Current Risk Estimate of Breast Implant–Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants

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Background: With breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) now accepted as a unique (iatrogenic) subtype of ALCL directly associated with textured breast implants, we are now at a point where a sound epidemiologic profile and risk estimate are required. The aim of this article is to provide a comprehensive and up-to-date global review of the available epidemiologic data and literature relating to the incidence, risk, and prevalence of BIA-ALCL.

Methods: All current literature relating to the epidemiology of BIA-ALCL was reviewed. Barriers relating to sound epidemiologic study were identified, and trends relating to geographical distribution, prevalence of breast implants, and implant characteristics were analyzed.

Results: Significant barriers exist to the accurate estimate of both the number of women with implants (denominator) and the number of cases of BIA-ALCL (numerator), including poor registries, underreporting, lack of awareness, cosmetic tourism, and fear of litigation. The incidence and risk of BIA-ALCL have increased dramatically from initial reports of 1 per million to current estimates of 1/2,832, and is largely dependant on the "population" (implant type and characteristics) examined and increased awareness of the disease.

Conclusions: Although many barriers stand in the way of calculating accurate estimates of the incidence and risk of developing BIA-ALCL, steady progress, international registries, and collegiality between research teams are for the first time allowing early estimates. Most striking is the exponential rise in incidence over the last decade, which can largely be explained by the increasingly specific implant subtypes examined—driven by our understanding of the pathologic mechanism of the disease. High-textured high-surface area implants (grade 4 surface) carry the highest risk of BIA-ALCL (1/2,832). (*Plast. Reconstr. Surg.* 143: 30S, 2019.)

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a rapidly emerging disease entity, uniquely iatrogenic in nature with indisputable evidence to its direct association with breast implants, in particular, those with a textured outer shell.[1] The first case of BIA-ALCL was reported by Keech and Creech[2] in 1997, and until recently remained relatively underreported. Over the last decade, with mounting evidence and growing concerns to the potential implication of breast implants as the root cause, there has been an exponential rise in public interest and published literature[3] (Table 1). The World

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Table 1. Global Numbers of BIA-ALCL Cases and Related Deaths

Country	Cases	Deaths
Argentina	6	
Australia	81	3
Belgium	10	
Brazil	3	1
Canada	25	
Chile	2	
China	0	
Colombia	6	
Czech Republic	1	
Denmark	7	
Egypt	1	
Finland	7	
France	55	3
Germany	7	
Ireland	1	
Israel	8	
Italy	28	
Japan	0	
Mexico	4	
Netherlands	40	1
New Zealand	13	1
Norway	3	
Romania	0	
Russia	2	
Singapore	0	
South Africa	1	
South Korea	1	
Spain	29	
Sweden	6	2
Switzerland	4	
Taiwan	Not reported	
Thailand	1	
Venezuela	2	
United Kingdom	45	1
United States	257	5
Total	656	17

As of November 2018, a total of 656 cases have been identified worldwide with 17 deaths reported.

Health Organization has recently listed BIA-ALCL as a unique disease entity and has cited evidence linking this unique lymphoma to breast implants. We are now at a point where a sound epidemiologic profile (and management approach) is required.[4] There are considerable challenges to defining epidemiology and risk, given incomplete data sets, lack of awareness, and poor penetrance of current registries. Based on the best available evidence, we hope to shed some light on the current risks and incidence of BIA-ALCL from a global perspective, discussing the implication of these findings.

DISEASE OVERVIEW

BIA-ALCL has only recently been identified as an emerging disease entity and represents a novel variant of the clinicopathologic subtypes of anaplastic large cell lymphoma (ALCL). Whereas systemic ALCL is an aggressive metastatic disease, BIA-ALCL is more akin to cutaneous ALCL with an indolent course, often identified during the early stages of the disease with lymphoma cells confined to a peri-implant seroma or capsular tissue.[5,6] BIA-ALCL is a purely T-cell lymphoma, distinct from primary breast lymphoma, which is a predominantly B cell in origin.[7–9] BIA-ALCL is also characterized by a unique antigenic profile, with all currently reported cases found to be anaplastic lymphoma kinase negative and CD30 positive.[3] The progression from seroma or effusion-limited disease to more advanced disease including the development of a capsular mass and metastasis is not clear. The increasing percentage of patients presenting with stage 1a (effusion limited) disease as the disease is diagnosed earlier may point to a natural slowing in progression at this stage, perhaps more in keeping with a lymphoproliferative precursor. It could also be that mass disease represents an altogether different subtype of BIA-ALCL with unique genetic or biological drivers.[10,11]

