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Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis

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Abstract

Objectives: Several epidemiological studies have investigated the link between silicone breast implants (SBIs) and autoimmune/rheumatic disorders, reporting inconsistent results. We aimed to evaluate the association between SBIs and the most clinically relevant autoimmune/rheumatic disorders using a large, population-based database.

Methods: In this cross-sectional study, we used the computerized databases of Maccabi Healthcare Services (MHS), which include up to 20 years of data on 2 million members. Women with SBIs were identified by procedure and diagnosis codes, clinical breast examinations and mammography referrals. Autoimmune/rheumatic disorders were identified using the International Classification of Diseases 9th revision (ICD-9) codes. Multivariable logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). A Cox's proportional hazards model was used to calculate the hazard ratios (HRs) and 95% CIs among a subgroup of SBI recipients for whom the year of SBIs insertion was available.

Results: We included 24 651 SBI recipients and 98 604 matched SBI-free women. The adjusted OR between SBIs and being diagnosed with any autoimmune/rheumatic disorders was 1.22 (95% CI 1.18–1.26). The strongest association with SBIs ($OR > 1.5$, $p < 0.001$) was recorded for Sjögren's syndrome, systemic sclerosis (SSc) and sarcoidosis (OR of 1.58, 1.63 and 1.98, respectively). Similar results were calculated when analysis was limited to women with no breast cancer history. A multivariable Cox regression

model yielded a HR of 1.45 (95% CI 1.21–1.73) for being diagnosed with at least one autoimmune/rheumatic disorder in women with SBI compared with those without.
Conclusions: SBIs seem to be associated with higher likelihood of autoimmune/rheumatic disorders diagnosis.

Key words: silicone, breast implants, silica, autoimmune diseases, autoimmunity, adjuvant

Key Messages

- In this large population-based study, we have demonstrated an association between silicone-based implants (SBIs) and the presence of autoimmune/rheumatic disorders.
- Sjögren's syndrome, systemic sclerosis (SSc) and sarcoidosis were the disorders most strongly associated with SBIs.
- Women with SBIs had an increased hazard ratio of 1.45 (95% confidence interval 1.21–1.73) for being diagnosed with at least one autoimmune/rheumatic disorder in comparison to women without SBIs.
- The indication for SBIs (reconstructive vs cosmetic) had no impact on the subsequent risk of being diagnosed with an autoimmune/rheumatic disorder.
- Our results highlight the need for further investigation of the antigenic/adjuvant activity of SBIs.

Introduction

Silicon (Si), a chemical element, is one of the major constituents of the Earth's crust and an important trace mineral in bone formation and mineralization.[1] Silica or silicon oxide is a chemical compound that is composed of one silicone atom and two atoms of oxygen (SiO_2) and appears naturally as quartz or sand.[1] Silicones are polymeric compounds sharing a silicon–oxygen chain with varying organic side-groups that can be linked together to form rubber-like materials that are used for many purposes, including dental applications, medical implants, lubrication and insulation.[2] Silicones have been in medical use since the 1960s in a variety of applications, such as breast and joint implants, testicular prostheses, intraocular lenses, suprapubic catheters, artificial cardiac valves, hydrocephalus shunts and others.[3] Silicone breast implants (SBIs) were first introduced in 1962 and, since then, have been surgically emplaced in millions of women. The main purpose of the vast majority of implantations is cosmetic, though a minority of SBIs are utilized as part of breast reconstructions following mastectomy due to breast malignancy.[4]

In contrast to an earlier perception that regarded silicone as a biologically inert material, today that notion has been refuted; various immunological effects induced by silicone have been reported.[5] Silicone gel can migrate outside the outer shell after SBI rupture and migration through an intact shell has also been demonstrated—the so-called 'gel bleed'.[5]

Silicon-containing particles that are then captured by macrophages have been shown to induce the release of IL-1β, activate the NALP3 inflammasome and B cells, and ultimately generate an imbalance of regulatory T cells, responder T cells and Th17 cells.[6] Furthermore, it has been demonstrated in animal studies that SBIs induce an adjuvant effect and increase the susceptibility to autoimmune/rheumatic disorders.[7] The mechanisms by which SBIs induce autoimmune phenomena are numerous and include dysregulation of the innate as well as adaptive immunity in those genetically predisposed for autoimmunity.[5]

Despite changes in the principal constituents of the SBIs during the past 50 years and their proven record of safety, a number of epidemiological studies, both cohort and case–control, have investigated the potential association between SBIs and autoimmunity, although their findings have been controversial and inconsistent.[5,7–10] In many reports, confounders weakened the strength of the alleged associations between SBIs and autoimmune/rheumatic disorder.

