Review Article

Current risk of breast implant-associated anaplastic large cell lymphoma: a systematic review of epidemiological studies

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Abstract: Recent epidemiological studies have attempted to accurately determine the risk of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). However, comparisons of previously published works are difficult due to widespread variations in reporting. We systematically review the epidemiology in order to better define the current risk of BIA-ALCL. Herein, we report the global epidemiology with an emphasis on the U.S. breast implant population while simultaneously assessing the oncologic safety of smooth-surface devices. In the current manuscript, a systematic review of PubMed and other scientific databases, as well as the grey literature, was conducted for epidemiologic studies on BIA-ALCL. Using analytical and descriptive epidemiology, we estimated the cumulative incidence and incidence rate of BIA-ALCL using a standardized approach. Cumulative incidence was reported at implant and patient-specific levels. The patient-specific cumulative risk within the U.S. market ranges from 1.79 per 1,000 (1:559) to 2.82 per 1,000 (1:355) patients with a textured implant. The implant-specific risk of Allergan textured devices ranges from 1:602–871 to 1:8,500, while the risk of commercially available Mentor Siltex implants is 1:50,000. No epidemiological study or regulatory agency reported a case of BIA-ALCL occurring exclusively with a smooth device. As such, with the removal of Allergan textured breast devices, this study demonstrates substantial gaps in the epidemiological knowledge of BIA-ALCL, including the current risk of commercially available textured breast implants in the U.S. market. Although the risk of BIA-ALCL is low, surgeons should exercise extreme caution when considering the use of a textured breast device for cosmetic or reconstructive purposes.

Keywords: Lymphoma; breast implants; breast implant-associated anaplastic large cell lymphoma (BIA-ALCL); epidemiology; systematic review

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Background

Since initial discovery in the mid-1990s (1,2), evidence linking a novel anaplastic lymphoma kinase-negative (ALK–) anaplastic large cell lymphoma and textured breast devices continues to accrue. Over the past decade, the field has made significant advances toward understanding the key clinicopathologic features of this breast implant associated-anaplastic large cell lymphoma (BIA-ALCL), including

the commonly delayed, spontaneous periprosthetic seroma rich in atypical CD30+ monoclonal T cells (3,4). If left untreated, these cells can coalesce and acquire characteristics typically associated with solid tumors—and can in very rare cases lead to patient demise (5,6). As such, a multidisciplinary team of pathologist, surgical oncologists and plastic surgeons helped adapt NCCN guidelines for the diagnosis and treatment of this emerging disease, which our group has discussed thoroughly in recent publications (7-9). While we continue to make strides in the understanding of the pathogenesis of BIA-ALCL, both the global and regional impact of the disease remains under considerable debate. Truly, the patient-level impact of a BIA-ALCL diagnosis is undeniably severe—including steep personal, emotional and financial costs (10,11)—but until the field reaches a clear consensus on the epidemiologic data surrounding the disease, we cannot adequately assess the safety of implant devices available to current and future cosmetic and reconstructive patients.

Understanding breast implant safety remains a shared goal of plastic and reconstructive surgeons and regulatory bodies alike. In 2011, the Food and Drug Administration (FDA) released their initial communication outlining the possible association of breast devices and lymphoma (12). At this time, epidemiologic risk estimates suggested the overall risk of developing BIA-ALCL from all breast devices was as low as 1:500,000 devices implanted. Over the next nine years, that risk figure has been revised as high as 1:600 for Allergan BIOCELL (Dublin, Ireland) devices (13). Indeed, the degree of device texturization has been linked to the development of the disease, and Allergan's salt-loss technique cultivates an exceedingly harsh outer shell compared to its counterparts (14). Not surprisingly, the updated US risk estimate for the Allergan textured supporting a six-fold increase in risk (15) compounded with non-renewal of Allergan's CE Mark in Europe led to the voluntary removal of the BIOCELL product from the US and global market in 2019. The removal of the BIOCELL device from the market raises several important questions—namely how much of the consensus risk estimate of BIA-ALCL is borne solely by BIOCELL device, and how much regional genetic and epigenetic differences affect patient outcomes. These questions could more appropriately be answered through rigorous systematic investigation of the available literature to establish both implant-specific and patient-specific risk factors for development of BIA-ALCL.

