

# Prospective cohort study of breast implants and the risk of connective-tissue diseases

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**Background** A 2000 meta-analysis indicated no overall association between breast implants and risk of connective-tissue diseases (CTDs). However, a large retrospective cohort study we previously conducted suggested, instead, a small increased risk of CTDs. Because of limitations inherent to the retrospective cohort study design, we sought clarification by conducting a prospective cohort study of the association of breast implants with CTD risk.

**Methods** Participants were 23 847 US women (mean age 56.6 years), 3950 of whom had breast implants and 19 897 did not. Women reported their breast implant status at baseline in 2001 and were followed for a median of 3.63 years. During follow-up, women reported incident CTD, confirmed using a CTD screening questionnaire (CSQ) and medical records.

**Results** In multivariate analyses, the rate ratios for self-reported CTD (113 vs 377 cases in the implanted and non-implanted group, respectively) were 1.60 [95% confidence interval (CI) 1.28–2.00], for CSQ-confirmed CTD (77 vs 226 cases), 1.80 (1.37–2.38) and for medical record confirmed CTD (21 vs 74 cases), 1.39 (0.82–2.35).

**Conclusions** Although this prospective cohort study represented a stronger design than the retrospective cohort study, the present data should still be viewed cautiously because of remaining methodological limitations, including the potential for differential self-reporting of CTD and CTD symptoms among women with and without breast implants, the difficulty of obtaining medical records for women reporting CTD and the low and possibly differential confirmation of self-reported disease against medical records. A reasonable conclusion is the lack of a large increase in CTD risk (e.g.  $\geq 2$ -fold) associated with breast implants.

**Keywords** Breast implants, cohort studies, connective-tissue diseases, women's health

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## Introduction

Cosmetic breast surgery has been performed for >100 years, with the silicone breast implant introduced in 1962.<sup>1</sup> Today, one of the most common cosmetic surgical procedures is breast augmentation: more than 260 000 US women underwent this procedure in 2005, more than a doubling of the number doing so in 1998.<sup>2</sup> In the UK, breast augmentation rates increased by 275% between 2002 and 2008.<sup>3</sup>

In the decades following the introduction of the silicone breast implant, several case reports and case series raised concerns about potential adverse health effects, particularly increased risks of connective-tissue diseases (CTDs), associated with such implants.<sup>4–6</sup> Although the interpretation of findings from these studies is difficult because there is no comparison group (women without silicone breast implants), the US Food and Drug Administration (FDA) in 1992 banned the use of silicone breast implants, except in clinical trials, citing inadequate data on their safety.<sup>5</sup>

Following the ban, case-control and cohort studies were conducted over the next several years to investigate whether breast implants did indeed increase the risks of CTDs.<sup>7–25</sup> Overall, these studies indicated no increased risks of CTDs among women with breast implants, compared with non-implanted women.<sup>1,26–28</sup> A meta-analysis of 13 studies published in 2000 estimated an adjusted summary rate ratio (RR) of 0.80 [95% confidence interval (CI) 0.62–1.04] for CTDs associated with breast implants.<sup>26</sup> For six studies that specifically examined silicone breast implants, the summary RR was 0.82 (95% CI 0.46–1.46).<sup>26</sup> These data led to the FDA lifting its ban in 2006, approving silicone-gel filled breast implants made by two companies, Allergan and Mentor.<sup>29</sup>

Although the studies utilizing appropriate comparison groups indicated no increased risks of CTDs with breast implants when viewed in totality, not all individual studies supported this. In particular, the results from two large studies departed from the overall findings, reporting, instead, increased risks of CTDs with RRs = 1.24 (95% CI 1.08–1.41) in a 1996 study<sup>18</sup> and 2.0 (95% CI 1.5–2.8) in a 2004 study.<sup>13</sup> The former finding was from a retrospective cohort study of almost 400 000 women conducted by our research group. Although this study is the largest study of breast implants and CTDs to date, its limitations included the retrospective assessment of breast implants (thus, recall of this may have been biased among women who went on to develop a CTD), lack of ascertainment of the type of breast implant (silicone vs non-silicone) and self-reported CTD.

We therefore conducted a prospective cohort study to investigate the association of breast implants with risk of CTDs, utilizing eligible women from the same population as the 1996 study, but addressing the limitations of the previous study listed above.

