Association of Breast Implants with Nonspecific Symptoms, Connective Tissue Diseases, and Allergic Reactions: A Retrospective Cohort Analysis

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Background: Given the rising media attention regarding various adverse conditions attributed to breast implants, the authors examined the association between breast implantation and the risk of being diagnosed with connective tissue diseases, allergic reactions, and nonspecific constitutional complaints in a cohort study with longitudinal follow-up.
Methods: Women enrolled in a regional military health care system between 2003 and 2012 were evaluated in this retrospective cohort study. A propensity score was generated to match women who underwent breast implantation with women who did not undergo breast implantation. The propensity score included age, social history, health care use, comorbidities, and medication use. Outcomes assessed included *International Classification of Diseases, Ninth Revision,* diagnoses codes for (1) nonspecific constitutional symptoms, (2) nonspecific cardiac conditions, (3) rheumatoid arthritis and systemic lupus erythematosus, (4) other connective tissue diseases, and (5) allergic reactions.
Results: Of 22,063 women included in the study (513 breast implants and 21,550 controls), we propensity score–matched 452 breast implant recipients with 452 nonrecipients. Odds ratios and 95 percent confidence intervals in breast implant recipients compared to nonrecipients were similar, including nonspecific constitutional symptoms (OR, 0.77; 95 percent CI, 0.53 to 1.13), nonspecific cardiac conditions (OR, 0.97; 95 percent CI, 0.69 to 1.37), rheumatoid arthritis and systemic lupus erythematosus (OR, 0.66; 95 percent CI, 0.33 to 1.31), other connective tissue diseases (OR, 1.02; 95 percent CI, 0.78 to 1.32), and allergic reactions (OR, 1.18; 95 percent CI, 0.84 to 1.66).
Conclusions: Women with breast implants did not have an increased likelihood of being diagnosed with nonspecific constitutional symptoms, connective tissue disorders, and/or allergic reaction conditions. (*Plast. Reconstr. Surg.* 147: 42e, 2021.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Although breast implants were introduced in the 1960s, controversy about breast implant safety has persisted for more than 60 years.[1] As this debate continues, over 330,000 cosmetic breast augmentation operations are currently performed annually in the United States alone.[2] Some of the reported concerns include increased risk of connective tissue diseases, including rheumatoid arthritis and Sjögren syndrome[3]; increased allergic reactions[4]; and a vague constellation of symptoms including fatigue, myalgia, chest pain, and fever, which has been dubbed with various terms such as "implant incompatibility syndrome," "siliconosis," and "silicone reactive disorder."[1,5]

Available studies associating breast implants with various adverse events suffer from methodologic flaws that curtail a robust conclusion. These limitations include failure to consider the relevant

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baseline characteristics of women included in the studies or failure to adequately adjust for likely confounders.[6] Another major limitation of large postapproval studies is the lack of a control group; thus, the rate of reported conditions was compared to historical data.[3] In addition, many of these studies commonly relied on patients' self-reporting that could not be verified by physicians.[7] Self-reporting became more problematic as studies demonstrated that women who underwent breast implantation differed in their psychological background, social habits, and demographic characteristics from those who did not,[8–10] representing unrecognized confounders. Conflict of interest from authors with ties to manufacturers of the devices or ties to litigations against the manufacturers can also complicate and/or confound study findings.

The objective of this study was to examine physician-diagnosed nonspecific constitutional and cardiac symptoms, connective tissue diseases, and allergic reactions in a retrospective cohort of women who underwent breast implantation in comparison to active comparators and who were followed within the same health care system with relatively homogenous access and standards of care. Tricare approves breast implant procedures in women for medical necessity and not for purely cosmetic reasons.[11]

PATIENTS AND METHODS

Study Design

This was a retrospective cohort study of patients enrolled in the San Antonio military area as Tricare Prime/Plus. This study was approved by the Institutional Review Board of the Dallas VA Hospital. We extracted archival data from October 1, 2003, to March 31, 2012, which encompassed administrative data of outpatient and inpatient encounters regardless of point-of-care location or affiliation and pharmacy data. Pharmacy data included details of dispensed medications regardless of pharmacy location or affiliation.[12] The reliability and reproducibility of Tricare data have been previously described.[13]

We included all women enrolled in the San Antonio area aged 30 to 85 years who were enrolled in Tricare Prime/Plus throughout the study period. All women in this study were followed in the regional Tricare system (military health care system) with relatively equal access to care.

