

## SILICONE BREAST IMPLANTS AND THE RISK OF CONNECTIVE-TISSUE DISEASES AND SYMPTOMS

JORGE SÁNCHEZ-GUERRERO, M.D., GRAHAM A. COLDITZ, M.B., B.S., DR.P.H., ELIZABETH W. KARLSON, M.D., DAVID J. HUNTER, M.B., B.S., SC.D., FRANK E. SPEIZER, M.D., AND MATTHEW H. LIANG, M.D., M.P.H.

**Abstract** *Background.* Silicone breast implants have been linked to a variety of illnesses, the most controversial of which are connective-tissue diseases and symptoms. To study this relation, we analyzed data from 14 years of follow-up of the Nurses' Health Study cohort.

*Methods.* Women who were free from connective-tissue disease in June 1976 were followed through May 31, 1990, before there was widespread media coverage of the possible association of breast implants and connective-tissue diseases. Information was collected through biennial and supplementary mailed questionnaires and blinded reviews of medical records with the use of standardized criteria. Relative risk, the measure of association, was defined as the incidence rate of connective-tissue disease among women with breast implants divided by the corresponding incidence rate among women without breast implants.

*Results.* Among 87,501 women who were eligible for follow-up, 516 were confirmed as having definite connective-tissue diseases and 1183 as having breast implants (of which 876 were silicone-gel-filled, 170 saline-filled, 67 double-lumen, 14 polyurethane-coated, and 56 of un-

known type). The mean ( $\pm$ SD) period of follow-up after surgery was  $9.9\pm 6.4$  years (range, 1 month to 40.5 years). Three of the patients with definite connective-tissue disease — all had rheumatoid arthritis — had implants (one silicone-gel-filled, one saline-filled, and one double-lumen). The age-adjusted relative risk of a definite connective-tissue disease among women with any type of implant was 0.6 (95 percent confidence interval, 0.2 to 2.0), as compared with women without implants. For women with silicone-gel-filled implants, the comparable relative risk was 0.3 (95 percent confidence interval, 0 to 1.9). The relative risk of self-reported signs or symptoms of connective-tissue disease for women with implants was 1.5 (95 percent confidence interval, 0.9 to 2.4); the risk of having any 1 of 41 signs, symptoms, or laboratory features of connective-tissue disease was 0.7 (95 percent confidence interval, 0.3 to 1.6).

*Conclusions.* In a large cohort study, we did not find an association between silicone breast implants and connective-tissue diseases, defined according to a variety of standardized criteria, or signs and symptoms of these diseases. (N Engl J Med 1995;332:1666-70.)

SINCE 1962, approximately 1 million to 2.2 million women in the United States and Canada have received silicone breast implants as part of reconstruction following surgery for breast cancer or prophylactic mastectomy or for cosmetic reasons.<sup>1,2</sup> Silicone breast implants have been linked to a variety of illnesses, the most controversial of which are connective-tissue diseases and symptoms.<sup>1-3</sup> Since 1982, at least 293 patients with connective-tissue diseases or rheumatic illnesses and silicone breast implants have been described in the English literature; many additional cases

have been reported in abstract form.<sup>4</sup> On April 16, 1992, the Food and Drug Administration banned further use of these devices, except for limited use in research settings.<sup>1</sup>

To study the relation between silicone breast implants and connective-tissue diseases, we analyzed data from 14 years of follow-up of the Nurses' Health Study cohort with respect to connective-tissue diseases that were diagnosed before June 1, 1990. Widespread media coverage in the United States of a possible association began in December 1990, after a program on the subject was aired on national television.<sup>5</sup>

### METHODS

#### The Nurses' Health Study Cohort

The Nurses' Health Study cohort was assembled in June 1976. Questionnaires were mailed to all registered nurses who were female, married, 30 to 55 years of age, and living in California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, or Texas. Seventy percent of the women invited to participate returned the base-line questionnaire. Information was sought on a variety of health conditions and practices. Subsequently, biennial questionnaires have been sent. The overall response rate to follow-up questionnaires has been more than 90 percent. The study protocol has been approved by the Human Research Committee of Brigham and Women's Hospital in Boston. All subjects have given informed consent.