## Methods

### Study subjects

Participants were from the 426 774 women comprising the eligible study population for our 1996 retrospective cohort study of breast implants and CTDs.<sup>18</sup> These women were individuals who returned a health questionnaire between 1992 and 1995, in response to an invitation to participate in the Women's Health Study, a completed randomized clinical trial (1992–2004) testing aspirin and vitamin E in the prevention of cardiovascular disease and cancer.<sup>30–32</sup> To reduce participant burden, we excluded 46 758 women participating in the Women's Health Study and another clinical trial, the Women's Antioxidant Cardiovascular Study, testing vitamins C and E and beta carotene in the secondary prevention of cardiovascular events, leaving 380 016 eligible women.<sup>33</sup>

We then selected all women, not known to be deceased, who reported a history of breast implants on their health questionnaire in 1992–95; these represented the exposed women ( $n = 10\,120$ ). For the unexposed comparison group, we randomly selected five women for each woman reporting breast implants, frequency matched on age ( $n = 50\,592$ ; for a few women, we were unable to obtain five matches). Our rationale for not using the entire cohort of 380 016 women was that the statistical information provided by this 5:1 match would be virtually identical to the full cohort, at substantially lower costs.

Beginning in April 2001, the baseline for the present study, we sent up to three mailings of a brief health questionnaire to the 60 712 women inquiring about socio-demographic factors, health habits and health history, including breast implants and CTDs [rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, dermatomyositis or polymyositis, Sjogren's syndrome and any other CTD—including mixed]. After excluding those deceased ( $n = 309$ ), those without valid mailing addresses ( $n = 5400$ ) and two duplicates, 55 001 remained eligible. A total of 32 439 women responded, an overall response rate of 59.0% (58.8% among the exposed; 59.0% among the unexposed).

Of the 32 439 women, we further excluded the following:

- (i) those declining to participate from the beginning ( $n = 1314$ );
- (ii) those missing updated information on breast implant history on the baseline questionnaire, 2001 (breast implant history was initially obtained in 1992–95;  $n = 46$ );
- (iii) those reporting a CTD diagnosis occurring before baseline, or were missing information on a CTD (in order to have a disease-free population at baseline;  $n = 3412$  who were older, heavier, more likely to smoke, less likely to consume alcohol, less likely to use post-menopausal hormones and less active than included women);

- (iv) those subsequently declining participation after enrolling (thus providing no follow-up information;  $n = 3816$ ); and
- (v) those providing a subsequent diagnosis of a CTD, but we were unable to obtain a date of diagnosis from the participant or their physicians ( $n = 4$ ).

Our final sample included 23 847 women; 3950 with breast implants and 19 897 without.

### Ascertainment of breast implants

On the baseline questionnaire in 2001, we asked whether women had ever had breast implants, and the year of the first procedure. For all women who responded affirmatively, we then sent a detailed questionnaire asking for further information, including a history of up to three breast implant surgeries/procedures, their date(s), reason(s) for the procedure(s), type of implant(s) and any complications experienced.

### Assessment of CTDs

At 1 and 2 years after the return of their baseline questionnaire, women were mailed a detachable postcard. They returned this if they had been diagnosed with myocardial infarction, stroke or transient ischemic attack, cancer, osteoarthritis, fibromyalgia or one of the following CTDs: RA, SLE, scleroderma, dermatomyositis or polymyositis, Sjogren's syndrome and any other CTD—including mixed—and also provided the diagnosis date(s). At the Year 3 and final follow-up, a brief health questionnaire, similar to that at baseline and including questions on CTD diagnosis, was mailed.

Because women returned their questionnaires and postcards in a staggered fashion, we included all final questionnaires up to October 2006. However, 90% of final questionnaires were received by April 2005.

We confirmed self-reported CTDs by two methods: using a validated CTD screening questionnaire (CSQ) for symptoms/signs of CTDs ('CSQ confirmed'), which has shown sensitivity of 83–96% for detecting CTDs and specificity of 83–93%,<sup>34</sup> and using medical records ('medical record confirmed'). Women who reported a CTD were first sent the CSQ; those who screened positive on the CSQ were then asked for permission to obtain medical records related to their CTD diagnosis.

