CRD summary
This review assessed the long-term risk of cardiovascular disease after radiotherapy for childhood cancer. The authors concluded that cardiovascular mortality is increased after irradiation, but the risks of clinical cardiovascular events are unclear and further research is required. The well-described methodological limitations of the included studies weaken the strength of the evidence but support the need for further research.

Authors' objectives
To determine the long-term risk of cardiovascular disease (CVD) after radiotherapy for childhood cancer.

Searching
MEDLINE (from 1966 to October 2002) and EMBASE (from 1980 to October 2002) were searched for studies reported in English, Dutch, French or German; the search terms were reported. The reference lists of all relevant reports and reviews were checked.

Study selection
Study designs of evaluations included in the review
Studies of any design were eligible for inclusion if they included more than 50 children. For cohort studies, either the entire cohort or part of the original cohort (selected using well-defined criteria) could be included. The included studies followed up patients for between 1 and 29 years.

Specific interventions included in the review
Studies of radiotherapy involving the heart region were eligible for inclusion. The included studies used chest, spinal radiation and abdominal radiation that included the heart region. Most of the included studies reported cointervention with potentially cardiotoxic anthracyclines; the proportion of children treated with anthracyclines ranged from 4 to 100%.

Participants included in the review
Studies that included children (aged 18 years or younger) treated for childhood cancers were eligible for inclusion. The included studies were in children with paediatric Hodgkin lymphoma, Wilm's tumour and various tumours. Most of the included studies followed up children from the start of treatment; others were in survivors of childhood cancer who entered the study at a fixed point after the treatment started.

Outcomes assessed in the review
Studies that reported clinical cardiovascular events (CVEs) or cardiovascular mortality (CVM) were eligible for inclusion. The review defined a clinical CVE as pericarditis, cardiomyopathy, congestive cardiac failure, proven coronary artery disease, valvular disease, conduction disorders, arrhythmias or autonomic function disorders; CVM was defined as death from any of these CVEs or sudden death.

How were decisions on the relevance of primary studies made?
Two reviewers selected studies for inclusion and resolved any disagreements through discussion, with the aid of a third reviewer where required. The authors of the studies were contacted to verify eligibility when necessary.

Assessment of study quality
The studies were assessed on the basis of formation of study group (adequacy of description, representative and start
Data extraction
Two reviewers extracted the data and resolved any disagreements through discussion. Attempts were made to avoid including overlapping data sets. Data were extracted or calculated to obtain the following: the cumulative incidence of CVE and CVM, standardised mortality ratio (SMR), standardised incidence ratio, absolute excess risk and actuarial risk (where adequate censored data were available). Relative risks (RRs) with 95% confidence intervals (CIs) were extracted if reported.

Methods of synthesis
How were the studies combined?
Full details of the characteristics and results of the included studies were summarised in the text of the review, with additional information presented in tabular format. Where appropriate, the ranges of outcome events of interest across studies were reported. Studies of paediatric Hodgkin lymphoma provided adequate data to calculate a pooled SMR.

How were differences between studies investigated?
Differences between the studies were described in the text and were apparent from inspection of the tables. SMRs with 95% CIs were presented graphically for each study.

Results of the review
Fourteen retrospective studies (n greater than 14,417) were included: 13 retrospective cohorts and one cohort with a nested case-control study (n=2,710). The number of patients in one study was unclear.

Methodological problems with the studies included poorly described study group, incomplete follow-up, no blinding of the outcome assessors, inadequate definition of risk estimation and lack of adjustment for other risk factors. Further details were given in the report.

The cumulative incidence of clinical CVE ranged from 0.3% to 22.8% (9 studies). Standardised incidence ratios could not be estimated from the data provided.

The cumulative incidence of CVM ranged from 0% to 3.5% (11 studies).

SMRs (adjusted for duration of follow-up, age and gender) ranged from 0 to 68, based on 6 studies of paediatric Hodgkin’s lymphoma. Four studies showed significantly increased SMRs after radiotherapy in comparison with the general population. The pooled SMR of 28.4 was based on 4 studies.

The absolute excess risk ranged from -0.4 to +17.7 excess cardiac deaths per 10,000 person-years adjusted for age, gender, race and calendar period (4 studies). The actuarial risk for CVM increased from 0.3% at 10 years to 10.2% after 25 years (2 studies).

The RR of CVD (both CVE and CVM) following radiation was reported in 3 studies. Two of the 3 studies showed a significantly increased risk with radiation compared with no radiation. In one study the risk of CVM was significantly greater in those given radiation compared with no radiation (RR 2.2, 95% CI: 1.2, 4.4, P<0.05) after adjusting for gender, age at diagnosis and follow-up time. One study found that the risks of clinical CVE were increased with increasing dose of radiation, for female patients and with anthracycline dose. In one study there was no difference in risk when adjusting for follow-up (RR 1.75, 95% CI: 0.56, 5.43, P=0.34).

Authors’ conclusions
The risk of CVM was greater after radiotherapy involving the heart region for childhood cancer, compared with the general population and patients who did not receive radiotherapy. The risk of CVE and risk factors for its development
after radiotherapy were unclear. Well-designed studies are required to accurately estimate the long-term risks and examine the factors associated with an increased risk of radiation-induced CVD.

**CRD commentary**

The review question was clear in terms of the intervention, participants and outcomes. Only two databases were searched and no attempts were made to locate unpublished studies; this might have resulted in the omission of relevant studies and raises the possibility of publication bias. Attempts were made to minimise language bias. Methods were used to minimise bias and error in the study selection, validity assessment and data extraction processes. Validity was assessed using specified established criteria and the results, which were reported in detail, highlighting methodological flaws in most of the included studies. Adequate information was given about each of the included studies. The methods used to calculate the risk of CVD appeared appropriate and the authors reported limitations in the results. The well-described methodological limitations of the included studies cast doubt on the robustness of the results for CMV, but support the need for further research.

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

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

**Research:** The authors stated that future studies should be well-designed with complete follow-up (greater than 90%), clear definitions of outcomes and uniform methods of detection of events, and should follow up all children receiving radiotherapy involving the heart region from the start of treatment. They stated that the incidence of clinical CVE and CMV should be compared with the general population by calculating SMRs and standardised incidence ratios, and with unexposed internal control groups. Studies need to estimate the risks over time and take account of other cardiotoxic treatments and prognostic factors using multivariate analysis.

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