Anaplastic Large Cell Lymphoma in the breast in women with breast implants

Citation for published version (APA):

de Boer, M. (2021). *Anaplastic Large Cell Lymphoma in the breast in women with breast implants: a multidisciplinary approach to answer epidemiological, clinical and biological questions*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20211210mb>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20211210mb](https://doi.org/10.26481/dis.20211210mb)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

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Anaplastic Large Cell Lymphoma in the breast in women with breast implants

A multidisciplinary approach to answer epidemiological, clinical and biological questions

Mintsje de Boer

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Cover: Ellen Hansen, idea by Mintsje de Boer
Layout: Dennis Hendriks || Proefschriftmaken.nl
Printing: Proefschriftmaken.nl
ISBN: 978-94-6423-476-3

This thesis was financially supported by the Amsterdam University Medical Center (AUMC), location VU: hemato-pathology, by the Maastricht University through the School for Oncology and Developmental Biology (GROW), and by the Maastricht University Medical Center (MUMC+) and by the Stichting Jules Coenegracht Sr.

Financial support from the Nederlandse Vereniging voor Plastische Chirurgie (NVPC) and Junior Vereniging Plastische Chirurgie (JVPC), Aleamed, Quamedical and Puregraft was received for the printing costs of this thesis.

Anaplastic Large Cell Lymphoma in the breast in women with breast implants

***A multidisciplinary approach to answer epidemiological,
clinical and biological questions***

Proefschrift

ter verkrijging van de graad van doctor

aan de Universiteit van Maastricht

op gezag van de Rector Magnificus, prof.dr. Rianne M. Letschert,

volgens het besluit van het College van Decanen,

in het openbaar te verdedigen op

vrijdag 10 december 2021, om 14.00 uur.

door

Mintsje de Boer

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CHAPTER

1

General introduction

Purposes and indications of breast implants

Breast implants are medical devices, consisting of a gel-like material in a flexible sac (after the Oxford dictionary). The device is designed to be implanted under the breast tissue or pectoralis muscle to increase breast size in underdeveloped, atrophic or deflated breasts, in transgender surgery (augmentation), to substitute breast tissue in case of impaired development (for example Poland's Syndrome), or to reconstruct breast tissue that has been removed for breast cancer or prophylactically in case of high genetic risk for breast cancer.^{1,2}

The main objective of a breast implant is to increase the patient's quality of life. In cosmetic as well as in reconstructive surgery it has been shown that the patient's self-esteem and health-related quality of life indeed benefit from breast implant surgery.³⁻⁵

History of breast implants

The current equivalent of the breast implant was introduced in the early 1960s by Cronin and Gerow. These implants were made of a cross-linked smooth silicone-containing elastomer-shell, filled with a viscous silicone gel and contained a dacron patch for adherence to the thoracic wall.¹ This first generation silastic gel implant was initially only used for cosmetic surgery in patients with atrophic or deflated breasts or in patients without breast development. Cronin and Gerow's device marked the beginning of the first of many generations of silicone gel breast implants. In the years thereafter, the design was optimized and several second-generation breast implants were developed, mainly characterized by thinner seamless shells, without dacron patches. These implants were filled with less viscous silicone gel to provide a 'natural feel'.² In the following years the use of breast implants expanded, as implants were also used for reconstructive purposes in breast cancer patients and women at high genetic risk.¹

In the 1980s the third-generation implants were developed. To improve on the tendency of rupture of second-generation implants and subsequent leakage of silicone, the strength and integrity of the shell was enhanced using multi-layered silicone elastomers.² The fourth-generation implants were introduced between 1986 and 1990 and included third generation technology, but with the introduction of textured surfacing. Capsular contraction was an often reported complaint in the previously used smooth-surfaced breast implants and textured implants aimed to reduce capsular formation by disrupting the planar arrangement of collagen.^{5,6} The most commonly used methods for breast implant surface texturing are now the salt-loss technique and the imprinting technique. In the salt-loss technique, sodium chloride is applied to the uncured silicone by dipping, spraying or sprinkling and washed away after curing of the silicone. The imprinting technique refers to the stamping of a structured foam into uncured silicone.⁷

The currently used implants known as fifth-generation implants, were introduced in 1992-1995. In these implants the silicone gel is more cohesive by increased cross-linking of the polymers to prevent leakage upon rupture and to retain shape ^{5,6}The techniques in the production and texturing of breast implants have been evolving throughout the past decades and each manufacturer has developed its own patented methods.

Current use and registration

Over the past five to six decades, breast implants have become increasingly popular and currently an estimated 10 million women worldwide have breast implants, the majority for cosmetic purposes (65-70%), and about one third for reconstructive purposes after mastectomy for breast cancer or high familial risk for breast cancer (e.g. germline *BRCA1/2* mutation carriership)⁸ As systematic (inter)national registration of breast implant use is lacking, exact numbers of women with breast implants per period and per country remain largely unknown. Registration of breast implants was recently initiated with breast implant registries from Australia, Austria, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, South Africa, the United Kingdom, and the United States, united in the International Collaboration of Breast Registry Activities (ICOBRA). In the Netherlands this initiative is represented by the Dutch Breast Implant Registry (DBIR).⁹ In April 2015, DBIR was nationally implemented. DBIR is an opt-out registry, meaning that registration is mandatory unless the patient actively objects. DBIR registers all patients undergoing breast implant surgery in the Netherlands; implantations, implant revisions and explantations. This audit system provides hospitals and private clinics with benchmarked information on quality and performance, and it can serve as a track-and-trace system in case of implant recalls.¹⁰

The currently available implants in the Netherlands have silicone or saline fillings, with a silicone or polyurethane shell and different types of textured or smooth surfaces. Well-known manufacturers are Allergan, Eurosilicone, Mentor, Motiva and Polytech, which all have a wide variety in types of implants. The 2019 annual report of DBIR shows that a predominance of textured silicone gel implants is used for cosmetic and reconstructive purposes, which is in line with other European countries but in contrast to the United States or Canada, where the majority of implants used has a smooth surface.¹⁰

Regulatory bodies

In the first period after the introduction of breast implants (1962), implant production was not regulated and the safety and quality of breast implants as medical devices was not monitored. In May 1976, the Federal Food Drug and Cosmetic Act (FDA) received the authority to review, approve and classify breast implants, as part of the Medical Device Amendments.^{2,11} Initially, breast implants were labeled as class II devices, but as a result

of safety and health concerns, the FDA classified breast implants as class III devices in 1982. In 1988 all breast implants were classified into class III, meaning that these medical devices required a PreMarket Approval Application (PMA).^{2,12} PMA's have to be based on valid clinical information and scientific analysis on sound scientific reasoning, showing a reasonable assurance of safety and effectiveness. The FDA currently uses a list of 52 points to assess the PMA and to decide on the approval.¹³ At the end of 1991, the General and Plastic Surgery Devices Panel of the FDA could not advise that implants were safe and effective since the implant manufacturers failed to provide adequate safety and effectiveness data for their implants in these PMA's. Therefore, in January 1992, the FDA called for a voluntary moratorium, until new safety information could be reviewed by the General and Plastic Surgery Devices panel. Only women enrolled in clinical studies for reconstruction after mastectomy, congenital deformities or replacement/revision surgery were allowed access to breast implants. Detailed in-depth investigations were conducted between 1992 and 2006, and various systematic reviews and meta-analysis reported a lack of evidence for an increased risk of systemic diseases in patients with breast implants. These studies could also not substantiate an increased risk for breast cancer in women with breast implants.^{14,15} Therefore, in 2006 the moratorium was lifted.

The FDA continues its regulatory actions and activities to monitor the safety and quality of breast implants, mainly by analyzing the perspectives of patients, manufacturers and scientific groups. New breast implant manufacturers and vendors wanting to obtain access to the USA market are required to produce an FDA-approved PMA.

In the EU the rules and regulations are somewhat different. Breast implants as medical devices are included in the Council Directive 93/42/EEC on Medical Devices (MDD) covered by the European Medical Device Regulation (MDR). For approval of the access to the European market, a medical device requires CE certification.¹⁶ The CE mark can be obtained when the device is in conformity with the general requirements as described in EU directives (MDD/MDR). Since breast implants are of higher risk, a so-called Notified Body is mandated to decide whether the device meets the legal requirements, based on the technical reports of the manufacturer.¹⁷ More specifically in the Netherlands, the Ministry of Health and Welfare has appointed 'DEKRA Certification' and 'DARE!! Medical Certifications' as Notified Bodies. Only after approval by these bodies, the CE marking may be obtained.^{16,17}

Both systems in the EU and USA have received criticism, mainly since manufacturers use safety and effectiveness data of existing products to claim equivalence for their new product and in this way obtain authorization for market access. In 2015 the RIVM compared both market authorization systems; it was concluded that there was no difference in the level of quality or safety of implants assessed by the American or the Dutch/European system.¹⁸

Breast implant-related complications and adverse events

Since the introduction of breast implants, several breast implant-related complications have been described. Direct implant-associated complications are rupture, subsequent leakage of silicone, bleeding or sweating of the silicone through the shell, infiltration and migration into surrounding tissues and beyond (regional lymph nodes), infection and capsular contracture.¹² However, already in the 1980s several concerns about the long-term safety of breast implants were raised. These concerns were based on reports of women who reported auto-immune and connective tissue diseases, rheumatological complaints as well as breast cancer after breast implant placement. Over the past 30 years, rheumatological symptoms in women with breast implants have been referred to as 'adjuvant breast disease', 'silicone implant compatibility syndrome', 'Auto-immune Syndrome Induced by Adjuvant (ASIA-syndrome)' or 'Silicone Implant Illness' (SII).^{14-15, 19-22} As discussed above, a voluntary moratorium was set between 1992-2006, but direct evidence for a causal association between breast implants and health complaints was not identified.¹² Proving a cause-effect relationship is a challenge, amongst others since the definition of fibromyalgia-like complaints is vague and the prevalence of these complaints in a general control group is relatively high. Moreover, published studies have not analyzed appropriate comparison groups, precluding conclusions about clinically relevant risks.²² In the past few years lay media in the Netherlands have regularly covered the subject of breast implant safety and implant-related health complaints. This attention has mainly caused a lot of anxiety, and women with implants who have developed health complaints feel misunderstood or not taken seriously. Well-defined and high quality research to collect epidemiological, clinical-translational and experimental evidence is needed to better inform the public and to draw well-founded conclusions about potential health risks. At present, neither epidemiological nor experimental studies have been able to confirm or refute a relationship between breast implants and health complaints.

The family of Anaplastic Large Cell Lymphomas:

Breast implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

Anaplastic large cell lymphomas (ALCLs) represent a group of malignancies which share morphological and immunophenotypic features. They are characterized by presence of large pleomorphic cells with kidney- or horseshoe-shaped nuclei, sharing a T-cell immunophenotype and expression of the lymphocyte activation marker CD30 (Figure 1). The clinical characteristics of the various members of the ALCL family are very different, however. Systemic-type ALCL presents as nodal disease and has either a good or poor prognosis depending on ALK1-status (5-year survival rates of $\geq 80\%$ versus $\leq 50\%$). Primary cutaneous ALCL is almost always ALK1-negative, but has an excellent prognosis (5-year survival exceeding 90%).²³ Anaplastic large cell lymphoma in the breast in women with

breast implants (or Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) as a generally accepted term) is the most recently recognized member of the ALCL family.

Figure 1. The cytopathological features of BIA-ALCL in a seroma aspirate are shown: The typical large immunoblast-like cells with kidney- or horseshoe-shaped nuclei.

1

In the 2016 WHO classification of lymphoid neoplasms Breast Implant Associated-ALCL (BIA-ALCL) was introduced as a new (provisional) entity. BIA-ALCL cells typically present as a late-onset seroma in the periprosthetic space (seroma-associated type).²³ Less often it presents with a mass in the periprosthetic capsule (tumor-associated type). The diagnosis is made by immunohistochemical analysis of the aspirated seroma or biopsy of the mass (Figure 2).²³

The reported time between implantation and diagnosis of BIA-ALCL is highly variable, i.e. between 0.4 and 35 years, with a median interval of 5.8-10.9 years.²⁴⁻²⁷ In most cases BIA-ALCL behaves as an indolent disease (Stage 1, seroma-associated), and explantation and capsulectomy are considered effective surgical therapy with complete remission in 90-95% of the cases.²⁶ When infiltration of lymphoma cells beyond the capsular tissue, into locoregional lymph nodes or systemic nodal and/or organ involvement is present, surgical treatment is not sufficient. In these cases, peripheral T-cell lymphoma specific chemotherapy, a combination of five agents (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; CHOEP) can be prescribed, as well as radiotherapy or high-dose chemotherapy with autologous stem cell transplantation.¹² Despite these approaches, outcome can be significantly poor, with a fatal outcome reported in various patients.²⁸⁻³¹ Clinical awareness for late-onset periprosthetic seroma is therefore of great importance and has increased significantly among clinicians during the last decade.

Figure 2. This image shows the breast implant and its adjacent periprosthetic space and capsule. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) can develop in the periprosthetic space as a seroma, or in the periprosthetic capsule as a mass. The procedure of aspirating or taking a biopsy of the lymphoma cells is shown.

Pathogenesis of Breast implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

Several potential triggers leading to the development of BIA-ALCL have been uncovered, however the pathogenesis of the disease is not completely understood. BIA-ALCL occurs in an inflammatory microenvironment in the periprosthetic space with lymphocyte infiltrates and a prominent Th1/Th17 phenotype. Th1/Th17 cells represent a differentiated subset of antigen-driven memory T helper cells, producing IL-17. These cells are involved in the mediation of the host defense against extracellular pathogens. Aberrant regulation of Th17 cells are implicated in the pathogenesis of inflammatory autoimmune disorders.³² In case of BIA-ALCL, silicone implant-related particulates (platinum), silicone leachables and bacteria in the implant adherent biofilm and possibly supported by the textured implant surface have been suggested as triggers for a Th17-driven response.

Risk of anaplastic large cell lymphoma in the breast in women with breast implants

The many international studies and papers describing single cases, case series and cohorts of women with breast implants, addressing risks and risk factors, pathogenesis and treatment options show the increasing clinical and scientific awareness of this subject.^{29-31, 33-35} The first study to indicate a clear association between ALCL in the breast and breast implants was a Dutch population-based case-control study performed in 2008. The relative risk for development of ALCL in the breast was 18-fold increase in women with breast implants, compared to women without breast implants.²⁹ The strengths of this study included the complete identification of women with ALCL in the breast in the period 1990- 2006, the

selection of control subjects from the same cohort, and the complete retrieval of information on breast prosthesis in all women, rendering selection bias unlikely. However, due to the rarity of ALCL in the breast, the number of cases was small ($n=11$).

Since then, an increasing number of international case series and cohorts studies have been reported, reflecting the trend of an increasing incidence of BIA-ALCL cases since 1997. However to date, the determination of accurate absolute risks has been challenging. Valid epidemiological studies require inclusion of all breast ALCL cases in a defined geographic area as well as information on the total number of women with breast implants in the same population (national or regional). The relatively uncommon occurrence of ALCL in the breast in the general population and incomplete registration of both the disease itself as well as the number of women receiving implants are major hurdles in relative and absolute risk estimation studies. The first two large case series reported covered 60 and 173 BIA-ALCL patients in 2014 and 2015, respectively. Most cases were extracted from the world literature, whereas in the latter study, 94 of 173 cases were not previously reported and collected mostly in the United States.^{27,36} These studies provided a broad overview of the current caseload, but were not suited for risk estimations. Later, several national studies from Australia combined with New Zealand and the United States were published.³²⁻³⁵ These studies provided absolute risks ranging from 2.03 per million women per year with textured breast implants³³ in the USA, to estimates ranging from 1:2,832 - 1:60,631 in Australia/New Zealand for different breast implant types.^{34,35} These studies were based on a set of opt-in reported BIA-ALCL cases (surveys to treating physicians only), without nationwide coverage, implying unreliable assessment of the numerator and lack of a control group of women with ALCL in the breast but without breast implants. Moreover, breast implant sales data were used to determine the number of women with breast implants and to calculate absolute risks. This choice is suboptimal since sales data lack historical information on market shares and do not provide information on primary placement, replacement surgery and unilateral versus bilateral use. At the start of the present PhD project, epidemiological studies with appropriate comparison groups had not been published after the first Dutch study in 2008. Therefore, the precise relative and absolute risks of breast-ALCL in women with implants were unknown at that time.

Aim of this thesis

In this thesis, we explored the following research questions with respect to BIA-ALCL:

1. What is the absolute risk for women with breast implants to develop breast-ALCL?
2. Can specific risk groups for BIA-ALCL be characterized?
3. How should serious adverse events as BIA-ALCL be registered to obtain a reliable surveillance system on the quality of breast implant care?
4. How can the diagnostic process of BIA-ALCL be standardized?
5. What are the molecular characteristics of BIA-ALCL, how do these relate to other classes of ALCL and which molecular pathways may be involved in BIA-ALCL oncogenesis?

Outline of this thesis

Chapter 2: Breast implant prevalence in the Dutch female population assessed by chest radiographs

In order to determine the absolute risk for women with breast implants to develop breast-ALCL, it was first necessary to reliably assess the number of women with breast implants. In this study we assessed breast implant prevalence in the Netherlands, with a novel method based on evaluation of routine chest radiographs. Subsequently, this information is used in chapter 3, where we calculate the absolute risk of BIA-ALCL.

Chapter 3: Breast implants and the risk of Anaplastic Large Cell Lymphoma in the breast

We investigated the relative and absolute risks of BIA-ALCL in the Netherlands using a population-based case-control study through PALGA from 1990-2016. The relative risk of ALCL in the breast associated with breast implants was derived from the case-control study, by comparing breast implant prevalence in cases with breast ALCL with that in a control group of women with other types of Non-Hodgkin Lymphoma (NHL) in the breast. By using the estimated number of women with breast implants in 2015 from chapter 2 and the trend-coefficient in implant sales we estimated the numbers of women with breast implants in the period 1965-2016. In combination with the number of women with BIA-ALCL as established in the case-control study we determined absolute risks of breast ALCL in women with implants.

Chapter 4: Reply: Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast

In chapter 4 we provide a reply to two letters to the editor in reaction to our epidemiological study (chapter 3). We discuss the importance of robust epidemiological studies in which the numerator and denominator are reliably retrieved, and the caution that is needed to associate BIA-ALCL with certain implant types.

Chapter 5: Letter to the editor: response to “Macrot textured Breast Implants with defined steps to Minimize Bacterial Contamination around the Device: Experience in 42.000 implants.”

Further to the reply in chapter 4, we stress the importance of well-designed epidemiological studies in this letter to the editor.

Chapter 6: The Dutch Breast Implant Register (DBIR): Registration of Breast Implant - Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), a proof of concept

We aimed to enhance timely identification and registration of new cases of BIA-ALCL, since we noticed a lack in actual database-based identification of BIA-ALCL cases in the

population. We assessed the registration potential of the Dutch Breast Implant Registry (DBIR) as a post-marketing surveillance system for breast implant-related complications such as BIA-ALCL, using validation by registration in PALGA.

Chapter 7: A Practical Cytological Approach to the Diagnosis of Breast-Implant Associated Anaplastic Large Cell Lymphoma

Cytomorphological and immunohistochemical analysis of aspirated seroma fluid is accepted as a screening and diagnostic approach for patients with breast implants who present with late-onset periprosthetic seroma (chapter 8). In this chapter we describe the diagnostic process of BIA-ALCL.

Chapter 8: Breast Implant-Associated Anaplastic Large-Cell Lymphoma in a Transgender Woman

The importance of clinical awareness and increased incidence of BIA-ALCL is demonstrated in this case report.

Chapter 9: Chromosome 20 loss is characteristic for Breast-implant Associated Anaplastic Large Cell Lymphoma

To study the genetic landscape of BIA-ALCL, we performed shallow next-generation sequencing and whole exome sequencing on a large series of formalin-fixed paraffin-embedded tumor specimens of BIA-ALCL patients and patients with non-implant ALCL to examine the biological and molecular characteristics of BIA-ALCL.

Chapter 10: Increased prevalence of BRCA1/2 mutations in women with macro-textured breast implants and anaplastic large cell lymphoma of the breast

An increasing number of women with *BRCA1/2* mutations opts for preventive risk-reduction mastectomy, with breast reconstruction using an implant. As we observed a relatively high number of women with known *BRCA* mutation carriership among the Dutch BIA-ALCL cohort, we performed an epidemiological study to examine if *BRCA1/2* mutation carriers with breast implants have a greater risk to develop breast-ALCL than non-*BRCA* mutation carriers with implants.

Chapter 11: General discussion

In chapter 11 all results of this thesis are reviewed and future perspectives are discussed.

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Breast Implant Prevalence in the Dutch Female Population Assessed by Chest Radiographs

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Background: Breast implant-related health problems are a subject of fierce debate. Reliable population-based estimates of implant prevalence rates are not available, however, due to a lack of historical registries and incomplete sales data, precluding absolute risk assessments.

Objective: This study aimed to describe the methodology of a novel procedure to determine Dutch breast implant prevalence, based on the evaluation of routine chest radiographs.

Methods: The validity of the new method was first examined in a separate study. Eight reviewers examined a series of 180 chest radiographs, with (n=60) or without (n=120) a breast implant confirmed by a CT or MRI scan. After a consensus meeting with best performing expert reviewers, we reviewed 3000 chest radiographs of women aged 20-70 years in two large regional hospitals in the Netherlands in 2015. To calculate the national breast implant prevalence, regional prevalence variations were corrected using the National Breast Cancer Screening Program.

Results: Eight reviewers scored with a median sensitivity of 71.7% (range 41.7-85.0%) and a median specificity of 94.6% (range 73.4-97.5%). After a consensus meeting and a re-evaluation by best performing expert-reviewers, sensitivity was 79.9% and specificity 99.2%. The estimated national prevalence of breast implants among women between 20-70 years was 3.0%, ranging from 1.7 % at 21-30 years to 3.9% between 51-60 years.

Conclusions: The novel method in this study was validated with a high sensitivity and specificity resulting in accurate prevalence estimates, providing the opportunity to conduct absolute risk assessment studies on the health consequences of breast implants.

Introduction

Silicone breast implants were first introduced in 1964 by Cronin and Gerow and have since been implicated with various adverse events, including malignancies and autoimmune disorders.¹ Of these, only the association with Anaplastic Large Cell Lymphoma in the breast (BIA-ALCL) has been unequivocally supported by formal epidemiological studies², while studies on associations with other disorders show highly variable results.^{3,4} These studies, especially when focussing on absolute risks of breast implant-related health problems, are hampered by lack of information on the prevalence of women with breast implants and thereby of the population at risk.⁵ Answering this seemingly simple question has proven to be a major challenge. Sales data are unreliable and incomplete since companies are reluctant to share sales data or market shares. In addition, the market is highly variable due to retraction from the market by producers due to bankruptcies. Moreover, sales data do not provide information on primary placement, replacement surgery and unilateral versus bilateral use. Breast implant surgery information from hospitals and clinics is also incomplete, since most implant surgery is performed in private clinics that do not maintain central administrative databases and remain outside the medical insurance system. Only recently, centralized national opt-out registries for breast implant surgery have been established in the Netherlands and Australia.^{6,7} The Dutch Breast Implant Registry (DBIR) started in 2015 and is a quality benchmark in breast implant care.⁸ It is a mandatory nationwide registration of all breast implant surgical procedures. In the future, such databases will be crucial to answer questions on breast implant-associated risks, but for now they cannot give sufficient information on implant prevalence.

In this study, we estimated breast implant prevalence in the Netherlands based on evaluation of routine chest radiographs. Chest radiographs are one of the most frequently requested diagnostic tests for a great diversity of indications in all adult age groups,⁹ and women with breast implants most likely have the same risk of mandating these diagnostics compared to women without implants. Therefore, screening chest radiographs for the presence of a breast implants was considered an unbiased method.⁹ Since silicone is a radiopaque substance, it may be assumed that breast implants can reliably be identified on chest radiographs and that they constitute a feasible screening tool.^{10,11}

The aim of this study was to provide a detailed description of the methodology of our novel approach. Firstly we performed a validation study to determine the diagnostic accuracy of breast implant assessment based on chest radiographs. Subsequently we conducted a large-scale chest radiograph evaluation study to assess the prevalence of breast implants by age in the Dutch population. Detailed information on the methodology used will allow broader applicability, which will benefit international studies assessing absolute risks of health problems associated with breast implants.

Methods

This fully anonymized study was approved by the Ethics Review Board in both participating institutions (Medical Spectrum Twente, Enschede and Maastricht University Medical centrum) and it was determined that the Dutch WMO does not apply to the study. The study was executed between December 2016 and October 2017.

Validation study

In order to evaluate the validity of assessing chest radiographs for the presence of breast implants, we used women with a breast implant confirmed by CT-scan or MRI-scan of the breast as the gold standard. Radiology databases of the Medical Spectrum Twente Hospital in Enschede and Zorg-Groep Twente Hospital in Hengelo, the Netherlands, were searched for CT and MRI reports of women (18-85 years, scanned between January 2013 and December 2015), using the search term 'breast implant'. We then selected women with a CT or MRI of the breast positive for a breast implant who had a simultaneously conducted chest radiograph ($\pm$ three months to CT / MRI of the breast).

Visual verification of the breast implant in each MRI and/or CT-scan was conducted by a radiologist. The conventional chest radiographs with an anterior-posterior and a lateral view in these women were selected. The same procedure was used to select a control group of women with a verified absence of a breast implant and with simultaneously conducted chest radiographs. The group of women with a simultaneously performed MRI and/or CT-scan with a proven breast implant *and* a chest radiograph was relatively small. Therefore, we selected the first consecutive 60 women with a CT/MRI established implant who had a simultaneous chest radiograph of good quality, meaning a anterior-posterior and lateral image and a completely depicted chest. For each of these 60 selected chest radiographs, two chest radiographs of women without breast implants, matched on age and gender (± 5 years) were manually selected. The manual identification of suitable negative controls (without breast implants based on CT/MRI images) for the validation study was performed as follow. We selected the first consecutive 120 women (based on date of radiological imaging) with a CT- or MRI-proven absence of breast implants, who also had a subsequent chest radiograph within three months from the CT/MRI of the breast. Absence of a breast implant on CT/MRI image was confirmed by a visual check of the CT/MRI-scan by a radiologist. Negative controls were selected from the same database as the 60 patients with proven presence of a breast implant. Exclusion criteria were poor image quality of chest radiographs; for instance impaired position of the chest on the image, incomplete inspiration or supine position. The 180 chest radiographs were assessed for the presence of breast implants in random order by two specialized breast radiologists, two plastic surgeons, two residents, and two medical students, without previous training. Series were assessed in dual-headed working stations with high-resolution (2.5 K · 2 K), high-brightness monitors according to routine working procedures. Characteristics

confirming implant presence were: 1. projection lines following the contour of the breast implant within the breast, with or without asymmetrical densities in the basal lung fields with a focal opacified aspect, with or without evident absence of ptosis in the breast (Figure 1); or 2. evident calcification in the periprosthetic capsule (Figure 2); or 3. the metal magnetized valve/port of the tissue expander (Figure 3).

Figure 1. Standard chest radiograph in posterior-anterior (1a) and lateral (1b) view made in 62 year old female due to a suspicion of bilateral pneumonia. The implant can be seen as asymmetrical densities in the basal lung fields with a focal opacified aspect (arrows).

Figure 2. Standard chest radiograph in posterior-anterior (2a) and lateral (2b) view made in 70 year old female due to a suspicion of exacerbated lung emphysema). The implant can be seen by the evident calcifications in the periprosthetic capsule (arrows).

Figure 3. Standard chest radiograph in posterior-anterior (1a) and lateral (1b) view made in 32 year old female due to a suspicion of bilateral pneumonia. The implant can be seen by the metal magnetized valve/port of the tissue expander (arrows).

Statistical analysis

A correct evaluation of the chest radiograph by the reviewer was defined as detection of the presence of at least one to potentially up to two breast implant(s). The specificity and sensitivity were calculated per reviewer. Specificity was the percentage of correctly negatively assessed chest radiographs among the 120 women without implant, while sensitivity was the percentage of correctly positively assessed chest radiographs among the 60 women with implants.

After the first validation round, three selected expert reviewers (sensitivity >70.0% and specificity of >80.0%) held a consensus meeting based on the uniform scoring rules with respect to the characteristics confirming a breast implant and re-evaluated all mutually discordant results in the validation series. We then determined, the estimated prevalence of breast implants as a function of the sensitivity (*sens*), the specificity (*spec*) and the presumed true prevalence (*p*) *estimated prevalence* = $(1-p)*(1-spec)+p*sens$.

We also examined whether the indication (reconstructive after breast amputation or cosmetic, i.e. the presence of a mammary gland) and the laterality (unilateral or bilateral) of the breast implant could be assessed reliably.

Prevalence Study

The study population consisted of two regional study series of women aged 20-70 years who had chest radiographs between January to December 2015 in the Medical Spectrum Twente Hospital (East) or the Maastricht University Medical Center (South) in the Netherlands. In these hospitals we selected two samples of *n*=1525 conventional chest radiographs (305 per 10-year age category), which allows for precise estimation of

a breast implant prevalence of at least 1% with a sufficiently narrow confidence interval (0.5%-1.5%).

Per hospital two expert reviewers, showing high sensitivity and specificity, independently assessed all chest radiographs per regional hospital for the presence of silicone breast implants. We selected reviewer A and B for the East region, and reviewer B and C for the South region. Series were assessed in dual-headed working stations with high-resolution (2.5 K · 2 K), high-brightness monitors. After independent assessment, consensus was reached for discordant results per two regional reviewers.

Breast implant prevalence per age group and per region (South or East) was calculated as the ratio of the number of positive chest radiographs by the total number of chest radiographs in the age-group.

Assessment of breast implant prevalence in the Netherlands in 2015

After assessing the breast implant prevalence rates per 10-year age group in the East and South of the Netherlands, the national breast implant prevalence in the general female population in the Netherlands was calculated by correcting for the other regions (North, West, Central region). Region-specific coefficients for breast implant prevalence were provided by the Dutch National Breast Cancer Screening Program (BCSP).^{12,13} The BCSP offers biannual mammography screening to Dutch females between age 50-75, with a national participation rate of 80%.^{13,14} Between May 2014 and May 2016, breast implant prevalence was monitored in participating women in all five regions of the Netherlands (i.e. North, East, South, West and Central).^{13,14} Since it is known that women with breast implants less often attend breast cancer population screening programs, we could not use these prevalences directly.¹⁴ However, we assumed that the relative differences between regions in BCSP-reported implant prevalence in the 50-75 year (mean age 60.6 years) female populations approximated regional differences in the general population. The region-specific coefficients in for BCSP-North was 0.6%, BCSP-East=0.7%, BCSP-South=1.0%, BCSP-West=1.1% and BCSP-Central=1.2%. For the Eastern and Southern regions, the age-specific breast implant prevalence was already determined in this study. For the Northern, Western and Central regions, both age-specific percentages of the East and the South were used as a baseline to extrapolate to a national breast implant prevalence. These age-specific baselines were multiplied by the regional BCSP-prevalences of the Northern, Western and Central regions and the regional population size.¹⁵ From the subsequent combined regional age-specific breast implant prevalences as derived from the South and East a mean breast implant prevalence was calculated.

Results

Validation Study

In the first part of the validation study, eight reviewers scored a median sensitivity of 71.7% (range 41.7-85.0%) and a median specificity of 94.6% (range 73.4-97.5%) (Table 1). Based on the CT/ MRI reports breast implants were bilateral in 65.0% of the women versus unilateral in 35.0% of the women in the positive group. Bilateral presence was correctly identified with a median score of 40.0% (range 28.6-77.1%), while unilateral presence was correctly identified with a median score of 50.0% (range 21.1-63.3%). Reviewers reported a cosmetic indication for a median percentage of 54.3% of women (range: 19.1-74.2%) and a reconstructive indication for a median percentage of 45.7% of women (25.8-80.9%). Indication was unknown for 12.5% of women (range 4.0-28.0%). No information on breast implant indications was available from the CT/MRI reports; however, results among reviewers were widely spread without an evident trend of agreement. Laterality and indication were therefore omitted from the prevalence study.

Since sensitivity and specificity were low for some reviewers, only the reviewers with a sensitivity of at least 70.0% (range 70.0-76.7%) and a specificity of at least 80.0% (range 81.7-95.8%), similar to the scores of the specialized breast radiologists (D&E), were selected for further participation in this study. The three selected reviewers (A,B,C) performed a consensus meeting and a blinded re-evaluation of mismatched positive and negative chest radiographs in the validation study. After this re-evaluation, sensitivity and specificity had increased to 79.9% and 99.2%, respectively. With these values, estimated implant prevalence would be 3.1% and 4.7%, for true prevalence rates of 3.0% and 5.0%, respectively.

Table 1. Sensitivity and specificity per reviewer in the validation study assessing the 180 chest radiographs.

Reviewer	A	B	C	D	E	F	G	H
Sensitivity (%)	71.7	76.7	71.7	71.7	70.0	85.0	46.7	41.7
Specificity (%)	81.7	94.2	94.2	95.0	95.8	73.4	96.7	97.5
Sensitivity after consensus meeting and re-evaluation(%)		79.9		-	-	-	-	-
Specificity after consensus meeting and re-evaluation (%)		99.2		-	-	-	-	-

Prevalence Study

In the two hospital populations we assessed a total of n=3,050 chest radiographs in women between 20-70 years of age (n=305 per age group, mean age 46.5 years). Indications for chest radiographs included cardio-pulmonary problems (64.6%) of which suspicion for pneumonia was a major indication, screening for tuberculosis (6.1%), trauma screening (8.6%), auto-immune diseases (5.6%), perioperative screening (3.3%), position of devices

other than breast implants (2.6%), abdominal indications (1.4%) and oncological indications (6.4%), of which breast carcinoma in 1.2% of the patients (n=36). Of these 36 women, seven women had a breast implant.