Cancer epidemiology plays an essential role in identifying and quantifying risk factors of a disease in order to guide the development of effective prevention strategies. Previous epidemiological studies have attempted to quantify the risk of BIA-ALCL accurately (13-16); however, comparisons of published studies are difficult due to a lack of well-defined study populations and widespread variations in the reporting of epidemiological parameters. Some have speculated that heterogeneity in risk estimates stems from the reliance on global sales data for incidence calculations and the lack of long-term follow-up for a disease which the median time to development is between 8–12 years following implantation. Despite an unclear risk profile for many American women, the evolving regulatory environment has led to a decline in implant-based reconstruction and an increase in implant-removal procedures for the first time this decade (17). Further, the FDA has now mandated a black box warning (*Table 1*) on all breast implants, regardless of filling (saline *vs.* silicone) or surface (textured *vs.* smooth), without significant clinical data to link smooth-textured implants to the disease (18). Therefore, the purpose of this study is to better define the risk of BIA-ALCL by systematically reviewing the epidemiological literature on the disease to clarify implant safety. Determining an accurate risk estimate for commercially available devices is essential for both patients and providers when considering the risks and benefits of using a textured breast device. This study also aims to definitively establish an exclusive association between textured-surface breast implants and foreign-body carcinogenesis that is BIA-ALCL while simultaneously demonstrating the oncologic safety of smooth devices. Herein, we report the global epidemiology of BIA-ALCL with a focus on the U.S. breast implant population while simultaneously assessing the possible association with smooth-surface devices. We hypothesize that Allergan BIOCELL devices carry a disproportionately higher risk profile than other manufacturers regardless of population studied, and that there is no clinical or pathologic data to support smooth textured devices in the development of BIA-ALCL. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/abs-20-96).

Methods

Search strategy

A systematic review of epidemiological population-based cohort studies on BIA-ALCL was conducted in PubMed, Google Scholar, and EMBASE databases between March

Table 1 U.S. Food and Drug Administration proposed warnings for breast implants

Description
Breast implants are not considered lifetime devices. The longer people have them, the greater the chances are that they will develop complications, some of which will require more surgery
Breast implants have been associated with the development of a cancer of the immune system called breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). This cancer occurs more commonly in patients with textured breast implants than smooth implants, although rates are not well defined. Some patients have died from BIA-ALCL
Patients receiving breast implants have reported a variety of systemic symptoms such as joint paint, muscle aches, confusion, chronic fatigue, autoimmune diseases and others. Individual patient risk for developing these symptoms has not been well established. Some patients report complete resolution of symptoms when the implants are removed without replacement

9–20, 2020 using a combination of BIA-ALCL and epidemiological-related search terms. Search parameters included the terms and Medical Subject Headings (MeSH) "breast implant-associated anaplastic large cell lymphoma", "breast implant(s)", "lymphoma", "epidemiology", "cancer epidemiology", "incidence, and cancer incidence". A search of the grey literature was also performed. Two independent reviewers screened titles, abstracts, and full texts of identified articles (RCD, MWC). Disagreement between reviewers prompted further investigation of text, and was resolved via discussion until there was 100% agreement on included studies. Citation chaining was performed using Web of Science. Critical appraisal of the evidence was conducted using a modified STrengthening Reporting of OBservational studies in Epidemiology (STROBE) checklist that was developed within the aims of the present study. The modified checklist was comprised of key quality factors including a risk-of-bias assessment and consisted of 10 total items. A single-point system was used to score each item. Quality scores were calculated for each article ranging from 0 (min score) to 10 (max score) in order to facilitate comparisons of the relative quality of each study. Higher scores were indicative of higher overall quality, while lower scores did not necessarily reflect poor study quality, but rather a lower relative quality assessment compared to other included studies. Global regulatory agency data were reviewed for epidemiological data related to BIA-ALCL that were not captured in the main search.

