Risk of Connective Tissue Disorders among Breast Implant Patients

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Received for publication December 12, 2003; accepted for publication April 15, 2004.

In a US retrospective cohort study (1960–1996), 351 (4.8%) of 7,234 patients with breast implants and 62 (2.9%) of 2,138 patients who had undergone other types of plastic surgery reported subsequent rheumatoid arthritis (RA), scleroderma, systemic lupus erythematosus, or Sjögren’s syndrome (relative risk = 2.0, 95% confidence interval (CI): 1.5, 2.8). Risks of RA, scleroderma, and Sjögren’s syndrome were elevated both before and after 1992, when the Food and Drug Administration changed the status of breast implants to investigational. When records for these diseases were retrieved (35–40% retrieval rate) and blindly reviewed, two expert rheumatologists assessed only a minority of the cases as being “likely” (e.g., regarding RA, 16.5% for implant patients and 23.5% for comparison patients). Recalculation of incidence rates using “likely” diagnoses found relative risks of 2.5 (95% CI: 0.8, 7.8) for RA, scleroderma, and Sjögren’s syndrome combined and 1.9 (95% CI: 0.6, 6.2) for RA only. When the proportions deemed “likely” were applied to all self-reports, the estimated relative risks were 2.0 (95% CI: 0.7, 5.4) for the three disorders combined and 1.3 (95% CI: 0.5, 3.8) for RA. These results indicate that self-reports of connective tissue disorders are influenced by reporting and surveillance biases. Given the diagnostic complexities of these diseases, excess risks, if they exist, may be beyond detection even in a study of this size.

arthritis, rheumatoid; breast implants; connective tissue diseases; risk; scleroderma, systemic; Sjögren’s syndrome

Abbreviations: CI, confidence interval; CTD(s), connective tissue disorders(s); RR, relative risk.

Considerable controversy has surrounded the long-term safety of silicone breast implants. Concerns regarding cancer risk have centered around breast cancer, hematopoietic malignancies, and sarcomas (1–4). Clinical reports (5–15) have raised additional concerns regarding the long-term risks of connective tissue disorders (CTDs). Although a number of epidemiologic investigations have assessed these relations (16–35), they have been hindered by methodological limitations, including small sample sizes, limited follow-up, and imprecise information on either the exposures or the outcomes of interest.

In 1992, the US Congress directed the National Institutes of Health to undertake an investigation to assess the long-term safety of silicone breast implants. In response, the National Cancer Institute designed an epidemiologic follow-up investigation focused on the relation between cosmetic breast implants and subsequent cancer occurrence and overall mortality patterns. Several previous publications addressed these initial research goals (1, 2, 36). While it was not the primary focus of the study, systematic follow-up of a large group of women who had received breast implants provided investigators with an opportunity to assess CTDs, many of which have received attention as possible consequences of exposure to silicone implants. In this paper, we address the impact of timing and types of breast implants on...
the long-term risks of various CTDs, considering both patient reports and medical verification of these conditions.

**MATERIALS AND METHODS**

This retrospective cohort study has been described previously (2, 36). Institutional review boards at the National Cancer Institute and the organizations involved in data collection approved the study. Eligible study subjects comprised women who had had initial bilateral augmentation mammoplasty before 1989 at one of 18 plastic surgery practices in six areas (Atlanta, Georgia; Birmingham, Alabama; Charlotte, North Carolina; Miami and Orlando, Florida; and Washington, DC). Since breast cancer was a primary outcome of interest, patients who had received implants following treatment for breast cancer were not included. A total of 13,488 eligible study subjects were identified, comprising all augmentation mammoplasty patients at each practice who met the eligibility criteria. In addition, 3,936 comparison subjects from these same practices were identified, comprising similar-aged patients who had undergone other types of plastic surgery not involving silicone during the same time period. The major types of plastic surgery included abdominoplasty or liposuction, blepharoplasty or rhytidectomy (operations for removal of wrinkles on the face and neck), and rhinoplasty, otoplasty, mentoplasty, or genioplasty (operations involving the nose, ear, or chin). The number of comparison patients was considerably lower than the number of implant patients, since the emphasis of the study was on cancer outcomes, for which external comparison incidence rates are available.

