Hormone therapy and risk of lung cancer: a meta-analysis

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CRD summary
This review concluded that, although there was no significant association between the overall use of hormone therapy and lung cancer risk, further research was needed to confirm the results. The authors’ conclusion about the need for further research is suitably cautious and reliable.

Authors' objectives
To examine the association between the use of hormone therapy and the risk of lung cancer.

Searching
PubMed, EMBASE, and The Cochrane Library were searched from inception up to April 2008; search terms were reported. Reference lists from relevant articles were checked. Only articles written in English were included.

Study selection
Case-control and cohort studies that reported on an association between hormone therapy use and lung cancer risk were eligible for inclusion. Studies were excluded if there was insufficient data, data on mortality only, or where standardised incidence ratios were reported.

In included studies, oestrogen only and oestrogen plus progesterone were the most commonly used hormone replacement therapy, although a variety of others were used. Comparators included women who were not using or had never used hormone replacement therapy. Duration of treatment was not reported in most of the studies. The range of enrolment periods was from 1969 to 2006. The mean age of included women was 51 years (range 18 to older than 76 years, where reported). All studies adjusted for smoking, all but one study adjusted for age, and other studies varied on the type and number of other adjustments made (details reported in the paper). Over half of the studies were conducted in North America.

Two reviewers independently selected studies for inclusion in the review. Disagreements were resolved by consensus or consultation with a third reviewer.

Assessment of study quality
The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale; an eight-item scale subdivided into three main areas: selection of the study groups (four items), ascertainment of either the exposure or outcome of interest (three items), and the comparability of the groups (one item). A maximum score of 9 was possible; high quality was defined as a score of 6 or more.

The authors did not state how many reviewers were involved in the assessment of study quality.

Data extraction
Odds ratios and relative risks with associated 95% confidence intervals were extracted. Where additional information was required, attempts were made to contact the authors of the primary studies.

Data extraction was conducted in duplicate.

Methods of synthesis
Pooled relative risks and odds ratios with 95% confidence intervals were calculated using a fixed-effect model (inverse variance method); if significant statistical heterogeneity was found, a random-effects model (DerSimonian and Laird) was used. Statistical heterogeneity was investigated using $I^2$; substantial heterogeneity was defined as $I^2$ of 50% or higher). Adjusted data were used whenever possible. Cumulative meta-analyses were performed.

Planned subgroup and sensitivity analyses were conducted according to type of hormone therapy, duration of hormone therapy, status of hormone use, smoking status, histology of lung cancer, study design, and study quality.
Begg's funnel plot and the Egger's test were used to investigate publication bias.

**Results of the review**

Eleven studies were included in the review (220,599 women) comprising eight case-control and three cohort studies. The mean Newcastle-Ottawa Scale score for quality was 5.7 (range 4 to 8). All three cohort studies and three case-control studies were considered to be of high methodological quality.

When all eleven studies were combined, the use of hormone therapy was not statistically significantly associated with risk of lung cancer (OR 0.87, 95% CI 0.74 to 1.02; \( I^2 = 68\% \)). There was no evidence of publication bias.

When study design was taken into account, a statistically significant reduction in lung cancer risk was found with hormone therapy (RR 0.81, 95% CI 0.68 to 0.97; \( I^2 = 55\% \)) in case-control studies, but no statistically significant association was found in the cohort studies. There was evidence of substantial heterogeneity in both subgroups.

Results of subgroup and sensitivity analyses and the cumulative analyses were also reported.

**Authors' conclusions**

Although no significant association was found between the use of hormone therapy and lung cancer risk, further research was needed to confirm these results given the potential bias of low-quality case-control studies included in the review.

**CRD commentary**

The review question was supported by clearly defined inclusion criteria. Several relevant databases were searched. Although only articles written in English were included, English abstracts of a number of foreign language papers were searched, which reduced the potential for language bias. No specific search for grey literature was undertaken. Methods used to select studies and extract data were likely to have minimised the possibility of error and bias; it was not clear whether similar steps were taken in the assessment of study quality.

Study quality was assessed using a standardised tool; full details were reported. Given the substantial clinical heterogeneity across the studies, the use of a fixed-effect model was questionable. Substantial statistical heterogeneity was found in a number of the analyses, and only a small number of studies contributed to the results of many of the analyses performed. Some of this heterogeneity may be explained by the fact that studies adjusted for different numbers and type of modifying variables, which impacted on the overall reliability of the pooled estimates.

The authors' conclusion about the need for further research is suitably cautious and reliable.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further prospective cohort studies were needed to evaluate the association between use of hormone therapy and lung cancer risk.

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