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Is there an association between the use of textured breast implants with anaplastic large cell lymphoma?

Existe associação do uso de implantes mamários texturizados com linfoma anaplásico de células grandes?

Juliana da Motta Girardi^{I,*} 

Gabriela Vilela de Brito^{II} 

ABSTRACT

Introduction: Anaplastic Large Cell Lymphoma (ALCL) is a rare type of non-Hodgkin's lymphoma and some reports have indicated a possible association between its occurrence and the implantation of breast implants, especially the textured ones. However, so far, little is known about the disease process and its relationship with breast implants. **Objective:** Thus, the aim of this study was to identify whether there is an association between the use of breast implants and the development of ALCL. **Method:** A systematic literature review was performed on the databases: Medline via PubMed, Cochrane Library, Embase and Virtual Health Library (BVS) in February 2019 using the terms "Breast Implantation" and "anaplastic large-cell lymphomas." **Results:** A total of 797 studies were identified, of which 12 were selected and included in the present study: 2 case-control studies, 5 retrospective database records, 1 prospective cohort and 4 systematic case report reviews. Case-control studies have shown increase the chance of ALCL in breast implant patients. In the reported cases of ALCL, most were relate to textured surface implants; however, data may be skewed as this is the best-selling type of prosthesis worldwide. Most of the procedures were performed for aesthetic reasons, followed by breast reconstruction after breast cancer and mastectomy. In these cases, it is not known whether reconstruction is a risk or aggravating factor for the development of ALCL. The data came from studies conducted in the United States of America - USA, Netherlands, Sweden, United Kingdom and Italy. **Conclusion:** To date, data indicate an association between breast implant and the development of ALCL; however, there is no way to establish a causal relationship.

KEYWORDS: Anaplastic Large Cell Lymphoma; Breast Implants; Association; Risk; Causal Relationship

RESUMO

Introdução: O linfoma anaplásico de células grandes (ALCL) é um tipo raro de linfoma não Hodgkin e alguns relatos têm apontado possível associação entre a sua ocorrência e a implantação de próteses mamárias, especialmente as texturizadas. Contudo até o momento, pouco se sabe sobre o processo da doença e sua relação com os implantes mamários. **Objetivo:** Identificar se há associação entre o uso de implantes mamários e o desenvolvimento de ALCL. **Método:** Foi feita uma revisão de literatura com busca sistemática nas bases de dados: Medline via PubMed, Cochrane Library, Embase e Biblioteca Virtual em Saúde (BVS) em fevereiro de 2019, utilizando os termos *Breast Implantation* e *anaplastic large-cell lymphomas*. **Resultados:** Ao todo foram identificados 797 estudos, dos quais 12 foram selecionados e incluídos no presente trabalho: dois estudos de caso-controle, cinco registros retrospectivos de banco de dados, um estudo de coorte prospectiva e quatro revisões sistemáticas de relatos de casos. Os estudos de caso-controle apontaram aumento da chance de ocorrência de ALCL nas pacientes com implante mamário. Nos casos de ALCL relatados, a maioria relaciona-se a implantes de superfície texturizada, entretanto os dados podem estar enviesados já que este é o tipo de prótese mais vendida em todo o mundo. Grande parte dos procedimentos foram realizados por motivos estéticos, seguidos de reconstrução mamária após câncer de mama e

^I Fundação Oswaldo Cruz (Fiocruz), Brasília, DF, Brasil

^{II} Secretaria de Estado de Saúde do Distrito Federal, Brasília, DF, Brasil

* E-mail: juliana.girardi@fiocruz.br



mastectomia. Nesses casos, não se sabe se a reconstrução é um fator de risco ou agravante para o desenvolvimento de ALCL. Os dados foram provenientes de estudos realizados nos Estados Unidos da América, Holanda, Suécia, Reino Unido e Itália. **Conclusões:** Até o momento, os dados apontaram associação entre o implante mamário e o desenvolvimento de ALCL, entretanto não há como se estabelecer relação causal.

PALAVRAS-CHAVE: Linfoma Anaplásico de Células Grandes; Implantes Mamários; Associação; Risco; Relação Causal

INTRODUCTION

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin's lymphoma (NHL) that involves cells of the immune system. ALCL is characterized by abnormal growth of T lymphocytes and is subdivided into systemic, cutaneous and pure ALCL¹. There are currently two major variants of ALCL: one expresses anaplastic lymphoma protein kinase (ALK+) and the other doesn't (ALK-). The latter is the most common variant. The expression of ALK protein by tumor cells is an independent prognostic factor for prediction of survival².

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is extremely rare. It affects the fibrotic capsule around the implant and its pathogeny is not yet well understood. It appears in the form of a seroma or mass³.

The first case of BIA-ALCL was reported in 1997¹. In the last two decades, there have been more than 300 documented reports of confirmed cases of BIA-ALCL. The exact number of cases is difficult to determine due to the absence of global data on breast implant sales and significant limitations in worldwide reporting of BIA-ALCL⁴.