#### Ascertainment of Exposure to Silicone Breast Implants

By 1992, the number of women still alive and participating in the study was 109,750. Among many other topics on the 1992 biennial questionnaire were questions about whether participants had ever had breast-implant surgery or silicone, paraffin, or collagen injections. After three mailings, 89,376 women (81.4 percent) returned the questionnaire, including 88,153 who answered the questions related to breast implants and injections. A supplementary question-

From the Departments of Rheumatology and Immunology (J.S.-G., E.W.K., M.H.L.) and Medicine (G.A.C., D.J.H., F.E.S., M.H.L.), Harvard Medical School; the Robert B. Brigham Multipurpose Arthritis and Musculoskeletal Diseases Center (J.S.-G., E.W.K., M.H.L.) and the Channing Laboratory (G.A.C., D.J.H., F.E.S.), Brigham and Women's Hospital; and the Department of Epidemiology, Harvard School of Public Health (G.A.C., D.J.H.) — all in Boston. Address reprint requests to Dr. Liang at Brigham and Women's Hospital, Dept. of Rheumatology and Immunology, 75 Francis St., Boston, MA 02115.

Supported by grants from the National Institutes of Health (CA40356-08S1, for the Supplement-Prospective Study of Diet and Cancer in Women; AR36308, for the Multipurpose Arthritis and Musculoskeletal Diseases Center; and AR42630, for the Effects of Silicone on the Immune Response Study). Dr. Sánchez-Guerrero was supported by a Research Fellowship Award from the Fogarty International Center (NIH 5F05 TW04573-02).

The Brigham and Women's Hospital has received grants from Dow Corning to study silicone breast implants in a separate study, the breast-implant substudy of the Women's Health Cohort Study, being conducted by the Division of Preventive Medicine. From these grants, Dr. Sánchez-Guerrero received \$7,500 toward tuition at the Harvard School of Public Health in September 1992 and Dr. Karlson received \$25,800 in salary and fringe-benefit support between February 1, 1994, and June 30, 1994. Dr. Liang received \$2,525 from four legal firms representing Dow Corning or McGhan for 8.5 hours of consulting between June 16, 1993, and August 26, 1994. The other authors have not received compensation from companies that manufacture breast implants or from lawyers involved in breast-implant litigation.

*Editor's note:* This disclosure statement is in accord with our usual policy but is somewhat more detailed because of the intense public controversy over the health effects of breast implants.

naire was sent to the 1861 women who reported having received breast implants of any sort or silicone, paraffin, or collagen injections. The supplementary questions were intended to confirm the breast-implant surgery and to ascertain whether it was unilateral or bilateral, the side of the implant, the reason for the surgery (cancer treatment, prophylaxis, cosmetic reasons, or other), type of implant, date (or dates) of surgery, and complications, if any. Although all breast implants are contained in silicone envelopes, there are differences in structure and filling. The implant types were categorized as silicone-gel-filled, saline-filled, double-lumen (a silicone-gel-filled envelope within a saline-filled envelope), polyurethane-coated (a silicone-gel-filled implant coated with polyurethane foam), other, or unknown.

Overall, 1809 of the 1861 women (97.2 percent) responded to the supplementary questionnaire; 330 without breast implants reported silicone, paraffin, or collagen injections; 117 reported breast-implant surgery after May 1990; 22 had received implants after the date of diagnosis of a connective-tissue disease; and 157 provided incomplete information about the breast-implant surgery. The remaining 1183 women with confirmed breast implants in May 1990 or earlier were included in the analysis. Researchers who entered data on implant history were blinded to information about the medical histories of the women.