Hence, in this cross-sectional study, we aimed to evaluate the association between SBIs and the most clinically relevant autoimmune/rheumatic disorders by performing a 'real-world' analysis using the computerized databases of the second largest health maintenance organization (HMO) in Israel.

Methods

Study design and settings

We conducted a cross-sectional study based on the computerized databases of Maccabi Healthcare Services (MHS), which include up to 20 years of data on 2 million members—a representative sample that accounts for 25%

of the Israeli population. Physician diagnoses are coded using the International Classification of Diseases 9th revised edition with clinical modifications (ICD-9-CM) codes, as well as internal MHS codes for sub-classification (Y codes). Research ethical approval was obtained from the institutional review board of the Bait Balev Medical Center.

Identifying women with SBIs

We identified patients as having SBIs according to procedure and diagnosis codes, clinical breast examinations and mammography referrals. For patients whose mammography referral suggested the presence of SBIs, the total number of indicative mammography referrals was calculated. Patients with SBIs were identified using a recorded diagnosis code indicating the presence of SBIs and were divided into two groups: patients with diagnosis codes that definitely indicate the presence of SBIs and patients with diagnosis codes that *suggest* the presence of SBIs (i.e. cases in which the description did not specify whether silicone implants were used or not). Patients identified using a recorded procedure code indicating the presence of SBIs were also divided into two groups, in the same manner as used for patients identified by the diagnosis codes. A text mining approach was used to pinpoint patients whose clinical breast examination suggested the presence of SBIs and/or the word 'silicone' was used in the free-text field in their examination form.

Exposed patients were divided into three categories: (i) 'Definite'—the patient was identified as a patient with SBIs from at least two different sources (e.g. mammography referral and positive breast clinical examination for implants) and/or had at least two mammography referrals suggestive of SBIs; (ii) 'Probable'—the patient was identified as a patient with SBIs from a single source (not including diagnosis and procedure codes that *suggest* the presence of SBIs); and (iii) 'Possible'—the patient was identified as a patient with SBIs only from diagnosis and/or procedure codes that suggest the presence of SBIs. For each patient, we collected the earliest date when SBIs were first captured in the information system.

Study population

Eligibility criteria for this study were: (i) identification of a woman as SBI recipient from at least one source, (ii) first documented with SBIs before 1 January 2016 (index date), (iii) at least 16 years old at the time first documented with SBIs and (iv) MHS member as of 1 January 2016. The SBI-free group included women with no record indicating the presence of SBIs who were MHS members as of the index date. Patients with missing data on socio-economic status (SES) or membership of less than 12 months before the index date were excluded from the analysis. The groups were frequency-matched by age and SES in a ratio of 1:4.

Study outcomes

The study included multiple autoimmune/rheumatic disorder outcomes: ankylosing spondylitis (AS), fibromyalgia/chronic fatigue syndrome, hypothyroidism, hyperthyroidism, multiple sclerosis (MS), psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA), sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma (SSc) and vasculitis (classified in different types). A patient was defined as being diagnosed with an autoimmune disease if she had at least two records of diagnoses of the same outcome in her medical record, made by a health professional any time before the index date. The diagnostic codes recorded in MHS database were previously used to identify patients diagnosed with RA[11] and psoriasis.[12]

Other variables

The following socio-demographic and clinical variables were assessed: age (on the index date), SES was based on a score ranked with 1 (lowest) to 10 derived for commercial purposes by Points Location Intelligence using geographic information systems (GIS) and data such as expenditures related to retail chains, credit cards and housing. SES was categorized into low,[1–4] medium[5–7] and high,[8–10] smoking status (ever smokers, never smokers) and other comorbid conditions, according to the MHS registries. The type of implants, whether silicone-gel or saline breast implants, has not been addressed in our study due the prominent preference of plastic surgeons to use silicone-gel implants and therefore, in Israel, saline implants are rarely used.[13]

