Breast implant associated ALCL

Epidemiology

H. Miles Prince

Peter MacCallum Cancer Centre

Melbourne, Australia

BREAST IMPLANT ASSOCIATED ALCL: History

- Originally described in 1997 – ALCL
- 2008: Dutch study demonstrated increased risk of ALCL with implants
- Other studies have not confirmed this (small numbers of events)
- FDA Report (2011) – 60 cases worldwide (literature + FDA reporting)
  - Incidence quoted approx: 1:80,000 risk??
  - Based on USA approx 10/year and 10mill+ procedures*
- Issue is not related to rupture risk (i.e. PIP implants and rupture – frequently used in France and no increased reports to date)

This figure is supposition only, there is no definitive correct number. Each company does not reveal their sales figure.

BACKGROUND

Breast Lymphomas

- 90% B cell: If localized = DLBCL, Burkitts, MZL
- 10% T cell
  - PTCL (NOS)
  - ALCL
    - Systemic – ALCL Alk pos
    - Systemic – ALCL Alk neg
    - Primary Cutaneous ALCL [Alk neg]
    - Implant associated ALCL [Alk neg]
  - other

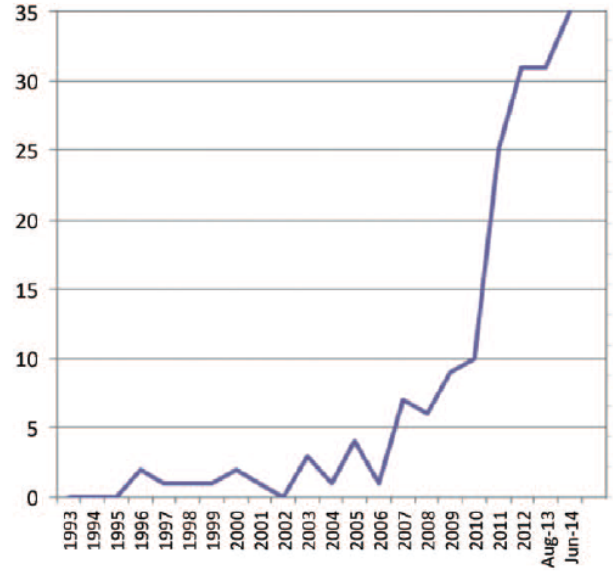

Fig. 3. Number of newly diagnosed patients per year (where date is known) through June 1, 2014.

Brody et al. Plast Glob Open 2015; 3e296

BACKGROUND

Breast Lymphomas

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    - Implant associated ALCL [Alk neg]
  - other

Better recognition?

Better reporting

Double-reporting?

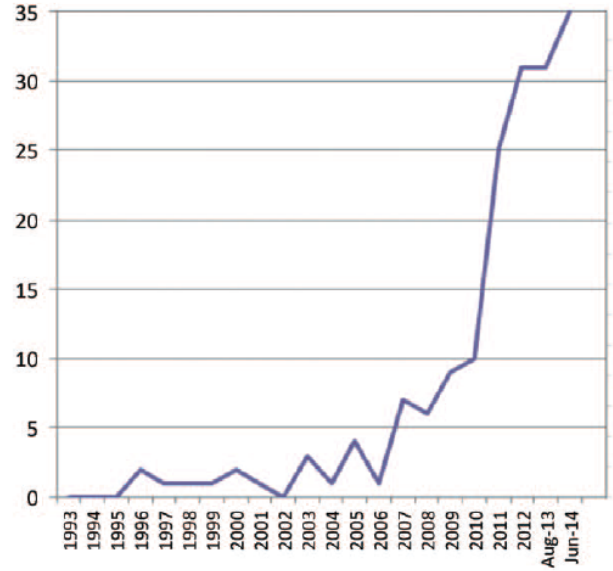


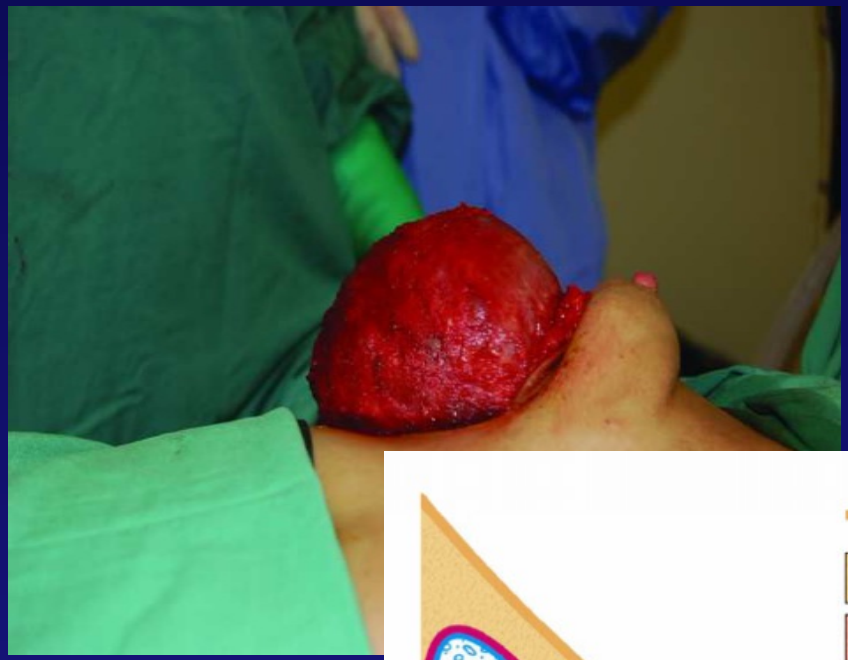
Fig. 3. Number of newly diagnosed patients per year (where date is known) through June 1, 2014.

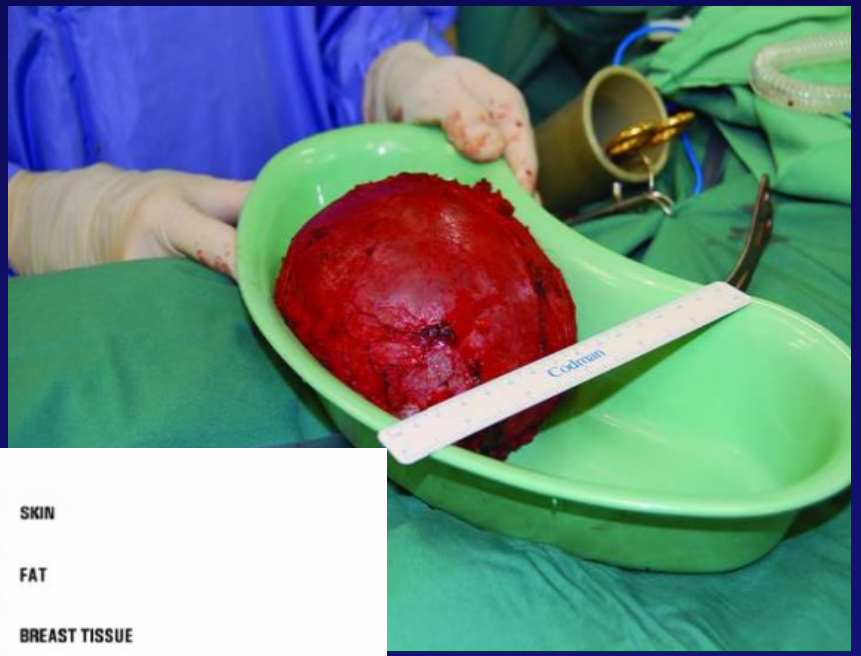
Brody et al. Plast Glob Open 2015; 3e296

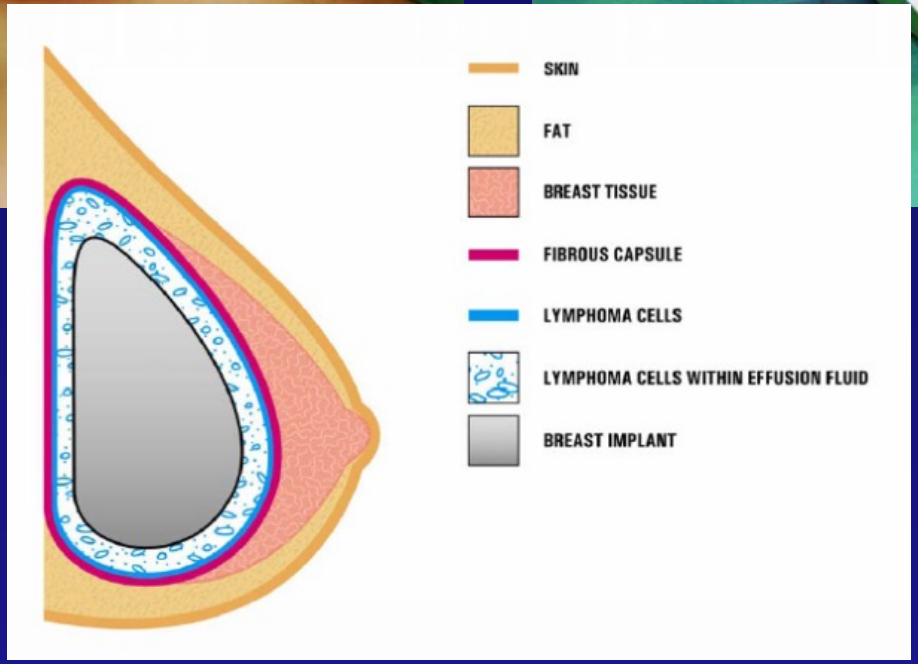
Types of implant-associated ALCL

- Mass-associated (often with effusion)
- No Mass-associated (seroma/effusion - almost always)

