Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis

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**BACKGROUND:** Various studies have reported an inverse relation between oral contraceptive (OC) use and the risk of colorectal cancer, but the issue is still open.

**METHODS:** In order to quantify the association between OC use and colorectal cancer risk, we performed a systematic review and meta-analysis of studies on this issue. We identified all relevant studies published, in English, as original articles up to December 2008 through a search of the literature using PubMed and EMBASE, and by reviewing the references from the retrieved articles.

**RESULTS:** The summary relative risk of colorectal cancer for ever versus never OC use was 0.82 (95% confidence interval, CI, 0.69–0.97) from 11 case–control studies, 0.81 (95% CI, 0.75–0.89) from seven cohort studies, and 0.81 (95% CI, 0.72–0.92) from all studies combined. The results were similar for colon and rectal cancer. No difference was evident according to duration of OC use both for colon and rectal cancer, although there is an indication that the protection is stronger for more recent use (OR = 0.70, 95% CI, 0.53–0.90, on the basis of four studies).

**CONCLUSION:** Epidemiological data consistently indicate that OC users have a reduced risk of colorectal cancer, and that the protection is greater for recent use in the absence, however, of a duration–risk relation.

**Key words:** colorectal cancer / epidemiology / meta-analysis / oral contraceptives / risk

**Introduction**

A role of reproductive factors on colorectal carcinogenesis has long been suggested, starting from the observation of an excess colorectal cancer in nuns (Fraumeni et al., 1969), and of an inverse relation between parity and colorectal cancer in several studies (La Vecchia and Franceschi, 1991). Epidemiological, metabolic and animal data also indicated that endogenous and exogenous hormones could affect colorectal cancer risk (McMichael and Potter, 1980). With reference to oral contraceptives (OCs), in a meta-analysis of epidemiological studies published up to June 2000, the pooled relative risk (RR) of colorectal cancer for ever OC use was 0.81 from eight case–control studies, 0.84 from four cohort studies and 0.82 (95% confidence interval, CI, 0.74–0.92) from all studies combined (Fernandez et al., 2001). However, no relation with duration of use was observed. The pattern of risk was similar for colon and rectal cancer.

Among more recent investigations, a Swiss case–control study on 131 women with colorectal cancer and 373 hospital controls reported an odds ratio (OR) of 0.8 for ever OC use (Levi et al., 2003), in the absence of consistent relation with duration and time since first or last
OC use. In a case–control study from Wisconsin, USA, including 1122 cases of colon cancer, 366 of rectal cancer and 4297 population controls, the overall OR for ever use was 0.89, with no difference between colon (OR = 0.87) and rectal (OR = 0.87) cancer (Nichols et al., 2005). No pattern in risk was seen according to duration of use, although the risk reduction was stronger for more recent use for rectal, but not colon, cancer. A case–control study from Canada on 1404 colorectal cancer cases and 1203 population controls found a significant reduced risk for ever use of OC (OR = 0.77), with no evidence, however, of a relation with duration of use (Campbell et al., 2007). The Oxford Family Planning Association cohort study including 17 032 women and 46 cases of colorectal cancer reported no association with OC use (Vessey et al., 2003). In a cohort study of 267 400 female textile workers in Shanghai, China, including 655 women with colon cancer, the RR was 1.09 for women who had ever used OC, in the absence of any trend in risk with duration of OC use (Rosenblatt et al., 2004). In the 2003 follow-up of the Royal College of General Practitioners’ OC Study (46 000 women, ~35 years follow-up) there were 323 cases of colorectal cancer, corresponding to a RR of 0.72 for ever OC users (Hannaford and Elliott, 2005). In a nested case–control study within that cohort there were 146 cases of colorectal cancer (Hannaford et al., 2007). The OR was 0.84 for ever users, with greater reduction in risk for current (OR = 0.38) than for former (OR = 0.89) users. In the 11-year follow-up of the Women’s Health Study, including 39 680 women and 267 cases of colorectal cancer, the RR for ever OC use was 0.67, with little evidence, however, of a duration–risk relation (Lin et al., 2007). In a cohort study of Canadian women within a breast cancer screening program, including 89 835 women followed for an average of 16.4 years, there were 1142 incident colorectal cancers (Kabat et al., 2008). The overall RR for ever OC use was 0.83, with no difference across colorectal subsites. There was no relation with duration of OC use.