Breast implant prevalence for the series in the East of the Netherlands was assessed by reviewer A and B and for the South of the Netherlands by reviewer B and C. Reviewer B performed in both regions. Before consensus, for the Eastern region reviewer A and B agreed on 37 women with a breast implant, whereas reviewer A reported one additional case and reviewer B reported one additional case. After consensus the additional case reported by reviewer B was accepted, for a total of 38 women with at least one breast implant among 1525 chest radiographs.

Before consensus for the Southern region, reviewer B and C agreed on 42 identical cases, whereas reviewer B reported three additional cases, not reported by reviewer C, and reviewer C reported one case not reported by reviewer B. After consensus four additional cases were added, for a total of 46 women with at least one implant among 1525 chest radiographs.

Interestingly, only in 35.7% (n=30) of the women with at least one breast implant in the chest radiograph, the radiological report mentioned the breast implant.

After consensus, observed prevalence rates in the Eastern and Southern region were 1.0% (n=3) and 2.3% (n=7), respectively, for 20-30 years, 3.6% (n=11) and 3.6% (n=11), respectively, for 31-40 years, 3.3% (n=10) and 3.9% (n=12), respectively, for 41-50 years, 3.0% (n=9) and 3.3% (n=10), respectively, for 51-60 years and 1.6% (n=5) and 2.0% (n=6), respectively, for 61-70 years. (Figure 4). Using these regional prevalence rates per age group, we extrapolated for the Northern, Western and Central region by using the region-specific coefficients of the BCSP, and the region-specific population size (Figure 4). We extrapolated for the Northern, Western and Central region as described in the methods. Subsequently, we estimated the mean national breast implant prevalence in 2015 among women between 20-70 years at 3.0%, and was 1.7% for 20-30 years, 3.5% for 31-40 years, 3.7% for 41-50 years, 3.9% for 51-60 years and 1.9% for 61-70 years (Figure 5).

Figure 4. Regional breast implant prevalence in the Netherlands per age-group.

This figure shows the region-specific breast implant prevalences (P) in women between 20-70 years. The Eastern and Southern regional prevalences were derived from the prevalence study, and both age-specific prevalences were multiplied by the region-specific coefficients of the Breast Cancer Screening Program Program (BCSP) and the regional population size to calculate a mean for the Northern, Western and Central region

Figure 5. Estimated national breast implant prevalence in the Netherlands in 2015 among women between 20-70 years of age.

The national breast implant prevalence (P) in Dutch women in the Netherlands between 20-70 years is shown, derived by combining differences in region-specific breast implant prevalence from the BCSP and regional prevalences from the prevalence study.

Discussion

Knowledge about breast implant prevalence is essential for assessing the absolute risk and public health impact of breast implant-related health problems. So far, data on the prevalence of breast implants were not available due to the absence of historical breast implant registries,⁸ and lack of reliable and complete historical implant sales data. Since there is a recently growing attention in the scientific and lay press for specific breast implant-related health problems such as BIA-ALCL,² we found it of great importance to assess breast implant prevalence, enabling reliable risk assessments in epidemiological studies. Searching the published literature we observed a lack of information regarding breast implant prevalence. Although the American Society of Plastic Surgery reports a prevalence of 4.9% for women with breast implants in 2010, with an estimated 300,000 - 400,000 breast implant procedures per year^{16,17}, the methodology or registration from which these numbers were derived were not clear. The Food and Drug Administration reported that, worldwide, from 1998 until 2011, approximately 5-10 million breast implants have been placed, but this estimate is relatively broad.⁴ As for the Netherlands, the BCSP data could have provided insight into national breast implant prevalences, however prevalence rates from the BCSP are an underestimation due to decreased participation of women with breast implants as a result of discomfort, risk of implant

rupture, and suboptimal mammography, clinical follow-up of women with breast cancer or high genetic risk for breast cancer, and a restricted participating age group (50-75 years, mean age 60.6 years).¹²⁻¹⁴ In summary, so far no studies or data sets were eligible to accurately derive breast implant prevalence, emphasizing that our report provides unique and novel information.

In this study, we assessed the prevalence of breast implants in the Dutch female population using a novel method based on routine chest radiographs, which we first validated with a sensitivity of 79.9% and a specificity of 99.2%. Prevalence was estimated at 3.0% among women between 20-70 years (Figure 5). Breast implant prevalence in this study varied by age, concurring with data in plastic surgery practices where most esthetic procedures are performed in women between 20-40 years of age, and reconstructive procedures are performed in older aged groups (50-70 years).^{16,17} Regional differences might be dependent on urban and rural differences in accessibility and acceptability of (cosmetic) breast surgery. Compared to the overall prevalence of hip and knee arthroplasty in the United States in 2010 of respectively 0.8% and 1.5%, or the prevalence of cardiac pacemakers exceeding 2.0% for patients aged over 75 years in Western Australian in 2005, we can conclude that breast implants are used extensively.^{18,19} Therefore, our data are key in providing answers to important questions about absolute risk assessment for breast implant-related health problems. Moreover, we provide a description of the detailed procedures used in our novel implant assessment method, as well as its validity. This is of prime importance for other investigators to obtain accurate estimates of breast implant prevalence, facilitating international epidemiological studies on breast implant-related health problems.

The current study differs from the present knowledge base since it establishes an age-specific nationwide breast implant prevalence independent from implant sales data. Since sales data are not representative for the number of women carrying breast implants, our approach contributes to new knowledge about breast implant prevalence, enabling adequate risk assessment. Furthermore, the strength of this study lies in the high sensitivity and specificity we demonstrated in the validation study. Because initial sensitivity and specificity were relatively low, it is of major importance to stress the need for expert reviewers, and to consider the significance of gaining experience and organize consensus meetings. After these procedures, sensitivity and specificity increased to 79.9% and 99.2% and these scores were obtained by radiologists, as well as by residents and medical students, providing excellent prospects for a wider applicability of our novel assessment procedure. To put these results into perspective; the sensitivity of a chest radiograph to detect tuberculosis or pneumonia is approximately 80%,^{20,21} while the sensitivity of a mammography for the detection of breast cancer is 77%.²² Even though laterality of the breast implant has proven difficult to assess, this has not hampered our objective to estimate the number of women with at least one breast implant, which is the relevant parameter when assessing absolute risk in breast implant-related problems. The

current literature in breast implant-related health problems focusses on the number of women with breast implant-related problems, and not on the number of breast implants associated with breast implant-related problems (in a, very likely, unequal number of women). This relates to the problems involved in deriving breast implant prevalence from sales data, since sales data do not disclose whether implants were implanted bilaterally or unilaterally or if they were used for revision surgery.

Limitations

A potential limitation of the large-scale prevalence study is selection bias due to the indication for the chest radiographs. For example, younger healthy females may undergo chest radiographs less frequently and the indication might be related to the presence/absence of breast implants. However, upon assessing the indications for the chest radiographs (i.e., malignancies) in comparison to trauma, suspected pneumonia, and work- or travel-related tuberculosis screening, the distribution of indications in younger age groups was comparable to older age groups, with the majority of indications being a suspicion of pneumonia. To our knowledge, there is no evidence that these indications are related to the presence of breast implants. Older age groups might more often undergo potential screening for lung-metastases in the context of primary breast carcinoma associated with breast reconstruction, which might have resulted in a higher breast implant prevalence. However, in this study, only 36 women (1.2% of the study population) underwent a chest radiograph for oncological examination of metastasized breast cancer or with a reported history of breast cancer, of these women 19.4% (n=7) had a breast implant. Another potential source of bias in the prevalence study is that we selected reviewers who were not specialized breast radiologists. However, we selected reviewers with a similar score as breast radiologists in the validation study, demonstrating that non-experienced individuals can be easily trained to perform our assessment method, which supports its broad applicability. Another potential limitation that might have influenced the prevalence study is a lack of actual breast implant assessment in the Northern, Western and Central region. However, we corrected for this using the regional BSCP-coefficients as well as the weight of the regional population size. Moreover, we selected a sample size to detect at least a prevalence of 1%, assuring the reliability of the identified 3,0%

Conclusion

With a validated novel method using routinely available chest radiographs we were able to derive accurate age-specific breast implant prevalence rates for Dutch women. The description of the methodology and validity of our measurement procedures enables wide application in other countries. This will benefit absolute risk assessments in epidemiological studies on the full spectrum of health consequences of breast implants.

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Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast

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Importance: Breast implants are among the most commonly used medical devices. Since 2008, the number of women with breast implants diagnosed with anaplastic large cell lymphoma in the breast (breast-ALCL) has strongly increased and several reports have suggested an association between breast implants and risk of breast-ALCL. However, relative and absolute risks of breast-ALCL in women with implants are still unknown, precluding evidence-based counseling about implants.

Objective: To determine relative and absolute risks of breast-ALCL in women with breast implants

Design: Through the population-based nationwide Dutch pathology registry we identified all patients diagnosed with primary non-Hodgkin lymphoma in the breast between 1990-2016 and retrieved clinical data, including breast implant status from the treating physicians. We estimated the odds ratio (OR) of ALCL associated with breast implants in a case-control design, comparing implant prevalence between women with breast-ALCL and women with other types of breast lymphoma. Cumulative risk of breast-ALCL was derived from the age-specific prevalence of breast implants in Dutch women, estimated from an examination of 3,000 chest X-rays and time trends from implant sales.

Setting: Population-based case-control study in the Netherlands

Participants: A nation-wide population-based series of Dutch female patients diagnosed with primary Non-Hodgkin lymphoma in the breast between 1990-2016.

Main outcome measure: Relative and absolute risks of breast-ALCL in women with breast implants

Results: Among 43 patients with breast-ALCL (median age 59 years), 32 had ipsilateral breast implants, compared to 1 among 146 women with other primary breast lymphomas (OR 421.8, 95% CI 52.6-3385.2). Implants among breast-ALCL cases were more often macro-textured (82%) than expected (44%) based on sales data ($P < 0.001$). The estimated prevalence of breast implants in 20-70 year-old women was 3.3%. Cumulative risks of breast-ALCL in women with implants were 29/million at 50 years and 82/million at 70 years. The number of women with implants needed to cause one breast-ALCL case before age 75 was 6920.

Conclusions and relevance: Breast implants are associated with strongly increased risk of breast-ALCL, but the absolute risk remains small. Our results emphasize the need for increased awareness among the public, medical professionals and regulatory bodies, stimulation of alternative cosmetic procedures and alertness to signs and symptoms of breast-ALCL in women with implants.

Introduction

Since the introduction of breast implants in the 1960s, their safety has been debated extensively, even resulting in a temporary ban (1992-2006) on silicone-gel implants for cosmetic indications by the Food and Drug Administration (FDA).¹ However, consistent associations of silicone breast implants with adverse events, such as breast cancer, autoimmune diseases, and connective tissue diseases have not been substantiated, as recently underlined by two meta-analyses.^{2,3} The risk for anaplastic large-cell lymphoma (ALCL) in the breast in relation to breast implants was not discussed in these studies.^{2,3}

In 2008, we reported the first epidemiological study showing an increased risk of breast-ALCL in association with breast implants (Odds Ratio (OR) of 18.2 (95% CI 2.1-156.8), based on five exposed cases.⁴ Since then, the number of reported cases has strongly increased to 173 unique cases reported in the literature by 2015⁵ and 359 international Medical Device Reports (MDRS) received by the FDA by February 2017.⁶ Breast-ALCL has been included as a provisional new disease entity in the most recent update of the WHO lymphoma classification.⁷

Epidemiological studies with appropriate comparison groups have not been published after 2008, likely due to the rarity of breast-ALCL. Most reports discussing risk estimations for breast-ALCL rely on clinical reporting of breast-ALCL cases with implants and lack valid data on the prevalence of women with implants in the population. Estimating the prevalence of (type of) breast implants has proven to be a true international challenge^{8,9}, as sales data are generally not released by companies and information on unilateral versus bilateral usage as well as use for prosthesis revisions are not known. Consequently, the precise relative and absolute risks of breast-ALCL in women with implants are unknown.

The nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) of the Netherlands provides the unique opportunity for complete nationwide ascertainment of all cases of breast-ALCL and other classes of primary breast lymphomas as a comparison population.¹⁰ To estimate absolute risks of breast-ALCL in women with breast implants, we determined age- and calendar year-specific implant prevalence rates using a large, random sample of chest X-rays in 2015.

Methods

Design and study population

We performed a case-control study comparing the prevalence of breast implants between women with primary breast-ALCL and women with primary breast lymphomas other than ALCL. We identified 782 female patients diagnosed with a histologically or cytologically proven non-Hodgkin lymphoma (NHL) of the breast in the Netherlands during 1990-2016. Identification was based on data from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) with nationwide coverage of all academic and non-academic centres since 1990.¹⁰ (eFigure 1).

Breast-ALCL cases

For the 47 primary breast-ALCL cases among the identified patients, all available pathology samples (cytological and histological slides and/or blocks) and reports were retrieved from the original pathology laboratories for review, including immunohistochemistry and T-cell receptor gene rearrangements. All patients with a previously reported lymphoma diagnosis prior to lymphoma diagnosis in the breast, were excluded. Additionally, anonymized clinical information was collected from treating physicians via PALGA. Breast as the primary site of involvement was confirmed in 43 patients.

Controls with other types of breast lymphoma

Control selection procedures were performed using methods as previously described.⁴ From 735 non-ALCL breast NHL cases, full pathology reports from the laboratories were reviewed to confirm the diagnosis. All patients with a previously reported lymphoma diagnosis, prior to lymphoma diagnosis in the breast ($n=325$) and with chronic and acute leukaemia as disseminated diseases per definition were excluded ($n=220$). Only patients classified as diffuse large B-cell lymphoma, Burkitt lymphoma, follicular lymphoma, nodal and mucosa-associated lymphoid tissue-type marginal zone lymphoma, and peripheral T-cell lymphoma not otherwise specified were included ($n=190$).

Questionnaire assessing clinical breast lymphoma characteristics and breast implant prevalence in cases and controls

Through PALGA, a standardized questionnaire was sent to the treating physicians (oncologists, surgeons, or plastic surgeons) of all potential breast-ALCL cases ($n=47$) and potential controls ($n=190$). The questionnaire assessed whether the breast was the primary site of involvement, features at lymphoma presentation including clinicopathological variants (i.e., tumor-forming or seroma-associated breast-ALCL)¹¹, lymphoma treatment and outcome, and breast implant presence and history. Physicians were asked to review the full medical history, interdisciplinary correspondence and chest imaging for any breast implant surgery. Additionally, information was collected on breast implant indications, type of breast implant, and implant revisions. Physician response was 100% for breast-ALCL cases and 92% for controls. Breast as primary site of involvement was confirmed in 43 breast-ALCL cases and 146 controls (eFigure 1).

Prevalence of breast implants in the general Dutch population 1965-2016

We determined regional age-specific breast implant prevalence in 3,000 women aged 20-70 years by review of chest X-rays performed in 2015 in two large hospitals in different regions of the Netherlands. X-rays were sampled randomly from radiology records, stratified by age (eFigure 2). The validity of assessing breast implant presence from chest X-rays was first examined using a chest X-ray series of patients with simultaneously performed CT-scans which had demonstrated the presence of breast implants (eMethods). Chest X-rays

were assessed by three reviewers who had demonstrated high sensitivity and specificity in the validation study (eMethods).

To account for regional variation in breast implant prevalence rates in the chest X-ray study, we used differences between region-specific breast implant prevalence rates from the National Breast Cancer Screening Program (BCSP) to derive nationwide breast implant prevalence rates (eFigure 2). Implant prevalence rates from the BCSP were not used as such since these are underestimates, due to the fact that women with breast implants participate less in population screening as a result of discomfort, risk of implant rupture, and suboptimal mammography.^{12,13}

Breast implant prevalence prior to 2015 was estimated by applying changes in implant sales to the 2015 age- and region-specific prevalence rates. Upon request to all currently active breast implant vendors, we obtained nearly complete sales data for the period 2010-2015, covering >95% of the Dutch market share for this period. The change in implant prevalence by calendar year was determined from the 2010-2015 nationwide sales data by calculating the average annual percentage change (AAPC) in a regression of the log-transformed number of sold implants per year on calendar year. AAPCs for the period 1965-2010 were calculated assuming a linear decrease of the log-transformed number of sold implants to zero in 1965, the start of breast implant use in the Netherlands (eFigure 3).¹⁴ The age-specific size of the female Dutch population was obtained from Statistics Netherlands (CBS).¹⁵

Statistical analysis

For assessment of the association between breast implants and breast-ALCL, we calculated the odds ratio (OR) between case-control status and breast implant status (in the ipsilateral breast) as an approximation of the relative risk, using unconditional logistic regression with adjustment for age and calendar year (continuous). The distribution of micro- and macro-textured silicone-filled implants was compared between breast-ALCL cases and Dutch sales data between 2010 and 2015 using Fisher's exact test. P-values below 5% were considered statistically significant.

We calculated the cumulative risk of breast-ALCL by age in women with breast implants and in the general Dutch female population without breast implants, using the number of breast-ALCL cases with or without breast implants and the age specific denominator of women with breast implants or the complete female Dutch population, respectively (eMethods).¹⁵ Cumulative risk to develop breast-ALCL up to age z was calculated as $P_{\text{crl}} = 1 - \exp(-\sum_x I_x \cdot c_x / n_x)$ where c_x and n_x are the numbers of cases and person-years in age-category x , respectively, I_x is the width of the x -th age interval and z is the upper limit of the last age category.¹⁶ As a sensitivity analysis, cumulative risk of breast-ALCL in women with implants was also calculated by multiplying the background incidence of breast-ALCL without implants in the general Dutch female population with the OR from our case-control study.

The number needed to harm was calculated as the inverse of the difference between the cumulative risk with breast implants and the cumulative risk in the general population at age 75 years. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC).¹⁷

Results

Case-control study: relative risk for ALCL associated with breast implants

Of 43 breast-ALCL patients (median age 59 years, range 24-87), 32 had an ipsilateral breast implant (median age 56 years, range 29-73), while in 11 patients no implant or implant history was noted. Of 146 controls (median age 61 years, range 24-89), one patient had a breast implant in the lymphoma-affected breast for a cosmetic indication, while one other patient had a breast implant for reconstructive purposes in the contralateral (not lymphoma-affected) breast (Table 1). This resulted in an OR of 421.8 [95% confidence interval (CI) 52.6-3385.2, $P < 0.001$] for breast-ALCL associated with a breast implant. The implant-related log OR increased by about 10% when adjusted for age and calendar year. A sensitivity analysis restricted to cases and controls not included in our previous report, showed 27 exposed cases and no exposed controls, resulting in an infinite OR ($P < 0.001$). Seven out of 43 ALCL cases had previous breast cancer (all 7 with breast implants), while 3/147 control patients had previous breast cancer, of whom none had implants.

Table 1. Diagnostic characteristics of 43 patients with primary ALCL in the breast and 146 patients with primary breast lymphomas other than ALCL included in the case-control study.

	Primary breast ALCL	Primary breast lymphomas other than ALCL*
Year of diagnosis		
1990-1995	1 (2,3%)	5 (3,4%)
1996-2000	6 (14,0%)	20 (13,7%)
2001-2005	3 (7,0%)	12 (8,2%)
2006-2010	9 (20,9%)	56 (38,4%)
2011-2016	24 (55,8%)	53 (36,3%)
Age at diagnosis (years)		
18-35	4 (9,3%)	13 (8,9%)
36-50	14 (32,6%)	36 (24,7%)
51-75	23 (53,5%)	74 (50,7%)
>75	2 (4,7%)	23 (15,8%)
Breast implant		
Yes	32 (74,4%)	1 (0,7%)
No	11 (25,6%)	145 (99,3%)

*including diffuse large B-cell lymphoma ($n=95$), Burkitt lymphoma ($n=7$), marginal zone lymphoma, mucosa associated lymphoid tissue-type ($n=22$), follicular lymphoma ($n=10$), nodal marginal zone lymphoma ($n=1$), indolent B-cell lymphoma, unclassifiable ($n=9$), peripheral T-cell lymphoma, not otherwise classified ($CD30$ negative, $n=3$).

Implant characteristics in patients with primary breast-ALCL

Patients received their first breast implants at a median interval of 13 years before lymphoma diagnosis (range 1-39 years). In 65% ($n=21/32$) of the patients, bilateral breast implants were

placed for cosmetic reasons. Thirty-one percent ($n=10/32$) had implants for reconstruction after mastectomy for breast cancer, including three patients with contralateral prophylactic procedures with implants, of whom two patients received breast implants after bilateral prophylactic mastectomy because of BRCA mutation carriership. One patient received breast implants as part of a gender transition program (Table 2, eTable 1, eFigure 4).¹⁸ Twenty-one patients received implants only once, while single ($n=3$) or multiple implant revisions ($n=8$) for leakage, rupture, or pain were necessary in 11 patients (Table 2, eTable 1).

Table 2. Implant characteristics of 32 patients with breast-ALCL with breast implants.

Breast-ALCL cases (N)		
Age at breast implant (years)		
21-30	10	
31-40	7	
41-50	8	
51-60	6	
>60	1	
Indications for implants		
Cosmetic	22	
Reconstruction after breast cancer surgery	7	
Reconstruction after prophylactic mastectomy	3	
Type of implant		
Macro-texture	Allergan/Inamed/McGhan	22
	Nagor	1
Microtexture	Eurosilicone	2
	Mentor	1
	PIP	1
	Sebbin	1
Unknown		4
Interval between first implant and ALCL diagnosis (years) (median interval 13 years, range (1-39 years))		
1-5	6	
6-10	5	
11-20	14	
21-30	5	
31-40	2	

We examined whether a specific type of implant was more strongly associated with breast-ALCL. Of the breast-ALCL patients, 82% had macro-textured implants upon diagnosis, while only 44% of all implants sold in the Netherlands in 2010-2015 were macro-textured ($P<0.001$) (eFigures 5a and 5b). Based on sales-data, macro-textured breast implants were introduced on the Dutch market around 1995. Eighteen percent of implants in breast-ALCL patients were micro-textured with a market share of 54%. No smooth or polyurethane covered implants were observed in breast-ALCL patients. All implants were permanent and silicone-filled; none were saline or hydrocellulose-filled. However, it should be noted that the use of such implants was very limited (0.1-1%). (eFigures 5a and 5b).

Clinicopathological characteristics of patients with breast-ALCL

Clinical and pathological characteristics did not differ significantly between implant-exposed patients and breast-ALCL patients without implant exposure, except for seroma-associated features uniquely in patients with implants (Fisher-exact test $P < 0.001$) (eTable 2, eResults). With a median follow-up of 33 months in the implant-exposed group (range 2-240 months), 29 women were in complete remission after first line ($n = 23$) or second line treatment ($n = 6$). Two patients died of disseminated disease after second line treatment (eTable 3). In the non-implant-exposed breast-ALCL group, 8 were in complete remission after first-line treatment ($n = 8$), and 3 patients died of disseminated disease (eTable 2).

Absolute risk assessment for ALCL associated with breast implants

The estimated prevalence of 20-70 year-old women with a breast implant in 2015 was 3.3%, ranging from 2.3% between 20-30 years, 4.0% between 31-40 years, 4.2% between 41-50 years, 3.6% between 51-60 years and 2.1% between 61-70 years (eFigure 2).

Cumulative risk of breast-ALCL in the general population increased with age and reached about 0,35 per million at an attained age of 75 years (Figure 1a). Among women with an implant, cumulative risk increased from about 29 per million at 50 years and 82 per million at 70 years (Figure 1b). The cumulative risks estimated using the alternative approach (based on the breast-ALCL background incidence and the breast implant-associated OR) did not essentially differ from this estimate (Figure 1b).

Figure 1. Regional breast implant prevalence in the Netherlands per age-group.

This figure shows the region-specific breast implant prevalences (P) in women between 20-70 years. The Eastern and Southern regional prevalences were derived from the prevalence study, and both age-specific prevalences were multiplied by the region-specific coefficients of the Breast Cancer Screening Program Program (BCSP) and the regional population size to calculate a mean for the Northern, Western and Central region

The number needed to harm, i.e. the number of women with implants needed to cause one breast-ALCL case before the age of 75 years, was 6,920.

The lack of reliable denominator data on textures precluded calculation of separate risks per implant type or vendor.

Discussion

In 2008, we reported the first relative risk estimate for breast-ALCL associated with breast implants, based on only 5 exposed cases.⁴ Based on what is the largest population-based study conducted thus far, with nationwide coverage of breast-ALCL cases in the period 1990-2016, we now confirm that implants strongly increase the risk of this rare type of lymphoma. Our relative risk estimate of over 400, implying an attributable risk approaching 100%, is highly suggestive of a direct or indirect causal role of the breast implant in breast implant-associated ALCL (BIA-ALCL). So far, various, not mutually exclusive causal factors have been suggested. Specifically, a local inflammatory response, elicited by silicone-derived products or specific bacterial species adherent to the prosthesis surface (biofilm) may play a role, possibly via an auto-immune response. Toxic products related to the production of breast implants have been implicated as direct mutagens.¹⁹⁻²¹ Whether certain groups of women have a genetically determined increased risk to develop lymphoma when exposed to breast implants, e.g. via a genetically determined altered or exaggerated local immunological response, remains hypothetical.²² A major increase in breast-ALCL incidence over time was noted, especially over the last 3-4 years (eFigure 4). Apart from a truly increased incidence²³, this rise may also have been influenced by increased awareness and earlier diagnosis of breast-ALCL in the context of breast implants among plastic surgeons and pathologists alike, since the subject has drawn major attention in the medical and lay literature in the past few years.

Rather than the relative risk to develop a rare disease, albeit of impressive magnitude, for women with breast implants, physicians and governmental organizations absolute risk estimates, as well as associations with specific types of implants are of most interest in order to possibly avoid or reduce risks. Thus far absolute risk estimates were not based on large population-based studies and reliable information on the prevalence of women with breast implants over time. Therefore, results of previous absolute risk calculations should be considered rough and potentially biased estimates.^{4,6,8,9} Using three complementary data sources (one-year point prevalence data for two Dutch regions, data on regional variation in breast implant prevalence based on the BCSP and national sales data), we could, for the first time, make an unbiased estimate of the age- and period-specific prevalence of breast implants in Dutch women. This key ingredient provided absolute risks of 29 BIA-ALCL cases per million women with implants at 50 years and about 82 per million at 70 years. This risk exceeds previous estimates by us and others 10-20-fold^{4,8}, but is unlikely to be an overestimation. Remarkably, our sensitivity analysis using another statistical approach resulted in very similar estimates.

The majority of BIA-ALCL cases ($n=24/32$) were associated with macro-textured implants, provided by various distributors over time. The current market share was 46%, indicating a possible increased risk of developing BIA-ALCL with macro-textured implants, as suggested by others based on case-reports and series.^{8,9,17,24} It should be noted,

however, that BIA-ALCL has also been observed in patients with micro-textured implants both in our study and by others, as well as possibly in smooth implants.⁶ Furthermore, our sales data lack historical information on market shares before 2010, as a result of a.o. bankruptcy or changing distributors with loss of product data files. These considerations preclude reliable conclusions on associations between implant types or vendors and the risk of developing BIA-ALCL.

Clinical information on the 32 BIA-ALCL patients with implants shows that the disease is not restricted to specific indications for receiving implants, as affected patients had implants for cosmetics reasons alone, for reconstruction in transgender surgery, after breast cancer surgery, and after prophylactic mastectomy for high breast cancer risk. As 3/32 BIA-ALCL patients were from families with high breast cancer risk, of whom two with proven BRCA-mutations, future studies should investigate the possibility that BRCA 1/2 mutations might increase the risk of BIA-ALCL.

Considering absolute risks of breast-ALCL of 1/35,000 at age 50 years, 1/12,000 at 70 years, and 1/7,000 at 75 years, with 3.3% of all women in the Netherlands having implants, our results affect a relatively large group of women, and therefore have multiple implications. Firstly, comprehensive counseling of women considering breast implants for cosmetic or reconstructive reasons should be mandatory, including communication of risks and symptoms (late seroma or mass) of BIA-ALCL, especially since outcome in early stage disease is usually excellent. Secondly, in our opinion, alternative (autologous) breast surgery procedures^{25,26} should be stimulated, and importantly, be reimbursed in specific groups of women, i.e. healthy women at high genetic breast cancer risk considering prophylactic mastectomy, women who had mastectomy for breast cancer and women who underwent explantation after silicone breast implant-related problems. Thirdly, the fact that the use of silicone breast implants - more than fifty years after their introduction - is again under debate due to increased risk of BIA-ALCL, implies a call for support of registry programs for breast implants and other medical devices, supported and funded independently as post-market monitoring systems.²⁷ Risk-benefit evaluations on breast implants will vary by indication and fall under the responsibility of national governmental and regulatory bodies. Collaboration between international research groups, registries, and governmental organizations to pool multidisciplinary data on BIA-ALCL cases and breast implant prevalence are essential to support these efforts.

Acknowledgements;

We are indebted to the many plastic surgeons, hematologists, general surgeons, and pathologists who provided clinical information and pathological material and data on all patients who have been under their care.

We thank the Dutch National Breast Cancer Screening Program, especially Mrs ten Voorde, for providing information on region-specific breast implant prevalence rates.

We thank the teams of radiologists, and especially dr. N van der Bijl, drs. M Middelkoop, and drs. N Hendriks of the Medical Spectrum Twente, Enschede, the Netherlands and drs. SA Schop and drs J Bosmans at the Maastricht University Medical Centre, Maastricht, the Netherlands for participating in the chest X-ray study.

We also wish to acknowledge the breast implant manufacturers and sales companies for making their classified sales information available for this study.

None of these acknowledged contributors have received any financial compensation.

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Supplements

1. eMethods:

1. Pathology review

All cytological preparations and histological biopsy and excision samples of potential breast-ALCL were reviewed by an experienced hematopathologist (DDJ). In all cases, CD30 and T-cell markers to support a T-cell immunofenotype were available. With sufficient material available to complete immunohistochemical evaluation, at least CD30, CD2, CD3, CD4, CD8, TIA1, granzyme B, ALK1, EBER and CD20 were included, and in selected cases molecular analysis (T-cell re-ceptor rearrangement analysis according to standard BIOMED2 technology) was performed.^{28,29} Local disease status was classified according to Clemens et al.³⁰

2. Case-control selection

Via the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) we identified 782 female patients diagnosed with a histologically or cytologically-proven non-Hodgkin lymphoma (NHL) of the breast in the Netherlands during 1990-2016.

For the period between 1990 and 2005, 398 eligible female patients, and for the period between 2006 and 2016, 384 eligible female patients were diagnosed. Of 782 subjects, only patients classified as anaplastic large cell lymphoma for the case group, and diffuse large B-cell lymphoma, Burkitt lymphoma, follicular lymphoma, nodal and mucosa-associated lymphoid tissue-type marginal zone lymphoma, and peripheral T-cell lymphoma not otherwise specified for the control group were included. 220 subjects were excluded based on other lymphoma types, including chronic lymphocytic leukemia and acute lymphoblastic leukemias as disseminated diseases per definition. Of the remaining 562 subjects, 325 were not confirmed as primary breast located lymphomas.

In the case group, 47 cases were selected; 4 were excluded since the breast was not confirmed as primary lymphoma location. In the control group, 190 controls were selected; 27 were excluded since the breast could not confirmed as primary lymphoma location, 15 controls were missing due to non-responding physicians, and 2 controls were lost to follow-up in medical follow-up records.

For the period between 1990 and 2005, eleven patients with breast-ALCL, among whom 5 with an implant, and 35 controls with non-Hodgkin lymphoma other than breast-ALCL, among whom 1 with an implant, were previously reported in our earlier study.⁴ Subsequently, 32 breast-ALCL cases, among whom 27 with an implant, and 110 controls among whom 1 with a breast implant (contralateral, non-lymphoma-affected), were diagnosed between 2006-2016 (Table 1). Seventy-seven % of breast-ALCL cases was identified between 2006-2016, implying a substantially increased incidence (eFigure 4).⁴

3. Estimation of the prevalence of women with breast implants

We assessed the point prevalence of breast implants per 10-year age group in the general female population in 2015 based on evaluation of 3000 chest X-rays in two cohorts of female patients (20-70 years), and we used the differences in region-specific breast implant prevalence from the BCSP (Breast Cancer Screen-ing Program) to derive a national breast implant prevalence (eFigure 2). The cohorts originated from two regional hospitals in the Netherlands (Maastricht University Medical Centre, Maastricht and Medical Spectrum Twente, Enschede). The validity (sensitivity and specificity) of this method was first examined in a separate validation study using a series of 180 X-rays, alternately positively (n=60) or negatively confirmed (n=120) for the presence of a breast implant by a simultaneously performed CT-scan. CT-scans demonstrating a breast implant were identified by a digital search of radiology reports of the Medical Spectrum Twente radiology database. Inter-observer reproducibility of eight blinded reviewers, including two specialized breast radiologists, two plastic surgeons, two plastic surgery residents, and two medical students, were assessed. Five out of eight reviewers completed the validation study satisfactorily with a median sensitivity of 72% (range 70-77%) and a median specificity of 94% (range 82-96%), of whom three were selected to participate in the prevalence study. To further improve specificity in the actual prevalence study, in case of discordance between two independent reviewers, consensus was reached during a specific reviewers' meeting.