### Validation of Breast-Implant Information

A validation study of self-reported information on breast implants was conducted for a random sample of 100 women. Permission was requested to review their medical records. Sixteen women did not give permission, the medical records for 11 were not available after multiple mailings, and the medical records for 6 were not received from the surgeon or hospital. For the 67 women whose medical records were obtained, we confirmed that surgery had been performed and ascertained which side the implant was on, the reason for the surgery, the type of implant (or implants), and the date (or dates) of surgery. Medical records were abstracted by physicians using a questionnaire identical to that completed by the subjects. Self-reports agreed with blinded record reviews at the following rates: surgery — 99 percent; side of the implant — left 91 percent, right 100 percent, and bilateral 99 percent; reason for the surgery — cancer 93 percent, prophylaxis 91 percent, and cosmetic reasons 95 percent; type of implant — silicone-gel-filled 100 percent, and saline-filled 89 percent; and date (or dates) of surgery — same date 78 percent, within one year 84 percent, and within two years 95 percent.

### Case Identification of Connective-Tissue Disease

Questions regarding rheumatic conditions that had occurred since 1976 were included on all questionnaires after 1980. There were specific questions about diagnosis by a physician of systemic lupus erythematosus in the 1982, 1984, 1986, and 1992 questionnaires; about rheumatoid arthritis in 1982 through 1992; about scleroderma, polymyositis, dermatomyositis, and Sjögren's syndrome in 1992; and about "other major illness diagnosed" on every biennial questionnaire.

In 1992, we mailed a screening questionnaire on connective-tissue disease<sup>6</sup> to participants who had reported any rheumatic, musculoskeletal, or connective-tissue disease before June 1, 1990, and had answered the 1992 questionnaire. These diseases included rheumatoid arthritis, scleroderma, morphea, systemic lupus erythematosus, dermatomyositis or polymyositis, Sjögren's syndrome, "connective tissue disease not further specified," or "any other arthritis (excluding osteoarthritis and fibromyalgia)." Those who did not respond initially were sent second and third mailings. Those who still did not respond were sent a shorter questionnaire, once or twice, asking specifically about the occurrence of these conditions, or were telephoned by trained interviewers who asked the same questions and sought permission to obtain further details regarding the diagnosis. Of the 5086 participants who were sent the screening questionnaire, 4598 (90 percent) responded to the mailings or telephone calls.

The screening questionnaire on connective-tissue disease<sup>6</sup> contained 30 questions about symptoms or signs of connective-tissue diseases ever experienced by the subject, based on the classification criteria of the American College of Rheumatology for rheumatoid

arthritis,<sup>7</sup> systemic lupus erythematosus,<sup>8</sup> and systemic sclerosis<sup>9</sup>; Alarcon-Segovia and Cardiel's criteria for mixed connective-tissue disease<sup>10</sup>; Bohan and Peter's criteria for inflammatory myositis<sup>11</sup>; and Fox et al.'s criteria for Sjögren's syndrome.<sup>12</sup> Validation of questionnaire data on 253 subjects with connective-tissue disease and 340 control subjects showed a sensitivity ranging from 83 to 96 percent and a specificity of 83 to 93 percent for detecting any of these six connective-tissue diseases.<sup>6</sup>

For this study, we used a more conservative screening rule to maximize sensitivity. A positive questionnaire was defined as one indicating at least two swollen joints for more than six weeks or at least three positive answers to questions about connective-tissue disease symptoms. Medical records were requested to validate the diagnoses for all subjects who had reported connective-tissue diseases and had positive questionnaires. Exposure information was separated from the medical records by a research assistant, and the records were then reviewed independently by two rheumatologists blinded to exposure. Definite connective-tissue disease was identified according to the standardized classification criteria on which the questionnaire was based. When the rheumatologists disagreed, the complete medical information was reviewed by a third independent rheumatologist and a final judgment was made by consensus of all three rheumatologists. The date of onset of the connective-tissue disease was the date of diagnosis indicated in the medical record. The analysis was based on records received through May 1994.

### Population for Analysis

Women for whom information on breast implants was missing or whose connective-tissue disease was diagnosed before 1976 or after May 1990 were excluded, leaving 87,501 women eligible for follow-up. The period from June 1976, the start of the study, through May 31, 1990, was chosen to avoid potential bias from the widespread news-media attention to this topic, which began in December 1990. During the 14-year period, we accrued 1,181,244 person-years of follow-up.

