Fast Track Article

Scleroderma and augmentation mammoplasty – a causal relationship?

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Abstract

Background: The studies implicating a causal relationship between silicone and scleroderma, other autoimmune diseases, and fibromyalgia-like symptoms have been largely descriptive with absence of appropriate controls and no consideration of potential confounders.

This case control study of augmentation mammoplasty and scleroderma represents an attempt to answer these deficiencies.

Aims: To compare the frequency and temporal relationship of augmentation mammoplasty in interviewed and deceased cases and interviewed controls. To determine the frequencies of exposure to non-augmentation mammoplasty silicone, and to determine the frequencies of mastectomy and breast lumpectomy in interviewed cases and controls.

Methods: Scleroderma cases and age-stratified general practice controls were interviewed using a prepilotted telephone questionnaire. Self-reported date/s of augmentation mammoplasty were ascertained, as were dates of onset of first and second scleroderma symptom/s and scleroderma diagnosis, where relevant. Comparison of socioeconomically adjusted rates was expressed in terms of rate ratios.

Results: Augmentation mammoplasty rates were comparable between interviewed cases and controls. No augmentation mammoplasty procedures were documented in deceased scleroderma patients' medical records. Rates of exposure to non-mammoplasty silicone, mastectomy and breast lumpectomy were comparable in interviewed cases and controls.

Conclusions: This study failed to demonstrate an association between silicone breast implantation and the subsequent development of scleroderma, to a relative risk level as low as 4.5 with 90% power. (Aust NZ J Med 1994; 24: 74-80.)

Key words: Scleroderma, augmentation mammoplasty, silicone.

INTRODUCTION

Scleroderma is an uncommon connective tissue disorder whose multifactorial aetiology remains poorly defined. It has been genetically linked to the HLA DRw52 antigen[1] and environmentally linked to silicone,[2-6] silicon dioxide (silica),[7,8] vinyl chloride,[9] epoxyresins,[10] aniline-contaminated rapeseed oil,[11] and drugs, including bleiomycin, pentazocine, and local and general inhalational anaesthetic agents.[12-17]

Silicone refers to a family of linear or cyclic, branched, or crosslinked polymers containing a repeating silicon-oxygen backbone.[18] Depending on the length of the backbone, the properties of the sidegroups and their interactions, silicone may exist in fluid, resin

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or elastomeric forms. The medical uses of silicones include breast, penile, testicular, and muscle implants, syringe lubrication, vitreous replacement fluid, body contour moulding, incorporation in drugs including antireflux/antacid medications, low friction coating on capsules, silastic (silicone elastomer) joint replacements, tendon grafts, lens implants, cardiac pacemakers, ventriculoperitoneal and arteriovenous shunts, rhinoplasty, and artificial heart valves.

Prior to 1962, when Cronin and Gerow introduced silicone breast implants,[19] mammoplasty procedures involved injection of paraffin, silicone, or petroleum derivatives directly into breast tissue. Many of the first anecdotal reports linking breast augmentation procedures and altered immunity pertained to paraffin injections. This state of altered immunity was a poorly defined condition named 'human adjuvant disease'.[20] Subsequently paraffin injections were also associated with the other disease outcomes – scleroderma, mixed connective tissue disease and morphea.[21]

Paraffin has been largely supplanted by silicone because of its chemical, oxidative and thermal stability.[18] Associations have also been made between connective tissue diseases and silicone, either whether injected directly into breast tissue[21–24] or as a gel-filled silicone breast implant.[24–28] Recently the saline-filled breast implant has also been implicated in the development of connective tissue diseases and fibro-myalgia-like symptoms.[29,30]

This comparative study of scleroderma and augmentation mammoplasty employed case-control methodology as part of a larger study investigating scleroderma epidemiology in Sydney. When the study was initiated in 1989, the nature of the association between silicone/paraffin and connective tissue disease was poorly defined. Little consideration was given to precise definition of exposure and outcome variables and data were not translated into disease rates. Although one of the least common of the connective tissue diseases, scleroderma is the most frequently reported with augmentation mammoplasty. Hence scleroderma was chosen as the most appropriate outcome variable and augmentation mammoplasty the exposure variable.