Sales data from 2010-2015 were provided by all currently active breast implant vendors on the Dutch market, representing >95% of the total market share for this period. After exclusion of the component of tissue expanders (temporary implants used as a first-stage prior to definitive breast reconstruction with a permanent breast implant), market shares per vendor were determined. Data prior to 2010 was not considered sufficiently reliable to reflect the breast implant market, since sales data from various breast implant vendors, active prior to 2010, were unavailable, due to bankruptcy or retraction of companies and introduction of others, resulting in major variations in the market.

Subsequently, we determined the average annual percentage change (AAPC) of implant sales during the period with available data (2010-2015) by regressing the log-transformed number of sold implants per year on calendar year.¹⁴ This estimated AAPC was used to extrapolate the number of sold implants in 2016. Corresponding numbers for the period 1965-2009 were extrapolated by applying an AAPC to the empirical 2010 data, which results in virtually no sold implants in 1965, the year the first implant was used in the Netherlands. The change in implant prevalence by calendar year was determined by using the AAPCs for the period 1965-2016, and by using the age-specific size of the female Dutch population from Statistics Netherlands (CBS), resulting in the estimation of the prevalence of women with breast implants for the period 1965-2016.

4. Calculation of cumulative risk

The cumulative risk for breast-ALCL by age in the general female population, as well as in women with breast implants, was calculated using the number of breast-ALCL cases in the general female population, as well as breast-ALCL cases in women with breast implants from PALGA. The age-specific size of the general female Dutch population was obtained from Statistics Netherlands (CBS)¹⁵, the age-specific size of the female population with breast implants was obtained as described in Supplementary methods 3. Cumulative risk to develop breast-ALCL up to age z was calculated as $P_{cri} = 1 - \exp(-\sum l_x * c_x / n_x)$ where c_x and n_x are the numbers of cases and person-years in age-category x , respectively, l_x is the width of the age interval and z is the upper limit of the last age category.¹⁶ For breast-ALCL risk in the general female population, cut-offs for age categories were 35, 45, 55, 65 and 75 years. For breast-ALCL risk among women with breast implants, cut-offs were 30, 40, 50, 60 and 70 years.

2. eResults

1. Lymphoma characteristics of breast-ALCL cases Exposed breast-ALCL cases

Thirty-two breast-ALCL patients were diagnosed between 1997 and 2016 at a median age of 56 years (range 29-73). Primary breast lymphoma was defined as 1) the dominant primary or main symptomatic location in the breast OR 2) the breast lesion the dominant site of involvement on PET-PDG scanning. Twenty-one patients presented with stage I, 5 patients presented with stage II, 3 with stage III, and 3 with stage IV disease.

In 15 patients, large polymorphous lymphoid cells were restricted to the seroma space (T1, according to Clemens et al.)³⁰, in 5 patients additionally minor infiltrative foci were noted in the periprosthetic fibrous capsule (T2). Twelve patients presented with a tumorous mass with infiltration into the breast parenchyma (T3/T4) and histological features as in non-implant-associated patients. In all cases, expression of CD30 was uniform and ALK1 was negative. A T-cell phenotype based on expression of at least one T-cell marker (CD3, CD2, CD5, CD7, CD4, CD8, GB7, TIA1) in the absence of B-cell marker expression (CD20, CD79a, PAX5) was confirmed.

Non-exposed breast-ALCL cases

Eleven primary breast-ALCL patients without an implant were diagnosed between 1994 and 2010 at a median age of 61 years (range 24-87). Primary breast lymphoma was defined as above. In all patients, ALCL, ALK- was confirmed according to the criteria of the WHO classification using morphological and immuno-histochemical markers as above and presented as a tumorous infiltrate in the breast parenchyma (T4).^{7,30}

2. Contralateral breast surgery in exposed breast-ALCL cases

In all patients except one, the implant at the affected side was removed together with the surrounding fibrous capsule. In 18 of 26 patients with bilateral implants, removal of the contralateral implant was performed, for which all patients except one received a contralateral capsulectomy. Eleven patients received no further treatment; the remaining patients received various chemotherapy regimens.

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4. Supplementary eFigures

Figure S1. Selection strategy of histologically or cytologically-proven primary non-Hodgkin lymphoma (NHL) of the breast in female patients diagnosed in the Netherlands between 1990-2016.

Initially, 782 patients for whom no previous lymphoma diagnosis was listed prior to breast lymphoma were identified. Of these 47 were diagnosed as ALCL and 190 as diffuse large B-cell lymphoma, Burkitt lymphoma, follicular lymphoma, nodal and mucosa-associated lymphoid tissue-type marginal zone lymphoma and peripheral T-cell lymphoma not otherwise specified and considered for this study. Of these, 59 patients were further excluded since primary breast localization could not be confirmed based on present clinical criteria and/or lack of sufficient clinical information thereof. Primary breast lymphoma was defined as 1) the dominant primary or main symptomatic location in the breast OR 2) the breast lesion the dominant site of involvement on PET-PDG scanning.

Figure S2a. Assessment of breast implant prevalence in the Netherlands in 2015, by A: Regional breast implant prevalence in 2015 in women between 20-70 as estimated from 3,000 chest X-rays in two large regional medical centers in the East and South of the Netherlands.

Part A shows breast implant point prevalence derived from the chest X-ray study performed in two regional referral hospitals in the Eastern and Southern regions of the Netherlands in women between 20-70 years old. Part B shows region-specific breast implant prevalence rates from the National Breast Cancer Screening Program (BCSP). In part C, national breast implant prevalence in the Netherlands is shown, derived by combining differences in region-specific breast implant prevalence from the BCSP and regional point prevalences from the chest X-ray study (part A and part B).

Figure S2b. Region-specific breast implant prevalence rates from the National Breast Cancer Screening Program (BCSP) and C: Derived estimation of breast implant prevalence in the Netherlands in 2015 in women between 20-70

Figure S2c. Derived estimation of breast implant prevalence in the Netherlands in 2015 in women between 20-70 years of age.

Figure S3. Estimated number of breast implants sold in the Netherlands by calendar year.

The average annual percentage change (AAPC) of sold breast implants between 2010-2015 (covering >95% of all sold breast implants) was used to extrapolate to the periods 1965-2009 (1965 as the year of the first implant used), and 2015-2016.

Figure S4. Incidence of breast-ALCL in patients with breast implants and reasons for breast implantation.

The incidence of breast-ALCL in patients with breast implants shows a strong increase between 1997 and 2016, most prominent after 2012. This increase may be caused by a higher frequency of breast-ALCL, or may in part be related to increased awareness of medical professionals and women with breast implants.

Figure S5a. Sales data of breast implants in the Netherlands between 2010 and 2015 by A: surface properties and B: filling properties.

Sales data were obtained from four manufactures (Allergan, Mentor, Polytech, Eurosilicone) active in the Dutch market between 2010 and 2015. This information covers approximately 95% of the market share in the Netherlands for the period of 2010-2015. Of one complying company, data were received for the period from 1995 to 2015, of one company for the period from 2009 to 2015, of one company for the period from 2007 to 2015 and of one company, who has only recently entered the Dutch market, from 2013-2015. Virtually no smooth and polyurethane implants or non-silicone filled implants were sold during this period, while macro- and micro-textured implants had largely similar market shares

Figure S5b. Sales data of breast implants in the Netherlands between 2010 and 2015 by filling properties.

5. eTables

eTable 1. Implant characteristics of 32 patients with breast-ALCL with breast implants.

Breast-ALCL cases (N)		
Year of breast implant		
1965-1975		1
1976-1985		4
1986-1995		6
1996-2005		14
2006-2015		7
Age at breast implant (years)		
21-30		10
31-40		7
41-50		8
51-60		6
>60		1
Indications for implants		
Cosmetic		22
Reconstruction after breast cancer surgery		7
Reconstruction after prophylactic mastectomy		3
Type of implant		
Macro-texture	Allergan/Inamed/McGhan	22
	Nagor	1
Microtexture	Eurosilicone	2
	Mentor	1
	PIP	1
	Sebbin	1
Unknown		4
Side of implant		
Unilateral		5
Bilateral		27
Interval between first implant and ALCL diagnosis (years) (median interval 13 years, range (1-39 years))		
1-5		6
6-10		5
11-20		14
21-30		5
31-40		2
Number of implant revisions		
None		21
Single		3
Multiple		8w
Indications for last revisional surgery		
Capsular contraction		4
Periprosthetic seroma	Inflammation-related	2
	Lymphoma-related	2
Unknown		3

eTable 2. Clinical characteristics and treatment of 43 patients with breast-ALCL with and without breast implants.

	Primary breast ALCL with breast implants (N=32)	Primary breast ALCL without breast implants (N=11)
Lymphoma localisation		
Unilateral	29	9
Bilateral	3	2
Type of ALCL		
Seroma-associated ¹¹	18	0
Mass forming ¹¹	14	11
Stage		
I	21	6
II	5	2
III	3	0
IV	3	3
Treatment		
First line surgical therapy only (excision or capsulectomy and explantation)	11	0
First line surgical therapy and chemotherapy and/or radiotherapy	12	10
Second line high dose chemotherapy and hematopoietic stem cell transplant	9	1
Treatment results		
Complete remission on first-line and or second-line treatment	29	8
Partial remission on first line and/or second line treatment	1	0
Progressive disease	2	3
Local relapse	0	0
Outcome		
Death due to lymphoma	2	3
Death of other causes	1	0
Alive without disease	23	8
Alive under active treatment	6	0

eTable 3. Clinicopathological characteristics of 32 patients with breast-ALCL with breast implants, diagnosed between 1990 and 2016.

A more detailed version of this table can be found online. All numeral characteristics refer to age or year of diagnosis of BIA-ALCL, etc. BI: breast implant. CR: complete remission, DOOC: death of other causes. DOD: death of disease. In the treatment section CHOP, CHOP, CAVmp/BV, IMVP, DHAP, VIM, BEAM refers to chemotherapy regimens received by the patient. ASCT: autologous stem cell transplantations.

Nr	Age	Year	Indication	BI side	BI at diagnosis	Interval between first BI and diagnosis (years)	Involved lymphoma sites at diagnosis	Stage at diagnosis	ALCL type: seroma or tumor-forming	TNM	Treatment	Outcome
1	38	1997	1984 Cosmetic augmentation	Bilateral	Unknown	13	Left breast	II	mass	T2N0M0	7x CAVmp/BV, explantation and capsulectomy after chemotherapy	CR
2	29	1999	1996 Cosmetic augmentation	Bilateral	Nagor, macrotextured, silicone	3	Right breast, right axillary lymph node	II	mass	T2N1M0	Explantation and capsulectomy bilateral, CHOP 6x, radiotherapy	CR, DOOC
3	49	2000	1977 Cosmetic augmentation	Bilateral	McGhan, macrotextured, silicone	23	Bilateral breasts	II	mass	T2N0M0	CHOP 3x, radiotherapy, -> PR followed by bilateral explantation and capsulectomy, IMVP 2x, BEAM/ASCT,	CR
4	53	2001	2000 Cosmetic augmentation	Bilateral	Rofill PIP Hydrogel, micro-textured	1	Left breast	I	mass	T2N0M0	Explantation and capsulectomy	CR
5	43	2005	1992 Cosmetic augmentation	Bilateral	McGhan, macrotextured, silicone	13	Right breast, right axillary and infradavicular lymph nodes, small bowel, right skull base	IV	mass	T2N2M1	CHOP 8x, DHAP-VIM-DHAP/MTX, explantation and capsulectomy/right	CR
6	47	2008	1988 Cosmetic augmentation	Bilateral	McGhan, macrotextured, silicone	20	Right breast, thoracic wall, right axillary lymph nodes	IIIE	combined seroma and mass	T3N2M1	Explantation and capsulectomy bilateral, CHOP 6x, DHAP+ASCT	CR
7	70	2010	1971 Cosmetic augmentation	Bilateral	Inamed CML 170, macrotextured, silicone	39	Right breast, right axillary lymph node	IIIE	seroma	T1N1M0	Explantation and capsulectomy	CR

eTable 3. Continued.

Nr	Age	Year	Indication	BI side	BI at diagnosis	Interval between first BI and diagnosis (years)	Involved lymphoma sites at diagnosis	Stage at diagnosis	ALCL type: seroma or tumor-forming	TNM	Treatment	Outcome
8	54	2010	1981 Right-sided mastectomy for breast cancer (reconstruction in 1984)	Right	McGhan, macro-textured, silicone	26	Right breast, right axillary and supra/infra-clavicular lymph nodes, sub pleural right	III	seroma	T1N2M0	2010 ABVD, 2011 Explantation and capsulectomy, right, adjuvant chemotherapy (DHAP - VIM - DHAP and BEAM) ASCT	CR
9	45	2011	2000 Cosmetic augmentation	Bilateral	Mentor Siltex, micro-textured, silicone,	11	Right breast	I	seroma	T1N0M0	Explantation and capsulectomy bilateral, CHOP 4, radiotherapy (45Gy)	CR
10	63	2011	1991 Cosmetic augmentation	Bilateral	Unknown	20	Bilateral breasts, mediastinal and abdominal lymph nodes	III	mass	T4N2M0	Explantation and capsulectomy, 8 CHOP, DHAP-VIM-VIM, radiotherapy	DOD
11	64	2012	2001 left-sided mastectomy for breast cancer	Left	McGhan 410 MF 375cc, macro-textured, silicone	11	Left breast	I	seroma	T1N0M0	Explantation and capsulectomy left, explantation right, 6x CHOP	CR
12	42	2012	2004 Cosmetic augmentation	Bilateral	Unknown	8	Left breast, upper abdominal lymph node	IV	mass	T4N1M1	CHOP 6, BEAM and ASCT	CR
13	48	2012	1998 Right-sided mastectomy for breast cancer, 2004 left-sided prophylactic mastectomy (BRCA2 mutation carrier)	1998 Right, 2004 bilateral	McGhan, macro-textured, silicone	14	Left breast	I	seroma	T1N0M0	Explantation and capsulectomy left, CHOP 6x	CR

14	35	2013	2008 Cosmetic augmentation	Bilateral	Eurosilicone type 81 micro-textured, silicone 260cc	5	Right breast	I	mass	T4N0M0	Explantation and capsulectomy bilateral, displatin	CR
15	67	2013	1987 Cosmetic augmentation	Bilateral	Inamed 110 330gr, macro-textured, silicone	26	Right breast	I	seroma	T1N0M0	Explantation and capsulectomy right, 6x CHOP	CR
16	55	2013	1987 Cosmetic augmentation	Bilateral	McGhan matrix 210cc macro-textured, silicone	26	Left breast	IE	mass	T4N0M0	Explantation and capsulectomy bilateral + 6 CHOP	CR
17	46	2014	2000 Cosmetic augmentation	Bilateral	McGhan 410 245cc, macro-textured, silicone	14	Left breast	IB	seroma	T1N0M0	Explantation right, Explantation and capsulectomy left	CR
18	40	2014	2002 Cosmetic augmentation	Bilateral	McGhan 120cc, macro-texture, silicone,	12	Left breast, left axillary lymph nodes	IIA-E	mass	T4N2M0	Explantation and capsulectomy bilateral, CHOP 5 DHAP 1	CR
19	72	2014	1977 Cosmetic augmentation using unknown type	Bilateral	McGhan, macro-textured, silicone	37	Left breast	I	seroma	T1N0M0	Explantation and capsulectomy left	CR
20	56	2014	2002 prophylactic mastectomy (BRCA1 mutation carrier)	Bilateral	Allergan, macro-textured silicone	12	Right breast	I	seroma	T1N0M0	Explantation and capsulectomy bilateral	CR
21	57	2014	2005 Cosmetic augmentation	Bilateral	Eurosilicone, micro-textured, silicone	9	Right breast	IE	seroma	T1N0M0	Bilateral explantation and capsulectomy, radiotherapy	PR
22	57	2014	2008 Right-sided mastectomy for breast cancer, 2014 left-sided mastectomy for breast cancer	Bilateral	Allergan type 410, macro-textured, silicone	6	Right breast	IE	mass	T3N0M0	Explantation and capsulectomy, CHOP 3x, radiotherapy	CR

eTable 3. Continued.

Nr	Age	Year	Indication	BI side	BI at diagnosis	Interval between first BI and diagnosis (years)	Involved lymphoma sites at diagnosis	Stage at diagnosis	ALCL type: seroma or tumor-forming	TNM	Treatment	Outcome
23	56	2015	2010 Right-sided mastectomy for breast cancer, left-sided prophylactic mastectomy (familial cancer, no proven mutation)	Bilateral	Mc Ghan 620 Mx, macro-textured, silicone	5	Left breast	I	seroma	T1N0M0	Explantation and capsulectomy, bilateral, radiotherapy (30 Gy)	CR
24	43	2015	1993 Cosmetic augmentation	Bilateral	Unknown	22	Right breast, right axillary lymph node	IA	mass	T4N1M0	Explantation and capsulectomy, bilateral, 6x CHOP, radiotherapy (40 Gy)	CR
25	73	2015	2003 Right-sided mastectomy for breast cancer	Right	McGhan 410, macro-textured, silicone	12	Right breast	I	seroma	T1N0M0	Explantation and capsulectomy	CR
26	64	2016	2012 Left-sided mastectomy for breast cancer, right-sided prophylactic mastectomy (proven BRCA1 mutation carrier)	Bilateral	Allergan, macro-textured, silicone	4	Left breast	I	combined seroma and mass	T3N0M0	Explantation and capsulectomy	CR
27	56	2016	2006 Cosmetic augmentation	Bilateral	Allergan 495 cc 410, macro-textured, silicone	10	Left breast	I	seroma	T1N0M0	Explantation and capsulectomy, CHOP 6x	CR
28	59	2016	2003 Left-sided mastectomy for breast cancer	Left	Inamed, macro-textured, silicone	13	Left breast	I	mass	T4N0M0	Explantation and capsulectomy	CR

29	56	2016	1998 Cosmetic augmentation	Bilateral	Allergan Natrelle Inspira macro-textured, silicone	18	Left breast	I	seroma	T1N0M0	Explantation and capsulectomy	CR
30	60	2016	2009 Left-sided mastectomy for breast cancer	Left	McGhan, macro-textured, silicone	7	Left breast	I	mass	T4N1M0	Explantation and capsulectomy	CR
31	48	2016	2012 Cosmetic augmentation	Bilateral	Sebbin 330 gr, micro-textured, silicone	4	Left breast	I	mass	T1N0M0	Explantation and capsulectomy	CR
32	56	2016	2001 Cosmetic augmentation	Bilateral	McGhan, macro-textured, silicone	15	Left and right breast, ab-dominal lym-phadenop-thy, bone	IV	mass	T3N2M1	Explantation and capsulectomy, CHOEP 6x + ASCT	CR

Reply: Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast

Daphne de Jong, Mintsje de Boer, Flora E. van Leeuwen

In Reply,

We appreciate the comments on our article.¹ Although relative cancer risk estimates are important for the understanding of oncogenetic processes, it is the excess absolute risk that should be the basis for health care decisions for patients and clinicians alike. Robust epidemiological studies to reliably determine the risk for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) are required to place the high relative risk in perspective. These studies fully depend on unbiased identification of BIA-ALCL and reference disease cases as can be retrieved from population-based, preferably national, comprehensive disease registries and on valid assessment of exposure. In the Netherlands, all these preconditions are available, permitting reliable epidemiological studies on the long-term effects of certain medical exposures on rare diseases, including breast-ALCL in women with breast implants.^{2,3} Various other published studies on risk assessment in BIA-ALCL are limited by bias from case registrations in nonmandatory (national) registries and international collaborative efforts based on poorly defined populations, dual entries in registries, and lack of central pathology review.^{4,5} Because implant registries have only been operational in the past few years and in few countries, reliable estimates of implant carrier prevalence, as well as the use of specific implant types over the past years, is largely lacking. These limitations lead to unpredictable overestimation and underestimation of absolute risks. Also, observed associations of BIA-ALCL with certain implant types should be approached with caution because not only is the use of textured vs smooth implants variable around the world and over time, also implant history in individual patients is often unknown. Considering that the interval between BIA-ALCL diagnosis and time of first implant is more than 10 years (mean, 13 years; range, 1-39 years) these aspects preclude strong statements and the issue should be considered unsettled for now.

Despite the low absolute risk, the high relative risk for women with breast implants to receive a diagnosis of BIA-ALCL is sufficient motivation to explore alternative procedures for breast augmentation and reconstruction. Autologous procedures, while giving good cosmetic results, bear the advantage of avoiding implantation of any foreign body material, smooth or textured, silicone or polyurethane, which is the safest choice with the current state of knowledge. Moreover, using autologous procedures guarantees complete independence from any implant manufacturing company, which may be considered an unplanned advantage when using this alternative. Complete independence from implant manufacturers is a prerequisite for unbiased research and conclusions that are beyond any scientific doubt. Indeed, our group has therefore only accepted (limited) funding from university and charitable foundations.

Breast implant-associated anaplastic large cell lymphoma is a very rare and intriguing disease, with generally a good prognosis after implant removal or capsulectomy as long as the disease is limited to the capsule. Scientific progress in the many aspects of this disease that are still unknown should be supported by (national) mandatory implant

registries and international collaboration. Women who consider breast implants today should primarily be well informed by their plastic surgeons on risks and alternatives to balance the advantages and risks and together come to a sound, personalized decision. No need for panic.

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Macro-textured Breast Implants with Defined Steps to Minimize Bacterial Contamination around the Device: Experience in 42,000 Implants

Mintsje de Boer, Michael Hauptmann, Daphne de Jong,
Flora E van Leeuwen, Hinne A Rakhorst, René RWJ van der Hulst

Dear Sir,

We have read the publication “Macrotextured Breast Implants with Defined Steps to Minimize Bacterial Contamination around the Device: Experience in 42.000 implants” with great interest.¹ Based on the hypothesis that the implant-related microbial biofilm plays a major role in the pathogenesis of BIA-ALCL, the authors suggest that a 14-point plan reduces the bacterial load/contamination associated with macrotextured breast implants and, as a consequence, may lower the risk of BIA-ALCL.²

In their study, 21,650 patients with 42,035 Biocell macrotextured breast implants were followed for a median of 11.7 years (range 1-14 years) and 353 patients with 704 polyurethane breast implants were followed for a median of 8.0 years (range 1-20 years). Eight surgeons who followed the 14-point plan report no cases of BIA-ALCL during the follow-up period of this study,¹ which represents an incidence rate of 0 per approximately 256,129 person-years, with an upper one-sided 95% confidence limit of about 12 per million person-years. Recently, we performed a population-based case-control study on all BIA-ALCL cases diagnosed between 1990 and 2016 in the Netherlands and observed a relative risk of 421.8, which, based on the cumulative absolute risk, corresponds to an incidence rate of 4 per million person-years among women who had received implants of any type following standard procedures.³ The data by Adams et al are therefore consistent with a substantially increased ALCL risk as observed in our study.

In our population-based series, only 11/32 cases (34%) were diagnosed with BIA-ALCL within 10 years after first implantation.³ The relatively short follow-up period of the series by Adams et al. may lead to an underestimation of the incidence of BIA-ALCL. Another possible confounding factor may be that a multicenter study of healthy individuals undergoing breast implants for primarily cosmetic reasons may contain incomplete follow-up information, which is essential for assessment of the true incidence of BIA-ALCL.

While we fully agree that optimizing surgical techniques remain essential to optimizing surgical results, the study by Adams et al. falls short of providing sound evidence that the 14-point approach reduces the risk of lymphoma in women with breast implants. Prospective clinical trials that are adequately powered for rigorous statistical analyses are needed to answer the important questions regarding lymphoma risk. Furthermore, a deeper exploration of the role of inflammation on lymphomagenesis is also warranted to fully understand the relationship between breast implants and lymphoma in the context of BIA-ALCL.

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The Dutch Breast Implant Registry: Registration of Breast Implant- Associated Anaplastic Large Cell Lymphoma - A Proof of Concept

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Background: The Dutch Breast Implant Registry (DBIR) was established in April of 2015 and currently contains information on 38,000 implants in 18,000 women. As a clinical registry, it evaluates the quality of breast implant surgery, including adverse events such as breast implant–associated (BIA) anaplastic large cell lymphoma (ALCL). To examine the efficacy of the DBIR, the capture rate of BIA-ALCL was compared to the registration of BIA-ALCL in the Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA) as a gold standard, in combination with matching these databases to obtain complementary information.

Methods: All BIA-ALCL patients diagnosed and registered in The Netherlands in 2016 and 2017 were identified separately in the PALGA and DBIR databases. In addition, both databases were matched using indirect key identifiers. Pathologic information from the PALGA and clinical and device characteristics from the DBIR were obtained for all patients.

Results: Matching of both databases gave a capture rate of BIA-ALCL in the DBIR of 100 percent ($n = 6$) in 2016 and 70 percent ($n = 7$) in 2017. In total, 17 patients were identified in the PALGA, of which 14 patients were also identified in the DBIR; three patients were not registered; and 10 patients were registered false-positive. Of all confirmed patients, symptoms, staging results, treatment, and implant information were registered.

Conclusions: Currently, the DBIR contains 2 full registration years and captures most of the BIA-ALCL patients despite overestimation. Therefore, pathology confirmation remains essential. By matching these databases, complementary clinical and implant information could be retrieved, establishing the DBIR as an essential postmarketing surveillance system for health risk assessments.

Introduction

Breast implants are class III (high-risk) medical devices that are among the most applied medical devices in plastic surgery.¹⁻³ Recently, we could determine that, in The Netherlands, 3.3 percent of all women between ages 20 and 70 years carry breast implants.⁴ Instigated by the ongoing

discussion on possible health risks in women with breast implants, national and international stake-holders have called for the need for nationally covering breast implant registries.³⁻¹¹ The recently proven significantly elevated risk for breast implant-associated (BIA) anaplastic large cell lymphoma (ALCL) has underpinned the timeliness of these registries.^{4,12,13} BIA-ALCL is a rare variant of T-cell non-Hodgkin lymphoma, occurring in the periprosthetic fluid or capsule of women with breast implants, with a calculated absolute risk of 1:35,000 at the age of 50 years to 1:7000 at the age of 75 years.⁴ Many aspects of this disease remain unresolved, of which identification of specific patient groups and implant associations that infer a higher risk may be the greatest challenges.

For meaningful studies in such a rare disease, a big-data approach is essential. In this light, use of breast implant registries with an almost complete regional or national coverage is an essential tool in evaluating breast implant-related serious adverse events. Currently, only the breast implant registries in Sweden (Swedish Breast Implant Registry, since 2014), Australia (Australian Breast Device Registry, since 2015), and The Netherlands (Dutch Breast Implant Registry, since 2015) seem to be eligible sources for big data.^{11,14,15}

The Dutch Breast Implant Registry (DBIR) is a national, prospective, opt-out registry, with mandatory registration of all breast implant surgery performed in The Netherlands.^{14,16,17} Since the start of the DBIR in April of 2015, approximately 18,000 patients and 38,000 breast implants have been registered until December of 2017. In contrast, the Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA) was established in 1971 as a comprehensive registration of all national pathology reports, containing coded histocytologic and cytopathologic information from all pathology laboratories in The Netherlands, providing nationwide coverage since 1990.¹⁸ We investigated the efficacy of the DBIR by measuring the capture rate of BIA-ALCL patients in the DBIR compared to the PALGA as a gold standard, providing an objective quality assessment of the national breast implant registration program. Second, we aimed to determine the compatibility of both databases in merging data, as a support for future research.

Patients and methods

Registries and Timeframe

Anonymized data for this cross-sectional study were obtained using two databases: the DBIR and the PALGA. The DBIR was implemented nationwide in April of 2015, and 2016 was the first full registration year in which “participation in the Dutch Breast Implant Registry”

was used as a national quality indicator by the Dutch Health Care Inspectorate. BIA-ALCL cases were selected from two corresponding full registration years in both registries, starting on January 1, 2016, up to and including December 31, 2017.

Case-Finding Strategies

All registered BIA-ALCL cases in The Netherlands were identified using the query “anaplastic large cell lymphoma” and “breast” in the PALGA database as described previously.^{4,19} In addition, all cases registered as a revision operation because of BIA-ALCL were selected from the DBIR.

These data were obtained after a centrally approved request by the scientific board of the DBIR, the Dutch Society of Plastic Surgery, and the scientific board of the PALGA. The Medical Research Involving Human Subjects Act does not apply to this study.^{18,19}

Matching Patients in the DBIR and the PALGA

After separate data collection from the PALGA and the DBIR, the output of the DBIR was validated using the identified cases in the PALGA database. Interdatabase comparison per identified case was performed manually, using three key variables: date of diagnosis (i.e., date of receipt of pathology samples) in the PALGA versus operation date in the DBIR (with a maximum range of 1 day), age at diagnosis in the PALGA versus age at surgery in the DBIR, and pathology laboratory in the PALGA versus hospital location in the DBIR.

Included Variables

Subsequently, data from the PALGA and the DBIR were merged. From the PALGA, information on the date of diagnosis, age at diagnosis, pathology laboratory, histopathologic and cytopathologic information on diagnosis, and detailed tumor characteristics was obtained. From the DBIR, clinical information at revision surgery was collected, including patient characteristics (i.e., age, American Society of Anesthesiologists classification, smoking, body mass index, and information on previous breast surgery and/or radiotherapy), surgery characteristics (i.e., hospital identification code, date of operation, side of operation, type of intervention, indication for intervention, and operative technique), and device characteristics (i.e., device type, year of implantation, country of implantation, and manufacturer).²⁰

Results

Capture Rate of BIA-ALCL

Between January 1, 2016, and December 31, 2017, 13,901 patients and 30,399 breast implants were registered in the DBIR (6336 patients and 12,854 implants in 2016; 7565 patients and 17,745 implants in 2017). Of the 13,901 patients, 4039 patients underwent an unexpected revision operation (2031 in 2016; 2008 in 2017). Registered implants were

composed of new implants and revision surgery of breast implants inserted before and after the start of the registry. In the registry, indications for revision surgery are collected and categorized as unexpected or planned, such as the exchange of a tissue expander for an implant or autologous tissue. Of the women with an unexpected breast implant revision in the DBIR, eight patients were reported to have BIA-ALCL in 2016 (0.3 percent) and 16 patients were reported to have BIA-ALCL in 2017 (0.8 percent). Between January 1, 2016, and December 31, 2017, 17 BIA-ALCL cases were identified in the PALGA (n = 7 in 2016; n = 10 in 2017).

Matching of the patients reported with BIA-ALCL in both databases was performed successfully. All seven patients reported in the PALGA database in 2016 were correctly registered in the DBIR (capture rate, 100 percent). In 2017, seven of 10 patients registered in the PALGA database were correctly registered in the DBIR, whereas three were missing (capture rate, 70 percent; n=3 false-negative cases for the DBIR). In both years, 10 additional patients were registered in the DBIR (n=1 in 2016, and n=9 in 2017). In these patients, BIA-ALCL diagnosis was not histologically or cytologically confirmed and therefore not reported correctly in the PALGA database. These cases were considered false-positive for the DBIR (Fig. 1).

Figure 1. Registered BIA-ALCL cases per year in DBIR and PALGA (2016 to 2017).

The number of registered BIA-ALCL cases per month in 2016 and 2017 in PALGA (dark green and dark blue), and the corresponding registrations in DBIR (light green and light blue). Registered cases in DBIR without a histopathological confirmation in PALGA were labeled false-positive (hatched).

Combining Clinical Information from Two Databases

Combined histocytologic findings and patient, surgery, and implant characteristics of confirmed BIA-ALCL patients are listed in Table 1.

Table 1. Complementary character of the DBIR and the PALGA database with histopathological, clinical and breast implant information per case (2016-2017).

Case	Pathological Report	Patient*	Surgery	Breast Implant (explanted)*
1	Periprosthetic seroma, CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T4N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 2, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: N/A. Year of implantation: N/A. Country of implantation: The Netherlands.
2	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type TNM: T1N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: N/A. Year of implantation: N/A. Country of implantation: Abroad (country unknown).
3	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T3N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Replacement with new implant. Indication for revision: Seroma and asymmetry. Additional findings: ALCL. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2013. Country of implantation: The Netherlands. NB: New implanted breast implant: Allergan, textured.
4	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: No.	Primary indication for breast implants: Aesthetic. Side & Intervention: Right - Explantation only. Indication for revision: Seroma/Hematoma. Additional findings: ALCL. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2016. Country of implantation: The Netherlands.
5	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: Asymmetry. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Sebbin Laboratoires. Year of implantation: 2012. Country of implantation: Belgium.

6	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T4N1M0	ASA classification: 2. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 2, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2009. Country of implantation: The Netherlands.
7	Periprosthetic seroma and capsule. CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type TNM: T3N2M1	ASA classification: 3. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: Seroma, Asymmetry, Breast pain. Device rupture: Yes. Silicone extravasation: Yes, intra- capsular. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2001. Country of implantation: The Netherlands.
8	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	Missing in DBIR		
9	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: N/A. BMI: 29. Previous RTx: No.	Primary indication for breast implants: N/A. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: N/A. Silicone extravasation: N/A. Capsular contracture: Grade 2, capsulectomy.	Type: N/A. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2007. Country of implantation: N/A.
10	Periprosthetic seroma CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: N/A. BMI: N/A. Previous RTx: No.	Primary indication for breast implants: Aesthetic. Side & Intervention: Left - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: Textured, silicone. Manufacturer: Allergan. Year of implantation: 2008. Country of implantation: N/A.
11	Periprosthetic seroma and capsule. CD30+, ALK1-. Anaplastic large cell lymphoma. Mass-associated type. TNM: T2N0M1	ASA classification: 3. Smoking: N/A. BMI: 23. Previous RTx: No.	Primary indication for breast implants: Aesthetic. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL and asymmetry. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 4, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: N/A. Year of implantation: 1999. Country of implantation: N/A.

