Breast Implant Rupture and Connective Tissue Disease: A Review of the Literature

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Background: Large-scale epidemiologic studies to date have not found any credible association between silicone breast implants and either well-defined connective tissue diseases or undefined or atypical connective tissue diseases. It has been hypothesized that implant rupture could prompt an immunologic reaction giving rise to autoimmune or related diseases. In this article, the authors review the available literature on implant ruptures and connective tissue disease.
Methods: Articles were identified from PubMed and by cross-checking reference lists of retrieved articles.
Results: Five publications were identified. In none of the studies were diseases or symptoms related to well-defined or ill-defined connective tissue diseases associated with rupture status.
Conclusions: There appears to be little scientific basis for any association between implant rupture and well-defined connective tissue disease or undefined or atypical connective tissue diseases. The concept of silicone-related disease was developed by rheumatologists based on highly selected groups of symptomatic breast implant patients seen in their practices. It is likely that nonspecific complications or symptoms related perhaps to capsular contracture or implant rupture may be misinterpreted as representing a systemic disease. (*Plast. Reconstr. Surg.* 120 (Suppl. 1): 62S, 2007.)

Anecdotal reports and case series have suggested that silicone implants may cause various diseases, in particular, connective tissue diseases, or a new "silicone adjuvant syndrome."[1–3] However, large-scale epidemiologic studies have consistently failed to demonstrate increased risks of these diseases among women with breast implants.[4–11] It has been hypothesized that women with long-term breast implantation and/or women with ruptured implants may experience increased exposure to silicone, which in turn could induce an immunologic reaction, leading to a higher risk of specific symptoms or systemic diseases.[2,12,13] We have reviewed the scientific literature on the subject of connective tissue disease in women with silicone breast implants, with specific focus on the relation to implant rupture.

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PATIENTS AND METHODS

We searched PubMed, EMBASE, and The Cochrane Library using the terms "silicone breast implants" and "connective tissue disease" and various combinations of different keywords such as "rupture," "adverse effect," and "extracapsular silicone." Manual searches using the related link facility extended the number of references identified. Additional references were identified by cross-checking the reference lists of the identified publications. Few of the retrieved references actually presented findings stratified by implant rupture status, which is the focus of this review.

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Breast Implants and Connective Tissue Disease

Several comprehensive reviews, meta-analyses, and recent updates of large epidemiologic studies have evaluated associations of breast implants and connective tissue diseases.[8,10,11,14–17] All reached the same conclusion that there is no credible association between silicone breast implants and either well-defined connective tissue diseases or undefined or atypical connective tissue diseases to date.

Ruptured Breast Implants and Connective Tissue Disease

Most of the studies on breast implants and connective tissue disease identified in the search for this review included highly selected groups of patients who were referred to rheumatologists because of symptoms or to plastic surgeons for explantation. To our knowledge, only five studies have reported on connective tissue disease or related symptoms evaluated by implant rupture status based on patients not thought to be selected by the clinical course or symptoms[18–22] (Table 1). Only one study exclusively included women with cosmetic breast implants ($n = 228$),[22] one study included primarily women with cosmetic implants (85 percent of 344 women),[18] and the other studies comprised fewer women, who either primarily or exclusively underwent reconstruction after breast cancer.[19–21]

Study I

In 2001, Brown et al.[18] assessed a number of self-reported symptoms and diseases among 344 women from two different plastic surgery clinics who were examined with magnetic resonance imaging to determine the status of their breast implants. In the first part of the study, implant rupture prevalence was determined: 236 women (68.6 percent) had at least one ruptured implant, and 73 of these (21.2 percent) had extracapsular silicone.[23] In the second published report, the women were categorized according to rupture status.[18] Neither rupture in general nor extracapsular rupture in particular was associated with an increase in self-reported symptoms, including joint symptoms, skin rash, cognitive disorder, fatigue, or hair loss. The women were also asked whether they had been diagnosed with any of seven rheumatic conditions: Raynaud's syndrome, chronic fatigue syndrome, Sjögren's syndrome, scleroderma, systemic lupus erythematosus, fibromyalgia, or other connective tissue disease. Rupture (intracapsular or extracapsular rupture) was not associated with an increase in any of these diseases. Extracapsular rupture was, however, associated with an increased reporting of fibromyalgia (odds ratio, 2.8; 95 percent confidence interval, 1.2 to 6.3) and Raynaud's syndrome (odds ratio, 4.2; 95 percent confidence interval, 1.1 to 16.0) (adjusted for implant characteristics) when compared with a combined group of women with intact implants or intracapsular ruptured implants.[18]