Since the classification criteria for connective-tissue diseases excluded patients with milder or atypical cases and those who did not fulfill the criteria early in their disease, the true incidence of the diseases could have been underestimated. We performed three additional analyses using less stringent case definitions that included (1) patients who reported a rheumatic disease on any biennial questionnaire; (2) patients who had a positive screening, as defined on the connective-tissue disease screening questionnaire; and (3) patients who had any 1 of 41 signs, symptoms, or laboratory features of a connective-tissue disease that were included in the six classification-criteria sets that were abstracted from the medical record.

We performed analyses according to type of implant: silicone-gel-filled, saline-filled, double-lumen, or polyurethane-coated.

### Statistical Analysis

For each participant, the number of person-years was assigned to the appropriate breast-implant category. Once a subject had surgery for a silicone breast implant, she was defined as having been exposed to silicone, regardless of whether an implant was subsequently removed. The number of person-years was calculated from 1976 until May 31, 1990, or until the date of diagnosis of any connective-tissue disease, whichever came first.

The analysis was based on incidence rates. Relative risk, the measure of association, was defined as the incidence rate of connective-tissue disease among women with breast implants divided by the corresponding incidence rate among women without breast implants. Age-specific rates were calculated in five-year categories of age and used to compute age-adjusted relative risks, with 95 percent confidence intervals.<sup>13</sup> When fewer than five cases involving exposure were observed, we calculated exact confidence intervals.<sup>14</sup>

## RESULTS

During the 1,181,244 person-years of follow-up, connective-tissue diseases were confirmed in 516 subjects. Among the 87,501 women in the analysis, 1183 (1.4 percent) reported having had some type of breast im-

plant between 1976 and May 31, 1990; gave complete information; and were free from connective-tissue disease before the implantation. Women with breast implants accounted for 11,170 person-years of follow-up. Information about the breast-implant surgery is summarized in Table 1.

The mean ( $\pm$ SD) period during which any kind of breast implant was in place was  $9.9 \pm 6.4$  years (range, 1 month to 40.5 years). Among women with silicone-gel-filled implants, the mean period was  $10.0 \pm 6.2$  years (range, 1 month to 37.5 years) (Table 2).

#### Definite Connective-Tissue Disease

Among the 516 women who met the criteria for connective-tissue disease, the observed incidence rate per 100,000 women was within the ranges reported in other studies (Table 3). Three of the patients with definite connective-tissue disease had breast implants (silicone-gel-filled in one, double-lumen in another, and saline-filled in the third). All had rheumatoid arthritis; their cases had no unusual features. The age-adjusted relative risk of any definite connective-tissue disease among the women with any type of breast implant, as compared with the women without breast implants, was 0.6 (95 percent confidence interval, 0.2 to 2.0) (Table 2).

We also examined risk according to the type of breast implant, specifically the silicone-gel-filled implants. One woman with a definite connective-tissue disease had silicone-gel-filled implants. The age-adjusted relative risk among women with such implants was 0.3 (95 percent confidence interval, 0.0 to 2.0) (Table 2). No patient with polyurethane-coated breast implants had any of the connective-tissue diseases studied.

The age-adjusted relative risk of rheumatoid arthritis was 0.9 (95 percent confidence interval, 0.3 to 2.6) with any breast implant, 0.4 (95 percent confidence interval, 0.1 to 2.4) with silicone-gel-filled breast im-

Table 2. Age-Adjusted Relative Risk of Connective-Tissue Disease among Women with Breast Implants as Compared with Women without Implants.

CASE TYPE	NO IMPLANT (N = 86,318)	BREAST IMPLANT	
		ANY TYPE (N = 1183)	SILICONE- GEL-FILLED* (N = 876)
Self-reported connective-tissue disease			
No. of cases	5054	32	21
Age-adjusted relative risk	1.0	0.7	0.6
95% Confidence interval		0.5–1.0	0.4–0.9
Self-reported signs or symptoms of connective-tissue disease†			
No. of cases	1277	17	11
Age-adjusted relative risk	1.0	1.5	1.2
95% Confidence interval		0.9–2.4	0.7–2.2
Documented signs or symptoms of connective-tissue disease‡			
No. of cases	898	6	4
Age-adjusted relative risk	1.0	0.7	0.6
95% Confidence interval		0.3–1.6	0.2–1.6
Definite connective-tissue disease			
No. of cases	513	3	1
Age-adjusted relative risk	1.0	0.6	0.3
95% Confidence interval		0.2–2.0	0.0–1.9
Duration of implant			
Mean ( $\pm$ SD) yr		9.9 $\pm$ 6.4	10.0 $\pm$ 6.2
Range		1 mo–40.5 yr	1 mo–37.5 yr

\*This category is a subgroup of "any type" of implant.

