Hormone replacement therapy and the sensitivity and specificity of breast cancer screening:

a review

Banks E

Authors' objectives
To investigate the relationship between use of hormone replacement therapy (HRT) and the risk of having breast cancer diagnosed between screenings (interval cancer) (sensitivity of screening) and the risk of false positive recall for screening following initial mammographic screening for breast cancer (specificity of screening).

Searching
MEDLINE and the Science Citation Index were searched up to 31 January 2000, with no language restrictions. No details of the search strategy were provided. The reference lists of identified papers were scanned and relevant (unspecified) journals were handsearched.

Study selection
Study designs of evaluations included in the review
Epidemiological studies were eligible for inclusion. Further details were not provided.

Specific interventions included in the review
Studies of mammographic breast cancer screening were eligible for inclusion.

Reference standard test against which the new test was compared
No inclusion criteria relating to the reference standard for diagnosis were specified. The diagnosis of breast cancer was taken as that presented within each study. The included studies defined breast cancer as invasive breast cancer only, or invasive breast cancer and ductal carcinoma in situ. All the studies related to cancers occurring within one year of screening, except for one study that covered a 2-year period.

Participants included in the review
The women included in the review were users and non-users of HRT who had received mammographic screening. Non-users of HRT included women who had never used HRT, as well as previous users of HRT.

Outcomes assessed in the review
Studies reporting the risk of interval breast cancer or risk of false positive recall were eligible for inclusion. The outcome measures calculated in the review were the sensitivity and specificity. Sensitivity was defined as the proportion of interval cancers among the total number of breast cancers detected at screening (interval plus screen-detected cancers). Specificity was defined as the proportion of women without breast cancer who had a false positive screen (during interval or at screening) among the total number of women without breast cancer (false positives and true negatives).

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

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

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
The data extracted included age of the participants, the number of screen-detected cancers and interval cancers in users and non-users of HRT, and the number of false positive recalls. Only data from women aged 50 years and older were extracted. Where possible, 1-year interval data were extracted. Crude relative proportions for the first and following round of screening were calculated where the results were presented separately for each screening round. These were combined as a weighted average to provide an overall relative proportion adjusted for screening round. For one study, the figures for sensitivity were used to back calculate crude data for the age group and interval of interest.

**Methods of synthesis**

How were the studies combined?
A narrative synthesis of the studies was undertaken. For each study, the relative proportion (RP) and 95% confidence interval (CI) of interval cancers and false positive recall were estimated for current users of HRT versus never users or current non-users of HRT.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the method of empirically weighted least-squares. Differences between the studies were also discussed in the narrative synthesis.

**Results of the review**

Seven epidemiological studies of 938 detected interval cancers were included in the review.

**Sensitivity.**

There were 367 interval cancers in women aged 50 years and older. The RP of interval cancers in HRT users versus never users or non-users ranged from 0.4 to 5.2 in the individual studies. In six of the 7 studies, the sensitivity of mammographic screening was lower in current users of HRT and the risk of interval cancer, compared with screen-detected cancer, was greater in this group than in never and non-users of HRT. There was statistically significant heterogeneity in this group of studies (P<0.05). The data were not adjusted for potential confounding factors such as age, menopause and time since menopause.

**Specificity.**

There were 8,878 cases of false positive recall in women aged 50 years and older. False positive recalls ranged from 2.1 to 14.7% in the individual studies. In three of the 5 studies reporting false positive recall, the rate was statistically significantly higher in current users of HRT compared with never users and non-users of HRT. There was no evidence of statistical heterogeneity (P>0.1). Most of the studies did not adjust for relevant potential confounding factors.

**Authors’ conclusions**

The sensitivity and specificity of breast cancer screening is more likely to be reduced for women using HRT than for women not using HRT. The magnitude of these effects is uncertain, as the results were not adjusted for important confounding factors.

**CRD commentary**

The review addressed an explicit research question, which was clearly defined by the inclusion criteria. Only two databases were searched and specific attempts to identify unpublished studies were not made. Consequently, studies might have been missed. In addition, although there were no language restrictions, there is a risk of publication bias. The study selection and data extraction processes do not appear to have been carried out in duplicate or checked by a second reviewer, thus introducing the risk of error and bias. Relevant details of the individual studies were given. However, more information on the HRT treatment, if available, would have aided the assessment of clinical heterogeneity. A systematic quality assessment was not carried out, though there was some discussion of study quality in the narrative synthesis. It was appropriate not to statistically pool the data. The author’s conclusions are suitably cautious given the limitations of the data.
Implications of the review for practice and research

Practice: The author stated that the evidence does not form an adequate basis for changes in screening policy.

Research: The author stated that good-quality research on the effect of HRT on risk of interval cancer and false positive recall is required. Future studies should have an adequate number of cases, control for confounding factors, investigate the effect of duration, dose and type of HRT, as well as how recently it was used. Methods offering improved detection of breast cancer in women currently using HRT need to be developed.

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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.