Treatment Groups

We identified two treatment groups: (1) women who underwent breast implantation (breast implant recipients); and (2) a control group of women who did not undergo breast implantation (nonrecipients). Women with breast implants were identified using CPT codes and/or *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure or diagnosis codes. (**See Appendix, Supplemental Digital Content 1**, which shows diagnosis and procedure codes used to define breast implantation, skin procedures, and outcomes, ***http://links.lww.com/PRS/E279***.) Identifying breast implant recipients using administrative codes is widely used in the literature.[14–16] In one study, *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure codes had 100 percent sensitivity and 100 percent positive predictive value for breast implant insertion.[15] For women who did not undergo breast implantation (control group), we used an active comparator design to mitigate immortal time bias and minimize confounding.[17,18] Thus, we selected women who did not undergo breast implantation but underwent a diagnostic or therapeutic skin or nail procedure biopsy, repair, or drainage, excluding genital areas, malignant lesions, and insertion of artificial material (**see Appendix, Supplemental Digital Content 1**, ***http://links.lww.com/PRS/E279***). Therefore, our exposure variable for the breast implant group was undergoing breast implantation; for the control group, undergoing a skin or nail procedure. The index date was the date of the first encounter with breast implant code or the date of the first encounter with skin or nail procedure code in each respective treatment group.

The study period was divided into two periods: the baseline period and the follow-up period. The baseline period encompassed the period from the first available medical encounter until the index date. The follow-up period started after the index date and extended until the date of the last encounter or the study end date. The baseline period was used to describe baseline characteristics of treatment groups, and the follow-up period was used to capture outcomes.

Outcomes

We used prespecified diagnosis groups to define our outcomes as outlined by the Agency for Healthcare Research and Quality Clinical Classifications software,[19] as follows:

1. Nonspecific constitutional symptoms: This outcome included Agency for Healthcare Research and Quality Clinical Classifications categories 246 (fever of unknown origin) and 252 (malaise and fatigue).
2. Nonspecific cardiac conditions: This outcome included Agency for Healthcare Research and Quality Clinical Classifications

categories 102 (nonspecific chest pain) and 104 (other and ill-defined heart disease).
3. Rheumatoid arthritis, systemic lupus erythematosus, and related diseases: This outcome included Agency for Healthcare Research and Quality Clinical Classifications categories 202 (rheumatoid arthritis and related disease) and 210 (systemic lupus erythematosus and connective tissue disorders).
4. Other connective tissue diseases: This outcome included Agency for Healthcare Research and Quality Clinical Classifications category 211 (other connective tissue disease, which includes enthesopathies; other disorders of synovium, tendon, and bursa; disorders of muscle, ligaments, and fasciae).
5. Allergic reactions: This outcome included Agency for Healthcare Research and Quality Clinical Classifications category 253 (allergic reactions).

