Menopausal hormone therapy (HT) in patients with breast cancer

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CRD summary
This review examined the effects of menopausal hormone therapy on cancer reoccurrence, cancer mortality and overall mortality in patients with breast cancer. The authors concluded that hormone therapy is not associated with an increased incidence of these outcomes. However, the reliability of this conclusion is limited by combining the results from studies of varying design.

Authors’ objectives
To assess the effect of menopausal hormone therapy (HT) on cancer reoccurrence, cancer-related mortality and overall mortality in patients with a diagnosis of breast cancer.

Searching
MEDLINE, CINAHL and HealthSTAR were searched from 1967 to 2001; the search terms were given. In addition, existing reviews were used to identify references and conference proceedings were handsearched. Pharmaceutical companies and experts in the field were contacted for ongoing trials. Non-English language reports were eligible.

Study selection

Study designs of evaluations included in the review
Controlled and uncontrolled studies were eligible for inclusion. Both prospective and retrospective studies were included in the review. The weighted mean duration of follow-up was 86 months (range: 26.4 to 228).

Specific interventions included in the review
Studies of HT for the treatment of menopausal symptoms were included in the review. The included studies used conjugated oestrogen (0.625 mg), transdermal oestradiol (0.05 mg patch), oral 17-beta-estradiol (1 mg) or estrified oestrogen (0.625 mg). All but one study also used progestins. The weighted average duration of treatment was 34 months (range of averages: 14.6 to 76.8).

Participants included in the review
Studies of patients with a diagnosis of breast cancer were eligible for inclusion. The mean age of the patients included in the review was 51 years. Most (68%) of the included patients were defined as being at low risk (node-negative on TNM staging system or stage 0 or 1 on Manchester system) for cancer reoccurrence, and 63% of those with known hormone (either oestrogen or progesterone) receptor status were hormone receptor-positive.

Outcomes assessed in the review
Studies that assessed cancer reoccurrence, cancer-related mortality and overall mortality were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the studies for relevance.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data. Authors were contacted where there was a possibility of multiple publications of the same study being included. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the controlled studies.
Methods of synthesis
How were the studies combined?
The proportion of hormone therapy-treated patients experiencing each outcome was calculated, along with 95% CIs, for all studies combined. The controlled studies were combined in a meta-analysis using the Mantel-Haenszel fixed-effect method to calculate pooled ORs for each outcome.

How were differences between studies investigated?
Controlled studies were combined in a separate analysis, in addition to being included in the analysis of all studies. The authors stated that they performed a heterogeneity test for the controlled studies, but no further details were provided.

Results of the review
Fifteen studies with 3,414 patients were included in the review. Seven studies were controlled (n=2,438) and eight were uncontrolled (n=976).

Cancer reoccurrence.
After approximately 7 years' follow-up, cancer reoccurrence occurred in 10% (95% CI: 8.4, 11.6) of HT patients (based on all studies).

When the controlled studies were pooled, patients on HT had a decreased risk of cancer reoccurrence in comparison with the control groups (OR 0.5, 95% CI: 0.2, 0.7). No statistically significant heterogeneity was found.

Cancer mortality.
After approximately 7 years' follow-up, cancer mortality occurred in 2.6% (95% CI: 1.8, 3.7) of HT patients (based on all studies).

When the controlled studies were pooled, patients on HT had a decreased risk of cancer mortality in comparison with the control groups (OR 0.3, 95% CI: 0.0, 0.6). No statistically significant heterogeneity was found.

All-cause mortality.
After approximately 7 years' follow-up, all-cause mortality was 4.5% (95% CI: 3.4, 5.8) of HT patients (based on all studies).

Statistically significant heterogeneity was found for the meta-analysis using data from controlled studies.

Authors' conclusions
The use of menopausal HT was not associated with increased cancer reoccurrence, cancer-related mortality or total mortality in patients with a diagnosis of breast cancer.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched a number of relevant sources to identify studies and took steps to identify unpublished trials, thereby reducing the likelihood of publication bias in the review. Appropriate methods were used to minimise error and bias in the study selection and data extraction processes. However, the validity of the primary studies was not assessed, which means that the quality of the evidence included in the review was not taken into consideration. In addition, it was not clear whether the controlled studies were randomised or had concurrent or historical controls.

The appropriateness of pooling controlled studies of variable design is questionable. Where non-randomised studies are included in a meta-analysis, an overestimate of a treatment effect can be obtained if, for example, patients with a better prognosis are allocated to the active treatment. There was no exploration of statistically significant heterogeneity where
this was found. For the above reasons, the results of the statistical pooling in this review should be considered with some caution, as should the conclusions based upon these results.

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

Practice: The authors stated that, while other treatments should be considered first, HT options should be reviewed for the subset of breast cancer survivors with refractory menopausal symptoms affecting their quality of life. They also stated that patients contemplating HT should be aware of the known risk and benefits of HT and the potential risks of breast cancer outcomes. The authors also stated that HT would not be recommended for patients taking aromatase inhibitors since its use had not been studied in these patients.

Research: The authors stated that future trials should focus on methods of safely distinguishing breast cancer survivors who may benefit from HT from those at substantial risk of reoccurrence.

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