>
<td>686 (53.8)</td>
<td>537 (55.2)</td>
<td>149 (49.5)</td>
</tr>
<tr>
<td>&gt;21</td>
<td>1,891 (49.9)</td>
<td>617 (46.2)</td>
<td>455 (44.8)</td>
<td>162 (50.5)</td>
</tr>
<tr>
<td>( \ell_{\text{trend}} )</td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>480 (11.2)</td>
<td>165 (12.1)</td>
<td>116 (12.1)</td>
<td>49 (12.2)</td>
</tr>
<tr>
<td>1-2</td>
<td>1,548 (36.3)</td>
<td>464 (33.0)</td>
<td>340 (31.2)</td>
<td>124 (37.8)</td>
</tr>
<tr>
<td>3-4</td>
<td>1,543 (36.2)</td>
<td>542 (38.3)</td>
<td>415 (29.4)</td>
<td>127 (35.4)</td>
</tr>
<tr>
<td>&gt;5**</td>
<td>697 (16.3)</td>
<td>300 (16.7)</td>
<td>240 (17.3)</td>
<td>60 (14.6)</td>
</tr>
<tr>
<td>( \ell_{\text{trend}} )</td>
<td></td>
<td></td>
<td>1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>2,819 (69.8)</td>
<td>1,283 (72.2)</td>
<td>975 (72.4)</td>
<td>308 (71.5)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1,222 (30.2)</td>
<td>157 (27.8)</td>
<td>112 (27.6)</td>
<td>45 (28.5)</td>
</tr>
<tr>
<td>( \ell_{\text{trend}} )</td>
<td></td>
<td></td>
<td>0.67 (0.47-0.97)</td>
<td>0.73 (0.38-1.40)</td>
</tr>
</tbody>
</table>

**Variable sums that do not equal the total \( N \) are due to missing data.

1Percentages are age-adjusted to the distribution of controls.

2Conditional on age and study of enrollment; adjusted for family history of colorectal cancer, BMI, education, screening, smoking, hormone replacement therapy, and age at first birth.

3Conditional on age and study of enrollment; adjusted for family history of colorectal cancer, BMI, education, screening, smoking, hormone replacement therapy, alcohol consumption, OC use, age at first birth and menopausal status.

4Conditional on age and study of enrollment; adjusted for family history of colorectal cancer, physical activity, education, screening, smoking, and hormone replacement therapy.

5Parous women only (Controls: \( n = 3,797 \) controls; Colon cancer: \( n = 992 \); Rectal cancer: \( n = 311 \)).

6P < 0.05 for the Wald test comparing colon and rectal associations; all other Wald tests for characteristics in this table have \( P > 0.05 \) (unless otherwise indicated).

7P = 0.08 for the Wald test comparing colon and rectal associations.

8P = 0.06 for the Wald test comparing colon and rectal associations.

9\( \ell_{\text{trend}} \) is the slope of the linear trend of the OR for the respective characteristic.
formulas. This trend could have attenuated the observed effect if one level of dosage but not the other was associated with colorectal cancer risk.

The lower case participation proportion (67%) occurred primarily because of death. Although bias is a possibility, for this to have occurred, women who were deceased at the time of enrollment would have had to have an OC use pattern that differed from living women. We cannot exclude this possibility; however, it seems unlikely.

Recall of OC use was unlikely to be differential for case and control women because the possible association among OC use, reproductive factors, and colorectal cancer risk is largely unknown. We observed strong associations with known confounders in our preliminary analysis. Although there were minor differences in the form of questions concerning colorectal cancer screening, physical activity, and alcohol consumption between the two waves of data collection, we are confident that our models rigorously adjust for these confounding variables. Our data analysis methods allowed us to anticipate and correct for sampling differences and secular trends between case-control studies.

Several mechanisms have been suggested for the protective effect seen among OC users and colon cancer. Bile acid secretion is potentially damaging to the colonic mucosa and may prompt the initiation or promotion of malignant growth (18, 39, 51). Supplemening exogenous estrogen decreases bile acid levels (51, 52). The absorption of bile acids in the proximal bowel provides support for a protective effect for colon but not rectal cancer (39, 51). Permanent shifts in endogenous hormone levels are also observed after pregnancy and influence hepatic cholesterol metabolism and bile production (18, 41, 51).

Colorectal cells (both normal and cancerous) may additionally be characterized by estrogen receptor status (52). Estrogen receptor genes can act as tumor suppressors in the presence of exogenous estrogen (39). Insulin-like growth factor has also been implicated in the development of colorectal cancer. Estrogen may down-regulate insulin-like growth factor and interrupt cell growth cycles (39). Substantial support for the protective role of estrogen in colorectal cancer risk has accumulated from studies that have repeatedly observed a protective association between postmenopausal hormone use and colorectal cancer (40, 52).

Conclusions. OC use and reproductive characteristics seem to modestly affect colon and rectal cancer risk. These findings support contributing roles of OC use and reproductive factors in colon and rectal cancer etiology.

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References