BIA-ALCL is most commonly detected during early stages of the disease, with approximately two thirds of cases presenting as a delayed (>1 year) implant-related seroma, one third as a capsular mass, and a very small number with metastatic disease.[3,12] Interestingly, the mean time from implant surgery to diagnosis is approximately 10 years, again indicative of its indolent nature.[12,13] Clinically, women present with breast pain, swelling, asymmetry, or a palpable mass, and in all cases, these symptoms must be investigated with diagnostic imaging.[3] Current recommendations suggest ultrasound as the first-line modality because it has similar specificity and sensitivity as more invasive techniques.[14] With confirmation of a seroma or mass, tissue specimens should be obtained via fine-needle aspiration or biopsy. As awareness of this disease is still variable, it can easily be overlooked if not considered in the initial differential diagnosis. It is, therefore, important that requests sent to the pathologist specifically ask for BIA-ALCL assessment.[3] Although lymphoma cells may be undetectable in subsequent seroma aspirates, this does not signify regression or resolution because it could be the result of a dilutional effect following the initial aspiration.

IMPLANT TEXTURE

The texturization of the outer shell of breast implants was first introduced in 1968 with the "Natural Y" implant which incorporated a 1.2–2 mm polyurethane foam coating on its outer surface.[15] This open pore texture was thought to

combat capsular contracture by promoting ingrowth of tissue. It was proposed that the foam texture prevented organized alignment of myofibroblasts, thereby interrupting the formation of a thick capsule and reduced immune response to the implant.[15] Following a voluntary moratorium by the Food and Drug Administration in 1991, on the polyurethane coating for fear of carcinogenicity, a number of alternative surface technologies to modify the outer silicone shell were introduced in an attempt to mimic the polyurethane surface texture. There are 3 processes for generating surface texture on the external silicone shell, salt loss, gas diffusion, and imprinting techniques.[16] A more recently released surface which claims a novel "nano" texture remains proprietary.[17]

The evidence that textured implants reduce capsular contracture remains controversial. Systematic reviews of comparative clinical studies concluded that texturization may reduce the incidence of early capsular contracture in subglandular augmentation.[18,19] One review identified 40 comparative clinical studies including 7 Food and Drug Administration core studies, 29 retrospective cohort studies, and 4 prospective cohort studies. Of these, only half had adequate description of implant type, surgical technique, and outcome assessment. Only 1 study had follow-up of patients to >5 years of age, but this was further limited by heterogeneity in patient selection and technique. It was not possible to compare incidence of rupture, rippling, asymmetry, implant failure, pain, and size change due to lack of comparative data.[18] Smaller comparative or split breast studies are evenly divided as to the benefit of texturization.[20–30] It is likely that the effect of surface technology is of some benefit but is one of many other factors that impact on outcomes. The effect of surgical technique, bacterial mitigation, and patient factors also needs to be taken into account.[31]

A new classification system for implant surfaces has been recently published and linked to potential for bacterial growth (Fig. 1).[32] The movement toward a more generic classification based on measurable parameters such as surface area and surface roughness rather than terms like "smooth (<10 μm)," "micro (10–50 μm)," and "macro (>50 μm)," used by the older International Organization for Standardization classification system, is preferable to allow more meaningful comparison of outcomes going forward. Interestingly, the risk for BIA-ALCL has been shown to be significantly higher for implants with grade 3 and 4 surfaces.

