CRD summary
The review concluded that external beam radiation therapy to the breast was associated with a statistically significantly lower axillary recurrence rate after negative sentinel lymph node biopsy. The review was based on observational studies of uncertain quality, which makes the reliability of the authors' conclusion unclear.

Authors' objectives
To determine the efficacy of external beam radiation therapy to the breast on the risk of axillary recurrence after negative sentinel lymph node biopsy.

Searching
PubMed, DARE, the Cochrane Library, and LILACS were searched without language restriction. Search terms were reported, but not search dates. References from selected articles were also checked.

Study selection
Prospective or retrospective cohort studies that reported follow-up data of patients with clinically node-negative breast carcinoma were eligible for inclusion. Eligible patients had undergone sentinel lymph node biopsy but had not received additional axillary treatment (surgical and/or external beam radiation therapy as part of initial treatment of the axilla). Studies were required to clearly report the initial local treatment of the breast cancer, including type of surgery and use of external beam radiation therapy. Patients with well-documented additional axillary treatment were excluded, as were studies where it was not clear whether additional treatment had been given. Adjuvant treatment (chemotherapy or hormone therapy) was not subject to review and did not form part of the inclusion/exclusion criteria.

The primary outcome was axillary recurrence, defined as the detection of metastatic disease in the axilla (without evidence of ipsilateral breast recurrence) after negative sentinel lymph node biopsy.

Over 80% of included patients received external beam radiation therapy (range 46.4% to 100%). Most patients receiving external beam radiation therapy did so as part of breast conserving treatment. One study reported the use of intraoperative radiotherapy in a subgroup of patients who had breast-conserving treatment.

Two reviewers independently selected studies for inclusion in the review and any disagreements were resolved through discussion.

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

Data extraction
Numbers of patients with axillary recurrence, as well as the number of patients with and without external beam radiation therapy, were extracted from each study. Efforts were made to contact the authors of the primary studies where additional information was required.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Where possible, studies were pooled in a meta-analysis using the hypergeometric-normal model to summarise the influence of external beam radiation therapy on axillary recurrence rate.

Subgroup analyses were performed to identify possible sources of heterogeneity for the percentage of patients treated...
with external beam radiation therapy (80%, 80 to 90%, and over 90%) and the length of follow-up (less than 24 months, 24 to 60 months, over 60 months). A L’Abbe plot was presented for effect of external beam radiation therapy to the breast on axillary recurrence rate.

Exploratory analyses on the influence of other therapies (chemotherapy and hormone therapy) on axillary recurrence were also performed.

**Results of the review**

Forty-five studies were included in the review (n=23,357 patients; 18,878 treated with external beam radiation therapy). Thirty studies reported on individual patients with axillary recurrence; these were included in the L’Abbe plot. Median follow-up ranged from 15 to 102 months.

Axillary recurrence after negative sentinel lymph node biopsy was identified in 127 patients (0.5%), of whom 73 had received external beam radiation therapy as part of their initial treatment. The median interval between sentinel lymph node biopsy and detection of axillary recurrence was 22 months (73 patients).

Of patients that received adjuvant therapy (2,286 chemotherapy and 3,197 hormone treatment), 28 developed axillary recurrence (including eight on chemotherapy and 14 on hormone therapy).

In pooled analysis, external beam radiation therapy was associated with a lower rate of axillary recurrence including intraoperative radiotherapy as external beam radiation therapy (OR 0.32, 95% CI 0.17 to 0.59), and excluding intraoperative radiotherapy as external beam radiation therapy (OR 0.29, 95% CI 0.16 to 0.55). Heterogeneity was found (variation between studies was 72%), but this was not statistically significant (p=0.33).

In a subgroup analysis based on length of follow-up, a clear effect on axillary recurrence was found for patients treated with external beam radiation therapy to the breast after 60 months (five studies) without evidence of statistical heterogeneity; significant heterogeneity was found for all other groups.

**Authors’ conclusions**

External beam radiation therapy to the breast was associated with a significantly lower axillary recurrence rate after negative sentinel lymph node biopsy.

**CRD commentary**

The review question was supported by clear inclusion criteria. Several relevant databases were searched with no language restrictions, although no attempts were made to search grey literature, so some studies may have been missed. Appropriate steps were taken to minimise error and bias at study selection, but it was not clear whether similar procedures were taken for data extraction.

The quality of the studies was not formally assessed. Not all trials appear to be represented in the L’Abbe and the symbols should indicate the weight of the trials. The observational design of the included studies precludes determining a cause between external beam radiation therapy and risk reduction in axillary recurrence.

The reliance on observational studies and the uncertain quality of these studies makes the reliability of the authors’ conclusion unclear.

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

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

**Research:** The authors stated that before considering possible changes in breast cancer treatment in sentinel lymph node-negative patients in order to prevent axillary recurrence, the impact of axillary recurrence on survival needs to be established. Multicentre trials with long-term follow-up of a large cohort of axillary recurrences are required. The authors also indicated that type of radiation therapy including radiation fields and doses, surgical technique, and tumour characteristics should be considered.
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Record Status
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.