US FDA Breast Implant Postapproval Studies

Long-term Outcomes in 99,993 Patients

Christopher J. Coroneos, MD, MSc, Jesse C. Selber, MD, MPH, Anaeze C. Offodile II, MD, MPH, Charles E. Butler, MD, and Mark W. Clemens, MD

Objective: To analyze the long-term safety and efficacy outcomes of patients with breast implants.

Summary Background Data: Research is ongoing regarding the safety of silicone breast implants. Despite the number of patients with breast implants followed by United States Food and Drug Administration large postapproval studies (LPAS), this database has not been thoroughly analyzed or reported.

Methods: This is a multicentered, cohort study. LPAS prospectively monitor long-term implant-related outcomes and systemic harms for silicone/saline implants from 2 manufacturers (Allergan and Mentor) placed for primary/revision augmentation/reconstruction. Systemic harms, self-harm, and reproductive outcomes are compared with normative data. Implant-related complications are analyzed by implant composition and operative indication in the short and long terms.

Results: LPAS data includes 99,993 patients, 56% of implants were silicone for primary augmentation. Long-term magnetic resonance imaging surveillance is under 5%. Compared with normative data, silicone implants are associated with higher rates of Sjogren syndrome (Standardized incidence ratio [SIR]8.14), scleroderma (SIR 7.00), rheumatoid arthritis (SIR5.96), stillbirth (SIR4.50), and melanoma (SIR3.71). One case of BI-ALCL is reported. There is no association with suicide. In the short term, rupture is higher for saline (2.5% vs. 0.5%, $P < 0.001$), and capsular contracture higher for silicone (5.0% vs. 2.8%, $P < 0.001$). At 7 years, reoperation rate is 11.7% for primary augmentation, and 25% for primary/revision reconstruction. Capsular contracture (III/IV) occurs in 7.2% of primary augmentations, 12.7% primary reconstructions, and is the most common reason for reoperation among augmentations.

Conclusions: This is the largest study of breast implant outcomes. Silicone implants are associated with an increased risk of certain rare harms; associations need to be further analyzed with patient-level data to provide conclusive evidence. Long-term safety and implant-related outcomes should inform patient and surgeon decision-making when selecting implants.

Keywords: breast implantation, breast implants, breast reconstruction

(*Ann Surg* 2019;269:30–36)

Responding to public opinion, the United States Food and Drug Administration (FDA) prohibited use of silicone gel-filled breast implants in 1992.[1] Concerns included incidence of cancer, connective tissue disease (CTD), and autoimmune disease. The Institute of Medicine subsequently concluded there was no evidence to support an association between breast implants and these systemic diseases.[2] Current generation silicone gel-filled implants were approved by the FDA in 2006[1] for two manufacturers: Allergan and Mentor Corp (Mentor).[3] While implant-specific local complications were adequately characterized at the time of approval, the FDA stipulated manufacturers conduct large postapproval studies (LPAS) monitoring outcomes for imaging surveillance, long-term safety and outcomes, and possible systemic harms due to silicone.

Postapproval studies include patients with silicone or saline breast implants for primary or secondary breast augmentation or reconstruction. Follow-up time horizon is 10 years. Overall, LPAS enrolled nearly 100,000 patients. Despite abundant data collection, and open public access, the LPAS database has yet to be thoroughly analyzed or reported; this manuscript represents the first report of those data. The existing literature is sponsored by industry,[4–8] and focused on a single manufacturer by design. Analyses have included follow-up from smaller FDA ''Core Study'' datasets,[4,5,7–9] studies primarily intended to investigate implant-specific, local complications geared toward FDA approval. These were not designed with adequate power to detect ''rare'' systemic harms, or with enough centers to be generalized to ''real-world'' effectiveness.

Breast implants are used in nearly 300,000 augmentations and 100,000 reconstructions annually in the United States,[10,11] however prospective research is ongoing regarding the safety of silicone gel-filled breast implants, with limitations in the existing evidence.[12] As a specialty, plastic surgery must increase its awareness of evidence-based practice.[13] It remains the specialty's duty to provide evidence to inform surgeons, patients, the general medical community, and public about the safety of its distinguishing medical device.[14] The purpose of this study is to comprehensively analyze long-term safety and implant-specific outcomes in patients with breast implants from the FDA LPAS database, including rare harms of CTD, neurological disease, autoimmune disease, cancer, self-harm, and reproductive health. Secondary outcomes include implant-specific complications, patient-reported outcomes, and compliance with imaging surveillance.

METHODS

Institutional review board approval was obtained by the authors' institution. This is a retrospective cohort study of prospectively collected data for patients receiving breast implants for primary or revision augmentation or reconstruction.

Data Sources

Data were obtained from reports of the FDA LPAS database.[1,15,16] This study is a secondary analysis of the existing open access data; this study has a number of limitations reflecting analysis of summary data. We are unable to account for the specific methodology of LPAS beyond what is publicly available,[15,16] or the differences between respective manufacturer protocols. This is especially important when considering outcomes assessment, loss to follow-up (LTFU), confounding, and other potential sources of bias.

From the Department of Plastic Surgery, MD Anderson Cancer Center, Houston, TX.