Statistical analysis

The socio-demographic and clinical characteristics of the study population are presented using descriptive statistics (N, % or median, IQR, as appropriate, after testing for normality). Any statistical difference between the groups was assessed by Mann-Whitney U and χ^2 tests when appropriate. Odds ratios (ORs) and 95% CIs for the association between SBIs presence and the diagnosis with a specific autoimmune/rheumatic disorder were evaluated using a multivariable logistic regression adjusted for age, SES, smoking status and breast-cancer history. Double-sided p-values less than 0.05 were considered statistically significant. We further tested our results and used the Bonferroni adjustment for multiple

tests by which p-values less than 0.004 were considered statistically significant. We additionally evaluated the association between SBI presence and diagnosis with at least one autoimmune/rheumatic disorder.

We performed a retrospective sensitivity analysis among a subgroup of SBI recipients (for whom we were able to capture the year of SBIs insertion as documented in clinical breast examinations) and their matched SBI-free group. For this analysis, retrospective follow-up began at the insertion year for SBI recipients and, for the matched SBI-free group, we assigned the mid-point year from the insertion years of SBI recipients in the same age and SES category as the year of the beginning of follow-up. Only patients who were free of any autoimmune/rheumatic disorder prior to the follow-up year and patients whose SBIs were inserted after 1998 were included in this analysis (a total of 1797 SBI recipients and 7109 SBI-free women). Patients were followed up until the earliest of the following events: diagnosis with an autoimmune/rheumatic or end of the study period (1 January 2016). We performed a Kaplan-Meier survival analysis and difference in survival as autoimmune/rheumatic disorder-free between the groups was tested using log-rank testing. The hazard ratio (HR) and 95% CI of patients with SBIs for being diagnosed with at least one autoimmune/rheumatic disorder was assessed using the Cox's proportional hazards model with years of follow-up used for the time scale. The model was adjusted for age at beginning follow-up year, SES, smoking status and breast-cancer history at the beginning of follow-up.

Two additional sensitivity analyses were performed using multivariable logistic regression as mentioned above: the first on patients who were included in the 'definite' category and their matched SBI-free group (11 495 and 45 980, respectively) and the second on patients who had no history of breast cancer and their matched breast-cancer-free SBI-free group (19 350 and 76 497, respectively).

Analyses were performed by the SPSS V.24.0 software for Windows.

Results

We identified 24 651 women with SBIs from the MHS database who met our inclusion criteria; 11 495 patients were categorized as 'definite', 11 511 as 'probable' and 1645 as 'possible' patients with SBIs. The SBI recipients were matched to 98 604 SBI-free women. SBI recipients were more likely to be ever smokers and have a history of breast cancer and other comorbidities (aside from diabetes) in comparison with the SBI-free group (Table 1).

Patients with SBIs were also more likely to be diagnosed with the following autoimmune/rheumatic disorders than the matched SBI-free group: hypothyroidism, psoriasis, hyperthyroidism, RA, fibromyalgia/chronic fatigue syndrome, Sjögren's syndrome, SSc, sarcoidosis and being diagnosed with at least one autoimmune/rheumatic disorder (Table 2).

In the multivariable model, the strongest association with SBIs (OR $>$ 1.5, $p < 0.001$) was recorded for: sarcoidosis [OR 1.98 (95% CI 1.50–2.60)], SSc [OR 1.63 (95% CI 1.26–2.11)] and Sjögren's syndrome [OR 1.58 (95% CI 1.26–1.97)]. These results remain strong, after we applied the Bonferroni adjustment for multiple tests (p-values < 0.004). The OR between SBIs and being diagnosed with any autoimmune/rheumatic disorder was 1.22 (95% CI 1.18–1.26) (Table 2).