Inclusion and exclusion criteria

Inclusion was limited to primary epidemiological research on BIA-ALCL reported in prospective cohort studies, case-series, case-control studies, conference proceedings, and abstracts, in an attempt to glean consensus among these known disparate populations. Articles comparing the risk of BIA-ALCL to other lymphomas (19) were excluded, as were articles in which the epidemiology of a previously described cohort had been recently published (16,20). Only articles in the English language were reviewed.

Data abstraction and quality assessment

Abstracted data included author, journal, year of publication, country, study period, number of incident cases, study design, study period, patient-specific cumulative incidence, implant-specific cumulative incidence, incidence rate (per 100,000 person-years). In cases where the incidence rate was reported differently (e.g., per 1,000 person-years), rates were standardized per 100,000 person-years, which is the conventional method for reporting cancer incidence rates (21). Analytical and descriptive epidemiology was used to estimate the cumulative incidence (i.e., risk) of BIA-ALCL according to patient and implant specificity. Cumulative incidence was reported at implant and patient-specific levels. Levels of evidence were ranked from highest to lowest according to the American Society of Plastic Surgeons evidence-based rating scales for prognostic/risk studies (*Table 2*). Regulatory agency-specific epidemiologic data were collected from Australia, Canada, the Netherlands, the U.S., and the U.K.

To investigate the possible association between smooth surface devices and BIA-ALCL, the FDA's Manufacturer User Facility Device Experience database, and the American Society of Plastic Surgeons (ASPS) Patient Registry and Outcomes For breast Implants and anaplastic large cell Lymphoma (ALCL) etiology and Epidemiology (PROFILE) registry were queried for reports of BIA-ALCL. PROFILE is a prospectively maintained database that collects data regarding breast implants and ALCL. MAUDE collects medical device reports on data related to suspected device-associated deaths, serious injuries, and malfunctions, and the limitations of MAUDE with regard to breast implant safety and BIA-ALCL have been previously described (22,23).

Results

An overview of the search is shown in *Figure 1*. The initial

Table 2 American Society of Plastic Surgeons evidence rating scale for prognostic/risk studies

Level of evidence	Description
I	High-quality, multi-centered or single-centered, prospective cohort or comparative study with adequate power; or a systematic review of these studies
II	Lesser-quality prospective cohort or comparative study; retrospective cohort or comparative study; untreated controls from a randomized controlled trial; or a systematic review of these studies
III	Case-control study; or systematic review of these studies
IV	Case series with pre-/post-test; or only post-test
V	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or "first principles"

