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## Hormone replacement therapy and ovarian cancer risk: a meta-analysis

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### CRD summary

The authors concluded that hormone replacement therapy could increase the risk of ovarian cancer. Although these conclusions reflected the results of the review, the possibility of missed studies, publication bias, lack of randomised trials and the unclear quality of included studies suggest the findings should be interpreted with caution.

### Authors' objectives

To assess the effects of hormone replacement therapy (HRT) on ovarian cancer risk.

### Searching

PubMed was searched from inception to May 2007; search terms were reported. Bibliographies of retrieved articles and previous meta-analyses were handsearched for additional studies.

### Study selection

Prospective or case-controlled studies that reported HRT use and presented data on ovarian cancer incidence in at least two groups as either relative risks (RR) or odds ratios (OR) or reported data from which these measures could be calculated were eligible for inclusion. The two groups had to be defined as patients who had ever used HRT and those who had never used HRT.

Included studies assessed oestrogen replacement therapy (ERT) and oestrogen-progestin replacement therapy (EPRT); most studies did not specify the type of HRT. Where stated, ages of patients ranged from 18 to 89 years of age. More than half of the included studies were undertaken in USA; other studies were conducted in Canada, Mexico, Australia, Greece, Italy, Sweden, Norway and UK.

Two authors independently selected studies for inclusion in the review.

### Assessment of study quality

The authors did not state that they assessed validity.

### Data extraction

Two authors independently extracted relative risks (RR) and 95% confidence intervals (CI) for cohort studies and odds ratios (OR) and 95% CI for case-control studies. Where studies reported relative risks for current and former users, data were combined to give a relative risk for ever users. Covariates that were controlled for in the analysis were extracted.

### Methods of synthesis

Relative risks, odds ratios and 95% CI were pooled in a random-effects meta-analysis (DerSimonian and Laird) weighted by inverse variance. The main analyses were stratified by study type and by current/former or ever HRT use. Statistical heterogeneity was assessed using  $Q$  and  $I^2$  statistics.

A sensitivity analysis was used for case-control studies to explore heterogeneity using stepwise omission of studies. Subgroup analyses were performed to take account of type of control subjects, type and duration of hormone use. Publication bias was assessed using Egger's regression test.

### Results of the review

Eight cohort (4,715 cases and 1,555,374 participants) and 19 case-control studies (8,240 cases and 20,996 controls) were included. Significant publication bias was evident for the case-control studies.

**Cohort studies:** There was a significantly increased risk of ovarian cancer for women who had ever used HRT

compared with those who had never used HRT (RR 1.24, 95% CI 1.15 to 1.34,  $I^2=0\%$ ; eight studies). There was a significantly increased risk of ovarian cancer among women with current hormone use compared with those who had never used HRT (RR 1.28, 95% CI 1.15 to 1.42  $I^2=14.5\%$ ; five studies). There was a significantly increased risk of ovarian cancer among current users of more than five years (RR 1.47, 95% CI 1.12 to 1.92,  $I^2=66\%$ ; three studies) compared with those of less than five years. A stronger risk of ovarian cancer was observed for ERT users (RR 1.51, 95% CI 1.21 to 1.88,  $I^2=0\%$ ; four studies) than for EPRT users (RR 1.24, 95% CI 1.00 to 1.54,  $I^2=0\%$ ; four studies).

**Case-control studies:** Women who were current or former users of HRT (ever used) had a significantly increased risk of ovarian cancer than those who had never used HRT (OR 1.19, 95% CI 1.02 to 1.40,  $I^2=78\%$ ; 19 studies). An increased risk of ovarian cancer was observed for ERT users (OR 1.19, 95% CI 1.01 to 1.40,  $I^2=0\%$ ; six studies) than for EPRT users.

There was no significantly increased risk of ovarian cancer associated with different durations of HRT use (less than five years, five to 10 years and more than 10 years). When population-based controls were analysed there was an increased risk (RR 1.17, 95% CI 1.01 to 1.35,  $I^2=44\%$ ; eight studies), but this was not significant for hospital-based controls (11 studies).

### Authors' conclusions

HRT use was associated with increased risk of ovarian cancer. These findings may expand the range of possible risks associated with HRT use. However, this positive association should be considered in the context of favorable effects on health from HRT.

### CRD commentary

The review question and the inclusion criteria were clear. The authors undertook a limited search. It was unclear whether language restrictions were applied and there was no search for unpublished studies. Language bias may have been present and some studies may have been missed. There was some evidence of publication bias for the case-control studies. Study selection and data extraction were carried out with sufficient attempts to minimise error and bias. Absence of any formal quality assessment of included trials limited interpretation of the reliability of the findings. It appeared that appropriate methods were used to pool the trials. Reasonable measures were used to assess and explore heterogeneity between studies.

The authors' conclusions reflected the results of the review, but the possibility of bias, lack of randomised trials and the unclear quality of included studies suggest the findings should be interpreted with caution.

### Implications of the review for practice and research

**Practice:** The authors stated that women who were considering hormone therapy should consider their own risk factors and preferences before making a decision.

**Research:** The authors stated that further further studies were required to clarify whether longer HRT use was associated with an increased risk of ovarian cancer.

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