Cervical cancer and use of hormonal contraceptives: a systematic review

CRD summary
This review concluded that longer durations of hormonal contraceptive use are associated with an increased risk of developing invasive or in situ cervical cancer. However, despite concerns about the review methodology and the variability of the studies, the authors' cautious conclusions seem reasonable given the data presented.

Authors' objectives
To examine the association between the use and duration of use of hormonal contraceptives and the development of invasive and in situ cervical cancer, with particular attention to human papilloma virus (HPV) infection.

Searching
MEDLINE was searched from January 1966 to July 2002; the search terms were reported. In addition, references from retrieved articles were checked. No language restrictions were applied, but only published, peer-reviewed studies were included in the review.

Study selection
Study designs of evaluations included in the review
Cohort or case-control studies were eligible for inclusion. Cohort studies reporting a measure of HPV infection had to include a minimum of 50 cases of invasive carcinoma, in situ carcinoma or CIN grade 3; those that failed to report a measure of HPV infection had to include a minimum of 100 cases. Case-control studies had to include either 100 cases of invasive carcinoma or 200 cases of in situ carcinoma or CIN grade 3.

Specific interventions included in the review
Studies reporting on the duration and use of hormonal contraceptives were eligible for inclusion. Hormonal contraceptives included oral contraceptives, depot medroxyprogesterone acetate injectables, progestagen-only pills, or monthly combined injectables. The majority of studies failed to report the specific formulation and dose of hormonal contraceptive, so it was impossible to distinguish between combined and progestagen-only interventions.

Participants included in the review
Inclusion criteria were not defined in terms of the participants. The participants were women with and without invasive or in situ cervical cancer, who have or have not used hormonal contraceptives and who may or may not have an HPV infection.

Outcomes assessed in the review
Eligible studies had to report the incidence of invasive cervical cancer, carcinoma in situ, or cervical intraepithelial neoplasia (CIN) grade 3. The studies also had to include data on the number of participants and present age-adjusted or age-matched relative risks (RRs) or odds ratios and their corresponding 95% confidence intervals (CIs).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The data were extracted and double checked to reduce the risk of errors. The most fully adjusted RRs were extracted.
and used in the analysis. For studies with multiple data points for duration or time since last use, data were combined into one data point using the generalised least-squares method, taking correlations between the two RRs into account. Similarly, studies where the results were reported separately for squamous and adenocarcinomas data were combined to give one data point. Where the data were reported separately for HPV-positive and -negative individuals, both sets of data were extracted.

Methods of synthesis
How were the studies combined?
The results were presented graphically, stratified according to duration of contraceptive use. Pooled RRs with 95% CIs were calculated according to the method of empirically weighted least-squares.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Analyses were carried out according to study design, duration of hormonal contraceptive use, time since last use, and adjustment for one or more specified potential confounding factors.

Results of the review
Twenty-eight studies (12,531 women with in situ or invasive cancer) were included in the review: 4 cohort studies and 24 case-control studies.

Oral contraceptive use was associated with an increased risk of cervical cancer compared with never users of oral contraceptives, and the risk increased with duration of use: the RR was 1.1 (95% CI: 1.1, 1.2) for less than 5 years’ use, 1.6 (95% CI: 1.4, 1.7) for 5 to 9 years’ use, and 2.2 (95% CI: 1.9, 2.4) for 10 years or more use. Within each of these groups the estimates of RR were consistently higher for cohort studies than for case-control studies.

When only HPV-positive women were assessed the corresponding RRs were similar: 0.9 (95% CI: 0.7, 1.2), 1.3 (95% CI: 1.0, 1.9) and 2.5 (95% CI: 1.6, 3.9). Similar RRs were also observed for invasive and in situ cancers, for squamous and adenocarcinoma, and for studies adjusted for HPV status, number of sexual partners, cervical screening, smoking and use of barrier contraceptives. For medium- and long-term users (at least 5 years), the risks were lower for women who had ceased oral contraceptive use at least 8 years ago (RR 1.4, 95% CI: 1.1, 1.9) than those who ceased less than 8 years ago (RR 2.1, 95% CI: 1.8, 2.4); similar but smaller effects were found for short-term users (less than 5 years). A number of the comparisons showed evidence of heterogeneity.

Additional data and figures are available on the Lancet website, but a journal subscription is required to access this information.

Authors’ conclusions
Limited data suggest that longer durations of hormonal contraceptive use are associated with an increased risk of developing cervical cancer.

CRD commentary
This review assessed a clear research question and searched a limited number of literature sources. Unpublished data and non-peer-reviewed studies were excluded from the review, suggesting that publication bias might affected the findings. Study validity was not assessed and it was unclear how studies were selected for inclusion in the review, although two reviewers double checked the extraction of data; it was therefore difficult to assess the reliability of the review methods.

There was evidence of both clinical and statistical heterogeneity between the studies, which questions the reliability of the effect sizes. The authors did, however, try to investigate the effects of several potential sources of heterogeneity, but the reliability of these findings is unclear given the statistical heterogeneity observed and the possibility that relevant data were missed. In addition, 10 large studies were excluded as they did not provide age-adjusted data and/or
information about the duration of use. The authors also commented that other relevant information was often missing from the included studies. Overall, despite the concerns about the review methodology and the heterogeneity between the studies, the reviewers’ cautious conclusions seem reasonable.

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

Practice: The authors stated that the public health implications of the findings are dependent on the long-term effects and these could not be properly evaluated from the published data.

Research: The authors stated that a 'collaborative re-analysis of individual data from all relevant studies' is required in order to provide reliable information about the effects of duration on the risk of developing cervical cancer within the different categories of time since last use.

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