Trained abstractors reviewed medical charts and entered data directly into laptop computers using standardized software. Information on vital status and location was sought through various tracing sources. In total, 10,778 (79.9 percent) of the implant patients and 3,214 (81.7 percent) of the comparison patients were traced, with 364 being identified as deceased (245 implant patients and 119 comparison subjects). Death certificates were obtained for 91.4 percent and 95.8 percent of the deceased implant and comparison patients, respectively.

Beginning in June 1995, subjects were sent mailed questionnaires requesting information on demographic factors, subsequent plastic surgeries, current health status, and lifestyle factors that could affect health. Respondents were asked whether they had ever received a physician’s diagnosis of rheumatoid arthritis, arthritis of another type, scleroderma, systemic lupus erythematosus, Sjögren’s syndrome, Raynaud’s phenomenon, fibrositis/fibromyalgia, vasculitis, chronic fatigue syndrome, or multiple sclerosis. They were also asked whether they had received any other CTD diagnosis and, if so, which one. For each condition, patients were asked to provide their age at first diagnosis and the physician’s name and address. Nonrespondents were given the opportunity to complete questionnaires by telephone. Questionnaires were obtained from 7,447 (70.7 percent) of the living implant patients and 2,203 (71.2 percent) of the comparison patients.

**Statistical methods**

Person-years were accrued beginning 1 year after initial plastic surgery and continuing through the earliest date of development of a CTD, the date on which the patient was last known to be alive and free of any CTD, or December 31, 1996. Patients with a CTD diagnosed prior to their initial plastic surgery were excluded from analysis of that disease; further evaluation that excluded such patients from all analyses showed no substantial changes in risk estimates. Poisson regression methods (37), as implemented in the Epicure AMFIT module (38), were used to calculate relative risks (implant patients vs. comparison patients), compute 95 percent confidence intervals, and adjust for potentially confounding variables. For all analyses, relative risks were adjusted for age at follow-up, calendar period of follow-up, and race. Other factors, such as age at surgery, year of surgery, time since surgery, or specific predictors of CTDs (education, family history), were included in the regression models, as necessary, for evaluation of their roles as potentially confounding factors or for examination of variations in the relative risk. The final analytical data set, which excluded subjects who developed CTDs within 1 year of initial plastic surgery (59 implant patients and 21 comparison patients) and persons of races other than White or Black (154 implant patients and 44 comparison patients), consisted of 7,234 implant patients and 2,138 comparison patients.

The mortality of the subjects through the end of 1997 was also examined (36).

**Medical review of reported CTDs**

We attempted to retrieve and review medical records for the CTDs that have been most consistently related to breast implants and for which patient reports indicated persistent elevations in risk over time. Notations regarding implants were blacked out, and extraneous information in the records of comparison patients was similarly marked, to blind the reviewing rheumatologists as to patient implant status. Using a standardized abstract form, two board-certified rheumatologists (L. M. B. and O. D.) reviewed the records to determine their adequacy and to assess whether the patient’s history, the physical examination, and radiographic and laboratory findings supported the diagnoses reported. The reviewers assessed the likelihood of each reported diagnosis (likely, unlikely, unable to assess). Instances of disagreement between reviewers were resolved by having both rheumatologists re-review the record and come to consensus. For diagnoses deemed “likely,” the reviewers determined whether standardized criteria for rheumatoid arthritis (39) or Sjögren’s syndrome (40) were met. For diagnoses deemed “unlikely,” the reviewers were asked to indicate a probable alternative diagnosis (chronic fatigue syndrome, fibromyalgia, osteoarthritis, other condition, no condition, or unknown).

**RESULTS**

Although implant patients were somewhat younger than comparison patients at the time of their plastic surgery (mean...
ages of 34.6 years and 41.5 years, respectively), the mean years of initial surgery were similar (1983.0 vs. 1984.3). The average length of follow-up was 12.1 years among the implant patients and 11.1 years among the comparison patients. The maximum lengths of follow-up were 31.6 years and 27.6 years among the implant and comparison patients, respectively.