Without tumor mass and effusion-associated

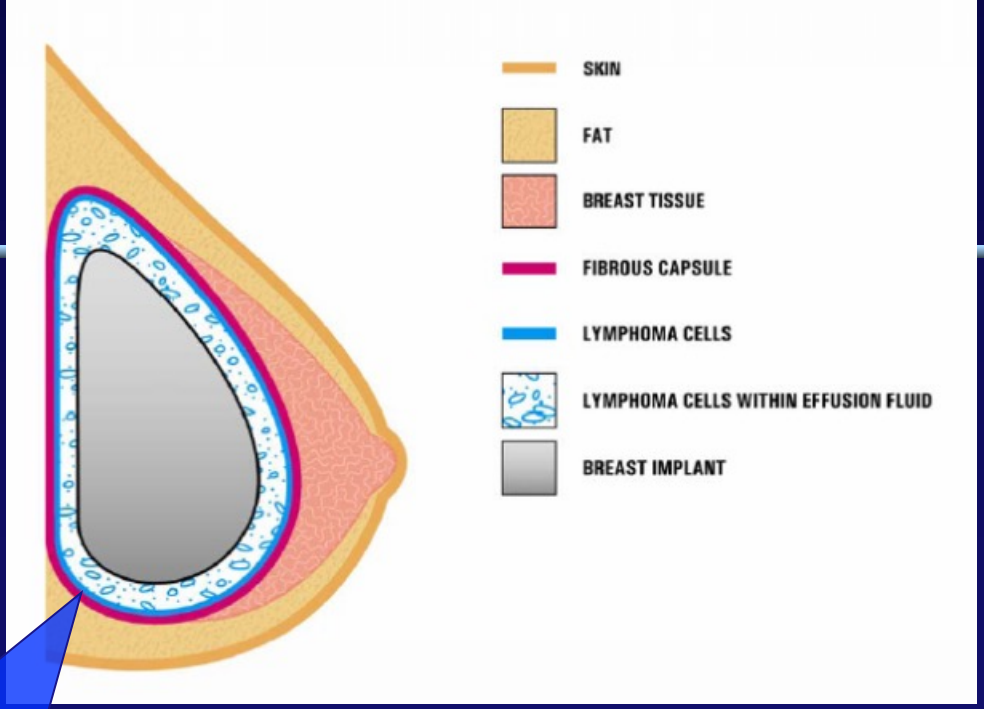


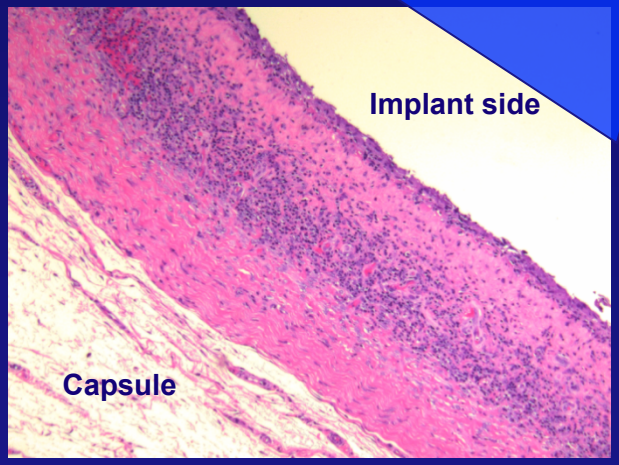


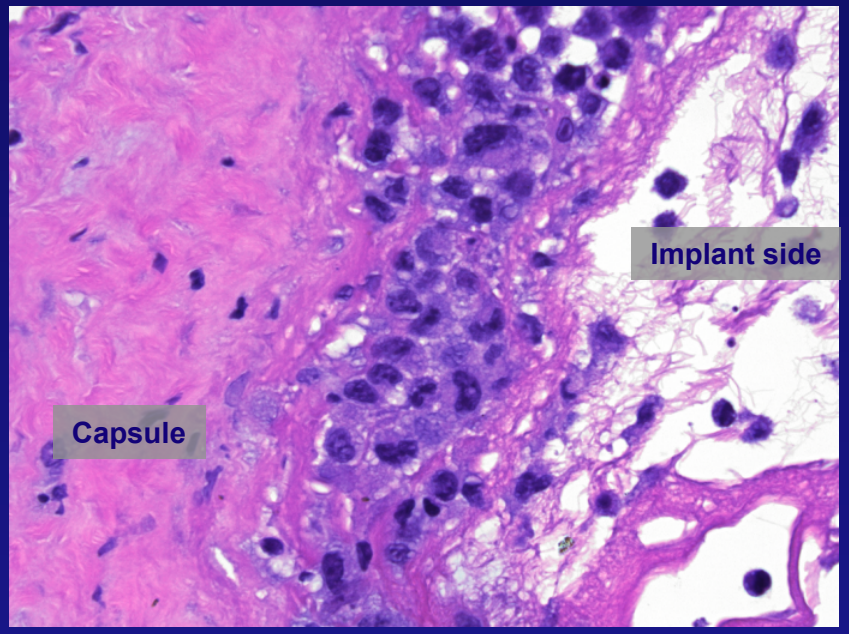


Thompson et al. 2010. Hematologica

Effusion-associated

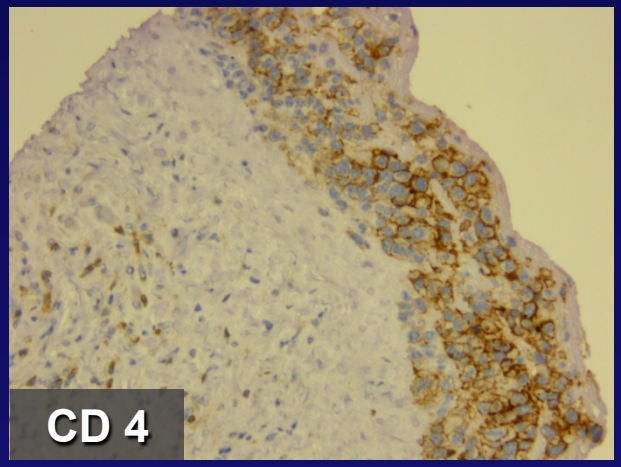


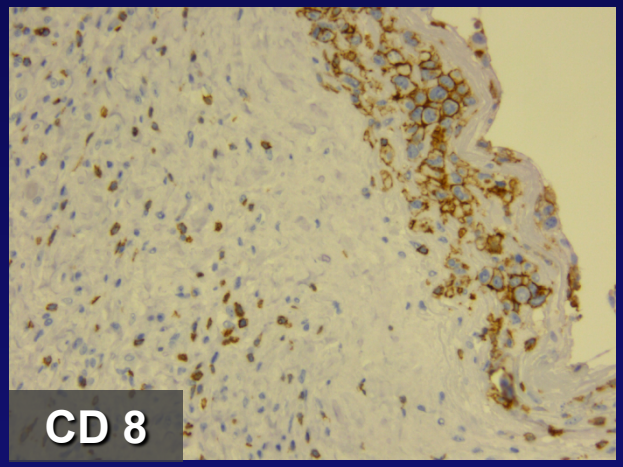


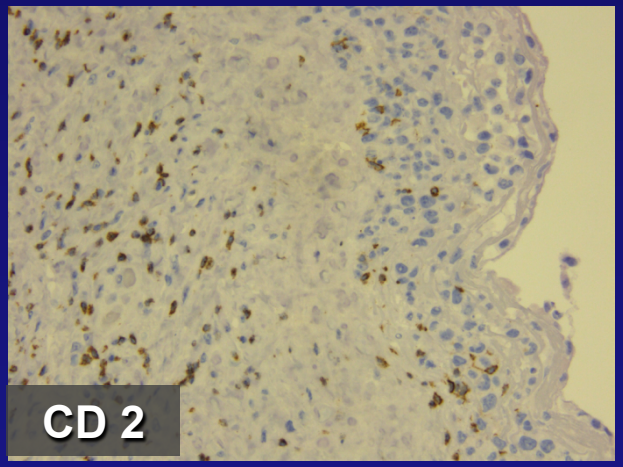


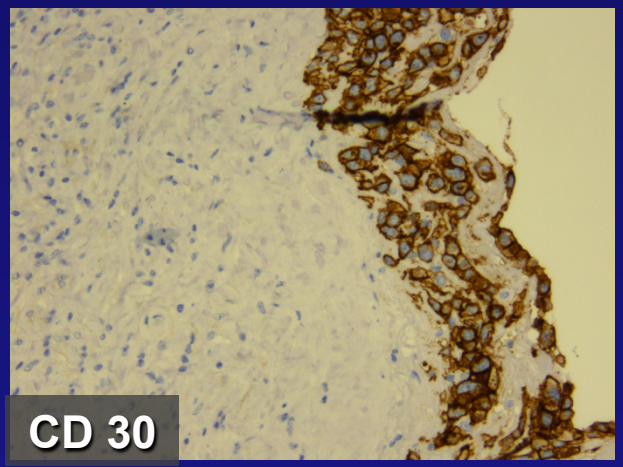
Thompson et al. 2010. Hematologica

Without tumor mass/Effusion-associated





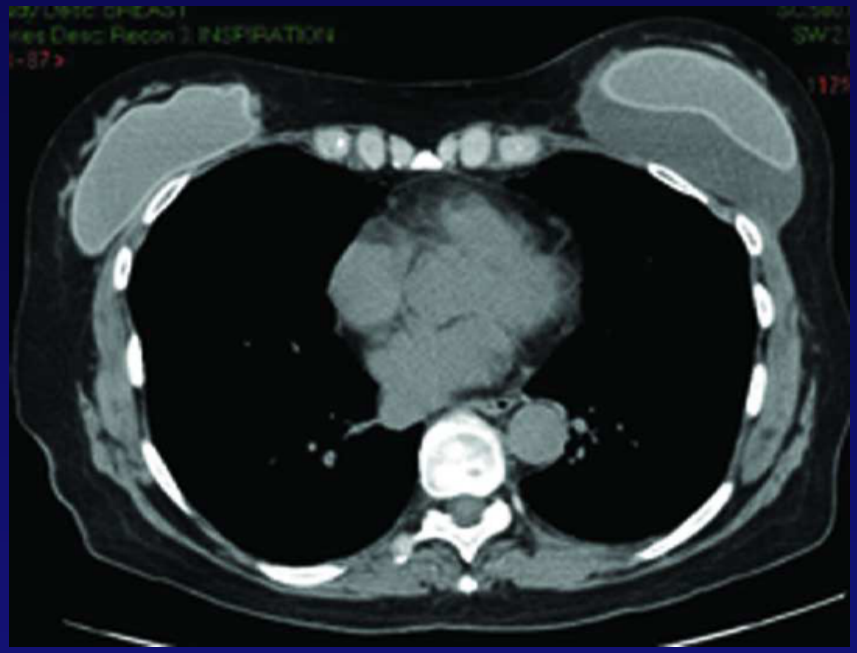


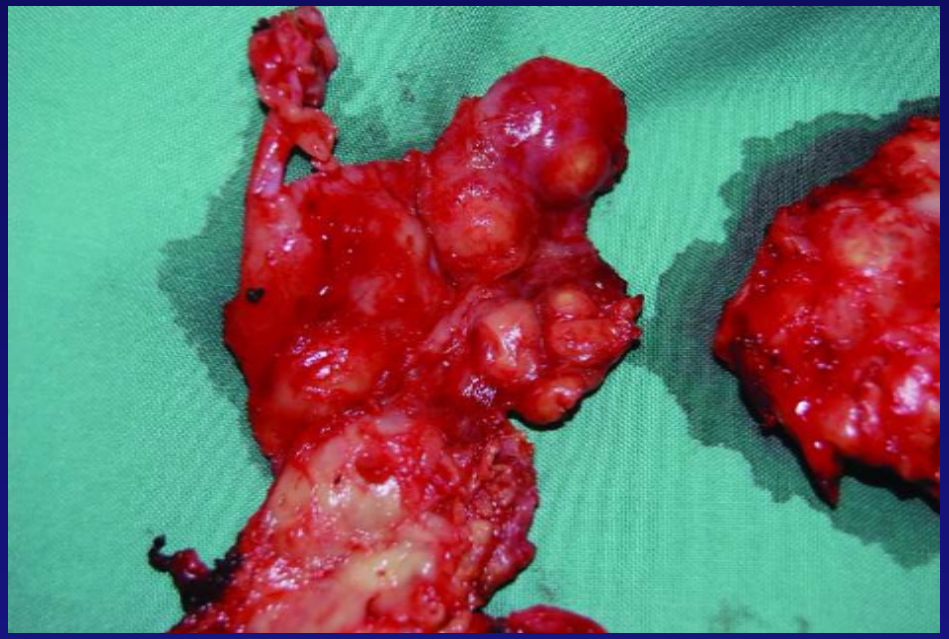


CD3 neg, EMA pos, Alk neg

Thompson et al. 2010. Hematologica

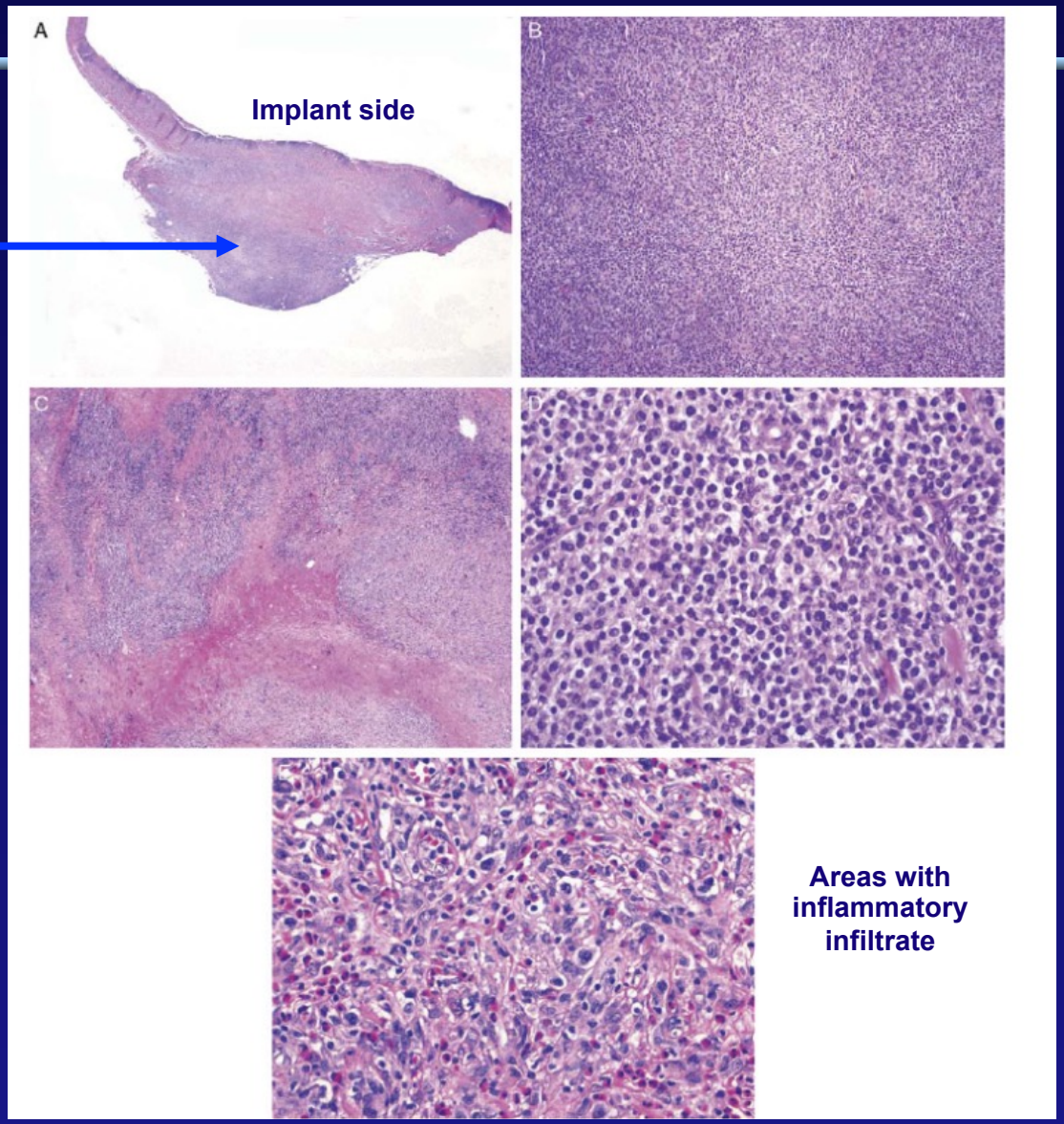
With tumor mass





With tumor mass

Diffuse Growth Pattern



Infiltrating soft tissue

Necrosis and sclerosis

Areas with inflammatory infiltrate

Immunophenotype

Anaplastic Large Cell Lymphoma Associated With Breast Implants: A Report of 13 Cases

Tariq N. Aladily, MD, L. Jeffrey Medeiros, MD,* Mitual B. Amin, MD,† Nisreen Haideri, MD,‡ Dongjiu Ye, MD,§ Sergio J. Azevedo, MD,‖ Jeffrey L. Jorgensen, MD, PhD,* Mariza de Peralta-Venturina, MD,¶ Eid B. Mustafa, MD,# Ken H. Young, MD, PhD,* M. James You, MD, PhD,* Luis E. Fayad, MD,** Ann Marie Blenc, MD,† and Roberto N. Miranda, MD**