There are several methodologic limitations in the study by Brown and colleagues.[17,22,24] Women with extracapsular ruptures were compared with an inappropriately combined group of women with intact implants and intracapsular ruptures, even though women with intracapsular rupture reported lower frequencies of fibromyalgia and Raynaud's syndrome than women with intact implants. From a biological and methodologic point of view, it would have been sounder to compare women with extracapsular ruptures to women with intact implants. Such comparisons would not have produced any statistically significant findings.[25] The magnetic resonance imaging study was based on a subgroup of a larger cohort obtained from volunteer plastic surgery clinics; reliance on volunteer clinics and low response rates raise questions about selection bias. In addition, the radiologic diagnosis of extracapsular rupture could be subject to misclassification; a subsequent study of the same patient series revealed lower interobserver agreement for the diagnosis of extracapsular silicone than for intracapsular silicone.[26] Finally, the investigators could not rule out the possibility that self-reported conditions had been diagnosed before implantation. This issue is crucial, as highlighted in a recent study by Wolfe and Anderson examining the frequency of silicone breast implants among patients in a rheumatic disease clinic.[27] The study found no association between implants and subsequent diagnosis of rheumatoid arthritis or fibromyalgia. However, silicone breast implants were more common in patients with a prior diagnosis of fibromyalgia than among controls, suggesting certain common characteristics among women who undergo breast augmentation and those diagnosed with fibromyalgia.[27]

Study II

In a Danish study, 271 women from a larger group of unselected breast implant women were randomly selected to undergo a magnetic resonance imaging examination to determine implant status.[28] Ruptured implants were observed in 97 of

Table 1. Studies Examining an Association between Silicone Breast Implant Rupture Diagnosed by Magnetic Resonance Imaging and Connective Tissue Disease or Related Disorders or Symptoms

Reference	Setting	Study Design	Study Population	Rupture Frequency	Main Results
Brown et al., 2001[18]	United States	Cohort study	344 women (85% had cosmetic implants)	236 women (69%) with ruptures, 73 (31%) with extracapsular rupture (21% of all women)	Comparison between women with extracapsular ruptures and a combined group of women with intact implants and intracapsular ruptures: fibromyalgia: OR = 2.8, 95% CI = 1.2–6.3; Raynaud's syndrome: OR = 4.2, 95% CI = 1.1–16.0; other CTD: OR = 2.7; 95% CI = 0.8–8.5
Berner et al., 2002[20]	Germany	Cross-sectional study	32 breast cancer patients reconstructed with silicone breast implants	13 (41%) with ruptures	Women with implant rupture compared with women with no implant rupture: No difference in self-report of 23 CTD-related symptoms Numbness/tingling in extremities was reported by: 44% with intact implants and 85% with ruptured implants ($p = 0.02$)
Gaubitz et al., 2002[21]	Germany	Cohort study	90 women with silicone breast implants (53% reconstruction after breast cancer surgery, 22% reconstruction after mastopathia surgery, and 25% cosmetic)	24 (27%) had ruptures; 13 (54%) of these had silicone in the liver with NMRS; 15 (23%) of those with intact implants had apparent silicone in the liver ($p = 0.006$)	No difference in 14 CTD-related symptoms stratified on implant status (with or without rupture); no difference in 12 CTD-related symptoms stratified on MRS-silicone in liver; two symptoms overreported by women with MRS silicone in liver: (1) tingling/numbness of the fingers in 82% with MRS silicone in the liver and in 52% without MRS silicone in the liver ($p = 0.006$); (2) photosensitivity in 57% with MRS silicone in the liver and 31% without MRS silicone in the liver ($p = 0.02$)
Contant et al., 2002[19]	The Netherlands	Cohort study	57 women with immediate breast reconstruction after mastectomy (half of the mastectomies were prophylactic)	Three women (0.7%) had rupture signs 1 yr after reconstruction	No difference in self-reported complaints or rheumatologic parameters by rupture status
Hölmich et al., 2003[22]	Denmark	Cohort study	238 women with cosmetic implants	92 (39%) with ruptures, 23 (25%) with extracapsular ruptures (10% of all women)	All women with ruptured implants compared to women with intact implants: risk of defined CTD*: OR = 0.9, 95% CI = 0.1–6.7; risk of undefined CTD: OR = 1.0, 95% CI = 0.3–3.0; women with extracapsular ruptures only, compared to women with intact implants: risk of defined CTD*: OR = 3.8, 95% CI = 0.4–35.1; risk of undefined CTD†: OR = 0.8, 95% CI = 0.1–4.5

