Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23257 women with ovarian cancer and 87303 controls
Beral V, Doll R, Hermon C, Peto R, Reeves G

CRD summary
The authors concluded that the use of oral contraception provides long-term protection against ovarian cancer, with longer use associated with a greater reduction in risk. The review was well conducted and these conclusions are likely to be reliable.

Authors' objectives
To investigate the relationship between the use of oral contraceptives and the subsequent risk of ovarian cancer.

Searching
MEDLINE, PubMed and EMBASE were searched to January 2006. Review articles and colleagues were also consulted to identify additional relevant studies. A writing group, a steering committee and a collaborative group were established: the principal investigators from each eligible study were invited to join the collaborative group.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from epidemiological studies, provided they included at least 100 cases (prospective studies) or 40 cases (cohort studies) of ovarian cancer.

Specific interventions included in the review
Epidemiological studies that included data on oral contraceptive use were eligible for inclusion. The mean duration of oral contraceptive use in the included studies was 4.4 years in women with ovarian cancer and 5 years in controls. The mean time since ceasing use was 18.6 years in cases. Calendar year of use was taken as a proxy for dose, with pre-1970, 1970 to 1979 and post-1980 taken as corresponding to high-, medium- and low-dose preparations, respectively. The authors stated that over 95% of contraceptives would have been combined oestrogen-progestagen preparations.

Participants included in the review
Eligible studies included women with malignant epithelial or non-epithelial ovarian cancer (cases) and women without ovarian cancer who had not undergone bilateral oophorectomy (controls), for whom recorded information on reproductive history and use of oral contraceptives was available.

Outcomes assessed in the review
Studies that evaluated the risk of ovarian cancer were eligible for inclusion in the review.

How were decisions on the relevance of primary studies made?
The relevance of the primary studies was established through contact with the principal investigators.

Assessment of study quality
Data provided by the primary investigators were collated and checked centrally, and any inconsistencies were corrected, where possible, by correspondence with the investigators. Investigators were sent data to be used in analyses for final confirmation. Studies were excluded if the primary investigators could not retrieve IPD or if the investigators could not be located.

Data extraction
IPD sought from principal investigators included: ovarian cancer, reproductive history, use of oral contraceptives, sociodemographic factors, reproductive and menstrual history, use of hormonal therapies for the menopause, height, weight, family history of breast and ovarian cancer, and use of alcohol and tobacco. Tumour histology was classified as non-epithelial and epithelial. Epithelial tumours were further subcategorised as borderline malignant or malignant.
Cohort studies were incorporated using a nested case-control design, with up to four randomly selected controls matched for follow-up duration, age and (if appropriate) location.

**Methods of synthesis**

How were the studies combined?

The Mantel-Haenszel method was used to calculate and combine odds ratios and associated variances. The analyses were stratified by study, study centre, age, parity and hysterectomy status. The odds ratios and relative risks (RRs) obtained were applied to published data on age-specific incidence and mortality rates for ovarian cancer, and used to calculate the public health effect of contraceptives.

How were differences between studies investigated?

Differences in treatment effects between studies were investigated by grouping studies in the meta-analysis according to study design and by the type of controls used (population versus hospital). Statistical heterogeneity was evaluated using the chi-squared test.

**Results of the review**

IPD from 45 studies were included: 13 prospective cohorts (7,726 cases and 32,201 controls) and 32 case-control studies (15,531 cases and 55,102 controls).

Women who had ever used oral contraceptives were significantly less likely to develop ovarian cancer than women who had never used oral contraceptives (RR 0.73, 95% confidence interval, CI: 0.70, 0.76, p<0.001). The longer they had used oral contraceptives, the lower their risk. The overall risk of ovarian cancer decreased by 20% (95% CI: 18, 23, p<0.0001) for each 5 years of use of oral contraceptives. This estimate was altered by less than 1% after adjusting for ethnicity, education, age at first birth, family history of breast cancer, age at menarche, menopausal status, use of hormone replacement therapy, height, weight, body mass index, use of alcohol or smoking, or all of these combined.

Reduced risk persisted but was attenuated over time. Proportional risk reductions per 5 years of use were 29% (95% CI: 23, 34) for use that had ceased less than 10 years previously, 19% (95% CI: 14, 24) for use that had ceased 10 to 19 years previously, and 15% (95% CI: 9, 21) for use that had ceased 20 to 29 years previously.

There was no evidence of a differential effect according to whether contraceptive use took place in the 1960s, 1970s or 1980s, even though the oestrogen dose had decreased substantially over time. Nor did the proportional risk reduction vary among different histological types (other than for mucinous tumours, for which incidence was little affected by oral contraceptive use).

The authors estimated that in high-income countries, 10 years' use of oral contraceptives would reduce the risk of ovarian cancer before the age of 75 years from 1.2 per 100 users to 0.8 and mortality from 0.7 to 0.5, compared with never-users.

Data from three published studies were not available. The authors estimated that data from these studies would have increased the cases by only another 3%, that their results did not differ from those reported and, consequently, that inclusion would not have materially altered the overall findings of the review.

**Authors' conclusions**

Oral contraception provides long-term protection against ovarian cancer, with longer use associated with greater reduction in risk.

**CRD commentary**

The objective of the review was clear and relevant sources and strategies were used in the literature search. A collaborative group of trial investigators was established to maximise the retrieval of IPD, thus enabling the accuracy of the data to be checked and the use of standard definitions across studies (as far as possible). Unavailable data are unlikely to have affected the findings. The data analysis and investigation of heterogeneity appear appropriate. The review was well conducted and the conclusions are likely to be reliable.
Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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