The issue, however, is still open, and the IARC Monograph on combined estrogen–progestogen contraceptives concluded that there was evidence for a lack of carcinogenicity of OC on colorectal cancer (IARC, 2007).

In order to provide a quantification of the association between OC use and colorectal cancer risk, we performed a comprehensive review and meta-analysis including all data published up to December 2008.

**Methods**

**Search strategy and selection criteria**

In the present meta-analysis, we included all case–control and cohort studies published as original articles in English up to December 2008. They were identified through a search of the literature using PubMed and EMBASE with the keywords: [‘oral contraceptives’ OR ‘exogenous hormones’] AND [‘colorectal’ OR ‘colon’ OR ‘rectal’ OR ‘rectum’] AND [‘cancer’ OR ‘neoplasm’] AND [‘case–control study’ OR ‘cohort study’]. We retrieved and assessed potentially relevant articles, and checked the reference lists of all papers of interest to identify additional relevant publications. Studies were considered only if they provided information on OC separately from hormone replacement therapy or other hormonal therapies. We did not assign quality scores to studies, and no study was excluded a priori for weakness of design or data quality. However, we performed sensitivity analyses, excluding studies which provided crude estimates or estimates adjusted for age and a few selected covariates only. Articles were reviewed and data were extracted and cross-checked independently by 2 investigators, and any disagreement was resolved by consensus among the 2. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis only the most recent or informative one.

For each study, we abstracted information on study design, country, number of subjects (cases, controls or cohort size), length of follow-up (for cohort studies), prevalence of OC use, confounders allowed for in the analysis, RR estimates for ever OC use, and (when available) for duration and recency of use, and corresponding 95% CIs. The primary analysis concerned the risk for ever versus never OC users; whenever possible, we also abstracted information on duration and recency of OC use. In most studies, the primary outcome was colorectal cancer, but some included colon cancer only, and others provided colon and rectal cancer separately. These were also considered, whenever possible.

**Statistical methods**

The measure of interest was the RR (or the OR in case–control studies), giving preference to RR estimates adjusted for multiple confounding factors. When RRs were not available in published papers, we computed unadjusted RRs from the exposure distributions as given in the papers. We derived summary estimates of the RR using fixed effect models (i.e. as weighed averages using the inverse of the variance of the log (RR) as weight), and we assessed the heterogeneity between studies using the Chi² test (Greenland, 1987). When significant heterogeneity (defined as a P-value for heterogeneity < 0.10) was found, we used a random effect model (i.e. as weighed averages using the sum of the inverse of the variance of the log (RR) and the moment estimator of the variance between studies as weight) (DerSimonian and Laird, 1986). We also calculated summary estimates for case–control and cohort studies separately. Since duration and recency of use were not uniformly reported, we first defined for each study two categories of duration (short-term, approximately <5 years; long-term use, approximately ≥5 years) and of recency (shorter time since last use, approximately <10 years; longer time since last use, approximately ≥10 years); then we pooled the risk estimates for these categories. We also computed pooled RR estimates for ≤5 and ≥5 years of duration of OC use, and for ≤10 and ≥10 years since last OC use. Inadequate information was available on the type of OC used.

We provided forest plots, in which a square was plotted for each study, whose center projection on the underlying scale corresponds to the study-specific RR. The area of the square is proportional to the inverse of the variance of the natural logarithm of the RR, and gives thus a measure of the amount of statistical information available from that particular estimate. A diamond was used to plot the summary RRs, whose center represents the RR and its extremes show the 95% CIs.

Publication bias was evaluated using funnel plots and quantified by the Egger’s test (Egger et al., 1997; Thornton and Lee, 2000).

