

Special Topic

# What's Your Micromort? A Patient-Oriented Analysis of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

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## Abstract

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) continues to be a rare and elusive malignancy. Because BIA-ALCL does not behave like traditional lymphomas, additional research needs to be conducted to further delineate the lymphoproliferative nature of BIA-ALCL. An estimated 35 million women worldwide have breast implants and the total reported deaths from BIA-ALCL is 12 to date. The term micromort was introduced in 1979 by Ronald Howard as a person's risk of dying as 1 in a million. Drinking 0.5 L of wine or walking 17 miles all increase your risk of death by 1 micromort. Risk of death from BIA-ALCL is 0.4 micromorts for a woman having bilateral breast implants. This information is important for counseling new patients and those presenting with delayed onset seromas.

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Anaplastic large cell lymphoma (ALCL) was first described in 1985 when atypical tumor cells consistently demonstrated the CD30 antigen. ALCL was added as a distinct entity in 1998 to the revised Kiel classification, and in 1994 was included in the Revised European American Lymphoma (REAL) classification. The REAL classification for ALCL then became the World Health Organization (WHO) classification in 2001.<sup>1</sup> The first published report of breast implant-associated ALCL (BIA-ALCL) was by Keech in 1997.<sup>2</sup> As more case reports were published, an increased awareness of BIA-ALCL was generated, leading to a proliferation of literature in an attempt to better understand and classify BIA-ALCL. In 2011, the Food and Drug Administration (FDA) identified a possible association between breast implants and the development of ALCL but it wasn't until 2016 that the WHO recognized BIA-ALCL as a unique type of T-cell lymphoma.<sup>3,4</sup>

The true number of global cases of BIA-ALCL continues to be difficult to determine. Many countries have created national registries to better track the diagnosis and prognosis of BIA-ALCL. Srinivasa et al conducted a recent review

of 40 national and international government authority databases to better understand the number of BIA-ALCL cases reported globally. Using the US Manufacturer and User Facility Device Experience (MAUDE) database they identified 258 unique cases of BIA-ALCL, 130 of which were confirmed with appropriate pathological markers (CD30+ and ALK-). Of these, 110 were reported within the United States and 20 internationally. A total of 5 deaths were reportedly associated with BIA-ALCL.<sup>5</sup> The current total number of known deaths related to BIA-ALCL is 12.<sup>6</sup> Despite ongoing research to understand the cause of BIA-ALCL, it continues to be a rare and elusive process.

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As more is learned about T-cells, more specific cellular characteristics have been identified including: abundant cytoplasm, vesicular irregular nuclei, frequent mitosis with the occasional “hallmark” cell being present.<sup>7</sup> Studies have identified changes in cellular morphology which are believed to be due to persistent low grade inflammation caused by chronic biofilm infection most closely linked to the bacteria *Ralstonia* spp.<sup>8-10</sup> More recent data also suggests that BIA-ALCL actually behaves as a lymphoproliferative disorder in which normal cells experiencing chronic inflammation undergo a progressive and predictable transformation into “pre-malignant” precursors before rarely transforming into end stage malignant lymphocytes.<sup>11</sup> Evaluation of isolated cells from the seroma fluid of 2 patients demonstrated the presence of CD30+ /ALK- lymphocytes which despite the expression of abnormal cellular markers, did not have the cellular features diagnostic for BIA-ALCL.<sup>12,13</sup> This progression from normal to pre-malignant to malignant very closely resembles the cellular transformation seen in cutaneous non-melanoma skin cancers. The clinical behavior of BIA-ALCL is largely benign; however, surgeons have had a paucity of data to use for good patient education on this disease.

The purpose of this study is to perform a micromort risk analysis of BIA-ALCL and make recommendations for its use in breast implant patient education.

## Study Data and Mathematical Analysis

It is difficult to determine the true incidence of BIA-ALCL because there are no good estimates of the actual number of patients with breast implants worldwide. The International Society of Aesthetic Plastic Surgery (ISAPS) estimated approximately 1.5 million women underwent breast augmentation surgery and 153,500 women had breast implants removed in 2015 worldwide.<sup>14</sup> ISAPS estimates that approximately 20% of these women underwent breast augmentation surgery in the United States, or about 300,000 women. Similar data provided by American Society of Plastic Surgeons (ASPS) estimates that 290,000 women underwent breast augmentation surgery in 2016, with approximately 30,000 removed in the same year for a net total of 260,000 women undergoing breast augmentation in 2016.<sup>15</sup> The American Society for Aesthetic Plastic Surgery (ASAPS) statistics correlate with the ASPS numbers in that 310,000 women underwent breast augmentation surgery and 43,000 women had implants removed in the same year.<sup>16</sup> According to the ASPS trend data there was a 37% increase in the number of breast augmentations from 2000 to 2016, or about 2.3%/year. For the purposes of this analysis,

it will be assumed that the number of patients having implants removed follows the same trend of 2.3%/year. Analyzing the numbers provided by both ASAPS and ASPS, an estimation can be made regarding the total number of patients undergoing breast augmentation surgery going back to 1980. The data estimates that only 2% of women aged 55 or older have implants placed for breast augmentation.<sup>15</sup>