12	Periprosthetic seroma, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	Missing in DBIR		
13	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	Missing in DBIR		
14	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: N/A. BMI: N/A. Previous RTx: N/A.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade N/A, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: Allergan. Year of implantation: 2004. Country of implantation: N/A.
15	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: N/A. Smoking: N/A. BMI: N/A. Previous RTx: No.	Primary indication for breast implants: N/A. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade 1, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: N/A. Manufacturer: CUI implants. Year of implantation: 2003. Country of implantation: N/A.
16	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: No. BMI: 32. Previous RTx: No.	Primary indication for breast implants: Reconstructive. Side & Intervention: Bilateral - Explantation only. Indication for revision: ALCL and seroma. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: N/A, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: Textured, silicone. Manufacturer: Allergan. Year of implantation: 2008. Country of implantation: the Netherlands.
17	Periprosthetic seroma and capsule, CD30+, ALK1-. Anaplastic large cell lymphoma. Seroma-associated type. TNM: T1N0M0	ASA classification: 1. Smoking: No. BMI: 26. Previous RTx: No.	Primary indication for breast implants: Reconstructive. Side & Intervention: Left - Replacement. Indication for revision: ALCL, seroma and asymmetry. Additional findings: No. Device rupture: No. Silicone extravasation: No. Capsular contracture: Grade N/A, capsulectomy.	Type: Permanent breast implant. Texture, coating, fill: Textured, silicone. Manufacturer: Allergan. Year of implantation: 2009. Country of implantation: the Netherlands. NB: new implanted breast implants: Allergan, smooth, silicone.

PALGA indicates Dutch Nationwide Network and Registry of Histo- and Cytopathology; DBIR, Dutch Breast Implant Registry; TNM, TNM classification of Malignant Tumours as by the Union for International Cancer Control's (21); ASA, American Association of Anesthesiologists; BMI, body mass index, RTx, radiotherapy; BIA-ALCL, breast-implant associated anaplastic large cell lymphoma; N/A, not available.

*Variables registered since September 2017: BMI and smoking, and from the explanted devices texture, coating, and fill.

incisional biopsy of a BIA- tumor mass. Of the 17 confirmed cases, median age at diagnosis and revision surgery was 56 years (interquartile range, 48 to 59 years; range, 33 to 75 years). Twelve patients presented with a seroma-associated type BIA-ALCL (T1N0M0), and five patients presented with a mass-associated type (T2 to T4), three of which had dissemination outside the breast.²¹ Median time from implantation to lymphoma diagnosis was 9 years (interquartile range, 5.5 to 13.5 years; range, 1 to 18 years). In 12 patients, BIA-ALCL was the indication for revision surgery and registration in the DBIR; in two patients, BIA-ALCL was an incidental finding at implant revision. Of five women, the primary indication for breast implants was known (n=3 aesthetic, n=2 reconstructive). Seven patients presented with asymmetry and seroma; in the other patients, the symptoms were not registered. The reported capsular contracture grade varied between grade I and grade IV (according to the Baker classification), and all patients underwent a capsulectomy and removal of the implant. Characteristics of the explanted implants were incomplete in the DBIR data set before September of 2017, as this information has only been registered for explanted devices since its most recent update in September of 2017.

The Accuracy of the DBIR: False-Positive and False-Negative Registrations

As derived from the DBIR and PALGA registration logs, the false-positive registrations in the DBIR (n=10) were entered based on a clinically suspected diagnosis of BIA-ALCL before histocytologic and/or cytopathologic assessment by the local and/or expert pathologist. However, once the negative pathology information became available, the registration was not corrected in the DBIR. The current registration procedure also explains the missing DBIR registrations (n=3), because novel lymphoma diagnoses were not updated in previously filed registrations at the time of surgery when lymphoma was not clinically suspected or realized. Even though the DBIR is an opt-out registry with mandatory registration for all board-certified plastic surgeons in The Netherlands since January 1, 2016, we cannot exclude that some institutions still fail to reach a complete registration rate. This was not the case for the three missed lymphoma patients, however.

Discussion

In the present study, the adverse event registration of BIA-ALCL in the DBIR was validated using histopathologically confirmed BIA-ALCL cases from the national pathology registration database (i.e., PALGA). This showed the efficacy of registration of BIA-ALCL in the DBIR to be 100 percent in 2016 and 70 percent in 2017, with a total of 10 patients reported as false-positive, underpinning the importance of histopathologic or cytopathologic confirmation. Furthermore, both databases could be matched, resulting in a larger data set with relevant variables for BIA-ALCL without the need for manual extraction of information from medical records. Data points included implant characteristics, surgery characteristics, and histopathologic information.^{4,12,13,22–24}

Quality Control Strategies for Breast Implants in the DBIR Design

The DBIR has three purposes, all aiming to improve health care quality and patient safety. Besides the evaluation of health care provided, it contains data for recall purposes and determines the performance of all registered devices.¹⁴ Because the quality and completeness of registered information depends on the accuracy of the registry and its users, control mechanisms are recommended.²⁵ To achieve maximal capture rates and improve data completeness, the DBIR uses an opt-out structure, and is “Registration in the Dutch Breast Implant Registry,” a mandatory quality indicator for the Dutch National Health Care Inspectorate since January of 2016. A structure of mandatory input in all registration fields guarantees data completeness. Besides quality control of submitted data, external validation of the registrations is at least as essential. Although no gold standard is known, several methods have been described, such as comparisons with locally held data, comparisons with other registries, or monitoring by dedicated personnel.^{26–28} In the DBIR, all registered implants used for implantation surgery have been compared with a selection of sales data from breast implant vendors in The Netherlands, resulting in an estimated capture rate of 75 percent in its first registration year (data not shown). However, validation of the capture rate of implants that are removed during revision surgery is more difficult, as validation tools with complete, reliable coverage for these operations are unavailable. Therefore, it was valuable to use the PALGA database, which has nationwide coverage, as an external validation tool for this particular group.

Complementarity of Databases

Matching pathologic data from the PALGA database with clinical and implant data from the DBIR proved the complementarity of both databases. Eventually, this could serve as a basic system, substituting for the manual collection of case-based information and minimizing the burden of double registration. Because the DBIR is a clinical audit, additional information such as body mass index, a history of smoking or previous radiotherapy of the breast, previous and subsequent implant operations, and additional findings at revision surgery is automatically asked for. Extensive information on other clinical history and (oncologic) follow-up, however, is not (yet) registered and needs to be extracted from medical records when necessary.

Optimizing the Quality of BIA-ALCL Diagnoses in the DBIR

This study has allowed us to identify various aspects of DBIR registration that will help to improve the quality of the database in the next registry update. Most importantly, 10 patients with a false-positive registration for BIA-ALCL were found and in three registered patients, the BIA-ALCL listings were missing and were considered false-negative. All misclassifications were caused by registrations based on clinical data at the time of surgery without manual correction after pathology reports were received. First, this underpins the importance of including cases with pathologically confirmed diagnoses in institutional and international/national databases in general. For the DBIR in particular, we

plan to include two registration fields for diagnosis: “BIA-ALCL pathologically confirmed” and “suspicion of BIA-ALCL, not pathologically confirmed.” All patients without a definite diagnosis will be automatically tagged and the reporting physician will receive an alert to update the registration based on a final pathologic diagnosis within 1 month after surgery. This procedure is currently being tested. To avoid false-negative registrations, all BIA-ALCL patients registered in the PALGA database will be matched to the DBIR periodically.

Limitations

A limitation is the fact that a minimum period of 3 years is indicated for a properly functioning clinical audit with reliable data.¹⁴ With 2 full registration years, the DBIR is still relatively young, and data completeness needs to improve. Increasing compliance, data validation, and awareness among plastic surgeons is continuously needed to ensure high-quality and completely registered data in the future.

Future Perspectives

The results from this study imply that breast implant registries can be used as an objective, national medical device evaluation system, without financial disclosures, to function as postmarketing surveillance systems, once the collected data have been validated.²⁹ Longitudinal long-term data collections in regular medical device post-approval studies often do not have a sufficient sample size to detect rare diseases such as BIA-ALCL, do not follow participants for a sufficient length of time, and are not equipped to identify influencing factors for the development or prevention of BIA-ALCL. Although matching the DBIR to the PALGA was executed manually for this study, a real-time patient-based matching process is ideally desired. For that, however, solid data validity and more advanced information and communication technology structures are required. A trusted third party may assist in this, but proven reliable search queries and key variables are essential when realizing an automatic matching process. Eventually, the concept of such a combined data set, either manually or automatically, might even be implemented internationally. However, different privacy laws could become an obstacle, requiring attention beforehand.

Conclusions

This study supports the potential of breast implant registries to identify serious adverse events, using BIA-ALCL as an example. Despite its short existence and still growing compliance, the DBIR proved to be effective as a registration system for BIA-ALCL. It showed a 100 percent match in its first registration year, and a 70 percent match in its second full registration year, as validated by the PALGA, albeit at the cost of false-positive registrations, emphasizing the importance of histopathologic confirmation of the diagnosis. By matching databases with patient-related, tissue-related, and implant-related information, reliable complementary data could be retrieved. In the future, a mature DBIR could provide complementary data that can be used for surveillance, monitoring, and to further study severe adverse events such as BIA-ALCL.

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A practical cytological approach to the diagnosis of breast-implant associated anaplastic large cell lymphoma

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The role of cytopathology in malignant lymphoma is largely restricted to primary screening in patients with lymphadenopathy of unknown causes and evaluation of relapse and transformation during follow-up of patients with known and fully classified malignant lymphoma. Few lymphoma diagnoses fully rely on cytology, although breast-implant associated anaplastic large cell lymphoma is currently the centre of clinical attention. Due to the major attention both in the medical and lay media for the recently substantiated high lymphoma risk in women with breast implants, cytopathology departments now frequently receive seroma fluid aspirates with this specific differential diagnostic consideration. In this review, we discuss clinico-pathological aspects of breast-implant associated anaplastic large cell lymphoma from a cytological point of view and provide guidelines for the processing of aspirates in daily practice and strategies for diagnostic work-up of seroma fluids.

Introduction

For comprehensive classification in the current World Health Organisation classification, histological assessment of representative biopsy samples of lymph node or extranodal sites is prerequisite for the majority of malignant lymphomas.¹ Cytological analysis primarily plays a role as a primary screening tool, for instance to exclude metastasis of solid malignancies or diagnose overtly reactive lymphoproliferations. Few malignant lymphomas present as fluid-based proliferations without any tumour mass: vitreous large B-cell lymphoma; HHV8+ primary effusion lymphoma; so-called fluid-overload-related large B-cell lymphoma (HHV8– primary effusion lymphoma); and breast-implant associated anaplastic large cell lymphoma (BIA-ALCL). In these cases, the diagnosis fully relies on cytological assessment.

Since the high relative risk for lymphoma has been described in women with breast implants, this disease has raised major concerns amongst plastic and reconstructive surgeons, regulating government bodies and the lay community.² BIA-ALCL is still a very rare disease, however. As a result of the higher awareness of the lymphoma risk, cytology departments now regularly receive cytological aspirates of seroma fluids from patients with breast implants with specifically inquiring to exclude BIA-ALCL. In this review, we discuss clinico-pathological aspects of BIA-ALCL from a cytological point of view and provide guidelines for the processing of aspirates in daily practice and strategies for diagnostic work-up of seroma fluids.

Presentation, incidence and risk of BIA-ALCL

BIA-ALCL is a rare T-cell non-Hodgkin lymphoma that has recently been added to the World Health Organisation classification as a distinct subgroup.¹ BIA-ALCL have now been recognised in the context of cosmetic augmentation (70%) and of breast reconstruction after breast cancer, both in the affected breast after contralateral prophylactic amputation (30%) and incidentally in transgender women.^{3,4} The lymphoma most often presents as late onset seroma (per definition more than 1 year after implantation), in which the tumour is confined to the periprosthetic fluid or may present as a tumourous mass. As long as the lymphoma remains confined to the seroma space, the outcome is excellent with explantation (removal of the implant and capsulectomy only).⁵ However, in 10%–20% of the patients, infiltration in the breast parenchyma and dissemination of the disease is present and despite systemic therapy, outcome is poor.⁵

Most reports on BIA-ALCL are complicated by lack of unbiased cohorts as reported series mostly rely on non-mandatory, clinical reporting of cases in institutional and (inter) national databases.^{6,7} In the Netherlands, all pathology reports are filed in the nationwide network and registry of histo- and cytopathology (PALGA Foundation) since 1989, providing a population-based, unbiased source for BIA-ALCL cases.⁸ From this database,

we have identified all cases of ALCL in the breast diagnosed since 1990 in the Netherlands and (in part retrospectively, since 2016 prospectively) could identify all BIA-ALCL (n = 42). This cohort is referred to as the Dutch BIA-ALCL cohort. Of 189 primary breast lymphomas identified from the PALGA database between 1990 and 2016, BIA-ALCL ranked second in frequency (23%), only exceeded by DLBCL (50%; Figure 1).

Figure 1. Distribution of classes of primary non-Hodgkin lymphoma in the breast, diagnosed in the Netherlands between 1990 and 2017.

ALCL, anaplastic large cell lymphoma; B-BHL, B-cell lymphoma unspecified; Burkitt, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MALT, mucosa associated lymphoid tissue-type lymphoma; NMZL, nodal marginal zone lymphoma; PTCL, peripheral T-cell lymphoma.

Moreover, as also reported worldwide, the incidence of BIA-ALCL showed a steep increase over the past 8 years and still shows a rising trend in 2018 (Figure 2).

Figure 2. Incidence of breast-implant associated anaplastic large cell lymphoma (BIA-ALCL) in women with breast implants, diagnosed in the Netherlands between 1990 and 2017.

Currently, 414 cases of BIA-ALCL are reported at the US Food and Drug Administration as per September 2017.⁷ The increased incidence may be due to various causes, including a true increased incidence, but is also likely to be due to the higher awareness amongst clinicians and pathologists.

Having reported on the relative risk for women with breast implants to develop BIA-ALCL, we recently completed an update of our previous epidemiological study now based on all reported cases between 1990 and 2016 and could estimate a relative risk of 421.8 (95%CI of 52.6 - 3385.2).⁹ Moreover, using a novel, reliable method to assess the breast implant prevalence, absolute cumulative risks of 29/1 000 000 and 82/1 000 000 women with implants at 50 years and at 70 years, respectively, could be estimated. This risk level is important, but not at all sufficiently high for panic and immediate action. In the first place, this risk level of approximately 1:7000 (at the life expectancy of Dutch women) implies the importance to provide comprehensive information to women considering breast implants with careful explanation of the pros and cons and alternative procedures for breast augmentation, but may not be supportive for an immediate ban on these medical devices.

A relative risk of over 400× strongly indicates a direct or indirect causative relation of the implant to lymphoma development (attributable risk). Toxic substances from the manufacturing procedures (eg, silicone polymerisation catalytic compounds) that are released from the implant material could directly play a role in the oncogenesis, while bacterial load or a specific composition of a periprosthetic biofilm adherent to the surface of the implant have been hypothesised as an indirect factor. Implant texture may be involved passively, facilitating the adherence of bacteria.¹⁰ An association with textured (rough surface) implants is very likely, but whether specific implant types are involved remains to be proven, despite public condemnation of specific brands.

What are the chances to catch a BIA-ALCL in daily practice?

The PALGA database (www.palgaopenbaredatabank.nl) can provide some insight on the chances to diagnose specific diseases in our daily practice.⁸

Plastic surgeons currently increasingly submit seroma aspirates with the specific question to evaluate a possible lymphoma diagnosis. Although cytology practices have the impression that they are flooded by cytological seroma aspirates, PALGA data show that the total number of aspirates for seroma has remained largely stable over the past 10 years. While the large majority concern early-onset seroma after breast cancer surgery, 5.5% are performed for seroma in the context of breast implants. Rare diagnoses of (relapsed) breast cancer were noted only outside the implant setting, while lymphoma was diagnosed both in the implant setting and incidentally outside the implant setting. Only in the implant-setting have gradually increased numbers of seroma aspirations been noted since 2016, but it may be too early to reliably assess a rising trend. Data from the Dutch Breast Implant Registry show a similar trend since 2015, but also here the period is too short to draw definite conclusions. To provide an estimate on the a priori chances to make a breast cancer diagnosis in a woman

with a breast implant, we can assume that of 15 600 newly diagnosed women with breast cancer in the Netherlands (www.rivm.nl), 315 carry an implant for cosmetic reasons. This is based on an implant carrier rate of 3.3% in the Dutch female population older than 18 years and 70% of implants placed for other reasons than malignancy as determined in a previous study. Approximately 10 women are diagnosed with BIA-ALCL per year. This indicates the very small a priori chance to diagnose BIA-ALCL in women with breast implants and should stress the awareness of breast cancer also in this group that is just a reflection of the general breast cancer risk in Dutch women. The seroma-context is highly characteristic, however, and should prompt attention.

A practical approach to patients with a breast implant-related seroma or mass

Standard diagnostic procedures for suspected BIA-ALCL have been proposed by various national governmental and medical professional bodies such as the National Comprehensive Cancer Network (NCCN, USA), the Institut National du Cancer (Inca, France) and the Netherlands Association for Plastic and Reconstructive Surgery (NVPC, the Netherlands) and are largely similar.¹¹⁻¹³ Any seroma occurring more than 1 year after implantation that is not readily explained by infection or trauma should be considered as suspicious for BIA-ALCL. Postoperative seromas occurring less than 1 year after the first implant are generally not part of the disease spectrum of BIA-ALCL. Obviously, this cut-off point is arbitrary and, in the Dutch BIA-ALCL cohort, the shortest interval between implant and lymphoma diagnosis was only 7.5 months, after which seroma with an infiltrative component in the capsular tissue was diagnosed. The range of the interval between last implantation and lymphoma diagnosis is highly variable and ranges between 1 and 39 years in the Dutch BIA-ALCL cohort, with a median of 13 years (Figure 3).

Figure 3. Interval between first breast implant and breast-implant associated anaplastic large cell lymphoma (BIA-ALCL) diagnosis of 42 confirmed BIA-ALCL cases diagnosed in the Netherlands between 1990 and 2017.

According to most guidelines, the initial workup of breast-implant associated seroma includes ultrasound evaluation in general accompanied by magnetic resonance imaging and, aspiration of seroma fluid by fine needle aspiration to send to the microbiology department for infectious causes and to the pathology department for cytological examination. In case of a mass in relation to the breast implant, cytological aspirate assessment should be geared towards adenocarcinoma as well as lymphoma diagnoses. It is generally recommended to involve experienced haematopathologists in the examination of seroma fluids or biopsies from implant-associated masses and include both smears for morphology and cell blocks for immunocytochemical studies.

Our experience

The Amsterdam VU University Medical Center is a reference centre for breast-implant related malignancies as member of the multidisciplinary Dutch BIA-ALCL Consortium. In the following section, we will share our experience and the strategy and techniques that we use to diagnose BIA-ALCL. In our laboratory, smears are air-dried and routinely stained with MayGrünwald Giemsa. Morphologically, BIA-ALCL consist of large immunoblast-like cells with conspicuous nucleoli and several degrees of nuclear pleomorphism (horseshoe shaped or embryoid).¹

Formalin-fixed paraffin-embedded cell blocks from seroma fluid are always made and sections are used for immunocytochemical evaluation. It is virtually always feasible to prepare a routine cell block from all varieties of cytological sample. Most currently used techniques are suitable for immunocytochemical staining as well as for molecular techniques, such as testing for clonality. Alcohol fixation offers good histological preservation but immunocytochemistry results are inferior to formalin fixation.¹⁴ For molecular techniques, however, alcohol fixation offers superior DNA quality.¹⁴ In our laboratory, cells in effusion fluids are prefixed in 4% formalin and thereafter mixed with agar before paraffin embedment. These paraffin blocks provide sections that are suitable for most routine immunocytochemical stainings. The results of clonality testing are also sufficient, but for fluorescent in situ hybridisation this procedure is less optimal.

Immunocytochemical stainings are only performed in cases where smears show at least some atypical cells, suspicious for malignancy. Since the large majority of breast lymphomas are of B- cell type, a panel of markers should be broader than just focused on BIA-ALCL. Moreover, poorly differentiated malignancies such as primary or metastatic carcinoma and melanoma and rarely (post- radiotherapy) (angio)sarcoma should be ruled out. To increase the efficiency and cost effectiveness of immunohistochemistry staining, the use of decision trees with algorithms and panels of markers is highly recommended.¹⁵ Our own preferred approach is listed in Figure 4.

Figure 4. Schematic flowchart for a practical diagnostic approach of periprosthetic seroma in women with breast implants to be used in daily practice.

CD30, which is characteristically uniformly positive in BIA-ALCL is a sensible first step to give a first direction in diagnosis. However, it should be noted that the marker is characteristic, but not specific and also expressed in various other lymphoid malignancies such as large B-cell lymphomas and in reactive lymphoid cells in chronic inflammatory processes as well as in rare instances in angiosarcoma.¹⁶ The spectrum of CD30 positive proliferations obviously is larger, but these may be of less relevance to the differential diagnosis of BIA-ALCL (Figure 5). If CD30 positive large atypical cells are observed, further characterization with additional markers such as T-cell and B-cell markers is needed. It should be noted that BIA-ALCL as also seen in other classes of ALCL is often marked by T-cell marker loss and CD3, CD2, CD5 and CD7 are very often not expressed, while CD4 and cytotoxic markers granzymeB and TIA1 are most often positive and contribute to the diagnosis (Table 1).

Table 1. Immunophenotypical features of 42 breast-implant associated anaplastic large cell lymphoma patients of the Dutch BIA-ALCL cohort, diagnosed between 1990 and 2017.

	Positive/total tested	Negative/total tested
CD30	100% (42/42)	-
ALK-1	-	100% (42/42)
CD3	28% (11/39)	72% (28/39)
CD2	41% (11/27)	59% (16/27)
CD5	30% (10/33)	70% (23/33)
CD7	-	100% (13/13)
CD4	79% (26/33)	21% (7/33)
CD8	7% (2/29)	93% (27/29)
Granzyme B	64% (14/22)	36% (8/22)
TIA-1	71% (15/21)	29% (6/21)

ALK1 is always negative and ALK expression should alert to a systemic T-cell lymphoma. In this respect, our experience is fully in line with series reported by others.^{1,3,5}

If the interpretation of the immunocytochemical stainings is ambiguous, molecular techniques such as immunoglobulin and T cell receptor gene rearrangement studies can be used as a tool to resolve diagnostic problems. In our hands, these techniques have also been performed successfully on cell blocks (Figure 6-8).

Figure 5. Cytopathological features of BIA-ALCL in seroma aspirates (ABC): May-Grünwald-Giemsa-stained smear with the typical large immunoblast-like cells with irregularly shaped nuclei (A), the atypical cells stain uniformly positive for CD30 (B), positive Granzyme B staining in ALCL (C).

Figure 6. Cytopathological features of a reactive lymphoid infiltrate with CD30 positive cells in a seroma aspirate. A few blast-like cells and some eosinophils, highlighted by arrows (A), some small blast-like cells stain with CD30 (B), in a background of small T cells positive for the cytotoxic marker granzyme B (C). In this case no T cell receptor rearrangement was found and the proliferation was diagnosed as a reactive, non-malignant infiltrate.

Figure 7. Cytopathological features of a reactive process with lymphohistiocytic reaction (ABC). Small lymphocytes admixed with macrophages (A), no CD30 staining (B), CD68 shows the large component of macrophages (C).

Figure 8. Cytopathological features of a reactive process with eosinophilic granulocytes (ABC). The aspirate contains only a few lymphocytes and eosinophils (A), no CD30 positive cells (B), in a background of small T cells, positive for CD3 (C).

Procedures following a cytological diagnosis of BIA-ALCL

BIA-ALCL can present as peri-implant effusion (seroma-type) and the other less frequent occurring type with a solid tumour mass. The latter has adverse prognostic features and might better be treated with systemic therapy.^{5,9} For optimal diagnosis of the solid type histological biopsies are the first choice. The same decision trees, algorithms or panels of stains as have been described in the embedded cytological material can be used. The morphology is that of a standard ALK-negative ALCL. In the seroma-associated type, histology of the capsules surrounding the implant is routinely performed after capsulectomy with or without re-implantation. Tumour cells can be very sparse, however, and special attention should be given to clumps of tumour cells adherent to the inner surface of the fibrous capsule and often related to fine clots. Varying degrees of capsular infiltration can be seen, which are better appreciated within the accompanying reactive lympho-histiocytic infiltrate using CD30 immunohistochemistry. We recommend standard investigation of capsules when removed, by taking sufficient sections, especially including fibrin clots adherent to the inner surface of the fibrous capsule.

Future directions

With the increasing numbers of seroma samples submitted to cytology departments and in view of the very low incidence of the BIA-ALCL, a screening method with high sensitivity and a reasonable specificity would be attractive as a time- and cost-effective tool. Any selected case may then be further worked-up for definite diagnosis according to the methods described above. Only few reports on the value of flow cytometry in the diagnostic workup of seroma-associated lymphoproliferations have been published, showing that this technique is in principle feasible.^{17,18} In the experience of one of our collaborating groups, using a combined panel of CD45, CD2, CD3, CD4, CD5, CD8, CD30 and CD33 in combination with forward/ side scatter (SSC) to select for large cells, lymphoma cells can indeed be recognised. This method depends on fresh material and seroma fluid should be processed within 12 hours after aspiration to remain viable for minimally another 24 hours in Dulbecco's modified Eagles medium with bovine serum albumin (personal communication, Dr M. Batstra, Reinier de Graaf Hospital, Delft, the Netherlands). It should be noted that this technique is highly dependent on experienced professionals to comprehensively analyse multiparameter flowcytometric data. Broader experience should provide data on sensitivity and specificity to determine the potential added value of flow cytometry for the evaluation of seroma fluids in daily practice. Data are too limited for meaningful conclusions thus far.

CD30-expressing lymphoid malignancies are known to shed soluble CD30 protein in fluids, including in peripheral blood and central nervous system fluid and can be demonstrated in patients with classical Hodgkin lymphoma, adult T-cell leukaemia and

systemic type ALCL using enzyme-linked immunosorbent assay techniques.¹⁹⁻²¹ Therefore, also soluble CD30 may be attractive as an alternative screening tool for seroma fluids and may be explored as a screening tool in the near future.

Acknowledgements

We thank Dr Esther van den Broek, PALGA Foundation, Houten, the Netherlands, for providing data on the frequency of reported seroma aspiration procedures within and outside the breast implant setting and Dr Babette Becherer, Dutch Institute for Clinical Auditing, Leiden, the Netherlands for sharing preliminary data from the Dutch Breast Implant Registry (DBIR).

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Breast Implant-Associated Anaplastic Large- Cell Lymphoma in a Transgender Woman

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Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare but serious complication in patients with breast implants. Patients are at risk of BIA-ALCL whether they receive breast implants for cosmetic reasons or for reconstructive purposes after surgery for breast cancer or prophylactic mastectomy. During the past decade, an increased number of reports have addressed BIA-ALCL. Herein, we describe BIA-ALCL in a transgender woman. The patient received breast implants as part of her gender transition and was diagnosed with BIA-ALCL 20 years later. The patient underwent several revisional operations in the 20 years after her primary breast surgery to treat unexplained pain with low-grade fever, severe capsular contracture (Baker grade III-IV), and several instances of implant rupture. In July 2016, the patient presented to our office with "late-onset" periprosthetic seroma 5 years after her last revisional breast surgery. She was diagnosed with BIA-ALCL without capsular invasion based on results of cytologic analysis of the peri-prosthetic seroma and histologic evaluation of the periprosthetic capsule. This diagnosis was verified further by results of immunohistochemical testing, which indicated expression of CD30 and T-cell markers in the periprosthetic seroma only. Our intentions with this case report are to demonstrate that all patients who undergo breast implantation, including transgender women, are at risk of BIA-ALCL and to highlight the importance of cytomorphologic and immunohistochemical screening of seroma fluid in patients with late-onset periprosthetic seroma.

Introduction

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare variant of T-cell non-Hodgkin lymphoma that occurs in the periprosthetic fluid or capsule of women who undergo breast implantation.¹⁻⁴ BIA-ALCL is included as a (provisional) entity in the 2016 nomenclature of the World Health Organization.⁵ When limited to the periprosthetic seroma or capsule, BIA-ALCL has an indolent clinical course, and explantation and capsulectomy may be adequate treatments.⁶ However, in approximately 10% of patients with BIA-ALCL, lymphoma dissemination occurs, which necessitates high-dose systemic chemotherapy and poses a risk of adverse prognosis.⁷ The pathogenesis of BIA-ALCL likely is multifactorial and associated with characteristics of the textured implant, features of the implant-related microbial biofilm (eg, its density and composition), and local immune response.⁸⁻¹¹

Approximately 200 cases of BIA-ALCL have been described worldwide; these cases have occurred in the context of cosmetic augmentation (54%-57% of all cases) or breast reconstruction after cancer related or prophylactic surgery (43%-45%).^{12,13} Herein, we highlight a unique at-risk population by describing a transgender woman with BIA-ALCL.

Case presentation

In July 2016, a 56-year-old transgender woman presented to our outpatient clinic with rapid enlargement of the left breast. Approximately 20 years prior to presentation, she had received bilateral breast augmentation with silicone-filled textured implants and penile inversion vaginoplasty as part of a gender transition. These procedures were performed in a single surgical session by a past staff physician of the Plastic Surgery Department of the VU Medical Center (Amsterdam, the Netherlands). The patient subsequently underwent multiple revisional breast surgeries to treat unexplained pain and low-grade fever, severe capsular contracture (Baker grade III-IV), and implant rupture (Table 1).

Figure 1. Ultrasonographic findings depicting seroma-associated BIA-ALCL of the left breast. Explantation of the left breast subsequently was performed. Note the seroma (red arrow) surrounding the periprosthetic space (yellow arrow). The implant is distinguishable by its folded surface. The blue arrow indicates the skin and subcutaneous layers.

Table 1. Implant-Related Surgical Procedures in a Transgender Woman.

Year	Age, y	Procedure	Reason for Procedure	Side of Surgery	Type of Prosthesis	Additional Information
1998	38	Neomammoplasty with implantation	Male-to-female gender transition	Bilateral	Nagor GFX ^a textured gel-filled implants; 460 cc; placed bilaterally	NA
1999	39-40	Explantation and reimplantation	Pain in left breast; low-grade fever	Left	Rofil ^b highly cohesive textured gel-filled implant; 460 cc; placed unilaterally on left side	Elevated erythrocyte sedimentation rate; small hypoechogenic structure, interpreted as postoperative seroma, on preoperative ultrasound examination of left breast
2012	52	Explantation, capsulectomy, and reimplantation	Baker grade 3 capsular contracture; bilateral implant rupture	Bilateral	Allergan Natrelle Inspira SoftTouch ^c textured gel-filled implant; 490 cc; placed bilaterally	Bilateral rupture of breast implants on preoperative ultrasound examination; results of postoperative pathology analysis of periprosthetic capsules indicated foreign-body reaction related to silicone particles; absence of T-lymphocytes that tested positive for CD30 or ALK
2015	56	Explantation and reimplantation	Implant rupture in right breast	Right	Allergan Natrelle Inspira SoftTouch ^c textured gel-filled implants; 490 cc; placed unilaterally on right side	No abnormalities of left breast; implant rupture and intracapsular hyperechoic seroma of right breast on preoperative ultrasound examination
2016	56	Explantation and capsulectomy	Progressive late-onset periprosthetic seroma of the left breast	Left	None	Results of cytopathologic assessment of periprosthetic seroma collected perioperatively indicated T-lymphocytes that tested positive for CD3 and ALK; diagnosis of seroma-associated BIA-ALCL

BIA-ALCL, breast implant–associated anaplastic large-cell lymphoma; NA, not applicable. aNagor Ltd., Cumbernauld, Glasgow, UK. bRofil, Breda, the Netherlands. cAllergan, Parsippany-Troy Hills, NJ.

“Late-onset” periprosthetic seroma, (i.e. after more than one year after implantation) of the left breast was noted on our examination and was confirmed by ultrasonographic findings (Figure 1). Unilateral explantation of the Natrelle Inspira SoftTouch device (textured, gel-filled, 490 cc; Allergan, Parsippany-Troy Hills, NJ) and complete capsulectomy were performed. Seroma fluid and capsular tissue were obtained for analysis at the VU University Medical Center Department of Pathology as part of routine patient care and processed as recommended by de Jong et al for late-onset seroma.¹⁴ Histologic findings of the capsular tissue showed presence of a small collection of atypical lymphoid cells adherent to the inner surface of the fibrous capsule. No infiltrating component of the tumor was observed, despite lymphohistiocytic inflammatory infiltrate in the capsule tissue. Large atypical lymphoid cells were abundant in the

seroma fluid. Immunocytologic results on the cytological preparations, were positive for CD30, CD2, and CD3 and negative for CD4, CD8, TIA1, granzyme B, ALK1, EBER, and B-cell markers, which confirmed the diagnosis of ALK-negative BIA-ALCL (Figure 2). We conducted a retrospective analysis of all available histologic specimens, including an immunohistochemical examination of capsular tissue excised at the patient's revisional breast surgery 4 years before presentation. Our findings indicated absence of lymphoma localization at that time.