TABLE 2. Immunophenotype and Molecular Findings in 13 Cases of ALCL Associated With Breast Implants

Case	CD45	CD3	CD43	CD4	CD8	CD5	CD2	CD7	EMA	CD30	CD15	ALK	TIA-1	Granzyme B	TCR
Group 1: patients who presented with effusion around the implant															
1	–	–	+	+	–	–	ND	ND	–	+	+	–	–	–	Monoclonal; biallelic
2	–	+	–	+	–	+	–	ND	–	+	–	–	+	–	ND
3	+	+	+	–	–	–	ND	–	–	+	+	–	+	+	ND
4	–	–	–	+	–	–	ND	–	ND	+	–	–	+	ND	Monoclonal
5	+	–	+	+	–	–	ND	ND	–	+	–	–	–	–	Monoclonal
6	+	–	–	–	ND	+	–	ND	–	+	–	–	–	–	Monoclonal
7	–	–	+	ND	ND	–	ND	ND	+	+	–	–	–	–	ND
8	–	–	+	+	ND	–	ND	ND	+	+	–	–	–	–	Monoclonal
9	–	–	+	+	–	–	+	–	ND	+	–	–	+	ND	ND
10	ND	–	+	+	–	–	–	–	+	+	–	–	+	+	ND
Group 2: patients who presented with a tumor mass and effusion															
11	ND	+	+	ND	ND	ND	ND	ND	ND	+	–	–	+	+	Monoclonal; biallelic
12	–	+	+	+	–	–	+	–	–	+	–	–	–	–	Monoclonal
13	+	–	+	+	–	–	–	ND	+	+	–	–	–	+	ND
Total (%)	4/11 (36%)	4/13 (31%)	10/13 (77%)	9/11 (82%)	0/9	2/12 (17%)	2/6 (33%)	0/5	4/10 (40%)	13/13 (100%)	2/13 (15%)	0/13	5/13 (38%)	4/11 (36%)	7/7 (100%)

(–) indicates negative; (+), positive; EMA, epithelial membrane antigen; ND, not done; TCR, T-cell receptor γ-chain gene rearrangement by polymerase chain reaction; TIA-1, T-cell intracellular antigen-1.