So far, little is known about the disease and its relationship to breast implants. Diagnoses are usually made during implant revision surgeries motivated by delayed or persistent seroma associated with breast pain or swelling. On average, BIA-ALCL develops 9 years after implantation of the prosthesis⁵.

Although Brazil is the second largest world market for breast implants, behind the United States only, there are no official national data on the disease¹. According to the Brazilian National Cancer Institute (INCA), the estimate of new cases of NHL for 2018 would be 10.180, of which 5.370 would occur in men and 4.810 in women⁶.

Since 2011, the Food and Drug Administration (FDA) has been investigating the possible association between this cancer and breast implants and fostering a national database of suspected cases⁴. In 2017, FDA data indicated that the majority (56.0%) of reported BIA-ALCL cases occurred in patients who had textured

implants; 7.0% in patients with smooth implants and in 36.0% of cases information was not available. In 50.0% of them, the filling of the prostheses was silicone; in 35.0% it was saline solution, and in 15.0% information was not available⁷.

The surfaces of breast implants have a stable outer layer of silicone elastomer and may have a smooth or textured surface. The filler may be silicone gel or saline solution⁸. The implant texture is an irregularity on the silicone surface designed to mimic the shape and the benefits of polyurethane implants, which have fewer complications⁴.

Since the FDA points out that most cases occurred in patients with textured implants, the aim of this study was to identify whether there is in fact an association between the use of breast implants, especially textured implants, and the development of ALCL.

METHOD

A literature review was done to identify whether scientific evidence suggested any association between the use of breast implants, especially textured implants, and the development of ALCL. Two research questions guided the work: i) "Do people with textured breast implants have a higher risk or chance of having ALCL compared to people with other types of breast implants?"; ii) "Do people with textured breast implants have a higher risk or chance of having ALCL compared to people without implants?"

To this end, in February 2019, structured searches were performed according to Table 1 in the following databases: Medline (via PubMed), Cochrane Library, Embase and Virtual Health Library (BVS).

Cohort, case-control studies, systematic reviews of case reports and observational database-type reports on patients with lymphoma and/or breast implants published in English, Portuguese or Spanish were considered eligible. There was no restriction regarding the date of publication.

Table 1. Search strategies for each database.

Database	Search strategy
Medline via PubMed	((“Breast Implantation” [Mesh]) OR (“Breast Implantation [Mesh]) OR (“Prostheses and Implants” [MESH])) AND ((“Lymphoma, Large-Cell, Anaplastic” [Mesh]) OR (anaplastic large-cell lymphomas) OR (cd30 anaplastic large-cell lymphoma) OR (ki-1 lymphomas))
Cochrane Library	Strategy 1
	Breast implants
	Strategy 2
Cochrane Library	Strategy 3
	Breast implantation
Embase	Lymphoma, Large-Cell, Anaplastic
BVS	((‘breast implant’/exp) OR (‘breast endoprosthesis’/exp) OR (‘breast prosthesis’/exp) OR (‘silicone breast implant’/exp)) AND (‘anaplastic large cell lymphoma’/exp))
	((Lymphoma, Large-Cell, Anaplastic) OR (Linfoma Anaplásico de Células Grandes) OR (Linfoma de Células Grandes Anaplásico) OR (Linfoma Anaplásico de Grandes Células CD30-Positivo) OR (Linfoma de Células Grandes Ki-1) OR (Lymphomas, Ki-1) OR (Systemic Anaplastic Large Cell Lymphoma)) AND ((Breast Implantation) OR (Prostheses and Implants) OR (Breast Implantation) OR (Implantes de Mama) OR (Prótese Interna de Mama))



The following types of studies were not selected: animal studies, *in vitro*, letters to the editor and studies whose full text was not available.

We excluded studies that: i) did not address patients with breast implants and ALCL; ii) did not study any of the following outcomes: incidence, prevalence, mortality, disease development time, contributing factors, risk or chance of BIA-ALCL.

The study selection process was conducted in two steps with the help of the Rayyan QCRI online tool (available at: <<https://rayyan.qcri.org/welcome>>). Initially, the studies were screened by two independent reviewers who read the titles and the abstracts. Then the selected papers were read in full. Those considered adequate according to the predetermined inclusion and exclusion criteria were included in the study. In cases of disagreement between the reviewers, the decision was made by consensus.

Data from the selected studies were extracted by collecting information on the population, the disease and breast implants.

RESULTS

Selection of studies

The literature search retrieved 797 studies, of which 112 were duplicate studies. Thus, 685 studies were screened by title and abstract according to the eligibility criteria above. Of these, 20 were selected for the reading of their full text. Papers that were potentially eligible but whose abstracts or full texts were not found were excluded from this review. A total of 12 studies met all established inclusion criteria. Details of the selection process and reasons for exclusion are illustrated in the Figure.

Characteristics of the studies

Of the 12 studies selected, most were retrospective observational studies. Two case-control studies, five retrospective database registration studies, one prospective cohort, and four systematic case report reviews were included.