Figure 2. Histocytologic and immunohistochemical analyses of seroma-associated BIA-ALCL.

- A Lymphoma cells with abnormal (kidney- or horseshoe-shaped) nuclei in hematoxylin and eosin (H&E) staining (original magnification x400).
- B Enlarged atypical lymphoid cells were abundant in the seroma fluid and had adhered to the capsule (H&E-staining, original magnification x400).
- C Tumor cells stained with anti-CD30 in seroma fluid, showing brown chromogen (original magnification x400).
- D Tumor cells stained with anti-CD3 antibodies in seroma fluid (original magnification x400).

Results of a complete standardized hemato-oncologic work-up, involving positron emission tomography–computed tomography, demonstrated lack of dissemination, suggesting stage IE lymphoma.⁶ The patient underwent explantation of the contralateral right breast implant; no oncologic treatment, such as chemotherapy or radiotherapy, was indicated. In accordance with international recommendations, follow-up was conducted in collaboration with the Departments of Hemato-oncology and Plastic and Reconstructive Surgery of the VU Medical Center (Amsterdam, the Netherlands).¹⁵ The patient was in complete remission 10 months postoperatively.

Discussion

In a case-cohort epidemiologic risk assessment conducted in the Netherlands from 1990 to 2005, our group found an odds ratio of 18.2 for ALCL in women with breast implants; the estimated absolute risk was 1:300,000 to 1:1,000,000.¹⁴ In recent years, plastic surgeons and pathologists have become more aware of BIA-ALCL, which has yielded in an increasing apparent incidence of this disease.¹⁶ The number of cosmetic breast augmentations with macrot textured implants also has grown, but in view of the

increasing market shares of these products, specific risk assessments in relation implant characteristics await further study.⁴ Therefore, the true incidence of BIA-ALCL may be increasing and may exceed current estimates.¹⁶ Transgender women have not formally been included in risk assessments of BIA-ALCL.^{13,14,16} To our knowledge, the current report is only the second description of BIA-ALCL in a transgender woman with breast implants.¹⁷

The prevalence of gender dysphoria in the general population is 1:10,000, and an estimated 60% to 70% of individuals who undergo male-to-female transition require breast implantation. (Cross-sex hormone therapy adequately enlarges the mammary glands in 30%-40% of transgender women.) Therefore, BIA-ALCL may be diagnosed more frequently in transgender women in the coming years.^{18,19}

Conclusions

Physicians must recognize that all patients with breast implants, including transgender women, are at risk of BIA-ALCL. Cytohistologic and immunohistochemical analysis of aspirated seroma fluid constitute the most sensitive screening and diagnostic approach for patients with breast implants who present with late-onset periprosthetic seroma.

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Chromosome 20 loss is characteristic of breast implant–associated anaplastic large cell lymphoma

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Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a very rare type of T-cell lymphoma that is uniquely caused by a single environmental stimulus. Here, we present a comprehensive genetic analysis of a relatively large series of BIA-ALCL (n=29), for which genome-wide chromosomal copy number aberrations (CNAs) and mutational profiles for a subset (n=7) were determined. For comparison, CNAs for anaplastic lymphoma kinase (ALK)⁻ nodal anaplastic large cell lymphomas (ALCLs; n=24) were obtained. CNAs were detected in 94% of BIA-ALCLs, with losses at chromosome 20q13.13 in 66% of the samples. Loss of 20q13.13 is characteristic of BIA-ALCL compared with other classes of ALCL, such as primary cutaneous ALCL and systemic type ALK⁺ and ALK⁻ ALCL. Mutational patterns confirm that the interleukin-6–JAK1–STAT3 pathway is deregulated. Although this is commonly observed across various types of T-cell lymphomas, the extent of deregulation is significantly higher in BIA-ALCL, as indicated by phosphorylated STAT3 immunohistochemistry. The characteristic loss of chromosome 20 in BIA-ALCL provides further justification to recognize BIA-ALCL as a separate disease entity. Moreover, CNA analysis may serve as a parameter for future diagnostic assays for women with breast implants to distinguish seroma caused by BIA-ALCL from other causes of seroma accumulation, such as infection or trauma.

Introduction

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a rare class of T-cell lymphoma and is listed as separate provisional entity in the World Health Organization classification.¹ In the past 10 years, the incidence of BIA-ALCL has dramatically increased, and lymphoma risk has become a matter of concern for national public health regulatory bodies worldwide. Previously, we showed that women with breast implants have a >400-fold increased relative risk to develop breast anaplastic large cell lymphoma (ALCL) than do women without breast implants, with an absolute lifetime risk of 1 in 7000.²

In most patients, BIA-ALCL is limited to the periprosthetic seroma space (seroma BIA-ALCL); progression is seen into the capsule or breast tissue (tumor BIA-ALCL) in only ~20% of patients.

BIA-ALCL belongs to the family of ALCL, which also includes systemic anaplastic lymphoma kinase (ALK)⁺ and ALK-negative or nodal-type ALCL (nALCL), and primary cutaneous ALCL (pcALCL).^{1,3}

The first molecular evidence for BIA-ALCL as a separate entity was published in 2019, based on gene expression in a set of 12 samples.⁴ Comprehensive molecular data for BIA-ALCL have been limited.⁴⁻⁹ Recently, a cohort of 34 BIA-ALCL cases analyzed by whole-exome sequencing (WES) showed recurrent mutations in the JAK-STAT pathway, epigenetic modifiers, and TP53.¹⁰ This study confirms findings from previous smaller series.⁵⁻⁹ Together, these reports demonstrate that recurrent activating mutations in the JAK-STAT pathway and epigenetic modifiers have major oncogenic importance. However, they are common among all ALCL family members^{4,10,11} and other T-cell lymphoma entities, including peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS),¹¹ and are not specific for BIA-ALCL.⁵⁻¹⁰ Because no statistically significant defining genomic characteristic unique to BIA-ALCL has been determined thus far, we complemented information on the genomic landscape of BIA-ALCL by analyzing chromosomal copy number aberrations (CNAs) using shallow whole-genome sequencing (WGS) (n=29), as well as mutations by WES (n=7), in a well-defined series of BIA-ALCL patients and compared the CNAs with a control cohort of ALK2 nALCL patients (n=24).

Study design

We identified all patients with BIA-ALCL diagnosed between 1990 and 2018 in The Netherlands (n=50).² Sufficient DNA could be isolated from 35 formalin-fixed paraffin-embedded samples from 29 patients, including seroma BIA-ALCL (n=13), tumor BIA-ALCL (n=10), and paired samples of seroma BIA-ALCL and tumor BIA-ALCL (n=6). As a control cohort, 24 ALK⁺ nALCL samples, of which 7 had localized in the breast but were not implant associated, and 17 were from other sites, were collected from the archives of the Department of Pathology Amsterdam UMC. DNA was processed for 50-bp single-ended shallow WGS on a HiSeq 4000 (Illumina, San

Diego CA), and CNAs and copy number load were calculated as previously described.¹² Based on the CNA profiles, the intratumoral heterogeneity was estimated (E.v.D., Tom van den Bosch, Kristiaan J. Lenos, Khalid El Makrini, Lisanne E. Nijman, Hendrik F. B. van Essen, Nico Lansu, Michiel Boekhout, Joris H. Hageman, Rebecca C. Fitzgerald, Jurriaan B. Tuynman, Hugo J. G. Snippert, Geert J. P. L. Kops, Jan Paul Medema, B.Y., Louis Vermeulen, and D.M.M., manuscript submitted May 2020). For WES, a SeqCap EZ MedExome targeted enrichment kit (Roche, Pleasanton, CA) was used. Detailed methods can be found as supplemental Methods.

Results and discussion

From 29 patients, 35 formalin-fixed paraffin-embedded samples, including 6 paired seroma and tumor pairs, could be included in this study. Twenty patients had breast implants for cosmetic reasons, 8 had implants after mastectomy for breast cancer, and 1 patient had implants after preventive mastectomy. Further clinicopathological information is listed in supplemental Tables 1 and 2.

CNAs in BIA-ALCL

Shallow WGS was performed for all BIA-ALCLs and 24 ALK2 nALCLs. CNAs were detected in 27 of 29 BIA-ALCL patients (94%) and in 23 of 24 ALK2 nALCL patients (96%) (supplemental Figure 1). The most frequent CNAs in BIA-ALCL were gain of chromosome 2p25-pter (48%) and losses of 8p (48%), 20p13-p12 (48%), and 20q13.12-q12.2 (66%) (Figure 1A). Chromosome 9p24 gains are detected in 27.5% of BIA-ALCLs, as also reported previously.¹³ The most frequent CNA, 20q13.12-q13.2 loss, had a smallest region of overlap of 3 Mb (Figure 1B). In 7 patients, this was combined with a 1.4-Mb subcentromeric gain of 20q11.21. Because these regions are highly gene dense, no specific or obvious driver-gene candidate could readily be identified. Only limited CNA data are available from published case series; chromosome 20 loss is reported in 10 of 15 cases.^{6,10,14} This further supports that chromosome 20 loss is indeed characteristic for BIA-ALCL and is not restricted to Dutch patients. The CNAs of BIA-ALCL were compared with ALK⁺ nALCL. Statistically significant differences were found for chromosome 19p13.3 loss (0% vs 25%; $P = .01$; false discovery rate [FDR], 0.03), 20p13-p12 loss (45% vs 8%; $P = .01$; FDR, 0.04), and 20q loss, with a peak at q13.13 (66% vs 13%; $P < .0001$; FDR, 0.0001). Chromosome 20 loss was not observed in any of the 7 primary breast ALK⁺ nALCLs outside of the breast implant context, indicating that this is not a site/organ-specific feature but is implant associated (supplemental Figure 2C). Next, we studied the CNA profile of BIA-ALCL in relation to pcALCL, ALK⁺ nALCL, and PTCL-NOS, based on publicly available CNA data from large series (supplemental Table 3).¹⁵⁻¹⁸ In pcALCL, ALK⁺ nALCL, and PTCL-NOS, chromosome 20q loss is a rare finding (9%, 10%, and 4%, respectively) and, therefore, can be considered highly characteristic for BIA-ALCL (all $P < .001$). In conclusion, partial loss of chromosome 20q provides further genetic justification to recognize BIA-ALCL as a separate disease entity.

Figure 1. CNAs in 29 BIA-ALCL and ALK2nALCL cases.

(A) CNA frequencies of 29 BIA-ALCL patient samples. Frequency of gains (red) and losses (blue) are shown on the y-axis, sorted in chromosomal order and by chromosomal position on the x-axis. The top 5 most frequent CNAs in BIA-ALCL are gains of chromosome 2p25-pter (48%) and 8q24-qter (45%) and losses of chromosome 8p (48%), 20p13-p12 (48%), and 20q13.12-q13.2 (66%). Of the 6 paired samples, only CNA of the seromas are included. (The same frequency plot is created for the CNAs of matching tumors; see supplemental Figure 2.) (B) Chromosome 20 CNAs with seroma BIA-ALCL (light blue) and tumor BIA-ALCL (magenta) on the y-axis and gains (red), losses (blue), and blacklisted regions (gray) by chromosomal position on the x-axis. The ideogram of chromosome 20 is given above the graph. The smallest region of overlap and, hence, the most frequently lost region, is at chromosomal band 20q13.13-13.2. (C) Comparison plot for CNAs between BIA-ALCL (filled; n=29) and ALK2 nALCL (lines, n=24). Gains (positive value, red) and losses (negative value, blue) are depicted, sorted by chromosomal position (x-axis). (D) Frequency plot of P value (pink) calculated with a 2-sided Wilcoxon rank-sum test with 10 000 permutations and false discovery rate (FDR, striped segments) of the difference in CNAs; the horizontal dotted lines show the significance thresholds (red: $P < .05$; blue: FDR > 0.1). If the difference in CNA level crosses the P value, and the FDR level is < 0.1 , the difference is considered significant. Significant differences are seen for losses at chromosome 19 20p, and 20q.

Differences between tumor BIA-ALCL and seroma BIA-ALCL

In comparison with tumor BIA-ALCL (n=16), seroma BIA-ALCL showed a significantly higher copy number load ($P = .008$) (Figure 2A). Individual seroma BIA-ALCL and tumor BIA-ALCL copy number profiles were marked by noninteger sublevels of CNAs, which are indicative of intratumoral copy number heterogeneity, hence multiple subclones (supplemental Figure 3). A heterogeneity measure (E.v.D., Tom van den Bosch, Kristiaan J. Lenos, Khalid El Makrini, Lisanne E. Nijman, Hendrik F. B. van Essen, Nico Lansu, Michiel Boekhout, Joris H. Hageman, Rebecca C. Fitzgerald, Jurriaan B. Tuynman, Hugo J. G. Snippert, Geert J. P. L. Kops, Jan Paul Medema, B.Y., Louis Vermeulen, and D.M.M., manuscript submitted May 2020) was significantly higher for seroma BIA-ALCL than for tumor BIA-ALCL ($P = .002$) (Figure 2B). This indicates that the higher copy number load of seroma BIA-ALCL is related to a higher level of subclonal variation with the synchronous presence of multiple subclones in seroma BIA-ALCL, with clonal selection upon infiltration in the breast parenchyma. In contrast, subcentromeric gains at chromosome 20 seem to be exclusively associated with seroma BIA-ALCL ($P = .007$; FDR, 0.09) (Figure 2C).

The mutational landscape of BIA-ALCL

Seven BIA-ALCL tumor and matched normal sample pairs were subjected to WES analysis. Mutations were detected in 400 genes across the 7 patient samples, of which 38 known pathogenic mutations, including STAT3 (n=2), JAK1, KMT2C, and MEF2A, which were also reported by other investigators⁵⁻¹⁰ (supplemental Figure 5; supplemental Table 5). Integration of mutation and CNA data show that the JAK1-STAT3 pathway was activated by gain-of-function mutations, as well as by chromosomal amplification (supplemental Figure 5C). Systemic deregulation of the JAK1-STAT3 pathway in BIA-ALCL is further underpinned by strong and uniform expression of phosphorylated STAT3, which is in contrast to a significantly lower and more heterogeneous phosphorylated STAT3 expression pattern within and between tumors in ALK⁺ nALCL ($P < .0001$) (supplemental Figure 6; supplemental Table 6). Further, combined chromosome 20 loss and mutation of local genes (NFATC2, NEURL2) was observed in 1 case.

Conclusions

We found that BIA-ALCL is characterized by loss of (part of) chromosome 20q and is present in a high percentage of patients, distinguishing this disease from other types of ALCL and PTCL-NOS. This feature may provide a supporting argument in diagnostically equivocal cases, especially in the differential diagnosis with other ALCL subtypes. CNA detection by next-generation sequencing has been shown to be a sensitive method in liquid biopsy analysis,¹⁹ whereas routine cytological assessment of seroma aspirates for cytomorphological features and CD30 immunocytology can be difficult to interpret. Therefore, omnipresent CNAs in BIA-ALCL may serve as a basis for a complementary diagnostic assay to differentiate lymphoma-associated seroma fluid from reactive effusions related to infection, trauma, or inflammatory response to implant rupture.²⁰

Figure 2. CNA comparison of seroma BIA-ALCL and tumor BIA-ALCL.

(A) Box plots of the percentage of the genome gained or lost in seroma BIA-ALCL (average 31%) and tumor BIA-ALCL (average 19%). Seroma BIA-ALCL has a significantly higher copy number load. Significance was calculated using the Wilcoxon rank-sum test for independent samples and paired samples separately, after which a weighted pooled P value was calculated ($P = .008$) (supplemental Table 2). (B) Heterogeneity of seroma BIA-ALCL (average 0.074) and tumor BIA-ALCL (average 0.041). Seroma BIA-ALCL is significantly more heterogeneous. A Wilcoxon rank-sum test was performed for independent samples and paired samples separately, after which a weighted pooled P value was calculated ($P = .002$) (supplemental Table 2). (C) Comparison plot for CNAs between seroma BIA-ALCL (filled) and tumor BIA-ALCL (lines). Gains (positive value, red) and losses (negative value, blue) are depicted, which are sorted by chromosomal position (x-axis). (D) Plot of P value calculated with a 2-sided Wilcoxon rank-sum test with 10 000 permutations (pink) and FDR (striped segments) of the difference in CNA frequencies. The horizontal dotted lines show the significance thresholds (red: $P < .05$; blue: FDR, 0.1). When the difference in CNA level crosses the P value and the FDR level is, 0.1, the difference is considered significant. A significant difference is seen for the subcentromeric gain of chromosome 20, which is present in 8 seroma BIA-ALCLs and missing in all tumor BIA-ALCLs. No statistically significant difference was observed for any other region.

Acknowledgements

The authors thank all pathologists, pathology laboratories, and the nationwide histo- and cytopathology registry of The Netherlands for providing tissue materials and data about patients who have been under their care. The authors also thank Yongsoo Kim for advice on WES analysis and Paul P. Eijk and H. (Dirk) F.B. van Essen (Tumor Genomic Analysis Core, Amsterdam UMC) for help and advice with next generation sequencing experiments. They also thank Titus Lotgering for creating the visual abstract.

This work was supported by Dutch Cancer Society grants KWF 2015- 7925, KWF 2015-7882, and KWF 2012-5711.

The funders had no role in the study design, material collection, analysis or interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

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Supplemental Methods

Patients and sample selection

From the nationwide histo- and cytopathology registry of the Netherlands (PALGA) we identified all patients with histologically or cytologically proven BIA-ALCL diagnosed between 1990 and 2018 (n=50). Of this cohort, 38 FFPE tumor samples of 32 patients could be retrieved, either from pre-operative seroma or at explantation. For 35 FFPE samples of 29 patients sufficient amount of DNA could be isolated, including seroma-BIA-ALCL (n=13), tumor-BIA-ALCL (n=10) and paired samples of synchronous seroma- and tumor-BIA-ALCL (n=6). For seven of the 29 BIA-ALCL patients, FFPE biopsy samples of matched normal tissue yielded sufficient amounts of DNA of adequate quality for inclusion in WES analysis.

Eleven patients with not-implant-associated ALK-negative nALCL in the breast were diagnosed in the same period in the Netherlands. For seven patients FFPE material was available for DNA isolation (median age at diagnosis 41 years; range 24-74 years). Patients all presented with tumor-forming lymphoma, of which three with stage I, two with stage II, and two with stage IV disease. In addition, 19 ALK-negative nALCLs were collected from the files of the Department of Pathology, AmsterdamUMC, location VUmc, Amsterdam, the Netherlands (median age at diagnose 63 years; range 37-83 years). Fourteen patients had nodal disease and five had localizations at various extranodal sites. Sufficient amounts of DNA for NGS analysis could be retrieved from FFPE tumor samples of 17 of 19 patients. The 24 ALK-negative nALCL samples (7 breast not- implant-associated and 17 from other sites) together are used as control cohort.

This fully de-identified study was centrally approved by the Central Medical Ethical Committee of VUmc (METC 2018-265). It was determined that the Medical Research Involving Human Subjects Act (WMO) does not apply and the study is in accordance with the General Data Protection Act.

DNA isolations and NGS library preparation

Seroma and/or tumor areas and normal tissue areas were marked by an expert hematopathologist (D.d.J.), and a semi-quantitative estimation of cellularity (<20%, 20-50% and >50%) was made (Supplemental Table 2) on hematoxylin-eosin and CD30 stained slides to achieve tumor cell enrichment. Five to ten 10 µm FFPE sections were separately microdissected and DNA was isolated with an QIAamp DNA FFPE Tissue kit (Qiagen, Hilden, Germany)². Subsequently, 100-300 ng DNA was fragmented to 250 bp using a Covaris ME220 (Covaris Inc, Woburn, MA, USA). Sequencing libraries were made with 100 ng DNA input using a KAPA or KAPA Hyper library preparation kit (KAPA Biosystems, Wilmington, MA, USA) (Supplemental Table 2) and with unique indexes (IDT, Coralville, IA, USA).

Shallow WGS for CNA analysis

Sequencing libraries were quantified with a TapeStation 4200 (Agilent, Waldbronn, Germany). Fifteen to 24 libraries were equimolar pooled to a concentration of 10 nmol/l per library and sequenced 50 bp single-ended on a HiSeq 4000 (Illumina, San Diego, CA, USA). Nine samples were processed twice and data was combined to obtain sufficient amount of reads (Supplemental Table 2). For CNA analysis, we obtained sufficient amount of reads with a mapping quality above 37, which ranged between 719,312 and 38,342,183, mean 9.605.085, this corresponds with a mean coverage between 0.01 and 0.66 with an average of 0.17, as determined with Picard tools (v.2.15.0) (<http://broadinstitute.github.io/picard>) (Supplemental Table 2). Sequencing reads were aligned against the reference genome (GRCh37/hg19) using Burrows-Wheeler Alignment tool (BWA) (v0.7.12)³ and duplicate reads were removed with Picard tools (v.2.15.0). Reads were binned in 100 kbp bins and corrected for GC-bias and mappability followed by blacklisting using the R-package QDNAseq (v.1.12.0)⁴. Subsequent analysis was done with R-packages NoWaves (v0.6)⁵ to reduce noise, DNACopy (v.1.50.1)⁶ to delineate segments, ACE (v.0)⁷ to determine cellularity, and CGHcall (v2.38.0)⁸ to call copy number alterations. To improve the consistency of CNA calling, ACE-determined cellularity percentages were used with a threshold set by visual inspection of the profiles to 20% to minimize false positive calls as it was noted that the bioinformatical method resulted in poor specificity in the lower cellularity ranges. This balance, at the cost of some loss of sensitivity, benefits a higher specificity and consistency of calling across all samples analyzed. After calling, CGHregions (v1.34.0) was used to reduce the number of data points by creation of regions on the set of samples with a maximal information loss of 2% allowed.⁹ For comparison between BIA-ALCL and ALK-negative ALCL, CGHtest (v1.1)¹⁰ was used, which implements a two-sided Wilcoxon Rank-Sum Test with 10,000 permutations including a false discovery rate (FDR) correction for multiple testing (R v3.4.1). The same was done for tumor-BIA-ALCL and seroma-BIA-ALCL.

Comparison of copy number load and heterogeneity

To calculate the copy number load, in other words, the percentage of the genome aberrant from normal, the Genome Instability Index (GII) was calculated per sample by taking the ratio of the number of altered bins as determined by CGHcall (v.2.38) over the total number of bins after blacklisting (n=24,573), resulting in the fraction of genome numerically aberrant, as previously described^{9,11}. Next, we used the copy number profile from a single sample to estimate the intra-tumoral heterogeneity¹². The difference in copy number load, heterogeneity, cellularity, and total number of reads of seroma-BIA-ALCL and tumor-BIA-ALCL both were statistically tested calculating a combined p-value as was described by Kuan and Huang¹³. For this, a separate p-value was calculated for the paired and the independent samples with a two-sided Wilcoxon Rank-Sum Test and subsequently combined with a weighted Z-test using the square root of the sample

size as weight. Observed differences in copy number load could not be explained by a difference in cellularity or total number of reads, and are therefore most likely not related to a difference in sensitivity of CNA detection (Supplemental Figure 4).

Comparison of CNAs with multiple subtypes of T-cell lymphoma

The CNA spectrum of BIA-ALCL was compared to publicly available CNA data of T-cell lymphomas other than ALK-negative ALCL, namely ALK-positive nALCL (n= 84)¹⁴⁻¹⁶, ALK-negative nALCL (n=62)^{14,15}, pcALCL (n=22)^{16,17} and peripheral T-cell lymphoma, not-otherwise specified (PTCL-NOS) (n=46)^{16,17}. Statistical comparison of 20q loss was performed with a two-sided Fisher exact test with Bonferonni multiple testing correction (R v3.4.1).

WES for mutation analysis

For 7 BIA-ALCL and paired normal samples, a total of 100-125 ng DNA sequencing libraries as prepared for shallow WGS were captured using a SeqCap EZ MedExome targeted enrichment kit (Roche, Pleasanton, CA, USA). Captured libraries were quantified using a TapeStation 4200 (Agilent, Waldbronn, Germany), equimolarly pooled to a concentration of 10 nmol/l per library and 150 bp paired-end sequenced on 2 lanes of a HiSeq 4000 (Illumina, San Diego, CA, USA). Pooled sequence reads were demultiplexed by bcl2fastq (v2.17.1.14) and subsequently trimmed with Cutadapt (v1.16)¹⁸, and aligned by BWA-mem (v0.7.12)³ against the reference genome (GRCh37/hg19). Query name-sorted reads of the same sample were combined and deduplicated with Picard MarkDuplicates (v2.15.0) (<https://broadinstitute.github.io/picard/>). Mutation calling was performed on tumor-normal pairs by GATK4 MuTect2 (v4.0.6.0) and filtered using default settings of FilterMutectCalls.¹⁹ Subsequently, calls were annotated with dbsnp (b151)²⁰, clinvar (20180701)²¹ and COSMIC (v84)²² information using SnpSift (v4.3.1)²³ and SnpEff (v4.3.1)²⁴ for functional effect prediction. Mutations with a minimal coverage of 10 reads in normal as well as tumor data and with at least 4 mutation supporting reads, of which minimal 1 forward and 1 reverse read, and an allele frequency of at least 5% were selected. Further, mutations which were reported to be false positives (Mucins) by Lawrence et al. were filtered out.²⁵ An average mean target coverage of 43.5x was obtained for DNA extracted from lymphoma FFPE tissue and 30x for DNA extracted from matched normal FFPE tissue (Supplemental Table 3). As a result of the sequence depth, mutation detection is limited for samples with low cellularity, whereby sub-clonal aberrations can be missed.

Immunohistochemistry

On 33 BIA-ALCL samples and 25 ALK-negative nALCL cases, immunohistochemistry for pSTAT3 was performed using standard diagnostic protocols. In brief, 3 µm sections were cut from FFPE tissue, dried, deparaffinized, rehydrated, and subjected to heat-mediated antigen retrieval. Subsequently, endogenous peroxidase was blocked after which the

primary antibody (pSTAT3Y705; clone D3A7, 1:200; Cell Signaling) was applied for 1 hour at room temperature (RT). The secondary antibody (BrightVision Poly-HRP-Anti Mouse/Rabbit IgG Biotin-free, one component, immunologic, Klinipath, Duiven, the Netherlands) was then applied for 30 minutes at RT after which visualisation was performed using bright 3,3'-diaminobenzidine. Haematoxylin was used as a nuclear counterstain. pSTAT3 expression was visually assessed for intensity as negative, weak (+), heterogeneous (++) and uniform strong (+++), and percentages of positive tumor cells were scored in 10% increments (D.d.J., N.J.H.).²⁶ A two-sided Wilcoxon Rank-Sum Test was performed in R (v.3.4.1) to compare expression levels between BIA-ALCL and ALK-negative nALCL. Additional relevant phenotypic markers, such as CD30, CD3, CD4, and CD8 were evaluated only if routinely performed for diagnostic purposes.

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Supplemental Table 1. Clinical features of BIA-ALCL patients.

	BIA-ALCL patients (N=29)
Age at diagnosis (years)	
21-30	1
31-40	3
41-50	7
51-60	11
>60	7
Median age at diagnosis	56 (29-75)
Indications for implants	
Cosmetic	20
Reconstruction after breast cancer surgery	8
Reconstruction after prophylactic mastectomy	1
Type of ALCL	
Seroma type -ALCL	13
Tumor-type -ALCL	10
Combined seroma and mass (pair)	6
TNM classification	
T1-3N0M0	14
T4N0M0	3
T1-4N1M0	7
T2-4N2M0	3
T2-3N2M1	2
Ann Arbor Stage	
I	19
II	5
III	2
IV	3
Treatment	
First line surgical therapy only (excision or capsulectomy and explantation)	12
First line surgical therapy and chemotherapy and/or radiotherapy	12
Second line high dose chemotherapy and hematopoietic stem cell transplant	5
Treatment results	
Complete remission on first-line and/or second-line treatment	26
Partial remission on first line and/or second line treatment	1
Progressive disease	1
Local relapse	1
Outcome	
Death of lymphoma	1
Death of other causes	1
Alive without disease	27

Supplemental Table 2: Sample characteristics, cellularity, genome instability and pSTAT immunohistochemistry results.

Table can be found in online supplements.

Supplemental Table 3. Most frequent and characteristic copy number aberrations in BIA-ALCL, ALK- nALCL, ALK+ nALCL, pcALCL and PTCL.

p-values of Fisher exact test with Bonferroni correction for loss of 20q, BIA-ALCL compared to ALKnegative ALCL: 3.2440e-07, pc-ALCL: 1.9236e-04, PTCL-NOS: 4.0320e-08, and ALK positive ALCL: 8.0520e-12. And for loss of 20p BIA-ALCL compared to ALK-negative ALCL: 4.1760e-05, pc-ALCL: 1.2560e-01, PTCL-NOS: 2.2824e-05, and ALK positive ALCL: 8.4280e-08.

Chr	region	BIA-ALCL n=29	ALK- ALCL n=24	ALK- ALCL 27/28	n=62	pc-ALCL 8,29	n=22	PTCL-NOS 8,29	n=46	ALK+ ALCL 27,29	n = 84
1p	1p36-pter	gain	5	21%	9	15%	4	18%	4	9%	2
1q	1q32-qter	gain	7	29%	17	27%	3	14%	9	20%	8
2p	2p25-pter	gain	6	25%	6	10%	3	14%	7	15%	6
6q	6q16-q22	loss	6	25%	17	27%	6	27%	13	28%	5
7q	7q22-qter	gain	8	33%	8	13%	7	32%	17	37%	8
8p	8p11-pter	loss	7	29%	8	13%	6	27%	11	24%	2
8q	8q24-qter	gain	5	21%	11	18%	3	14%	13	28%	5
9p	9p21-pter	loss	2	8%	5	8%	2	9%	14	30%	7
13q	13q21	loss	6	25%	14	23%	3	14%	15	33%	10
13q	13q34-qter	loss	7	29%	13	21%	5	23%	11	24%	7
15q	15q	loss	5	21%	5	8%	1	5%	4	9%	3
17p	17p12-pter	loss	10	42%	14	23%	3	14%	7	15%	4
17q	17cen-q21	gain	8	33%	8	13%	4	18%	13	28%	7
20p	20p12	loss	2	8%	3 *	5%	3	14%	1 *	2%	1 *
20q	20q13	loss	3	13%	6 *	10%	2 *	9%	2 *	4%	2 *

Supplemental Table 4. Sequencing coverage metrics WES.

	BIA-ALCL			Normal		
	Mean target coverage	Percentage 10x coverage	Percentage 30x coverage	Mean target coverage	Percentage 10x coverage	Percentage 30x coverage
BIA-ALCL 7	42	95	58	22	83	19
BIA-ALCL 9	47	96	70	29	91	37
BIA-ALCL 16	41	95	61	20	80	16
BIA-ALCL 20	38	94	50	33	93	47
BIA-ALCL 21	38	95	54	26	89	30
BIA-ALCL 26	44	88	41	33	93	45
BIA-ALCL 28	55	95	59	48	96	67

Supplemental Table 5: Overview of high and moderate impact mutations of all patients.

Table can be found in online supplements.

Supplemental Table 6. Summary of immunohistochemistry pSTAT staining intensity.

	BIA-ALCL	ALK-negative nALCL
Negative	0	11
Weak	2	2
Heterogeneous	3	8
Uniformly strong	22	4

Supplemental Figure 1.

Copy number profiles of all patients: 35 BIA-ALCL plots from 29 patients and 24 ALK negative ALCL plots. Black dots indicate normalized log₂ read count (y-axis) per chromosomal position (x-axis), each dot represents a region of 100 kb. Orange lines indicate segments, vertical bars indicate the probability of gain (red, reversed bars) or loss (blue) (left y-axis) of a segment, and probabilities >0.5 are called and included in further analysis. Tick marks on top of the x-axis indicate high level amplifications (e.g., sample BIA-ALCL 7 chromosome 6). Various (low) level amplifications including EPHA3 (BIA-ALCL 5-S), JAK1 (BIA-ALCL 16-T), JAK2, CD274, and PDCD1LG2 (BIA-ALCL 27-S) were noted. Of these the alterations at 9p24 have been reported previously and may result in high expression of PDL1, PDL2, or both. In the title above the plot, the total number of uniquely aligned reads with a mapping quality above 37 is indicated per sample; 6 billion reads corresponds to a coverage of approximately 0.1x; the coverage per sample is as indicated in Supplemental Table 2. The standard deviation of a profile, denoted by σ , and the theoretically expected standard deviation based on read counting, denoted by $E\sigma$, are given above each profile (according to Scheinin et al., 20144). CNA analysis is performed in our diagnostic laboratory under ISO accreditation on a weekly basis and can be applied as a diagnostic test to detect omnipresent chromosomal aberrations in BIA-ALCL.

In this thesis two copy number profiles of a seroma and tumor BIA-ALCL case are given as example. The rest of the CNA profiles can be found in the online supplements.

Supplemental Figure 2. CNAs in BIA-ALCL and ALK-negative nALCL cases.

(A) CNAs frequencies of 29 BIA-ALCL patient samples. Of the 6 paired samples only CNA of the tumors are included (the same frequency plot is created where the CNAs of the matching seromas are used, see Figure 1). Frequency of gains (red) and losses (blue) are shown on the y-axis, sorted in chromosomal order and by chromosomal position on the x-axis. The top 6 most frequent CNAs in BIA-ALCL are gains of chromosome 2p25-pter (48%), 8q24-qter (38%) and 21q22.3 (41%) and losses of chromosome 8p (38%), 20p13-p12 (48%) and 20q13.12-q13.2 (62%) (B) Frequency plot of copy number alterations in 24 ALK-negative nALCL with the top 5 most frequent CNAs gain of 1q23.2 (33%), 6p21.2 (38%), 7q (33%) and 17q (33%) and loss of chromosome 17p13 (42%). (c) Frequency plot of copy number alterations in 7 not-implant-associated ALK-negative breast-ALCL which does not show any noticeable differences from the whole cohort of ALKnegative nALCL.