Biology: proven malignant capacity

Breast Implant-Associated, ALK-Negative, T-Cell, Anaplastic, Large-Cell Lymphoma: Establishment and Characterization of a Model Cell Line (TLBR-1) for This Newly Emerging Clinical Entity

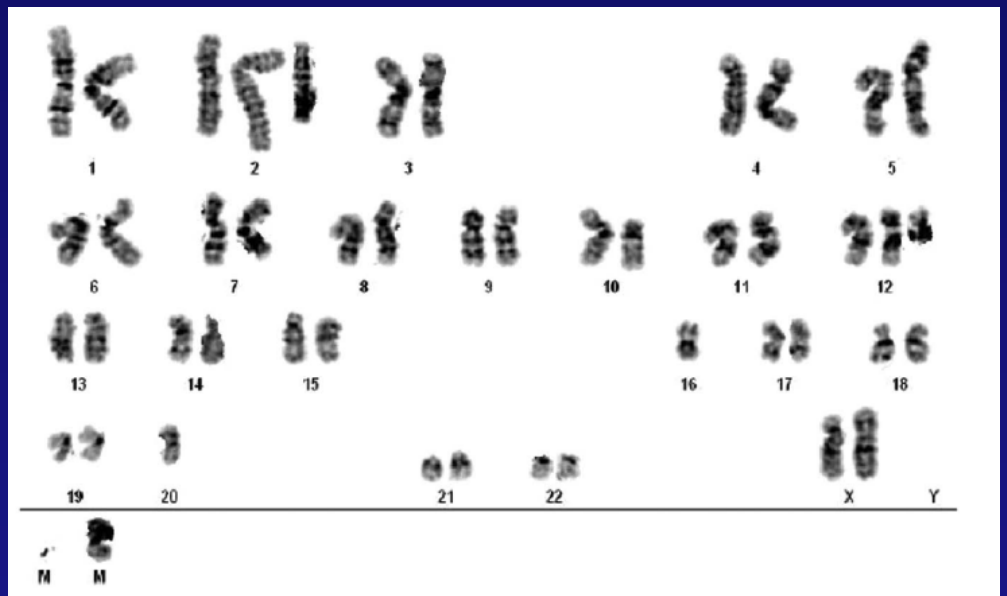
Melissa G. Lechner, BA[1]; Stephen Lade, MD[2]; Daniel J. Liebertz, MD[1]; H. Miles Prince, MD[2]; Garry S. Brody, MD[3]; Howard R. Webster, MD[4]; and Alan L. Epstein, MD, PhD[1]

BACKGROUND: Primary lymphomas of the breast are very rare (0.2-1.5% of breast malignancies) and the vast majority (95%) are of B-cell origin. Recently, 40 cases of clinically indolent anaplastic large-cell kinase (ALK)-negative, T-cell, anaplastic, non-Hodgkin lymphomas (T-ALCL) have been reported worldwide. **METHODS:** A tumor biopsy specimen from a patient in this series was obtained for characterization. By using a human stromal feeder layer and IL-2, a novel cell line, TLBR-1, was established from this biopsy and investigated by using cytogenetics and various biomolecular methods. **RESULTS:** Immunoperoxidase staining of the tumor biopsy showed a CD30/CD8/CD4 coexpressing T-cell population that was epithelial membrane antigen (EMA)$^+$ and perforin$^+$. Multiplex polymerase chain reaction (PCR) of TCRγ genes showed monoclonality that suggested a T-cell origin, yet pan-T markers CD2/5/7, anaplastic large-cell kinase (ALK)-1, pancytokeratins, CD20, CD56, and Epstein-Barr virus (EBV) by in situ hybridization (ISH) were negative. TLBR-1 is IL-2 dependent, has a relatively long doubling time (55 hours), and displays different cellular shapes in culture. Cytogenetic analysis of tumor and TLBR-1 cells confirmed a highly anaplastic cell population with a modal number of 47 chromosomes lacking t(2;5). PCR screens for EBV and human T-lymphotropic virus types 1 and 2 (HTLV-1/2) were negative. Fluorescence-activated cell-sorting (FACS) analysis showed strong positivity for CD4/8, CD30, CD71, and CD26 expression, and antigen presentation (HLA-DR$^+$CD80$^+$CD86$^+$), IL-2 signaling (CD25$^+$CD122$^+$), and NK (CD56$^+$) markers, and Western blots demonstrated strong Notch1 expression. Severe combined immunodeficiency (SCID) mouse TLBR-1 heterotransplants recapitulated the histology and marker characteristics of the original tumor. **CONCLUSIONS:** TLBR-1, a novel ALK-negative, T-cell, anaplastic, large-cell lymphoma, closely resembles the original biopsy and represents an important tool for studying this newly recognized disease entity. ***Cancer* 2011;117:1478–89.**

Biology: proven malignant capacity

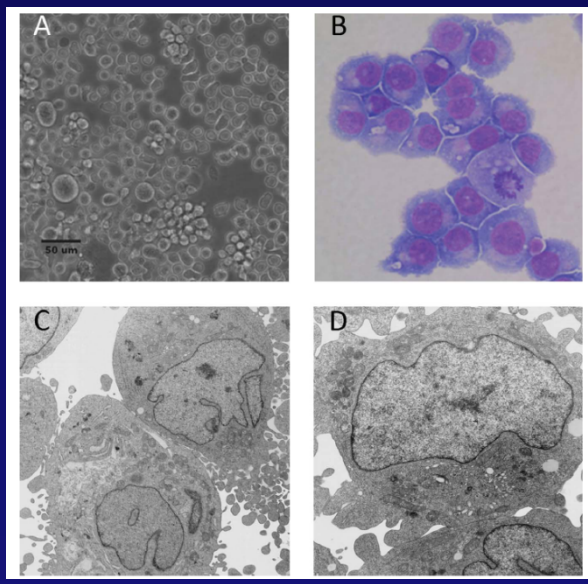
Table 2. Comparison of Patient Tumor and TLBR-1 Cell Line to Primary Systemic, Primary Cutaneous, and Seroma-Associated ALCLs

	Primary Systemic ALCL	Primary Cutaneous ALCL	Seroma-Associated ALCL	Primary Tumor Specimen	TLBR-1 Cell Line & SCID Heterotransplant
CD30	+	+	+	+	+
TCRγ monoclonality	+	+	+	+	+
ALK	+ (60-80%)	- (Rarely +)	- (Rarely +)	-	-
t(2;5)	+ (60-80%)	-	-	-	-
EMA	+	-	+	+	Weak
Clinical course	Aggressive	Indolent	Indolent	Indolent	NA



48,XX,+add(2)(q21),dup(2)(q31q35),add(5)(p13),del(10)(p11.2p13),+der(?12)t(12;17)(q13;q21),-16,-20,+mar1-2[5]

Figure 5. Karyotype of TLBR-1. The TLBR-1 stemline population demonstrated partial trisomy 2, deletion of 10p, an unbalanced translocation between chromosomes 12 and 17, and monosomy 16 and 20. Three clonal subpopulations showed additional abnormalities in the form of the addition of unknown genetic material to the short arms of chromosomes 16, 15, and 13 (data not shown).



LAB#: G092361

DATE COLLECTED 02/06/2009
DATE RECEIVED 02/06/2009

CLINICAL NOTES
Lymphoma Arising Around Breast Implant (In Effusion)

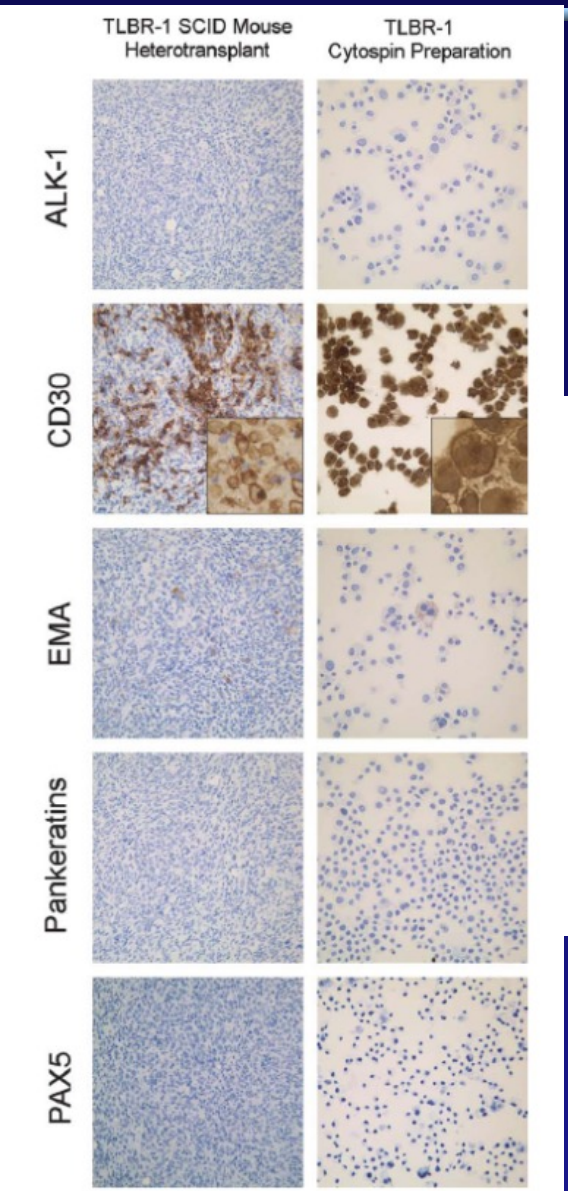
SPECIMEN
Fluid

CULTURE TYPE
Overnight 72hr Stim(TPA/PHA)

ANALYSIS
G-Banding
Cells fully analysed: 15
Total cells examined: 15
Chromosome Band Resolution: 250 (Average)

KARYOTYPE:
49,XX,+2,add(2)(q?33),del(2)(q?31),add(5)(p13),del(10)(p11.2),
add(16)(p11.2),-20,+21,idic(21)(p11.2),+mar1,+mar2[12]/
86-95,idemx2[cp3]