The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

Reprints: Mark W. Clemens, MD, Department of Plastic Surgery, MD Anderson Cancer Center, 1400 Pressler Street, Unit 1488, Houston, TX 77030.
E-mail: mwclemens@mdanderson.org.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0003-4932/18/26901-0030
DOI: 10.1097/SLA.0000000000002990

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

LPAS inclusion was limited to women 22 years of age or older receiving unilateral or bilateral silicone or saline implants for primary or revision breast augmentation, and women 18 years of age or older for primary or revision breast reconstruction following cancer resection, trauma, or congenital absence.

Allergan patients were recruited from February 2007 to March 2010 from 873 sites, receiving FDA PMA#P020056 Natrelle silicone gel-filled, or saline breast implants.[17] Mentor patients were recruited from February 2007 to July 2009 from 2342 sites, receiving FDA PMA#P030053 MemoryGel silicone gel-filled, or saline breast implants.[18] All clinical outcome data including deaths, very rare adverse events (eg, connective tissue disease), rare target adverse events, and local complications were reported to the FDA at predefined intervals. All reported events represent new diagnoses or symptoms versus baseline for each outcome. For each manufacturer, outcomes were assessed at 3 to 4 postoperative visits at predefined intervals, and remote (mail, telephone, internet) annual patient-reported questionnaires.

Outcomes

Outcome data of interest was abstracted from LPAS summary reporting by a single reviewer using an electronic form designed a priori, and checked by a second reviewer. Baseline data included patient demographics, operative technique, and implant characteristics. The primary outcome is rare harm, including CTD, neurological, autoimmune disease, cancer, self-harm/wellbeing/satisfaction (suicide, BREAST-Q), and reproduction (fertility/offspring outcomes). Secondary outcomes include imaging surveillance, local complications, and reoperation.

Statistical Analysis

Baseline enrollment included patients under age 22 undergoing primary augmentation; 556 patients were removed from short-term Mentor analyses for not meeting eligibility criteria. For Allergan, 97 patients not meeting criteria could not be isolated, and were included in short-term analyses. Long-term implant-related events are calculated using the Kaplan–Meier estimate of cumulative incidence.

Systemic harm rates in the study population are calculated per 10,000 person-years. For Allergan, person-years are estimated from 2-year follow-up rates. For Mentor patients, rates include cases self-identified by patient-reported questionnaires. Normative population rates for systemic harms, self-harm, and reproductive outcomes are obtained from the literature; rates reflect LPAS demographics for female sex, age, and race in the United States.[19–38] LPAS data is expressed relative to normative population rates using standardized incidence ratios (SIRs). One sample exact Poisson tests are used to compare event rates in the LPAS population to normative rates in the general population; 95% confidence intervals are calculated using a Poisson distribution with 2-sided tests. Incidence of harms 2 times that of normative data is considered clinically important, decided a priori. Chi-squared tests are used to analyze categorical variables. *P* values less than 0.05 are significant; values are not adjusted. Analyses are performed in R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Large postapproval studies include 99,993 patients, summarized by operative indication and manufacturer (Table 1). Allergan enrolled 41,342 patients with silicone implants and 15,646 with saline; Mentor enrolled 41,975 with silicone and 1030 with saline. The majority of patients received silicone implants for primary augmentation (56%). Overall, 72% of patients underwent primary augmentation, 15% revision augmentation, 10% primary reconstruction, and 3% revision reconstruction. Patient demographics, operative technique, and implant characteristics are summarized (Table 2). All implants included are round. For Mentor, submuscular pocket is most common for all indications. Implant size and texture are not available for Mentor.

TABLE 1. Patients Enrolled in LPAS

	Allergan		Mentor		
	Silicone	Saline	Silicone	Saline	Total
Primary aug	29,886	14,447	26,674	930	71,937
Revision aug	6033	970	8365	76	15,444
Primary recon	4714	184	5031	13	9942
Revision recon	709	44	1757	9	2519
Unknown	0	1	148	2	151
Total	41,342	15,646	41,975	1030	99,993

Follow-up and Surveillance

Clinical follow-up by year and indication are summarized (eTable1 and 2 in the Supplement, http://links.lww.com/SLA/B485). There is significant attrition in follow-up: 2-year 60.5% for silicone and 45.1% for saline (Allergan), 3-year 21.1% for silicone and 9.6% saline (Mentor), and 7-year combined 20.1% (Mentor). Compliance with surveillance magnetic resonance imaging (MRI) for silicone is summarized (eTable3, http://links.lww.com/SLA/B485). Overall compliance is poor, 5.2% for 3-year baseline and under 5% at 5 years and thereafter. Among 2051 patients undergoing MRI surveillance by Mentor, 6.4% have evidence of rupture. At 7 years, rupture is detected in 0.7% of primary and 2.8% of revision augmentations, 2.2% of primary and 2.6% of revision reconstructions.