Using the more conservative data from ASPS which estimates 290,000 women had implants placed and 30,000 had implants removed in 2016, for a net total of 260,000 in the United States. Since the United States is responsible for placing 20% of implants worldwide, in 2016 there were 1,300,000 women who underwent breast augmentation surgery worldwide, or 2.6 million implants. With 2% less implants placed each year prior to 2016, there were 1,270,000 women with implants (2,470,000 implants) placed in 2015, which is consistent with ISAPS data (a net of 1,350,000 augmentation patients for 2015, 2.7 million implants).<sup>14</sup> Using this confirmed number we performed an annual regression back to 1980.

When summation of all years from 1980 until 2016 is calculated, there are currently 33,000,000 women with implants in place worldwide. This is still a very conservative estimate as it does not account for implants placed for reconstructive purposes or pre-1980 implants.

The percentage of textured implants was estimated from available data. The European, Asian, and Australian markets use nearly 100% textured devices as reported from the Austrian Breast Implant Register which states that 97% of breast implants placed are textured devices.<sup>17</sup> Percentages from the United States are more difficult to come by and can be estimated based off of Allergan’s and Sientra’s core studies.<sup>18,19</sup> Based off of their 10-year and 9-year data respectively for all comers (cosmetic and reconstructive) 53.2% of patients had smooth implants placed while 46.8% had textured implants. More recent data from Sientra show that 26% of total implants sold in 2015 were textured, an increase from 8.1% in 2011.<sup>20</sup> Prior to 2011, the US market likely used approximately 8% textured implants based on available data.

The final calculation of the total worldwide number of patients with implants in our analysis estimates 35 million patients with breast implants (roughly 70 million implants). To calculate the total number of textured implants worldwide it is assumed that 97% of non-US implants are textured while 8% of those used in the United States are also textured. Of these 35 million patients, there are 650,000 patients with textured implants in the United States and 25 million patients outside of the United States, for a total of 26 million patients. This number does not account for the 2.5 million patients who have undergone breast reconstruction in the United States with a textured device.<sup>15</sup>

A conservative global estimate is that approximately 30 million patients have textured breast implants in place.

## Micromort Concept and BIA-ALCL Analysis

A micromort is a unit of risk defined as a one-in-a-million chance of death, introduced by Ronald A. Howard in 1979 who established the concept of decision analysis.<sup>21,22</sup> Many common daily activities have already been studied for micromorts per unit of exposure. Simply getting out of bed when you are 20 years old increases risk of death by 1 micromort, driving a car 1 hour per day increases risk of death by 2 micromorts, and running a marathon increases risk of death by 8 micromorts per run.<sup>23</sup> These units of risk assessment are commonly used for evaluation of high-risk activities such as skydiving and mountaineering, or even more common activities such as riding a bicycle for 10 miles or smoking one pack of cigarettes a day.

Using the estimated 30 million patients with textured breast implants (from above) and 12 reported deaths from BIA-ALCL, the risk of death from BIA-ALCL is 0.4 micromorts per patient (with bilateral textured implants) or 0.2 micromorts per textured implant.

## DISCUSSION

The micromort risk assessment for BIA-ALCL requires an accurate estimation of the number of breast implants currently in place worldwide. Many lecturers estimate the number of patients with breast implants at 5 to 10 million, or 10 to 20 million implants.<sup>24</sup> Per our conservative estimates, there are at least 33 million women with implants in place worldwide, and this only accounts for those patients undergoing cosmetic, not reconstructive surgery. If a woman was 18 when she underwent breast augmentation in 1980, she would be 55 today. And because only 2% of women older than 55 undergo breast augmentation, we only included the number of breast implants placed over the last 37 years. Using the same calculations above, there were 110,000 breast reconstructions performed in the United States in 2016.<sup>15</sup> Of these, 110,000 breast reconstructions, 54% to 92% were prosthetic based reconstructions.<sup>25-27</sup> If the number of breast reconstructions each year follows the same depreciations and global percentages, then there have been approximately 15 million breast reconstructions performed worldwide over the last 37 years. The actual number of implants worldwide could feasibly be 15 to 20 million higher than our estimates, totaling close to 50 million, especially when taking into consideration those women undergoing reconstructive breast surgery.