Biology: proven malignant capacity



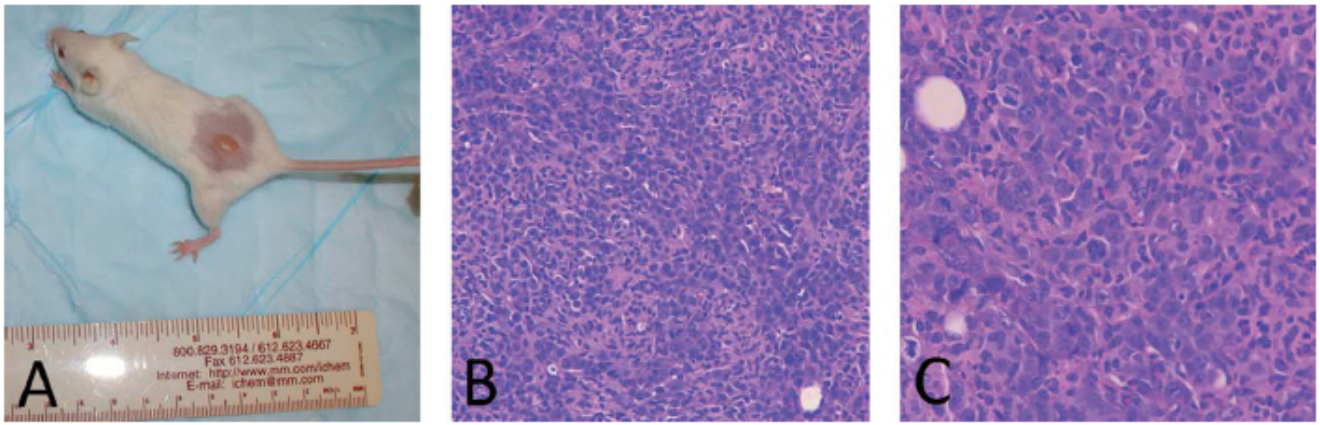


Figure 3. Heterotransplantation of TLBR-1 cell line. (A) Appearance of subcutaneous TLBR-1 tumor in SCID mouse. (B and C) Low and high magnification of TLBR-1 SCID tumor demonstrating similar morphological features to the original biopsy (hematoxylin and eosin [H&E] stain ×200 and ×400 original magnification).

2011: FDA recognizes risk

U.S. Department of Health & Human Services

U.S. Food and Drug Administration
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- Implants and Prosthetics
- Breast Implants
- Regulatory History of Breast Implants in the U.S.
- Saline-Filled Breast Implants
- Silicone Gel-Filled Breast Implants
- Labeling for Approved Breast Implants
- Breast Implant Surgery
- Risks of Breast Implants
- Breast Implant Complications Booklet
- Anaplastic Large Cell Lymphoma (ALCL)
- Other Resources

Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses

January 2011

PDF Printer Version

Center for Devices and Radiological Health
U.S. Food and Drug Administration

Table of Contents

Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses

Executive Summary

Reports in the scientific community have suggested a possible association between anaplastic large cell lymphoma (ALCL) and breast implants. In this document we summarize the scientific data the FDA used to assess the possible association. It represents our current understanding, based on the published scientific literature on ALCL in women with breast implants and information gathered through the FDA's contact with other regulatory authorities, scientific experts, and breast implant manufacturers. The document includes the FDA's analyses of the data and steps we plan to take to better understand and characterize the possible association.

Although ALCL is extremely rare, the FDA believes that women with breast implants may have a very small but increased risk of developing this disease in the scar capsule adjacent to the implant. Based on available information, it is not possible to confirm with statistical certainty that breast implants cause ALCL. At this time, data appear to indicate that the incidence of ALCL is very low, even in breast implant patients. Currently it is not possible to identify a type of implant (silicone versus saline) or a reason for implant (reconstruction versus aesthetic augmentation) associated with a smaller or greater risk.

The FDA is interested in learning more about the actual incidence of ALCL in women with breast implants, the characteristics of breast implants that might increase the risk of ALCL, and the pathological characteristics and clinical features of ALCL in women with breast implants. To this end, FDA is collaborating with the American Society of Plastic Surgeons to establish a registry of cases of women with breast implants who have been diagnosed with ALCL.

Health care providers should be aware ALCL in women with breast implants is a very rare condition; when it occurs, it has been identified most frequently in patients undergoing implant revision operations for late onset, persistent seroma. The FDA does not recommend prophylactic breast implant removal in patients without symptoms or other abnormalities. Current recommendations are described below. As we learn more about ALCL in women with breast implants, these recommendations may change.

- Consider the possibility of ALCL when you have a patient with late onset, persistent peri-implant seroma. In some cases, patients presented with capsular contracture or masses adjacent to the breast implant. If you have a patient with suspected ALCL, refer her to an appropriate specialist for evaluation. When testing for ALCL, collect fresh seroma fluid and representative portions of the capsule and send for pathology tests to rule out ALCL. Diagnostic evaluation should include cytological evaluation of seroma fluid with Wright Giemsa stained smears and cell block immunohistochemistry testing for cluster of differentiation (CD) and Anaplastic Lymphoma Kinase (ALK) markers.
- Report all confirmed cases of ALCL in women with breast implants to the FDA. In some cases, the FDA

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Internet | 100%

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm

FDA assessment (34 cases detailed) Total n=60

Table 1. Characteristics of 34 Unique Cases of ALCL in Women with Breast Implants		
Age (years)	Median	51
	Range	28-87
	No age specified	8
Type of Implant	Silicone	24
	Saline	7
	No implant type specified	3
Texture of Implant	Textured	4
	Smooth	0
	No surface texture specified	30
Time from Implant to ALCL Diagnosis (years)	Median	8
	Range	1-23
	No time to diagnosis specified	11
Reason for Implant	Reconstruction	11
	Augmentation	19
	No reason specified	4

- There is a possible association between breast implants and ALCL
- At this time, it is not possible to identify a specific type of implant associated with a lower or higher risk of ALCL
- There is uncertainly about the true cause of ALCL in women with breast implants

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm

Published Reviews: Miranda et al. N=60

VOLUME 32 · NUMBER 2 · JANUARY 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast Implant–Associated Anaplastic Large-Cell Lymphoma: Long-Term Follow-Up of 60 Patients

Roberto N. Miranda, Tariq N. Aladily, H. Miles Prince, Rashmi Kanagal-Shamanna, Daphne de Jong, Luis E. Fayad, Mitual B. Amin, Nisreen Haideri, Govind Bhagat, Glen S. Brooks, David A. Shifrin, Dennis P. O'Malley, Chan Y. Cheah, Carlos E. Bacchi, Gabriela Gualco, Shiyong Li, John A. Keech Jr, Ephram P. Hochberg, Matthew J. Carty, Summer E. Hanson, Eid Mustafa, Steven Sanchez, John T. Manning Jr, Zijun Y. Xu-Monette, Alonso R. Miranda, Patricia Fox, Roland L. Bassett, Jorge J. Castillo, Brady E. Beltran, Jan Paul de Boer, Zaher Chakhachiro, Dongjiu Ye, Douglas Clark, Ken H. Young, and L. Jeffrey Medeiros

Patients and Methods

We reviewed the literature for all published cases of breast implant–associated ALCL from 1997 to December 2012 and contacted corresponding authors to update clinical follow-up.

Conclusion

Most patients with breast implant–associated ALCL who had disease confined within the fibrous capsule achieved complete remission. Proper management for these patients may be limited to capsulectomy and implant removal. Patients who present with a mass have a more aggressive clinical course that may be fatal, justifying cytotoxic chemotherapy in addition to removal of implants.

Table 1. Breast Implant–Associated ALCL (1997-2012): Clinicopathologic Features of 60 Patients

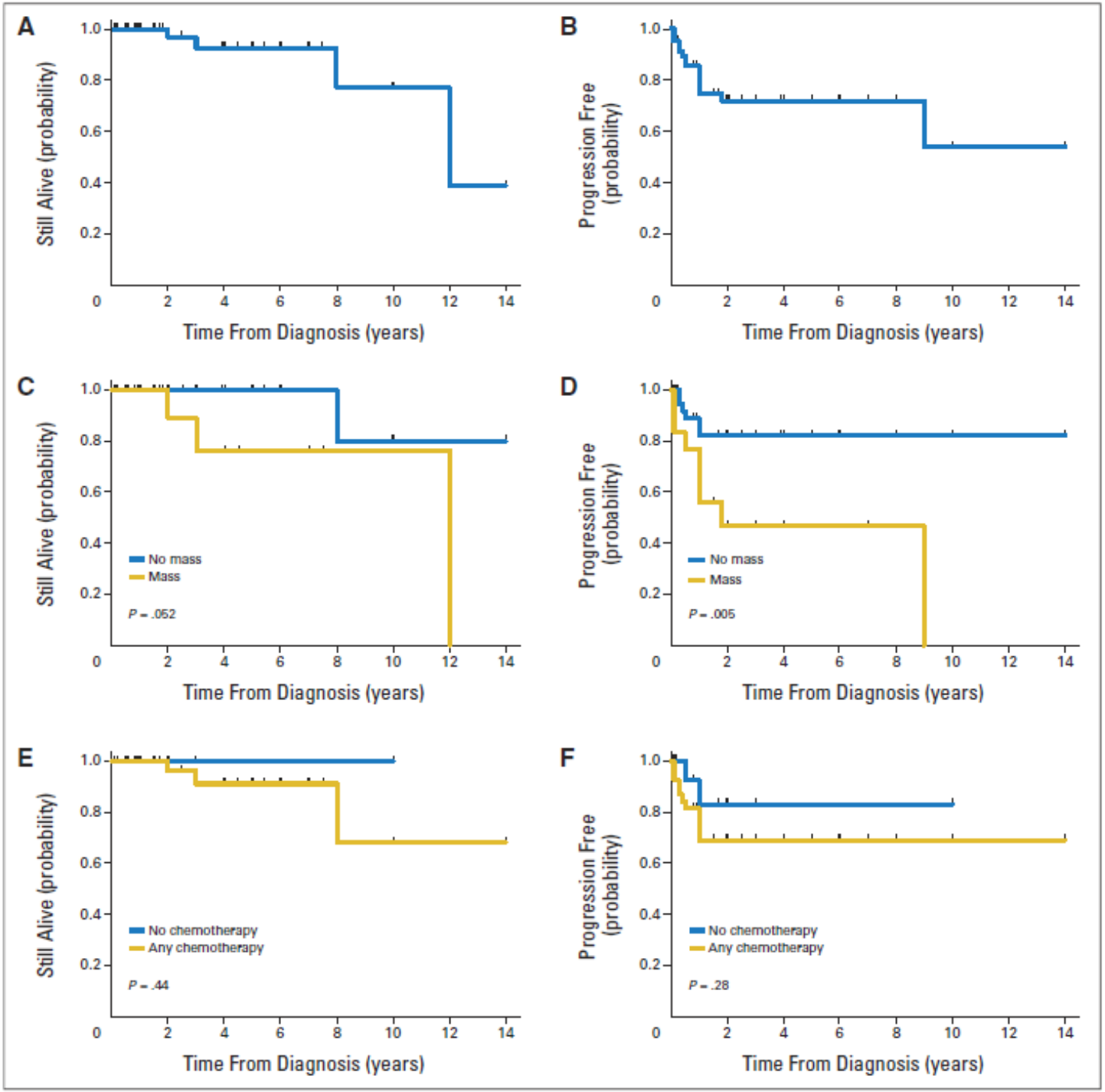
Clinical Features	No.	%
Age, years		
Median		52
Range		28-87
Side		
Right	31	
Left	20	
Bilateral	1	
Reason for implants		
Cosmetic	34	
Breast cancer	26	
Stage I	5	
Stage II	3	
Stage III	1	
Carcinoma in situ	6	
Stage, NA	11	
Therapy for breast cancer		
Surgical approach	22	
Radical mastectomy	9	
Mastectomy	8	
Lumpectomy	2	
NA	4	
Chemotherapy or radiation		
Yes	15	
No	5	
NA	6	
Type of implant	51	
Silicone	23	
Saline	28	
Texture of implant		
Textured	21	
NA	39	
Interval to lymphoma diagnosis, years	59	
Median		9
Mean		10.9
Range		1-32
Clinical presentation		
Effusion	42	
Mass	18	
Tumor size, cm	9	
Mean		3.2
Median		2
Range		0.5-10
Not specified	3	
NA	6	
Axillary lymphadenopathy	29	
Yes	10	34
Positive	6	
Negative	4	
No	19	66
Stage of disease at presentation	59	
I	49	83
II	6	10
IV	4	7
NA	1	