The studies reported data from the United States, the Netherlands, Sweden, the United Kingdom, and Italy. In most studies, the procedure had an esthetic purpose, followed by breast reconstruction after breast carcinoma or prophylactic mastectomy.

The most reported implants were textured surface implants. However, in many (about 50.0% of cases), information on implant type, surface and filling was unknown. McGhan, Allergan, and Mentor are some of the manufacturers that most appeared in the studies.

The main characteristics of the included studies are presented in Table 2 and the main results are in Table 3.

Case-control studies

We selected two case-control studies, both conducted in the Netherlands, whose estimated odds ratios (OR) were high, indicating a high chance of women with breast implants having ALCL. Both sought to identify whether the chance of ALCL was associated with breast implants. Importantly, the OR

expresses whether the chance of having the disease (in this case, ALCL) in the exposed group is higher (or lower) than in the unexposed group.

The study by Daphne et al.⁹ was done in two parts. In the first, a survey of the Pathologisch Anatomisch Landelijk Geautomatiseerd Archief (PALGA) population database was conducted for nationally diagnosed patients with breast lymphoma diagnosed between 1990 and 2006. Then a nested case-control study was carried out. In the first part, 11 women diagnosed with ALCL were identified, of which eight had unilateral breast involvement and three, bilateral.

For the case-control study, a conditional logistic regression analysis was performed to estimate the ALCL OR associated with the breast implant, whose value was 18.2 (95% CI: 2.1-156.8). The results suggested an association between silicone breast implants and the development of ALCL. Although this 18-fold increase and the development of ALCL may cause significant concern among women with breast implants, it should be noted that the chance remains low due to the rare occurrence of breast ALCL in the population (11 cases in 17 years in the Netherlands, whose population is 8 million women). The incidence of breast ALCL is estimated to range from 0.1 to 0.3 per 100,000 women with prostheses per year (five cases in 1.7-5.1 million person-years)⁹.

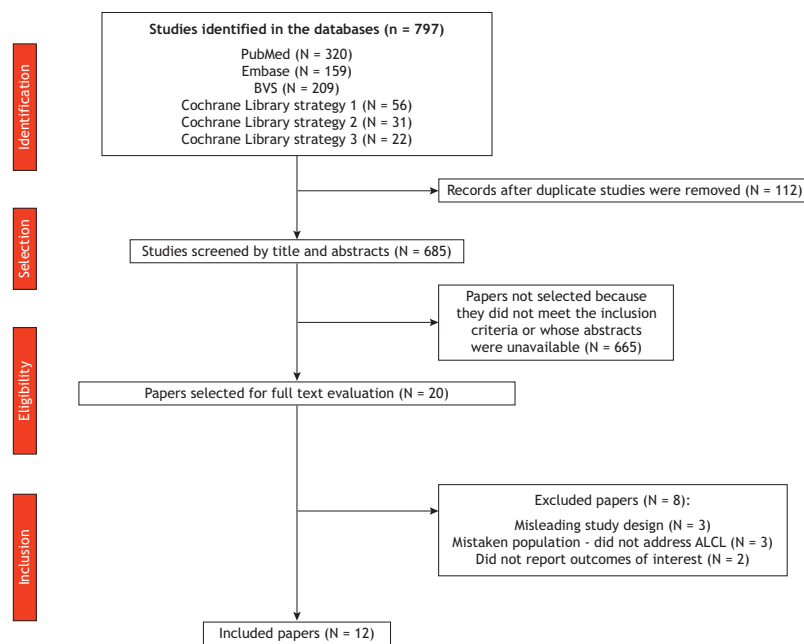
The study points out that if silicone implants are also associated with breast lymphomas other than ALCL, the strength of the association between breast implants and breast ALCL may have been underestimated.

The study by Boer et al.¹⁰ analyzed whether there was a specific type of implant that could be more associated with ALCL. Forty-three patients were identified with breast ALCL, of which 32 had ipsilateral breast implants and seven had breast cancer prior to the breast prosthesis. Of the 146 controls, one patient had a breast implant (for esthetic purposes) in the breast affected by the lymphoma. This resulted in an OR of 421.8 (95% CI: 52.6-3.385.2; P <0.001) for BIA-ALCL. Therefore, the authors stated that implants greatly increase the chance of this rare type of lymphoma.

In the study, the estimated prevalence of women aged 20 to 70 years with breast implants was 3.3% in 2015. Cumulative risks of BIA-ALCL in women with implants were 29 per million in 50-year-olds and 82 per million in 70-year-olds; in other words, it is much higher in older women. The average age of women with BIA-ALCL was between 18-75 years, but the highest number of reported cases was between 51-75 years. The number of women with implants required for a case of breast ALCL before age 75 was 6,920, which indicates how rare the disease is. Most of the diagnosed cases occurred between 2011-2016. The largest percentage of implants corresponded to macrot textured implants from Allergan, Inamed and McGhan¹⁰.

Retrospective database studies

We retrieved retrospective database studies, of which most (3/5) had been done in the United States. The reports of these studies



ALCL: anaplastic large cell lymphoma.