In the retrospective sensitivity analysis that was limited to SBI recipients with a documented year of implants insertion and their matched SBI-free group, the multivariable Cox regression model yielded a HR of 1.45 (95% CI 1.21–1.73) for being diagnosed with at least one autoimmune/rheumatic disorder for SBI recipients compared with SBI-free women. The Kaplan–Meier survival analysis revealed higher survival (p-value < 0.001) as autoimmune/rheumatic

Table 1. Demographic and clinical characteristics of the study population

Variable		SBI-free women ($n = 98\,604$), N (%)	SBI recipients ($n = 24\,651$), N (%)	Total study population ($n = 123\,255$), N (%)	p-value
Age (IQR)		47 (40–58)	47 (40–57)	47 (40–58)	0.54
SES	Low	8300 (8.42)	2075 (8.42)	10 375 (8.42)	1.000
	Medium	54 848 (55.62)	13 712 (55.62)	68 560 (55.62)	
	High	35 456 (35.96)	8864 (35.96)	44 320 (35.96)	
Current/past smokers		13 078 (13.26)	3930 (15.94)	17 008 (13.80)	<0.001
Comorbidities	Breast cancer	1347 (1.37)	5301 (21.50)	6648 (5.39)	<0.001
	Cancer	5958 (6.04)	6679 (27.09)	12 637 (10.25)	<0.001
	Cardiovascular disease	5563 (5.64)	1615 (6.55)	7178 (5.82)	<0.001
	Diabetes	7073 (7.17)	1409 (5.72)	8482 (6.88)	<0.001

Table 2. Proportions, unadjusted and adjusted[a] odds ratios for autoimmune/rheumatic diseases among SBI recipients in comparison to SBI-free women

Autoimmune/rheumatic disorder	SBI-free women, ($n = 98\,604$), *N* (%)	SBI recipients ($n = 24\,651$), *N* (%)	Unadjusted OR (95% CI)	Adjusted[a]	
				OR (95% CI)	*p*-value
Any autoimmune/rheumatic disorder	22 634 (22.95)	6510 (26.41)	1.20 (1.17–1.24)	1.22 (1.18–1.26)	<0.001
Systemic lupus erythematosus	457 (0.46)	117 (0.47)	1.02 (0.84–1.26)	1.05 (0.84–1.30)	0.677
Hypothyroidism	10 870 (11.02)	2979 (12.08)	1.11 (1.06–1.16)	1.10 (1.05–1.16)	<0.001
Psoriasis	4594 (4.66)	1293 (5.25)	1.13 (1.06–1.21)	1.13 (1.05–1.21)	0.001
Hyperthyroidism	2945 (2.99)	870 (3.53)	1.19 (1.10–1.28)	1.16 (1.07–1.26)	0.001
Psoriatic arthritis	201 (0.20)	54 (0.22)	1.07 (0.80–1.45)	1.17 (0.85–1.61)	0.339
Rheumatoid arthritis	970 (0.98)	278 (1.13)	1.15 (1.00–1.31)	1.19 (1.03–1.38)	0.018
Vasculitis[b]	115 (0.12)	32 (0.13)	0.90 (0.61–1.33)	1.22 (0.80–1.87)	0.362
Ankylosing spondylitis	155 (0.16)	41 (0.17)	1.06 (0.75–1.49)	1.23 (0.85–1.79)	0.269
Fibromyalgia/chronic fatigue syndrome	6106 (6.19)	1997 (8.10)	1.34 (1.27–1.41)	1.37 (1.29–1.45)	<0.001
Multiple sclerosis	303 (0.31)	93 (0.38)	1.23 (0.97–1.55)	1.41 (1.11–1.80)	0.005
Sjögren's syndrome	344 (0.35)	123 (0.50)	1.43 (1.17–1.76)	1.58 (1.26–1.97)	<0.001
Systemic sclerosis (scleroderma)	242 (0.25)	101 (0.41)	1.67 (1.33–2.11)	1.63 (1.26–2.11)	<0.001
Sarcoidosis	187 (0.19)	93 (0.38)	1.99 (1.55–2.56)	1.98 (1.50–2.60)	<0.001

[a]Adjusted for: age (cont.), socio-economic status (low, medium, high), smoking status (never smoked, current/past smoker) and breast-cancer history (no, yes).
[b]Diagnosed with ≥1 of the followings: Takayasu disease, temporal arteritis, granulomatosis with polyangiitis and microscopic polyangiitis (Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), polyarteritis nodosa.

disorder-free among the SBI-free group compared with the SBI-recipients group. The survival rate as autoimmune/rheumatic disorder-free after 10 years of follow-up was 89.2% among the SBI-recipients group compared with 92.4% among the SBI-free group (Figure 1) .