Mass vs.

No-mass

chemoRx vs.

No-chemoRx



Epidemiology: Dutch Study 2008

OR = 18.25

(95%CI: 2.1 – 156.8)

5 cases of ALCL associated with implants

Anaplastic Large-Cell Lymphoma in Women With Breast Implants

Daphne de Jong, MD, PhD
Wies L. E. Vasmel, MD, PhD
Jan Paul de Boer, MD, PhD
Gideon Verhave, MD
Ellis Barbé, MD
Mariel K. Casparie, MD, PhD
Flora E. van Leeuwen, PhD

Context Recently, we identified 2 patients with anaplastic large T-cell lymphoma (ALCL) negative for tyrosine kinase anaplastic lymphoma kinase (ALK-negative) in the fibrous capsule of silicone breast prostheses, placed for cosmetic reasons. Similar cases have been reported in the literature. Although an increased risk of ALCL in patients with breast prostheses has been speculated, no studies have been conducted so far.

Objective To determine whether ALCL risk is associated with breast prostheses.

Design A search for all patients with lymphoma in the breast diagnosed in the Netherlands between 1990 and 2006 was performed through the population-based nationwide pathology database. Subsequently, we performed an individually matched case-control study. Conditional logistic regression analysis was performed to estimate the relative risk of ALCL associated with breast prostheses.

Setting and Patients Eleven patients with breast ALCL were identified in the registry. For each case patient with ALCL in the breast, we selected 1 to 5 controls with other lymphomas in the breast, matched on age and year of diagnosis. For all cases and controls (n=35), pathological and clinical information was obtained with special emphasis on the presence of a breast prosthesis.

Main Outcome Measure Association between breast implants and ALCL of the breast.

Results The 11 patients with ALCL of the breast were diagnosed between 1994 and 2006 at a median age of 40 years (range, 24-68 years). In 5 of these patients, bilateral silicone breast prostheses had been placed 1 to 23 years before diagnosis. All received prostheses for cosmetic reasons. Lymphoma classes of 35 eligible control patients were 12 diffuse large B-cell lymphomas, including 1 T-cell rich B-cell lymphoma; 5 Burkitt lymphomas; 10 mucosa-associated lymphoid tissue–type lymphoma; 3 follicular lymphomas; 3 peripheral T-cell lymphomas; and 2 indolent B-cell lymphomas, unclassified. One of 35 control patients had a breast implant placed before diagnosis of lymphoma. The odds ratio for ALCL associated with breast prostheses was 18.2 (95% confidence interval, 2.1-156.8).

Conclusions These preliminary findings suggest an association between silicone breast prostheses and ALCL, although the absolute risk is exceedingly low due to the rare occurrence of ALCL of the breast (11 cases in the Netherlands in 17 years). These findings require confirmation in other studies.

JAMA. 2008;300(17):2030-2035 www.jama.com

SINCE THE LATE 1970S, SILICONE breast implants have been under constant challenge for suspected association with systemic disease and malignancy.[1-4] Although no health risk had been proven, the use of silicone-filled breast implants was banned by the US Food and Drug Administration in 1992. Saline-filled, silicone-covered implants stayed on the market. Also with these implants, contracture and rupture are frequent events, and interference with breast cancer detection may be a problem. Large observational epidemiological studies in populations in Canada and Sweden have not shown consistent associations with breast cancer or other specific cancer sites or with autoimmune disease.[5,6]

Several cases of non-Hodgkin lymphoma in women with breast implants have been described. Of these,

OR = 18.25

(95%CI: 2.1 – 156.8)

Implant Type?

Table 1. Clinical Information on 11 Patients With Anaplastic Large T-cell Lymphoma With Dominant Breast Involvement (5 Patients With a Breast Implant)

Patient	Age at Diagnosis, y	Year of Diagnosis	Stage	Breast Involvement	Other Involved Sites	Breast Implant		
						Placement, y	Removal or Replacement, y	Prosthesis Type
1	41	1997	II	Left	Left subscapular lymph node			
2	38	1994	I	Left				
3	61	2006	IV	Bilateral	Left axillary and supraclavicular lymph nodes, bilateral inguinal lymph nodes, lung			
4	31	2002	I	Right				
5	68	1998	I	Right				
6	53	2001	I	Left		2000		Rofil PIP Hydrogel
7	49	2000	II	Bilateral		1977	1988, 1995, 1998 Bilateral replacement	Textured silicone McGhan
8	43	2005	IV	Right	Right infraclavicular lymph node, right skull base	1992	2007 Removal of left side implant	Textured silicone McGhan
9	29	1999	II	Right	Right axillary lymph node	1996		Textured silicone Nagor R
10	38	1997	I	Right		1984	1994 Bilateral replacement	Unknown
11	24	1996	IV	Bilateral	Left axillary, mediastinal and upper abdominal lymph nodes, lung			

Table 2. Clinical Information on 35 Patients With Non-Hodgkin Lymphoma Other Than Anaplastic Large T-cell Lymphoma With Dominant Breast Involvement

Matched Control to Case	Age at Diagnosis, y	Year of Diagnosis	Diagnosis	Stage	Breast Localization	Other Involved Sites	Previous Malignancies	Placement of Breast Implant and Type
1	44	1996	MALT	IE	Left			
1	39	1999	DLBCL	IE	Left			
1	43	1998	Follicular lymphoma	IV	Right	Mediastinal and abdominal lymph nodes, bone marrow		1984, textured silicone McGhan
2	36	1992	DLBCL	IE	Left		Unknown	
3	61	2004	Follicular lymphoma	IIE	Left			
3	62	2004	DLBCL	IIE	Right	Right axillary lymph node	Cervical carcinoma in 1988, lung cancer, NSCLC in 2003	
4	31	2003	Burkitt lymphoma	IE	Right		Unknown	
4	32	2002	Burkitt lymphoma	IIE	Bilateral	Cervical lymph nodes		
4	28	2003	DLBCL	IE	Right			
5	68	1998	DLBCL	IE	Left			
5	66	1997	TCRBCL	IIIA	Right	Unknown		
5	69	1997	MALT	IE	Left			
5	70	1997	MALT	IE	Left		Pancreatic carcinoma in 1990	
5	70	1997	Indolent B-NHL	IE	Left			
6	55	2001	DLBCL	IIIE	Right	Right axillary and para-aortal lymph nodes	Unknown	
6	54	2002	MALT	IIE	Left	Skin	Unknown	
6	55	2000	MALT	IE	Right		Unknown	
6	55	2000	DLBCL	IE	Left			
6	55	2000	MALT	IIIE	Right	Abdominal lymph nodes		
7	51	1999	MALT	IE	Left			
7	50	1998	DLBCL	IE	Right		Unknown	
7	48	1998	DLBCL	IE	Right			
7	50	1998	Burkitt lymphoma	IE	Right			
8	42	2001	Indolent B-NHL	IIIE	Left	Iliac lymph nodes, soft tissue abdominal wall		
8	41	2003	MALT	IE	Left			
8	38	2003	Follicular lymphoma	IV	Bilateral	Bilateral axillary and inguinal lymph nodes, bone marrow		
9	33	1999	MALT	IE	Right			
9	26	1999	PTCL	IVB	Bilateral	Generalized lymph adenopathy		
9	32	1997	Burkitt lymphoma	IV	Right	Ovaria, cecum	Unknown	
10	34	1995	DLBCL	IE	Left			
10	37	1999	DLBCL	IIE	Right	Mediastinal lymph nodes		
10	38	1995	Burkitt lymphoma	IV	Left	Stomach, cerebro-spinal fluid		
10	39	1995	MALT	IE	Left			
11	24	1997	PTCL	IIIE	Left	Mediastinal and abdominal lymph nodes	Pituitary adenoma in 1986	
11	25	1994	PTCL	IE	Right			

Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; NSCLC, non-small-cell lung cancer; PTCL, peripheral T-cell lymphoma; TCRBCL, T-cell rich B-cell lymphoma.