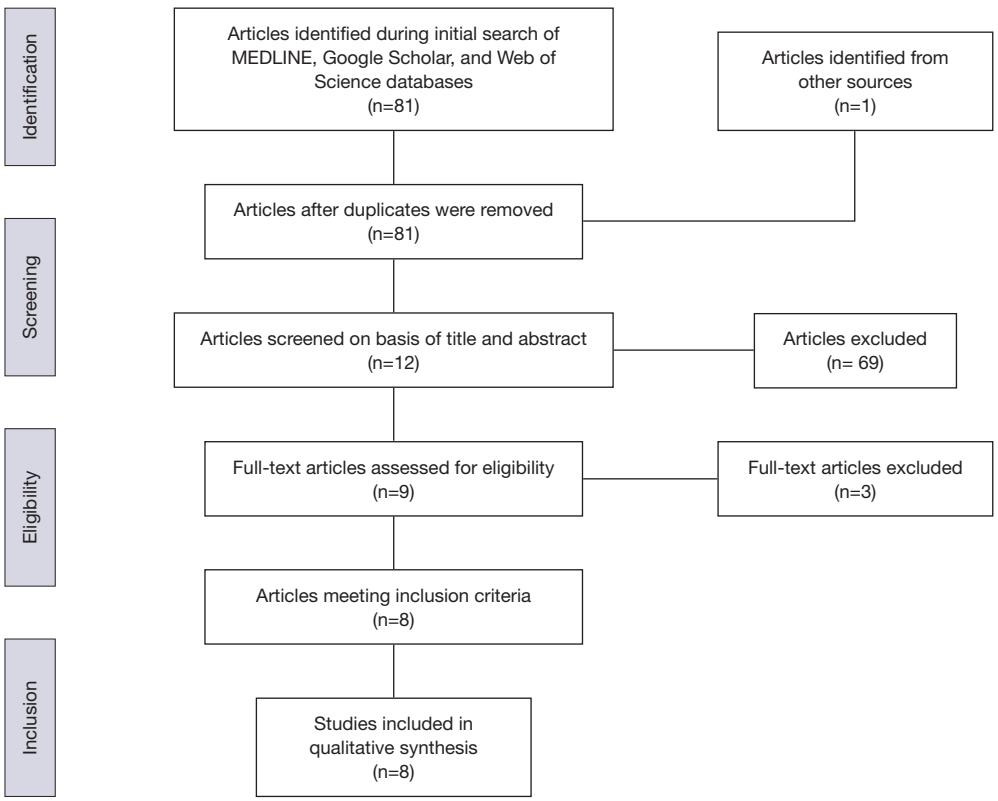

Figure 1 PRISMA flow diagram.

search generated 81 articles. One additional article was identified in a conference proceeding. Titles and abstracts from 12 articles were further reviewed to assess for study eligibility. The full text from nine articles were reviewed. After meeting study inclusion criteria, eight articles underwent quality assessment and data abstraction (*Table 3*). Disease incidence was reported in seven studies while incidence rates were described in two studies. Included studies differed in two main ways: study design and the reporting of incidence and incidence rates.

U.S. epidemiology of BIA-ALCL

Patient-specific risk

Two studies have examined the incidence of BIA-ALCL within the U.S. breast implant population. Both studies are exclusive to the reconstructive cohort, which introduces selection bias. The first study is a recent prospective

Table 3 Summary of epidemiological studies on BIA-ALCL

Author	Year	Country	Study design	Study period	Level of evidence	BIA-ALCL cases	Sample size	Patient specific incidence	Standardized patient specific incidence	Implant specific incidence	Standardized implant specific incidence	Incidence rate (person-years)	Quality assessment (max score 10)
Largent *et al.*	2011	USA	Retrospective	1994–2007	II	3	NR	NR	N/A	NR	N/A	1.46 per 100,000	6
McGuire *et al.*	2016	USA	Prospective cohort	–2014	II	4 initially (now 8)	17,656	1:2,207 Allergan	0.45 per 1,000 Allergan	NR	N/A	NR	8
Cordeiro *et al.*	2020	USA	Retrospective cohort	1992–2019	III	10	3,456	1:355	2.81 per 1,000	1:602 Allergan	1.66 per 1,000 Allergan	NR	5
Nelson *et al.*	2020	USA	Retrospective cohort	1991–2017	III	11	9,373	1:559	1.79 per 1,000	1:871 Allergan	1.15 per 1,000 Allergan	NR	7
De Boer *et al.*	2018	The Netherlands	Retrospective cohort	1990–2016	III	43	3,000	1:6,920 at 75 years of age	0.14 per 1,000	NR	N/A	NR	8
Campanale *et al.*	2018	Italy	Retrospective cohort	2015–2017	III	22	10,000,000	2.8 per 100,000	0.028 per 1,000	NR	N/A	NR	6
Loch-Wilkinson *et al.*	2019	Australia	Retrospective	2015–2019	III	104	?	NR	N/A	1:9,457 Silimed; 1:36,730 Mentor	0.11 per 1,000 Silimed; 0.03 per 1,000 Mentor	NR	7
Doren *et al.*	2018	USA	Case series	1996–2015	IV	100	3,000,000	NR	N/A	1:8,500 Allergan; 1:51,000 Mentor	0.12 per 1,000 Allergan; 0.02 per 1,000 Mentor	2.03 per million; (0.203 per 100,000)	8