†The signs and symptoms are those included in the screening questionnaire on connective-tissue disease.<sup>6</sup>

‡Data were derived from the medical-record review. Documented signs and symptoms included proximal weakness, a high creatine kinase concentration, positive electromyogram, positive muscle biopsy, proximal scleroderma, sclerodactyly, digital scars, bibasilar lung fibrosis, malar or discoid rash, photosensitivity, nasopharyngeal ulcers, nonerosive arthritis, pleuritis, pericarditis, proteinuria, renal casts, seizures, psychosis, hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia, positive test for lupus erythematosus, antibodies to double-stranded DNA, biologic false positive serologic test for syphilis, positive test for anti-cardiolipin antibody, positive antinuclear-antibody test, Raynaud's phenomenon, morning stiffness for more than one hour, arthritis in three or more joint areas, arthritis in hand joints, rheumatoid nodules, positive rheumatoid-factor tests, radiographic changes characteristic of rheumatoid arthritis, keratoconjunctivitis, xerostomia, salivary-gland biopsy positive for Sjögren's syndrome, and anti-Ro, anti-La, anti-extractable-nuclear-antigen, and anti-U1-RNP antibodies.

Table 1. Breast-Implant Surgery in 1183 Women from the Nurses' Health Study.

VARIABLE	NO. OF WOMEN (%)
Indication	
Cosmetic reasons	587 (50)
Cancer	387 (33)
Prophylaxis	138 (12)
Unknown	71 (6)
Type	
Silicone-gel-filled	876 (74)
Saline-filled	170 (14)
Double-lumen	67 (6)
Polyurethane-coated	14 (1)
Unknown	56 (5)
No. of operations*	
1	911
2	191
3	52
4	29
Side	
Unilateral	224 (19)
Right	112
Left	112
Bilateral	937 (79)
Unknown	22 (2)

\*Each operation was counted as one, irrespective of whether a bilateral operation was performed.

plants, and 1.4 (95 percent confidence interval, 0.2 to 9.7) with saline-filled implants, as compared with no breast implants. No patients with scleroderma, systemic lupus erythematosus, inflammatory myositis, mixed connective-tissue disease, or Sjögren's syndrome had any type of breast implant.

#### Risk of Connective-Tissue Disease or Symptoms Based on Less Stringent Diagnostic Criteria

We studied women with possible early, milder, or atypical forms of connective-tissue disease or with any sign or symptom of a connective-tissue disease who did not meet standard classification criteria (Table 2). These groups were not mutually exclusive.

Since 1976, 5087 women have reported having a connective-tissue disease or rheumatic disorder on the biennial questionnaires. Thirty-two had some type of breast implant, including 21 with silicone-gel-filled implants. The age-adjusted relative risk of any connective-tissue disease was 0.7 (95 percent confidence interval, 0.5 to 1.0) for those with breast implants as compared with those without breast implants. For wom-

Table 3. Incidence Rates of Connective-Tissue Diseases in the Nurses' Health Study (1976 to 1990).

DISEASE	NURSES' HEALTH STUDY		INCIDENCE RANGE IN OTHER STUDIES†
	NO. OF CASES	INCIDENCE RATE*	
Rheumatoid arthritis	392	33.2	24–50
Systemic lupus erythematosus	96	8.1	1.8–7.6
Scleroderma	14	1.2	0.4–1.9
Polymyositis or dermatomyositis	12	1.0	0.5–1.1
Sjögren's syndrome	2	—	—
Mixed connective-tissue disease	0	—	—
Any connective-tissue disease	516	43.68	—

\*Rates are per 100,000 person-years.