**Self-reported conditions**

Three hundred fifty-one (4.8 percent) of the implant patients and 62 (2.9 percent) of the comparison patients reported a diagnosis of one of four major CTDs (rheumatoid arthritis, scleroderma, systemic lupus erythematosus, or Sjögren’s syndrome), generating a relative risk of 2.0 (95 percent confidence interval (CI): 1.5, 2.8) (table 1). Significant risk elevations were noted for rheumatoid arthritis (relative risk (RR) = 1.9, 95 percent CI: 1.4, 2.7), systemic lupus erythematosus (RR = 2.1, 95 percent CI: 1.1, 4.2), and Sjögren’s syndrome (RR = 11.7, 95 percent CI: 2.5, 54.9). Scleroderma was associated with a threefold risk on the basis of 23 implant patients and three comparison subjects. The maximum lengths of follow-up were 31.6 years and 27.6 years among the implant and comparison patients, respectively.

We analyzed disease associations according to whether the diseases were reportedly diagnosed prior to or during/after 1992, when the Food and Drug Administration changed the status of breast implants to investigational. The overall risk of the major CTDs was higher for conditions diagnosed during or after 1992 (RR = 2.6) as compared with before 1992 (RR = 1.7), although both risks were significant (table 2). The risks were similar in the two time periods for rheumatoid arthritis, scleroderma, and Sjögren’s syndrome, but for a number of conditions the risks were substantially higher for diagnoses occurring in the later period. This was true for lupus, Raynaud’s phenomenon, fibromyalgia, chronic fatigue syndrome, and “other CTDs.” However, the risk of chronic fatigue syndrome was significantly elevated in both the earlier and the later time periods. Only for one condition, vasculitis, was the relative risk higher (though nonsignificant) for diagnoses in the earlier time period (RR = 2.6), on the basis of 10 reported cases among the implant patients.

In additional analyses, we examined risks for conditions with sufficient numbers of exposed persons by age at, calendar period of, and years since initial implantation (table

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**TABLE 1. Relative risk of self-reported connective tissue disorders and other conditions among patients with breast implants in comparison with other plastic surgery patients, southeastern United States, 1960–1996**

<table>
<thead>
<tr>
<th>Condition*</th>
<th>No. of implant patients $(n = 7,234)$ (87,199 person-years)</th>
<th>No. of comparison patients $(n = 2,138)$ (23,724 person-years)</th>
<th>Relative risk†</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue disorders</td>
<td>351</td>
<td>62</td>
<td>2.0</td>
<td>1.5, 2.8</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>258</td>
<td>49</td>
<td>1.9</td>
<td>1.4, 2.7</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>23</td>
<td>3</td>
<td>3.0</td>
<td>0.8, 10.9</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>72</td>
<td>10</td>
<td>2.1</td>
<td>1.1, 4.2</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>43</td>
<td>2</td>
<td>11.7</td>
<td>2.5, 54.9</td>
</tr>
<tr>
<td>Other conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other arthritis</td>
<td>724</td>
<td>201</td>
<td>1.3</td>
<td>1.1, 1.6</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>97</td>
<td>10</td>
<td>2.6</td>
<td>1.3, 5.1</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>311</td>
<td>57</td>
<td>1.3</td>
<td>0.9, 1.7</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>21</td>
<td>4</td>
<td>1.4</td>
<td>0.5, 4.6</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>246</td>
<td>27</td>
<td>2.4</td>
<td>1.6, 3.6</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>26</td>
<td>5</td>
<td>0.7</td>
<td>0.2, 1.9</td>
</tr>
<tr>
<td>Other disorders</td>
<td>202</td>
<td>24</td>
<td>2.5</td>
<td>1.6, 3.9</td>
</tr>
</tbody>
</table>

* Conditions are not mutually exclusive.
† Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960–1964, ..., 1990–1994, 1995–1996), and race (White or Black).
For the major CTDs, there was no evidence of a trend in risk according to any of these parameters. This was also generally true when individual conditions were considered, although for several conditions (e.g., scleroderma, Sjögren’s syndrome) the risks were difficult to interpret because of small numbers. We also examined the effects of timing of