To increase the specificity of our outcomes, we required two separate encounters with the appropriate diagnosis code to identify conditions.[20–22] The Agency for Healthcare Research and Quality Clinical Classifications is a diagnosis and procedure categorization scheme that is based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes, which categorizes thousands of *International Classification of Diseases, Ninth Revision, Clinical Modification* codes into a limited number of disease categories, enabling more useful identification of a population's comorbidities.[19] The method of creation and validation of the Agency for Healthcare Research and Quality Clinical Classifications has previously been published.[23–27] The Agency for Healthcare Research and Quality Clinical Classifications disease categories have been widely used for comorbidity-risk adjustment and estimating outcomes,[28–32] predicting mortality,[32,33] and costs and use estimates.[34–37]

Data and Statistical Analyses

Patients' baseline comorbidities were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes as defined by the Agency for Healthcare Research and Quality Clinical Classifications and by the Charlson Comorbidity Index and its components using the Deyo method.[38] Using propensity scores, we matched breast implant recipients to similar nonrecipients using 61 variables, including age, social habits, duration of baseline and follow-up periods, comorbidities, and use of different classes of medications (Table 1).[39]

Table 1. Baseline Characteristics of Women with Breast Implants and Those Without

	Before Matching		Propensity Score–Matched Cohort		
	Breast Implantation (%)	No Breast Implantation (%)	Breast Implantation (%)	No Breast Implantation (%)	*p*
Patient demographics					
No.	513	21,550	452	452	
Mean age ± SD, yr	40.3 ± 14	43.5 ± 19	40 ± 15	41 ± 17	0.47
Smoking*	80 (16)	2655 (12)	72 (16)	73 (16)	>0.99
Alcohol-related disorders†	6 (1)	278 (1)	5 (1)	6 (1)	>0.99
Substance-related disorders†	17 (3)	284 (1)	14 (3)	13 (3)	>0.99
Family history of heart disease‡	13 (3)	449 (2)	11 (2)	16 (4)	0.44
Overweight/obese†	165 (32)	5297 (25)	141 (31)	145 (32)	0.83
Comorbidities in the baseline period§					
Mean Charlson Comorbidity Index ± SD	2.18 ± 2.7	0.89 ± 1.6	1.89 ± 2.52	1.83 ± 2.45	0.67‖
Myocardial infarction	4 (1)	378 (2)	4 (1)	4 (1)	>0.99
Congestive heart failure	5 (1)	597 (3)	4 (1)	6 (1)	0.75
Peripheral vascular disease	13 (3)	673 (3)	11 (2)	10 (2)	>0.99
Cardiovascular diseases	14 (3)	922 (4)	13 (3)	14 (3)	>0.99
Dementia	0 (0)	179 (1)	0 (0)	0 (0)	
Chronic obstructive lung diseases	75 (15)	3170 (15)	68 (15)	72 (16)	0.78
Rheumatologic diseases	16 (3)	643 (3)	11 (2)	16 (4)	0.44
Peptic ulcer diseases	7 (1)	276 (1)	6 (1)	3 (1)	0.51
Mild liver diseases	0 (0)	134 (1)	0 (0)	0 (0)	
Diabetes mellitus	36 (7)	3086 (14)	32 (7)	33 (7)	>0.99
Diabetes mellitus with complications	64 (13)	2487 (12)	58 (13)	48 (11)	0.35
Hemiplegia or paraplegia	3 (1)	91 (0)	3 (1)	2 (0)	>0.99
Kidney diseases	7 (1)	341 (2)	4 (1)	4 (1)	>0.99
Malignant neoplasms	247 (48)	1127 (5)	186 (41)	191 (42)	0.79
Severe liver diseases	0 (0)	33 (0)	0	0	
Metastatic neoplasm	51 (10)	163 (1)	34 (8)	30 (7)	0.70
AIDS/HIV	0 (0)	8 (0)	0 (0)	0 (0)	

(*Continued*)