Medical records were independently reviewed by two board-certified rheumatologists blinded to breast implant status; the reviewers met to discuss and resolve any discrepancies. CTDs were confirmed according to the American College of Rheumatology (ACR) classification criteria for RA and SLE,<sup>35,36</sup> preliminary ACR criteria for scleroderma,<sup>37</sup> and published studies of classification criteria for dermatomyositis or polymyositis, Sjogren's syndrome and mixed CTD.<sup>38–40</sup>

### Statistical analyses

We first compared characteristics of women with and without breast implants. We then used Cox proportional hazards models to estimate the hazard rate ratios of a CTD associated with breast implants. We defined CTDs based on three levels of diagnosis, from the least to the most precise: self-reported CTDs, CTDs that satisfied screening criteria on the CSQ<sup>34</sup> and CTDs confirmed using medical records. Follow-up time was calculated from the date of return of the baseline questionnaire to the latest follow-up questionnaire/postcard for women without a CTD; for women with a CTD, this was calculated to the self-reported date of diagnosis (self-reported and CSQ-confirmed CTD) or date of diagnosis on medical records (medical record confirmed CTD). We first adjusted models for age only, and then also for body mass index (BMI) (continuous variable), smoking (never, past, current) and use of post-menopausal hormones (never, past, current), factors associated with breast implants in the present study, which also have been associated with risk of CTDs. A second multivariate model further adjusted for history of breast cancer.

Because the numbers of several CTD outcomes were small, we conducted sensitivity analyses using propensity score modelling<sup>41</sup> to more efficiently control for potential confounders listed above, as well as additional variables associated with breast implants in the present study that have not been clearly linked to CTD risk. The propensity score model included age, age squared, BMI (<23, 23–24.9, 25–26.9, 27–29.9,  $\geq 30$  kg/m<sup>2</sup>), smoking (never, past, current), use of post-menopausal hormones (never, past, current), high cholesterol, hypertension (both no, yes), alcohol intake (g/day) and physical activity (<200, 200–599, 600–1499,  $\geq 1500$  kcal/day). A second propensity score model also included history of breast cancer.

We then estimated the RRs of CTDs according to the duration of breast implants at baseline (<10, 10 to <20 and  $\geq 20$  years), as well as the type of breast implant (silicone, saline, other and unknown) reported.

## Results

Table 1 compares the characteristics of women with and without breast implants. Their ages were similar, due to age-matching, but women with implants were leaner, more likely to smoke, to consume more alcohol, to be post-menopausal and using post-menopausal hormones and be more active. They were less likely to have a history of hypertension or high cholesterol. As expected, a history of breast cancer was more common in implanted women.

We sent women reporting breast implants a more detailed questionnaire requesting further information regarding their implants, and 3781 women (95.7%)

**Table 1** Characteristics of women according to breast implant status

	Breast implant (n = 3950)	No breast implant (n = 19 897)	P-value <sup>a</sup>
Mean age (SD)	57.0 (8.4)	56.5 (9.2)	0.22
Mean BMI, kg/m <sup>2</sup> (SD)	24.7 (4.6)	27.0 (5.9)	<0.0001
Smoking, %			
Never	52.4	57.5	<0.0001
Past	38.0	35.0	
Current	9.6	7.5	
Mean alcohol consumption, g/day (SD)	5.5 (9.6)	4.1 (8.4)	<0.0001
<b>Menopausal status, %</b>			
Post-menopausal	82.4	76.5	<0.0001
Pre-menopausal	15.2	20.4	
Not sure	2.4	3.1	
<b>Post-menopausal hormone use, %</b>			
Never	32.8	35.4	0.0002
Past	14.8	15.9	
Current	52.4	48.7	
Mean physical activity, kcal/week (SD)	1219 (1400)	1102 (1290)	<0.0001
History of hypertension, %	23.5	30.3	<0.0001
History of high cholesterol, %	31.9	35.3	<0.0001
History of breast cancer, %	28.2	4.9	<0.0001

<sup>a</sup>Using the Wilcoxon rank sum test for continuous variables and chi-squared test for categorical variables. SD, standard deviation.

responded. Of these, 2626 women reported having silicone gel implants (69.5%); 1384 women, saline implants (36.6%); and 528 women, both (14.0%). Regarding reasons for having breast implants, 1866 (49.4%) did so to enhance breast size, 1202 (31.8%) for reconstruction following mastectomy, and the remainder cited other reasons (including post-childbirth sagging, asymmetry and cysts). The median duration of implants was 17.1 (25th to 75th percentile, 12.7–23.0) years.

During follow-up [median 3.63 (25th to 75th percentile, 3.54–3.68) years], 113 women (2.9%) from the implanted group reported a diagnosis of any CTD, as did 377 women (1.9%) from the group without breast implants.