EPIDEMIOLOGIC CHALLENGES

To date, determination of an accurate risk assessment of BIA-ALCL has been elusive. Multiple variables and the relative uncommon occurrence of this disease make valid epidemiologic

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Gas Diffusion	Salt Loss (Nagotex)	Imprinting	Smooth/Nano
Surface Area	High	Intermediate	Intermediate	Low	Low	Minimal
Roughness	High	Intermediate	Low	Low	Low	Minimal
SURFACE TYPE	4	3	3	2	2	1

Fig. 1. Functional classification of breast implant surface based on surface area and roughness.[32]

studies difficult. Estimates of the risk of BIA-ALCL hinge on accurate measures of the prevalence of women with breast implants and implant type (smooth versus textured): Denominator and the number of actually cases of BIA-ALCL in a given population: Numerator. Both numerator and denominator for BIA-ALCL could be more accurately recorded by national registries, but this is impacted by the voluntary (opt-in) nature[33] of many registries.

Figure 2 outlines the factors that impact on the risk calculation.

DENOMINATOR

Multiple factors impact on the denominator. These include poor records, a lack of systematic

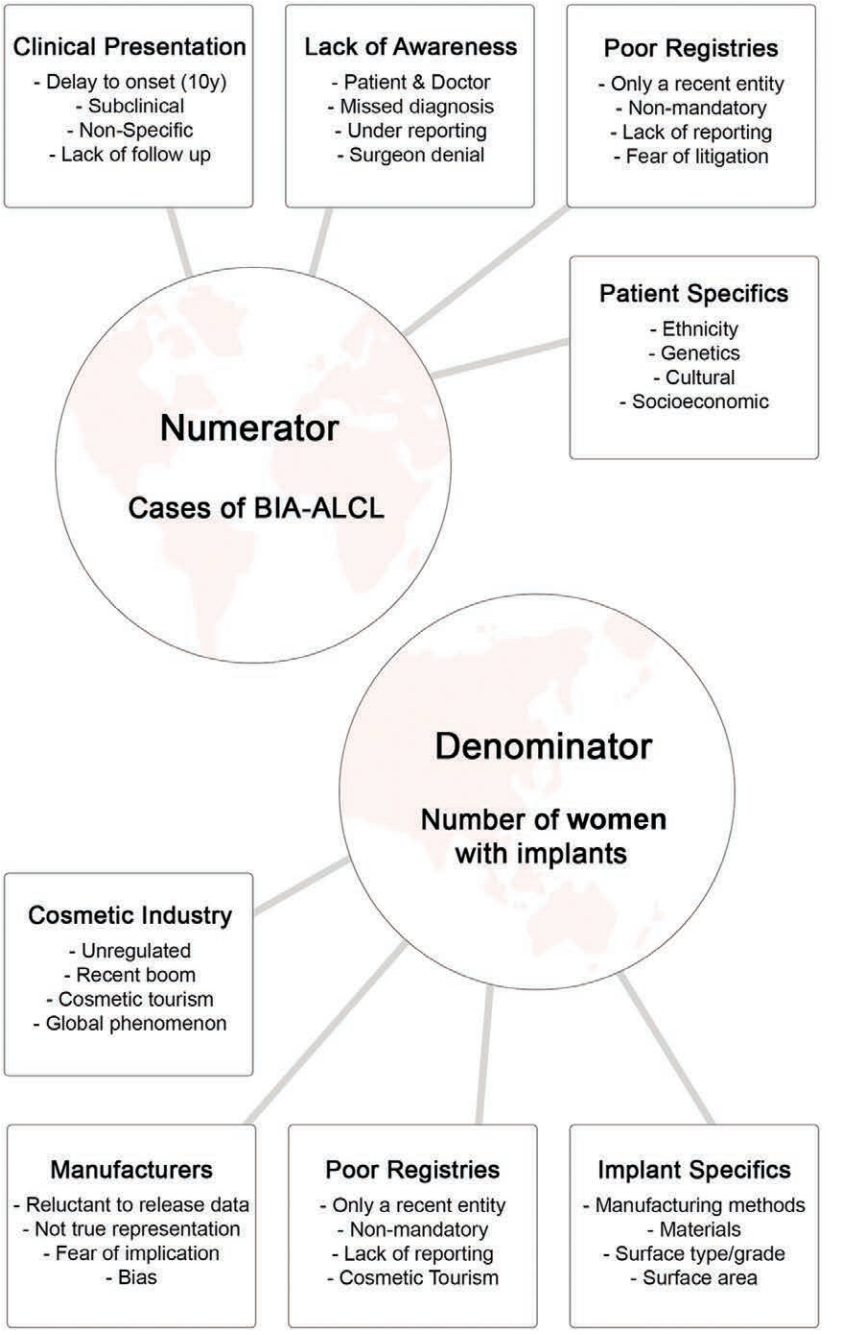

Fig. 2. Factors that influence the risk calculation in BIA-ALCL.

follow-up, and reporting of adverse events, an unregulated boom in cosmetic tourism and the entry of many disparate practitioners. Two methods of prevalence analysis have been utilized to date: reliance on company-reported sales data and radiologic sampling of a random population. Implant sales are not readily released by companies who are keen to protect their commercial position. Moreover, these numbers tend to be lost due to bankruptcy or changing distributors, both being frequent occurrences. Reliance on these data is prone to bias and in no way equates to the true number of implants inserted as sales of implant numbers may not necessarily correlate with actual implants utilized nor with the number of women having them. Radiologic estimates of prevalence using a random sample of patients with imaging confirming the presence of implants is another methodology. This method, however, is quite time consuming and relies on extrapolation of a small sample size.

NUMERATOR

With regard to determining the numerator, the true incidence of BIA-ALCL is also difficult. Although the numbers would appear to suggest a recent increase, these figures may be artificially inflated by the recent increased awareness of this disease leading to more diagnoses, in combination with an increase in the number of breast augmentation procedures performed. The number of reported cases, however, may be prone to underreporting because true diagnosis relies on clinical suspicion confirmed by accurate pathologic confirmation, which may further cloud accurate epidemiologic investigation.[34] Poor awareness of implant-associated lymphoma by surgeons (by not suspecting a seroma to be BIA-ALCL) and by pathologists (by not testing for ALK and CD30 status) may have led to a significant underreporting, for fear of litigation or additional cost, and/or missed diagnoses. Further, in light of its indolent nature, there is no way of calculating the number of women with breast implants currently suffering from subclinical early-stage disease and the crossover between inflammatory benign seroma and early seroma, effusion-limited BIA-ALCL.