†Range of incidence rates reported in 10 other studies.<sup>15-24</sup>

en with silicone-gel-filled implants, the age-adjusted relative risk was 0.6 (95 percent confidence interval, 0.4 to 0.9).

Signs or symptoms of connective-tissue disease were reported on the screening questionnaire by 1294 women, including 17 with some type of breast implant and 11 with silicone-gel-filled implants. Of these 17 patients, 3 fulfilled the classification criteria for rheumatoid arthritis on review of the medical records. Two patients, one with symptoms of arthritis and Raynaud's phenomenon and another with Raynaud's phenomenon alone, could not be classified as representing definite cases. Nine patients had other rheumatic or musculoskeletal conditions (five had osteoarthritis, one chondrocalcinosis, one trochanteric bursitis, one cervical strain, and one familial Mediterranean fever). In three patients, no evidence of rheumatic disease or symptoms could be found. The age-adjusted relative risk of self-reported signs or symptoms of connective-tissue disease was 1.5 (95 percent confidence interval, 0.9 to 2.4) among the women with any type of breast implant as compared with those without implants (Table 2). For the women with silicone-gel-filled breast implants, the age-adjusted relative risk was 1.2 (95 percent confidence interval, 0.7 to 2.2).

We also studied 904 participants with any of 41 signs, symptoms, or laboratory findings seen in connective-tissue diseases that were validated by review of the medical records (Table 2). Six of these women had some type of breast implant, including four with silicone-gel-filled breast implants. As compared with the group without breast implants, their age-adjusted relative risk of having the signs or symptoms of connective-tissue disease was 0.7 (95 percent confidence interval, 0.3 to 1.6) with any breast implant and 0.6 (95 percent confidence interval, 0.2 to 1.6) with silicone-gel-filled breast implants. The analyses for other implant types had similar results (data not shown).

## DISCUSSION

In this large cohort study, we did not find an increased risk of any connective-tissue disease or of 41 signs or symptoms of connective-tissue disease among

women with any breast implant or with specific types of breast implants. Connective-tissue diseases occur infrequently. For this and other reasons, our study cannot be considered definitively negative. The upper bound of the 95 percent confidence interval for the relative risk of definite connective-tissue disease (2.0), for example, does not exclude minor associations that would still be of public health importance. Since information on exposure was based on self-report, there may have been some misclassification of breast-implant surgery. However, we found high rates of agreement between self-reports and medical records in our validation study of self-reported breast implants.

In all epidemiologic studies of rheumatic diseases, diagnosis is a major problem. We identified and confirmed cases through a multistep procedure and blinded medical-record review. Sixty-five percent of the 904 subjects who had any signs or symptoms of connective-tissue disease as determined by chart review had seen physicians who were active members of the American College of Rheumatology. The observed incidence of connective-tissue diseases was within ranges previously reported in population-based studies.<sup>15-24</sup> The application of strict criteria for any connective-tissue disease may exclude some true cases or milder cases and hence underestimate the true incidence of disease. With a rare disease, a slight underestimation of the incidence rate is less important in a study of etiology than is the misclassification of participants without disease as having disease.<sup>25</sup> In this situation, misclassification adds a small number of true cases to the very large number of true non-cases and has a negligible influence on estimates of the exposure among the non-cases. Less specific criteria might add non-cases. Since the number of cases is relatively small, the non-cases could make up an appreciable proportion of the total cases. Thus, the distribution of exposure among cases might be inaccurate. If the misclassification is random, the risk estimate will be driven toward the null value.

We found no association between breast implants and previously reported signs and symptoms,<sup>26-29</sup> such as Raynaud's phenomenon, photosensitivity, arthritis, morning stiffness, xerostomia, dry eyes, sclerodactyly, positive antinuclear-antibody tests, and positive rheumatoid-factor tests. We could not study subjective and largely unverifiable symptoms, such as fatigue, decreased ability to sleep, frequent sore throats, cognitive deficits, arthralgias, lymphadenopathy, or dizziness, or diseases such as fibromyalgia.

