Radiation-induced cardiac toxicity after therapy for breast cancer: interaction between treatment era and follow-up duration
Demirci S, Nam J, Hubbs J L, Nguyen T, Marks L B

CRD summary
In this review, the authors concluded that radiotherapy in the treatment of breast cancer was associated with long-term increases in cardiac morbidity and mortality. There was insufficient information provided about the conduct of the review and the quality of the included studies to assess the accuracy and reliability of the authors' conclusions.

Authors' objectives
To assess the interaction between treatment era and follow-up duration on the reported effect of radiotherapy on cardiac events in patients treated for breast cancer.

Searching
The database MEDLINE was searched to December 2007 to locate relevant English-language studies; search terms were reported. Reference lists of retrieved articles were also searched.

Study selection
Randomised controlled trials (RCTs) evaluating patients treated with radiotherapy for breast cancer and subsequent treatment-related cardiac morbidity and mortality, were eligible for inclusion. Studies were excluded from the review if they: were published as abstracts only; failed to provide adequate information on the numbers of patients irradiated; failed to report cardiac toxicity in clearly designated risk units (hazard ratio, relative risk, odds ratio, incidence ratio and risk ratio); evaluated cardiac toxicity by the analysis of radiographic changes (for example, by single photon emission computed tomography or magnetic resonance imaging).

RCTs, cancer registry database studies, and institutional reviews were included. Cardiac toxicity was assessed by comparing patients who had received radiotherapy to those who had not; patients who received radiotherapy for left-sided breast cancer compared to patients who received radiotherapy for right-sided breast cancer; and evaluations of both of the other comparisons. Varying definitions of cardiac toxicity and different cardiac endpoints were reported including overall cardiac mortality/morbidity and specific cardiac diseases (myocardial infarction, ischaemic heart disease, cardiovascular disease and valvular heart disease).

Two reviewers independently and collaboratively reviewed the abstracts and selected the full text articles for inclusion in the review.

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

Data extraction
Data were collected from trials that reported cardiac toxicity risk in clear designated risk units (hazard ratio, relative risk, odds ratio, incidence ratio and risk ratio). Where median follow-up duration was not specifically reported, the reviewers estimated follow-up durations using other information provided in each study. To examine the relationships between the treatment era, duration of follow-up and the risk of cardiac morbidity or mortality, the authors compared the trials by the following groupings: commencing before or after 1980, and with follow-up duration less than or greater then 10 years.

The reviewers did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Simple and weighted means of the risk unit data were extracted from the studies and compared with the independent samples t-test. These results were presented in a narrative summary. The reported risks and their relationship to the commencement date of radiotherapy and follow-up duration were also presented graphically.

**Results of the review**

Nineteen published reports comprising five randomised controlled trials (RCTs, n= 6,806 patients), nine cancer registry database studies (n=460,890 patients) and five single-and multi-institutional trials (n= 15,146 patients) were included. The years of radiotherapy treatment commencement ranged from 1968 to 2002, with a median follow-up of 4.6 to 20 years.

**Cardiac mortality:**

There were statistically significant differences in the relative risk of cardiac mortality between trials that commenced before 1980 (simple mean 1.47, weighted mean 1.28; p<0.001, 10 trials) and those commencing during or after 1980 (simple mean 1.40, weighted mean 1.30; p<0.001, three trials).

There were statistically significant increases in the relative risk of cardiac mortality observed where the median follow-up was more than 10 years (simple mean 1.62, weighted mean 1.42; p<0.001, nine trials) compared to the relative risk in which median follow-up was less than 10 years (simple mean 1.00, weighted mean 1.16, p<0.001, four trials).

For the comparison of trials commencing prior to 1980 with those beginning after 1980 with less than 10 years of follow-up, there were no statistically significant reductions in the relative risk of cardiac mortality over time. When trials of different eras (pre- or post-1980) with more than 10 years of follow-up were compared, there was no appreciable reduction observed in the relative risk of cardiac mortality. Only one study commenced after 1980 with more than 10 years of follow-up.

**Cardiac morbidity:**

There were statistically significant differences in the relative risk of cardiac mortality between trials that commenced before 1980 (simple mean 1.7, weighted mean 1.63; p=0.007, four trials) and trials commencing during or after 1980 (simple mean 1.13, weighted mean 1.05; p<0.001, six trials).

The relative risk of cardiac morbidity was significantly higher in the trials with a median follow-up of greater than 10 years (simple mean 1.17, weighted mean 1.54; p<0.001, five trials) compared to the trials with less than 10 years follow-up (simple mean 0.90, weighted mean 1.02, p<0.001, five trials).

For the comparison of studies with less than 10 years of follow-up that commenced either before or after 1980, there was no apparent increase in relative risk. All the trials with more than 10 years of follow-up reported high cardiac morbidity relative risks, but there was limited data from the studies commencing during or after 1980.

**Authors' conclusions**

Radiotherapy in the treatment of breast cancer was associated with long-term increases in cardiac morbidity and mortality. Although modern techniques may have decreased this risk, the long term safety of this treatment for breast cancer is uncertain.

**CRD commentary**

The review addressed a clear question and the criteria for including studies in the review were stipulated. The literature search was confined to published English-language studies, and there were no attempts to identify unpublished studies; so relevant studies may have been missed and language and publication bias cannot be ruled out. The steps taken to minimise errors and bias appeared to be applied in the selection of studies, but not for further aspects of the review process. There were some discrepancies in the inclusion criteria pertaining to eligible study designs and the studies actually included in the review. Some studies were excluded because of difficulty in extracting the results, which may lead to bias. The statistical comparisons conducted by the reviewers did not appear to be fully reported, which may lead to bias in interpreting the results. The relative risks for a number of differing cardiac conditions across a variety of study types were combined, which may not have been appropriate. The uncertain quality of the included studies,
missing data, and the conduct of the review, makes it difficult to draw any conclusions from the evidence presented, and the reliability of the authors' conclusions is unclear.

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

**Practice:** The authors stated that for patients being treated with radiotherapy for breast cancer, it remains important to minimise cardiac exposure during treatment.

**Research:** The authors stated that longer term follow-up of modern methods of radiation treatment is necessary, to determine the risk of cardiac morbidity and mortality after treatment.

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