**Results**

From the initial literature search we identified and checked 57 abstracts; 18 articles were considered of interest and full-text were retrieved for detailed evaluation; references of these articles were reviewed and 11 additional relevant studies were identified; six of these articles were subsequently excluded from the meta-analysis (since they were based on the same study population), thus leaving
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country, study acronym</th>
<th>No. of cases &amp; Colorectum</th>
<th>No. of controls</th>
<th>Source of information</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss et al. (1981)</td>
<td>Washington State, USA</td>
<td>143</td>
<td>707</td>
<td>Interview</td>
<td>Age</td>
</tr>
<tr>
<td>Potter and McMichael (1983)</td>
<td>Adelaide, Australia</td>
<td>155</td>
<td>99</td>
<td>56</td>
<td>311</td>
</tr>
<tr>
<td>Furner et al. (1989)</td>
<td>Chicago, USA</td>
<td>90</td>
<td>208</td>
<td>Medical records + interview + self-reported</td>
<td>—</td>
</tr>
<tr>
<td>Kune et al. (1990)</td>
<td>Melbourne, Australia</td>
<td>190</td>
<td>108</td>
<td>82</td>
<td>200</td>
</tr>
<tr>
<td>Peters et al. (1990)</td>
<td>Los Angeles, USA</td>
<td>—</td>
<td>327</td>
<td>327</td>
<td>Interview</td>
</tr>
<tr>
<td>Wu-Williams et al. (1991)</td>
<td>North America and China</td>
<td>395</td>
<td>192</td>
<td>203</td>
<td>1112</td>
</tr>
<tr>
<td>Jacobs et al. (1994)</td>
<td>Seattle, USA</td>
<td>—</td>
<td>193</td>
<td>—</td>
<td>194</td>
</tr>
<tr>
<td>Kampman et al. (1994)</td>
<td>The Netherlands</td>
<td>—</td>
<td>102</td>
<td>123</td>
<td>Interview</td>
</tr>
<tr>
<td>Kampman et al. (1997)</td>
<td>USA, KPMC</td>
<td>—</td>
<td>894</td>
<td>—</td>
<td>1120</td>
</tr>
<tr>
<td>Fernandez et al. (1996)</td>
<td>Italy</td>
<td>709</td>
<td>—</td>
<td>—</td>
<td>992</td>
</tr>
<tr>
<td>Talamini et al. (1998)</td>
<td>Italy</td>
<td>507</td>
<td>—</td>
<td>—</td>
<td>2081</td>
</tr>
<tr>
<td>Fernandez et al. (1998)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Italy</td>
<td>—</td>
<td>803</td>
<td>429</td>
<td>2793</td>
</tr>
<tr>
<td>Levi et al. (2003)</td>
<td>Switzerland</td>
<td>131</td>
<td>—</td>
<td>—</td>
<td>373</td>
</tr>
<tr>
<td>Nichols et al. (2005)</td>
<td>Wisconsin, USA</td>
<td>1488</td>
<td>1112</td>
<td>366</td>
<td>4297</td>
</tr>
<tr>
<td>Campbell et al. (2007)</td>
<td>Canada</td>
<td>1404</td>
<td>—</td>
<td>—</td>
<td>1203</td>
</tr>
</tbody>
</table>

KPMC: Kaiser Permanente Medical Care.

<sup>a</sup>Pooled data from Fernandez et al. (1996) and Talamini et al. (1998).