Table 1. *Continued*

	Before Matching		Propensity Score–Matched Cohort		
	Breast Implantation (%)	No Breast Implantation (%)	Breast Implantation (%)	No Breast Implantation (%)	*p*
Health care use					
Mean duration of baseline period ± SD, yr	4.6 ± 2.3	3.3 ± 2.4	4.4 ± 2.3	4.4 ± 2.3	0.90†
Mean duration of follow-up period ± SD, yr	2.9 ± 2.4	3.9 ± 2.5	2.95 ± 2.4	2.94 ± 2.4	0.91†
Medications at baseline					
Statins	101 (20)	5144 (24)	86 (19)	86 (19)	>0.99
Nonstatin lipid-lowering drugs	32 (6)	1623 (8)	26 (6)	29 (6)	0.78
Beta-blocker	52 (10)	3081 (14)	46 (10)	54 (12)	0.46
Diuretic	99 (19)	4844 (23)	85 (19)	90 (20)	0.74
Calcium channel blocker	44 (9)	2682 (12)	39 (9)	46 (10)	0.49
ACE/ARB	90 (18)	5393 (25)	77 (17)	84 (19)	0.60
Other antihypertensive medications	14 (3)	608 (3)	9 (2)	14 (3)	0.40
Oral hypoglycemic	19 (4)	1687 (8)	18 (4)	21 (5)	0.74
Insulins	6 (1)	674 (3)	6 (1)	8 (2)	0.79
Aspirin	56 (11)	3669 (17)	51 (11)	48 (11)	0.83
Antiplatelet agents (other than aspirin)	5 (1)	621 (3)	5 (1)	3 (1)	0.73
Warfarin	16 (3)	558 (3)	11 (2)	19 (4)	0.19
NSAID	436 (85)	14737(68)	378 (84)	380 (84)	0.93
SSRI	205 (40)	4922 (23)	172 (38)	178 (39)	0.73
Antipsychotic	19 (4)	538 (3)	18 (4)	13 (3)	0.47
Sedatives	298 (58)	6337 (29)	252 (56)	253 (56)	>0.99
Tricyclic antidepressants	3 (1)	68 (0)	3 (1)	3 (1)	>0.99
Systemic corticosteroid	164 (32)	3452 (16)	127 (28)	126 (28)	>0.99
Hormone replacement therapy	100 (20)	4528 (21)	92 (20)	88 (20)	0.80
Testosterone	6 (1)	27 (0)	3 (1)	1 (0)	0.62
Cytochrome p450¶	71 (14)	2099 (10)	58 (13)	59 (13)	>0.99
Bisphosphonate	44 (9)	2192 (10)	38 (8)	39 (9)	>0.99
Proton pump inhibitors	196 (38)	6946 (32)	170 (38)	154 (34)	0.30
Smoking cessation medications	40 (8)	791 (4)	34 (8)	37 (8)	0.81
Radiotherapy	52 (10)	267 (1)	38 (8)	40 (9)	0.91
Chemotherapy	92 (18)	319 (2)	58 (13)	56 (12)	0.92
Occurrence of outcomes of interest during baseline period					
Malaise and fatigue	115 (22)	3173 (15)	99 (22)	109 (24)	0.48
Fever of unknown cause	42 (8)	1183 (6)	39 (9)	34 (8)	0.63
Nonspecific chest pain	123 (24)	4180 (19)	105 (23)	110 (24)	0.76
Ill-defined heart disease	12 (2)	906 (4)	10 (2)	10 (2)	>0.99
Rheumatoid arthritis and SLE	26 (5)	805 (4)	20 (4)	24 (5)	0.64
Other connective tissue diseases	335 (65)	10854 (50)	290 (64)	294 (65)	0.84
Allergic reactions	169 (33)	5946 (28)	149 (33)	139 (31)	0.52

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; NSAID, nonsteroidal antiinflammatory drug; SSRI, selective serotonin reuptake inhibitor; SLE, systemic lupus erythematosus.

*Smoking as defined using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 3051 and V1582.

†Diagnoses as defined by the Agency for Health Research and Quality Clinical Classifications software disease and procedure categories using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

‡Family history of cardiovascular disease was defined using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes V171, V1749, V174, V1741, and V173.

§Diagnosis is based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes as identified in Clinical Classification Software of the Agency for Health Research and Quality. The Charlson Comorbidity Index was calculated using the Deyo method.[38]

‖Using the Mann-Whitney *U* test.