We mailed a CSQ<sup>34</sup> to all women who reported a CTD diagnosis, and received completed questionnaires from 93 women (82.3%) reporting breast implants, and 287 women (76.1%) without breast implants. In the breast implant group, 77 women (82.8%) screened positive for a potential CTD, whereas 226 women (78.8%) without implants did so. Thus, women with breast implants were more likely to return a CSQ, and also more likely to screen positive for CTDs.

We requested medical records for women who screened positive on the CSQ, and were able to obtain them for 41 (53.3%) and 138 (61.1%) women with and without breast implants, respectively. Medical records confirmed CTD diagnoses in 21 women with breast implants and 74 women without breast implants, representing 51.2% (21 of 41) and 53.6% (74 of 138), respectively, for whom medical records were received, and 27.3% (21 of 77) and 32.7% (74 of 226), respectively, for whom CSQs screened positive. Medical record confirmed CTD represented 18.6% (21 of 113) and 19.6% (74 of 377), respectively, of all self-reported CTD. Thus, a lower proportion of medical records were obtained for women with breast implants compared with non-implanted women, and medical record confirmation of a CTD also tended to be lower in women with breast implants.

Table 2 presents the RRs of CTDs, comparing women with and without implants. Of the CTDs, RA was the most commonly reported CTD, numbering 54 and 218 cases, respectively, in the two groups. With increasing strictness of criteria for confirmation, the numbers of confirmed CTD dropped steadily. With self-reported events, there was a 52–60% increase in risk for all CTDs, depending on covariate adjustment. For RA, the RRs ranged from 1.25 to 1.39; for the other individual CTDs, the numbers of cases were small and yielded results with wide CIs. With CSQ-confirmed CTD, we continued to observe an increase in risk (73–80%) of all CTDs. For all CTDs confirmed on medical record review, breast implants were associated with a 43% increase in risk (95% CI 0.88–2.33) in age-adjusted analysis, which was further attenuated to a 39% increase (0.82–2.35) after additional adjustments for BMI, smoking and post-menopausal hormone use.

In a secondary analysis accepting a diagnosis of a CTD by the participant's treating physician (i.e. not using strict study criteria adjudicated by study rheumatologists; *n* = 24 and 82 among women with and without implants, respectively), the corresponding RR of any CTD associated with breast implants was 1.44 (0.89–2.35), similar to the 1.39 for CTDs confirmed using strict study criteria.

Because history of breast cancer was a strong predictor of CTD in the present study, in another secondary analysis, we examined the association of breast implants with CTD, stratifying women by such a history. The results were not notably different, considering the wide CIs, among women without and with a history of breast cancer (data not shown). For example, the multivariate RR for all self-reported CTDs among women without a history of breast cancer was 1.66 (1.28–2.16); among women with a history, 1.30 (0.72–2.34) (in this latter group, there were 34 exposed cases and 22 unexposed cases).

In a sensitivity analysis that used propensity score modelling to more efficiently control for potential confounders as well as additional variables associated

**Table 2** RRs (95% CIs) of CTDs among women with breast implants

	All CTDs	RA	SLE	Scleroderma	Sjogren's syndrome	Dermatomyositis/polymyositis	Other CTDs (including mixed)
<b>Self-reported events</b>	(n = 113; 377) <sup>a</sup>	(n = 54; 218)	(n = 8; 19)	(n = 2; 10)	(n = 19; 43)	(n = 7; 9)	(n = 40; 115)
Age-adjusted RR	1.52 (1.23–1.87)	1.25 (0.93–1.68)	2.15 (0.94–4.90)	–	2.23 (1.30–3.83)	3.93 (1.46–10.6)	1.76 (1.23–2.52)
Multivariate RR1 <sup>b</sup>	1.60 (1.28–2.00)	1.32 (0.96–1.82)	2.04 (0.88–4.74)	–	2.28 (1.31–3.97)	3.97 (1.44–10.9)	1.80 (1.24–2.63)
Multivariate RR2 <sup>c</sup>	1.60 (1.26–2.03)	1.39 (0.99–1.97)	2.27 (0.93–5.54)	–	2.16 (1.18–3.99)	2.24 (0.69–7.27)	1.85 (1.24–2.75)
<b>Events confirmed using CSQ<sup>34</sup></b>	(n = 77; 226)	(n = 23; 86)	(n = 4; 11)	(n = 1; 4)	(n = 13; 25)	(n = 4; 5)	(n = 4; 8)
Age-adjusted RR	1.73 (1.33–2.34)	1.36 (0.86–2.15)	–	–	2.63 (1.34–5.14)	–	–
Multivariate RR1 <sup>b</sup>	1.80 (1.37–2.38)	1.39 (0.84–2.28)	–	–	2.80 (1.40–5.60)	–	–
Multivariate RR2 <sup>c</sup>	1.75 (1.30–2.36)	1.31 (0.76–2.24)	–	–	2.78 (1.29–5.98)	–	–
<b>Events confirmed using medical records</b>	(n = 21; 74)	(n = 12; 32)	(n = 2; 2)	(n = 1; 4)	(n = 0; 6)	(n = 0; 1)	(n = 7; 30)
Age-adjusted RR	1.43 (0.88–2.33)	1.89 (0.98–3.68)	–	–	–	–	1.18 (0.52–2.68)
Multivariate RR1 <sup>b</sup>	1.39 (0.82–2.35)	1.76 (0.83–3.75)	–	–	–	–	1.23 (0.53–2.83)
Multivariate RR2 <sup>c</sup>	1.21 (0.68–2.15)	1.30 (0.56–3.04)	–	–	–	–	1.46 (0.62–3.45)