There were five study aims, the first of which was to compare the self-reported rates of augmentation mammoplasty in interviewed female cases and controls. The second was to determine the rates of augmentation mammoplasty in deceased female scleroderma patients. The third was to determine and quantitate the temporal relationship between augmentation mammoplasty and scleroderma onset in interviewed female cases in which augmentation mammoplasty preceded scleroderma onset. The fourth was to determine the frequencies of exposure in interviewed cases and controls to non-augmentation mammoplasty silicone with respect to insulin dependent diabetes mellitus, silicone non-breast implant prostheses (including joint replacements, pacemakers, valve replacements, intraocular lenses, and ventriculoperitoneal shunts), and antireflux/antacid use. The fifth was to determine the frequencies of mastectomy and breast lumpectomy in interviewed cases and controls, which might have indicated the need for silicone breast prostheses in both groups.

METHODS

Cases

In order to satisfy study entry requirements a scleroderma case had to satisfy each of five entry criteria:

1 Scleroderma or CREST syndrome was a premortem clinical diagnosis and made on or before 31 December 1988.

2a Either the patient's disease had to satisfy the American College of Rheumatology's Preliminary Criteria for the Classification of Systemic Sclerosis (Scleroderma)[31]; or

2b The patient had sclerodactyly and at least two of the following to suggest systemic disease: Raynaud's phenomenon, oesophageal dysmotility, calcinosis, telangiectasia(e), bilateral basal pulmonary fibrosis or an elevated antinuclear antibody titre.

3 The patient must have resided in Sydney for at least 6 consecutive months within the study time frame.

4 If the patient migrated from Sydney the diagnosis of scleroderma must have been made prior to emigration.

5 If the patient migrated to Sydney the major reason for such migration to Sydney must not have been for scleroderma management. Excluded were patients with mixed connective tissue disease, morphea or other localised forms of scleroderma, and those with sclerodema. Cases were obtained from the following six sources – death certification data, all public and most large private hospitals within Sydney, private rooms of physicians, dermatologists and vascular surgeons, membership of the Scleroderma Association of NSW, and medical laboratories performing antinuclear antibody tests.

Controls

A control was a living Sydney resident sex and age-stratified (+/- 5 years) with a living case. Each control must have resided in Sydney for at least six consecutive months during the study period and must have attended his/her Sydney general practitioner since January, 1990. Excluded were either those Sydney residents with scleroderma or CREST or those Sydney residents with a psychiatric history. Ascertainment

of controls was through the auspices of 28 randomly chosen Sydney general medical practitioners.

Instrument

The instrument used was a prepilotted telephone questionnaire specifically designed for this study.

Interviewed cases and controls were initially asked the following open-ended question in relation to their past surgical and medical history – 'What illnesses or operations have you ever had and when?' – which provided data relating to breast-implant and non-breast implant silicone-related exposure. These included cardiac pacemaker insertions and valve replacements, joint replacements, cataract lens extractions with or without intraocular lens replacement, diabetes mellitus and pernicious anaemia, mastectomy and breast lumpectomy. Interviewed female cases were later asked the directed question – 'Have you ever had an operation to make your breasts bigger – called augmentation mammoplasty? Yes/No/other. If Yes when?'.

Augmentation mammoplasty status in deceased female scleroderma cases was ascertained by perusal of such patients' medical records.

Use of antireflux/antacid medications, which may contain silicone (dimethicone), was estimated in answer to the following: 'What tablets, pills or potions are you on at the moment?'

Ethical committee approval for the study was obtained from all public hospitals within Sydney and the large private hospitals. Consent was also obtained from the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons, the Royal Australian College of General Practitioners and the Australasian College of Dermatology.

Statistical Analysis

Frequencies of non-augmentation mammoplasty silicone exposure between interviewed cases and controls were expressed in terms of rate ratios, with appropriately determined 95% confidence limits.

Socioeconomic status adjustment of augmentation mammoplasty rates in interviewed cases was performed using the technique of indirect standardisation.[32]

Results

A total of 315 cases and 371 controls were interviewed, of whom 251 and 289 respectively were female. Of the latter 540 patients, the number who had augmentation mammoplasty, their socioeconomic status, number of procedures, prosthetic type/s where known, and the temporal relationship with scleroderma onset, where relevant, are documented in Table 1.