BIA-ALCL, breast implant-associated anaplastic large cell lymphoma.

outcomes study from a single surgeon's experience operating on more than 3,500 patients (13). The second included study is a published conference abstract presents findings on BIA-ALCL at a single institution (24). Collectively, these studies report patient-specific cumulative risk within the U.S. ranges from 1.79 per 1,000 (1:559) (24) to 2.82 per 1,000 (1:355) (13) patients with a textured surface implant. Thus, the overall cumulative risk estimate for developing BIA-ALCL in patients with textured breast implants in the U.S. settles between 0.003% to 0.29% at 20 years and 26 years, respectively. When considering the cumulative risk from the time of implantation, proportions ranged from 0.00 at 5 years, 0.002 at 10 years, 0.007 at 15 years, and 0.011 at 20 years (13), while other estimates suggest a cumulative risk estimate of 4.4 per 1,000 patients at 10–12 years and 9.4 per 1,000 patients at 14–16 years (24).

Implant-specific risk

With Allergan BIOCELL implants' removal from the market, there is increased need to understand current implant-specific risks for developing ALCL. Using analytical and descriptive epidemiology and the data provided in Doren *et al.* (15), we calculated manufacturer specific risks in the U.S. breast implant population. U.S. implant-specific risks are less heterogeneous than global risk estimates with incidences, ranging from 1:602–871 to 1:8,500 with textured implants, which exclusively report Allergan (Dublin, Ireland) textured devices (13,15,25). The risk estimate for Mentor (Mentor Worldwide LLC, Irvine, Calif.) Siltex implants is 1:51,000. Despite focused investigation of the literature, implant-specific risks for other currently available textured devices (e.g., Sientra, Santa Barbara, Calif.) in the U.S. market have not been reported. Stevens *et al.* estimate a global combined risk of BIA-ALCL for Sientra (Santa Barbara, Calif.) and Silimed (Rio de Janeiro, Brazil.) implants at 1:200,000 (26,27). In the US, Sientra has been commercially available for approximately eight years since 2012, and importantly has not yet achieved the average time interval (9–10 years) for the development of BIA-ALCL. To date, five cases of BIA-ALCL with Sientra implants have been reported in the US. US sales data has not been made available by the company despite request. Based upon reported annualized sales revenue compared to total market, Sientra represents less than 5% of the US market, and therefore the number of Sientra BIA-ALCL cases encountered to date should be taken in the context of a shortened follow up period and marginal market share.

Incidence rate

U.S. specific incidence rates vary from 0.311 cases per 1,000 person-years (95% CI: 0.118–0.503) (13) to 1.46 per 100,000 person-years (95% CI: 0.30–0.43) (28) to 2.03 cases per 1 million person-years [1.86 per million (Allergan); 0.33 per million (Mentor)] (15). Following conversion, the standardized incidence rate determined by the present study of BIA-ALCL in the U.S. ranges from 0.203 per 100,000 person-years to 31.1 per 100,000 person-years, indicating that the cumulative risk of BIA-ALCL is higher than previously thought. When considering incidence rates according to U.S. manufacturer specificity, a 5.67-fold difference for Allergan Biocell (1.87 per 1 million person-years) compared to Mentor Siltex (0.33 per 1 million person-years) implants was reported (P<0.001) (15).