¶Medications that inhibit the cytochrome p450 system as identified in a recent U.S. Food and Drug Administration warning.[39]

Propensity Score Matching

A propensity score was created using a logistic regression model and covariates were tested for balance among treatment groups as described previously.[40,41] We performed 1:1 nearest neighbor matching with a caliper of 0.0001.

Primary Analysis

We examined odds ratios of outcomes among breast implant recipients and nonrecipients in the propensity score–matched cohort using conditional logistic regression analysis.

Secondary Analysis

We performed the following analyses:

1. We examined the odds ratio of outcomes among breast implant recipients and nonrecipients in the propensity score cohort with five or more encounters for these outcomes. Because some of these outcomes were very common, we hypothesized that breast implants recipients might have a higher frequency of these outcomes in comparison to nonrecipients; thus,

considering higher frequency of these conditions rather than their mere presence may be important.
2. Overall cohort analysis: We examined the odds ratio of outcomes among breast implant recipients and nonrecipients in the whole cohort using logistic regression analysis and adjusting for propensity score.
3. Overall cohort analysis with five or more encounters: We examined the odds ratio of outcomes among breast implant recipients and nonrecipients in the whole cohort using logistic regression analysis and adjusting for propensity score.

Categorical variables of treatment groups were compared using the chi-square test and continuous variables were compared using the *t* test if data had normal distribution and the Mann-Whitney test if data were not distributed normally. Comparisons were considered to be statistically significant for values of $p < 0.05$. Statistical analyses were performed using IBM SPSS Version 25 (IBM Corp., Armonk, N.Y.) and propensity score creation and matching were performed using STATA version 15 (StataCorp, College Station, Texas). This study was approved by the Institutional Review Board at the VA North Texas Health Care System.

RESULTS

A total of 22,270 women, who had undergone either breast implants or skin or nail procedures (control group), were identified. We excluded 207 subjects who had no available follow-up (index date was date of last encounter); two received breast implants and 205 received skin or nail procedures. The remaining 22,063 were included in the propensity score matching (513 breast implant recipients and 21,550 nonrecipients).

Breast implant recipients (before propensity score matching) in comparison with nonrecipients were younger (mean age, 40.3 years versus 43.5 years), had a smoking history (16 percent versus 12 percent), had substance-related disorders (3 percent versus 1 percent), and had a higher Charlson Comorbidity Index (2.18 ± 2.7 versus 0.89 ± 1.6). Before propensity score matching, there was a high preponderance of malignant neoplasms in the breast implant recipient group (48 percent versus 5 percent), because Tricare approved breast implantation for medical necessity only; such a difference was equalized with propensity score matching.

Propensity Score–Matched Results

We propensity score–matched 452 breast implant recipients with 452 nonrecipients, with no residual differences between groups (Table 1). In the propensity score–matched cohort, breast implant recipients in comparison to nonrecipients had a similar odds ratio of nonspecific constitutional symptoms (OR, 0.77; 95 percent CI, 0.53 to 1.13); nonspecific cardiac conditions (OR, 0.97; 95 percent CI, 0.69 to 1.37); rheumatoid arthritis, systemic lupus erythematosus, and related diseases (OR, 0.66; 95 percent CI, 0.33 to 1.31); other connective tissue diseases (OR, 1.02; 95 percent CI, 0.78 to 1.32); and allergic reactions (OR, 1.18; 95 percent CI, 0.84 to 1.66). Table 2 depicts outcomes in the propensity score–matched cohort.

