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

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### CRD summary

This review concluded that women who had ever used oral contraceptives had a lower risk of colorectal cancer than those who have never used oral contraceptives. Given potential for bias in included studies, lack of a quality assessment and the relatively small number of women on which the primary analyses were based, the reliability of the conclusions is uncertain.

### Authors' objectives

To assess the relationship between oral contraceptive use and colorectal cancer risk.

### Searching

PubMed and EMBASE were searched for English-language papers to December 2008. Additional handsearching of reference lists was performed. Search terms were reported.

### Study selection

Case control and cohort studies that assessed an association between oral contraceptive used and colorectal cancer risk were considered for inclusion if studies provided information on oral contraceptive separately from other hormonal therapies. If multiple papers reported data on the same sample, only one paper was included.

Most studies used interview as the main source of information; self-report and medical records were also used. Most studies were conducted in North America and Western Europe. No patient characteristics, details of oral contraceptive regimens used or information on the stage of colorectal cancer identified were provided. Confounding factors adjusted for in each study were reported. All studies adjusted for age; other factors considered varied across studies.

Articles were selected independently by two reviewers. Disagreements between authors were resolved by consensus.

### Assessment of study quality

There was no assessment of study quality.

### Data extraction

Two reviewers independently extracted risk ratios (RRs) from cohort studies and odds ratios (OR) from case-control studies, with 95% confidence intervals (CI), for colorectal cancer, colon cancer and rectal cancer. Data for participants who had either ever used or never used oral contraceptives were extracted where such information was available.

### Methods of synthesis

Pooled risk ratios (for cohort studies) and pooled odds ratios (for case-control studies) and 95% CIs were calculated. Statistical heterogeneity was assessed using a  $X^2$  test ( $p < 0.10$ ) and if identified a random-effects rather than fixed-effect model was used. Risk ratios were used when both study types were combined. Studies were classified on duration of use (<five years and  $\geq$ five years) and recency (<10 years and  $\geq$ 10 years since last use), and pooled estimates were calculated for these. Sensitivity analysis was performed to assess the effect of studies that provided poorer estimates or did not control for many covariates on overall results. Publication bias was assessed using funnel plots and the Egger's test.

### Results of the review

Twenty four populations across 23 studies were included in the review: 14 case control ( $n=24,001$ , range 225 to 5,785); and nine cohort studies ( $n=652,810$ , range 10,671 to 267,400). Follow-up in the cohort studies ranged from four to 35 years. Fourteen studies reported colon cancers, eight reported rectal cancers and 18 reported colorectal cancers.

Never use versus ever use: Compared to never oral contraceptive users, ever users had a statistically significantly lower risk of colorectal cancer (RR 0.81, 95% CI 0.72 to 0.92; 18 studies), colon cancer (RR 0.85, 95% CI 0.79 to 0.93; 15

populations, 14 studies) and rectal cancer (RR 0.80, 95% CI 0.70 to 0.92; nine populations, eight studies). These findings were similar to those derived from case-control and cohort studies separately; results for rectal cancer from cohort studies was not statistically significant.

**Duration:** Studies that compared risks of these outcomes against duration of oral contraceptive use did not identify a statistically significant difference between those who used oral contraceptives for up to five years and those who used oral contraceptives for five years or longer.

**Recency:** Women who had last used oral contraceptive less than 10 years ago had a statistically significantly lower risk (RR 0.51, 95% CI 0.35 to 0.74) of developing colorectal cancer than women who had last used oral contraceptives 10 years or more ago (RR 0.77, 95% CI 0.60 to 0.99; three studies).

Heterogeneity was observed only for colorectal cancer assessed in case-control studies. There was no evidence of publication bias; results of the Egger's test were not reported. No results of the sensitivity analyses were reported.

### **Authors' conclusions**

The meta-analysis confirmed that women who had ever used oral contraceptives had approximately a 20% lower risk of colorectal cancer than those who had never used oral contraceptives.

### **CRD commentary**

The research question was clear and supported by broad (although relevant) inclusion criteria. More than one database was searched, as were reference lists in relevant publications. Only studies in English were included, which increased risk of language bias. There was no specific search for unpublished studies and publication bias could not be ruled out; the authors investigated this, but did not report all the results of the investigation. Selection of papers and data extraction were conducted in duplicate, which reduced risks of error and bias. Although the authors stated that odds ratios were extracted for case-control studies and risk ratios for cohort studies, risk ratios were reported for both study types. It was unclear whether risk ratios were calculated for all studies or whether odds ratio was assumed to be comparable to risk ratio and used as such; the latter assumption is only reliable for low-prevalence outcomes. There was a lack of study detail on population characteristics, oral contraceptive regimens and losses to follow-up (which may be of particular concern given the long follow-up period of some studies). Trial quality was not assessed and insufficient study details were provided for the reader to assess quality. Much of the evidence was from case control studies, which are prone to certain biases (particularly selection bias). Therefore, risk of bias within the studies cannot be ruled out. Although population sizes of many included studies were large, the primary analyses of ever-users and never-users of oral contraceptives seemed to be based on only a small proportion of the women. Given the limitations mentioned, the reliability of the conclusions is uncertain.

### **Implications of the review for practice and research**

The authors did not state any implications for practice and further research.

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