In the sensitivity analysis that was limited to SBI recipients of the 'definite' category and their matched SBI-free group, the strongest association with SBIs ($OR > 1.5$, $p < 0.05$) was recorded for: sarcoidosis [OR 1.95 (95% CI 1.27–2.99)], MS [OR 1.64 (95% CI 1.16–2.32)] and Sjögren's syndrome [OR 1.61 (95% CI 1.15–2.26)]. The OR between SBIs and being diagnosed with any autoimmune/rheumatic disorder was 1.22 (95% CI 1.16–1.29). In the sensitivity analysis that included only SBIs with no-breast-cancer-history recipients and their matched breast-cancer-free SBI-free women, the strongest association with SBIs ($OR > 1.5$, $p < 0.05$) was recorded for: sarcoidosis [OR 2.15 (95% CI 1.59–2.91)], SSc [OR 1.64 (95% CI 1.24– 2.17)] and Sjögren's syndrome [OR 1.62 (95% CI 1.27–2.05)]. The OR between SBIs and being diagnosed with any autoimmune/rheumatic disorder was 1.23 (95% CI 1.18–1.28). The results of these two sensitivity analyses are detailed in the Supplementary Appendix (Table A), available as Supplementary data at *IJE* online.

A comparison of the results from the three multivariable logistic regression models revealed that the strongest association with SBIs ($OR > 1.5$, $p < 0.05$) in all three analyses was recorded for sarcoidosis, SSc and Sjögren's syndrome, with the exception of the sensitivity analysis limited to SBI recipients in the 'definite' category and their matched SBI-free group, in which the OR for SSc was lower than 1.5 ($p > 0.05$). The OR for any autoimmune/rheumatic disorder was identical in all three analyses (OR 1.2, $p < 0.001$) (Figure 2).

Discussion

In our large population-based study, aside from demonstrating an association between SBIs and the presence of any autoimmune/rheumatic disorder, disease-specific stratification revealed a prominent link between SBIs, sarcoidosis and SSc. In addition, a very interesting finding of our study is that an increased OR for having an autoimmune/rheumatic disorder was found in women with SBIs regardless of their indication for SBIs (reconstructive or cosmetic reasons).

In the past few decades, there has been a growing body of evidence linking SBIs to various adverse effects, including inducement of autoimmunity and various systemic symptoms.[14] This issue has generated considerable controversy in the literature, ranging from substantial criticism to outright denial that SBIs may be associated with injurious outcomes. However, despite the abundance of large-scale epidemiological studies conducted with the goal of evaluating the association between SBIs and autoimmune/rheumatic disorders, the results remain inconclusive and the debate regarding the safety of SBIs rages on.[5,10,14]

SBIs have been linked to systemic clinical symptoms reminiscent of autoimmune/rheumatic disorders, such as fatigue, weakness, musculoskeletal pain, morning stiffness,