Supplemental Figure 3. Absolute copy number profiles of samples with low and high level of heterogeneity.

Absolute copy number profile, with on the y-axis the absolute copy number and on the x-axis the chromosomal position. Absolute copy numbers are estimated by scaling the relative copy number signals of chromosomal segments (orange lines) to optimally fit the integers. In parallel, tumor cell percentage (cellularity) is calculated⁵. Segments not fitting integers indicate subclonal alterations, the measure of the goodness of fit is used to determine the level of heterogeneity. (A) Example of a sample with low level of heterogeneity (0.034), almost all chromosomal segments fitted on integer copy numbers. (B) Example of a sample with a high level of heterogeneity (0.157), large proportion of the chromosomal segments did not fit integer copy number levels.

Supplemental Figure 4. Boxplot of cellularity and total reads of seroma- and tumor-BIA-ALCL.

(A) Boxplots of the cellularity in seroma-BIA-ALCL (average 34%) and tumor-BIA-ALCL (average 38%). No significant difference is observed. Significance was calculated by a Wilcoxon Rank-Sum Test for independent samples and paired samples separately, where after a weighted pooled p-value is calculated, p-value=0.99. (Supplemental Table 2) (B) Total number of uniquely aligned reads with a mapping quality above 37, seroma-BIA-ALCL (average 9.497.740) and tumor-BIA-ALCL (average 11.583.368). No significant difference is observed. Wilcoxon Rank-Sum Test is performed for independent samples and paired samples separately, where after a weighted pooled p-value is calculated, p-value = 0.38.

Supplemental Figure 5. Mutations in BIA-ALCL.

(A-G) Circos plots of 4 tumor-BIA-ALCL (T) and 3 seroma-BIA-ALCL (S) cases analyzed by WES combining information on mutations and copy number alterations. Copy number gains are depicted in red and losses in blue, names of the mutated genes with functional impact are depicted around the ideogram, genes mentioned in the main text are indicated in red. More details of the mutations can be found in supplementary table 5.

Supplemental Figure 5. continued.

Supplemental Figure 6. Immunohistochemical stainings.

Exemplary immunohistochemical sections photographed with original magnification 400x of: 1 BIA-ALCL, 1 ALK-negative ALCL localized in the breast, and 2 ALK-negative nALCL cases using pSTAT3, CD30 and HE stainings. Most BIA-ALCL had uniform strong pSTAT3 staining, Heterogeneous weak staining is shown in the ALK-negative casus, and a negative example is shown with internal control of blood vessel (arrow).

Increased prevalence of BRCA1/2 mutations in women with macro-textured breast implants and anaplastic large cell lymphoma of the breast

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Women with a germline mutation in the *BRCA1* or *BRCA2* genes have high cumulative risks of developing breast cancer before the age of 80 years, i.e., around 72% and 69%, respectively.¹ To reduce risk, an increasing proportion of *BRCA1/2* mutation carriers opt for preventive mastectomy and reconstruction with breast implants. However, breast implants are associated with a strongly increased relative risk (Odds Ratio = 400) of anaplastic large-cell lymphoma (BIA-ALCL), with a low absolute risk of 1/7000 at age 75 years.²⁻⁴ Host susceptibility factors for BIA-ALCL are largely unknown. As we observed several women with *BRCA1/2* mutations, implants and BIA-ALCL, we examined whether *BRCA1/2* mutation carriership increases the risk of BIA-ALCL in women with implants.

In December 2018, we identified 49 confirmed cases of BIA-ALCL (median age 55 years, range 29-75) via the Dutch nationwide Pathology Database (PALGA); methods were detailed before.² Reasons for breast implants were cosmetic (n=32), reconstruction after breast cancer surgery (n=15) or prophylactic mastectomy (n=2). All BIA-ALCL cases with reconstruction after breast cancer received macro-textured implants, while cosmetic cases also received other implant types (Table 1). Median interval between insertion of implants to development of BIA-ALCL was 11 years (range 3-39). Based on medical records of all BIA-ALCL cases, six women had *BRCA1/2* mutations (*BRCA1* n=4, *BRCA2* n=2). Of the 15 BIA-ALCL cases following breast cancer reconstruction, four (26.7%, CI95% 7.8-55.1) carried *BRCA1/2* mutations (median age at breast cancer diagnosis 51, range 26-60) (Table 1). To further examine the prevalence of *BRCA1/2* mutation carriers in our cohort, we could analyze germline DNA from 18/49 women with BIA-ALCL (Supplementary methods). Biopsy material of one of six known *BRCA1/2* mutation carriers was included and the mutation confirmed. No germline mutations were observed in the remaining women. Therefore, the prevalence of *BRCA1/2* mutations in our entire BIA-ALCL series is at least 12.2% (6/49, 95% CI 4.6-24.8).

We compared the 26.7% prevalence of *BRCA1/2* mutations in BIA-ALCL cases after reconstruction for breast cancer (~30% of our cohort) with the expected prevalence, based on recently published age-specific prevalence rates of *BRCA1/2* mutations in an unselected Dutch breast cancer cohort diagnosed before 50 years.⁵ However, 8/15 women in our cohort were diagnosed with breast cancer after age 49 (median age 54, range 50-60). Since no literature is available on *BRCA1/2* prevalence for this age group, we chose to apply the estimate for women aged 45-49 years as the best available approximation (Table 2).⁵ Based on these data, 5.1% (95% CI 4.6-5.7) of BIA-ALCL cases with breast implants after breast cancer surgery would be expected to carry a *BRCA1/2* mutation.⁵ This is significantly lower than our observed estimate of 26.7% (p=.006). Since the prevalence of *BRCA1/2* mutations decreases with older age at breast cancer diagnosis,^{5,6} the calculated expected 5.1% prevalence overestimates the true expected *BRCA1/2* prevalence in breast cancer

patients in our cohort of women with BIA-ALCL, rendering the true difference with our observed prevalence an underestimation.

Table 2. Age-specific prevalence of *BRCA1/2* mutation carriers among breast cancer cases as observed in van den Broek11 and number of BIA-ALCL cases with breast cancer by age.

	Age at breast cancer diagnosis				
	Age <35	Age 35-39	Age 40-44	Age 45-49	Age >50 years*
Expected prevalence of <i>BRCA1/2</i> mutations in breast cancer patients (%) ¹¹	10.7	6.1	4.3	2.4	2.4*
Observed BIA-ALCL patients per age category (n)	1	2	1	3	8

*: Prevalence for age 45-49 years was also used for the group aged > 50 years to best approximate prevalence since specific data for this age group are unknown.¹¹

The prevalence of *BRCA1/2* mutation carriers among BIA-ALCL cases with breast cancer was estimated as the geometric mean of age-specific *BRCA1/2* prevalences among BIA-ALCL cases multiplied by 100/61 to correct for the incomplete mutation testing panel.¹¹ Calculation: $(.1069 \times .0612^2 \times .0432 \times .024^{11})^{(1/15)} = 0.0312$. After correction: $0.0312 \times 100/61 = 5.1$ (95%CI 4.6-5.7)

Subsequently, to determine the risk of BIA-ALCL in *BRCA1/2* mutation carriers and non-carriers we calculated the expected proportion of *BRCA1/2* mutations in women with breast implants in the general population (Supplementary methods). For women with implants for cosmetic reasons (approximately 70% of the cohort), we assumed the prevalence to be similar to the general population, for which we used a recently reported estimate of 0.5% (95% CI 0.5-0.6) based on 50,726 women of predominantly European ancestry⁶ with *BRCA1/2* mutations, as classified in ClinVar.⁷ This estimate is in line with other similar studies.⁹⁻¹⁰ By combining the above expected *BRCA1/2* prevalence rates for cosmetic and reconstructive cases with our previously reported overall cumulative risk of BIA-ALCL of 1/7000 at the age of 75 years², we estimated the number of women with breast implants with and without *BRCA1/2* mutations. Based on (at least) four *BRCA1/2* mutation carriers with BIA-ALCL, and 43 non-carrier BIA-ALCL cases, we then determined the absolute risk of developing BIA-ALCL in *BRCA1/2* mutation carriers to be approximately 1/1551 (95% CI 1/5692 - 1/606) before the age of 75 years, compared with 1/7507 (95% CI 1/10,373 - 1/5573) in non-carriers with a breast implant (Odds Ratio=4.8, 95% CI 1.7-13.5, $p=.012$). It should be noted that the BIA-ALCL risk of 1/1551 for women with a *BRCA1/2* mutation may be underestimated, since 1) the expected age-specific *BRCA1/2* mutation prevalence in women with breast cancer aged 50-60 was overestimated, and 2) we could only determine *BRCA1/2* mutation status in 18/49 BIA-ALCL cases.

We excluded the two *BRCA1/2* cases with bilateral prophylactic mastectomy (BPM) from the risk calculation above, as *BRCA1/2* mutation carriership was the a-priori indication for BPM and subsequent breast reconstruction. Nationwide data from the Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON) indicates that 1,950

Dutch *BRCA1/2* mutation carriers underwent BPM, with approximately 75% having a reconstruction with implants.¹¹ Therefore, the observation of two women with BIA-ALCL in this population (~1/730) further supports our findings of increased risk of BIA-ALCL in *BRCA1/2* mutation carriers.

The currently estimated risk for BIA-ALCL in women with *BRCA1/2* mutations applies to the Dutch population and these findings need to be validated in other BIA-ALCL series. Recently, a prospective single institution study from Memorial Sloan Kettering Cancer Center, NY, USA presented an exceptionally high risk for BIA-ALCL in women with implants after breast cancer surgery (1/355).¹² At least five of ten BIA-ALCL cases had a previous contralateral prophylactic mastectomy.¹³ Possibly, this high risk is at least partly related to specific features, including genetic characteristics, of the patient population in the adherence area of this single institution.

Our study has several limitations. If *BRCA1/2* mutation carriers with breast cancer would more often undergo mastectomy (with reconstruction) than lumpectomy, we may have overestimated BIA-ALCL risk in carriers compared to non-carriers. However, a recent Dutch study shows that breast cancer recurrence rates in *BRCA1/2* mutation carriers (and non-carriers) do not differ between mastectomy and lumpectomy, suggesting that this bias may be small.¹⁴ Next, we did not account for the number of implants per woman, although *BRCA1/2* mutation carriers with breast cancer likely have a higher rate of bilateral implants than non-*BRCA1/2* breast cancer patients because of increased rates of contralateral breast cancer and prophylactic contralateral mastectomy.¹⁵ Higher bilateral implant prevalence may have led to some overestimation of our calculated BIA-ALCL risk in *BRCA1/2* mutation carriers. The extent of this bias is unclear, however, as we actually do not know whether bilateral implants increase risk of BIA-ALCL compared to unilateral implants. Thirdly, *BRCA1/2* mutation testing could only be performed in 18/49 women; as a consequence, our risk estimates are conservative. Strengths of our study include the complete nationwide ascertainment of BIA-ALCL cases, histopathological confirmation of all cases and the availability of complete clinical data, including implant type. Since all breast cancer patients in this study, both *BRCA1/2* carriers and non-carriers, had macro-textured breast implants, confounding by 'high-risk' implant-types can be excluded.¹⁶⁻¹⁹

This study has been performed in the context of a breast cancer population with macro-textured breast implants. If validated in larger international cohorts, the results of this study may have important implications for breast reconstruction options after breast cancer surgery and prophylactic mastectomy in women with established *BRCA1/2* mutations. Such implications would include personalized patient information for *BRCA1/2* mutation carriers opting for implants and promotion of alternative autologous breast reconstruction procedures.

Acknowledgements

We thank dr. Hans Gille of the AmsterdamUMC and Prof. dr. Marjanka Schmidt of the Netherlands Cancer Institute and Prof. dr. Peter Devilee of the Leiden University Medical Center for valuable discussions in the analysis and interpretation of our data. We thank the many plastic surgeons, hematologists and pathologists who provided clinical information, pathology material and data on their patients. Specifically Drs. Vasmel, Tick, Pruijt, Stevens, Kok, Lavrencic and Visser are acknowledged for their support. We thank Dr. Overbeek, dr. van den Broek, Dr. Gijsbers, epidemiologists of the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands (PALGA Foundation) for their ongoing contributions and support. We thank dr. Matti A. Rookus from the Department of Epidemiology and Biostatistics, Netherlands Cancer Institute for her contribution.

Table 1. Clinical characteristics of 17 women with Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) after breast reconstruction for breast cancer and/or bilateral or contralateral prophylactic mastectomy because of breast cancer risk.

Case	BRCA mutation information	Age at breast cancer	Reason for breast implant insertion	Age at breast implant insertion	Breast implant type and location*	Other breast cancer treatment	Interval to BIA-ALCL	BIA-ALCL lymphoma sites
1	BRCA1 mutation, details not disclosed	N.A.	Bilateral prophylactic mastectomy	46	Bilateral, Allergan, macro-textured, silicone	N.A.	10	Left breast
2	BRCA1 gene 5396 + 1G -> A	N.A.	Bilateral prophylactic mastectomy	44	Bilateral, Allergan, macro-textured, silicone	N.A.	12	Right breast
3	BRCA2 gene 8295T -> A (cys2689end, exon18)	35	Right-sided mastectomy for breast cancer; six years later left-sided prophylactic mastectomy	35 & 40	Bilateral, McGhan, macro-textured, silicone	Chemotherapy and radiotherapy	8	Left breast
4	BRCA1 exon 11 c.4097-1G>A splicing (49%) at Alamut/NCBI (confirmed mutation in MLPA/NGS analysis in this study)	60	Left-sided mastectomy for breast cancer and right-sided prophylactic mastectomy	60	Bilateral, Allergan, macro-textured, silicone	None	4 & 6	Left breast
5	Heterozygous c.5722_5723delCT p.(Leu1908Argfs*2) exon 11 v.BRCA2	37	Right-sided mastectomy for breast cancer and left-sided prophylactic mastectomy	47	Bilateral, Allergan, macro-textured, silicone	Radiotherapy	13	Left breast, axillary lymph node
6	c.66dupA p.Glu23fs BRCA1, exon 2	40	Right-sided mastectomy for breast cancer and left-sided prophylactic mastectomy	40	Bilateral, Allergan, macro-textured, silicone	Chemotherapy	9	Left breast
7	N.A.	26	Right-sided mastectomy for breast cancer (reconstruction 3 years later)	29	Right, McGhan, macro-textured, silicone	Chemotherapy and radiotherapy	26	Right breast and axilla, right lung
8	N.A.	49	Right-sided mastectomy for breast cancer and left-sided prophylactic mastectomy (familial cancer, no proven mutation)	49	Bilateral, McGhan, macro-textured, silicone	None	7	Right breast
9	N.A.	56	Right-sided mastectomy for breast cancer, left-sided prophylactic mastectomy (familial cancer, no proven mutation)	56	Bilateral, McGhan, macro-textured, silicone	Chemotherapy	5	Left breast
10	N.A.	51	Right-sided mastectomy for breast cancer, six years later left-sided mastectomy for breast cancer	51	Bilateral, Allergan, macro-textured, silicone	None	6	Right breast

Table 1. Continued.

Case	BRCA mutation information	Age at breast cancer	Reason for breast implant insertion	Age at breast implant insertion	Breast implant type and location*	Other breast cancer treatment	Interval to BIA-ALCL	BIA-ALCL lymphoma sites
11	N.A.	46	Left-sided mastectomy for breast cancer	46	Left, Inamed, macro-textured, silicone	None	13	Left breast
12	N.A.	48	Right-sided breast cancer, one year later left-sided prophylactic mastectomy left with subsequent reconstruction	49	Bilateral, Allergan, macro-textured, silicone	Chemotherapy and hormonal therapy	9	Left breast
13	N.A.	51	Left-sided mastectomy for breast cancer, reconstruction two years later	53	Left, McGhan, macro-textured, silicone	Chemotherapy and hormonal therapy	7	Left breast
14	N.A.	51	Left sided mastectomy for breast cancer, reconstruction in 2009	53	Left, Allergan, macrotextured, silicone,	None	8	Left breast
15	N.A.	52	Left-sided mastectomy for mammary carcinoma breast, right-sided mastectomy for pain/mastopathy	52	Bilateral, McGhan, macro-textured, silicone	None	12	Left breast
16	N.A.	59	Right-sided mastectomy for breast cancer	61	Righ, McGhan, macro-textured, silicone	Hormonal therapy	12	Right breast
17	N.A.	57	Right-sided mastectomy for breast cancer, contralateral side augmentation	61	Bilateral McGhan, macrotextured, silicone	Hormonal therapy	14	Right breast

Implant type in the remaining 32 BIA-ALCL cases who received breast implants for cosmetics purposes was Allergan/Inamed/McGhan (n=15), Eurosilicone (n=3), Rofil PIP (n=1), Monobloc (n=1), Sebbin (n=1), Mentor (n=1), Nagor (n=1) and unknown (n=9). Other detailed information on these cases can be found in the supplements of reference 2.

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Supplemental material

Methods and results for the additional *BRCA1/2* mutation testing in 18 BIA-ALCL patients.

We further examined the prevalence of *BRCA1/2* mutation carriers in our cohort by analyzing germline DNA from formalin-fixed paraffin-embedded non-malignant tissues from biopsies as available from 18/49 women with BIA-ALCL. DNA of two cases with breast-ALCL without breast implants was analyzed as a control. Normal tissue areas were marked by an expert hematopathologist (D.d.J.) on hematoxylin-eosin and CD30 stained slides to exclude tumor contamination. Five to ten 10 µm FFPE sections were separately micro-dissected and DNA was isolated with an QIAamp DNA FFPE Tissue kit (Qiagen, Hilden, Germany). After DNA extraction, protocols were applied that are also used for diagnostic purposes in daily practice. We used multiplex ligation-dependent probe amplification to determine copy number variations. For *BRCA1/2* copy number variations we used the following probe mixes P087-C1/D1 for *BRCA1* and P045-C1 for *BRCA2* (MRC-Holland, Amsterdam, Netherlands). The MLPA was performed according to the manufacturer's instructions. Capillary electrophoresis was performed using the ABI 3730XL (ThermoFisher Scientific, Waltham, Massachusetts, United States). Coffalyser software (MRC-Holland, Amsterdam, Netherlands) was used for analysis.

For targeted sequencing of *BRCA1* and *BRCA2*, we used Oncomine™ *BRCA* Research Assay, Manual Library Preparation (ThermoFisher Scientific, Waltham, Massachusetts, United States). DNA libraries were made using Ion AmpliSeq library kit 2.0™ (ThermoFisher Scientific, Waltham, Massachusetts, United States) according to the manufacturer's instructions. We used 20 ng input DNA. Libraries were barcoded (Ion Xpress Barcodes adapters kit, Life Technologies) and quantified using the Qubit dsDNA HS assay kit. DNA libraries were sequenced on a 316/318 chip in the Personal Genome Machine (PGM) system (ThermoFisher Scientific, Waltham, Massachusetts, United States) Torrent suite software v5.10.1 was used for signal processing, run quality report and BAM files generation. Sequences were then analyzed using SeqNext software v4.1.2 (JSI Medical Systems GmbH, Ettenheim, Germany).

This pseudonymized study was centrally approved by the Institutional Review Boards of PALGA and the Amsterdam University Medical Center (METC 2018-265). Biopsy material of one of six known *BRCA1/2* mutation carriers was included and this germline mutation was confirmed (Supplemental Table 1, sample number 8). No germline mutations were observed in the remaining patients. In two patients we found an amplification of exon 1 in *BRCA1* as a known non-pathogenic variant. In six patients, homozygous absence of PCR product of exon 1 of *BRCA2* was observed, suggestive of deletion. However, this finding could not be confirmed in matching peripheral blood samples from 2 patients and was considered as an FFPE-related artifact. In 3 patients NGS analysis found non-pathogenic variants in *BRCA2* (Supplemental Table 1).

Table S1. Results of MLPA and NGS testing in 18 women with Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) after breast reconstruction due to breast cancer and/or bilateral or contralateral prophylactic mastectomy because of breast cancer risk.

BIA-ALCL Sample	Reason for breast implant	Results MLPA for copy number variation in <i>BRCA1</i> or <i>BRCA2</i>	Result NGS
1	Cosmetic	No alterations	No mutations
2	Cosmetic	Amplification exon 1 <i>BRCA1</i>	<i>BRCA2</i> intron 5 c.475+8_475+9insA (26%) Intron, benign
3	Cosmetic	Scatttering	No mutations
4	Cosmetic	Deletion exon 1 <i>BRCA 2</i>	No mutations
5	Cosmetic	Scatttering	<i>BRCA2</i> exon 4 c.353G>A p.R118H (47%), polymorphism/non-pathogenic variant
6	Reconstruction	No alterations	No mutations
7	Cosmetic	No alterations	No mutations
8	Reconstruction (confirmed <i>BRCA-1</i> mutation carrier)	Amplification upstream exon 1 <i>BRCA1</i>	<i>BRCA1</i> exon 11 c.4097-1G>A splicing (49%) Alamut/NCBI
9	Reconstruction	Deletion exon 1 <i>BRCA 2</i>	No mutations
10	Cosmetic	No alterations	<i>BRCA2</i> exon 11 c.3417G>T; p.K1139N (48%), benign/non-pathogenic variant
11	Cosmetic	Deletion exon 1 <i>BRCA 2</i>	No mutations
12	Cosmetic	Deletion exon 1 <i>BRCA 2</i>	No mutations
13	Reconstruction	Probes upstream exon 1 <i>BRCA2</i> decreased	No mutations
14	Cosmetic	No alterations	No mutations
15	Reconstruction	Deletion exon 1 <i>BRCA 2</i>	No mutations
16	Cosmetic	No alterations	No mutations
17	Reconstruction	Deletion exon 1 <i>BRCA 2</i>	No mutations
18	Cosmetic	No alterations	No mutations
Breast ALCL without a breast implant 1	N.A.	No alterations	No mutations
Breast ALCL without a breast implant 2	N.A.	No alterations	No mutations

Methods and outcome of the risk calculation

To determine whether *BRCA1/2* mutation carriers have an increased risk to develop BIA-ALCL relative to non-carriers, we compared the prevalence of *BRCA1/2* mutations in women with breast implants who did and did not develop BIA-ALCL. Among all BIA-ALCL patients, the prevalence of *BRCA1/2* carriers was 12.2% based on the Dutch nationwide Pathology Database (PALGA) and our clinical data collection.¹ Among women without BIA-ALCL but with breast implants, calculations of expected *BRCA1/2* prevalence were performed separately for women with breast implants for cosmetic and reconstructive purposes. For women with implants for cosmetic reasons (approximately 70% of the cohort), we assumed the prevalence to be similar to the general population and used a recently reported estimate of 0.5% (95% CI 0.47-0.59) from 50,726 women of predominantly European ancestry² with *BRCA1/2* mutations, as classified in ClinVar.³ This estimate is consistent with other relevant studies.⁴⁻⁶ For women with implants after breast cancer surgery (~30% of the cohort), we calculated the geometric mean *BRCA1/2* mutation prevalence from published data in an unselected Dutch breast cancer cohort diagnosed <50 years⁷, weighted by the age at breast cancer diagnosis of our BIA-ALCL cases (n=15, median age 51, Table 2): $(.1069 \cdot .0612^2 \cdot .0432 \cdot .024^{11})^{(1/15)} = .0312$. The resulting prevalence was adjusted by 100/61 to correct for the incomplete mutation testing panel⁷, i.e. $.0312 \cdot 100/61 = 5.12\%$. Based on these data, 5.1% (95% CI 4.6-5.7) of women with breast implants after breast cancer surgery would be expected to be *BRCA1/2* mutation carriers.

By combining these expected *BRCA1/2* prevalence rates, we calculated the denominators of women with breast implants with and without *BRCA1/2* mutations. Fractions of 0.5% and 5.1% of respectively 70% and 30% of 47 BIA-ALCL cases were multiplied with our previously reported overall cumulative risk of BIA-ALCL of 1/7000 at the age of 75 years.^{1,8} Based on (at least) four *BRCA1/2* mutation carriers with BIA-ALCL among an estimated 6205 carriers with implants, and 43 non-*BRCA1/2* carrier BIA-ALCL cases among an estimated 322795 non-carriers with implants, we determined the absolute risk of developing BIA-ALCL in *BRCA1/2* mutation carriers to be approximately 1/1551 (95% CI 1/5692 - 1/606) before the age of 75 years compared to 1/7507 (95% CI 1/10,373 - 1/5573) in non-*BRCA* carriers with a breast implant (Odds Ratio=4.84, 95% CI 1.74-13.49, p=.012).

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General Discussion

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General discussion

In this thesis, a number of questions has been addressed. The risk to develop Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) has been estimated, specific risk factors for BIA-ALCL among women with breast implants have been described, the molecular oncogenesis of BIA-ALCL has been studied and the importance of robust, longitudinal, population-based breast implant registries has been evaluated. Some answers have been given, but also new questions have been raised: can breast implants be considered sufficiently safe and can we continue to use them? Can we convincingly support that specific implants carry an unacceptable higher risk that justifies that these be withdrawn from the market? Do women with breast implants need to be screened for BIA-ALCL, and should women with high risk implants undergo preventive explantation? Which of the options for breast reconstruction or breast implant replacement may be most appropriate? Do we need different recommendations for women with *BRCA1/2* mutation carriership who consider implants after bilateral prophylactic mastectomy? Do we have insight into the complex pathogenesis of BIA-ALCL and does this provide clues for specific treatment and prevention? In the following discussion we will address these questions.

1. Breast implant usage and safety and consequences for public health

1.1 Which factors influence decisions: risks and alternatives

Acceptable risk determinations are rarely easy and obvious ones as also recognized.^{1,2} They depend on formal analyses, expert opinions, matters of public health and public pressure from society. Acceptable risks are not absolute and depend on specific target populations, specific exposures and involuntary or voluntarily exposure.³ In the Netherlands, the National Health Council decides on the legal threshold value of carcinogens.⁴ However, for many carcinogenic substances no safe health-based threshold value can be determined since the attributable role in disease pathogenesis is hard to establish. Therefore, the threshold value is derived from a risk assessment approach. It concerns an 'occupational exposure limit' (Dutch: streefrisico) and 'maximum allowable risk' (Dutch: verbodsrisko). The National Health council has set the target risk of cancer at 1 in a million exposed persons per year.⁴ A risk of 1 in 10,000 exposed persons is used as the maximum allowable risk.^{4,5} These threshold values have, for example, been used for employees exposed to exhaust gas of diesel engines, and chromium-compounds in paint.^{4,5}

As estimated in chapter 3 of this thesis, the potential risk of BIA-ALCL (in)directly caused by a medical device is 1:7,000 in women with breast implants who have reached the age of 75 years, with a relative risk of (OR) > 400. For example, the relative and/or absolute risks of small cell lung cancer associated with smoking are OR = 111⁶ or 1-2:1000⁷, and that of clear cell adenocarcinoma of the vagina associated with diethylstilbestrol (DES) is OR = 400⁸ or 1:1000 (age 34⁹). When we set the maximum acceptable risk of cancer

at the agreed 1 in 10,000, the conclusion then should be that breast implants for elective purposes cannot be considered safe. However this threshold of 1:10,000, by which breast implants would not be permissible, is arbitrary and context-dependent. The reason for a breast implant and thus the degree of avoidable exposure differs among women. In women who undergo mastectomy for breast cancer or high genetic risk of breast cancer, breast implant surgery is performed as a reconstructive option of a functional part of the body that has to be removed for medical necessity. These women experience health advantages in terms of improved quality of life and body perception by having breast implants. The balance of pro's and con's for a breast implant may differ, depending on the indication, urgency and medical context in women undergoing a preventive mastectomy (high familial risk or *BRCA* 1/2) versus women having breast cancer. On the other hand, women who undergo a cosmetic procedure may be able to make a more conscious choice and have a higher acceptance of breast implant-related risks, since they will also experience increased body perception and quality of life. Subsequently, the extent to which breast implants can be avoided or substituted by alternatives is not as straightforward as it may seem, even though it is an elective medical device and implantation is not an absolute must as compared to other implants as a pacemaker or vascular stent. Autologous procedures are an alternative, but autologous fat transfer by lipofilling or free flap surgery may not always be possible due to unsuitable or absent donor sites in the abdominal, lumbar, thigh or gluteal regions. Moreover, it may require extensive or multiple surgeries and recovery, which might not be an option for patients with severe co-morbidities.

From an individual woman's perspective, the health advantages of a breast implant might outweigh the low a-priori risk of BIA-ALCL and potential health disadvantages of developing BIA-ALCL, which is well treatable when diagnosed early. The balance between benefits and risks is subjective, and may differ for certain risk factors, such as implant type or genetic susceptibility; see next paragraphs). Since BIA-ALCL has become a known disease entity, the current standard practice for plastic surgeons in the Netherlands is to provide the patient with detailed information about BIA-ALCL as given in this thesis, and to obtain adequate informed consent from women who consider a breast implant afterwards. This ultimately helps women to help balance their personal risks and benefits and is essential in current shared decision-making.

1.2. Risk estimates and high risk breast implants: comparison of different studies

Since plastic surgeons and pathologists have become aware of BIA-ALCL as a new disease entity, various international research groups have collected case series to calculate the risk of BIA-ALCL and to identify risk factors. Since 2017, an Australian research group has identified BIA-ALCL cases in the Pacific, and almost yearly provided an update of risks and the implant-associated number of cases.¹⁰ In an updated report from 2020 they found absolute risks ranging between 1:2,436 to 1:14,741 per implant type.¹¹ American studies in 2017, using the PROFILE database (Patient Registry and Outcomes For breast Implants

and anaplastic large cell Lymphoma etiology and Epidemiology), showed an incidence rate of 2.03 per 1 million person-years (203 per 100 million person-years) and a lifetime prevalence of 33 per 1 million persons with textured breast implants.¹² In these American and Australian studies, sales data of breast implant vendor companies were used for the calculations. Sales data, however, are not reliable for a number of reasons: data are generally not released by all companies and information on unilateral versus bilateral usage as well as use for prosthesis revisions are unknown, sales data lack historical information on market shares, and as a result of bankruptcy or changing distributors product data files are lost and consequently nationwide sales data are not complete. Moreover, the way these sales data are used to derive at the outcome and the exact calculation was not transparent (also when asking the authors by email by one of our consortium group members).

In this thesis, we used three complementary data sources (1-year point prevalence data for 2 Dutch regions, data on regional variation in breast implant prevalence based on the Breast Cancer Screening Program (BCSP) and national sales data), and were therefore able to make an unbiased estimate of the age- and period-specific prevalence of breast implants in Dutch women. Our sensitivity analysis using another statistical approach (see chapter 3) resulted in very similar estimates. Therefore, results of previous absolute risk calculations should be considered as rough and potentially biased estimates.

The outer surface of breast implants has been classified by vendors and plastic surgeons into smooth, micro- and macro-texture, although internationally accepted, objective or strict criteria for these features are lacking. Implants of Allergan/Biocell, Polyurethane-covered implants and several implant types of Eurosilicone and Nagor are generally identified as macro-textured implants, while implants of Mentor/Siltech are named microtextured implants.^{11,13} Smooth implants, or nano-textured implants are labelled as implants with low to none surface roughness.^{11,13} Despite the indicated lack of an internationally accepted classification, we will use the widely used and accepted terms of smooth, micro- and microtexture to further discuss the literature on this subject.

In 2018 in the Dutch BIA-ALCL cohort, we observed that 23/32 (82% of known associated implants) of women with BIA-ALCL had macro-textured implants at diagnosis, whereas only 45% of all implants sold in the Netherlands in 2010-2015 were macro-textured ($P < .001$).¹⁴ We concluded, however, that no strong conclusions could be drawn from this observation since historical sales data were very much incomplete and adjustment for year of implant could therefore not be performed. In the Australian study, implant associated risks were estimated at one in 2,436 (95%CI 1,888-3,200) for Allergan Biocell, compared to one in 1,947 (95%CI 1,199-3,406) for Silimed polyurethane, one in 5,164 (95%CI 2,506-12,844) for Nagor, and one in 14,741 (95%CI 7,640-39,153) for Mentor Siltech.¹¹ These calculations are based upon (incomplete) sales data and the denominators of different textured implants in the population remains unknown, precluding definitive conclusions. However, based on a growing number of studies, there is an international

trend to suggest that so-called macro-textured breast implants, i.e. Biocell implants of Allergan and to a lesser extent Polyurethane implants, are associated with an increased risk of BIA-ALCL.^{11,10-12,14-19} However, comparison of several types of texture is trivial and solid studies with uniform definitions and outcome measures proving that specific types of textured breast implants are related to a greater risk for the development of BIA-ALCL are absent. Several systems to classify implant texture have been proposed; being the ISO 14607 2018 classification, surface area assessment on 10 mm CT diameter discs, roughness assessed by scanning electron microscopy (SEM), and a combination of SEM and laser confocal microscopy.²⁰ However, the evident trend of the majority of BIA-ALCL cases being associated with macro-textured implants, led most national regulatory bodies and ministries to decide that macro-textured breast implants carry a higher BIA-ALCL risk than smooth and micro-textured implants.