Although there appears to be an overwhelming number of barriers preventing sound epidemiologic study (Fig. 2), recent persistent efforts have started to make headway in forming methods of extracting more reliable data sets. A number of national and international registries are now beginning to generate early data. The Patient Registry and Outcomes for Breast Implants and ALCL Etiology and Epidemiology (PROFILE), a collaborative effort with the American Society of Plastic Surgery and the Plastic Surgery Foundation, is a good example of where collaboration between clinical societies and regulators is able to quickly garner reliable information on confirmed cases. Governments are starting to take notice with the French National Agency for Medicines and Health Products Safety recently instigating a mandate for all manufacturers of textured breast implants to perform biocompatibility testing and report their findings. International collaborative efforts between research teams are allowing higher powered studies with pooling of resources and data. What can be said is that in light of the aforementioned barriers, the incidence of breast implant–associated lymphoma is likely to be an underestimate.

With acceptance and awareness of BIA-ALCL as a true disease entity, we are likely to see a dramatic increase in detection and reporting. Coupled with an ever-expanding incidence of women with breast implants among the global population, we will undoubtedly see a steady rise in disease notifications (Fig. 3).

CURRENT EPIDEMIOLOGIC DATA

Prevalence of Breast Implants

In order to calculate the incidence and risk of developing BIA-ALCL, the prevalence of women with breast implants needs to be known. Current conservative estimates suggest that ≥35 million women worldwide have textured breast implants, with 1.5 million breast implants inserted last year alone (International Society of Aesthetic Plastic Surgery global survey – 2016). The trend is upward, but significant geographical variations are expected due to cultural acceptance, medical tourism rates, and the socioeconomic state of a given region. The highest prevalence of breast implants exists among the western world, with the use of breast implants steadily increasing since their introduction in the 1960s. The United States have the highest prevalence and highest rates of cosmetic surgery—breast augmentation being the number 1 procedure performed, with a recent estimate of >550,000 implants placed per year.[35] Data obtained from sales registries in Australia and New Zealand would suggest a prevalence of 3.99%, whereas epidemiologic data obtained in the Netherlands have reported 3.3% of the population.[36] Current estimates of the number of women