### TABLE 2. Relative risk* of self-reported connective tissue disorders and other conditions among patients with breast implants in comparison with other plastic surgery patients, by period of diagnosis, southeastern United States, 1960–1996

<table>
<thead>
<tr>
<th>Condition</th>
<th>Before 1992</th>
<th>During or after 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases observed†</td>
<td>RR‡</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>185</td>
<td>1.7</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>13</td>
<td>2.6</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>29</td>
<td>0.9</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>12</td>
<td>12.1</td>
</tr>
<tr>
<td>Other conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other arthritis</td>
<td>397</td>
<td>1.3</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>47</td>
<td>1.8</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>156</td>
<td>0.9</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>10</td>
<td>2.6</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>123</td>
<td>1.9</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>Other disorders</td>
<td>82</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960–1964, ..., 1990–1994, 1995–1996), and race (White or Black).
† Number of breast implant patients with the disorder.
‡ RR, relative risk; CI, confidence interval.

### TABLE 3. Relative risk* of self-reported connective tissue disorders and other conditions among patients with breast implants in comparison with other plastic surgery patients, according to various time parameters of initial implantation, southeastern United States, 1960–1996

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age (years) at initial implantation</th>
<th>Calendar year of initial implantation</th>
<th>No. of years since initial implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue disorders</td>
<td>2.3 (94)</td>
<td>2.0 (89)</td>
<td>3.9‡ (83)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.9 (68)</td>
<td>4.0 (63)</td>
<td>4.2‡ (68)</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>∞ (3)</td>
<td>0.9 (7)</td>
<td>∞ (6)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>4.3 (28)</td>
<td>0.9 (20)</td>
<td>1.2 (6)</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>∞ (9)</td>
<td>∞ (8)</td>
<td>∞ (12)</td>
</tr>
<tr>
<td>Other conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other arthritis</td>
<td>1.8 (162)</td>
<td>1.4 (176)</td>
<td>1.5 (181)</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>3.4 (37)</td>
<td>1.3 (20)</td>
<td>4.2 (24)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1.3 (103)</td>
<td>1.0 (96)</td>
<td>1.3 (69)</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>1.6 (97)</td>
<td>1.3 (59)</td>
<td>3.1 (47)</td>
</tr>
</tbody>
</table>

* Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960–1964, ..., 1990–1994, 1995–1996), and race (White or Black).
† Numbers in parentheses, number of breast implant patients with the disorder.
‡ 95% confidence interval excluded 1.0.
implantation according to whether conditions were diagnosed prior to or during/after 1992. Given the evidence that breast implants deteriorate over time, we focused on relations by the number of years since initial implantation. This analysis showed no relation with years since implantation for diseases diagnosed prior to 1992 but increasing risks after this time (e.g., for the major CTDs, in comparison with women with less than 5 years of follow-up, the risks were 1.5, 1.6, and 2.0 for 5–9, 10–14, and ≥15 years of follow-up, respectively; comparable risks for women diagnosed before 1992 were 1.2, 1.3, and 0.8). This post-1992 pattern largely reflected trends for rheumatoid arthritis.

Given that rates of location and response varied depending on the source of patients, we subdivided medical practices from which patients were recruited according to their average rates of location (<75 percent, 75–84 percent, and ≥85 percent) and questionnaire completion (<70 percent, 70–74 percent, and ≥75 percent). There appeared to be no consistent pattern of risk according to these groupings. We further grouped practices according to the combination of location rate and response rate. The relative risk for the major CTDs was 2.4 for practices with the highest rates and 1.9 for practices with the lowest rates. We also examined risks for the demographic subgroup with the highest questionnaire response rate (≥70 percent)—namely, older White subjects who had undergone surgery after 1981. The risk of major CTDs, as well as the risk of most individual diseases, was similar to overall risks (for the major CTDs, RR = 1.8, 95 percent CI: 1.0, 3.1).