<sup>a</sup>Number of events among women with breast implants; number of events among women without breast implants. Where the number of exposed cases is 5 or less, the RR is not provided due to small sample size.

<sup>b</sup>Adjusted for age, BMI, smoking and post-menopausal hormone use.

<sup>c</sup>Additionally adjusted for history of breast cancer.

with breast implants in the present study, we obtained similar results to those in Table 2 (data not shown). For example, the RR for all CTDs confirmed on medical record review from a model using propensity scores that did not include history of breast cancer was 1.40 (0.83–2.37); from a model including history of breast cancer, 1.21 (0.69–2.13).

We then examined the risk of CTD according to duration of breast implants (Table 3). There were no clear trends by duration for CTD confirmed using different degrees of strictness.

Finally, we examined the risk of developing CTD according to type of breast implant (Table 4). There were only two cases of CTD confirmed on medical record review among women with saline implants. For CSQ-confirmed CTD, the multivariate-adjusted RR with silicone breast implants was 2.03 (1.50–2.73); for saline implants, 1.45 (0.79–2.66).

## Discussion

In this large prospective cohort study, we observed a 60% increase (95% CI 1.28–2.00) in risk of self-reported CTD among women with breast implants, which attenuated to a 39% increase (0.82–2.35) for CTD confirmed using medical records. Although we had hoped that the present study would provide more definitive findings compared with our 1996 retrospective cohort study,<sup>18</sup> methodological limitations inherent to research involving such studies, discussed below, indicate that these results should be viewed with caution. An important lesson learnt is the difficulty of conducting unbiased research related to breast implants and CTDs. Perhaps the most reasonable conclusion that can be drawn from the present results is that there does not appear to be a large increase in risk of a CTD, say ≥2-fold, associated with breast implants, and with silicone breast implants in particular.

The first methodological concern relates to response rates. The response rate among eligible women was low (59%), but this alone was unlikely to result in bias as the low rate was approximately the same in women with and without implants. When women reported the occurrence of a CTD, they were sent a screening questionnaire for CTDs, the CSQ.<sup>34</sup> Response to this CSQ was differential, higher in women with than without implants (82 vs 76%), which could most likely lead to a bias away from the null. Women screening positive on the CSQ were asked for permission to review their medical records. The receipt of medical records was low, and differential, between implanted and non-implanted women (53 vs 61%), which could most likely lead to a bias towards the null.

A second methodological concern is the ascertainment of CTDs. Although the study was prospective in nature, women with breast implants might be more aware of symptoms and seek medical help, leading to increased reporting of symptoms and diagnosis