The 5514 women who died during the 14-year study period could not be studied because information about breast-implant surgery was not available for them. It is unlikely that this potential limitation biased the results, unless women with breast implants and connective-tissue disease died at a higher rate than women with connective-tissue disease who did not have breast implants.

Our results are based on data about registered nurses, about 95 percent of whom were white. Whether

these results can be generalized to include other women may be questioned. In 1989, a national survey of 40,000 households in the United States found that approximately 60 percent of breast implantations were performed for cosmetic reasons and that 95 percent of women with implants were white.<sup>30</sup> The prevalence of breast implants was higher in the South and West than in other regions of the country and increased with household income. Furthermore, the breast-implant rate in our cohort, 1.4 percent, is within the range of 0.7 to 2.0 percent estimated for U.S. women. For these reasons, the women in our study are likely to be representative of women in the United States who have breast implants.

Our results are consistent with the findings of published epidemiologic studies of breast implants and rheumatic diseases<sup>31-36</sup> and reports in abstract form.<sup>37-40</sup> In a population-based retrospective cohort study,<sup>31</sup> 749 women in Olmsted County, Minnesota, who received breast implants between January 1964 and December 31, 1991, were followed for a mean of 7.8 years and compared with 1498 control women of similar age without implants. In 5 case subjects, as compared with 10 in the control group, one of the specified connective-tissue diseases was diagnosed (relative risk, 1.06; 95 percent confidence interval, 0.34 to 2.97).

In conclusion, we found no evidence of an association between silicone breast implants and either connective-tissue diseases defined according to a variety of standardized criteria or signs or symptoms of connective-tissue disease.

We are indebted to the nurses in this study for their continuing participation; to Barbara Egan, Karen Corsano, and Mary Scamman for expert assistance; and to Dr. Peter H. Schur for reviewing this manuscript.