Figure. Flowchart of the results of search, selection and inclusion of studies.

contained the most common characteristics of the patients, like the types of implants, in which breast the lymphoma was detected, the time of diagnosis, the average age of the patients and the main symptoms. They all reported silicone or saline solution implants, in which much of the surface was textured.

The study by Srinivasa *et al.*¹¹ used international databases from Brazil, Canada, China, Colombia, Japan, Mexico, European Union Member States, New Zealand, South Korea and Italy, as well as a search in the International Manufacturer and User Facility Device Experience database (MAUDE), fostered by 40 countries, where a total of 459 medical device reports were reviewed between 2010 and 2015. These reports contain information about adverse events, suspected device-associated deaths, serious injuries, and malformations. Lymph node metastasis was reported in 16 (6.2%) cases, whereas in 12 (4.7%) no lymph node metastasis was specified. It is noteworthy that the bases of Brazil (Health Surveillance Notification System - Notivisa), Canada (Vigilance Adverse Reaction Online Database - VAROD), China (China Food and Drug Administration - CFDA), Colombia (Ministry of Health and Social Protection), Japan (Pharmaceuticals and Medical Devices Agency - PMDA), Mexico (*Secretaria de Salud*) and South Korea (Ministry of Food and Drug Safety - MFDS) did not report any cases of BIA-ALCL.

The study by Popplewell *et al.*¹² analyzed archives of patients with primary T-cell lymphoma between 1999 and 2007. These documents came from the Department of Hematopoietic Cell Pathology and Hematology of the United States City of Hope Pathology database. Eight cases of BIA-ALCL were detected, of which seven expressed ALK- and a single case was ALCL ALK+, a 15-year-old patient who did not have breast implants. Symptoms reported by the patients were swelling, fluid accumulation in the breast and increased mass. The authors concluded that there is a strong

inclination toward ALCL ALK- histology in the occurrence of primary T-cell lymphoma associated with breast implants.

The study by Doren *et al.*⁵ reviewed 100 documented BIA-ALCL cases from 1996-2015 in the United States. Based on that, they determined an incidence of 2.03 cases per 1 million person-years with textured breast implants and a prevalence of one in 30.000 women with textured implants.

Assuming that breast implant-associated ALCL occurs only with textured implants, the risk of developing it is much higher than the risk of developing primary ALCL with breast tissue involvement in the general population (67.6 times higher), considering the incidence of 3.00 per 100 million per year, according to the literature.

The study points to association, but not causality. And its limitation is the fact that the disease occurs predominantly in people with textured implants, since it uses United States sales data for textured implants from Allergan and Mentor but does not evaluate other types of implants⁵.

The study by Dashevsky *et al.*¹³ assessed the hospital information system of a United States cancer center to review the electronic medical records of women diagnosed with BIA-ALCL between 2010 and 2016 and who had undergone breast reconstruction or cosmetic augmentation at the institution. The study points out that it is not possible to establish any correlation with the breast implant texture given the small number of cases.

Although most breast implants were bilateral (10/11, 91.0%), patients only developed unilateral BIA-ALCL. In 56.0% of cases, BIA-ALCL was diagnosed on the same side as the previous cancer¹³.

The study by Campanale *et al.*¹⁴ reported Italian cases of BIA-ALCL recorded in the Dispovigilance database, an initiative of the Italian



Table 2. Characteristics of the included studies.