TABLE 2. Patient Demographics, Operative Techniques, and Implant Characteristics

	Allergan	Mentor	
	Combined	Silicone	Saline
Age (mean years)	35	–	–
Age over 30 (%)	–	78.2	49.8
Height (mean feet/inches)	5'5"	5'5"	5'3"
Weight (mean pounds)	130	130	129
Caucasian (%)	71	77.8	56.5
Hispanic (%)	13	9.9	26.5
Asian (%)	5	4.5	7.7
Black/African American (%)	3	1.1	4
Native America/Alaska (%)	–	2.5	0.9
Unknown/other (%)	6	2.1	4.6
College education or greater (%)	72.1	75.6	63.9
Married (%)	51.8	59.5	44.2
Professional occupation (%)	45.2	–	–
No tobacco history (%)	57	55.6	62
Among smokers, <10 cigarettes/d (%)	67.5	–	–
No alcohol	19.5	29.3	38.9
<3 alcoholic drinks/wk (%)	63.3	–	–
Bilateral (%)	95.9	95.1	98.6
Inframammary (%)	54	58.6*	26.9*
Periareolar	22.8	–	–
Mastectomy scar	–	72.8†	57.9†
Partial submuscular pocket	58.9	–	–
Complete submuscular pocket	29.3	–	–
Smooth shell	91.3	–	–
300–399cc	42.4	–	–

*Includes only primary augmentations.
†Includes only primary reconstructions.

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 3. Rare Systemic Harms Compared With the General Population

	Manufacturer*,†	Study Events	Study Event Rate (Per 10,000 Person Yr)	General Population Event Rate (Per 10,000 Person Yr)	SIR	SIR 95% CI	*P* Value
Fibromyalgia	Allergan	9	1.8	112.8	0.02	0.01–0.03	<0.001
	Mentor	307	28.4	112.8	0.25	0.22–0.28	<0.001
Rheumatoid arthritis	Allergan	4	0.8	5.4	0.15	0.04–0.38	<0.001
	Mentor	349	32.2	5.4	5.96	5.35–6.62	<0.001
Scleroderma	Mentor	46	4.2	0.6	7.00	5.12–9.34	<0.001
Sjogren syndrome	Mentor	62	5.7	0.7	8.14	6.24–10.44	<0.001
Systemic lupus erythematosus	Allergan	3	0.6	5.4	0.11	0.02–0.32	<0.001
	Mentor	66	6.0	5.4	1.11	0.86–1.41	0.398
Cancer	Allergan	80	16.0	41.3	0.39	0.31–0.48	<0.001
	Mentor	532	63.8	41.3	1.54	1.42–1.68	<0.001
Breast cancer	Mentor	116	13.9	12.5	1.11	0.92–1.33	0.26
Lung cancer	Mentor	5	0.6	5.2	0.12	0.04–0.27	<0.001
Brain cancer	Mentor	3	0.4	0.6	0.67	0.14–1.95	0.639
Melanoma	Mentor	65	7.8	2.1	3.71	2.87–4.73	<0.001
Neurological disorder	Allergan	18	3.6	22.5	0.16	0.09–0.25	<0.001
	Mentor	394	35.8	22.5	1.59	1.44–1.76	<0.001
Multiple sclerosis	Mentor	47	4.3	2.5	1.72	1.26–2.29	0.001
Myositis	Mentor	17	1.5	0.8	1.88	1.09–3.00	0.018

*Allergan follow-up 2 years.
†Mentor follow-up 7 years.

Systemic Harms

Incidence rates for systemic harms for silicone are summarized and compared with the general population (Table 3). Harms are not reported for saline. Diagnoses with rates double the general population (SIR greater than 2.0) include Mentor patients with Sjogren syndrome (SIR: 8.14, 95% CI: 6.24–10.44, $P < 0.001$), scleroderma (SIR: 7.00, 95% CI: 5.12–9.34, $P < 0.001$), rheumatoid arthritis (SIR: 5.96, 95% CI: 5.35–6.62, $P < 0.001$), and melanoma (SIR: 3.71, 95% CI: 2.87–4.73, $P < 0.001$). SIRs less than 2.0 but with statistically increased associations are overall cancer diagnosis, neurological disorder, multiple sclerosis, and myositis. Silicone implants are associated with statistically decreased rates of fibromyalgia, and lung cancer.

Allergan data is limited given fewer reported diagnoses, and 2-year follow-up (Table 3). Descriptively, Allergan reports patients receiving silicone implants for revision reconstruction have SIRs over 2.0 for scleroderma, Sjogren syndrome, and dermatomyositis/polymyositis compared with normative at 7-year follow-up. Primary/revision augmentation and primary reconstruction groups have SIRs less than 2.0 though numerical values are not reported. However, Allergan descriptively reports more rheumatologic events and symptoms with silicone implants than saline.

There is 1 case of breast implant associated anaplastic large cell lymphoma (BI-ALCL) reported by Mentor; implant characteristics are unknown.

Self-harm, Wellbeing, and Satisfaction

Mentor reports the suicide rate for patients with silicone implants is 0.01% overall (5 cases), similar to the general population, $P > 0.999$. Similarly, Allergan reports suicide rates under 0.1% for patients with silicone implants for any indication.

Allergan reports 4-year BREAST-Q outcomes for 12,758 patients with silicone implants and 1393 with saline for all indications. For both silicone and saline, median ''satisfaction with breast'' scores were baseline 33.3 baseline, 1-year 94.4, and 4-year 88.9. Median ''psychosocial well-being'' scores were baseline 66.7 silicone/58.3 saline, 1-year 97.2 for silicone/saline, and 4-year 91.7 silicone/88.9 saline.