Anaplastic Large Cell Lymphoma Occurring in Women with Breast Implants: Analysis of 173 Cases

Garry S. Brody, M.D., M.Sc.
Dennis Deapen, Dr.Ph.
Clive R. Taylor, M.D., D.Phil.
Lauren Pinter-Brown, M.D.
Sarah Rose House-Lightner, B.A.
James S. Andersen, M.D.
Grant Carlson, M.D.
Melissa G. Lechner, Ph.D.
Alan L. Epstein, M.D., Ph.D.

Los Angeles and Duarte, Calif.; Atlanta, Ga.; and Boston, Mass.

Background: The first silicone breast implant was inserted in 1962. In 1997, the first case of anaplastic large cell lymphoma (ALCL) in association with a silicone breast implant was reported. The authors reviewed 37 articles in the world literature reporting on 79 patients and collected another 94 unreported cases as of the date of submission.

Methods: The world literature was reviewed. Missing clinical and laboratory information was solicited from the authors and treating physicians. As several different specialties were involved, information was not in one place. Many (but not all) authors and treating physicians were responsive, resulting in incomplete data.

Results: ALCL lesions first presented as late peri-implant seromas, a mass attached to the capsule, tumor erosion through the skin, in a regional node, or discovered during revision surgery. The clinical course varied widely from a single positive cytology result followed by apparent spontaneous resolution, to disseminated treatment-resistant tumor and death. There was no preference for saline or silicone fill or for cosmetic or reconstructive indications. Where implant history was known, the patient had received at least one textured-surface device. Extracapsular dissemination occurred in 18 cases; nine of those were fatal. Histochemical markers were primarily CD-30^{+} and Alk-1^{-}. Other markers occurred at a lower frequency. Risk estimates ranged from one in 500,000 to one in 3 million women with implants.

Conclusion: Breast implant–associated ALCL is a novel manifestation of site- and material-specific lymphoma originating in a specific scar location, presenting a wide array of diverse characteristics and suggesting a multifactorial cause. (*Plast. Reconstr. Surg.* 135: 695, 2015.)

Brody et al. Plast Reconstr Surg

2015; 135: 695

- **79 reported + 94 unreported (personal communication)**
- **no denominator**
  - **Double reporting?**
  - **USA and other**
- **Limited demographic data**
- **Pathology not confirmed**
- **Confirms that at least 150+ cases exist**

Table 1. ALCL Demographics and Numerical Data (where known)

Country	Company	Implant Fill	Presentation	Indication	Side
United States, 112	Allergan*, 97	Saline, 48	Seroma, 104	Cosmetic, 75	Left, 52
Australia, 20	Mentor, 3	Silicone, 61	Mass, 11	Reconstruction, 62	Right, 89
France, 9	Mentor and Allergan, 3	Polyurethane, 4	Seroma and mass, 11		Bilateral, 5
Canada, 5	Sientra, 1		Skin erosion, 3		Reconstruction, tumor side, 57
Holland, 5	PIP†, 5	Axillary notes, 8			Reconstruction, opposite side, 5
Britain, 9	Nagor, 3	At surgery, 6			
Brazil, 4		Disseminated, 10			
New Zealand, 3					
Iran, 2					
Italy, 2					
Israel, 1					
Denmark, 1					

Brody et al. Plast Reconstr Surg 2015; 135: 695

Cancer Epidemiology, Biomarkers & Prevention

Null Results in Brief

Breast Implants and Anaplastic Large-Cell Lymphoma: A Danish Population-Based Cohort Study

Maja Ølholm Vase[1], Søren Friis[4], Andrea Bautz[4], Knud Bendix[2], Henrik Toft Sørensen[3], and Francesco d'Amore[1]

Abstract

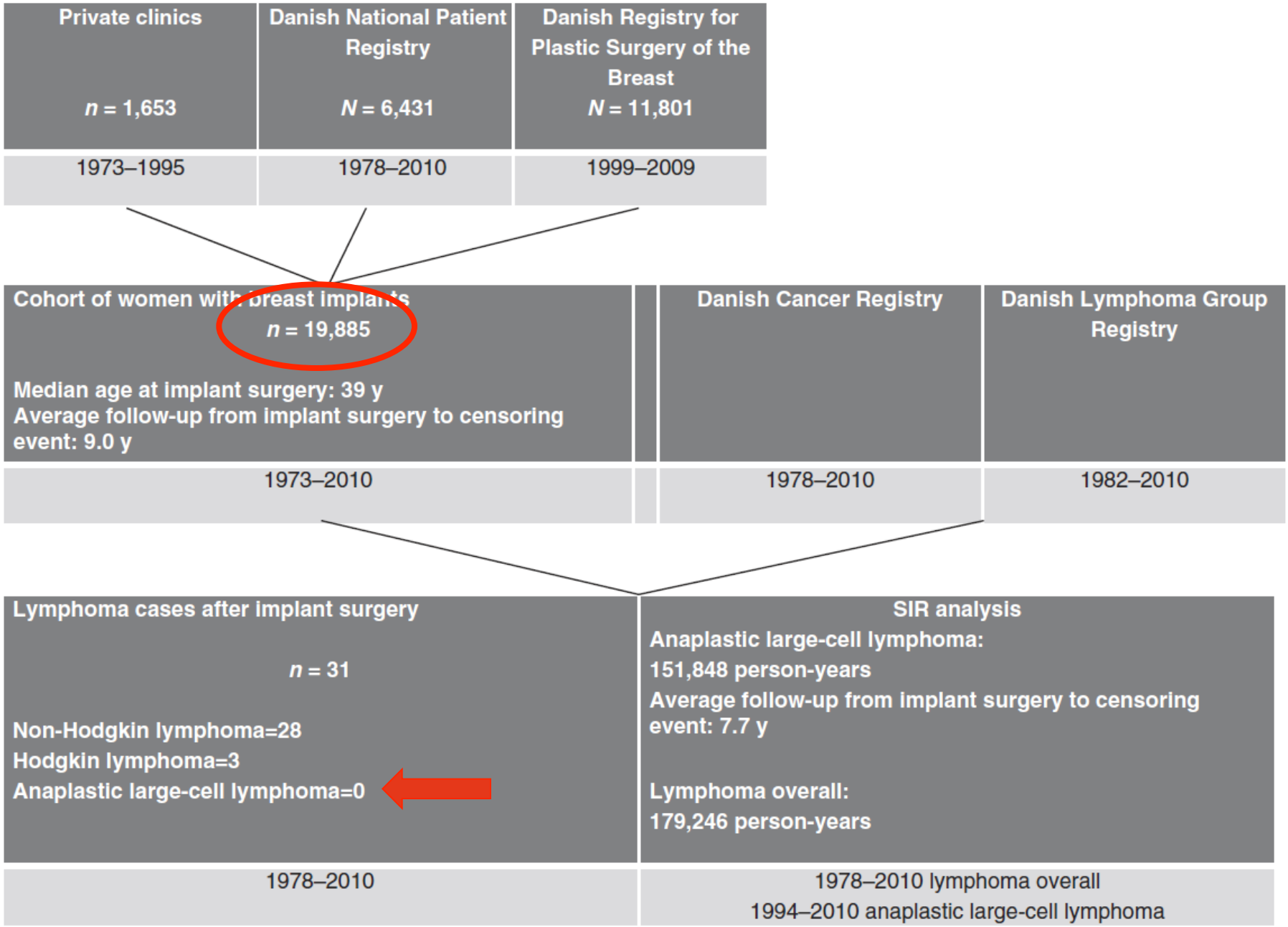
Background: A potential link between breast implants and anaplastic large-cell lymphoma (ALCL) has been suggested.

Methods: We examined lymphoma occurrence in a nationwide cohort of 19,885 Danish women who underwent breast implant surgery during 1973–2010. Standardized incidence ratios (SIR), with 95% confidence intervals (CI), for ALCL and lymphoma overall associated with breast implantation were calculated.

Results: During 179,246 person-years of follow-up, we observed 31 cases of lymphoma among cohort members. No cases of ALCL were identified. SIRs for ALCL and lymphoma overall were zero (95% CI, 0–10.3) and 1.20 (95% CI, 0.82–1.70), respectively.

Conclusions: In our nationwide cohort study, we did not find an increased risk of lymphoma in general, or ALCL in particular, among Danish women who underwent breast implantation. However, our evaluation of ALCL risk was limited by the rarity of the disease.

Impact: Our results do not support an association between breast implants and ALCL and are consistent with other studies on cancer risk and breast implants. *Cancer Epidemiol Biomarkers Prev; 22(11); 2126–9. ©2013 AACR.*


Private clinics
n = 1,653
Danish National Patient Registry
N = 6,431
Danish Registry for Plastic Surgery of the Breast
N = 11,801
1973–1995
1978–2010
1999–2009
Cohort of women with breast implants
n = 19,885
Median age at implant surgery: 39 y
Average follow-up from implant surgery to censoring event: 9.0 y
Danish Cancer Registry
Danish Lymphoma Group Registry
1973–2010
1978–2010
1982–2010
Lymphoma cases after implant surgery
n = 31
Non-Hodgkin lymphoma=28
Hodgkin lymphoma=3
Anaplastic large-cell lymphoma=0
SIR analysis
Anaplastic large-cell lymphoma:
151,848 person-years
Average follow-up from implant surgery to censoring event: 7.7 y
Lymphoma overall:
179,246 person-years
1978–2010
1978–2010 lymphoma overall
1994–2010 anaplastic large-cell lymphoma

Breast Implant–associated Anaplastic Large Cell Lymphoma: Updated Results from a Structured Expert Consultation Process

Benjamin Kim, MD, MPhil*†
Zachary S. Predmore, BA*
Soeren Mattke, MD, DSc*
Kristin van Busum, MPA*
Courtney A. Gidengil, MD, MPH*‡