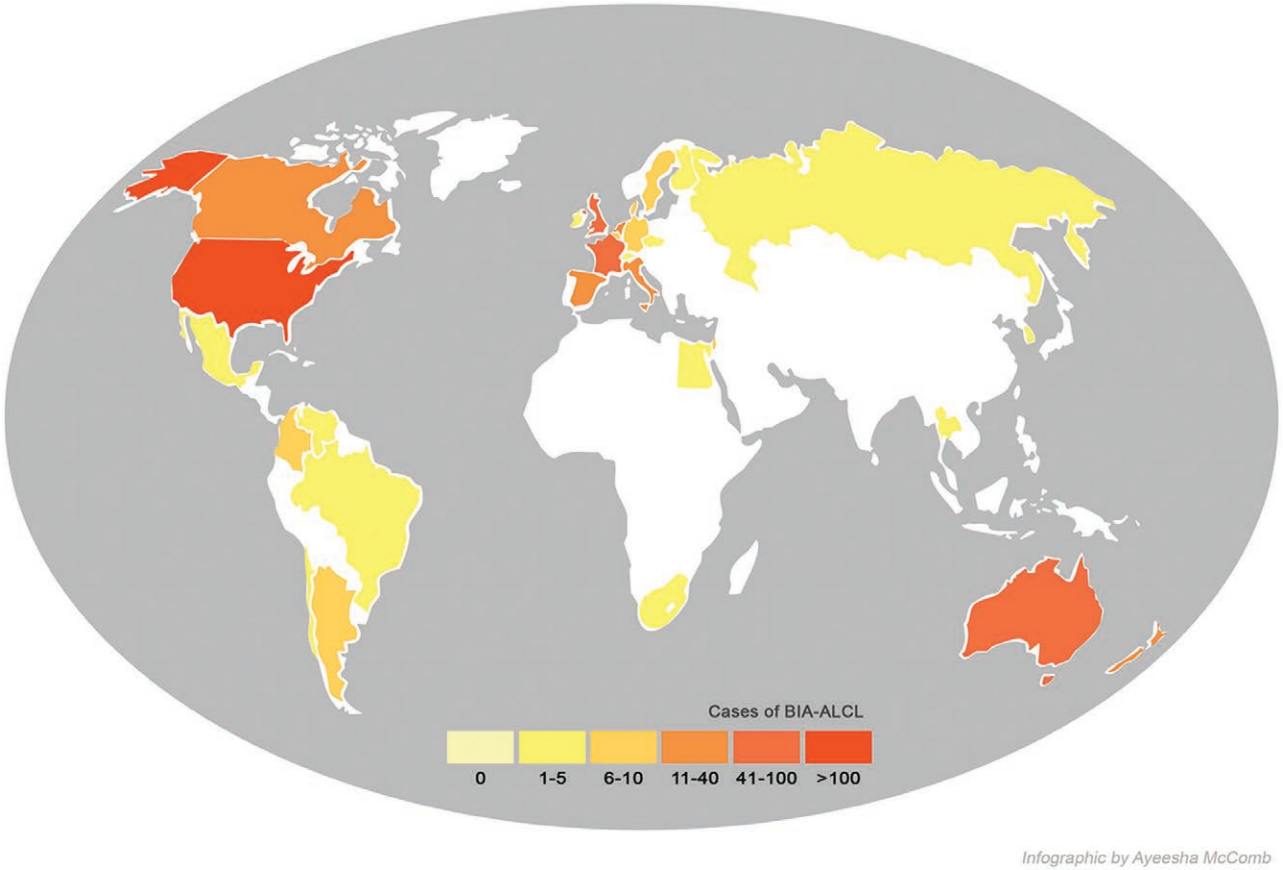

Fig. 3. Global snapshot of confirmed cases as of September 10, 2018. Sourced from global BIA-ALCL network.