1.3 Actions of regulatory bodies

In December 2018, Allergan did not apply for or receive renewed CE certifications for Biocell breast implants and their use in Europe was no longer allowed.²¹ Subsequently, in France the use of all macro-textured implants was banned in April 2019 (Allergan/Biocell, Sebbin, Arion/Monobloc, Polytech, Eurosilicone, Nagor).¹⁸ While waiting for a re-appraisal of all available information on this subject by the RIVM in response to the French decision, the Dutch Ministry of Health temporarily advised NVPC members against the use of macro-textured implants.^{21,22} The RIVM concluded, however, that the current evidence does not scientifically support a ban of all macro-textured implants, despite the dominant association of Biocell implants with BIA-ALCL, and stated there was no evidence for an increased risk for other macro-textured implants such as polyurethane implants.²² Main arguments for this decision were that there were less BIA-ALCL cases associated with other types of macro-textured implants, leading to a risk that was not comparable to that of Biocell implants, even though usage of other types of macro-textured implants in the Netherlands was lower than Biocell use. Moreover, it remains unclear to which degree the texture of the implant affects the pathogenesis of BIA-ALCL, especially when no uniform classification is present.²²

Between May and September 2019, macro-textured Biocell implants, as well as Polytech polyurethane implants, Eurosilicone implants, Nagor implants and Sebbin implants were suspended for a period of six months in Australia.²³ In this period, the Therapeutic Goods Administration (TGA) reevaluated additional information provided by the vendors of different breast implants. Biocell implants were officially recalled permanently in August 2019²⁴, and other implants were automatically taken from the market by the TGA or by the vendor itself.²⁵ For Polytech (Polyurethane) and the Eurosilicone/Crystalline Paragel implants the period for reevaluation was extended until October 2020, but afterwards also officially recalled. In practice Biocell breast implants, as well as Sebbin, Nagor, Eurosilicone and Polytech were returned to the supplier, and are no

longer available and permitted for use.^{24,25} Patients with any of these breast implants in situ were advised to be aware of the symptoms of BIA-ALCL and seek advice from a health professional if they notice any changes.²⁴

In July 2019, the FDA requested Allergan to recall all textured breast implants as evidence indicated that 'Biocell breast implants were linked to significant patient harm' and use was subsequently prohibited in the USA.²⁶

Currently, Biocell breast implants are no longer used anywhere worldwide. For several other implants which might be categorized as macro-textured,¹¹ usage is not specifically restricted as in Australia and France however. It would not be acceptable for medical professionals as well as for the community of all women with breast implants and those considering to have breast implants, for specific breast implant types to be allowed in certain countries and prohibited in other countries, especially within the EU. In Europe, regulatory decisions on breast implant use and safety are made at the EU level and should be based on valid and inter-comparable risk assessments between various European countries. (Inter)national breast implant registries are therefore needed to provide robust international epidemiological data and to obtain comparable and comprehensive information.

1.4 Screening and preventive explantation

From a public health perspective, regular screening of all women with breast implants for BIA-ALCL is not effective.²⁷ BIA-ALCL can be detected early when women and physicians are alert to symptoms. When detected early BIA-ALCL is well treatable, has an excellent prognosis and the mortality rate is low. The a-priori chance of 1/7000 at age 75 years¹⁴ implies a high number needed to screen to identify a single case of BIA-ALCL, which is not a realistic option. Also, actively informing, and subsequent screening of women with breast implants (or presumably high risk implants) for BIA-ALCL is not possible in the Netherlands, since in the past women with breast implants have not been registered prospectively and can therefore not be contacted. In the future, the Dutch Breast Implant Registry (DBIR) may play a role to identify and contact (groups of) women with breast implants. DBIR was only started in 2015 and does therefore not include women who received breast implants in the past. Within the General Data Protection Regulation (GDPR), DBIR is not designed to directly link registry data to individual patients, but can provide linkage data to hospitals or clinics, which can inform individual patients.²⁸ The cost-effectiveness and requirements for this process are currently being investigated. In 2019 the Dutch Ministry of Health, in close collaboration with the NVPC and Dutch Breast Cancer patient association (BVN), has actively informed women on signs and symptoms of BIA-ALCL by a campaign in the lay press, in order to create awareness. Breast implant vendors were not involved in this campaign to avoid conflicts of interest.²⁹ In contrast, in the USA in June 2020, Allergan launched a campaign to inform American women about the Biocell recall and advised

women who were not informed on their implant type to contact their surgeon, hospital or the Allergan Aesthetics Department.³⁰

At this time the FDA, TGA as well as other health authorities in the EU, have not recommended preventive removal or replacement of high risk breast implants in asymptomatic patients because of the low incidence of BIA-ALCL, costs and potential risks associated with explantation surgery.²⁵ The same applied for PIP implants in 2014; these implants had an unexpectedly high risk of rupture and leakage and the EU/SCHENHIR report underlined the risk-benefit considerations of preventive explantations, arguing against explantation in asymptomatic women.³¹ However, women with high risk implants may request removal. These women should obtain adequate information about the potential complications of surgery and provide informed consent before explantation. As a benefit, women who undergo explantation likely experience a relief in fear and a risk-reduction for the chance to develop BIA-ALCL or other breast implant-related complications. At this moment, Dutch health insurance only covers explantation surgery upon severe capsular contracture, extra-capsular leakage of silicone in case of a ruptured implant, symptoms of Breast Implant Illness (BII) with other diseases ruled out by a physician or rheumatologist, and BIA-ALCL diagnosis. Women opting for a preventive explantation will therefore not always be reimbursed, which holds for subsequent reconstructive alternative procedure as well.²⁶ As a consequence, women may experience decreased quality of life or body perception. This is the case for women with implants for cosmetic reasons, and for women who underwent mastectomy, of which *BRCA1/2* mutation carriers are a specific subgroup. These women undergo prophylactic mastectomy as a risk-reduction strategy for breast cancer often at a young age. Breast reconstruction using breast implants is a then quick and accessible option to restore the breast and body contour. When our finding of an increased risk of BIA-ALCL in *BRCA1/2* mutation carriers with implants (1;1551 carriers) is validated in other international cohorts, this may result in a shift in the risk-benefit balance of explantation surgery for *BRCA1/2* carriers. After all, these women underwent a risk-reducing mastectomy, but may involuntarily and unknowingly have contracted a new risk for another malignancy. For these women preventive explantation and subsequent autologous reconstruction should then be promoted and reimbursed as a feasible alternative.

1.5 Reconstruction or reimplantation after BIA-ALCL diagnosis

In women with BIA-ALCL, explantation and capsulectomy is the gold standard for treatment, with 95% 5-year survival of women achieving complete remission without further therapy in stage I disease.^{32,33} The psychological impact and related body image consequences of explantation are substantial and should not be underestimated and many women will request an alternative reconstruction. There is no consensus on methods and timing. A single case study of eighteen patients addresses this issue. Smooth breast implants, reduction mastopexy of the in situ breast or autologous procedures (free flap surgery or

autologous fat transfer (lipofilling) was performed.³⁴ For disease that was confined to the periprosthetic capsule, immediate reconstruction was suggested as a safe option, whereas a delayed reconstruction for more advanced disease was advised.³⁴ In general, it is advised that a reconstructive plan should be the result of informed consent and shared decision-making, followed by long-term surveillance, likely beyond 5 years.³⁵ In the Dutch cohort of BIA-ALCL cases in 2018, 5 women (stage I (n=4, stage III (n=1) underwent immediate reconstruction with a textured breast implant. Recurrent disease was found in one patient with stage I disease after 2 years, the remaining patients remained disease-free (July 2020).

The advice to use smooth implants is interesting. While the majority of BIA-ALCL cases is associated with macro-textured implants,³⁴ the FDA reports that 28 of 733 confirmed cases of BIA-ALCL worldwide (until August 2020) were associated with smooth implants. The FDA also states that 8 of these 28 patients had a prior textured implant, 9 had previous implants with unknown texture, 10 had an unknown prior implant history, and 1 patient has a history of one smooth implant and no known textured implant.³⁶ Whether these data justify the use of smooth implants as best practice is debatable. It is unknown if a prior textured implant bears a residual pathogenic effect after explantation and total capsulectomy. Moreover, the total number of women with smooth breast implants, remains unknown, making it difficult to put this argument into perspective. It is estimated that approximately 87% of the currently used breast implants in the USA have a smooth surface, partially due to a historical preference for smooth silicone breast implants as a result of FDA-issued moratorium on silicone breast implants between 1992-2006.³⁷ The longer term of use of smooth implants in the U.S., argues against the possibility that the low reported number of BIA-ALCL cases in the context of smooth implants is due to a (too) short exposure time.

Beside smooth breast implants, alternative reconstructive procedures without breast implants such as autologous free flap reconstruction or autologous augmentation using lipofilling might also be an option. For patients after mastectomy breast reconstruction using free flap transfer from the abdominal or thigh region (Deep Inferior Epigastric Artery Perforator flap (DIEP) or Lateral Thigh Perforator (LTP) would be an adequate option. Flap reconstruction is not a common or reimbursed option for cosmetic augmentations. For these patients lipofilling could be more appropriate. Lipofilling is not reimbursed as a standard treatment for reconstructive purposes yet, but only available for patients participating in the BREAST-trial in the Netherlands. In this trial, the quality and esthetic outcome of Breast Reconstruction with External pre-expansion and Autologous fat transfer is compared to the standard therapy with breast implants. In view of the various complications of breast implants, an increasing demand for sustainable autologous breast surgery is expected, including a need for reimbursement of such procedures.

2. Biological mechanisms in the pathogenesis of BIA-ALCL

2.1 The genomic landscape of BIA-ALCL

Comprehensive next generation (NGS) and whole exome sequencing (WES) data for BIA-ALCL are scarce and incomplete in part due to the low incidence of the disease and limited numbers of cases available for such studies. From a large French cohort (n=34 cases analyzed by WES and/or targeted NGS), and various smaller series studied by targeted NGS (or more limited assays), mutations in the JAK/STAT pathway, including JAK1, STAT3 and STAT5B were identified as most important recurring alterations. Further, a lower rate of mutations in TP53, KMT2C, DNMT3a and other epigenetic modifiers are reported.³⁸⁻⁴⁰ Deregulation of the JAK/STAT signaling pathway has been identified as an important oncogenetic factor in BIA-ALCL, but deregulation of this pathway is also common in ALCL family members as well as in other T-cell lymphomas. Therefore, this finding is important and whilst JAK/STAT deregulation is characteristic and essential in the oncogenesis of BIA-ALCL, it is not specific. In our study, we focus on the complementary information from shallow sequencing NGS to evaluate copy-number (n=29). Data were compared to those from 24 cases of nodal-ALCL, ALK1-. Our main findings included loss of chromosome 20q13.13 in 66% of BIA-ALCL with a significantly higher frequency than in other types ALCL, as identified in our 24 cases of nodal ALCL (13%), as well as in PTCL-NOS as reported in the literature (4-10%).⁴¹ Further significantly different alterations were seen at 19p13.3 and 20p13-p12. Together with clinical arguments, this further justifies to include BIA-ALCL to be recognized as a disease entity in its own right in the next update of the WHO classification. We identified mutational patterns in 9 patients using WES confirming deregulation of the IL6-JAK1-STAT3 pathway as described by others. The level of deregulations may be higher in BIA-ALCL, however as indicated by strong pSTAT3 immunohistochemistry as compared to nodal-ALCL.³⁸⁻⁴⁰ We observed some indication that seroma-BIA-ALCL may be marked by a significantly higher copy number load and subclonal heterogeneity compared to tumor-BIA-ALCL, which is considered a more progressed form of disease. This may suggest a synchronous presence of various subclones in the seroma fluid and subsequent clonal selection upon infiltration and progression. In reverse, the overall mutational load in tumor-BIA-ALCLs may be higher than in the seroma-BIA-ALCLs. If this observation can be validated in larger series this could suggest that clonal evolution upon infiltration and progression go hand-in-hand with an increased mutational rate. If this feature would also be predictive of progressive disease remains to be seen.

2.2 Does genetic predisposition play a role in BIA-ALCL?

In the Dutch BIA-ALCL cohort we observed that 6 of 49 BIA-ALCL cases were diagnosed in women with confirmed *BRCA1/2* mutations. Consequently, we could calculate an estimated risk for *BRCA1/2* carriers with implants to develop BIA-ALCL before the age of 75: approximately 1/1551, compared with 1/7507 in non-carriers with a breast implant (OR =4.8, p=.012).⁴² This estimation might be an underestimate since the expected age-specific *BRCA1/2* mutation prevalence in women with breast cancer aged 50-60 was

overestimated due to lack of population data for this age group. Also, we could only determine *BRCA1/2* mutation status in 18/49 BIA-ALCL cases (chapter 10). The mechanism or role of *BRCA1/2* mutations in the pathogenesis of BIA-ALCL is not yet clear. *BRCA1/2* genes are tumor suppressor genes with an important DNA repair function and breast cancer in these patients is associated with homozygous inactivation. Based on copy number alterations (CNA) profiles of BIA-ALCL in *BRCA1/2* mutation carriers, we did not observe specific losses of *BRCA1* or *BRCA2* loci that might be suggestive of homozygous inactivation, and therefore the mechanisms underlying the increased risk for BIA-ALCL in *BRCA1/2* mutation carriers remains to be clarified.

Apart from *BRCA1/2* mutation carriership, also incidental patients with *TP53* germline mutations have been reported.^{43,44} In view of the low prevalence of germline *TP53* mutation carriership in the population, a genetic predisposing role for *TP53* cannot be excluded, but is unlikely to explain the development of a substantial number of BIA-ALCL cases.

2.3 The multifactorial oncogenesis of BIA-ALCL

The oncogenesis of BIA-ALCL is likely multifactorial and not all factors are completely understood. Besides the genetic predisposition, the presence of the silicone breast implant and the subsequent elicited immune response and the role of implant texture and adherent substances play a role.

The natural response by the body of encapsulating the silicone implant is a T-cell driven inflammation process, known as the foreign body response, resulting in the fibrous periprosthetic capsule⁴⁵. The available studies on this subject have shown the expression of TH1 and TH17 related cytokines by intra-capsular T-cells when compared to peripheral blood T-cells.⁴⁶ These cytokines are associated with inflammation by extracellular pathogens. Identical expressed cytokines by BIA-ALCL cells are identified.^{47,48,49} This supports the evidence that BIA-ALCL cells may derive from the Th1/Th17 cells derived response to pathogens in the periprosthetic capsule. The origin of the extracellular pathogen, and the specific immune response which is elicited are unknown. It is important to identify whether stimuli in or around the breast implant elicit a specific immune response, causing the T-cells in the periprosthetic infiltrate to be the precursors of BIA-ALCL. No experimental papers or conclusive evidence have been identified to confirm or refute the toxicological role of (bleeding) silicone in BIA-ALCL patients.⁵⁰⁻⁵³ A recent paper suggested particulate shedding of breast implants, especially particulates of rough textured surfaces implants, to cause increased pathogenic inflammation over time and being a precursor of BIA-ALCL.⁵⁴ The role of platinum as a toxic product in the context of BIA-ALCL has also not been investigated. Platinum is a catalyst in the production of silicone, and it can induce DNA-adducts, which on turn can cause mutations in DNA coding for oncogenes, which might stimulate oncogenesis in BIA-ALCL.⁵⁵

As mentioned before, there is epidemiological evidence supporting the role of specific textured implants in the pathogenesis in BIA-ALCL^{10-12, 14-19}, indicating the need for evidence to explain the precise causal or facilitating factor of the texture. Several studies have shown that textured implants are prone to develop increased bacterial load compared to smooth implants, possibly when contaminated upon introduction.^{56,57} In the clinical setting, the initial periprosthetic contamination of the breast implant may occur upon introduction of the breast implant and, in later stage, via spilling of bacteria via the nipple, possible (wound) infections or trauma. This contamination may explain why a higher number of lymphocytes was found in the peri-implant infiltrates of textured implants when compared to smooth implants in a pig model.⁵⁸ Moreover these infiltrates showed a significantly higher ratio of T-cells versus B-cells in textured implants when compared to smooth implants.⁵⁹ These studies suggest a facilitating role for textured implants in terms of increased bacterial load and inflammatory reaction. The causal relation between bacteria, inflammation, T-cell hyperplasia and lymphomagenesis, has been demonstrated in gastric MALT-lymphoma associated with gram-negative *Helicobacter Pylori* bacteria, as well as Staphylococcal Super-antigen endotoxins (SE) colonizing the skin in cutaneous T-cell lymphomas. Eradication therapy in both situations is associated with improvement⁶⁰. When examining whether a specific microbiome plays a role in BIA-ALCL, one group found that the microbiome in the biofilm of periprosthetic capsules in BIA-ALCL cases compared to non-BIA-ALCL capsules had significantly higher numbers of gram-negative bacteria (*Ralstonia* spp).⁶¹ This might imply a role for specific bacteria in the pathogenesis of BIA-ALCL, similar to MALT lymphoma or cutaneous T-cell lymphoma, however these results have not been validated since.

3. Clinical implications and recommendations

The main results of this thesis are the findings regarding the prevalence of breast implants in our population and the risk for developing BIA-ALCL (chapters 2&3). This implies that approximately 200,000 women with breast implants, and a smaller group of women who may be opting for breast implants are affected by the results of our research. For the latter group of women we recommend plastic surgeons to provide information explaining the risks of the disease, the signs and symptoms of a periprosthetic seroma or tumor, and when indicated diagnostic methods, the potential treatment and outcomes, and the possibility of alternative autologous procedures. For women who return for check-up consultation we recommend informing these women about BIA-ALCL, and to communicate the importance of alertness about signs and symptoms of BIA-ALCL. We have found that retrospective identification of women with breast implants is not possible, and therefore actively informing all women with breast implants about BIA-ALCL is not feasible. In 2019, this led the Dutch Ministry of Health to communicate the signs and symptoms of BIA-ALCL, and the recall of Biocell/Allergan implants due to increased incidence of BIA-ALCL, via lay press such (Libelle, Linda) and NVPC/Dutch Breast Cancer patient association

(BVN) websites. The Dutch Breast Implant Registry (DBIR) has been implemented in 2015 and since then prospective registration of women with breast implants and subsequent adverse events is possible. We found that 100 and 70% of BIA-ALCL cases were registered in 2016 and 2017 respectively (chapter 6). A strong recommendation is therefore to register identified BIA-ALCL cases in this implant registry. For future international research this is of immense importance, since studies to identify high risk implants can most efficiently be performed through breast implant registries. Denominator data derived from other sources will be less reliable, and the methodology and outcome of such risk assessments have to be reviewed strictly (chapter 4&5).

With regard to our biological studies, we found that BIA-ALCL is characterized by loss of chromosome 20q and present in a high percentage of patients, distinguishing this disease from other types of ALCL and PTCL-NOS (chapter 9). When validated, the detection of loss of chromosome 20q13.13 will provide the WHO with the evidence to recognize BIA-ALCL as a separate disease entity. Moreover, loss of chromosome 20q may prove a sensitive, time- and cost-effective screening method of periprosthetic seroma. This may have great clinical implications, since nowadays we observe an increasing number of seroma samples in Cytology departments, which may pose differential diagnostic challenges (chapter 7).

Lastly, we identified an increased risk of BIA-ALCL in *BRCA1/2* carriers compared to non-carriers, i.e., 1/1551 before the age 75 years (chapter 10). These results still have to be validated; however upon counselling of women with a *BRCA1/2* gene mutation for breast reconstruction, it is important that physicians are aware of this potential risk and can provide detailed answers to questions on this topic. Moreover, stimulation and reimbursement of alternative autologous breast reconstruction procedures might be of increased importance for these women.

4. Future research

It is likely that with the right interventions the incidence of BIA-ALCL will reach its peak in the next decade. The identification of direct causal factors and mechanisms will help to eliminate the disease, but we need to take into account that the induction period for breast implants causing BIA-ALCL is quite long, up to 13 years (range 1-39). Future research in BIA-ALCL should have a multi-disciplinary scientific approach to identify these causal factors and mechanisms with implications for prevention. Prospective, disclosure-free international collaborative studies using breast implant registries linked to disease registries are needed to have adequate power for epidemiological research to examine patient-related biological risk factors such as age at implant, pregnancy, presence of other (auto-immune) diseases, and implant specific risks factors (texture, filling, brand). This will enable internationally uniform banning or permission of different breast implant types on the market. These studies cannot be executed without a standardized international

classification for texture and type of breast implants. Ultimately, reduced use of high risk implant types will decrease the incidence of BIA-ALCL.

Experimental basic research into the role of breast implant-related substances such as silicone and platinum has not yet been performed, but is essential to demonstrate or refute the toxicological influence of the breast implant in the pathogenesis of BIA-ALCL. It will prove difficult to establish an in vitro- or animal model designed to examine the causal role of these substances in the lymphomagenesis of BIA-ALCL, but experimental data on the toxicological effect of silicone and platinum is needed.

Moreover, the role of bacteria and a specific microbiome in the pathogenesis of BIA-ALCL has to be explored further. The extension of the hypothesis concerning the role of bacteria in MALT lymphoma or cutaneous T-cell lymphoma to BIA-ALCL is interesting, and preliminary data show an overrepresentation of specific bacteria in BIA-ALCL specimens. However, these data have to be validated. If the role of specific bacteria in the development of BIA-ALCL can be confirmed, improved surgical or antimicrobial techniques may prevent specific bacterial contamination of the implant.

Biological studies will have to validate the loss of chromosome 20q13.13 as unique for BIA-ALCL and thus prove its significance in sensitive screening of periprosthetic seromas. These international NGS and/or WES studies will also have to focus on determining other molecular characteristics of BIA-ALCL on chromosomal or gene level in order to further mark it as a separate disease entity, since no other studies have been able to do so yet.

As stated before, we observed an increased risk of BIA-ALCL of 1/1551 in *BRCA1/2* carriers with implants, compared with 1/7507 in non-carriers. Follow-up research should examine whether this increased risk can be validated in other international cohorts and what the exact mechanism is by which the presence of *BRCA1/2* gene mutations causes the increased risk of BIA-ALCL. This may ultimately lead to recommending women with a specific genetic background to refrain from using a breast implant. As a logical consequence autologous breast procedures have to be reimbursed in these patients. Moreover, it has to be examined how alternative autologous breast procedures can become tailor-made treatment with high accessibility and comparable surgical, esthetic, physical and psychological outcomes for women with breast implants.

Researchers and breast implant registries should be financially supported to advance the knowledge about these research areas in BIA-ALCL risk and pathogenesis and be given the opportunity to serve as research partners and provide objective, scientific information as a basis for evidence-based guidelines and international regulations. Governmental bodies and health authorities, in collaboration with research groups, should take the lead in the discussions about research policy and call for uniform and comprehensive research methods in order to make well-founded regulatory decisions regarding breast implants.

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CHAPTER

12

Paragraph of impact

1. Research: What is the main goal of the research described in the thesis and what are the main results and conclusions?

In our project, we have aimed to define the risk for Dutch women with breast implants to develop Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL); a rare form of lymph node cancer. We aimed to explore if there are specific groups of women may run a higher risk than we found in the general population. For that purpose, we first identified how many Dutch women actually carry breast implants for cosmetic or medical reasons, since this feature was unknown at the start of our project. Based on a measurement in two large regional medical centers and combining information from various national database sources, we found that 3.0% of women between 20-70 years carry breast implants, ranging from 1.7% in women between 21-30 years to a maximum of 3.9% in women between 51-60 years and with considerable regional variation. This data was used to calculate the risk of BIA-ALCL, which was found to be 1 in 7,000 Dutch women with breast implants to develop BIA-ALCL before the age of 75 years. It was not possible to make a firm statement about implant-specific risks, since information on implant use in the past was largely lacking. However, we did see that implants associated with BIA-ALCL cases were more often macro-textured. This is in line with other international studies on implant-associated BIA-ALCL risks.

Next, we observed a remarkable high percentage of women (12.2%) in the Dutch BIA-ALCL cohort with *BRCA1/2* carriership; a gene that is associated with increased risk to develop breast cancer. Therefore, we assessed whether *BRCA1/2* carriership was an additional risk factor for the development of BIA-ALCL. Indeed, we found that women with *BRCA1/2* mutations and breast implants had a significantly higher risk to develop BIA-ALCL before the age of 75 years, compared to non-carriers (1/1551 vs 1/7507). It is important to note that these findings must first be validated in other international cohorts. If validated, for these women alternative breast reconstruction procedures may be a safer choice and may be promoted in the future.

During our studies, the Dutch Breast Implant Registry (DBIR) was launched as a quality tool to monitor implant use in the Netherlands. We explored the contribution of DBIR to reliably identify newly diagnosed BIA-ALCL patients. We found that in its first two years (2016 and 2017) registration rates were almost complete, Registration flaws were observed, however, especially false-positive registrations. Our results were used to improve the procedures and thereby the quality of the database. Also, we proposed a diagnostic algorithm to support the reliability of cytological diagnosis by pathologists,

Finally, we performed studies on the biology of BIA-ALCL to shed light on the molecular alterations that may cause this disease. Thereby, we investigated the genomic landscape of chromosomal and gene alterations in the DNA of BIA-ALCL tumor cells. We found specific chromosomal changes (loss of 20q13.13) that were only rarely found in other types of T-cell lymphomas. Gene mutations were less specific, but shed light on

the immunological processes that are involved in the development of BIA-ALCL(IL6-JAK1-STAT3) and support our understanding of the disease.

2. Relevance: What is the (potential) contribution of the results of this research to science, and if applicable to social sectors and societal challenges?

Societal impact

Our studies on risk assessment have contributed important information that has served as a basis for national and international policy making by the Dutch RIVM, the French ANSM, the European SCHEER, and indirectly the American FDA and Australian TGA. In the underlying documentation of policy reports by these organizations, our studies are widely cited. (See also chapter 11: Discussion, section Actions of regulatory bodies). Most importantly, macro-textured breast implants (Allergan / Biocell) have not received renewed CE certifications and their use is thereby banned in Europe since 2018.

Our studies on risk assessment have received wide attention in lay press and popular scientific media ranging from Nieuwsuur, NOS, NRC, MedicalResearch.com, newsweek.com and NEJM Journal watch. To mitigate the unrest among women with breast implants by providing optimal, reliable information, the Dutch Ministry of Health has launched a program to pro-actively inform women on signs and symptoms of BIA-ALCL by a comprehensive campaign in the lay press. Amongst others, our studies have been used as a source of information for patient information documents and informed consent.

Contribution to science

Our biological studies (chapter 9) have contributed to the delineation of BIA-ALCL as a disease entity and thereby contributed to decisions in the WHO Classification for Hematological malignancies for which an update is expected in 2022. Moreover, our work stresses the importance of thorough epidemiological investigation. Opt-in cases series or cohort studies without a control population of breast lymphomas (ALCL and other types) as well as thorough knowledge on the denominator of women with breast implants can no longer be the standard. In future BIA-ALCL research, and more generally plastic surgery research on breast implant usage and safety, it is important to come up with a sound study design and reliable input data prior to analysis or drawing up the conclusions.

3. Target group: For whom are the research results interesting and relevant? And why?

The results of this thesis are relevant for all women who have breast implants and for those women who are considering breast implants for any reason, cosmetic, reconstruction after mastectomy for breast cancer or for high familial risk for breast cancer. In this thesis we have calculated that approximately 3.0% of the female Dutch

population between the ages of 20-70 years carry breast implants. This implies that the information in this thesis is relevant for 1 in 30 women. Specifically, the situation for women with BRCA carriership are a major concern as these women likely have a significantly additional increased risks for BIA-ALCL. Awareness amongst this population should be increased, in which patient advocacy organizations may play a major role. A discussion on the use of alternatives including autologous breast reconstruction (reconstruction with own tissue) and smooth implants should be a subject of discussion.

In addition, the results of our research are relevant for specialists dealing with patients with BIA-ALCL; being the general practitioner, the plastic surgeon, the pathologist and the (hemato) oncologist. It is important for these doctors to recognize clinical symptoms, to use the correct diagnostics and to be aware of various treatment strategies. Due to the multidisciplinary nature of our research group, these professional associations have been represented, and all members have been informed when the research results were published.

4. Activity: How can these target groups be involved in and informed about the research results, so that the acquired knowledge can be used in the future?

Relevant patient associations (BVN, Oncogen) have already been involved in the development of dedicated patient information letters and information videos to present the facts in an appropriate context. Involvement of other advocacy groups should be considered.

As mentioned earlier in this chapter, we consider regulators such as the RIVM, IGZ and VWS also as a target group. Our research, in addition to several international sources with comparative outcomes, has led to changes in regulations and therefore in the use of breast implants. (See also chapter 11: Discussion, section Actions of regulatory bodies).

CHAPTER

13

Summary /
Nederlandse Samenvatting

Summary

In **chapter 1**, we provide an introduction to “Breast Implant-Associated Anaplastic Large Cell Lymphoma” (BIA-ALCL); a lymphoma that arises in the periprosthetic seroma or capsule of a breast implant. The purpose of this thesis is to provide a broad multidisciplinary overview of different aspects of BIA-ALCL and to answer epidemiological, clinical and biological questions with respect to the risk, pathogenesis, diagnostics and prognosis of BIA-ALCL. Important topics to be addressed in this thesis are the prevalence of breast implants and the risk of and risk factors for BIA-ALCL in women with breast implants. Subsequently, we focus on immunohistochemical diagnostics and potential registration systems for this disease. Moreover, we examined the molecular oncogenesis and the possible genetic susceptibility for BIA-ALCL. Insight obtained from this thesis is expected to benefit the care for women with breast implants and patients with BIA-ALCL.

The aim of **chapter 2** is to assess the prevalence of women with breast implants in the Netherlands, since reliable population-based estimates of breast implant prevalence rates are not available, complicating absolute risk assessment of breast implant-related complications. Randomly selected chest radiographs from women aged 20-70 years in 2015 were assessed for the presence of a breast implants. The accuracy of this method was first proven by eight reviewers with a sensitivity of 79.9% and a specificity of 99.2%. Subsequently, a series of 1500 chest radiograph from the East (MST, Enschede) and South (MUMC+ Maastricht) Dutch regions was assessed to determine breast implant prevalence. To derive a national breast implant prevalence rate, regional differences from the nationwide Breast Cancer Screening Program (East, South, West, North, Central) were used to extrapolate the findings from the East and South regions. Our conclusions are that on average 3.0% of Dutch women have a breast implant, ranging from 1.7% at 21 to 30 years to 3.9% between 51 and 60 years.

Chapter 3 describes the epidemiology of BIA-ALCL in the Netherlands. All primary breast lymphomas between 1990 and 2016 were identified from PALGA (the Dutch Pathology database) and breast implant presence was determined for all these cases. The relative risk (OR) was calculated in a case-control study: among a total of 43 patients with primary ALCL in the breast, 32 had a breast implant, compared to 1 of 146 patients with other types of primary lymphomas in the breast (OR = 422). The median interval between breast implantation and diagnosis of BIA-ALCL was 13 years (range 1-39). Using the prevalence of breast implants from chapter 2, combined with the time trend in sales data, the absolute cumulative risk for BIA-ALCL in women with breast implants was calculated: 1 per 35,000 at 50 years, 1 per 12,000 at 70 years and 1 per 7,000 at 75 years. It is not possible to calculate implant-specific risks in this study due to the lack of data on the denominator of women with specific types of implants, but we observed that implants among BIA-

ALCL cases were more often macro-textured: 23 of 28 BIA-ALCL cases with known texture (82%), compared to sales data: 49,193 of 109,449 (45%) sold implants between 2010-2015 ($P < .001$).

In **chapter 4** we provide a reply to two letters to the Editor in reaction to our epidemiological study (chapter 3). We discuss the importance of robust epidemiological studies in which the numerator and denominator are reliably retrieved. Moreover, we stress the need for further sound internationally pooled epidemiological studies to examine the associations between specific implant types and risk of BIA-ALCL.

In **chapter 5** we present a letter to the Editor, commenting on a study in which a 14-point plan was proposed aiming to reduce the bacterial load/contamination around textured breast implants, which might lower the risk of BIA-ALCL. The authors presented no cases of BIA-ALCL in a cohort of women with 42,000 implants and stated that the 14 point plan is successful in reducing BIA-ALCL. In our reply we state that this study falls short in providing evidence that the 14-point approach indeed reduces the risk of BIA-ALCL since the study was not adequately powered for rigorous evaluation of the hypothesis put forward by the authors. Again we stress the need for adequate registration of implants as well as BIA-ALCL as a tool to enable adequate epidemiological studies on the subject of BIA-ALCL.

Optimal post-marketing surveillance is important for high quality evaluation of medical implants, since the clinical approval studies only run for a few years. In **chapter 6** the registration potential of the Dutch Breast Implant Registry (DBIR) was compared with the nationwide pathology database (PALGA, chapter 3). We obtained clinical information for BIA-ALCL cases registered in DBIR for the years 2016 and 2017. Registration rates were 100% and 70%, respectively, when compared to PALGA. We conclude that the use of both databases has important complementary value, which will benefit the collection of detailed case information in future research.

Chapter 7 examined the increase in cytological aspirates of periprosthetic seromas in the pathology labs. The clinical pathology aspects of BIA-ALCL were described from a cytological-diagnostic point of view, we provided guidance for the handling and processing of these aspirates, and a diagnostic algorithm for evaluating these preparations was provided (Figure 4 of chapter 7).

In **chapter 8** the clinical scenario of an unexplained periprosthetic seroma in a women with breast implants is described. In this case report, the importance and difficulties of cytological examination of periprosthetic seromas are discussed. The report also suggests the potential increase in incidence of BIA-ALCL, due to its occurrence in a relative minority (transgender women).