Authors	Location	Period	Population	N (BIA-ALCL)	Reason for the procedure	Type of implant	Type of filling	Manufacturer
Case-control studies								
Boer <i>et al.</i> , 2018	Netherlands	1990-2016	Patients diagnosed with primary non-Hodgkin's breast lymphoma, either breast ALCL or other types of breast lymphoma	Cases (n = 32) Controls (n = 146)	Esthetic (n = 22) Reconstruction after prophylactic mastectomy (n = 3) Reconstruction after mastectomy due to breast CA (n = 7)	Macrotextured: 23/32 (72.0%) Microtextured: 5/32 (16.0%) Unknown: 4/32 (12.0%)	MI	Eurosilicone Allergan McGhan Mentor Inamed Nagor Sebbin PIP
Daphne <i>et al.</i> , 2008	Netherlands	1990-2006	Women with histopathological diagnosis of ALCL	Cases (n = 11) Controls (n = 35)	All esthetic	Textured: 3/11 (27.0%)	Hydrogel: 1/11 (9.0%) Unknown: 1/11 (9.0%)	McGhan, Nagor Rofit PIP
Retrospective database studies								
Srinivasa <i>et al.</i> , 2017	40 countries	2010-2015	Database information: The International Manufacturer and User Facility Device Experience - MAUDE database	258	Reconstruction (n = 58) Esthetic (n = 97) Not specified (n = 103)	Textured: 129/258 (50.0%) Smooth: 11/258 (4.0%) Unknown: 115/258 (45.0%) History of both 3 (1.0%)	Saline: 104/258 (40.0%) Silicone: 90/258 (35.0%) Unknown: 64/258 (25.0%)	Allergan: 161/229* (70.3%) Cui: 1/229 (0.4%) Inamed: 4/229 (1.7%) McGhan: 19/229 (8.3%) Mentor: 20/229 (8.7%) Silimed: 1/229 (0.4%) McGhan/Allergan: 1/229 (0.4%) Unknown: 22/229 (9.6%)
Popplewell <i>et al.</i> , 2011	USA	1999-2007	Database information: City of Hope Pathology database	8	Esthetic (n = 6) Unknown (n = 2)	Textured: 1/8 (12.5%)	Saline: 2/8 (25.0%) Silicone: 1/8 (12.5%) Unknown: 2/8 (25.0%)	McGhan for the textured
Doren <i>et al.</i> , 2017	USA	1996-2015	Women with implant-associated cancer Literature data from all documented USA BIA-ALCL cases	100	Esthetic (n = 49) Mastectomy (n = 44) Unknown (n = 7)	Textured: 51/100 (51.0%)	Unknown: 49/100 (49.0%)	Allergan and Mentor
Dashevsky <i>et al.</i> , 2018	USA	2010-2016	Women undergoing breast reconstruction or esthetic augmentation Database information: Large US Cancer Center	11	Esthetic reasons (n = 2) Reconstruction after carcinoma (n = 9)	Textured: 7/11 (63.0%), of which: - Textured saline: 4/11 (36.3%) - Textured silicone: 2/11 (18.2%) - Unknown textured material: 1/11 (9.1%) Unknown: 4/11 (36.0%), of which: - Silicone unknown texture: 3/11 (27.3%)	Saline: 4/11 (36.3%) Silicone: 5/11 (45.5%) Unknown: 2/11 (18.2%)	MI
Campanale <i>et al.</i> , 2017	Italy	2014-2017	Adults with BIA-ALCL Italian database information: Disposition	22, of which 21 in women	Reconstruction (n = 14; 63.6%) Esthetic (n = 8; 36.3%)	Textured: 22/22 (100.0%)	Silicone: 20/22 (91.0%) Saline and silicone double lumen filling: 1/22 (4.5%) Silicone and polyurethane: 1/22 (4.5%)	MI
Prospective cohort studies								
Wang <i>et al.</i> , 2015	USA	1995-2012	Women with ALCL who worked in public schools	2	MI	MI	Saline and silicone	MI

continue



continuation

Authors	Location	Period	Population	N (BIA-ALCL)	Reason for the procedure	Type of implant	Type of filling	Manufacturer
Systematic reviews of case reports								
Story <i>et al.</i> , 2013	USA	1990-2012	People with ALCL and breast implant	39	MI	MI	MI	MI
Rupani <i>et al.</i> , 2015	United Kingdom	1995-2014	People with breast implant and hematopoietic malignancies	71	Esthetic (n = 41) Breast reconstruction (n = 27) Unknown (n = 3)	Textured: 24/71 (33.8%)	Saline: 29/71 (41.0%) Silicone: 30/71 (42.0%) Silicone and saline: 3/71 (4.3%) Hydrogel: 1/71 (1.4%) Unknown: 8/71 (11.3%)	MI
Kim <i>et al.</i> , 2011	USA	1966-2010	Population with breast implants and ALCL or other non-Hodgkin lymphomas	29	Implant replacement (n = 7; 24.0%) Reconstruction (n = 5, 17.0%)	Textured: 6/29 (20.7%) Unknown: 23/29 (79.3%)	Saline: 16/29 (55.0%) Silicone: 11/29 (38.0%) Not informed: 2/29 (7.0%)	McGhan: 4/29 (14.0%) Nagor 2/29 (7.0%) Rofli PIP hydrogel: 1/29 (3.0%) Not reported: 22/29 (76.0%)
Jewell <i>et al.</i> , 2011	USA	1990-2010	Patients with breast implants and diagnosis of ALCL with breast tissue impairment (BIA-ALCL)	27	Esthetic (n = 14; 52.0%) Reconstruction (n = 11; 41.0%) Unknown (n = 2; 7.0%)	Textured: 5/27 (18.5%)	Saline: 13/27 (48.15%) Silicone: 12/27 (44.45%) Hydrogel: 1/27 (3.70%) Unknown: 1/27 (3.70%)	MI
Case-control studies								
Boer <i>et al.</i> , 2018	Netherlands	1990-2016	Patients diagnosed with primary non-Hodgkin's breast lymphoma, either breast ALCL or other types of breast lymphoma	Cases (n = 32) Controls (n = 146)	Esthetic (n = 22) Reconstruction after prophylactic mastectomy (n = 3) Reconstruction after mastectomy due to breast CA (n = 7)	Macrotextured: 23/32 (72.0%) Microtextured: 5/32 (16.0%) Unknown: 4/32 (12.0%)	MI	Eurosilicone Allergan McGhan Mentor PIP Inamed Nagor Sebbin
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continue								