**Table 3** RRs (95% CIs) of all CTDs among women with breast implants, according to duration of implants

	No breast implants	Duration of breast implants (years)			P for trend across duration
		<10	10 to <20	≥20	
<b>Self-reported events</b>					
Number of cases	377	10	61	41	
Age-adjusted RR	1.00 (referent)	1.23 (0.66–2.31)	1.68 (1.28–2.20)	1.40 (1.02–1.94)	0.97
Multivariate RR <sup>a</sup>	1.00 (referent)	1.34 (0.69–2.61)	1.73 (1.29–2.30)	1.53 (1.10–2.13)	0.80
<b>Events confirmed using CSQ<sup>34</sup></b>					
Number of cases	226	7	43	26	
Age-adjusted RR	1.00 (referent)	1.44 (0.68–3.05)	1.98 (1.43–2.74)	1.49 (0.99–2.23)	0.62
Multivariate RR <sup>a</sup>	1.00 (referent)	1.52 (0.67–3.44)	2.00 (1.41–2.85)	1.64 (1.08–2.47)	0.59
<b>Events confirmed using medical records</b>					
Number of cases	74	3	12	6	
Age-adjusted RR	1.00 (referent)	1.90 (0.60–6.02)	1.68 (0.91–3.09)	1.04 (0.45–2.40)	0.31
Multivariate RR <sup>a</sup>	1.00 (referent)	1.54 (0.38–6.32)	1.61 (0.83–3.14)	1.14 (0.49–2.64)	0.42

<sup>a</sup>Adjusted for age, BMI, smoking, post-menopausal hormone use.

**Table 4** RRs (95% CIs) of all CTDs among women with breast implants, according to type of implants

	No breast implants	Implant type			
		Silicone implants <sup>a</sup>	Saline implants	Other	Unknown
<b>Self-reported events</b>					
Number of cases	377	84	20	2	7
Age-adjusted RR	1.00 (referent)	1.60 (1.26–2.02)	1.34 (0.86–2.11)	2.98 (0.74–12.0)	1.13 (0.54–2.39)
Multivariate RR <sup>b</sup>	1.00 (referent)	1.68 (1.31–2.15)	1.48 (0.93–2.36)	3.69 (0.92–14.8)	1.07 (0.48–2.41)
<b>Events confirmed using CSQ<sup>34</sup></b>					
Number of cases	226	62	12	0	3
Age-adjusted RR	1.00 (referent)	1.97 (1.49–2.61)	1.34 (0.75–2.40)	–	0.81 (0.26–2.51)
Multivariate RR <sup>b</sup>	1.00 (referent)	2.03 (1.50–2.73)	1.45 (0.79–2.67)	–	0.90 (0.29–2.83)
<b>Events confirmed using medical records</b>					
Number of cases	74	18	2	0	1
Age-adjusted RR	1.00 (referent)	1.74 (1.04–2.91)	0.68 (0.17–2.79)	–	0.82 (0.11–5.88)
Multivariate RR <sup>b</sup>	1.00 (referent)	1.63 (0.93–2.86)	0.79 (0.19–3.25)	–	0.92 (0.13–6.60)

<sup>a</sup>Includes double lumen and polyurethane-coated silicone implants.

<sup>b</sup>Adjusted for age, BMI, smoking and post-menopausal hormone use.

of CTD and a potential bias away from the null. When ascertaining CSQ-confirmed CTD, the proportion confirmed (among women who returned CSQs) was higher among women with than without implants (83 vs 79%), in line with the bias expected. With regard to medical record confirmation, the proportion of CTDs confirmed among those for whom medical records were obtained was low, and lower among women with than without implants (51 vs 54%), also congruent with the expected bias (i.e. CTDs rely in large part on symptoms to establish a diagnosis, and in the clinical setting, a diagnosis may be made with less stringent—fewer—criteria that those used in

research<sup>35–40,42</sup>). When calculated as a proportion of all women who reported CTD, the confirmation rate with medical records was very low, but similar among women with and without implants (19 vs 20%). This very low rate was not unique to the present study; previous studies have reported medical record confirmation of self-reported CTD of between 10 and 24%.<sup>13,23,43</sup> The overall rate of RA (the most common CTD) confirmed by medical records in the present study was 53 per 100 000 person-years, lower than the 73–130 per 100 000 comparably aged women per year reported in population-based studies.<sup>44</sup> Incidence rates may be lower because of incomplete response

rates, the stringent research criteria used as well as the 'healthy participant' effect—individuals who choose to participate in research studies tend to be healthier than the general population.

Thus, it is unclear in this study what the net effect of the different potential sources of bias might be on the relation between breast implants and CTD risk.

