Chemotherapy-induced cognitive impairment in women with breast cancer: a critique of the literature

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CRD summary
This review investigated chemotherapy-induced cognitive impairment in women with breast cancer. The authors concluded that although the data suggest that chemotherapy-induced cognitive impairments occur, the evidence is limited and further studies are required. The authors’ cautious conclusions seem appropriate. However, it is unclear whether the same results would have been obtained had a more comprehensive search strategy been used.

Authors’ objectives
To review the evidence for chemotherapy-induced cognitive impairments in women with breast cancer.

Searching
PubMed was searched from 1966 to June 2004 for studies published in the English language. The reference lists of identified studies were checked for further relevant articles. Details of the search strategy were not reported.

Study selection
Study designs of evaluations included in the review
No inclusion criteria for study design were specified.

Specific interventions included in the review
Studies of chemotherapy were eligible for inclusion. The chemotherapy regimens included were: cyclophosphamide, methotrexate and 5-fluorouracil (CMF); cyclophosphamide, doxorubicin and 5-fluorouracil (CAF); doxorubicin and cyclophosphamide; cyclophosphamide, epirubicin and 5-fluorouracil; 5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC); FEC plus cyclophosphamide, thiotepa and carboplatin; and CMF plus CAF.

Some participants received tamoxifen. Of those who had previously received chemotherapy, 205 had received standard-dose chemotherapy and 34 had received high-dose chemotherapy.

Participants included in the review
Studies of women with breast cancer were eligible for inclusion. The participants included in the review were either breast cancer survivors who had completed chemotherapy 6.5 to 10 years previously, or women currently receiving chemotherapy for breast cancer. Most of the studies included control participants, some of whom were women with breast cancer who had only received surgery or radiotherapy, and some of whom were healthy women. The mean age of all participants ranged from approximately 42 to 60 years. One study compared survivors who had previously received chemotherapy with those currently receiving chemotherapy without a separate control group.

Outcomes assessed in the review
Outcomes relating to cognitive function were eligible for inclusion. The outcomes included in the review incorporated 43 different tests and sub-tests (details reported). Each neuropsychological test used was assigned to one specific cognitive domain: attention and concentration, executive function, information processing speed, language, motor function, visuospatial skill, verbal memory or visual memory.

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

Assessment of study quality
The authors stated that each study was critiqued in terms of design and methodologic issues. However, no specific
criteria for this assessment were stated.

The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

**Data extraction**

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Where available, the age and educational level of participants was recorded as this can affect performance in cognitive tests. Baseline differences in participant characteristics between the study groups were also recorded.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a narrative which discussed the findings according to the eight identified cognitive domains.

How were differences between studies investigated?
Differences between the studies were described in the data tables and discussed within the text of the review.

**Results of the review**

Nine studies (n=720) were included in the review: one uncontrolled longitudinal study and 8 cross-sectional studies, three of which were prospective and five retrospective.

The authors reported methodological limitations in all of the studies. Problems with selection bias and confounding were of particular concern.

Studies of survivors (8 studies).

Three out of 7 studies found a significant impairment in attention; 3 of 6 studies found a significant impairment in executive function; 5 of 6 studies found a significant impairment in speed of information processing; 3 of 6 studies found a significant impairment in language; 5 of 7 studies found a significant impairment in motor function; 2 of 7 studies found a significant impairment in visuospatial skill; 3 of 7 studies found a significant impairment in verbal memory; and 4 of 6 studies found a significant impairment in visual memory.

Studies of patients receiving chemotherapy (3 studies).

None of the 3 studies found a significant impairment in attention, executive function or motor function. The one study that assessed speed of processing and visual memory found no significant impairment. Two of 3 studies found a significant impairment in language, one of 3 studies found a significant impairment in visuospatial skill, and one of 3 studies found a significant impairment in verbal memory.

**Authors' conclusions**

Although the data suggested that chemotherapy-induced impairments in cognitive function do occur in some women with breast cancer, differences in time since treatment, chemotherapy regimen, menopausal status and neuropsychological tests limit comparisons amongst the various studies. Further studies need to be conducted before definitive conclusions can be made.

**CRD commentary**

The authors set out a clear objective and this was supported by broad inclusion criteria. No inclusion criteria for study design were stated. Only one electronic database was searched and studies were limited to those published in English; this suggests that relevant studies might have been missed. Publication bias was not assessed. It was unclear whether the authors took appropriate measures to minimise bias in the study selection and data extraction processes. Although the
authors commented on the methodological quality of the studies, no specific assessment criteria were stated and the process did not appear to have been systematic.

Details of the studies were clearly presented. The narrative synthesis was appropriate given the considerable differences between studies in terms of the participants, interventions, outcome measures and study designs. The authors’ cautious conclusions seem appropriate given the limitations of the data presented. However, it is not clear whether the same results would have been obtained had a more comprehensive search strategy and more systematic review methods been used.

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

**Practice:** The authors stated that the potential effects of chemotherapy on cognitive therapy may influence the patients’ ability to give informed consent, identify treatment toxicities, learn self-care measures and perform self-care behaviours. They also stated that such effects have an influence on a patient’s experience of treatment and their return to normal life after treatment.

**Research:** The authors stated that the use of conceptual models or theoretical frameworks would help identify variables that explain or predict relationships between chemotherapy, clinical and patient characteristics, and cognitive impairment. They stated that the use of qualitative research methods would improve the understanding and complexity of patients’ experiences with cognitive impairments. In addition, further research to identify which tests are most reliable, sensitive and specific for detecting chemotherapy-induced cognitive deficits is needed. The authors suggested that instruments with a demonstrable ability to detect deficits should be used, but where instruments that possess sufficient sensitivity or specificity have not been identified, multiple measures may be used. The authors also stated that additional research is needed to confirm the hypothesis that chemotherapy-induced deficits decrease over time.

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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.