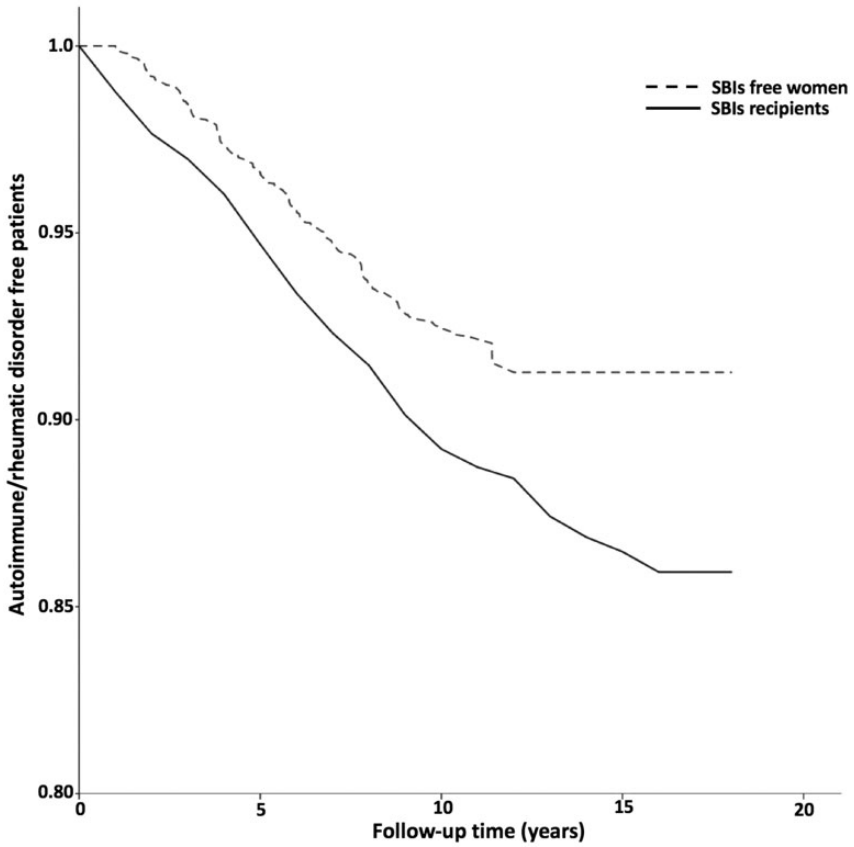

Figure 1. Kaplan–Meier plot for time to diagnosis with an autoimmune/rheumatic disorder according to SBIs status (SBI recipients vs SBI-free women, $n = 8906$). *P*-value from log-rank test <0.001. SBIs, silicone breast implants.

dry eyes and mouth.[5] In fact, Cohen *et al.*[5] showed that 30–50% of patients with so-called SBIs-related disease have Raynaud's phenomenon, occasionally presenting with nail-fold abnormalities on capillaroscopy, which is suggestive of scleroderma, rather than primary Raynaud's phenomenon. Additionally, the presence of anti-nuclear antibodies (ANAs) and a variety of other antibodies in SBI recipients has been demonstrated.[19]

The link between silicone and autoimmune/rheumatic disorders has also been replicated in animal model studies.[15,16] Silicone-gel or silicone-oil implantation has been found to lead to an increase in anti-ds-DNA antibodies titers in MRL lpr/lpr mice,[15] whereas, in the collagen-induced arthritis mouse model, it triggered an increased susceptibility to arthritis.[17] Similarly, silicone-gel injection induced proteinuria and autoimmune hemolytic anemia in NZB mice, although no such reaction was found in non-susceptible animals.[16]

Our findings are compatible with the results of a study[18] among 10 830 female health professionals with SBIs who were found to have a relative risk (RR) of 1.24 (95% CI 1.08–1.41) for any self-reported connective tissue disease (CTD) in comparison with SBI-free health professionals. Furthermore, an increased risk of Sjögren's syndrome and RA in women with SBIs has recently been demonstrated in an extensive meta-analysis of 32 studies.[14] Nevertheless, despite these findings, the conclusion was that the current evidence for an association between SBIs and CTDs is insufficient, mostly due to a lack of consistent estimates and adequate adjustment for potential confounders.[14] However, when scouring the literature, hundreds of cases of CTD/autoimmune reactions following silicone-gel breast implantation have been reported.[5,7,19] Specifically, as in our study, sarcoidosis has been repeatedly linked to SBIs, probably due to misinterpretation of clinical and histopathological findings as sarcoidosis rather than sarcoid-like disease induced by silicone resulting from thoracic lymph node and tissue silicone infiltration.[20,21]

In recent years, many reports and series dealing with silicone-based adjuvants have been described in the literature.[22–24] Indeed, it has been shown that SBIs may act as an adjuvant and induce both local and systemic reactions. Silicone has been demonstrated to trigger a local foreign-body reaction characterized by infiltration of inflammatory cells such as macrophages, giant cells and T cells,[20,25] and to promote the production of various autoantibodies and