Of the patients who received breast implants, 49.7 percent received silicone gel implants, 34.1 percent received double lumen implants, 12.2 percent received saline implants, and 3.9 percent received other/unspecified types of implants. The relative risk of major CTDs was 2.4 for silicone gel implants (210 events among implant patients; 95 percent CI: 1.8, 3.4), 1.8 for double lumen implants (100 events; 95 percent CI: 1.3, 2.6), 1.7 for saline implants (34 events; 95 percent CI: 1.0, 2.7), and 0.9 for other/unspecified implants (seven events; 95 percent CI: 0.4, 2.1). Risks of individual diseases were also generally somewhat higher for women with silicone gel implants, although the differences by implant type were not significant.

Examination of causes of death showed that none of the implant or comparison patients had a CTD as an underlying or contributory cause of death.

Rheumatologic review of conditions

We attempted to confirm diagnoses of rheumatoid arthritis, scleroderma, and Sjögren’s syndrome in physicians’ records. Permission for record retrieval was obtained from 70.4 percent of implant patients and 53.7 percent of comparison patients. We retrieved 56.4 percent and 65.5 percent of these patients’ records, respectively; the records comprised 114 patients with rheumatoid arthritis, eight with scleroderma, and 20 with Sjögren’s syndrome.

Most diagnoses were insufficiently supported, either because the records were incomplete or because clinical criteria were not met (table 4). Consensus review found the diagnosis of rheumatoid arthritis to be “unlikely” for 71.1 percent of implant patients and 64.7 percent of comparison patients. The diagnosis was supported for 16.5 percent of

<table>
<thead>
<tr>
<th>Condition and rheumatologists’ assessment of diagnosis</th>
<th>All patients No.</th>
<th>Patients with breast implants No.</th>
<th>Comparison patients No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>(n = 114)*</td>
<td>(n = 97)</td>
<td>(n = 17)</td>
</tr>
<tr>
<td>Likely</td>
<td>20</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Unlikely</td>
<td>80</td>
<td>69</td>
<td>11</td>
</tr>
<tr>
<td>Unassessable</td>
<td>13</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>No consensus</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>(n = 8)</td>
<td>(n = 7)</td>
<td>(n = 1)</td>
</tr>
<tr>
<td>Likely</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Unlikely</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Unassessable</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>(n = 20)</td>
<td>(n = 19)</td>
<td>(n = 1)</td>
</tr>
<tr>
<td>Likely</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Unlikely</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Unassessable</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

* Number of medical records that were reviewed by the rheumatologists. In standard chi-squared testing, none of the tests for differences produced significant results.

implant patients and 23.5 percent of comparison patients. American College of Rheumatology criteria (39) were met by eight of the 16 implant patients and three of the four comparison patients with “likely” diagnoses.

Given the rarity of scleroderma and Sjögren’s syndrome, reports were difficult to assess, particularly among comparison subjects. Furthermore, a number of reports of both diseases were classified as unassessable. For Sjögren’s syndrome, this was often due to the absence of diagnostic tests, including biopsies and serologic testing needed to distinguish Sjögren’s syndrome from other causes of xerostomia and dry eyes.

For those records with diagnoses assessed as unlikely, each reviewer was asked to assign a probable alternative diagnosis. For reports of rheumatoid arthritis, osteoarthritis was assigned most often among the implant patients (37.7 percent), followed by fibromyalgia (24.6 percent) and both osteoarthritis and fibromyalgia (14.5 percent). Comparable percentages among the comparison patients were 63.6 percent, 0 percent, and 9.1 percent. Among the seven unlikely reported cases of Sjögren’s syndrome among implant patients, two were considered potential cases of fibromyalgia, one was considered osteoarthritis, and one was considered both diseases. Both reported cases of unlikely scleroderma among the implant patients were considered possible cases of fibromyalgia.

Range of risk estimates

We calculated incidence rates and relative risks for diseases that were considered likely by both reviewers (table 5). For rheumatoid arthritis, scleroderma, and Sjögren’s syndrome combined, the relative risk was 2.5 (95 percent CI: 0.8, 7.8) on the basis of 24 implant patients and four comparison patients. Rheumatoid arthritis was the major contributor to this risk, occurring among 16 implant patients and four comparison patients (RR = 1.9, 95 percent CI: 0.6, 6.2). For comparative purposes, the relative risks based on self-reports were 2.2 (95 percent CI: 1.6, 3.0) for all three conditions and 1.9 (95 percent CI: 1.4, 2.7) for rheumatoid arthritis. The absence of confirmed cases of either scleroderma or Sjögren’s syndrome among the comparison patients precluded derivation of reliable point estimates, but the lower 95 percent confidence limits for both of these risks were 0.4.