in North America with breast implants range from 1 to 2 million, representing 1% of the adult female population. Recent dramatic growth of the cosmetic industry within the Asian subcontinent has seen an exponential rise in breast implant surgery, with the South Korean market now reported to perform the third highest number of cosmetic procedures per year behind the United States and Brazil. The recent rise in breast implant surgery is not confined to the Asian market, with regional data suggesting that this is a global phenomenon. Cosmetic surgery is becoming an available "commodity," with increasing acceptance and ease of access, fuelled by powerful marketing strategies, online media, and the current perception of the "ideal" body image.

Incidence and Risk of BIA-ALCL

The first case of BIA-ALCL was reported in 1997 by Keech and Creech,[2] and with increasing awareness of the disease, subsequent case reports and case series have emerged with increasing frequency. De Jong et al.,[37] in 2008, were the first to publish a report identifying an increased risk of ALCL in association with breast implants (odds ratio, 18.2; 95% CI, 2.1–156.8), and have more recently published a powerful population-based (The Netherlands) case—control study, reporting a relative risk for breast-ALCL in women with breast implants of 421.8 (95% CI), with an absolute cumulative risk of 1 per 35,000 at the age of 50 years, 1 per 12,000 at the age of 70 years, and 1 per 7,000 at the age of 75 years. Further statistical analysis was able to determine that the number of women with implants required to cause 1 case of breast-ALCL, the number needed to harm, was 6,920.[36] It is important to note that this study did not distinguish between smooth and textured implants, which is likely to have caused an underestimation of the true incidence and risk. Doren et al.[13] have released the first U.S population-based report demonstrating a significantly higher risk of developing breast-ALCL around a textured breast implant—reporting an incidence of 2.03 per million women per year, 67.6 times higher than that of primary ALCL of the breast, with a lifetime prevalence of 1 in 30,000 for women with textured breast implants.[13] Further, based on sales figures

of Allergan and Mentor implants, Doren et al.[13] estimate that there are approximately 3 million women with textured breast implants in the current U.S. population. Recent data from Australia and New Zealand have revealed a dramatic rise in the frequency of diagnosis and incidence of BIA-ALCL. Fifty-six cases in total had been confirmed by 2017 with a subsequent 26 new cases of BIA-ALCL diagnosed between January 2017 and April 2018 representing a 47% increase in diagnosis. The estimated incidence has subsequently been revised from 1 in 300,000 to 1 in 1,000–10,000 patients.[38]

Variations Between Geographical Locations and Ethnicity/Demographics

An analysis of global BIA-ALCL cases by Brody et al.[1] has revealed a substantial variation of incidence around the world, with the lowest relative incidence in the Eurozone, China, and Brazil. Currently, the highest reported incidence is in Australia and New Zealand (1/2,832 depending on implant type), whereas BIA-ALCL has been found to be extremely rare in people of Asian, African, and Native American descent.[1] Scandinavian countries, with excellent implant registries, until recently had almost no reported cases of the disease.[39,40] Interestingly, manufacturers estimate that 70%–80% of implants sold in Europe are textured.[1] Hence, it would appear that, as with most tumor-related diseases, genetic predisposition and ethnicity may play an important role.[41]

Differences Between Implant Types

Texture grading is typically defined by industry. A large number of new terms have seen the light since ALCL has gained in attention.