Secondary Analysis

Table 3 depicts outcomes in secondary analyses. In the secondary analysis, breast implant

Table 2. Comparison of Outcomes of Breast Implant Recipients to Nonrecipients in the Propensity Score–Matched Cohort

	Breast Implantation (%)	No Breast Implantation (%)	OR (95% CI)	*p*
No.	452	452		
Primary analysis				
Nonspecific constitutional symptoms	57 (12.6)	71 (15.7)	0.77 (0.53–1.13)	0.18
Nonspecific cardiac conditions	76 (16.8)	78 (17.3)	0.97 (0.69–1.37)	0.86
RA, SLE, and related diseases	14 (3.1)	21 (4.6)	0.66 (0.33–1.31)	0.23
Other connective tissue diseases	205 (45.4)	203 (44.9)	1.02 (0.78–1.32)	0.98
Allergic reactions	87 (19.2)	76 (16.8)	1.18 (0.84–1.66)	0.34
Secondary analysis				
Nonspecific constitutional symptoms ≥5 encounters	12 (2.7)	22 (4.9)	0.53 (0.26–1.09)	0.09
Nonspecific cardiac conditions ≥5 encounters	41 (9.1)	40 (8.8)	1.03 (0.65–1.62)	0.910
RA, SLE, and related diseases ≥5 encounters	10 (2.2)	13 (2.9)	0.76 (0.33–1.76)	0.53
Other connective tissue diseases ≥5 encounters	140 (31.0)	149 (33.0)	0.91 (0.69–1.21)	0.52
Allergic reactions ≥5 encounters	34 (7.5)	22 (4.9)	1.59 (0.92–2.76)	0.10

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Table 3. Comparison of Outcomes of Breast Implant Recipients to Nonrecipients in the Overall Cohort

Outcomes	Breast Implantation (%)	No Breast Implantation (%)	Adjusted OR* (95% CI)	*p*
No.	513	21,550		
Nonspecific constitutional symptoms	63 (12.3)	3232 (15.0)	0.92 (0.69–1.22)	0.55
Nonspecific cardiac conditions	86 (16.8)	4620 (21.4)	1.02 (0.80–1.31)	0.86
RA, SLE, and related diseases	16 (3.1)	942 (4.4)	0.82 (0.48–1.39)	0.46
Other connective tissue diseases	226 (44.1)	11374 (52.8)	0.90 (0.75–1.09)	0.29
Allergic reactions	92 (17.9)	4754 (22.1)	0.95 (0.75–1.21)	0.69
Five or more encounters				
Nonspecific constitutional symptoms ≥5 encounters	14 (2.7)	1120 (5.2)	0.53 (0.30–0.93)	0.03
Nonspecific cardiac conditions ≥5 encounters	43 (8.4)	2510 (11.6)	1.07 (0.77–1.48)	0.70
RA, SLE, and related diseases ≥5 encounters	12 (2.3)	684 (3.2)	0.87 (0.48–1.60)	0.66
Other connective tissue diseases ≥5 encounters	153 (29.8)	7851 (36.4)	0.97 (0.79–1.20)	0.80
Allergic reactions ≥5 encounters	35 (6.8)	1645 (7.6)	1.18 (0.82–1.71)	0.37

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
*OR adjusted for propensity score.

recipients in comparison to nonrecipients had no significant difference in odds ratio of outcomes for more than five encounters in the propensity score cohort. Similarly, in the overall cohort, odds ratios of outcomes were not significantly different in breast implant recipients in comparison to nonrecipients except for one outcome, that of nonspecific constitutional symptoms resulting in greater than five encounters, which was found to be lower in breast implant recipients (OR, 0.53; 95 percent CI, 0.30 to 0.93).

DISCUSSION

In this retrospective cohort study of women enrolled in a Tricare population, we found no increased odds of nonspecific constitutional or cardiac symptoms, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue diseases, or allergic reactions in breast implant recipients when compared to a matched active comparator group of nonrecipients. Secondary analyses demonstrated consistent findings. It is important to note that women included in our study were Tricare enrollees; Tricare approves breast implant procedures for medical necessity and not for purely cosmetic reasons.[11]