continuation

Authors	Location	Period	Population	N (BIA-ALCL)	Reason for the procedure	Type of implant	Type of filling	Manufacturer
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Campanale <i>et al.</i> , 2017	Italy	2014- 2017	Adults with BIA-ALCL Italian database information: Disproportion	22, of which 21 in women	Reconstruction (n = 14; 63.6%) Esthetic (n = 8; 36.3%)	Textured: 22/22 (100.0%)	Silicone: 20/22 (91.0%) Saline and silicone double lumen filling: 1/22 (4.5%) Silicone and polyurethane: 1/22 (4.5%)	MI
Wang <i>et al.</i> , 2015	USA	1995- 2012	Women with ALCL who worked in public schools	2	MI	MI	Saline and silicone	MI
Story <i>et al.</i> , 2013	USA	1990- 2012	People with ALCL and breast implant	39	MI	MI	MI	MI
Rupani <i>et al.</i> , 2015	United Kingdom	1995- 2014	People with breast implant and hematopoietic malignancies	71	Esthetic (n = 41) Breast reconstruction (n = 27) Unknown (n = 3)	Textured: 24/71 (33.8%)	Saline: 29/71 (41.0%) Silicone: 30/71 (42.0%) Silicone and saline: 3/71 (4.3%) Hydrogel: 1/71 (1.4%) Unknown: 8/71 (11.3%)	MI
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BIA-ALCL: breast implant associated with anaplastic large cell lymphoma; ALCL: anaplastic large cell lymphoma; N: number of cases; MI: missing information; PIP: Poly Implant Prothèse.
* Total of 229 MDR reports (medical device reports) that had information on the implant manufacturer.



Table 3. Main results of the studies found.

Authors	Location	Period	Mean age (years)	N (BIA-ALCL)	ALCL development time - diagnosis (years)	Manifestation (mass, seroma, CC)	ALK+	ALK-
Case-control studies								
Boer <i>et al.</i> , 2018	Netherlands	1990-2016	18-75	Cases (n = 32)	11-20	MI	MI	MI
Daphne <i>et al.</i> , 2008	Netherlands	1990-2006	40.0 (ranging from 24-68)	Cases (n = 11)	1-23	MI	MI	MI
Retrospective database studies								
Srinivasa <i>et al.</i> , 2017	40 countries	2010-2015	MI	258	10.08	Seroma (n = 134, 51.9%) Mass (n = 28, 10.8%) CC (n = 29, 11.2%)	MI	MI
Popplewell <i>et al.</i> , 2011	USA	1999-2007	45.0 (ranging from 32-62)	8	On average 7 years after implant surgery	MI	7 cases were ALK-	1 ALK+ case (patient without implant)
Doren <i>et al.</i> , 2017	USA	1996-2105	53.2 ± 12.3	100	10.7 ± 4.6	MI	MI	MI
Dashevsky <i>et al.</i> , 2018	USA	2010-2016	54.0 (ranging from 35-77)	11	On average 10 (ranging from 6-14)	MI	MI	MI
Campanale <i>et al.</i> , 2017	Italy	2014-2017	49.6 (ranging from 30-71)	22, of which 21 in women	6.8 (ranging from 1-22)	Seroma: 16 patients; seroma and lymphadenopathy: 1 patient; CC: 2 patients; seroma and capsular contracture: 1 patient; seroma and palpable node: 1 patient	MI	MI
Prospective cohort studies								
Wang <i>et al.</i> , 2015	USA	1995-2012	MI	2	20	MI	MI	MI
Systematic reviews of case reports								
Story <i>et al.</i> , 2013	USA	1990-2012	51.0 (28-87)	39	MI	Symptoms: 34 patients CC: 2/34 (6.0%) Mass: 12/34 (35.0%) Periprosthetic: 18/34 (53.0%) Others: 2/34 (15.0%)	1/36 (3.0%)*	35/36 (97.0%)*
Rupani <i>et al.</i> , 2015	United Kingdom	1995-2014	51.4 (28-87)	71	1 to 32	CC: 11/71 (16.0%) Mass: 14/71 (20.0%) CC: 2/29 (7.0%) Mass: 7/29 (24.0%) Seroma: 14/29 (48.0%) Pain: 6/29 (21.0%)	1/71 (3.0%)	66/71 (4.2%)
Kim <i>et al.</i> , 2011	USA	1966-2010	50.5 (28-87)	29	11.7 (1-23)	CC: 2/29 (7.0%) Mass: 7/29 (24.0%) Seroma: 14/29 (48.0%) Pain: 6/29 (21.0%)	MI	25/29 (86.0%)
Jewell <i>et al.</i> , 2011	USA	1990-2010	51.0 (28-87)	27	9 (1-23)	CC: 2/14 (7.0%)* Mass: 3/14 (21.0%)* Pain and swelling: 1/14* (7.0%)	MI	Majority

BIA-ALCL: breast implant associated anaplastic large cell lymphoma; ALCL: anaplastic large cell lymphoma; N: number of cases; CC: capsular contracture; ALK+: presence of anaplastic lymphoma protein kinase; ALK-: absence of anaplastic lymphoma protein kinase; MI: missing information.

* Data only of those who implanted the prosthesis for esthetic purposes.