OR, odds ratio; CI, confidence interval; CTD, connective tissue disease; MRS, magnetic resonance spectroscopy; NMRS, nuclear magnetic resonance spectroscopy.
*Defined connective tissue disease includes Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and dermatomyositis/polymyositis.
†Undefined connective tissue disease includes ill-defined rheumatologic symptoms (e.g., fibromyalgia).

the 271 women (36 percent) examined and in 141 of the 533 implants (27 percent) examined. Of the 141 ruptures, 110 (78 percent) were intracapsular and 31 (22 percent) were extracapsular. The extracapsular ruptures affected 23 women, or 8 percent of the study participants. An additional 32 implants (6 percent) in 19 women were diagnosed as possibly ruptured. For the subsequent study on symptoms and diseases, the latter group was excluded, along with 14 women who had not provided questionnaire data, yielding 238 study participants, 92 with ruptured implants and 146 with intact implants.[22] One year before the magnetic resonance imaging examination, the study women completed a questionnaire that collected information on medical history (including prior surgery) and postimplant history of 28 specific diseases and numerous symptoms. Blood was drawn at the time of the magnetic resonance imaging examination. All samples were analyzed for antinuclear antibodies, rheumatoid factor immunoglobulin M antibodies, and cardiolipin immunoglobulin G and immunoglobulin M antibodies.

Overall, there were no statistically significant differences in self-reported diseases occurring after implantation when comparing women with ruptured implants to women with intact implants, with most of the odds ratios close to unity. Two women in the ruptured group (both with extracapsular ruptured implants) and three women with intact implants reported a diagnosis of definite connective tissue disease, yielding an odds ratio for definite connective tissue disease of 0.9 (95 percent confidence interval, 0.1 to 6.7) comparing women with ruptures (intracapsular and extracapsular) with women with intact implants, and 3.8 (95 percent confidence interval, 0.4 to 35.1) for women with extracapsular ruptures only versus women with intact implants (adjusted for the woman's age and implant characteristics). There were no reported cases of scleroderma or polymyositis/dermatomyositis.

Eleven women with intact implants and 10 women with ruptured implants (two had extracapsular rupture) reported undefined connective tissue disease or other chronic conditions of an inflammatory nature, yielding an adjusted odds ratio of 1.0 (95 percent confidence interval, 0.3 to 3.0), comparing women with ruptures (intracapsular and extracapsular combined) with women with intact implants, and 0.8 (95 percent confidence interval, 0.1 to 4.5) when only women with extracapsular ruptures were compared with women with intact implants. The diagnoses constituting the group of undefined connective tissue disease or other chronic conditions included fibromyalgia: one case in the intact group and one case in the ruptured group (an intracapsular rupture). The remaining conditions were postinfectious arthritis, cystitis, sinusitis, hidrosadenitis, eczema, herpes, psoriasis, and epicondylitis. Large but similar proportions of women with or without ruptured implants reported unspecified neck, back, or shoulder pain (41 percent of participants overall). Cognitive problems (34 percent), joint or muscle symptoms (26 and 20 percent, respectively), and fatigue (17 percent) were also common complaints in all groups; however, women with ruptured implants, or with extracapsular ruptures in particular, were not more likely to report symptoms than women with intact implants after adjusting for age and implant characteristics, with the exception of breast hardness (capsular contracture), which was reported in excess among women with extracapsular rupture (odds ratio, 6.3; 95 percent confidence interval, 1.7 to 23.5). Fourteen percent of the women overall were antinuclear antibody–positive, 11 percent had positive rheumatoid factor immunoglobulin M antibodies, and 6 percent and 9 percent had positive cardiolipin immunoglobulin G and immunoglobulin M antibodies, respectively. The proportion of women positive for the various blood tests did not differ between women with intact implants and women with ruptured or extracapsular ruptured implants.

Shortcomings in the Danish study include its relatively small size and low statistical precision regarding rare diseases and symptoms. The study had high sensitivity (89 percent) and specificity (97 percent) for identifying ruptured and intact implants.[29] The information on self-reported diseases and symptoms and the blood samples were obtained on average 1 year before the magnetic resonance imaging examination, and even though almost all ruptures were likely present at that time, a few ruptures may have occurred in the interim, leading to a possibility of misclassification of rupture status and thus an attenuation of risk estimates.