Global epidemiology of BIA-ALCL

Patient-specific risk

Global risk estimates of BIA-ALCL, according to international regulatory agencies, are summarized in *Table 4*. In the Netherlands, the age-adjusted incidence of BIA-ALCL from a textured device is approximately 1:6,920 patients with a textured implant at 75 years of age (29). The Australian Therapeutic Goods Administration previously reported an implant risk estimate of 1:1,000–1:10,000 patients; however, this risk widened to 1:2,500 to 1:25,000 patients with a textured breast implant (30,31). The Italian-specific incidence is 2.8 per 100,000 patients (31). The breakdown of country-specific cases and related deaths in *Table 4* reinforces the distribution.

Implant-specific risk

Manufacturer-specific implant risk is outlined in *Table 5*. Interestingly, each country reports different implant-specific risk, highlighting the multiple factors beyond implant type that lead to the development of ALCL. For example, in Australia, the current implant-specific risk of BIA-ALCL varies widely, ranging from 1:2,832–1:86,029 implants (16,32). When titrating Australian risk profiles down according to manufacturer, the highest risk was in Silimed polyurethane implant (1:2,832; 95% CI: 1,582–5,673), followed by Allergan Biocell (1:3,345; 95% CI: 2,475–4,642) and finally Mentor Siltex (1:86,029; 95% CI: 15,440–1,301,759) implants. Health Canada, the Canadian equivalent of the U.S. FDA, currently estimates an overall risk of 1:24,177 implants (33). This distills down to a manufacturer-specific risk of 1:3,565 (Allergan Biocell) and

Table 4 Summary of global regulatory agency risk estimates of BIA-ALCL

Country	Source	Risk
Australia	Australian Therapeutic Good Administration	1:2,500–1:25,000 patients
Canada	Health Canada	Overall: 1:24,177; 1:3,565 (Allergan); 1:16,703 (Mentor)
United Kingdom	Medicines and Healthcare Products Regulatory Agency	1:24,000 (implants)
United States	Food and Drug Administration	1:3,817–1:30,000

BIA-ALCL, breast implant-associated anaplastic large cell lymphoma.

Table 5 Manufacturer-specific global risk estimates of BIA-ALCL

Manufacturer	Textured implant type	Texturization method	Global risk
Allergan	Biocell	Salt loss	1:602 to 1:8,500
Mentor	Siltex	Negative imprint	1:6,703 to 1:86,029
Sientra		Heat vulcanization	TBD
Silimed	Polyurethane	Foam-coated	1:2,832

Currently 5 US Sientra BIA-ALCL cases to date. Availability of Sientra implants has not reached the average follow up for disease development and represents less than 5% of US market share. BIA-ALCL, breast implant-associated anaplastic large cell lymphoma.

1:16,703 (Mentor Siltex) in the Canadian breast implant population, which translates to a 16.52 increased risk of Biocell implants. In the United Kingdom, the total risk of BIA-ALCL has been calculated as 1:24,000 implants inserted, but manufacturer-specific risk profiles remain to be investigated (34).

BIA-ALCL is exclusively associated with textured-surface breast implants

U.S. and non-U.S. population-based, and case-control studies, in combination with a review of government databases, consistently revealed an association between textured-surface breast implants and the incidence of BIA-ALCL. Importantly, not a single epidemiological study or government database reported a case of BIA-ALCL occurring solely in the context of a smooth surface breast implant. That is, all ALCL cases associated with implanted breast devices included a positive history of textured device.