** Status available for 36 patients.



government's health authority (Ministry of Health) to monitor, investigate and understand the true incidence of BIA-ALCL and identify medical devices that may be associated with the disease and its clinical and pathological aspects. In 2015, the estimated incidence of BIA-ALCL in the Italian population was 2.8 cases per 100.000 patients.

It is noteworthy that data were collected in 2017, however, diagnoses were made between 2010 and 2016 and prostheses were placed between 1994 and 2012. Five cases were staged as advanced-stage cancers.

Prospective cohort studies

The study by Wang *et al.*¹⁵ assessed the association between breast implants and the incidence of T-cell lymphoma in the California Teachers Study (CTS) cohort, which included 123.392 female public school workers. Of this total, ten women were diagnosed with ALCL, and only two reported having breast implants - either saline or silicone. The implant was associated with a 10.9-fold increase in the specific risk of developing ALCL (HR = 10.9; 95% CI: 2.18-54.00). None had a family history of lymphoma or identified celiac disease. The detected primary site of ALCL in one was the breast and in the other the multiple lymph nodes. No other study participant diagnosed with any other T-cell lymphoma subtype reported the use of breast implants, nor did any other T-cell lymphoma identified in the cohort had the breast as the primary site.

The data confirmed an association between breast implants and ALCL risk, but the occurrence of ALCL among women with breast implants remained extremely low.

Systematic reviews of case reports

The study by Story *et al.*¹⁶ performed a search on the PubMed, Embase, FDA and Web of Knowledge databases from 1990 to 2012. The study included 23 case reports that described 39 patients with ALCL in the vicinity of the implant - either gel, silicone or saline.

The symptoms presented were available for 34 patients, and the most common was swelling of the affected breast, which was associated with pain in some patients. Of these, 18 (53.0%) had periprosthetic fluid (1 year after implantation), 12 (35.0%) had palpable mass and four (12.0%) had other manifestations. Of these 34 patients, one had both periprosthetic fluid and palpable mass. Breast implants were removed from most patients where such information was available (26 of 28 patients, 93.0%). Two patients (7.0%) kept their implants¹⁶.

Follow-up time was available for 20 patients. It ranged from 7 to 108 months, with an average of 30 months. Twenty-three patients (79.0%) had complete response to the treatment, four had unknown response (14.0%) and two died (7.0%). For these two, there was impairment beyond the primary site at the time of diagnosis, including nodal and systemic involvement¹⁶.

The study by Rupani *et al.*¹⁷ reviewed and analyzed the published literature on hematopoietic malignancies associated with breast implants. The searches were performed at PubMed between 1995 and 2014, and retrieved 83 cases of lymphoma associated with breast implants, of which 71 were ALCL.

Of the 71 cases of ALCL, 66 were ALK-. The results showed no association with any particular type of implant. The study suggested that the most aggressive cases and the low mortality rate may be related to the presence of breast masses¹⁷.

Compiled data suggest that there is a low risk of developing ALCL. However, there must be greater public awareness of the association between breast implants and the development of ALCL, and patients who want breast implants should be informed about the risk¹⁷.

The study by Kim *et al.*¹⁸ reviewed reports of reported cases of non-Hodgkin's lymphoma in patients with breast implants. Searches were performed in the PubMed, Embase and Web of Science databases. Thirty-four papers were included in the study reporting 36 cases of non-Hodgkin's lymphoma in breast implant patients, of which 29 (81.0%) were ALCL.

Of the 29 cases of ALCL, in 20 (69.0%) the affected implant was removed and in one case (3.0%) the implant was maintained. In the remaining eight cases (26.0%), there was no information available on the subject. Most reports of ALCL (n = 21, 72.0%) did not indicate whether or not the capsule was associated with the inflammation. Twenty-five of the 29 ALCL cases (86.0%) were negative for ALK¹⁸.

In most cases (16 of 29, 55.17%), the right breast was affected, followed by the left breast (12 of 29 cases, 41.98%). Only one patient (3.45%) had bilateral manifestation. Regarding the location of the implant, few cases had such information; most cases (27 of 29, 93.00%) did not report this.

Of patients who had had cancer before, the mean time between the first cancer and the diagnosis of ALCL was 14.7 years (ranging from 7 to 32 years) - according to data from 10 cases. Two patients out of 29 (7.0%) had a history of previous T-cell lymphoma and the mean time between T-cell lymphoma manifestation and diagnosis of ALCL was 1.8 year (ranging from 1 to 2.5 years)¹⁸.

In the study by Jewell *et al.*¹⁹, the search was conducted on PubMed and limited to papers in English published between January 1990 and October 2010. The objective of the study was to identify published cases of breast-associated ALCL. Studies on cutaneous ALCL that did not involve periprosthetic breast tissue were excluded.

A total of 18 publications were retrieved. They described 27 cases of ALCL in patients with silicone gel and saline implants. Similar ratios of patients had both fill prostheses¹⁹.

