Authors' objectives
To evaluate the role of taxanes for the management of breast cancer.

Searching
Cancerlit and MEDLINE were searched. Additional material was sought in bibliographies of the published trials and from the author's personal notes. Published trials and reports that were presented at scientific meetings were eligible for inclusion. No details were given of the dates searched or the keywords used.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Studies evaluating taxanes were eligible. The included studies examined the following regimens:

- paclitaxel (135 to 250 mg/m2), given as an infusion over time periods ranging from 3 to 96 hours;
- cyclophosphamide, methotrexate, 5-fluorouracil and prednisone combination;
- doxorubicin alone;
- paclitaxel plus doxorubicin;
- 5-fluorouracil, doxorubicin and cyclophosphamide combination;
- paclitaxel plus trastuzumab;
- doxorubicin plus docetaxel;
- doxorubicin plus cyclophosphamide;
- mitomycin plus vinblastine;
- methotrexate plus 5-fluorouracil; and
- 5-fluorouracil plus vinorelbine.

The regimens were used as second-line therapy, neoadjuvant therapy, and adjuvant therapy. Cointerventions included surgery (mastectomy, lumpectomy and axillary dissection), local irradiation, and filgrastim for infection or neutropenia.

Participants included in the review
Women with early or advanced breast cancer were eligible. The participants included women with the following: metastatic breast cancer; metastatic and locally advanced breast cancer; clinical stage II-III disease and operable breast cancer; anthracycline-resistant breast cancer; metastatic breast cancer that overexpressed the HER2/neu protein. Women who had failed prior alkylator-based therapy were also included.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of the outcomes. Survival and incidence of grade 3 or 4 toxicity were
assessed for all studies. For trials of women with metastatic or locally advanced disease, the additional outcomes assessed were response rate, median time to disease progression, and quality of life (if performed). For studies involving adjuvant or neoadjuvant therapy, response rate (for neoadjuvant only) and disease-free survival were assessed. Primary studies evaluated the following outcomes: median time to progression; median survival; tumour response; progression-free interval; visceral metastases; resistant disease; toxicity; and quality of life. The latter was assessed using the EORTC QLQ-C30 tool, the Rotterdam Symptoms Check List, and global health scores.

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

Assessment of study quality
The primary studies were restricted to RCTs. The statistical power to achieve the primary objective of the individual study was assessed. The author does not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following information were tabulated: author; sample size; details of the intervention; and median survival and median time to progression per treatment arm.

Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken with studies grouped according to the following characteristics of the participants and interventions: dose and schedule of paclitaxel and docetaxel for advanced cancer; first-line therapy for metastatic breast cancer; second-line therapy; neoadjuvant therapy; and adjuvant therapy.

How were differences between studies investigated?
Some differences between the studies were discussed in the text. Summarising the studies was complicated by the diversity of the interventions, with no two studies comparing similar regimens in patients with similar characteristics. Only studies supporting the author's conclusions are reported below.

Results of the review
Eighteen RCTs (9,032 women) were included.

Optimal dose of paclitaxel for metastatic breast cancer (5 RCTs, 2,208 patients).

The RCTs compared different doses and different regimens. The most favourable therapeutic index was obtained using 175 mg/m² of paclitaxel, administered as an intravenous infusion over 3 hours every 3 weeks. Higher doses or longer infusion periods were associated with greater toxicity without a clear survival benefit.

3-hour versus 24-hour infusion of paclitaxel (2 RCTs).

One RCT involving 563 patients with stage III B or stage IV breast cancer compared 3- and 24-hour infusions of paclitaxel (250 mg/m²). After 4 cycles, the 24-hour infusion produced a significantly higher response rate (51 versus 41%), similar median progression-free survival (7.2 versus 6.3 months), and similar median overall survival (21.9 versus 21.1 months). Grade 4 toxicity was more common in the 24-hour infusion arm (23 versus 12%). The other RCT (521 patients) found no difference in response rates (29 versus 31%) between the 24- and 3-hour infusions (175 mg/m²). However, it did find a statistically-significant increase for the 24-hour infusion in median time to progression (4.6 versus 3.8 months; p=0.021) and for median survival (13.4 versus 9.8 months; p=0.021). The 24-hour infusion was
associated with significantly more grade 4 neutropenia, mucositis, and any diarrhoea. The 3-hour infusion was associated with significantly more neuropathy.

3-hour versus 96-hour infusion of paclitaxel (1 RCT, 179 patients).

The single RCT found no significant difference between the treatment arms.

Doses of 175 versus 135 mg/m² paclitaxel over 3 hours (1 RCT, 471 patients).

Increased toxicity (grade 3 to 4 leucopenia, neuropathy, febrile neutropenia, grade 3 myalgia or arthralgia) was found in the higher dose arm. However, there was no significant difference between the treatment arms in terms of the overall response rate (29 versus 22%) or median survival (11.7 versus 10.5 months). The quality of life-adjusted time to progression analysis favoured the higher dose (175 mg/m²) arm. Doses of 175 versus 210 versus 250 mg/m² paclitaxel over 3 hours (1 RCT, 474 patients).