Discussion

This systematic review provides a detailed examination of existing epidemiologic data on US-specific and global risk of BIA-ALCL. In lieu of a conventional systematic review based on randomized clinical trials, this comprehensive review is comprised of epidemiological observational studies of BIA-ALCL in the breast implant population. The heterogeneity of reported data prevented meta-analysis and limited the calculation of combined risk estimate. However, we were able to draw comparisons between studies by standardizing epidemiological parameters whenever possible. Our study demonstrates the risk of BIA-ALCL varies substantially, especially when considering incidence according to manufacturer type. In the U.S. market, the average lifetime risk of BIA-ALCL ranges from 1:355–1:51,000 patients with a textured surface breast implant. Allergan's Biocell implants carry that highest manufacturer-specific risk at 1:2,207–1:8,500 (15,25), followed by Mentor Siltex implants at 1:51,000. This confirms the nearly six-fold increase in the risk of BIA-ALCL when comparing Allergan Biocell to Mentor Siltex breast implants ($P<0.001$) across all populations, not just within the US. These data, among others, weighed heavily on the decision for the U.S. FDA to issue a Class 1 recall, the most serious type of recall, on all Allergan textured breast devices, and the findings of this study support the FDAs decision—based on the available data.

Texturization plays a critical role in the malignant transformation of BIA-ALCL. Yet, regulatory agencies remain reluctant to acquit smooth surface devices, despite the lack of available evidence to support smooth devices in the pathogenesis of the disease. Similarly, we did not find a single case of BIA-ALCL that had been reported to PROFILE where a patient had a pure history of a

smooth implant. As of July 2019, FDA's MAUDE database acknowledged 457 unique medical device reports with a BIA-ALCL diagnosis, of which 26 are recognized as occurring with a smooth device (35). Of those, 12 have an unknown prior implant history, 7 have a history of a prior textured implant, and in 7 cases surface characteristics were unknown. Contradicting these reports, this systematic review found no published reports of the disease occurring exclusively with a smooth-surface device. Moreover, this study failed to identify a single case of BIA-ALCL associated with a smooth device in any registry or government database where a patient had not already been exposed to a textured device, which includes exposure to a textured tissue expander. FDA currently denies any association between textured expanders and BIA-ALCL; however, it is important to note that PROFILE does recognize two cases of ALCL have occurred in patients receiving tissue expander breast reconstruction with a textured-surface expander followed by permanent implant exchange with smooth surface implants (36). Therefore, the findings of this study strengthen the claim that smooth-type implants have no independent association with BIA-ALCL.

With the removal of Allergan textured devices from the U.S. and other markets worldwide, much of the currently available epidemiologic data incompletely characterizes implant-specific risks in individuals considering the use of a non-Allergan textured breast device for breast reconstruction or cosmetic augmentation. Our study identified the Mentor specific risk profile to be 1:51,000 devices implanted. To date, only a single non-epidemiologic U.S. based study has reported a combined 20-year, worldwide risk of BIA-ALCL for Sientra and Silimed (Rio de Janeiro, Brazil) of 1:200,000 implants (26,27). Based upon reported annualized sales revenue compared to total market, Sientra represents less than 5% of the US market, and therefore the number of Sientra BIA-ALCL cases encountered to date should be taken in the context of a shortened follow up period and marginal market share. Taken together, the current risk of BIA-ALCL for commercially available textured devices likely falls around 1:50,000. However, as median disease presentation occurs between 8–12 years after device implantation, that future cases will likely continue to accrue. Further, it is unclear what is the upper and lower limit of that risk estimate and how it stratifies according to manufacturer type or if these findings are generalizable to the U.S. population. Combined with the removal of Allergan devices from the U.S. market, these data, along with a limited number of other risk estimates, do little to inform safety profiles required to engage in productive risk-benefit discussions for patients considering breast augmentation or breast reconstruction with a textured surface device. Future risk assessment studies on currently available breast devices are warranted.

The present study also identified clustering of cases in the U.S., Australia and New Zealand, the U.K., the Netherlands, and France, with widespread geographic variation in global risk estimates. The highest number of cases occurred in the U.S., which accounts for 1 out of every 2.6 cases (38.4%) worldwide, despite textured breast devices accounting for less than 10% of sales in the U.S. market, and may account for closer to 50% of sales in other countries, including Italy (27). Australia is also a predominantly textured device market, yet it only accounts for 1:7 cases (14.3%). These differences in clustering and subsequent risk profiles could result from increased awareness, improved surveillance, access to care, and long-term follow-up, rather than epidemiologic or pathologic phenomena. Until better long-term surveillance programs develop in the US, definitive assertions about population-specific risk profiles will remain limited.

