Menopausal hormone therapy and risk of lung cancer: systematic review and meta-analysis

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CRD summary
This review found that ever use of hormone therapy in non-smoking women may increase the risk of adenocarcinoma of the lung and that oestrogen/progestin therapy increased the risk of lung cancer. The first of these conclusions was based on two non-RCT studies of unknown size and quality. The reliability of the conclusions is unclear.

Authors' objectives
To investigate whether menopausal hormone therapy is related to increasing lung cancer rates in women.

Searching
MEDLINE, CANCERLIT, EMBASE, Scopus and The Cochrane Library were searched from inception to July 2008. Search terms were reported. Bibliographies of retrieved trials, relevant systematic reviews and previous systematic searches on similar topics were searched for additional studies. Editorials, supplements, books, abstract books and proceedings of major menopause meetings were searched from 2003 to 2008. No language restrictions were applied. Studies published as abstracts were eligible only if they reported sufficient statistical data.

Study selection
Cohort studies, case-control studies, cancer registry studies and randomised controlled trials (RCTs) that assessed the association between ever use of any type of hormone therapy and lung cancer were eligible for inclusion. Studies had to report risk of lung cancer by duration of use, or increase of risk within a given time interval for oestrogen replacement therapy, oestrogen/progestin therapy, or hormone therapy.

Included studies were conducted in USA, Italy, UK, Germany, Taiwan, Canada, Japan, Sweden and Finland. Most studies did not provide data on smoking status or discriminate between different histological diagnoses.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
US Preventive Services Task Force criteria were used to assess study quality. It appeared that quality assessment was performed independently by multiple reviewers and disagreements resolved through consensus (exact details were lacking).

Data extraction
Two reviewers independently extracted data to calculate risk ratios (RR) together with 95% confidence intervals (CIs). Disagreements were resolved through consensus.

Methods of synthesis
Summary risk ratios and 95% CIs were estimated using a fixed-effect model based on the general-variance method. Slopes for both individual studies and summary slopes were estimated using inverse variance-weighted least squares estimate to estimate summary slopes of increase of risk per year of use. Heterogeneity was assessed using $Q$ and $I^2$ statistics. All analyses were stratified according to type of hormone therapy and lung cancer subtype.

Results of the review
Eighteen studies were included in the review: three RCTs, six cohort studies, one nested case-control study and eight case-control studies.

Ever use of hormone therapy (17 studies):

Ever use of hormone therapy (any type) was associated with a significant decrease in the risk of all subtypes of lung cancer (RR 0.80, 95% CI 0.72 to 0.89; eight studies). When analysis was stratified according to type of cancer there
was no association between hormone therapy and adenocarcinoma (four studies), small cell carcinoma (three studies) and squamous carcinoma (two studies). There was an increased risk of non-small cell carcinoma (RR 0.71, 95% CI 0.61 to 0.82; four studies). There was no evidence of heterogeneity ($I^2=0\%$) for any of these analyses.

When the analysis was restricted to non-smokers (seven studies) or to smokers (six studies) there was no association between hormone therapy and all subtypes of lung cancer. However, there was an increased risk of adenocarcinoma in non-smoking women (RR 1.76, 95% CI 1.07 to 2.90; two studies). Use of oestrogen therapy and all subtypes of lung cancer was associated with a decreased risk of lung cancer (RR 0.73, 95% CI 0.61 to 0.87; three studies). Use of oestrogen/progestin therapy was not associated with lung cancer risk for all studies combined (five studies), but was associated with an increased risk when the analysis was restricted to the two RCTs (RR 1.36, 95% CI 1.03 to 1.79).

### Duration of use of hormone therapy (four studies):

Two studies that reported data for all subtypes of lung cancer combined reported a small but significant decrease of risk (4.7% per year of hormone therapy use). There was no significant difference in risk for three studies that assessed adenocarcinoma. Stratification based on smoking status did not provide significant findings.

### Authors’ conclusions

Ever use of hormone therapy in non-smoking women may increase the risk of adenocarcinoma of the lung. Data from RCTs suggest that oestrogen/progestin therapy increases the risk of lung cancer.

### CRD commentary

The review addressed a focused question and inclusion criteria were clearly defined. Extensive literature searches were conducted and these included attempts to identify unpublished studies. Appropriate steps were taken to minimise bias and errors at all stages of the review process. Study quality was reported to have been assessed, but the exact items considered and results of the quality assessment were not reported and so the reliability of the included studies remained unclear. Very few details of the included studies (such as sample size and participant details) were reported, which made it difficult to determine the generalisability of the review findings. Data were pooled from studies that used different designs; the appropriateness of this was questionable. Only one of the analyses was reported separately for RCTs and the results from these studies were in the opposite direction to those from studies of other designs.

The authors’ primary conclusions were based on two non-RCT studies of unknown size and quality. The reliability of their conclusions is unclear.

### Implications of the review for practice and research

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

**Research:** The authors stated that dedicated studies designed to more adequately delineate the role of menopausal hormone therapy were necessary to substantiate whether use of such therapy was a risk factor for adenocarcinoma or other types of lung cancer.

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### Bibliographic details


### PubMedID

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.