Given concerns that we were unable to retrieve all of the medical records for self-reported conditions, we also derived estimates of risk for all patients using confirmation rates based on patients with retrieved records. This analysis gave us an estimated relative risk of 2.0 (95 percent CI: 0.7, 5.4) for all three conditions and 1.3 (95 percent CI: 0.5, 3.8) for rheumatoid arthritis.

DISCUSSION

The design of this investigation and the characteristics of the assembled cohort offered many advantages for studying cancer risk and cause-specific mortality in relation to cosmetic breast implant surgery, the primary objectives of the study. These features include large numbers of implant patients (representing all patients from specific practices), extended follow-up, a practice-based comparison group, and the availability of questionnaire information on covariates. These features provide advantages in assessing the relation
of breast implants to CTDs as well. However, in contrast to
the relation between cancer and mortality, there are no well-
accepted age-, race-, sex-, and calendar-time-specific popu-
lation incidence rates for CTDs. Thus, our study was depend-
ton comparisons of rates in the implant and comparison
patients; for rare diagnoses (the majority), this involved
small numbers and unreliable rates. In addition, the complex
clinical presentation of many CTDs and the variable criteria
used to diagnose these diseases make reliable identification
of cases difficult.

In interpreting the results of this study, potential effects of
selection, recall, and surveillance biases must be considered.
Of particular concern is the fact that many of the disease
relations were primarily associations with conditions report-
edly diagnosed in 1992 or later. The difference in risks
between the two time periods was most apparent for lupus,
Raynaud’s phenomenon, fibromyalgia, and chronic fatigue
syndrome, the most graphic example being lupus: The rela-
tive risk was 0.9 in the era prior to extensive publicity and
5.9 afterward. Although trends by time of diagnosis could
reflect the influence of implant leakage, given the evidence
depending on patients over time (41), specific analyses
that addressed relations by latency showed increasing risks’
being restricted to post-1992 diagnoses. This suggests that
the publicity surrounding possible disease associations in the
early 1990s may have contributed to the observed time
trends.

Three conditions—rheumatoid arthritis, scleroderma, and
Sjögren’s syndrome—continued to show elevations in risk
even in the earlier time period and were of concern given
speculations from other investigations of a link with breast
implants. However, self-reports of CTDs for all patients,
with or without implants, are subject to reporting and diag-
nostic biases and must be cautiously interpreted. Our
confirmed risks were dependent on obtaining consent to
retrieve records and on retrieving the relevant records when
consent was received—challenges also experienced in
another investigation (42). In analysis based on confirmed
records, which involved considerably smaller sample sizes
and may have been influenced by a variety of selection
factors, the risk for the three conditions was 2.5; it dropped
to 2.0 when we also factored in completeness of record
retrieval. Both estimates were nonsignificant. Recognized
differences in lifestyle factors between implant and compar-
ison patients (43) further complicated the interpretation of
these risks, especially given the absence of many identified
risk factors for these CTDs. Thus, the influence that
confounding factors might have had on the risk estimates
cannot be dismissed.

We had the most power to evaluate risks for rheumatoid
arthritis. On the basis of self-reports, we saw no trends in risk
with any time-related parameters, including interval since
implantation. This raises questions regarding biologic plau-
sibility. Several investigations have suggested small but
nonsignificant risk increases for this disease among implant
patients (17, 23, 27, 35), though several other cohort (28–30)
and case-control (21, 44) studies have not supported a
connection. However, many of these investigations had
small sample sizes and short follow-up times. In one of the
investigations that suggested a small increase in risk (23),
subsequent confirmation of reported CTDs found evidence
of overreporting; only 22.7 percent of the self-reported cases
were confirmed (42). This was similar to our investigation,
wherein retrieval of medical records confirmed only 17
percent of the reported cases, possibly reflecting a lack of
awareness by the public of differences between rheumatoid
arthritis and other types of arthritis (e.g., osteoarthritis).