Unfortunately, there is a misconception held by few that clustering of BIA-ALCL cases is indicative of poor breast implant technique. Further, the relatively high rates of ALCL reported in the recent single-surgeon cohort have wrongfully reignited this discussion. The authors of the present study were not able to uncover a single, rigorous scientific study that revealed an association between surgical technique and BIA-ALCL tumorigenesis. As such we vehemently oppose reports linking surgeon technique to ALCL, as this dangerous association threatens to undermine the reporting of future ALCL cases required to build robust outcomes databases for scientific investigation. Previous studies have also suggested that genetics may account for differences in worldwide incidence, citing the lack of clustering in the Asian breast implant population as evidence (32,37). This concept has recently been challenged with reports of BIA-ALCL emerging in this population (38). While genetics, more specifically epigenetics, may account for geographic variations in cumulative risk found in the present study, the current evidence does not support such a concept at this time.

Limitations

The current study is only as strong as the quality of data

that were abstracted during the search. Retrospective designs have limited previous epidemiological studies of BIA-ALCL, along with data produced from extrapolated denominators based on inaccurate implant sales figures. Assessing data obtained using differing methodologies combined with the heterogeneity of data, prevented the standardization of all epidemiological parameters across studies or assess temporal trends in the risk of the disease. Other potential limitations include incomplete clinical data, and a lack of long-term follow-up—which remains the most critical limitation that must be addressed to improve the conclusions of future studies. Without better, standardized long-term follow-up protocols to examine a disease than in most cases takes 8–12 years to develop, we will never know the true implant risk profile for our patient population, all of may act as potential sources of bias in the present study.

This systematic review also limited inclusion criteria to articles exclusively disseminated in the English language. As such, it is possible, although highly improbable, that epidemiological studies on BIA-ALCL may exist in other languages. Additionally, the lack of reported cases of BIA-ALCL with smooth devices precluded a calculation of the relative risk of smooth *vs.* textured devices, which we acknowledge as an important consideration concerning the FDAs proposal to include a black boxed warning on all implant devices. In this regard, we ask all surgeons to review their outcome reporting practices, and would encourage reading about national efforts to establish implant registries (PROFILE, MAUDE) as referenced in this text.

Conclusions

This is the first systematic review on the epidemiology of BIA-ALCL in the breast implant population. Of great concern, this systematic review identified substantial gaps in the epidemiological knowledge of BIA-ALCL. We assert that a greater standardization of reporting outcomes, and improving long-term patient follow-up will help establish more robust data from which to study the impact of ALCL across the US and global population. The data in the present study demonstrated significant global geographic and manufacturer-specific variation in the risk of the disease, but confirmed the notion that Allergan textured devices carry substantially higher risk profiles than their counterparts—regardless of population studied. This conclusion should help practitioners inform their unique patient population about the current understanding of breast-implant safety. Regarding non-Allergan devices, further investigation of demographic, epigenetic, and environmental risk factors, including implant surface characteristics, may account for population-specific differences and is therefore warranted. With the removal of Allergan textured devices, this study also found that the current risk of commercially available textured-surface breast implants, specifically in the U.S. market, is not well-defined and impairs the ability to provide a thorough informed consent thereby threatening patient safety. Patients and providers should exercise extreme caution when considering the use of a textured breast device for cosmetic or reconstructive purposes. The implant selection decision should remain a shared discussion between patient and physician, but at this time only smooth-type implants carry no independent risk of the development of BIA-ALCL. Although these data suggest that smooth-surface breast implants are oncologically safe, more extensive prospective studies are needed before definitive conclusions may be drawn.

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Footnote

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Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/abs-20-96

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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