A third methodological concern relates to the rare occurrence of the disease studied, particularly the individual CTDs. The present study represents the second largest prospective cohort study to date, with only the study by Brinton *et al.*<sup>13</sup> recording a larger number of CTD cases confirmed on medical record review. Even with a cohort of almost 24 000 women, nearly 4000 with implants, followed for 3.6 years, there were few cases of CTD, and particularly scleroderma, the disease most commonly linked to breast implants in case reports and case series.<sup>1</sup> We combined the individual CTDs to obtain larger numbers of events, but the CTDs likely have different etiologies. Additionally, the present study only focused on classical CTDs, and did not seek information on other kinds of autoimmune diseases (e.g. atypical CTD or novel constellation of signs and symptoms in women with silicone breast implants) that also have been postulated to be linked to implants.<sup>1</sup>

The present study does possess a number of strengths, including its prospective design which, although not completely removing bias as discussed above, nonetheless can mitigate some bias, compared with case-control studies or retrospective cohort studies. It also used several levels of confirmation of CTD, from self-report to medical record confirmed disease. Although medical records were retrieved from only 53–61% of whom we requested records, this compares well with other studies. For example, in the largest prospective cohort study to date by Brinton *et al.*,<sup>13</sup> medical record retrieval was 35–40%. Finally, the present study collected information on the kinds of implants, allowing differentiation of implants containing silicone, whereas about half of the available studies do not have this information.<sup>26</sup>

The results from this study are not congruent with the findings from previous meta-analyses and reviews, which have reported no increase in CTD risk with breast implants, and silicone breast implants in

particular.<sup>1,26–28</sup> They are more in line with our earlier retrospective cohort study<sup>18</sup> that reported a 24% increase in risk, and a recent large prospective cohort study<sup>13</sup> that reported a 2-fold increase in risk, both of which also possessed many of the same methodological limitations of the present study. The different results across studies likely reflect their different study designs, the small sample sizes of many studies, limited duration of follow-up after breast implants and imprecise ascertainment of breast implants and/or CTD.

In conclusion, this study highlights the complexity of conducting research in the area of breast implants and CTD, particularly with regard to the rarity of the individual diseases of interest, the potential for differential self-reporting of CTD and CTD symptoms among women with and without breast implants, the difficulty of obtaining medical records for participants who reported CTD, and the low and possibly differential confirmation of self-reported disease against medical records. In view of these methodological issues, it is unlikely that future observational epidemiological studies will be able to detect small to moderate increases in risk, whereas randomized clinical trials that can do so are unethical. Perhaps the best advance that we can make is merely to exclude the likelihood of large increases in CTD risk associated with breast implants.

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### KEY MESSAGES

- Conducting research in the area of breast implants and risk of developing connective-tissue diseases (CTD) is challenging because of several methodologic issues.
- In view of these methodologic issues, it is unlikely that future observational epidemiologic studies will be able to detect any small to moderate increases in CTD risk, while randomized clinical trials which can do so are unethical.
- A reasonable conclusion is the lack of a large increase in CTD risk associated with breast implants.

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# Commentary: In pursuit of the 'best' possible evidence in investigations of breast implants and connective tissue disease

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Clinical medicine and public health organizations rely on epidemiology to play an integral role in evidence-based medicine. As epidemiologists, we are constantly striving to provide the best evidence with the goal of influencing public health and clinical practice for the better. With this overall objective in mind, studies are planned in excruciating detail and executed with painstaking care. After the data are collected and all analyses have been conducted, results are prepared for public dissemination. Sometimes, even when the optimal study has been conducted given the study population and subject matter, the investigators are left to excoriate their work in the 'strengths and limitations' section of the paper. The investigators do this even if their evidence is the best possible evidence and an improvement over prior evidence.

In the current edition of the *International Journal of Epidemiology*, Lee *et al.*<sup>1</sup> provide an excellent example of how they present the best possible evidence when faced with complicated study design issues. They investigated the risk of connective tissue disease

(CTD) associated with breast implants. CTDs have poorly understood aetiologies and vast, complex symptomatology. Considering the exposure, not only are breast implants a sensitive topic in society, but also the methods to study them are complex. There are no registries to easily identify women with implants, thus any study participant has her motivation questioned—perhaps she is only participating because of adverse symptoms she is experiencing. Those with implants are a mix of those who are electively choosing them (assumed physically 'healthy') and women who have been affected by cancer. Additionally, availability of implant types (saline and silicone) has varied over time and an individual woman may have multiple types over time. Presenting the best possible evidence becomes a massive challenge when confronted with the burden of dealing with judgement in the public health arena, in which: (i) randomized control trials (RCTs) are held by many clinicians and other individuals as a 'gold standard' and the only 'real' evidence that