The unadjusted rates for augmentation mammoplasty in interviewed cases and controls were 4/251 (1.59%) and 5/289 (1.73%) respectively. Socioeconomic status was a scleroderma disease determinant in Sydney (unpublished data) and socioeconomic status was recognised as a potential confounder for the mammoplasty – scleroderma relationship. Therefore the crude rate for augmentation mammoplasty in

TABLE 1
Self-Reported Rates of Augmentation Mammoplasty in Interviewed Cases and Controls

Cases/ Controls	DOB	SES	Date at onset of first symptoms	Date at onset of second symptoms	Date at disease diagnosis	Disease subtype	Surgical procedure, prosthetic type, and date of surgery
Cases							
1	1952	5	1981	1981	1984	Limited	AM (Sal) 1983 AM (Sal) 1987*
2	1926	6	1981	1985	1987	Limited	AM (NM)
3	1942	3	1963	1975	1984	Limited	AM (Si) 1982† RI 1985 RI 1991‡
4	1944	6	1986	NM	1987	Limited	AM 1977 RI 1984§ AM 1988
Controls							
1	1947	5	—	—			AM 1975
2	1929	6	—	—		—	AM 1990
3	1948	6		—	—	—	AM 1976
4	1940	2	—	—	—	—	AM
5	1936	5	—	—	—	—	AM 1973 RI and R 1980 R 1983

Abbreviations: DOB: Date of birth; SES: socioeconomic status, ASCO: Australian Classification of Occupations, AM: augmentation mammoplasty; RI: removal of implant; R: readjustment of implant; RI&R: removal of implant and reinsertion/replacement; Sal: saline implant; Si: silicone implant
*operation performed because insertion of a larger prosthesis was requested
†operation was preceded by breast carcinomas. Treatment included bilateral mastectomy procedures
‡implants were removed because 'implants kept repeating and moving out of place'
§implants were both removed due to 'hardening' around the left implant.

interviewed cases was adjusted for socioeconomic-status, using socioeconomic status-specific rates for augmentation mammoplasty in interviewed controls as standard rates. The socioeconomic status-adjusted rate of augmentation mammoplasty in interviewed scleroderma patients was 1.54% (95% CI 0.03-3.04%), similar to that (1.73%) in interviewed controls (rate ratio = 0.89; 95% CI 0.23-3.41). Using direct standardisation procedures to adjust for socioeconomic status, the adjusted rate of augmentation mammoplasty in the Australian population was 1.68% (95% CI 1.65-1.71).

A past surgical history of augmentation mammoplasty was recorded in no medical records of 213 deceased female scleroderma patients.

Of the four interviewed scleroderma patients with self-reported augmentation mammoplasty, Cases 1 and 3 had augmentation mammoplasty procedures which postdated the onset of both first and second disease symptoms. Case 1 had the onset of first and second disease symptoms, Raynaud's phenomenon and polyarthralgia respectively, aged 29 and 30 years. The first augmentation mammoplasty procedure occurred when the patient was aged 31 years. Scleroderma was diagnosed four years later. The first and second disease symptoms for Case 3 were Raynaud's phenomenon aged 21 years, and the co-occurrence of increased skin sensitivity, indigestion and fingertip ulceration aged 33 years. Breast augmentation surgery was first performed seven years later. Scleroderma was eventually diagnosed two years after breast augmentation. Therefore in Cases 1 and 3 the occurrence of scleroderma-related symptoms predating augmentation mammoplasty surgery mitigated against the causal role of augmentation mammoplasty.

Only Case 4 and possibly Case 2 satisfied the Bradford-Hill[33] criterion of temporality with respect to disease causation with a preclinical phase between breast augmentation and first disease symptoms in Case 4 of nine years.

Of the five interviewed controls who had had breast augmentation procedures, none answered the question relating to Raynaud's phenomenon ('Have you ever had at least one finger or toe go a waxy white colour if it gets cold or you get upset?') in the affirmative, although one patient (Control 5) complained of cold blue toes but not fingers with the cold. This symptom predated augmentation mammoplasty surgery. The rates of non-augmentation mammoplasty silicone exposure were indirectly assessed in interviewed male and female cases and controls. These included rates of insulin-dependent diabetes mellitus, and silicone elastomer and other silicone non-breast implant prostheses including joint replacements, pacemakers, valve replacements, and ventriculoperitoneal shunts, and use of antacids. Rates of mastectomy and breast lumpectomy were also included as these potentially reflected rates of undisclosed breast augmentation for other than cosmetic reasons. Results are documented in Table 2.

