Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin

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CRD summary
The authors concluded that estrogen therapy use increased ovarian cancer in a duration-dependent manner; adding progestins appeared to reduce this effect to some extent. The conclusions appeared to be supported by the evidence but the limited search, lack of reporting of review methods and study quality, and reliance upon predominantly observational studies mean that findings should be interpreted with caution.

Authors' objectives
To examine the relationship between oestrogen-only and oestrogen plus progestin menopausal hormone therapy and the risk of ovarian cancer.

Searching
PubMed was searched through to December 2007 for studies published in English. Search terms were reported. Reference lists were screened and addition studies were traced through the 'related articles' link.

Study selection
Randomised controlled trials (RCTs), cohort studies and population-based case control studies of oestrogen-only and oestrogen plus progestin hormone therapy were eligible for inclusion, if they restricted analysis to invasive epithelial ovarian cancers or combined invasive and borderline epithelial ovarian cancers. Studies had to report data separately for oestrogen-only and oestrogen plus progestin hormone therapy and to report the duration of hormone use. Three studies conducted in the early 1980's when sequential oestrogen plus progestin hormone use was just starting that did not report data separately were included and data assumed to apply to oestrogen-only therapy. Studies that used hospital controls were excluded.

Most studies were conducted in North America; others were set in Europe and Australia. Controls were obtained from national survey populations, population or electoral registries and random digit dialling. Cancer ascertainment were mostly obtained from cancer registries or death certificates. Where reported, studies included patients with invasive and low malignant potential ovarian cancer. Data were obtained using in-person interviews or self-administered questionnaires. The duration of hormone use ranged from one to over 20 years.

The authors did not state how 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
For each study, adjusted relative risks with 95% confidence intervals were extracted in relation to duration of oestrogen-only and oestrogen plus progestin hormone therapy use. Risk estimates of ovarian cancer per year of hormone use were extracted or estimated (methods were reported). In the review, data for duration of use of less than one year were combined with never used data.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks per five years of hormone use and 95% confidence intervals were calculated using fixed-effect and random-effects models. Differences between oestrogen-only and oestrogen plus progestin menopausal hormone therapy
use in ovarian cancer risk were compared within the ten studies that provided data for both types of hormone therapy; pooled weighted differences in RR5 were calculated. Heterogeneity was apparently assessed but methods were not reported. The influence of menopause type was discussed. Publication bias was assessed using funnel plots.

Results of the review
Fourteen studies were included (n was unclear but more than 1,419,833 participants). These included one RCT (n=16,608), five cohort studies (n=1,384,941) and eight population-based case control studies (n at least 13,345).

The authors stated that all studies adjusted for appropriate potential confounders in their analysis. Results were similar for fixed-effect and random-effects models. Results from only fixed-effect models were presented.

Oestrogen-only and oestrogen plus progestin hormone therapy: The risk of ovarian cancer was significantly increased among oestrogen-only users (relative risk per five years of hormone use 1.22, 95% confidence interval (CI): 1.18 to 1.27; 13 studies) and oestrogen plus progestin hormone therapy users (relative risk per five years of hormone use 1.10, 95% CI: 1.04 to 1.16; 11 studies). There was no evidence of heterogeneity or publication bias for either analysis.

Oestrogen-only versus oestrogen plus progestin hormone therapy: The risk of ovarian cancer was significantly higher among oestrogen-only compared to oestrogen plus progestin users (p=0.004; 10 studies). Results were similar for the five studies in which duration of use was similar for both types of hormone oestrogen plus progestin therapy (p=0.011).

Authors’ conclusions
Oestrogen use increased the risk of ovarian cancer in a duration-dependent manner and it appeared that adding progestins reduced this effect to some extent.

CRD commentary
The review question was stated and appropriate inclusion criteria were defined. Limiting the search to English language published studies identified in one database plus references and linked articles may have resulted in the omission of other relevant studies and raised the potential for publication and language bias. However, no evidence of publication bias was found. Methods used to select studies and extract data were not described, so it is not known whether efforts were made to reduce reviewer errors and bias. Study validity was not assessed, so results from these studies and any synthesis may not be reliable.

Other than duration of oestrogen-only therapy/oestrogen plus progestin therapy use, no information was provided about participants. No information was provided about which potential confounders were adjusted for in individual studies. Data were pooled using meta-analysis and heterogeneity was assessed. Studies were predominantly observational and adjustments were made for potential confounders. The authors’ conclusions appeared to be supported by the evidence, but the limited search, lack of reporting of review methods and study quality, and reliance upon predominantly observational studies mean that findings should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is required to determine the association between hormone therapy use and histological subtypes of ovarian cancer and stage of disease and the effects of past and current hormone therapy use.

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Bibliographic details