Our findings are in contrast to a large recently published prospective postapproval study (99,993 patients followed for up to 10 years), which showed an increased incidence of Sjögren syndrome (standardized incidence ratio, 8.14), scleroderma (standardized incidence ratio, 7.00), and rheumatoid arthritis (standardized incidence ratio, 5.96).[3] However, a significant proportion of reported conditions were based on patient self-report and were not physician verified; this is especially concerning in rheumatic and autoimmune conditions because of misclassification and misdiagnosis.[42] In addition, there was no control group in this postapproval study; rather, the incidence rate was compared to normative data, raising concerns about comparability between breast implant recipients and the general population. Moreover, the study was fraught with poor compliance within the study protocol (compliance rate <5 percent at 5 years) and a high attrition rate (>60 percent at 2 years of some breast implant subgroups).[3] Consequently, some of the postapproval study results were difficult to conceive; for example, whereas the standardized incidence ratio of rheumatoid arthritis in breast implant recipients of a specific manufacturer (Mentor Corp., Santa Barbara, Calif.) in comparison to normative data from the general population was 5.96, the standardized incidence ratio of rheumatoid arthritis in breast implant recipients of a different manufacturer (Allergan, Inc., Dublin, Ireland) was 0.15 ($p < 0.001$), suggesting Allergan breast implant recipients in some manner were protected against the development of rheumatoid arthritis. Of note, the prior 5-year safety data of the same postapproval studies did not find an increased incidence of any adverse events.[43]

To our knowledge, our study is the first to use propensity score matching to match treatment groups on several relevant baseline characteristics to minimize confounders. We also used active comparator design to minimize confounding. Instead of including all women who did not undergo breast implantation, we selected those who underwent skin or nail procedures; we used the date of such procedures to identify index date, baseline period, and follow-up period. Such a design is called active comparator design and has

been shown to minimize immortal time bias and confounding.[17,18] We then used propensity score to match women with breast implants with those without breast implants on an extensive host of baseline characteristics to ensure their comparability, including presence of malignancy, metastatic neoplasm, radiotherapy and chemotherapy, health care use measures, and many others. Our outcomes were physician verified, limiting selective reporting bias. Despite the relatively small size of our study, it seems adequate to examine our outcomes of interest given the high rate of reported adverse events in some publications. For example, using the reported standardized incidence ratio of rheumatoid arthritis of 5.96 in breast implant recipients in a recent postapproval study,[3] our propensity score–matched cohort would have greater than 99 percent power to detect differences at an alpha level of 0.05.

Our study has several limitations, including its relatively small size, which may limit its power to demonstrate the event occurrence. We used *International Classification of Diseases, Ninth Revision*, codes to define our outcomes; whereas use of *International Classification of Diseases, Ninth Revision*, codes to define connective tissue disease has been validated and is widely used,[20,44] their use to identify nonspecific constitutional symptoms reported with breast implants has not been validated. However, there is no well-established definition for the so-called breast implant syndrome or its different components. Our population was a Tricare population, and was undergoing breast implantation secondary to what was considered medical necessity, such as reconstruction after surgery, not for pure cosmetic reasons, which may limit generalizability of our results. Because our study included women who underwent breast implantation to treat medical conditions, they were generally more medically ill than women in other studies. This sicker population experienced a high incidence of our outcomes at both baseline and during the follow-up period, which may further limit generalizability. In addition, women who sought breast implantation for purely cosmetic purposes may not have reported it and may not be captured in Tricare data, resulting in contamination in the control group. However, we expect that the large sample size of the control group (>21,000 women) may dilute the effect of such contamination. Use of administrative data to identify breast implant recipients cannot account for different types of breast implants, which might have changed during the study period.

CONCLUSIONS

Our findings demonstrated no increased associated risk of nonspecific constitutional or cardiac symptoms, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue diseases, or allergic reactions in breast implant recipients in comparison to matched controls. Although these results offer assurance to women who had undergone breast implantion for medical reasons, potential future studies should focus on the individual factors that may predispose women to develop these symptoms and conditions.

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DISCLAIMER

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