Although >500 cases of BIA-ALCL have been confirmed worldwide, no cases have been reported in women exposed to smooth implants only.[11,13,42] The cases reported in women with smooth implants have had textured implants before revision surgery to smooth implants. Brody et al.[1] reviewed all current BIA-ALCL literature, analyzing 173 cases of the disease, and noted that where the clinical history was known, the patient had received ≥1 textured surface device. Further, no reports of the disease have been identified before the introduction of surface-textured implants.[1] Loch-Wilkinson et al.[11] have subsequently investigated implant-specific risks of BIA-ALCL in Australia and New Zealand—81 cases of BIA-ALCL were diagnosed between 2007 and 2018 with all cases related to textured implants. Most significantly, the vast majority of these cases, 85%, were related to higher surface area textures. The reported risk was 1:2,832 for polyurethane, 1:3,817 for Biocell, and 1:60,631 for Siltex-textured implants. Further, the most recent update of this study in 2018 reports that the risk of developing BIA-ALCL is approximately 16.5 times higher for Biocell and 23.4 times higher with polyurethane (Silimed, Rio De Janeiro, Brazil) implants, compared with Siltex-textured devices (Table 2).[34] Magnusson et al.[34] have gone on to assess the related risk of BIA-ALCL with surface area and degree of texture. Reporting that no cases have been associated with grade 1 textured implants, whereas 78.9% of cases were associated with grade 3 or 4 textured implants. Analysis of implant type with sales data for the 3 implant types has confirmed that the highest risk for BIA-ALCL in Australia and New Zealand is for implants with a grade 4 surface—shown to have the highest surface area and surface roughness; possibly potentiating the growth of both Gram-positive and Gram-negative bacteria. Silimed polyurethane (grade 4 surface) is now associated with the highest risk of developing BIA-ALCL, with an incidence of 1 case for every 2,832 implants used.[34] Doren et al.[13] recently performed a retrospective review of 100 confirmed cases of implant-associated ALCL in the United States, with comparison to textured breast implant sales figures. Again, they were able to confirm the association with textured implants, with an incidence 67.6 times that of primary breast ALCL. Further, they report on a potential link to the method of implant texturing, finding that a significantly higher

Table 2. Types of Implants by Manufacturer, Their Texture Type, Surface Area, Surface Grade, and Relative Risk Compared With Mentor Siltex

Manufacturer	Texture Type	Surface Area	Surface Grade	Relative Risk (Compared to Mentor Siltex)
Silimed	Polyurethane	High	4	23.4
Allergan/Inamed	Biocell	Intermediate	3	16.5
Mentor	Siltex	Low	2	1
Mentor	Smooth	Minimal	1	0

proportion of cases were associated with salt-loss implants compared with negative-imprint stamping techniques.[13] No preference for saline- or silicone-filled implants, or for cosmetic or reconstructive indications, has yet been identified.

Although the number needed to harm approximately 7,000 implants appears relatively small, the global increase in implant surgery coupled with a current worldwide predictive prevalence of upward of 35 million women, and a substantially higher incidence depending on implant type, these numbers become significant (Table 3).

DISCUSSION

Although there have been wide variations in the estimation of risk for BIA-ALCL, it is important to note that these numbers still predictive as the complexities of this newly emerging disease entity are fully appreciated. Much can be explained by analyzing the evolution of our comprehension and understanding the etiology of BIA-ALCL, which in turn has influenced research methodology. Initial epidemiologic reports were not only hindered by small study populations, inaccurate and unconfirmed reporting, and lack of awareness, but importance of implant and patient-specific characteristics were not fully understood. Estimates of risk have increased studies began to focus on textured implants alone.[1] Further differentiation between specific manufacturers and implant types has again lead to a comparative rise in the risk depending on implant type.[34,43] In light of these recent developments, it is most likely that the risk of BIA-ALCL is directly proportional to the surface texture and surface area of the breast implant—implicated indirectly through the propensity to harbor microorganism and form an indolent inflammatory biofilm, eventually triggering T-cell transformation. There will undoubtedly be further clinical, implant, and patient characteristics that emerge with associated risks, such as manufacturing methods and materials (Table 3).

With an increased awareness of the disease among patient and clinicians, a dramatic rise in the number of identified cases has now emerged, reflective of increased surveillance and reporting.[3,34] It is likely that BIA-ALCL is on the "take off" phase of identifying cases and will continue to experience an exponential rise. Unfortunately, truly accurate epidemiologic numbers will only become apparent once the rate in diagnosis plateaus. With greater numbers, accurate reporting, and increased penetrance of registries, the ability to further be identify and quantify risk factors associated with developing BIA-ALCL will be delineated. Dramatic variation between regions signals that ethnicity and genetic factors are implicated.[41]

It is currently, not appropriate to quote a global risk for this disease, in light of the reported geographic and ethnic variations.