<sup>b</sup>Matching variables.
### Table II  Cohort studies on OCs and colorectal cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country, study acronym</th>
<th>No. of cancers/deaths</th>
<th>Source of information</th>
<th>Follow-up</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez et al. (1997)</td>
<td>USA, NHS</td>
<td>501</td>
<td>Self-reported</td>
<td>12 years</td>
<td>Age, body mass index, physical exercise, smoking, alcohol, meat, aspirin, family history of cancer, menstrual factors</td>
</tr>
<tr>
<td>Bostick et al. (1994)</td>
<td>Iowa, USA, WHS</td>
<td>212</td>
<td>Self-reported</td>
<td>4 years</td>
<td>Age, height, energy intake, vitamin, parity</td>
</tr>
<tr>
<td>Troisi et al. (1997)</td>
<td>USA, BCDDP</td>
<td>330</td>
<td>Interview</td>
<td>10 years</td>
<td>Age</td>
</tr>
<tr>
<td>Van Wayenburg et al. (2000)</td>
<td>Netherlands</td>
<td>95</td>
<td>Self-reported</td>
<td>18 years</td>
<td>Age, socioeconomic status, body mass index, smoking, age at first birth, type of menopause</td>
</tr>
<tr>
<td>Vessey et al. (2003)</td>
<td>UK, OPFA</td>
<td>46</td>
<td>Interview</td>
<td>30 years</td>
<td>Age, social class, smoking, parity</td>
</tr>
<tr>
<td>Rosenblatt et al. (2004)</td>
<td>China</td>
<td>655</td>
<td>Interview</td>
<td>10 years</td>
<td>Age, parity</td>
</tr>
<tr>
<td>Hannaford and Elliot (2005)b</td>
<td>UK, RCGP OC</td>
<td>146</td>
<td>Medical records</td>
<td>35 years</td>
<td>Age, social class, smoking, parity, hormone replacement therapy</td>
</tr>
<tr>
<td>Hannaford et al. (2007)</td>
<td>UK, RCGP OC</td>
<td>323</td>
<td>Medical records</td>
<td>35 years</td>
<td>Age, social class, smoking, parity, hormone replacement therapy</td>
</tr>
<tr>
<td>Lin et al. (2007)</td>
<td>USA, WHI</td>
<td>267</td>
<td>Self-reported</td>
<td>11 years</td>
<td>Age, body mass index, physical activity, smoking, alcohol, meat, vitamin supplementation, family history of cancer, history of benign colorectal polyps, aspirin, treatment assignment, hormone replacement therapy</td>
</tr>
<tr>
<td>Kabat et al. (2008)</td>
<td>Canada, CNBSS</td>
<td>1142</td>
<td>Self-reported</td>
<td>16 years</td>
<td>Age, education, body mass index, smoking, menopausal status, hormone replacement therapy</td>
</tr>
</tbody>
</table>

BCDDP: Breast Cancer Detection Demonstration Project; CNBSS: Canadian National Breast Screening Study; NHS: Nurses’ Health Study; OPFA: Oxford Family Planning Association; OC: Oral contraceptives; RCGP: Royal College of General Practitioners; WHI: Women’s Health Initiative; WHS: Women Health Study.

*Deaths.

bNested case–control study within the RCGP OC cohort.
23 independent studies, 14 case–control and nine cohort studies (Appendix 1). The main characteristic of the 14 case–control studies (Weiss et al., 1981; Furner et al., 1989; Kune et al., 1990; Peters et al., 1990; Franceschi et al., 1991; Wu-Williams et al., 1991; Jacobs et al., 1994; Kampman et al., 1994; Fernandez et al., 1996, 1998; Kampman et al., 1997; Talamini et al., 1998; Levi et al., 2003; Nichols et al., 2005; Campbell et al., 2007) included in the meta-analysis are given in Table I. Corresponding information for the nine cohort investigations (Bostick et al., 1994; Martinez et al., 1997; Troisi et al., 1997; van Wayenburg et al., 2000; Vessey et al., 2003; Rosenblatt et al., 2004; Hannaford and Elliott, 2005; Hannaford et al., 2007; Lin et al., 2007; Kabat et al., 2008) are given in Table II. The Tables include the study reference, country and acronym; the number of cases/deaths by colorectal subsites; the number of controls (or cohort size and years of follow-up for cohort studies); the source of information (interview-administered questionnaire; self-reported; medical records); and the variables allowed for in the analyses information.

Figure 1 shows the RRs of colorectal cancer for ever versus never use of OCs as compared with never users in case–control and cohort studies.*Data not given. CI: confidence interval. NA: North America.