Reproduction

Mentor reports 3133 pregnancies among patients receiving silicone implants, resulting in 1710 offspring. Fetal and newborn outcomes are summarized and compared with the general population (Table 4). The rate of stillbirth (SIR: 4.50, 95% CI:

TABLE 4. Reproductive Health Compared With the General Population

	Study Events	Study Event Rate (%)	General Population Event Rate (%)	SIR	SIR 95% CI	*P* Value
Miscarriage	416	13.3	14	0.95	0.86–1.05	0.304
Stillbirth	85	2.7	0.6	4.50	3.59–5.56	<0.001
Preterm birth	234	13.7	10.4	1.32	1.15–1.50	<0.001
Low birth weight	155	9.1	8.2	1.11	0.94–1.30	0.19
Neonatal intensive care	194	11.3	6.4	1.77	1.53–2.03	<0.001
Any birth defect/congenital malformation	27	1.6	3	0.53	0.35–0.78	<0.001
Cleft palate	1	0.1	0.06	1.00	0.03–5.57	>0.999
Cleft lip	0	0.0	–	–	–	–
Esophageal deformity	1	0.1	0.04	1.50	0.04–8.36	0.487
Pyloric stenosis	0	0.0	–	–	–	–
Neural tube defect	0	0.0	–	–	–	–

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

3.59–5.56, $P < 0.001$) is more than double the general population. SIRs less than 2.0 but statistically increased are also demonstrated for preterm birth, and neonatal intensive care. Silicone implants are associated with statistically decreased rates of birth defect/congenital malformation.

Local Complications and Reoperation

Local, implant-specific complications, and reoperation are summarized (Table 5). Allergan reports silicone and saline outcomes pooled for all indications. At 2 years, rupture is higher for saline implants, 2.5% versus 0.5% silicone, $P < 0.001$. Capsular contracture (III/IV) is higher for silicone, 5.0% versus 2.8% saline, $P < 0.001$. Mentor reports silicone outcomes stratified by indication. At 3 years, rupture and capsular contracture (III/IV) are highest among revision augmentations, 1.0% and 11.8% respectively, $P < 0.001$. Seven-year follow-up (n) by indication is not reported, precluding statistical comparison. Event rates are higher in reconstruction versus augmentation, and revision versus primary surgery. Grade III/IV capsular contracture ranges from 7.2% to 18.3%, clinically suspected rupture 8.2% to 15.6%, infection 3.3% to 6.3%, and breast pain 19.6% to 29.6%. Five-year reporting for Allergan is limited, varying by indication: infection 0.3% to 1.9%, and rupture 1.4% to 2.6%.

Short-term reoperation and implant removal are higher for silicone (6.5% and 3.4% at 2 years, $P < 0.001$) and in primary reconstruction (20.4% and 13.5% at 3 years, $P < 0.001$). Etiology of implant removal is summarized for Allergan (eTable 4, http://links.lww.com/SLA/B485) and Mentor (eTable 5, http://links.lww.com/SLA/B485). The most common reason for both manufacturers is desire for size/style change. At 7 years, the reoperation rate for primary augmentation is 11.7%, revision 18.9%, most commonly for capsular contracture and patient requested size change (primary: 26.8%/21.0%, revision: 31.1%/19.9%, respectively). Reoperation for primary reconstruction is 24.7%, revision 26.6%, most commonly for asymmetry and capsular contracture (primary: 22.1%/20.0%, revision: 24.4%/21.4%, respectively). Altogether at 7-year follow-up, 35.9% of primary augmentations experience a complication and/or reoperation, and greater than 50% of revision augmentations and primary/revision reconstructions.

DISCUSSION

This is the largest, most comprehensive study of patient safety and implant-specific outcomes for breast implants reported in the literature. Long-term outcomes are obtained from reports of FDA LPAS data. Analyses include rare harms that Core Studies were not adequately powered to detect, and have never before been reported. Silicone breast implants are associated with increased rates of Sjogren syndrome (SIR: 8.14), scleroderma (SIR 7.00), rheumatoid arthritis (SIR: 5.96), stillbirth (SIR: 4.50), and melanoma (SIR: 3.71), greater than double the general population. It is critical patient-level data from the LPAS database be made available for unbiased analysis of these harms, resolving the existing weaknesses in and debate over the evidence. LPAS were multicenter effectiveness studies, reflecting generalizable outcomes for implant-specific complications, and compliance with imaging surveillance; these outcomes are valuable in informing surgeons and patients.

Our study agrees with a meta-analysis by Balk et al,[12] which pooled outcomes for silicone implants from 32 observational studies; associations were found for rheumatoid arthritis, Sjogren syndrome, and Raynaud syndrome (a main feature of CREST syndrome, the limited cutaneous form of scleroderma). Results in our study show a greater effect size for these same CTDs. That meta-analysis is limited primarily by inconsistency of the pooled studies, as well as indirectness (some studies included saline), bias from potential confounders, and LTFU. LPAS data in our study is self-reported, and similarly limited by the inability to account for confounders and LTFU. A large demographic study found a significant association between implants and poly/dermatomyositis, scleroderma, and Sjogren syndrome, which disappeared when only 22.7% of self-reported diagnoses could be confirmed.[39,40] A previous descriptive review similarly concluded no association between silicone implants and CTD.[41]