There was no significant difference between the treatment arms in terms of the response rates: the response rates were 22, 26 and 21% for doses of 175, 210 and 250 mg/m², respectively. The 175 mg/m² arm was associated with significantly less grade 4 granulocytopenia, grade 3 sensory neuropathy, grade 3 motor neuropathy and grade 3 myalgias, than the other regimens.

Taxanes as first-line therapy for metastatic disease (7 RCTs, 2,479 patients).

The response rates across the treatment arms ranged from 15 to 68%, and the median time to progression ranged from 4.1 to 8.7 months.

The addition of trastuzumab to paclitaxel resulted in improved survival in women with metastatic breast cancer that overexpressed the HER2/neu protein. The single RCT (178 patients) reported a significant increase in response rate (38 versus 15%), median time to progression (6.7 versus 2.5 months), and median response duration (8.3 versus 4.3 months) in the combination therapy arm. The following adverse reactions were significantly more common in the combination arm: cardiac dysfunction, fever, chills, abdominal pain, infection, nausea, diarrhoea, cough, rhinitis, sinusitis and rash. Quality of life was not assessed.

Taxanes as second-line therapy (3 RCTs, 850 patients).

The response rates across the treatment arms ranged from 12.1 to 42.1%, and the median time to progression ranged from 2.6 to 6.0 months.

Two RCTs looked at the effect of using docetaxel (100 mg/m²) as second-line therapy for anthracycline-resistant disease. One RCT (392 patients) found statistical improvements in the response rate (30 versus 12%; p<0.05), median time to progression (4.4 versus 2.6 months; p<0.05) and median survival (11.4 versus 8.7 months; p<0.05), when docetaxel was compared with mitomycin plus vinblastine. There was no difference in the global health scores between the treatment arms. Docetaxel was associated with more grade 3 to 4 neutropenia, infection, stomatitis, skin rash, nail disorders, diarrhoea, asthenia, and neurosensory toxicity.

The other RCT (283 patients, 199 included in the analysis) found statistical improvements in the response rate (42 versus 19%; p<0.05) and median time to progression (6.0 versus 3.0 months; p<0.05), when docetaxel was compared with methotrexate plus 5-fluorouracil. Docetaxel was associated with greater rates of leucopenia, infection, asthenia, fluid retention, nail toxicity, and neuropathy.

Another RCT (175 patients) found no significant difference between docetaxel and a combination of vinorelbine and 5-fluorouracil

Early-stage breast cancer.

One RCT (3,121 patients) found that, compared with 4 cycles of doxorubicin, 4 cycles of doxorubicin followed by 4 cycles of paclitaxel increased the disease-free survival at 2 years (90 versus 86%; p<0.05) and improved the survival in
women with axillary-node positive breast cancer.

**Authors' conclusions**
Taxanes improved survival in patients with early-stage breast cancer and selected patients with metastatic breast cancer.

**CRD commentary**
The aims were stated, and the inclusion criteria were defined in terms of the study design, interventions, and participants. Two relevant databases were searched and unpublished trials were eligible for inclusion. However, no details were given of the keywords used or the dates searched, and it was not reported whether any language restrictions were applied.

The methods used to select the studies were not reported. The included studies were limited to RCTs, but no subsequent formal validity assessment was undertaken. Some relevant data were tabulated, with additional material provided in the text of the review. However, the methods used to extract the data were not described. A narrative review was appropriate given the differences between the studies in terms of the participants and interventions.

The review was limited by the following: the lack of detail relating to the methodology of the review process; the lack of a formal validity assessment of the included studies; insufficient definition of the outcome measures; the evidence of specific regimens tended to be based on one trial; and the difficulty in combining the studies, due to the diversity of the regimens compared in different patient populations. These limitations should be taken into account when considering the author's conclusions.

**Implications of the review for practice and research**
Practice: The author states that the most favourable therapeutic index was obtained using 175 mg/m² paclitaxel given as a 3-hour infusion every 3 weeks, and docetaxel (60 to 100 mg/m²) given as a 1-hour infusion every 3 weeks. The author also states that improved survival was associated with the following: 4 cycles of paclitaxel (175 mg/m² every 3 weeks) following 4 cycles of conventional doxorubicin-cyclophosphamide for axillary-node positive operable breast cancer; trastuzumab added to paclitaxel as first-line therapy for metastatic breast cancer that overexpressed HER2/neu; and docetaxel given as second-line therapy for anthracycline-resistant disease.

Research: The author states that further research is needed to identify the efficacy of docetaxel compared with paclitaxel; the optimal dose of docetaxel; the role of weekly taxane therapy; the role of trastuzumab plus taxanes in early disease; and whether taxanes are more effective when given concomitantly or sequentially in patients with early-stage disease.

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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.