Study III

A study from a German radiology institute examined 32 breast cancer patients who underwent reconstruction with silicone breast implants and compared them with a control group of 64 other breast cancer patients selected by a matched-pair technique from the pool of 1100 breast cancer patients without implants treated at the same institution.[20] Both groups of patients were re-

cruited during routine follow-up magnetic resonance imaging mammograms. A comprehensive self-administered questionnaire focused on rheumatic and autoimmune symptoms. The majority of symptoms were reported equally often in the two study groups (19 symptoms); however, six symptoms were reported more often in the women who underwent breast reconstruction: numbness/tingling sensation in the extremities, swelling of the fingers, change of color of the fingers, dry oropharynx, vertigo, and hot flashes. Only numbness/tingling in the extremities was positively associated with implant rupture diagnosed by magnetic resonance imaging ($p = 0.02$), whereas all other symptoms ($n = 23$) were found to the same extent among women with intact implants and women with ruptured implants. The actual number of women reporting conditions were not presented in the article; however, the authors reported that 41 percent of all 32 implant patients had defective implants after an average implantation time of 7 years, 59.4 percent had tingling sensations, and 44 percent of patients with intact implants and 85 percent of those with ruptured implants had numbness/tingling sensations. Subsequent evaluation with peripheral arterial blood pressure measurements and oscillography showed that none of the patients with finger color changes had typical Raynaud's phenomenon. The women who had undergone reconstruction were younger than controls, and additional analyses showed an age association with hot flashes. The authors concluded that the many symptoms reported were common in middle-aged women, regardless of exposure to silicone implants.[20]

Study IV

In a second study by the same group, 90 women with silicone breast implants (reconstruction after breast cancer surgery, 53 percent; reconstruction after mastopathia surgery, 22 percent; and the remainder cosmetic) were examined with magnetic resonance imaging to identify implant rupture. Approximately 40 percent of participants were members of an association of "silicone-damaged women."[21] It is not stated whether there was an overlap in study participants with the previous study. There were no significant differences between women with intact implants and women with ruptured implants with regard to clinical symptoms, the data for which were gathered by means of a comprehensive self-administered questionnaire focusing on rheumatologic symptoms. Clinically, two patients had had rheumatoid arthritis before silicone breast implantation, whereas the other patients revealed no typical symptoms of arthritis or connective tissue disease at clinical examination by a rheumatologist. Ruptured implants had on average been in situ in 11.2 years compared with 8.2 years for the intact implants. In addition, magnetic resonance spectroscopy was used to identify apparent silicone in the liver. Of 24 patients (26.6 percent) with ruptured implants, 13 (54.2 percent) had apparent silicone detected in the liver by magnetic resonance spectroscopy. Of the 66 patients with intact implants, 15 (22.7 percent) had apparent silicone in the liver. The patients with magnetic resonance spectroscopic evidence of silicone in the liver had a similar complaint pattern to that of those without magnetic resonance spectroscopic evidence of silicone in the liver, with the exception of tingling/numbness of the fingers (82.1 and 51.6 percent, respectively; $p = 0.006$) and photosensitivity (57 and 31 percent, respectively; $p = 0.02$).

The authors concluded that implant rupture status had no major impact on rheumatic symptoms of women with silicone breast implants but recommended further investigation of the neuropathy-associated symptoms.[21] The identification of silicone in the liver by magnetic resonance spectroscopy is somewhat controversial, and the method has been debated.[30] The association of implant rupture with numbness/tingling sensations in the extremities observed in the first study, and the association of the same symptoms with apparent silicone in the liver detected with magnetic resonance spectroscopy in this study, is difficult to interpret. Such symptoms, if more than a chance finding, could in theory be part of a generalized disease such as scleroderma or other connective tissue diseases or a neurologic disorder. However, large epidemiologic studies of neurologic diseases in breast augmented women have not found any associations with silicone implants,[31,32] and studies evaluating implants and connective tissue diseases have likewise not found an increased risk.[7,8,10,11] Selective recruitment of some patients for this study from the silicone-damaged women groups can bias results, and the above findings should be considered cautiously.