The main characteristic of the 14 case–control studies (Weiss et al., 1981; Furner et al., 1989; Kune et al., 1990; Peters et al., 1990; Franceschi et al., 1991; Wu-Williams et al., 1991; Jacobs et al., 1994; Kampman et al., 1994; Fernandez et al., 1996, 1998; Kampman et al., 1997; Talamini et al., 1998; Levi et al., 2003; Nichols et al., 2005; Campbell et al., 2007) included in the meta-analysis are given in Table I. Corresponding information for the nine cohort investigations (Bostick et al., 1994; Martinez et al., 1997; Troisi et al., 1997; van Wayenburg et al., 2000; Vessey et al., 2003; Rosenblatt et al., 2004; Hannaford and Elliott, 2005; Hannaford et al., 2007; Lin et al., 2007; Kabat et al., 2008) are given in Table II. The Tables include the study reference, country and acronym; the number of cases/deaths by colorectal subsites; the number of controls (or cohort size and years of follow-up for cohort studies); the source of information (interview-administered questionnaire; self-reported; medical records); and the variables allowed for in the analyses information.

Figure 1 shows the RRs of colorectal cancer for ever OC users as compared with never users in case–control and cohort studies, and overall. The summary RR from 11 case–control studies was 0.82 (95% CI, 0.69–0.97), with significant heterogeneity across studies ($\chi^2 = 111.6, \text{10 df, } P < 0.001$). This heterogeneity was largely explained by two earlier studies (Weiss et al., 1981; Kune et al., 1990), one of which included in the reference category OC users for $\leq 1$ year (Weiss et al., 1981). The summary RR from seven cohort studies was 0.81 (95% CI, 0.75–0.89), in the absence again of significant heterogeneity. Overall, the RR from all studies combined was 0.81 (95% CI, 0.72–0.92), with significant heterogeneity between studies ($\chi^2 = 116.9, \text{17 df, } P < 0.001$).

Considering colon cancer, the summary RR was 0.85 (95% CI, 0.75–0.96) from 10 case–control studies, 0.86 (95% CI, 0.77–0.95) from five cohort studies, and 0.85 (95% CI, 0.79–0.93) from all studies (Fig. 2). No significant heterogeneity across studies was observed.

For rectal cancer, the summary RR was 0.80 (95% CI, 0.57–1.13) from six case–control studies, 0.80 (95% CI, 0.66–0.96) from three cohort studies and 0.80 (95% CI, 0.70–0.92) from all studies, again in the absence of significant heterogeneity (Fig. 3).
1989; Wu-Williams et al., 1991) or which adjusted for age and a few selected covariates only (Weiss et al., 1981; Potter and McMichael, 1983; Jacobs et al., 1994; Troisi et al., 1997). Corresponding figures, were 0.82 (95% CI, 0.75–0.89) for colon and 0.82 (95% CI, 0.66–1.03) for rectal cancer (data not shown).

Table III shows the summary RR according to duration and recency of OC use. Twelve studies provided information on duration of use and colorectal cancer; their pooled RR was 0.88 (95% CI, 0.77–1.01) for short-term use, and 0.86 (95% CI, 0.74–1.00) for long-term use. No difference was evident according to duration of OC use for cancer of the colon (RR = 0.90 for short-term and 0.87 for long-term use, based on 10 studies) and of the rectum (RR = 0.94 for short-term and 0.99 for long-term use, based on six studies) (Table III). Corresponding RRs for duration of use <5 years or ≥5 years were 0.84 (95% CI, 0.75–0.94) and 0.83 (95% CI, 0.74–0.94) for colorectal cancer (based on seven studies) (data not shown). Only four studies provided information on recency of OC use and colorectal cancer risk, and the overall RR was 0.70 (95% CI, 0.53–0.90) for short time since last use and 0.87 (95% CI, 0.77–0.99) for long time since last use (Table III). The RRs were 0.51 (95% CI, 0.35–0.74) for <10 years since last use and 0.77 (95% CI, 0.60–0.99) for ≥10 years since last use (based on three studies) (data not shown).