A 2-pronged approach is required to manage the 1 distinct subsets of women "at risk"; those who currently have high-textured high-surface area implants, and those looking to receive breast implants for cosmetic or reconstructive purposes, education, follow-up, and screening will be imperative.

On the plus side, science and evidence are at a point where modification and mitigation of some risk factors can be addressed. Fortunately, the majority of cases (around 80%) usually present during the early stages of the disease, which is imminently curable with surgical excision alone.[6,44] There will undoubtedly be a shift in surgeon selection of implant type, which, along with the current emerging trends, will drive various manufacturing changes to implant design,

Table 3. Epidemiologic Progression: With an Increasingly Specific Focus on Type of Implant and Implant Characteristics the Risk Estimate Has Dramatically Increased

Year	Study Type	Population	Risk Estimate	Reference
1997	Case report (1)	Textured saline implant	Association	Keech and Creech[2]
2008	Case control (5)	All implants	1–3/million	De Jong et al.[37]
2011	Case series (34)	All implants	1/3 million	U.S. Food and Drug Administration[35]
2014	Case series (71)	All implants	1/500,000	Ye et al.[41]
2018	Case control (43)	All implants*	1/35,000	De Boer et al.[36]
2016	Cases series (100)	Textured implants	1/30,000	Doren et al.[13]
2017	Case series (55)	High surface area textured implants	1/4,000	Loch-Wilkinson et al.[11]
2018	Case series (81)	Grade 4 surface implants	1/3,000	Magnusson et al.[34]

*It is important to note that the Netherlands is a near-95% textured implant market; thus, the reported risk estimate for all implants is representative of the risk for textured implants.

materials, and surface texture. Interestingly, evidence has emerged which reveals that meticulous and vigilant adherence to the 14-point plan can significantly reduce risks, which lends substantial support to the current theory of a bacterially driven transformation of T cells into malignancy.[43] Although the 14-point plan is yet to be examined exclusively in the context of BIA-ALCL, prevention of implant contamination has been shown as a significant strategy for reducing capsular contracture and so has other benefits.

RECOMMENDATIONS

In light of the current literature, we would strongly suggest that all patients undergoing breast implant surgery with a textured device must provide informed educated consent that includes a discussion of the risks of BIA-ALCL, with patient and implant-specific risks assessed and discussed before surgery.[45] At this time, we would advise that the relatively higher risk associated with textured high-surface area (grades 3 and 4) implants be communicated clearly to patients and the balance of risk and benefits be clearly articulated.[11] Provision of education relating to the signs and symptoms of BIA-ALCL is imperative to ensure that women receiving implants are vigilant in their monitoring; cases diagnosed during the early stages of the disease are imminently curable with surgical intervention alone.[36,44]

As the pathologic mechanism continues to unravel, we will begin to develop a disease profile with established relative and absolute contraindications. A number of cases have recently been linked to women with JAK/STAT acquired and germline mutations[46] and with the Li-Fraumeni syndrome, who carry the p53 oncogene mutation.[47,48] In such cases, and in women following mastectomy for breast cancer, reconstruction with textured breast implants would be inadvisable. It may be that we will see a shift away from breast implant reconstruction, especially in reconstructive cases, with a trend toward autologous techniques—driven by both patient and surgeon preference.

The most powerful resource with regard to surveillance, tracking, and detailed epidemiology profiling is the adherence to registries and mandatory reporting. Unfortunately, those that are currently in place lack adequate penetrance because they have only been in practice for a relatively short duration and adherence is at the surgeon's discretion.

CONCLUSIONS

We are beginning to better understand the relative risk and prevalence of BIA-ALCL. We predict a continued increase in the number of confirmed cases, most likely a combination of raised awareness leading to more frequent detection and/or a true rise in incidence with the growth of cosmetic breast augmentation. Proxy analysis using sales data and population radiology surveillance in combination with capture of reported cases have shown a differential risk with higher grade surface texture. There are likely to be advances in the understanding of pathophysiology and the role of patient genetics and/or microbiome in the near future.

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