Study V

The last study, which was designed to directly evaluate connective tissue disease occurrence among women with silicone breast implant according to rupture status, is a Dutch prospective study including 57 women who had undergone immediate breast reconstruction after mastectomy (approximately half of the mastectomies were

prophylactic).[19] Before and 1 year after implantation, the women had blood drawn for analysis for antinuclear antibodies and they filled out a self-administered questionnaire checking for numerous rheumatologic symptoms. In addition, a magnetic resonance imaging examination was performed 1 month and 1 year after breast reconstruction. None of the women experienced a change in antinuclear antibody status 1 year after implantation, but there was an increase in the proportion of women reporting symptoms related to Sjögren's syndrome, symptoms indicative of rheumatoid arthritis and Raynaud's syndrome, and undefined complaints. Three implants (in three women) had rupture signs at the second magnetic resonance imaging examination, but none of the three women had any changes in antinuclear antibodies or complaints related to Sjögren's syndrome, rheumatoid arthritis, Raynaud's syndrome, or undefined complaints.[19] The study is of limited use in this context because of the very small number of ruptures. Another limitation is that the study population consisted of women with breast cancer or a genetic predisposition to develop breast cancer. The impact of receiving a serious diagnosis or undergoing mastectomy may in itself lead to an increase in the number of reported symptoms. Inclusion of a comparison group of women undergoing mastectomy without reconstruction would have aided in the interpretation of the results.

Another study[33] claiming to investigate symptoms according to implant rupture status is mentioned here for completeness, but is based exclusively on highly selected symptomatic women with silicone breast implants, which detracts seriously from its credibility. Vermeulen and Scholte recruited participants for the study from readers of a Dutch silicone implant support group magazine. Only women who had undergone revision surgery and who knew about their implant status were included. These women were compared with a group of women with diagnosed chronic fatigue syndrome to evaluate whether the symptom profile among the two groups was comparable. The majority of the responders (72 percent) reported debilitating chronic fatigue, with a different complaint pattern than the typical chronic fatigue syndrome patients, including more muscle and joint pain but lower frequencies of the other characteristic symptoms. The second aim of the study was to correlate implant rupture with symptoms. An excess reporting of debilitating chronic fatigue, postexertional malaise, multijoint pain, and impaired short-term memory was found among those with ruptured implants compared with those stating to have intact implants. It was concluded that the pattern of silicone-induced complaints differed from that in patients with chronic fatigue syndrome, and that additional studies are needed to more precisely elucidate the pathophysiology of the disease caused by silicone gel breast implants.[33]

It is not possible to conclude anything about causality based on such a highly selected study group as in the Vermeulen and Scholte study. This study does not add any credible information to the evaluation of possible associations of ruptured silicone breast implants and connective tissue diseases.

SUMMARY

Any woman with silicone breast implants is at risk of some exposure to silicone. Thus, it is unlikely that various general symptoms or systemic diseases should be associated only with implant rupture and not be observed (albeit at lower frequency) among women with intact implants as well. Magnetic resonance imaging–based studies of unselected women with implants have observed relatively high numbers of undiagnosed implant rupture (i.e., silent ruptures).[23,28] The actual risk of rupture was found to be associated primarily with implant time in situ (implant age), but also with other implant characteristics. In the study by Brown et al., 55 percent of 687 implants with a median age of 10.8 years (range, 8.4 to 13.9 years) were ruptured.[23] In the similar Danish study, 26 percent of 533 implants with a median age of 12 years (range, 3 to 25 years) were ruptured.[28] In a subsequent incidence study with a repeated magnetic resonance imaging examination, the rupture incidence was measured to be 2.3 ruptures per 100 implant years (95 percent confidence interval, 1.1 to 3.4) for modern third-generation implants.[34] Two recent magnetic resonance imaging studies of modern third- and fourth-generation implants found lower rupture prevalences: 8 percent of third-generation implants with a median implantation time of 11 years were ruptured,[35] and 1 percent of the new cohesive (fourth-generation) implants were ruptured after a median implantation time of 6 years.[36] Based on knowledge of the above studies, it is likely that a substantial proportion of the women studied in past large cohort and case-control investigations evaluating associations between early generation implants and connective tissue diseases had undiagnosed ruptured implants at the time of study. Because no excess risk of connective tissue disease or rheumatologic conditions has been identified overall in these epidemiologic studies, any potential ex-

cess risk attributable to ruptured implants in particular is likely small.

As can be seen from this review of implant rupture and connective tissue diseases, there appears to be little scientific basis for any association between implant rupture and well-defined connective tissue disease or undefined or atypical connective tissue disease. The concept of a new silicone-related disorder has been developed among rheumatologists based on symptomatic breast implant patients; reliable information cannot be derived from such selective groups of women with implants. We believe it is more likely that nonspecific complications or symptoms resulting perhaps from capsular contracture or implant rupture may be misinterpreted as representing a systemic disease.

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