Authors' objectives
To determine if use of postmenopausal hormone replacement therapy (HRT) increases the risk of invasive epithelial ovarian carcinoma.

Searching
MEDLINE was searched for English language articles published between January 1966 and June 1997 using the following MeSH terms: ovarian neoplasms; estrogen replacement therapy; estrogens; hormone replacement therapy; post menopausal estrogens; post-menopausal hormones; non-contraceptive hormones; non-contraceptive estrogens; and the textword term ovarian cancer. Bibliographies of relevant articles were searched and experts were consulted. Only English language articles were included.

Study selection
Study designs of evaluations included in the review
Studies that examined the association between the use of postmenopausal estrogen and the risk of ovarian cancer were included if they met the following eligibility criteria: cases were age matched to controls or results were age adjusted. Hospital-based and population-based case-control studies and cohort studies were included. Reasons were given for exclusion of identified studies.

Specific interventions included in the review
HRT including unopposed estrogens and combination estrogen plus progestin therapy was studied. Where stated, duration of use ranged from less than one year to more than ten years.

Participants included in the review
Postmenopausal women were studied. Women with bilateral salpingo-oophorectomy were excluded.

Outcomes assessed in the review
The incidence of invasive and borderline ovarian carcinoma were assessed.

How were decisions on the relevance of primary studies made?
One author reviewed all identified studies to select studies examining the association between HRT use and the development of ovarian cancer. Eligible studies were then examined by two unblinded reviewers to determine eligibility according to pre-established eligibility criteria. Where necessary, authors were contacted for additional information to determine eligibility for inclusion.

Assessment of study quality
No formal assessment of validity was undertaken.

Data extraction
The following data were extracted: type of study; source of controls; years of enrolment; adjusted covariates; tumour histology; hormone use; duration of hormone use; and the odds ratio (OR) or relative risk (RR) and 95% confidence intervals by duration of use. Two independent blinded reviewers extracted the data.

Methods of synthesis
How were the studies combined?
Summary RRs and 95% CI were calculated using a fixed-effect model.
How were differences between studies investigated?
Studies were stratified by whether they included patients with invasive ovarian cancer, borderline ovarian tumours or both. Studies were grouped according to source of control (hospital or population based) and summary RR estimated for each group. Ovarian cancer risk associated with duration of use was evaluated by estimating the RR for the following categories: ever use of HRT for < 1 year; 1 to 5 years; 6 to 10 years; and > 10 years. When two or more risk estimates were available for the same category, a summary risk estimate was calculated for that category. All summary estimated were tested for statistical heterogeneity with P ≤ 0.10 being regarded as statistically significant. Potential sources of heterogeneity were investigated by sequentially removing one study at a time and recalculating the summary estimate. Summary estimates were calculated with and without studies enrolling patients with borderline malignancies.

Results of the review
Ten studies (9 case-control studies and one cohort study) of invasive epithelial ovarian cancer (256257 cases), 1 case control study of invasive and borderline cancers (1684 patients) and 1 case control study with borderline cancers only (2882 patients) were included.

Overall (10 studies): Ever use of HRT was associated with an increased risk of developing invasive epithelial ovarian cancer. RR = 1.15 (95% CI: 1.05, 1.27). Significant heterogeneity was present (P = 0.08). Removal of either one of three studies resulted in homogeneous results (P > 0.10) with little effect on the pooled RR. Inclusion of studies with invasive or borderline carcinoma produced similar results with RR = 1.14 (95% CI: 1.04, 1.24). Heterogeneity was not significant (P > 0.10). Considering only case-control studies and grouping studies by source of control group did not substantially alter the results.

Use of HRT for more than 10 years was associated with the greatest risk of ovarian cancer, but the increased risk did not reach statistical significance. No trend on increasing risk with increased duration of use was observed. Duration > 10 years (6 studies): RR = 1.14 (95% CI: 1.04, 1.24). Significant heterogeneity was found (P = 0.05). After exclusion of either of two studies heterogeneity was no longer present. Inclusion of studies with invasive or borderline carcinoma did not substantially alter the results.

Duration < 1 year (4 studies): RR = 1.12 (95% CI: 0.92, 1.36).

Duration 1 to 5 years (6 studies): RR = 0.95 (95% CI: 0.79, 1.14).

Duration 6 to 10 years (6 studies): RR = 1.02 (95% CI: 0.81, 1.29).

No statistical evidence for heterogeneity.

Due to insufficient data it was not possible to calculate either the effect of different doses of hormone therapy or the risk of ovarian cancer in women who had discontinued use of HRT to see if risk of invasive ovarian cancer returns to baseline.

Authors' conclusions
Prolonged use of hormone therapy by post-menopausal women may be associated with an increased risk of developing epithelial carcinoma of the ovary.

CRD commentary
The aims and inclusion criteria were stated. Relevant information on the primary studies was presented in tabular format. Results were clearly presented. Statistical heterogeneity was assessed and investigation of this heterogeneity undertaken. The discussion included consideration of potential causes of unexplained heterogeneity and discusses the following limitations of the review: summary findings were based on the results of a limited number of published studies and may be susceptible to publication bias; none of the included studies was a randomised controlled trial and confounding may have been introduced into the results due to differences between users and nonusers; and surveillance bias may have affected individual study results. The authors point out that there was not enough
epidemiological evidence to infer causality since a statistically significant trend of increasing ovarian cancer risk with duration of use was not found.

By limiting the literature search to English language studies identified in one database, other relevant studies may have been omitted. Validity of included studies was not formally assessed.

The authors' conclusions were supported by the evidence.

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

Practice: The authors consider that women should understand the impact of HRT on osteoporosis, cardiovascular disease, and cancers of the breast, endometrium and ovary so they can weigh their own risk factors and preferences and arrive at a personal decision about taking postmenopausal hormones.

Research: The authors do not report any research implications.

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**Bibliographic details**


**PubMedID**

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**Other publications of related interest**

This additional commentary may also be of interest. Thacker HL. Review: postmenopausal hormone replacement therapy is associated with increased invasive ovarian cancer, especially after long-term use. ACP J Club 1999;130:23.

**Indexing Status**

Subject indexing assigned by NLM

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