TABLE 2
Exposure Status to Potentially Silicone-Containing Non-Augmentation Mammoplasty Medical Products in Interviewed Cases and Controls

Potential silicone exposure from other than augmentation mammoplasty prostheses	Cases $n=315$ (%)	Controls $n=371$ (%)
Cardiac valve replacements	2 (0.6)	3 (0.8)
Pacemaker	2† (0.6)	0 (0.0)
Silastic joint replacement	4‡ (1.3)	3 (0.8)
Insulin-dependent diabetes mellitus	1 (0.3)	3 (0.8)
Pernicious anaemia	1 (0.3)	0 (0.0)
Silicone tubing		
haemodialysis AV shunt	1§ (0.3)	0 (0.0)
hydrocephalus VP shunt	0 (0.0)	1 (0.3)
Cataract extractions +/- intraocular lens	14¶ (4.4)	7 (1.9)
Other silicone prostheses	0 (0.0)	0 (0.0)
Occupational handling of breast prostheses	2 (0.6)	1 (0.3)
Antacid use		
peptic ulcer	16 (5.1)	17 (4.6)
hiatus hernia	12** (3.8)	15 (4.0)
current antacid use	10 (3.2)	6 (1.6)
Mastectomy	4 (1.3)	7 (1.9)
Breast lumpectomy	13 (4.1)	25 (6.7)

*Valve replacement postdated onset of second disease symptoms in both instances.
†Pacemaker insertion postdated scleroderma diagnosis in both cases.
‡Silastic joint replacement postdated disease diagnosis in at least one case.
§AV shunt postdated disease diagnosis.
¶Of these, eleven postdated disease diagnosis.
**These twelve cases refer to those whose symptoms or diagnosis of hiatus hernia predated the onset of scleroderma second disease symptoms.

DISCUSSION

The critical issue in the silicone augmentation mammoplasty – scleroderma controversy is whether this association occurs at a rate exceeded by chance.

Previously this could only be estimated from USA data, where comparison of both observed and expected rates of scleroderma in patients with augmentation mammoplasty was possible.

The expected rate, which assumes no significant relationship between augmentation mammoplasty and scleroderma, ranges between 1/5,000[34] and 1/50,000,[35] these boundaries representing the cumulative lifetime female-specific incidence rate (prevalence rate) and the annual female-specific incidence rate respectively. However, greater precision can be applied to this expected rate estimation, assuming the abovementioned annual female-specific scleroderma incidence rate, a mean age at augmentation mammoplasty approximating 40 years, and a mean expected lifespan approximating 80 years. This estimate, 40/50,000,

(0.8/10,000) more closely approximates the female-specific prevalence rate than the female-specific incidence rate. Using USA data which estimate that between one and two million US women have had augmentation mammoplasty,[36] and the 'cumulative' incidence rate of 0.8/10,000 females, the number of scleroderma cases arising purely by chance in the population of between 1-2 million breast-augmented women approximates 80-160.

However, the observed number of scleroderma cases with augmentation mammoplasty published to date, approximating 40 (3-6, 26-28, 30), provides an observed prevalence rate of 0.2-0.4/10,000. Therefore comparison of the observed and expected rates of augmentation mammoplasty-positive scleroderma patients using US data do not support the hypothesis that scleroderma and augmentation mammoplasty co-occur at a rate exceeded by chance. However, this estimate has inherent flaws. No explanation has been given as to the derivation of the US rate denominator estimate of one to two million women. Similarly the rate numerator estimates rely on published instances of breast-augmented women with scleroderma and these estimates also may underrepresent the true number to an unknown extent.