Manufacturers are consistent in terms of patient-reported rheumatologic symptoms; even after their own age-adjusted analysis, more symptoms are experienced by patients with silicone implants. Allergan reports ''higher standard incidence ratios (SIRs) were observed in the revision-reconstruction cohort for scleroderma, Sjogren's syndrome, and dermatomyositis/polymyositis'' at 7 years, without quantification.[15] Further, ''∼500 [sic] possible [rheumatologic] events in silicone vs less than 5 events occur in saline, and some symptoms occurred more frequently in the silicone cohort compared to the saline cohort, even after an age-adjusted analysis.''[15] This parallels patient information for Mentor silicone implants, ''significant increases were found for fatigue, exhaustion, joint swelling, joint pain, numbness of hands, frequent muscle cramps, and the combined categories of fatigue, pain, and fibromyalgia-like symptoms in primary augmentation patients, and for joint pain in

TABLE 5. Local Complications and Reoperation

	Allergan			Mentor					Mentor			
	Silicone	Saline		Silicone					Silicone			
Indication	All		*P* Value	Primary Augment	Revision Augment	Primary Recon	Revision Recon	*P* Value	Primary Augment	Revision Augment	Primary Recon	Revision Recon
N	41,342	15,646	–	26,118	8365	5031	1757	–	–	–	–	–
Time (yr)	2	2	–	3	3	3	3	–	7	7	7	7
Follow-up (%)	60.5	45.1	–	20	19	29	28	–	–	–	–	–
Rupture (%)	0.5	2.5	*P*<0.001	0.2	1.0	0.4	0.7	*P*<0.001	8.2*	14.2*	12.5*	15.6*
Capsular contracture (III/IV) (%)	5.0	2.8	*P*<0.001	5.3	11.8	9.1	10.0	*P*<0.001	7.2	18.0	12.7	18.3
Breast pain (%)	–	–	–	–	–	–	–	–	19.6	25.0	29.6	27.8
Infection (%)	–	–	–	–	–	–	–	–	3.3	4.0	6.3	5.9
Reoperation (%)	6.5	4.5	*P*<0.001	10.8	14.6	20.4	17.7	*P*<0.001	11.7	18.9	24.7	26.6
Implant removal (%)	3.4	2.4	*P*<0.001	5.0	7.7	13.5	11.7	*P*<0.001	6.2	12.5	15.9	17.4
Any complication and/or reoperation (%)	–	–	–	–	–	–	–	–	35.9	50.8	53.4	58.5

*Clinically suspected.

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

revision-augmentation patients. These increases were not found to be related to simply getting older over time.''[42]

A separate publication of LPAS data sponsored by Allergan reported no significantly higher rate of CTD, or any systemic harm investigated in our study at 5 years.[6] This data is not included in public LPAS reporting.[1,15] All Allergan diagnoses had to be confirmed by a physician, and analyses were adjusted for a number of covariates in each case.[6]

A common criticism of patient-reported data is that diagnoses are not confirmed by a physician, and may not be true events. However, we believe patient-reported symptoms are important to plastic surgeons and surgical oncologists alike, mirroring what practically occurs. In everyday practice, patients with silicone breast implants may present with these symptoms, and ultimately be referred to a rheumatologist for assessment. Even if patient-reports are not believed to be true events, these outcomes demonstrate the proportion of patients who will be referred for evaluation of their symptoms, regardless of whether a diagnosis is ultimately confirmed.

There is 1 case of BI-ALCL reported by Mentor.[16] The number needed to harm for BI-ALCL is estimated to be 58,140 for all breast implants.[43] To date, BI-ALCL is only reported as a sequela of textured implants; available data did not distinguish between textured versus smooth. A separate publication by Allergan reported no BI-ALCL cases, however it is unclear whether BI-ALCL was a tracked outcome.[6] The association between silicone implants and melanoma (SIR: 3.17) is inconsistent with previous literature which demonstrates no relationship.[44–46] The 65 reported melanoma cases also drive the elevated rate of overall cancer. Our study found no association between silicone implants and breast cancer, contrary to previous literature demonstrating decreased rates;[12,44–47] patient confounders and implant-related metabolic factors are hypothesized for this observed reduction.[12,48,49] The decreased rate of lung cancer in this study disagrees with the literature supporting no association or an increased rate,[50] owing to increased rates of smoking in the implant population.[12] Similar to the literature, there is no association with brain cancer in our study.[51] The association with multiple sclerosis and overall neurological disease is not supported by the literature.[12,52,53]

Reproductive outcomes are inconsistent. There is an increased rate of stillbirth, but no association with miscarriage versus the general population. Moreover, CTD is known to be associated with higher rates of stillbirth.[54] There are increased rates of preterm birth and neonatal intensive care, but no association with low birth weight. There is no evidence of poor reproductive outcomes in the literature,[12] despite studies not adjusting for alcohol or smoking status.[55] At baseline, women pursuing breast augmentation have been demonstrated to be more likely to smoke, have a prematurely terminated pregnancy, and fewer overall live births.[56]

Our study finds no association between breast implants and suicide. Suicide and psychiatric outcomes have been a major focus of breast implant research, with a possible association addressed by the FDA in 2011.[1] Analyses are thought to be confounded by socioeconomic status, self-esteem, psychological distress, and psychotherapy among implant patients.[1,12,57] A meta-analysis found that despite reports of increased suicide rates, studies adjusted for covariates did not demonstrate an association.[12] While BREAST-Q outcomes for satisfaction and psychosocial well-being were improved postoperatively, analyses included both augmentations and reconstructions.