**Discussion**

The present meta-analysis confirms that ever OC users have an approximate 20% reduction in colorectal cancer risk as compared with never OC users (Fernandez et al., 2001; IARC, 2007). The risk reduction is similar for colon and rectal cancer, and is consistently reported in case–control and cohort studies. However, longer duration of OC use is not associated with a greater reduction in risk, but there is a suggestion that the protection is stronger for more recent use.

Observational studies considered in this meta-analysis are prone to various sources of bias. However, differential underreporting of OC use by cases is unlikely in case–control studies, since the potential association between OC and colorectal cancer risk was unknown in most study populations and the results were similar in case–control and cohort studies. With reference to confounding, apart from a few earlier studies, most investigations provided multivariate analysis.
estimates, including allowance for socioeconomic factors, reproductive variables as well as other potential confounding factors for colorectal cancer. Exclusion from the analyses of a few studies which provided only crude estimates or estimates adjusted for a few covariates did not meaningfully modify the pooled estimates, thus ruling out a major effect of confounding factors. Scanty information was available on type of OC. No consistent pattern of trends was, however, observed across calendar year of use, which in most countries is a valid proxy of type of preparation, since first-generation OCs (used in the 1960s) were characterized by high estrogen levels, and subsequent generation OC (used since the early 1970s) had decreased levels of estrogens and progestins (IARC, 2007).

Publication bias is also possible, with selective reporting of favorable findings. Although we did not search for unpublished data, there was no evidence of significant asymmetry in the funnel plots, thus supporting the validity of our results (Egger et al., 1997; Thornton and Lee, 2000).

Various biological mechanisms for the protective effect of OCs on colorectal cancer have been suggested (Newcomb et al., 2008). Female hormones may reduce the synthesis and secretion of bile acids, which are considered carcinogenic on the colonic epithelium (McMichael and Potter, 1980, 1985). Estrogens inhibit colon carcinogenesis in animal models, and estrogen receptors α and β have been identified in normal and neoplastic colon epithelial cells (Campbell-Thompson et al., 2001; Di Leo et al., 2001). Estrogens may also reduce circulating levels of insulin-like growth factor-I (IGF-I) and IGF binding protein-3, in turn linked to an increased risk of colorectal cancer (Giovannucci, 2001). Moreover, estrogen-plus-progestin use has been related to a decrease in microsatellite instability (Newcomb et al., 2007). A regression of colorectal adenoma has also been shown in a case of familial adenomatosis polyposis after the administration of OCs (Giardiello et al., 2005). The protective role of OC on colorectal cancer is also consistent with the evidence of a protective role of hormonal replacement therapy (Chlebowski et al., 2004; La Vecchia et al., 2005; IARC, 2007). Moreover, the data from this meta-analysis are consistent with recent trends in colorectal cancer mortality in Europe (Bosetti et al., 2008), North America (Jemal et al., 2008) and Japan (Qiu et al., 2009) showing larger decreases in rates in women than in men (particularly in middle-age), and within Europe more favorable patterns in countries

**Figure 3** Summary RRs of rectal cancer for ever versus never use of OCs from case–control and cohort studies.
*Data not given. CI: confidence interval. NA: north America.
(such as the UK and other northern European countries) where OC had been used earlier and most widely (Levi et al., 2004).

The available epidemiological data thus consistently indicate that OC users have a reduced risk of colorectal cancer, and that the protection is greater for recent use in the absence, however, of a duration-risk relation. A better understanding of any potential relation between OC use and colorectal cancer may therefore help informed choice of contraception (IARC, 2007).

### Authors’ Role

C.B. supervised the work and wrote the manuscript; F.B. performed the analysis; E.N. revised the draft manuscript; C.L.V. had the original idea of the study and revised the draft manuscript.

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### References


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Appendix I
Flowchart of selection of studies for the meta-analysis.

57 Articles identified in MEDLINE

39 Articles excluded (title and/or abstract not relevant or not satisfying the inclusion criteria)

18 Articles identified for possible inclusion

11 Additional articles identified from the retrieved articles

29 Full-text articles considered for inclusion

6 articles excluded (duplicate report of the same study population)

23 independent studies included in the meta-analysis (14 case-control studies; 9 cohort studies)