Background: Despite increased cases published on breast implant–associated anaplastic large cell lymphoma (BIA-ALCL), important clinical issues remain unanswered. We conducted a second structured expert consultation process to rate statements related to the diagnosis, management, and surveillance of this disease, based on their interpretation of published evidence.
Methods: A multidisciplinary panel of 12 experts was selected based on nominations from national specialty societies, academic department heads, and recognized researchers in the United States.
Results: Panelists agreed that (1) this disease should be called "BIA-ALCL"; (2) late seromas occurring >1 year after breast implantation should be evaluated via ultrasound, and if a seroma is present, the fluid should be aspirated and sent for culture, cytology, flow cytometry, and cell block to an experienced hematopathologist; (3) surgical removal of the affected implant and capsule (as completely as possible) should occur, which is sufficient to eradicate capsule-confined BIA-ALCL; (4) surveillance should consist of clinical follow-up at least every 6 months for at least 5 years and breast ultrasound yearly for at least 2 years; and (5) BIA-ALCL is generally a biologically indolent disease with a good prognosis, unless it extends beyond the capsule and/or presents as a mass. They firmly disagreed with statements that chemotherapy and radiation therapy should be given to all patients with BIA-ALCL.
Conclusions: Our assessment yielded consistent results on a number of key, incompletely addressed issues regarding BIA-ALCL, but additional research is needed to support these statement ratings and enhance our understanding of the biology, treatment, and outcomes associated with this disease. *(Plast Reconstr Surg Glob Open 2015;3:e296; doi: 10.1097/GOX.0000000000000268; Published online 28 January 2015)*

Kim et al. Plast Glob Open 2015; 3e296

Table 1. National Specialty Societies Providing Panel Nominations

Specialty Society	Field of Expertise
National Comprehensive Cancer Network	Oncology (Clinical)
American Association for Cancer Research	Oncology (Research)
American Society of Hematology	Oncology (Hematology)
Leukemia & Lymphoma Society	Oncology (Lymphoma)
Lymphoma Research Foundation	Oncology (Lymphoma)
American Society for Investigative Pathology	Pathology (Experimental)
Society for Hematopathology/European Association for Haematopathology	Pathology (Hematopathology)
American Society of Plastic Surgeons	Surgery (Plastic)
Society of Surgical Oncology	Surgery (Oncology)
American Society of Breast Surgeons	Surgery (Breast)
American Society of Radiation Oncology	Radiation Oncology

Table 2. Affiliations of Structured Expert Panel Members

Institution
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
National Cancer Institute, Bethesda, Md.
Duke University, Durham, N.C.
University of Michigan, Ann Arbor, Mich.
University of Colorado, Aurora, Colo.
University of Nebraska, Omaha, Neb.
M.D. Anderson Cancer Center, Houston, Tex.
University of California San Francisco, San Francisco, Calif.
Stanford University, Palo Alto, Calif.
University of California Los Angeles, Los Angeles, Calif.

	Median									Dispersion
	Disagree			Uncertain			Agree			
Nomenclature										
The best nomenclature for implant-associated ALCL is "Breast Implant-Associated Anaplastic Large Cell Lymphoma."	1	2	3	4	5	6	7	8	9	**0.83**
Risk Factors - Patient										
Patients of certain ethnic backgrounds – such as Scandinavian – are more likely to develop breast implant-associated ALCL than those of other ethnic backgrounds.	1	2	3	4	5	6	7	8	9	**0.67**
Overweight or obese women are more likely to develop breast implant-associated ALCL than women who are normal or underweight.	1.5		3	4	5	6	7	8	9	**0.75**
Patients with certain HLA types are more likely to develop breast implant-associated ALCL than others who do not have such HLA types.	1	2	3	4	5	6	7	8	9	**0.92**
Patients with a history of autoimmune disease (e.g. psoriasis, Sjogren's syndrome, celiac disease) are at higher risk of developing breast implant-associated ALCL than those without a history of autoimmune disease.	1	2	3	4	5	6	7	8	9	**0.50**
Patients with a history of breast cancer are at higher risk of developing breast implant-associated ALCL than patients without a history of breast cancer.	1	2	3	4	5	6	7	8	9	1.33
Patients with a history of lymphoma or lymphoma-related conditions (e.g. mycosis fungoides, Sezary syndrome) are at higher risk of developing breast implant-associated ALCL than patients without a history of lymphoma.	1	2	3	4	5	6	7	8	9	**0.50**
Patients with a history of ALCL in other parts of their body prior to the development of breast implant-associated ALCL have an underlying predisposition to developing ALCL that is triggered by the breast implant.	1	2	3	4	5	6	7	8	9	**0.42**

Kim et al. Plast Glob Open 2015; 3e296

Risk Factors - Implant										
There is a positive correlation between length of time with a breast implant and risk of developing breast implant-associated ALCL.	1	2	3	4	5	6	7	8	9	*2.83*
Any type of breast implant, regardless of cover, surface, fill, or manufacturer, can be associated with the development of breast implant-associated ALCL.	1	2	3	4	5	6	7	8	9	*2.17*
Polyurethane-covered implants increase the risk of breast implant-associated ALCL development more than silicone-covered implants.	1	2	3	4	5	6	7	8	9	1.91
Silicone-filled breast implants are more likely to be associated with breast implant-associated ALCL than saline-filled implants.	1	2	3	4	5	6	7	8	9	1.17
Larger implants are associated with higher risks of breast implant-associated ALCL development than smaller implants.	1	2	3	4	5	6	7	8	9	**0.83**
Rupture or evident leakage of silicone-filled breast implants is more likely to cause breast implant-associated ALCL than implants that are intact without obvious leakage.	1	2	3	4	5	6	7	8	9	**0.33**
Breast implants with textured covers are more likely to be associated with breast implant-associated ALCL than those with smooth covers.	1	2	3	4	5	6	7	8	9	**0.50**

Kim et al. Plast Glob Open 2015; 3e296

Epidemiology: A truly international story

League table of breast implants in 2013

		Procedures/ annum	Female Population (million)	Augmentation rate	ALCL Reported Cases	ALCL Risk over 15 years
1	USA*	313K	158	1:500	112	1:42,000
2	Brazil*	226K	100	1:440	4	1:848,000
3	Mexico*	58K	58	1:1000		
4	Germany*	55K	40	1:730		
5	Colombia*	44K	22.5	1:500		
6	Spain*	38K	23.5	1:620		
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9	Italy*	16K	30	1:1875	2	1:120,000
10	Iran*	11K	40	1:3640	2	1:83,000
	Australia	13K	11	1:850	20	1:10,000
	Denmark	0.7K	2.25	1:3214	0	1:100,000+
	Netherlands	?	9	?	5	

*As reported to The International Society of Aesthetic Plastic Surgery (ISAPS) in 2013

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Issues (1)

- Incidence varies from country to country
  - Under-reporting
  - Reporting bias
  - Numerous countries do not report breast augmentation figures (unknown denominator)
  - WE CAN SAY 150+ CASES HAVE OCCURED – but detailed information is available on only 60 cases (Miranda et al JCO 2014)

Table 1. ALCL Demographics and Numerical Data (where known)

Country	Company	Implant Fill	Presentation	Indication	Side
United States, 112	Allergan*, 97	Saline, 48	Seroma, 104	Cosmetic, 75	Left, 52
Australia, 20	Mentor, 3	Silicone, 61	Mass, 11	Reconstruction, 62	Right, 89
France, 9	Mentor and Allergan, 3	Polyurethane, 4	Seroma and mass, 11		Bilateral, 5
Canada, 5	Sientra, 1		Skin erosion, 3		Reconstruction, tumor side, 57
Holland, 5	PIP†, 5	Axillary notes, 8			Reconstruction, opposite side, 5
Britain, 9	Nagor, 3	At surgery, 6			
Brazil, 4		Disseminated, 10			
New Zealand, 3					
Iran, 2					
Italy, 2					
Israel, 1					
Denmark, 1					

Issues (1)

- Incidence varies from country to country
  - Under-reporting
  - Reporting bias
  - Numerous countries do not report breast augmentation figures (unknown denominator)
- Risk Calculation is variable
  - Risk is reported as anything from **1:800,000 to 1:10,000**
  - A conservative 20 million breast implants have been performed and 150 cases, therefore risk is at least **1:80,000**

	Procedures/ annum	Female Population (million)	Augmentation rate	Reported Cases	Risk over 15 years
USA	313K	158	1:500	112	1:42,000
Brazil	226K	100	1:440	4	1:848,000
Italy	16K	30	1:1875	2	1:120,000
Iran	11K	40	1:3640	2	1:83,000
Australia	13K	11	1:850	20	1:10,000

Issues (2)

- For registries must have at least 100,000 procedures to be meaningful
  - Denmark = 19,885 and no cases
  - Australia unknown (approx 250,000 over last 15 years minimum) and 20 cases

- Variables that may be important?
  - Usually 4 years + post implant – will it increase?
  - Geography - suggests a region/ethnic/HLA? - effect
    - 2 asians only reported
    - 1 Native American
    - 0 African American
    - Relatively few in Sth America
    - Australia/NZ over-represented

Issues (3)

- Both malignant and non-malignant indications
- Textured > non-textured ??
  - Not reported before textured
  - varies from country to country
    - US mostly smooth (70-80%)
    - Europe and Australia mostly textured (70-80%)
  - opinion varies but pendulum is toward textured increasing risk
  - Saline and silicone – varies from country to country

- Aetiology unknown - ? Bacterial biofilm implicated – activates T lymphocytes*

*Hu et al. Plastic and Reconstructive Surgery. 2015 v135; 319-329

SUMMARY

- Breast implants are associated with ALCL of the breast
  - Risk likely at least 1:80,000
    - 1:10,000 in Australia
    - 1: 300,000+ in Brazil?
  - Usually 4 years + post implant
  - Both malignant and non-malignant indications for implant affected
  - Textured > non-textured (probable)
  - Saline and silicone (unknown)
- Consistently CD30pos, Alk neg, TCRpos
- Two types:
  - Mass associated/Tissue: poorer prognosis – more aggressive therapy
  - Non-Mass associated = Effusion-associated
    - E-A is not perfect term as often mass/tissue lesions also have effusion
    - Also called seroma-associated
    - Relatively indolent
    - What is the best Rx? – Capsulectomy (+/- radiotherapy)
    - Similar to primary cutaneous ALCL (Alk neg, indolent, observe, respond to MTX?)
    - Cell line and xenograft model – hopefully give insight

THANK YOU!