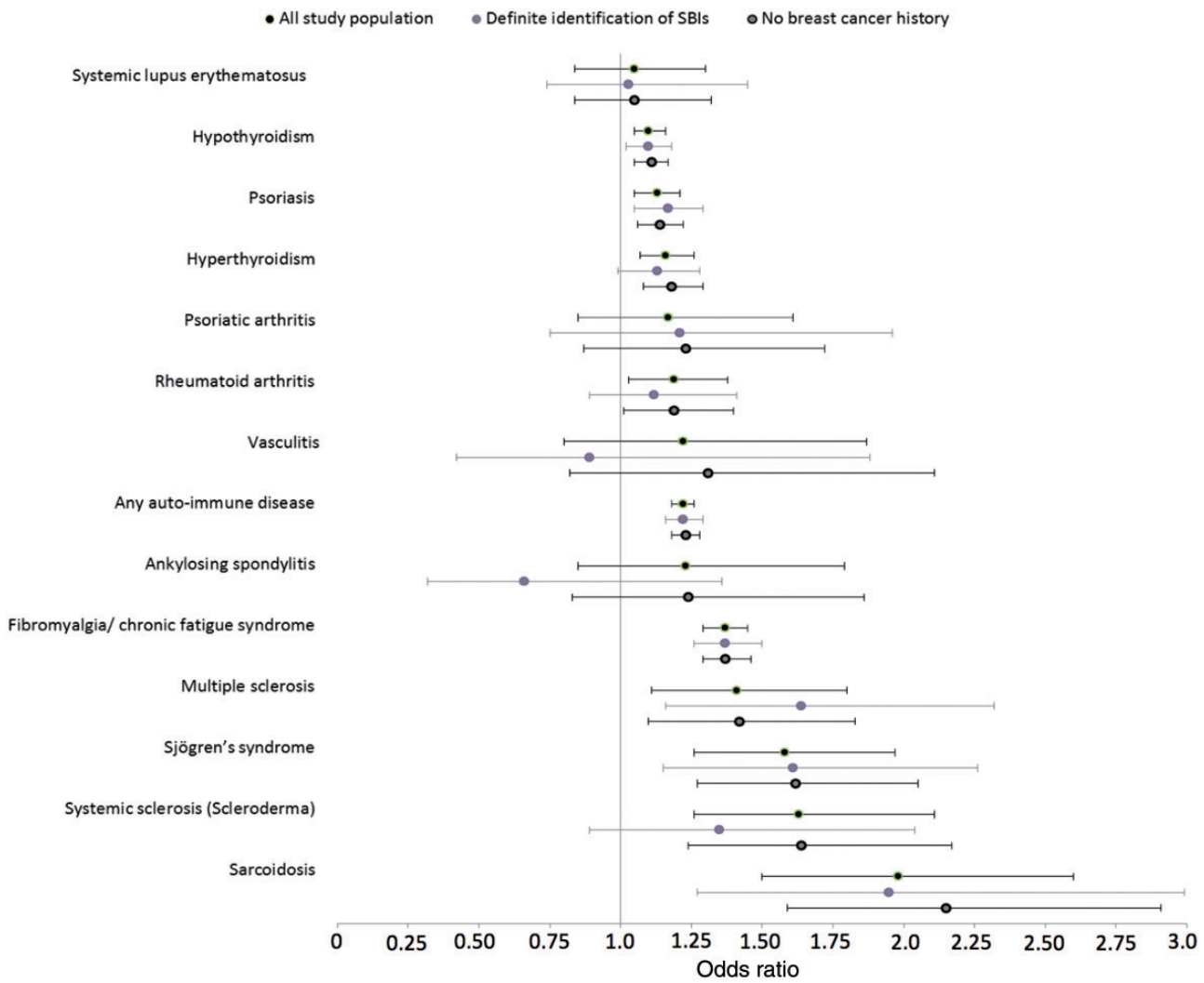

Figure 2. Adjusted (for age, socio-economic status, smoking status, breast cancer) odds ratios (95% confidence interval) for autoimmune/rheumatic disorders among SBI recipients in comparison to SBI-free women in three different multivariate analysis.

systemic symptoms on a systemic level. Previous reports have detected high levels of autoantibodies in asymptomatic SBI recipients, such as elevated titers of autoantibodies directed to SSA/SSB, histone-ribosomal-phosphate and cardiolipin.[26,27] Moreover, the cellular immune response directed against collagen (type I and III), fibronectin and fibrinogen were found to occur more frequently and intensely in women with SBIs.[28]