The US FDA recommends MRI surveillance of silicone implants 3 years postoperatively and every 2 years thereafter to assess for integrity/rupture. LPAS are effectiveness studies, and demonstrate compliance is less than 5% at 5 years. Imaging is a financial burden to patients and an ineffective screening tool, and therefore initial assessment with ultrasound is an optimal alternative in economic analysis.[58]

Short-term analyses for Allergan data could not be stratified by indication, and short and long-term for Mentor did not include saline. Long-term implant-specific outcomes in our study deliver practical expectations. For patients, specific rates of complications and reoperation can be provided by intervention within 7 years. In primary augmentation at least ''one-in-nine'' patients undergo reoperation (11.7%). In reconstruction reoperation is ''one-in-four'' (24.7–26.6%). Altogether, ''one-in-three'' (35.9%) of primary augmentations and ''more than half'' (50.8–58.5%) of revision augmentations, primary/revision reconstructions will experience some degree of morbidity in the form of a complication and/or reoperation. For surgeons, capsular contracture is confirmed to be the greatest long-term source of morbidity and reoperation. Outcomes in our study could not be stratified by relevant implant characteristics. Minimizing capsular contracture is an ongoing research priority.[59,60] Our outcomes are similar to those reported from Core Study data.[7,9]

Limitations

Our study has a number of limitations inherent to observational and summarized data. Given the summarized LPAS data, we were limited to the data that is publicly reported.[6,12] Methodological details of LPAS are limited. We are unable to comment on outcome assessment, dealing with LTFU, other potential sources of bias, or differences between Allergan and Mentor's protocols. All outcomes are not available from both manufacturers. Patients could not be analyzed on an individual level. It is accepted that women with breast implants have a number of distinct baseline factors and comorbidities.[61,62] This is especially important in adjusting analyses for known covariates or potential confounders among rare harms, where adjusted primary studies and Allergan sponsored publication report the most conservative results. Outcomes in subgroups of implant characteristics, operative details, and specific clinical combinations (eg, silicone fill, round shape, textured shell, subgladular pocket, inframammary approach) could not be isolated from summary data.

Additionally, data relied on self-reporting, notably for diagnoses for systemic harms and reproductive outcomes in Mentor patients. In contrast, Allergan diagnoses required confirmation with the diagnosing physician. Self-reporting of CTD,[39] melanoma,[63] and skin cancer[64] may be imprecise. Patients with symptoms or belief in a disease may be more likely to complete questionnaires.

Further, all analyses rely on indirect comparisons. Allergan and Mentor outcomes should not be directly compared since they were collected under different protocols; superiority analysis would require a head-to-head trial. Comparisons to normative data cannot be matched on a patient-level due to summary reporting. Data did not allow for comparisons between silicone and saline for many outcomes.

Finally, there is significant attrition in long-term follow-up rates and missing outcome data; patients who continue follow-up may systematically differ from those lost to follow-up. While LPAS were designed accounting for 35% LTFU,[65] this was exceeded in some subgroups. Appreciable rates of LTFU are similarly observed in Postapproval Studies from other specialties.[66,67] This limits our interpretation of study results.

CONCLUSION

This is the largest study of breast implant outcomes reported in the literature. Data was obtained from US FDA Large Postapproval Studies, which enrolled nearly 100,000 patients and captured imaging surveillance, long-term implant-specific outcomes, and rare harms over an adequate time-horizon. This study demonstrates silicone implants are associated with an increased risk of certain systemic harms. These associations are not conclusive given limitations of LPAS reporting. Further, summary data is unable to deliver

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

outcome profiles for implants in specific clinical scenarios. To resolve the remaining uncertainty in the evidence base, it is important that LPAS data be analyzed on a patient-level, and in an unbiased manner. It remains the plastic surgery community's duty to provide definitive evidence for the risks associated with breast implants.