Results from the current study suggest that the prevalence rates of breast augmentation in scleroderma females are similar to those in age-matched and socioeconomically-stratified Sydney controls. That is, they fail to support the concept of a causal association between breast augmentation and scleroderma. Assuming a required significance estimate of <0.05, a conservative two-tailed distribution, a control population rate of augmentation mammoplasty approaching 2%, and a sample size approximating 250, the study had 90% power to detect relative risks as low as 4.5 (80% power to detect relative risks approximating 3.5). Different methods were utilised to obtain augmentation mammoplasty data between living and deceased cases. However, assuming these differing methodologies were highly concordant, a metaanalysis of both living and deceased cases lowered the relative risks still further, approximating three (90% power) and 2.5 (80% power). As data collection was largely completed by 1991, the responses from cases and controls were thought to have largely avoided possible reporting or other bias consequent to media involvement.

Other important results from the current study suggested no significantly differential rates of exposure to non-augmentation mammoplasty-related medical uses of silicone nor possible requirements for breast augmentation following breast lumpectomy or mastectomy procedures. Type Two errors, however, cannot be discounted.

Breast augmentation was a sensitive issue to both interviewed cases and controls. Two of four cases and two of five controls failed to disclose augmentation mammoplasty surgery in the initial open-ended question pertaining to past surgical and medical history but disclosed it in the subsequent direct questioning regarding breast augmentation.

Problems inherent in this study include its lack of power to detect relative risks lower than 2.5-3, problems relating to augmentation mammoplasty data being self-reported and unverified in terms of false-positive and false-negative reporting, and the extent to which the augmentation mammoplasty rates in the Sydney general practice controls are representative of those in the Sydney community.

The rates of breast augmentation in the female controls, approximated 1.7%, possibly higher than expected. Augmentation mammoplasty procedures are largely performed in the private health care sector and are theoretically biased towards those in higher socioeconomic strata. Of interest, therefore, was the observation that the socioeconomic distribution amongst augmentation mammoplasty-positive controls was comparable in both the highest (ASCO Groups 1,2 and 3) and middle socioeconomic strata (ASCO groups 4,5 and 6) – 1.7% and 2.3% respectively. If covert selection bias operated such that the general practice controls overestimated the true extent of breast augmentation in the Sydney community, then the lack of difference between interviewed cases and controls might be contributed to by such bias.

This study has failed to demonstrate a significant relationship between augmentation mammoplasty and scleroderma. However, the indirect evidence in favour of such a causal association between (silicone) augmentation mammoplasty and scleroderma includes the frequency with which it is associated with scleroderma and its associated nucleolar and anticentromere ANA staining patterns in contrast to other more common connective tissue diseases,[30] the recent association between with a previously unidentified precipitin line on immune blotting[37] and the observation that in some instances there is improvement in disease following prosthesis explanation. Although the first and second observations cannot be denied, the third observation pertaining to some disease reversibility following removal of the exposure agent is considered weaker because in some instances no account is taken of either the natural history of the disease progressing from its oedematous to indurative phase, or the influence of medications such as steroids, or D-penicillamine.

If an apparent causal association were found between scleroderma and (silicone) augmentation mammoplasty the importance of two important confounders, general or local anaesthesia, and microcrystalline ('fumed') silica, incorporated within the silicone elastomer as a

reinforcing filler, has to be considered. Isolated descriptive studies exist linking local anaesthesia,[12] and the general anaesthetic agents, trichloroethylene and trichloroethane, to scleroderma[13-15] Although the latter are not widely used in Australia they bear structural similarity to halothane which has enjoyed more widespread usage. Crystalline silica may induce silicosis, whose pathology is similar in some respects to that of scleroderma. Microcrystalline ('fumed') silica, a component of the silicone elastomer, has been recently associated in animal studies with a 'highly reactive cellular response,'[38] and silica has also been incriminated as a scleroderma inducer.[7,8]

The relationship between augmentation mammoplasty, silicone and scleroderma remains contentious. However, this study provides useful guidelines. It has demonstrated no association between augmentation mammoplasty and scleroderma to levels of relative risk higher than 4.5 with reasonable certainty, and no association between augmentation mammoplasty and scleroderma to levels as low as 2.5 with lower levels of certainty. The study provides the first Australian prevalence rate estimates for augmentation mammoplasty and the distribution by socioeconomic status. Finally, the study has not demonstrated significantly differential rates of exposure to non-augmentation-related medical uses of silicone. ■

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