One of the main supporting factors of the causal relationship between SBIs and consequential risk of developing autoimmune/rheumatic disorders is the high percentage of symptom improvement in women with SBI-related disease after explantation.[5,7] de Boer *et al.*[29] revealed that 63% of SBI recipients who developed a subsequent autoimmune response experienced significant relief of systemic symptoms, such as arthralgia, myalgia, fatigue and neurological symptoms, during an observation period of 14 months following explantation. It is probable that the removal of the nociceptive signal triggered by the adjuvant qualities of the SBI prompts a regression of the immune reaction, leading to symptom relief. Nevertheless, although the majority of symptomatic women experienced clinical improvement, this was not the case for patients who had already been diagnosed with a well-defined autoimmune/rheumatic disorder following SBI. This finding implies that, once silicone particles have already infiltrated distant lymph nodes, such as in the axilla or inguinal regions, they continue to produce an inflammatory response, even after explantation of the original silicone implant.

Despite the various reports in the literature having suggested a link between SBIs and autoimmune/rheumatic disorders, many other studies conducted on this issue found the evidence for such an association to be lacking. One population-based retrospective study, which followed 749 women with SBIs and 1498 controls for a mean period of 7.8 years, showed no significant difference between the two groups with respect to the risk of developing CTDs

(HR 1.10, 95% CI 0.37–3.23), whereas only morning stiffness was found to be higher amongst women with SBIs (RR 1.81, 95% CI 1.11–2.9).[30] Another study by Sanchez-Guerrero *et al.*[31] analysed data of 14 years of follow-up of more than 80 000 subjects of the Nurses' Health Study cohort and concluded that there was no link between SBIs and CTDs. Yet this study primarily relied on self-report information (biennial and supplementary mailed questionnaires). A meta-analysis by Janowsky *et al.* that included 20 observational studies found no evidence of an association between SBIs and autoimmune/rheumatic conditions.[10]

It is clear that any attempt to establish a cause-and-effect relationship between an agent and a medical disorder is a complex endeavour, especially in the case of autoimmune/rheumatic disorders that are not extremely prevalent in the general population and often their aetiology is multifactorial. Proof of causality requires the existence of two components: a statistically significant association and a plausible mechanism that accounts for the association. Thus, it is apparent that, although the results of various studies including our own point to a clear relationship between SBIs and subsequent development of autoimmune/rheumatic disorders and several *in-vitro* studies and animal models have suggested various mechanisms by which silicone may induce autoimmune reactions, the evidence for a definite causal effect between SBIs and autoimmune/rheumatic disorders is still in the process of accumulation.

Our study has several strengths, the greatest of which is that all diagnoses recorded in the database were made by health professionals, as opposed to diagnoses based on self-reported symptoms as used by previous studies on SBIs.[18,31] Another strength is its large sample size, allowing sufficient statistical power to investigate disease with relatively low occurrence.

Our study also has several limitations: since the date of the SBIs insertion itself was not documented in MHS databases, we used a cross-sectional design, which prevented us from establishing a temporal relation between SBIs and diagnosis with an autoimmune/rheumatic disorder. However, in the retrospective sensitivity analysis that we performed among the subgroup of SBI recipients for whom we were able to capture the year of SBIs insertion, we revealed a positive association between the presence of SBIs and the risk of being diagnosed with at least one autoimmune/rheumatic disorder, indicating a possible temporal relation. Another limitation of our study is that some of the interventions that are performed outside of the MHS setting were not captured and included, so, despite our extensive attempts to identify all the relevant subjects, we probably failed to identify all of them due to lack of proper medical documentation in MHS databases. Information regarding the current prevalence of SBIs among Israeli women was unavailable and therefore we were unable to estimate the expected number of women with SBIs among MHS members. In addition, we cannot rule out the possibility of residual confounding. Previous studies have found various factors associated with the development of each autoimmune/rheumatic disorder. In the setting of our study, we were able to adjust for major confounders (age, SES, smoking status and breast-cancer history) and to perform several sensitivity analyses, which may help reduce the threat of residual confounding.

In conclusion, our data found an association between having SBIs and a higher likelihood of being diagnosed with various autoimmune/rheumatic disorders, regardless of the indication for SBIs, in particular sarcoidosis, systemic sclerosis and Sjögren's syndrome.

Supplementary Data

Supplementary data are available at *IJE* online.

Conflict of interest: None declared.

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