The most common clinical manifestation was unilateral breast swelling related to late periprosthetic fluid collection (1 year after implant placement). The swollen breast was sometimes reported to be painful and tender to the touch, but rarely with mass or capsular contracture. Furthermore, constitutional symptoms (fever, weight loss and night sweats) were rarely reported. In patients diagnosed with ALCL without late periprosthetic fluid (n = 14), the presentation at diagnosis varied: three had mass; one, pain and swelling; and two, capsular contracture¹⁹.

Implant texture was reported in only five cases (all with textured surface), thus hindering the determination of any association pattern between ALCL and implant texturing. Most of the cases were ALK-. Most patients (59.0%) had no disseminated disease



and were disease-free after a median follow-up of 16 months (ranging from 7 to 48 months) after therapy¹⁹.

An association, with no evidence of causality, has been reported between breast implants and the development of ALCL. However, further studies are needed to confirm that association. Breast-associated ALCL rarely occurred in women with and without breast implants, with and without a history of cancer, with and without the presence of late periprosthetic fluid and with different implant types (not limited to a specific type of prosthesis)¹⁹.

DISCUSSION

Little evidence was found to answer the research questions. Most do not relate the type of texture to lymphoma or the type of implant.

The evidence found had limitations. Among them, the following stand out:

1. Small number of studies done so far with good methodological quality and that addressed the research questions. Most of the information comes from case reports, a type of study not selected for this synthesis;
2. Small number of BIA-ALCL studied in the studies (small sample), which does not enable much inference, since the statistical power of small samples is reduced. The fact that this is a rare carcinoma also contributes to the scarcity of results in this matter;
3. Most studies did not have the appropriate length to enable observation of the outcome of interest - follow-up for at least 10 years, which is the time required for the development of ALCL according to the literature.

To date, data indicate that breast implants increase the risk and/or chance of BIA-ALCL. Results indicated association but not causal relationship. It is noteworthy that, even if there is an increase in the number of BIA-ALCL, there is still lack of data to infer more about the occurrence of BIA-ALCL, since the ALCL sample is small because it is a rare disease.

It is important to highlight that case-control studies are ideal designs for rare diseases, once they start the investigation from the effect (the disease) and retrospectively assess risk factors (the causes). Thus, they enable the simultaneous investigation of different hypotheses of cause and origin of the disease, in addition to identification of prevalence¹⁴. The results of the studies indicated much higher odds (high OR) of ALCL in patients with breast implants, but they are not stratified by implant type and texture. Further studies with appropriate follow-up periods are needed, with more women, generations, statistical power, different types of implants and manufacturing companies, so that we can better assess these questions.

A United States epidemiological study revealed the prevalence of 33 BIA-ALCL cases per 1 million people with textured breast implants. Australian literature reports a higher incidence than the United States. In Asia there are almost no reported cases, and in Latin America, only a few^{19,18}. Furthermore, the fact that most of the data comes from the United States is probably

related to the FDA alert and the fact that the United States is the country with the most breast implant surgeries. The possibility of underreporting in other countries should also be considered.

It is important to consider that virtually all studies have shown a higher rate of samples with textured implants than smooth implants. This is because textured implants sell approximately 85.0% more than smooth implants worldwide. For this reason, because of the small number of existing cases (n) and because there are few good quality studies available, it cannot be stated that textured implants are directly associated with ALCL, nor can a biunivocal relationship be established¹⁷.

No studies were found that explored the relationship of capsular contracture and BIA-ALCL. Studies have been found that reported capsular contracture, but it is not known whether it is in fact a risk factor or whether there is a causal relationship with BIA-ALCL.

Implications for practice and research

Given that the results of the review indicate that further studies are needed to assess the role of textured implants in the etiology of ALCL, research support is a way to obtain more qualified data for statistical assessment. Furthermore, the incentive for the creation of a collaborative database, as pointed out in some studies, is fundamental for the regulators of several countries to keep mandatory data of these patients containing information ranging from the product itself to clinical manifestations. With that, regulatory authorities would be able to monitor these patients' outcomes, detect potential health-related problems, and intervene with regulatory measures as needed.

These measures can be encouraged not only by health authorities, but also by national and international societies of related medical specialties.

Studies that address the Brazilian series of BIA-ALCL are needed, as well as rigorous scientific studies that can detect and explore any potential causal relationship between breast implants and the onset of BIA-ALCL. In addition, genetic studies on the population affected by BIA-ALCL could clarify why only a few patients with breast implants develop the disease.

CONCLUSIONS

The data have shown an association between the development of ALCL and breast implants, but no causal relationship can be determined. ALCL is a rare type of lymphoma whose case-related data are scarce. Moreover, it has occurred in a small number of patients with breast implants. Although the possibility of a woman with breast implants having BIA-ALCL is low, comprehensive information on the risk of the disease should be given to all patients involved. The risks and benefits should be informed by the physician and discussed with the patients who intend to undergo breast implant surgery.

Importantly, the study contributes to alert physicians, health-care professionals and patients about the safety and protection of patients who may have breast implants in the future, so that they are vigilant about the issue.



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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.



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