Further complicating the interpretation of self-reports of
rheumatoid arthritis in our study was the fact that a some-
what higher percentage of cases were confirmed in the
comparison patients than in the implant patients. When anal-
yses were restricted to cases judged likely by the two rheu-
matologists, the risk fell to less than 2 and became
nonsignificant. Furthermore, when we factored in our ability
to retrieve records to confirm self-reports, our estimate of
risk was 1.3, also not significant.

On the basis of clinical studies, the CTD that has been
most consistently related to breast implants is scleroderma.
This condition is difficult to study epidemiologically given
its rarity in the general population, with estimates of annual
disease incidence in females of 1.6 cases per 100,000 (45). In
the largest cohort study, a relative risk of 1.84 (95 percent
CI: 0.98, 3.5) was found on the basis of 10 observed cases
among implant patients (23). The relation of this condition
to breast implants has frequently been assessed in case-control
investigations, with most not showing a relation (16, 21, 24,
46). In our study, 23 implant patients and three comparison
patients reported scleroderma, resulting in a nonsignificant
threefold risk elevation. Of the retrieved medical records,
only 29 percent of cases among the implant patients were
assessed as likely, for a total of two confirmed cases. The
one comparison patient record failed to support the diag-
nosis. Thus, with no reliable estimate of comparison rates,
we cannot address the likelihood of an association. What is
clear is that any excess risk of scleroderma in implant recip-
cients, if present, is likely to be small in absolute terms.

Sjögren’s syndrome was also of concern on the basis of
prior clinical and epidemiologic literature, as well as prelim-
inary self-report findings in this study. This is also a rare
condition, with an annual estimated incidence of four cases
per 100,000 population (47). One meta-analysis (48) noted a
significant increase in this condition, largely reflecting risks
from one investigation (23). Our relative risk for Sjögren’s
syndrome based on self-reports was the largest of any
observed, but whether any excess risk would remain for vali-
dated diagnoses is unclear. As with scleroderma, any
increase in absolute risk, should it remain, would be small.

In this investigation, we also assessed the risks of fibromy-
algia and vasculitis, because implant patients have reported
symptoms often associated with these diseases (49–51).
Furthermore, one study found a relation between implant
leakage and increased risk of fibromyalgia (41). Self-reports
of fibromyalgia or vasculitis were not found to be related to
any sizeable risk in our study. However, chronic fatigue
syndrome was associated with a modest increase in risk. This
relation, though substantially more pronounced for diag-
noses reported during or after 1992, was also present for
earlier diagnoses. The diagnostic complexities of chronic
fatigue syndrome are well recognized (52); the symptoms
leading to medical assistance and the criteria used to confirm
the disease are associated with considerable uncertainty. Since this was not a condition that we attempted to confirm, we were unable to assess the extent to which defining criteria were present.

Our study was designed to assess only established CTDs. However, clinical observations (49–51, 53–55) have suggested that breast implants may lead to a new condition that does not meet established criteria for a recognized CTD. Although results from a case-control investigation provided some support for this (56), several recent record-linkage studies in Scandinavia failed to note unusual symptoms among women with breast implants (57, 58). Study of the issue is complex, especially since the suggestion of this entity is usually prompted by the presence of a breast implant. Appropriate evaluation would require a study design that included standardized histories and examinations in a large sample of implant patients and appropriate comparison patients.

This investigation confirmed the complexities of evaluating the relation between breast implants and the risk of CTDs. It is clear that a variety of selection and reporting biases may be involved, as evidenced in the present study by overreporting of conditions by both implant and comparison patients and the difficulty of confirming conditions according to defined clinical criteria. Our investigation had the most power to address relations with rheumatoid arthritis. Therefore, it is of interest that our risk estimates (on the basis of cases considered likely by expert chart review) were between 1.3 and 1.9 and not statistically significant. Confidence intervals in previous studies addressing the relation between breast implants and the risk of rheumatoid arthritis, and connective tissue diseases in a clinical practice. J Clin Epidemiol 1995;48:571–82.

REFERENCES


