Meta-analysis of the relation between silicone breast implants and the risk of connective tissue diseases
Janowsky E C, Kupper L L, Hulka B S

Authors' objectives
To investigate the possible relation between silicone breast implants and the risk of autoimmune conditions or connective tissue diseases.

Searching
Searches were conducted of MEDLINE (January 1966 to May 1998), Toxline (January 1985 to May 1998), Current Contents Search (July 1997 to May 1998), and Dissertation Abstracts Online (January 1992 to May 1998). Keywords included 'breast implant', 'breast augmentation', 'breast reconstruction', 'mammoplasty' and 'mammaplasty', 'rheumatic diseases', 'connective tissue disease', 'autoimmune disease', 'systemic sclerosis', 'scleroderma', 'lupus', 'dermatomyositis', 'sarcoidosis', 'rheumatoid arthritis', 'fibromyalgia', 'Sjogren', and 'polymyositis'. Citations in other meta-analyses and reviews were also used as a source of studies. All searches were limited to reports published in English.

Study selection
Study designs of evaluations included in the review
Cohort studies, case-control studies and cross-sectional studies. To be included studies had to have an internal comparison group and numbers available for construction of 2 by 2 tables to establish categories of disease and implants.

Specific interventions included in the review
Breast implants, including silicone-gel-filled breast implants.

Participants included in the review
Women with breast implants compared to control group women without breast implants. Women who had had direct injections of any material in to the breast, including silicone, were excluded from the analysis.

Outcomes assessed in the review
The disease variables assessed were the presence or absence of the following disease entities: rheumatoid arthritis, systemic lupus erythematosus, scleroderma or systemic sclerosis, Sjogren's syndrome, dermatomyositis or polymyositis; all definite connective-tissue diseases combined, as defined in each study. A category of other autoimmune or rheumatic conditions included undifferentiated connective tissue disease or mixed connective tissue disease, and signs and symptoms of other autoimmune or rheumatic conditions such as joint pain or swelling, or both, as defined in each study.

How were decisions on the relevance of primary studies made?
All potentially relevant papers were reviewed independently by all investigators.

Assessment of study quality
No systematic assessment of quality was undertaken, although aspects of quality were mentioned.

Data extraction
Data were abstracted independently by two reviewers using standardised data abstraction forms. Disagreements were resolved by discussion.
Methods of synthesis
How were the studies combined?
The basic data used in the unadjusted analyses (exact methods) were 2x2 tables of exposure variables (presence or absence of any breast implant) and disease variables for each study. Separate analyses were combined to produce summary estimates of the odds ratio (OR) and confidence limits for all connective tissue disease combined, for specific diseases, and for other autoimmune or rheumatic conditions. For adjusted analyses (approximate, large sample methods), the data needed from each study were the adjusted relative risk (RR) or odds ratio and standard error. If a chi-squared test for homogeneity between studies had P less than or equal to 0.01 an estimated summary adjusted RR was computed, weighted by study size. Meta-analysis was performed using these methods for all implants and separately for silicone-gel implants only. Fixed-effect models were used in the meta-analysis. The potential for publication bias was examined by constructing a funnel plot.

How were differences between studies investigated?
In the unadjusted analyses, stratified analyses involving three variables (cohort design versus other study design; year of diagnosis before or later than 1992; and validation of disease through medical records or not) as well as influence analysis was used to search for sources of heterogeneity. In the adjusted analyses, a chi square test for homogeneity was used.

Results of the review
Nine cohort studies (including 14,542 women with implants and 103,778 women without implants), nine case-control studies (including 3715 cases and 11,474 controls), and two cross-sectional studies (including 26,562 cases and 387,246 controls) were included.

The summary adjusted RR of individual connective tissue diseases associated with breast implants was 1.04 (95% CI 0.72, 1.51) for rheumatoid arthritis (7 studies), 0.65 (95% CI 0.35, 1.23) for lupus erythematosus (4 studies), 1.01 (95% CI 0.59, 1.73) for scleroderma or systemic sclerosis (4 studies), 1.42 (95% CI 0.65, 3.11) for Sjogren's syndrome (3 studies), and 1.52 (95% CI 0.97, 2.37) for dermatomyositis or polymyositis (1 study). The summary adjusted RR of all definite connective tissue disease combined, associated with breast implants, was 0.80 (95% CI 0.65, 3.11), and for other autoimmune or rheumatic conditions was 0.95 (95% CI 0.74, 1.25). There was no evidence, therefore, that breast implants were associated with a significant increase in any of these categories. Nor was there any evidence of significantly increased risk in the unadjusted analyses or in the analyses restricted to silicone-gel-filled implants. Funnel plots showed no evidence of publication bias.

Authors' conclusions
There was no evidence of an association between breast implants in general, or silicone-gel-filled implants specifically, and any of the individual connective tissues diseases, all definite connective tissue diseases combined, or other autoimmune or rheumatic conditions.

CRD commentary
The review addresses a clear question. The search strategy is adequate, although there is potential for language bias. The authors did investigate publication bias and found no evidence of it. The individual studies included in the review are presented clearly in tables, although it would have been helpful to have listed the type of implant used in each study. It is not explicit whether the tabulated outcome events were mutually exclusive within each study. There was no apparent systematic assessment of the quality of the included studies, although relevant aspects are mentioned in the results and discussion. The methods used for data analysis are clearly described and appear to be appropriate. Homogeneity was investigated whenever data were pooled in meta-analyses, and potential sources of heterogeneity were explored. In order to judge the strength of the evidence, it would have been helpful if the number of participants and the type of studies included in each meta-analysis, not only the number of studies, was presented. The conclusions do appear to be supported by the evidence presented.

Implications of the review for practice and research
Practice: The authors state that the elimination of implants would not be likely to reduce the incidence of connective tissue disease.

Research: The authors do not state any implications for research.

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