**Table 1.** BIA-ALCL Micromort Risk Compared to Risk of Other Common Activities

Activity	Micromort	Relative value to BIA-ALCL micromort
BIA-ALCL micromort	0.4	-
Skiing 1 day in the US	0.77	2×
Drinking 0.5 liters of wine	1	2.5×
Living 2 days in NYC	1	2.5×
Riding a bike 17 miles	1	2.5×
Traveling 230 miles by car	1	2.5×
1000 miles by plane	1	2.5×
Driving a car 1 hour per day	2	5×
Driving a car 8 hours per day	16	40×

BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; NYC, New York City; US, United States

Our calculated micromort risk for BIA-ALCL is 0.4. Compared to other daily activities (Table 1) which increased risk of death by 1 micromort ( $2 \times$  BIA-ALCL micromort) include: drinking 0.5 liters of wine, smoking 1.4 cigarettes, living 2 days in Boston or New York in 1979, drinking water in Miami for 1 year, eating 40 tablespoons of peanut butter, walking 17 miles, riding a bicycle 17 miles, traveling by car for 230 miles or by jet for 1000 miles.<sup>22,28</sup> Skiing 1 day in the US carries a  $2 \times$  higher micromort risk (0.77) than the micromort risk of death from BIA-ALCL in a patient who had bilateral breast implants over their lifetime. Compared to many common daily activities, the micromort risk from BIA-ALCL is minimal in comparison. This analysis is not surprising given the observed clinical course of most BIA-ALCL patients; however, this begs the question of why BIA-ALCL is being called what it is. The cumulative micromort risk from basal cell carcinoma (BCC) is 6.17 micromorts/year or 228 micromorts. The cumulative micromort risk from colon cancer is 152 micromorts/year or 5624 micromorts,  $14,060 \times$  the micromort risk BIA-ALCL.

Furthermore, current research is underway to better understand the progression and nature of BIA-ALCL. Recent findings by Kadin are helping to make a strong case for reclassification of BIA-ALCL as a lymphoproliferative disorder.<sup>11</sup> Even though specific cell markers (specifically CD30) are present on cells aspirated from implant associated seromas, many of these cells do not yet display the cellular features diagnostic for BIA-ALCL.<sup>13</sup>

The findings of this study are especially important for patient education. The clear lymphoproliferative nature of BIA-ALCL, along with the calculated risks associated with its diagnosis, should be used for discussion during new

consultations or at the time of presentation for evaluation of delayed onset seromas. Given that there has yet to be a documented case of BIA-ALCL with a smooth surface only implant, a preoperative patient who has chosen a smooth implant can be counselled accordingly. The risk of death in a woman with a smooth breast implant is essentially zero with our current knowledge regarding BIA-ALCL. The data from this analysis is relevant to patients with textured devices and as we learn more there will be more clarity in the breakdown for the varying degrees of texture, which may carry different risk.

Following the 2017 FDA update that did not qualify much of the information presented, news reports were published that largely provided patients with misinformation and a picture of the BIA-ALCL entity that is not reality.<sup>3,29</sup> Although there is a risk of death from BIA-ALCL, this risk is minimal compared to many other activities we perform daily. Patients can better frame the actual risk, which is currently skewed significantly due to the current classification and the lack of understanding of this rare disease. This discussion should be an integral patient of the patient education and informed consent process.

There are some limitations of this study due to the paucity of data both regarding the etiology and disease progression of BIA-ALCL as well as the true number of patients worldwide with breast implants. The estimates made within this paper are based on data collected from ASAPS, ISAPS, and ASPS annual data, and we believe these data are conservative and sound. Despite being from 3 sources with variations in the number of patients who underwent bilateral breast augmentation, as well as the number of patients who had implants removed, the net number of patients with breast implants each year is relatively consistent across all three groups. Nonetheless, the accuracy of these estimates cannot be completely verified. Ongoing research to help better understand the progression of BIA-ALCL will afford new insight for patient education.

Lastly, surgeons should also be wary in attempts to classify this disease as something that it obviously is not. The WHO should immediately amend the classification of BIA-ALCL as a lymphoproliferative disease solely based on current research and risk data, including this study which demonstrates an incongruity between the current classification and the behavior of the disease.

## CONCLUSION

It is important that we as educators do not react, but instead research and respond. When talking with patients about BIA-ALCL we need to use the data on hand to educate breast implant patients that BIA-ALCL is generally a reactive, generally benign behaving disease which is easily

treatable with surgery.<sup>30</sup> The cases of death which have occurred to date were typically in patients where they were not diagnosed and treated appropriately or in a timely fashion. When talking with patients about their risks, it is helpful to explain that their micromort risk from skiing for 1 day is a 2 × higher micromort risk than having a textured breast implant for their lifetime or that traveling 8 hours by car carries a 40 × higher micromort risk than having two breast implants for their lifetime. This information should be yet another tool we can provide to our patients to make sure they are aware and informed of the true risks associated with the procedures we perform.

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