## REFERENCES

- Kessler DA. The basis of the FDA's decision on breast implants. *N Engl J Med* 1992;326:1713-5.
- Independent Advisory Committee on Silicone-Gel-Filled Breast Implants. Summary of the report on silicone-gel-filled breast implants. *Can Med Assoc J* 1992;147:1141-6.
- Angell M. Do breast implants cause systemic disease? Science in the courtroom. *N Engl J Med* 1994;330:1748-9.
- Sánchez-Guerrero J, Schur PH, Sergeant JS, Liang MH. Silicone breast implants and rheumatic disease: clinical, immunological and epidemiologic studies. *Arthritis Rheum* 1994;37:158-68.
- Hazards of silicone breast implants. *Face-to-Face*, December 10, 1990. Columbia Broadcasting System.
- Karlson EW, Sanchez-Guerrero J, Wright EA, et al. A connective tissue disease screening questionnaire (CSQ) for population studies. *Ann Epidemiol* (in press).
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
- Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581-90.
- Alarcon-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease: study of 593 patients. *J Rheumatol* 1989;16:328-34.
- Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;292:344-7.
- Fox RI, Robinson C, Curd J, Michelson P, Bone R, Howell FV. First International Symposium on Sjogren's Syndrome: suggested criteria for classification. *Scand J Rheumatol Suppl* 1986;61:28-30.
- Rothman KJ, Boice JD. *Epidemiologic analysis with a programmable calculator*. Washington, D.C.: Public Health Service, 1979. (NIH publication no. 79-1649.)
- Stata reference manual: release 3.1, 6th ed. College Station, Tex.: Stata Corporation, 1993.
- Dugowson CE, Koepsell TD, Voigt LF, Bley L, Nelson JL, Daling JR. Rheumatoid arthritis in women: incidence rates in group health cooperative, Seattle, Washington, 1987-1989. *Arthritis Rheum* 1991;34:1502-7.
- Symmons DPM, Barrett EM, Chakravorty K, Scott DGI, Silman AJ. The incidence of rheumatoid arthritis in Norfolk, England. *Arthritis Rheum* 1992;35:S126. abstract.
- Fessel WJ. Systemic lupus erythematosus in the community: incidence, prevalence, outcome, and first symptoms; the high prevalence in black women. *Arch Intern Med* 1974;134:1027-35.
- Michet CJ Jr, McKenna CH, Elveback LR, Kaslow RA, Kurland LT. Epidemiology of systemic lupus erythematosus and other connective tissue diseases in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc* 1985;60:105-13.
- Oddis CV, Conte CG, Steen VD, Medsger TA. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963-1982. *J Rheumatol* 1990;17:1329-34.
- Hochberg MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970-1977. *Arthritis Rheum* 1985;28:80-6.
- Medsger TA Jr, Masi AT. Epidemiology of systemic sclerosis (scleroderma). *Ann Intern Med* 1971;74:714-21.
- Steen V, Conte C, Santoro D, Casterline GLZ, Oddis CV, Medsger TA Jr. Twenty-year incidence survey of systemic sclerosis. *Arthritis Rheum* 1988;31:S57. abstract.
- Silman AJ, Jannini S, Symmons D, Bacon P. An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol* 1988;27:286-90.
- Medsger TA Jr, Dawson WN Jr, Masi AT. The epidemiology of polymyositis. *Am J Med* 1970;48:715-23.
- Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 1986;123:894-900.
- Borenstein D. Siliconosis: a spectrum of illness. *Semin Arthritis Rheum* 1994;24:Suppl 1:1-7.
- Vasey FB, Havice DL, Bocanegra TS, et al. Clinical findings in symptomatic women with silicone breast implants. *Semin Arthritis Rheum* 1994;24:Suppl 1:22-8.
- Solomon G. A clinical and laboratory profile of symptomatic women with silicone breast implants. *Semin Arthritis Rheum* 1994;24:Suppl 1:29-37.
- Freundlich B, Altman C, Sandorfi N, Greenberg M, Tomaszewski J. A profile of symptomatic patients with silicone breast implants: a Sjögren's-like syndrome. *Semin Arthritis Rheum* 1994;24:Suppl 1:44-53.
- Cook RR, Delongchamp RR, Woodbury MA, Perkins LL, Harrison MC. The prevalence of women with breast implants in the United States — 1989. *J Clin Epidemiol* 1995;48:519-25.
- Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Melton LJ III. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994;330:1697-702.
- Giltay EJ, Bernelot Moens HJ, Riley AH, Tan RG. Silicone breast prostheses and rheumatic symptoms: a retrospective follow up study. *Ann Rheum Dis* 1994;53:194-6.
- Weisman MH, Vecchione TR, Albert D, Moore LT, Mueller MR. Connective-tissue disease following breast augmentation: a preliminary test of the human adjuvant disease hypothesis. *Plast Reconstr Surg* 1988;82:626-30.
- Bridges AJ, Conley C, Wang G, Burns DE, Vasey FB. A clinical and immunologic evaluation of women with silicone breast implants and symptoms of rheumatic disease. *Ann Intern Med* 1993;118:929-36.
- Wells KE, Cruse CW, Baker JL Jr, et al. The health status of women following cosmetic surgery. *Plast Reconstr Surg* 1994;93:907-12.
- Strom BL, Reidenberg MM, Freundlich B, Schinnar R. Breast silicone implants and risk of systemic lupus erythematosus. *J Clin Epidemiol* 1994;47:1211-4.
- Wigley FM, Miller R, Hochberg MC, Steen V. Augmentation mammoplasty in patients with systemic sclerosis: data from the Baltimore Scleroderma Research Center and Pittsburgh Scleroderma Data Bank. *Arthritis Rheum* 1992;35:S46. abstract.
- Goldman JA, Lamm SH, Cooper W, Cooper L. Breast implants are not associated with an excess of connective tissue disease (CTD). *Arthritis Rheum* 1992;35:S65. abstract.
- Hochberg MC, Perlmutter DL, White B, et al. The association of augmentation mammoplasty with systemic sclerosis: results from a multi-center case-control study. *Arthritis Rheum* 1994;37:1249. abstract.
- Dugowson CE, Daling J, Koepsell TD, Voigt L, Nelson JL. Silicone breast implants and risk for rheumatoid arthritis. *Arthritis Rheum* 1992;35:S66. abstract.