REFERENCES

1. Center for Devices and Radiological Health U.S. Food and Drug Administration. FDA Update on the Safety of Silicone Gel-Filled Breast Implants. 2011.
2. Bondurant S, Enster V, Herdman R. *Safety of Silicone Breast Implants.* Washington DC: National Academy Press; 1999.
3. Maxwell GP, Gabriel A. The evolution of breast implants. *Plast Reconstr Surg*. 2014;134:12S–17S.
4. Hammond D, Vargo J, Wixtrom R, et al. Long-term clinical performance of Memoryshape® breast implants in breast augmentation and reconstruction: prospective data through 10 years. *Plast Reconstr Surg*. 2015;135:1255.
5. Hammond DC, Migliori MM, Caplin DA, et al. Mentor Contour Profile Gel implants: clinical outcomes at 6 years. *Plast Reconstr Surg*. 2012;129:1381–1391.
6. Singh N, Picha GJ, Hardas B, et al. Five-year safety data for more than 55,000 subjects following breast implantation: comparison of rare adverse event rates with silicone implants versus national norms and saline implants. *Plast Reconstr Surg*. 2017;140:666–679.
7. Spear SL, Murphy DK, Allergan Silicone Breast Implant U.S. Core Clinical Study Group. Natrelle round silicone breast implants: Core Study results at 10 years. *Plast Reconstr Surg*. 2014;133:1354–1361.
8. Maxwell GP, Van Natta BW, Bengtson BP, et al. Ten-year results from the Natrelle 410 anatomical form-stable silicone breast implant core study. *Aesthetic Surg J*. 2015;35:145–155.
9. Calobrace MB, Schwartz MR, Zeidler KR, et al. Long-term safety of textured and smooth breast implants. *Aesthetic Surg J*. 2017;38:38–48.
10. Loyo-Berrios N. Building national infrastructure for postmarket surveillance of silicone breast implants Available at: www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM360961.pdf. 2013. Accessed November 10, 2017.
11. Cosmetic Surgery National Data Bank Statistics. *Aesthetic Surg J*. 2017;37:1–29.
12. Balk EM, Earley A, Avendano EA, et al. Long-term health outcomes in women with silicone gel breast implants: a systematic review. *Ann Intern Med*. 2016;164:164–175.
13. Eaves FF, Rohrich RJ, Sykes JM. Taking evidence-based plastic surgery to the next level: report of the second summit on evidence-based plastic surgery. *Plast Reconstr Surg*. 2013;132:227–235.
14. Thoma A, Kaur MN, Hong CJ, et al. Methodological guide to adopting new aesthetic surgical innovations. *Aesthet Surg J*. 2015;35:308–318.
15. Allergan. Post-Approval Studies (PAS). 2017–11-06. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?-t_id=90235&c_id=73. Accessed November 11, 2017.
16. Mentor Corp. Post-Approval Studies (PAS). 2017-11-06. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?t_id=90325&c_id=72. Accessed November 11, 2017.
17. Allergan. Premarket Approval (PMA) Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P020056. Accessed November 11, 2017.
18. Mentor Corp. Premarket Approval (PMA) Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P030053. Accessed November 11, 2017.
19. Weir PT, Harlan GA, Nkoy FL, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. *J Clin Rheumatol*. 2006;12:124–128.
20. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am*. 2001;27:269–281.
21. Wallin MT, Culpepper WJ, Coffman P, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. *Brain*. 2012;135:1778–1785.
22. Furst DE, Amato AA, Iorga R. et al. Epidemiology of adult idiopathic inflammatory myopathies in a U.S. managed care plan. *Muscle Nerve*. 2012;45:676–683.
23. Centers for Disease Control and Prevention. Fatal Injury Reports, National, Regional and State, 1981 – 2015. WISQARS. Available at: https://webappa.cdc.gov/sasweb/ncipc/mortrate.html. Accessed October 12, 2017.
24. Regan L, Rai R. Epidemiology and the medical causes of miscarriage. *Baillieres Best Pract Res Clin Obstet Gynaecol*. 2000;14:839–854.
25. Wang X, Chen C, Wang L, et al. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril*. 2003;79:577–584.
26. Ferré C, Callaghan W, Olson C, et al. Effects of maternal age and age-specific preterm birth rates on overall preterm birth rates—United States, 2007 and 2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:1181–1184.
27. Mai CT, Cassell CH, Meyer RE, et al. Birth defects data from population-based birth defects surveillance programs in the United States, 2007 to 2011: highlighting orofacial clefts. *Birth Defects Res A Clin Mol Teratol*. 2014;100:895–904.
28. Holmes LB. Current concepts in genetics. Congenital malformations. *N Engl J Med*. 1976;295:204–207.
29. Leppig KA, Werler MM, Cann CI, et al. Predictive value of minor anomalies. I. Association with major malformations. *J Pediatr*. 1987;110:531–537.
30. Marden PM, Smith DW, McDonald MJ. Congenital anomalies in the newborn infant, including minor variations. a study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. *J Pediatr*. 1964;64:357–371.
31. Chifflot H, Fautrel B, Sordet C, et al. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum*. 2008;37:223–235.
32. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol*. 2012;24:165–170.
33. Pillemer SR, Matteson EL, Jacobsson LT, et al. Incidence of physician-diagnosed primary Sjögren syndrome in residents of Olmsted County, Minnesota. *Mayo Clin Proc*. 2001;76:593–599.
34. Chakravarty EF, Bush TM, Manzi S, et al. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum*. 2007;56:2092–2094.
35. NIH National Cancer Institute. Cancer Statistics Available at: https://www.cancer.gov/about-cancer/understanding/statistics. 2017. Accessed January 12, 2017.
36. Jemal A, Siegel R, Ward E, et al. Cancer statistics. *CA Cancer J Clin*. 2008;58:71–96.
37. Deorah S, Lynch CF, Sibenaller ZA, et al. Trends in brain cancer incidence and survival in the United States: surveillance, Epidemiology, and End Results Program, 1973 to 2001. *Neurosurg Focus*. 2006;20:E1.
38. Borlongan CV, Burns J, Tajiri N, et al. Epidemiological survey-based formulae to approximate incidence and prevalence of neurological disorders in the United States: a meta-analysis. *PLoS One*. 2013;8:e78490.
39. Karlson EW, Lee IM, Cook NR, et al. Comparison of self-reported diagnosis of connective tissue disease with medical records in female health professionals: the Women's Health Cohort Study. *Am J Epidemiol*. 1999;150:652–660.
40. Hennekens CH, Lee IM, Cook NR, et al. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. *JAMA*. 1996;275:616–621.
41. Lipworth L, Holmich LR, McLaughlin JK. Silicone breast implants and connective tissue disease: no association. *Semin Immunopathol*. 2011;33:287–294.
42. Mentor Corp. Important Information for Augmentation Patients About Mentor MemoryGel(Silicone Gel-Filled Breast Implants Available at: https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM245622.pdf. 2009. Accessed November 2, 2018.
43. Nava MB, Adams WP, Botti G, et al. MBN 2016 Aesthetic Breast Meeting BIA-ALCL Consensus Conference Report. *Plast Reconstr Surg*. 2018;141:40–48.
44. Friis S, Hölmich LR, McLaughlin JK, et al. Cancer risk among Danish women with cosmetic breast implants. *Int J Cancer*. 2006;118:998–1003.
45. McLaughlin JK, Lipworth L, Fryzek JP, et al. Long-term cancer risk among Swedish women with cosmetic breast implants: an update of a nationwide study. *J Natl Cancer Inst*. 2006;98:557–560.
46. Deapen DM, Brody GS. Cancer risk among cosmetic breast implant patients: an update of the Los Angeles study. *Plast Reconstr Surg*. 2012;129:575e–576e.
47. Rubin JP, Landfair AS, Shestak K, et al. Health characteristics of postmenopausal women with breast implants. *Plast Reconstr Surg*. 2010;125:799–810.

© *2018 Wolters Kluwer Health, Inc. All rights reserved.*

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

48. Deapen DM, Pike MC, Casagrande JT, et al. The relationship between breast cancer and augmentation mammaplasty: an epidemiologic study. *Plast Reconstr Surg*. 1986;77:361–368.
49. Brisson J, Holowaty EJ, Villeneuve PJ, et al. Cancer incidence in a cohort of Ontario and Quebec women having bilateral breast augmentation. *Int J Cancer*. 2006;118:2854–2862.
50. Brinton LA, Lubin JH, Burich MC, et al. Cancer risk at sites other than the breast following augmentation mammoplasty. *Ann Epidemiol*. 2001;11:248–256.
51. McLaughlin JK, Lipworth L. Brain cancer and cosmetic breast implants: a review of the epidemiologic evidence. *Ann Plast Surg*. 2004;52:115–117.
52. Winther JF, Friis S, Bach FW, et al. Neurological disease among women with silicone breast implants in Denmark. *Acta Neurol Scand*. 2001;103:93–96.
53. Nyrén O, McLaughlin JK, Yin L, et al. Breast implants and risk of neurologic disease: a population-based cohort study in Sweden. *Neurology*. 1998;50:956–961.
54. Reddy UM, Goldenberg R, Silver R, et al. Stillbirth classification—developing an international consensus for research: executive summary of a National Institute of Child Health and Human Development workshop. *Obstet Gynecol*. 2009;114:901–914.
55. Signorello LB, Fryzek JP, Blot WJ, et al. Offspring health risk after cosmetic breast implantation in Sweden. *Ann Plast Surg*. 2001;46:279–286.
56. Fryzek JP, Weiderpass E, Signorello LB, et al. Characteristics of women with cosmetic breast augmentation surgery compared with breast reduction surgery patients and women in the general population of Sweden. *Ann Plast Surg*. 2000;45:349–356.
57. Sarwer DB, LaRossa D, Bartlett SP, et al. Body image concerns of breast augmentation patients. *Plast Reconstr Surg*. 2003;112:83–90.
58. Chung KC, Malay S, Shauver MJ, et al. Economic analysis of screening strategies for rupture of silicone gel breast implants. *Plast Reconstr Surg*. 2012;130:225–237.
59. Stevens WG, Nahabedian MY, Calobrace MB, et al. Risk factor analysis for capsular contracture: a 5-year Sientra study analysis using round, smooth, and textured implants for breast augmentation. *Plast Reconstr Surg*. 2013;132:1115–1123.
60. Liu X, Zhou L, Pan F, et al. Comparison of the postoperative incidence rate of capsular contracture among different breast implants: a cumulative meta-analysis. *PLoS One*. 2015;10:e0116071.
61. Cook LS, Daling JR, Voigt LF, et al. Characteristics of women with and without breast augmentation. *JAMA*. 1997;277:1612–1617.
62. Brinton LA, Brown SL, Colton T, et al. Characteristics of a population of women with breast implants compared with women seeking other types of plastic surgery. *Plast Reconstr Surg*. 2000;105:919–927.
63. Bergmann MM, Calle EE, Mervis CA, et al. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. *Am J Epidemiol*. 1998;147:556–562.
64. Sommer LL, Eminger LA, Lawrence N. The accuracy of self-reported skin cancer diagnosis: room for improvement. *Dermatol Surg*. 2016;42:1110–1111.
65. Krulewitch CJ. General and Plastic Surgery Devices General Issues Advisory Panel Discussion of Silicone Gel-Filled Breast Implants (SGBIs) Post-Approval Studies, the Present and the Future Available at: https://pdfs.semanticscholar.org/presentation/b67a/a73e25a2aa8c052f2a5a487bb2ed4f25d68a.pdf. 2011. Accessed June 17, 2018.
66. Post-Approval Studies (PAS) P060018/PAS001. 2018-06-11.
67. Post-Approval Studies (PAS) P020031/PAS001. 2018-06-11.

© 2018 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.