In **chapter 9** the molecular oncogenesis of BIA-ALCL is investigated. In 29 BIA-ALCL samples (both seroma and tumor-BIA-ALCL) and 24 nodal ALCL control samples shallow Next-Generation-Sequencing (sNGS) was used to identify copy number alterations (CNAs). In addition, 7 BIA-ALCL samples were examined for mutations by Whole-Exome-Sequencing (WES). CNAs were detected in 94% of BIA-ALCL cases, with losses at chromosome 20q13.13 in 66% of the samples. In our opinion, this finding provides further justification to recognize BIA-ALCL as a separate disease entity caused by specific driver mechanisms, of which CNAs appear to be dominant. Mutational patterns confirmed that the IL6-JAK1-STAT3 pathway was deregulated. Although this is commonly observed across various types of T-cell lymphomas, the extent of deregulation is significantly higher in BIA-ALCL, as indicated by pSTAT3 immunohistochemistry.

In **chapter 10**, the genetic background of the BIA-ALCL cohort is further examined. Of 49 confirmed BIA-ALCL cases between 1990-2018, 6 women had *BRCA1/2* mutations (12.2%). Of the 15 BIA-ALCL cases following breast cancer reconstruction, 4 women (26.7%), had *BRCA1/2* mutations. We compared the 26.7% prevalence of *BRCA1/2* mutations in BIA-ALCL cases after reconstruction with the expected prevalence in a breast cancer cohort with similar age distribution as our BIA-ALCL series, which was 5.1%. Hence, the prevalence of *BRCA1/2* mutations among BIA-ALCL cases was significantly increased ($p=0.006$). Subsequently, we determined the absolute risk of developing BIA-ALCL in *BRCA1/2* mutation carriers with breast implants to be approximately 1/1551 (95% CI 1/5692 - 1/606) before the age of 75 years, compared with 1/7507 (95% CI 1/10,373 - 1/5573) in non-carriers with a breast implant (Odds Ratio=4.8, 95% CI 1.7-13.5, $p=.012$). Our findings are based on a cohort of women with macro-textured implants and have to be validated in other international cohorts. If confirmed, our results imply the need for personalized patient information for *BRCA1/2* mutation carriers opting for implants and promotion of alternative autologous breast reconstruction procedures in the future.

Finally, **Chapter 11** contains the general discussion of our findings, with the clinical implications and recommendations for future research.

Nederlandse samenvatting

In **hoofdstuk 1**, wordt een introductie gegeven over “Breast Implant-Associated Anaplastic Large Cell Lymphoma” (BIA-ALCL). Dat is een vorm van lymfeklierkanker die specifiek geassocieerd is met borstprothesen. Het doel van het onderzoek dat in dit proefschrift beschreven wordt, is om epidemiologische, klinische en biologische vragen rond BIA-ALCL te beantwoorden en daarmee een breed multidisciplinair inzicht te geven in deze zeldzame ziekte. Belangrijke aspecten hierbij zijn betrouwbare risicoberekeningen voor BIA-ALCL, waarbij ook een objectieve prevalentie-schatting van borst-implantaten bij Nederlandse vrouwen een rol heeft gespeeld. Daarnaast is er gekeken naar protocollen voor betrouwbare diagnostiek. De mogelijkheden en optimalisatie van landelijke databases voor borstprothesen, en voor aandoeningen die hiermee geassocieerd kunnen zijn (zoals bijvoorbeeld BIA-ALCL), zijn geëvalueerd. Deze zijn immers essentieel voor toekomstig onderzoek. In het laatste deel van dit proefschrift wordt ingegaan op de moleculaire aspecten van BIA-ALCL en een mogelijke genetische predispositie voor de ontwikkeling van BIA-ALCL. We verwachten dat de inzichten die met dit proefschrift verkregen zijn bijdragen om de zorg voor vrouwen met borstprothesen en vrouwen met BIA-ALCL te verbeteren.

Het doel van **hoofdstuk 2** is om de prevalentie van vrouwen met borstimplantaten in Nederland te bepalen. Dit was een noodzakelijke stap, omdat hierover geen objectieve gegevens bekend waren, maar het gegeven essentieel is voor betrouwbare risicoberekeningen voor aandoeningen die mogelijk het gevolg zijn, of gerelateerd zijn aan borstprothesen. Eerst onderzochten we of de aanwezigheid van borstprothesen betrouwbaar bepaald kan worden op basis van standaard thoraxfoto's van vrouwen van 20-70 jaar oud. Dit bleek betrouwbaar te kunnen met een sensitiviteit van 79,9% en een specificiteit van 99,2%. Hierna werd een geselecteerde serie van 1500 thoraxfoto's uit 2015 van vrouwen tussen 20 en 70 jaar oud uit de regio's Oost (Medisch Spectrum Twente, Enschede) en Zuid (Maastricht Universitair Medisch Centrum+, Maastricht) beoordeeld om de prevalentie van borstprothesen te bepalen. De bevindingen uit de regio's Oost en Zuid werden geëxtrapoleerd naar een landelijke prevalentie met behulp van de regionale verschillen in borstprothese prevalentie, zoals die bekend waren uit het landelijke screeningsprogramma voor borstkanker (Oost, Zuid, West, Noord, Centraal). Op basis van deze gegevens werd geconcludeerd dat gemiddeld 3,0% van de Nederlandse vrouwen een borstprothese heeft, variërend van 1,7% van de vrouwen tussen 21 en 30 jaar tot 3,9% voor vrouwen tussen 51 en 60 jaar.

Hoofdstuk 3 beschrijft de epidemiologie van BIA-ALCL in Nederland. Alle primaire borst-lymfomen tussen 1990 en 2016 werden geïdentificeerd via PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief) en voor deze casus werd de aanwezigheid

van borstimplantaten bepaald. Het relatieve risico (OR) werd berekend in een case-control studie: van 43 patiënten met primaire ALCL in de borst hadden 32 patiënten een borstimplantaat, vergeleken met 1 van de 146 patiënten met andere typen primair lymfoom in de borst (OR = 422). Het mediane interval tussen de eerste borstprothese en diagnose van BIA-ALCL was 13 jaar (range 1-39 jaar). Gebruikmakend van de prevalentie van borstimplantaten uit hoofdstuk 2, gecombineerd met de trend van verkoopcijfers over de tijd, kon ook het absolute cumulatieve risico voor BIA-ALCL bij vrouwen met borstimplantaten worden berekend: 1 op 35.000 voor vrouwen voor de leeftijd van 50 jaar, 1 op 12.000 voor vrouwen voor 70 jaar en 1 per 7.000 voor vrouwen voor 75 jaar. Het bepalen van prothese-specifieke risico's was niet mogelijk doordat betrouwbare gegevens over het aantal Nederlandse vrouwen met specifieke soorten prothesen niet beschikbaar waren, zeker niet voor de relevante tijdsperiodes van meer dan 10 jaar geleden. Wel viel op, dat prothesen ten tijde van de BIA-ALCL diagnose vaker macro-getextureerd waren, te weten 23 van 28 BIA-ALCL casus waarbij het prothese-type bekend was (82%). Ten opzichte van verkoopgegevens (49.193 van 109.449 (45%) verkochte prothesen tussen 2010-2015) suggereert dat een overrepresentatie ($p < .001$).

Hoofdstuk 4 is een reflectie op 'Letters to the Editor' naar aanleiding van ons epidemiologische studie (hoofdstuk 3). We bespreken het belang van adequate epidemiologische studies waarin de teller en de noemer betrouwbaar moeten worden achterhaald. Bovendien benadrukken we de noodzaak van verdere degelijke internationaal gepoolde epidemiologische studies om de associaties tussen specifieke prothese types en het risico van BIA-ALCL te onderzoeken.

In **hoofdstuk 5** presenteren we een 'Letter to the Editor' waarin we een onderzoek becommentariëren waarin een 14-punts stappenplan werd voorgesteld om de bacteriële load rond getextureerde borstprothesen te verminderen, met als doel het risico op BIA-ALCL te verlagen. De auteurs schrijven dat zij in een cohort van vrouwen met 42.000 prothesen geen BIA-ALCL casus diagnosticeerden, en stellen dat dit stappenplan dus een succesvolle risicoreductie op BIA-ALCL oplevert. In de Letter stellen we dat de studie echter niet adequaat ontworpen is om te bewijzen dat het stappenplan inderdaad het risico op BIA-ALCL vermindert. Het aantal patiënten en het aantal jaren follow-up is hiervoor ruim onvoldoende. Opnieuw benadrukken we de noodzaak van een volledige en betrouwbare registratie van implantaten en van BIA-ALCL als voorwaarde voor epidemiologische studies op het gebied van zeldzame ziektes, zoals ook BIA-ALCL.

Post-marketingsurveillance is een voorwaarde voor de evaluatie van medische implantaten, aangezien klinische studies voorafgaand aan de toelating tot de markt slechts een beperkte periode in kaart brengen en latere complicaties of gevolgen nog onbekend blijven. In **hoofdstuk 6** is het registratiepotentieel van de Nederlandse Borstimplantaten

Registratie (DBIR) vergeleken met de landelijke pathologie database (PALGA, hoofdstuk 3). Voor de jaren 2016 en 2017 bleek de registratie graad in DBIR respectievelijk 100% en 70% vergeleken met PALGA. In DBIR werden zowel patiënten gemist als was er sprake van fout-positieve registratie. Zorgvuldige koppeling tussen beide databases kan de kwaliteit van registratie in de toekomst verbeteren. Daarmee kunnen beide databases voorzien in complementaire gegevens en toekomstig onderzoek met gedetailleerde casusinformatie mogelijk maken.

Hoofdstuk 7 wordt de toename van cytologische aspiraten van periprothetische seromen in de pathologie laboratoria sinds de introductie van BIA-ALCL gerapporteerd. We beschrijven de klinische pathologische aspecten van BIA-ALCL vanuit een cytologisch-diagnostisch oogpunt, en we geven richtlijnen voor het verwerken van deze aspiraten en een diagnostisch algoritme voor beoordeling (Figuur 4 van hoofdstuk 7).

In **hoofdstuk 8** wordt het klinische scenario van een onverklaard periprothetisch seroom bij een vrouw met borstprothesen beschreven. In dit case report worden het belang, maar ook de moeilijkheden van cytologisch onderzoek van periprothetische seromen besproken. Het is een van de eerste beschrijvingen van BIA-ALCL bij een transvrouw.

In **hoofdstuk 9** wordt de moleculaire oncogenese van BIA-ALCL onderzocht. In 29 BIA-ALCL-samples (zowel seroma- als tumor-BIA-ALCL) en 24 nodale ALCL-controle samples werd shallow Next-Generation-Sequencing (sNGS) toegepast om Copy Numbers Alterations (CNA's) te identificeren. Daarnaast werden 7 BIA-ALCL-samples onderzocht op mutaties door middel van Whole-Exome-Sequencing (WES). CNA's werden gedetecteerd in 94% van de BIA-ALCL patiënten, met een verlies van chromosoom 20q13.13 in 66%. Deze verandering kwam nauwelijks voor bij de nodale ALCL en daarmee is deze verandering dus heel karakteristiek voor BIA-ALCL. Dit biedt naar onze mening verdere rechtvaardiging om BIA-ALCL te erkennen als een aparte ziekte-entiteit. De gevonden mutaties bevestigden gegevens van anderen, dat de IL6-JAK1-STAT3-cellulaire signaleringsroute gedereguleerd is. Hoewel dit mechanisme niet specifiek is en ook bij andere typen T-cel lymfomen voorkomt, is de mate van deze deregulatie wel significant hoger bij BIA-ALCL, zoals aangetoond met behulp van pSTAT3 immunohistochemie.

In **hoofdstuk 10** werd de genetische achtergrond van het BIA-ALCL-cohort verder onderzocht. Van de 49 bevestigde BIA-ALCL casus tussen 1990-2018 hadden 6 vrouwen een *BRCA1/2* mutatie (12,2%). Van 4/15 (26,7%) BIA-ALCL casus na reconstructie van borstkanker waren *BRCA1/2* mutatiedragers. De verwachte prevalentie van *BRCA1/2* mutatiedragerschap in een borstkanker-cohort met een vergelijkbare leeftijdsverdeling als onze BIA-ALCL-serie is echter maar 5,1% en daarmee is het dus waarschijnlijk, dat vrouwen met *BRCA1/2* mutatiedragerschap een hoger risico op BIA-ALCL hebben (p

= 0,006). Vervolgens werd het absolute risico op het ontwikkelen van BIA-ALCL bij *BRCA1/2* mutatiedragers met borstimplantaten berekend; dit is 1/1551 (95% BI 1/5692 - 1/606) vóór de leeftijd van 75 jaar, vergeleken met 1/7507 (95% BI 1/10.373 - 1/5573) bij niet-dragers met een borstimplantaat (Odds Ratio = 4,8, 95% BI 1,7-13,5, $p = 0,012$). Onze bevindingen zijn afkomstig uit een cohort van vrouwen met macro-getextureerde implantaten en moeten gevalideerd worden in andere internationale cohorten. Wanneer bevestigd, impliceren onze resultaten dat vrouwen met *BRCA1/2* mutatie die kiezen voor borstprothesen aanvullende voorlichting moeten krijgen en dat autologe borstreconstructie als alternatief besproken dient te worden.

Hoofdstuk 11, tenslotte, bevat de algemene discussie met de uit deze thesis voortvloeiende conclusies, klinische implicaties en aanbevelingen voor toekomstig onderzoek.

CHAPTER

14

Acknowledgements

Acknowledgements

Allereerst wil ik alle plastisch chirurgen, pathologen, oncologisch mamma chirurgen en (hemato)-oncologen bedanken die hebben meegeholpen aan het aanleveren van (klinische) informatie en pathologie materiaal. Hetzelfde geldt voor geheel pathologie-Nederland, te weten lokale medewerkers van pathologie laboratoria en HUB-medewerkers van PALGA; dank voor jullie hulp met het verzamelen van gegevens en materiaal. Zonder deze hulp zou de totstandkoming van de artikelen in dit proefschrift niet mogelijk zijn geweest.

Ook de patiënten die toestemming hebben gegeven om mee te werken aan dit onderzoek verdienen een zeer speciaal woord van dank; het doormaken van een ziekte, of de herinnering hieraan, vraagt vaak al meer dan genoeg aandacht. Meewerken aan onderzoek is daarom niet vanzelfsprekend: jullie bijdrage is onmisbaar gebleken.

Beste René, professor RRWJ van der Hulst. Dank voor je geloof in mij! Zonder jouw steun en de input die je veelal achter de schermen geeft, was het voor mij niet mogelijk om dit proefschrift of mijn opleiding tot plastisch chirurg te doen. Als opleider heb je oog voor de persoon, voor het vallen en opstaan, en ben je altijd empathisch en eerlijk; het is enorm fijn om zo'n warme opleidingssfeer te genieten! Hoe je alle klinische, wetenschappelijke, organisatorische en dan ook nog sport-activiteiten weet te combineren, daar kan ik alleen maar naar gissen. Ik ben trots dat ik mijn opleiding in het MUMC+/Viecuri/Zuyderland mag doen, waar qua kliniek en wetenschap zoveel gebeurt, en ik kijk ernaar uit de komende jaren van alle stafleden in onze regio veel te leren!

Beste Daphne, professor D de Jong. Wat heb ik genoten van onze dagen in je kantoor op de VU, waarbij je me hielp met het analyseren van data en schijven van manuscripten. Door jouw begeleiding, waarbij je me tips gaf over hoe je je doelen voor ogen houdt en hoe je om gaat met moeilijke situaties, voel ik me nog dagelijks geholpen. Je nuchtere kijk op de soms beladen onderwerpen die we tegenkwamen tijdens dit promotietraject zorgden voor een hele fijne begeleiding. Hoe vaak we wel niet hebben besproken dat dit onderzoek ons met name zoveel plezier heeft gebracht, blijft heel speciaal. Ik wens je heel veel succes tijdens je werk-sabbatical in het buitenland, maar hoop vooral daarna weer met je te kunnen samenwerken, omdat ik hoop dat we met ons consortium de activiteiten in de toekomst kunnen uitbouwen !

Beste Floor, Professor FE van Leeuwen. Ik heb het tijdens mijn gehele promotietraject zo knap gevonden hoe je met ogenschijnlijk groot gemak voor moeilijke vraagstukken een epidemiologische studie en dus oplossing kunt verzinnen. Zoals een collega ooit gekscherend zei: "Vraag het aan Floor, ze rekent dit voor je uit op de achterkant van een bierviltje". Ook heb ik veel respect voor je grote staat van wetenschappelijke dienst. Dit

illustreerde zich bijvoorbeeld doordat je tijdens een van je vele revisies van mijn artikelen verwees naar een vroegere collega en opleider. Ik mocht het woord 'very' niet gebruiken in wetenschappelijk jargon, want de data zou wel voor zichzelf spreken als iets 'zeer' duidelijk was. Elke keer als ik vervolgens met de trein vanuit Maastricht aankwam in het Antoni van Leeuwenhoek, liep ik langs het naar deze collega gemaakte bronzen beeld in de centrale hal en moest ik hier aan denken. Het was voor mij een eer om met je te mogen samenwerken en ik hoop dat we dit in de toekomst kunnen voortzetten!

Aan jullie beide, Floor en Daphne: wat was het heerlijk om dit dankwoord te schrijven, in het Nederlands, wetend dat jullie dit niet mochten reviseren! Alvast mijn excuus voor de waarschijnlijke stijl en spelfouten! ;-) Heel veel dank voor jullie geweldige hulp bij het reviseren van de artikelen; door jullie input zijn bepaalde stukken Engelse tekst taalkundig op en top geworden!

Beste Hinne, Dr. Rakhorst. Ik herinner me nog zo goed onze eerste onderzoeksmeeting over BIA-ALCL op het NVPC kantoor in Utrecht. Nadien de refereer-avonden bij je thuis in Twente samen met jouw andere onderzoekers, of de ritten in de auto van het MST of ZGT naar de NVPC Utrecht. Het stimuleerde enorm om tijdens die autoritten effectief werk te verzetten of telefonisch te overleggen met collega's in het land. Jouw mantra om te werken wanneer andere mensen rusten zal ik niet vergeten; er komt sinds mijn opleidingstijd niet altijd evenveel van terecht, maar ik beloof dat dit in de toekomst weer zal komen! Het is in elk geval ongelofelijk hoeveel energie jij kunt steken in je werk en onderzoeksactiviteiten; je bent hierin een groot voorbeeld!

Promotie-commissie. Geachte leden van de beoordelingscommissie prof. dr. M van Engeland, Prof dr. B van Kiemeney, prof dr. en voorzitter VCG Tjan-Heijnen, en in het bijzonder prof. dr. MAM Mureau, die in de toekomst ook mee zal gaan werken aan het onderzoek dat verricht wordt binnen ons BIA-ALCL onderzoeksconsortium. Hartelijk dank voor het lezen en beoordelen van mijn manuscript en het feit dat jullie allen graag aanwezig willen zijn als opponenten tijdens de verdediging. Ik kijk uit ernaar uit om met jullie van gedachten te wisselen tijdens de officiële verdediging.

Leden van BIA-ALCL onderzoeksconsortium. Dit proefschrift is een team effort geweest en zou eigenlijk een groeps promotie kunnen zijn. Het verzamelen van data en het schrijven van alle artikelen was zonder jullie hulp en connecties niet mogelijk geweest; ik heb aan den lijve ondervonden hoe ontzettend goed het multidisciplinaire karakter van onze groep hieraan heeft bijgedragen. Zonder jullie als team zou ik dit proefschrift niet hebben kunnen verwezenlijken; hiervoor ben ik jullie oneindig dankbaar. Naast alle wetenschappelijke input waren alle vergaderingen en de veelvuldige Thaise etentjes ontzettend gezellig.

Dr. Jan Paul de Boer, dank dat je me hebt geholpen om de classificaties en therapieën voor lymfomen iets meer te begrijpen, en dat je altijd beschikbaar bent als we worden gecontacteerd met vragen over nieuwe BIA-ALCL casus. Ook veel dank voor je hulp wanneer ik in het AvL was om dossierstudie te doen, en natuurlijk dat ik dan mocht werken in je o zo gezellige en mooi versierde kantoor.

Nathalie Hijmering; als ik al dacht dat ik alle data goed op orde had en goed gecategoriseerd, dan was jij in dit alles net nog een stapje verder en beter. Wat heb ik daar veel aan gehad, dank! Je wordt zeker gemist in de VU, maar bent volgens mij ook erg op je plek bij je nieuwe baan. Ik hoop je weer te zien tijdens mijn verdediging. Dr. Lucy Overbeek, we hebben uiteindelijk maar kort samengewerkt tijdens je laatste werkperiode bij PALGA, maar ik heb veel van je geleerd en veel aan je tips en tricks gehad ten tijde van de intermediair procedures die met behulp van PALGA zijn uitgevoerd.

Prof. Dr. Michael Hauptmann; inmiddels werkt u aan de Universiteit in Brandenburg maar ook aan u ben ik veel dank verschuldigd. Alle statistiek in de JAMA paper, en de BRCA paper: zonder uw hulp had ik de uitkomsten zoals die in de data verscholen waren niet (zo snel) kunnen extraheren. Ik heb pas tijdens mijn promotietraject begrepen wat het klinische belang is van degelijk opgezette studies, en het hierdoor daadwerkelijk kunnen berekenen van uitkomsten die van waarde blijken.

Prof. dr. Bauke Ylstra, dank dat ik in Januari 2019 een maand lang op jullie afdeling in het Cancer Center heb mogen werken aan onze biologische paper. Ik heb veel bewondering voor het technische (en voor mij redelijk ingewikkelde) karakter van het werk dat door jouw vakgroep gedaan wordt, waarbij je wel mag zeggen dat de manier waarop jullie DNA analyse uitvoeren als pionieren te beschouwen is. Je enthousiasme hierover is aanstekelijk!

Graag wil ik ook alle co-auteurs van de publicaties in dit proefschrift bedanken; zonder jullie bijdrage en input hadden deze artikelen niet geschreven kunnen worden. Een speciaal woord van dank voor Tjitske Los de Vries, Babette Becherer en Michele van Middelkoop; met jullie heb ik nauw samenwerkt en ik wil jullie bedanken voor de gezelligheid en jullie hulp. We zullen elkaar nog tegenkomen in de toekomst verwacht ik, en daar kijk ik naar uit! Tevens wil ik nogmaals PALGA bedanken voor alle hulp bij de intermediair procedures en in het bijzonder Annette Gijsbers.

Van de afdeling Tumor Genome Analysis core van het Amsterdam UMC-locatie VUmc wil ik graag Paul Eijk en Dirk van Essen bedanken voor hun inbreng en advies in de sequencing experimenten voor de biologische paper. Tevens wil ik graag Matias Mendeville, Marit Roemer, Erik van Dijk en Phylcia Stathi bedanken voor hun hulp bij deze paper; voor een

plastisch chirurg in opleiding is de materie van een dergelijke paper lastig te begrijpen, maar jullie hebben me geholpen om het te bevatten.

Vervolgens wil ik ook graag de studenten bedanken die me hebben geholpen met data verwerking en literatuur searches tijdens dit promotie traject, te weten: Arthur Sernee, Sara Salassa en Eveline Meinen.

Naast alle wetenschappelijke steun van promotors, copromotors, het team van het BIA-ALCL consortium, is ook financiële steun een belangrijk onderdeel van een promotietraject. Ondanks dat ik mijn promotietraject volledig naast mijn Geneeskunde studie en assistenten-tijd heb verricht, heb ik begin 2017 een kwartaal full-time kunnen werken aan alle onderzoeken. De Jules Coenegracht Sr stichting uit Maastricht heeft dit destijds mogelijk gemaakt. Als stille partner ben ik hen hiervoor veel dank verschuldigd.

Hiernaast wil ik graag dr. Heuts bedanken. Beste Esther, tijdens mijn tijd als semi-arts en als ANIOS was je altijd beschikbaar als luisterend oor en heb je me erg geholpen door advies te geven over hoe mijn promotie traject aan te pakken. Hiernaast heb je me inhoudelijk geholpen door mee te helpen met de discussie over de biologische achtergrond van BIA-ALCL en door mee te schrijven aan de subsidie aanvraag voor de Jules Coenegracht Sr stichting. Je hebt hierdoor gezorgd voor net dat extra duwtje in de rug, waardoor dit promotietraject nu is afgerond. We zullen daar zeker de komende zomer- en winterbijscholingen op proosten!

Aan alle lieve chirurgie collega's in Viecuri, te weten de stafleden, collega arts-assistenten, verpleegkundigen op verpleegafdelingen en de poli, de dames op het secretariaat, en de collega's op de IC en de SEH. Ik kijk met een enorm fijn gevoel terug op mijn tijd bij de vooropleiding bij jullie. Het was machtig mooi; altijd gezellig, wat een grappen, nog leerzaam ook, en dan die bizarre COVID-tijd. Als ik terugben in Venlo om nu weer met de Plastische mee te opereren, is het welkom altijd warm! Bovendien betekent het werken in het MUMC+ dat ik met oud collega-assistenten weer opnieuw op die heerlijk gezellige manier mag samenwerken. Speciaal voor mijn carpool collega's; de borrels en diners houden we erin!

Beste John, Dr. Sawor. Mijn tijd als ANIOS in Venlo was onvergetelijk. Wat heb ik daar ontzettend veel van je geleerd. Over positief blijven tijdens je poli's en operaties, zodat als het een keertje tegenzit, de rest van je collega's jou er door heen trekken met de altijd positieve sfeer die er heerst. Het liefst met de foute music playlist aan. Maar ook je technische skills zoals de befaamde glijknoop, je coachende manier van opereren, altijd weer iets willen verzinnen waardoor iets handiger of slimmer kan, jezelf blijven verbeteren

en willen blijven leren. Om over je onuitputtelijke energie om te sporten maar niet te spreken. Ik ben erg blij dat je ja hebt gezegd om mijn paranimf te zijn.

Dan ook een speciaal woord van dank voor de allerliefste plastische poli verpleegkundigen en assistenten in Venlo; lieve Hanny, Anita, Janine, Gabrielle, Ira, en niet te vergeten Inge! Door de gezelligheid en de hele fijne samenwerking was mijn tijd als ANIOS Plastische in het VieCuri onvergetelijk en vloog de tijd voorbij. Toen ik de overstap maakte naar de vooropleiding was het altijd even thuiskomen als ik bij jullie kon langskomen voor een koffie, hapje of drankje. Nu ik weer in het MUMC+ werk, is dat als ik af en toe weer een dagje meeloop in het Viecuri niet anders. Ik heb echt een hele fijne tijd gehad bij jullie! Bedankt daarvoor!

Graag wil ik ook alle stafleden van het team Plastische Chirurgie in de regio bedanken voor hun hulp, het vertrouwen, de interesse en jullie enthousiasme, of dit nu is tijdens klinische werkzaamheden of tijdens een borrel of winterbijscholing! Bedankt dat ik mijn opleiding in jullie regio mag doen; ik vind dit een grote eer en heb heel veel zin om de komende jaren veel van jullie te leren op alle vlakken van de Plastische Chirurgie zoals die in onze regio in de hele breedte, en op hoog niveau, worden uitgeoefend.

Aan mijn collega- assistenten, Renee, Chao, Anouk, Jop, Nadine, Jip, Tert, Tim, Sander, Lisa, Ennie: dank voor het warme bad waarin ik viel na het terugkomen uit de vooropleiding. Ik weet zeker dat we nog veel plezier zullen hebben met elkaar de komende jaren! Ook dank aan alle oud assistent collega's (uit zowel Maastricht als Eindhoven) die me op weg hebben geholpen als semi-arts, jonge ANIOS en nu nog steeds, te weten: Vincent, Patrick, Michelle, Volkan, Lisette, Juliette, Tiara Rutger, Laura, An, Marijke, Alexander, Martijn, Maarten en Tert!

Lieve dames op het secretariaat: Cecile, Jolanda, Mariëlle, en ook Nelly en Petra. Dank voor alle keren dat jullie hebben geholpen om praktische, logistiek of administratieve dingen voor mij te regelen en voor de altijd gezellige gesprekjes! Ook de dames op de poli; Lilian, Debbie en Antoinette; dank voor jullie hulp op de poli en de gezelligheid tijdens een kopje koffie tussendoor. Al jullie moeite en inbreng is altijd heel fijn!

Aan de dispuutsgenoten (Goldbull) en vrienden uit Weert (Nichtendisco/ND) van Alout. De voortgang en het afmaken van dit proefschrift ging natuurlijk niet sneller dankzij jullie, maar des te fijner is altijd jullie gezelschap. Bij dit gezelschap hoort inmiddels een groeiend aantal heel leuke, lieve en knappe dames, met als logisch gevolg weer een gestaag toenemende hoeveelheid Goldbull of ND - babies, die ik allemaal niet zou willen missen!

Mijn Maastrichtse vriendinnetjes, Ashley, Elke, Lieke, Maartje en Suus. Maartje kende ik natuurlijk als sinds 2014, toen we samen begonnen met onderzoek doen bij de Plastische Chirurgie, maar wat ben ik blij dat ik jullie heb mogen leren kennen in de afgelopen jaren. Als de kroegen straks weer opengaan in Maastricht, Den Haag of Geetbets, dan gaan wij ze onveilig maken!

Mijn Friese vriendinnetjes, Astrid, Mirle en Sieuwke, ik zie jullie helaas niet zoveel als ik zou willen, maar als ik jullie zie is het altijd als vanouds, en daar ben ik erg dankbaar voor. Nu dit proefschrift is afgerond zal ik meer tijd hebben om in het mooie Friesland te zijn en jullie te zien!

Dan mijn knappe Sjengies; lieve Britt, Eva, Jolijn en Tess. Waar zou ik zijn zonder jullie, altijd zo lief, geïnteresseerd, gezellig en eerlijk. Het is alsof het gisteren was dat we elkaar leerden kennen op UNS 40, en sindsdien heb ik altijd met jullie het allergrootste plezier. Of dat nu is als we in Maastricht of Amsterdam zijn (en snel Engeland!), of dat nu is als we borrelen, eten, op stap zijn, dronken zijn of brak zijn. Ik kan niet wachten om post-corona in 2022 hopelijk met z'n elven weer op vakantie te kunnen met de mannen en met baby Jaxon. Aan jou, lieve Britt, een speciaal woord van dank omdat op deze dag mijn paranimf wilt zijn! Nog even, dan ben jij ook zover, en dan steun ik je net zo hard als jij mij!

Lieve Tony en Sonja, bedankt voor jullie hartelijke welkom in de familie Ramselaar in 2013 en de interesse voor mijn werk en promotieonderzoek. Het is altijd gezellig tijdens de etentjes die eerder in Weert waren, en nu meer in Amsterdam en omstreken, en hopelijk delen we volgend jaar weer meer van deze momenten.

Lisa, lief schoonzusje! Omdat je iets verder weg woont, zien we elkaar niet zo vaak, maar we halen dit altijd dubbel en dwars in tijdens de feestdagen, en wat is het dan een feestje om in de Jopenkerk in Haarlem even samen bij te kletsen. Op het moment van schrijven van dit dankwoord heb ik COVID-technisch goede hoop dat het lukt voor jou om aanwezig te zijn bij mijn verdediging;)

Lieve Marianne en Willem, en schoonfamilie Hoogenstrijd en Nieberg. Bedankt voor het thuis-gevoel dat ik altijd ervaar als ik in Haarlem ben, en jullie oprechte interesse in alle zaken die Alout en mij bezighouden. De (kerst)borrels die tot laat in de avond duren, samen met Merijn, Folkert en Inge, Gemma en Thijs en Charlotte, zijn voor in de boeken! Ook jullie lieve Kees en Greetje wil ik heel hartelijk bedanken: voor jullie altijd grote interesse, alle artikelen die jullie doorsturen en bovendien wil ik mijn oprechte bewondering voor jullie grote belezenheid! Ook zonder jullie steun was dit proefschrift niet op papier verschenen.

Jolanda en Sybren, de rest van de gehele familie Schreuder, en natuurlijk Sofi en Albin. Stiekem noem ik jullie altijd mijn peetfamilie, maar in elk geval Sybren voelt zich te jong voor de rol van peetvader ;). Jolanda, dank voor het voorbeeld dat je, vaak onbewust, voor mij bent geweest. Ik bewonder je arbeidsethos en je grote hart! Heel fijn dat jullie bij de verdediging kunnen zijn. De zomers in FP, samen met Sofi en de hele familie, zijn waarschijnlijk de mooiste van mijn leven. Heerlijk! Soms wens ik dat ik weer opnieuw student was;). Lieve Jannie en Wim, bedankt voor jullie hartelijkheid en gezelligheid tijdens deze zomers (en alle andere momenten); jullie hebben het hartstikke fijn in Portugal, maar toch hoop ik jullie snel weer te zien!

Leave mem, lieve muttie. Dank voor alles wat je voor me over hebt gehad en hebt gedaan! Altijd geïnteresseerd en vragen hoe het ging met de voortgang van mijn studie en promotie-onderzoek, waarschijnlijk soms ook lichtjes gissend of het ooit nog af zou komen;). Alout en ik genieten altijd zo van jouw moederlijke zorgzaamheid, inclusief Friese oranjekoek; iets waarvoor ik je wellicht niet altijd genoeg bedankt, maar wat altijd enorm heerlijk en fijn is. Ook was jouw en Jurrie's hulp tijdens onze recente verhuizing onmisbaar en zeer gewaardeerd. Ik ben heel trots op hoe je je door alles heen hebt geslagen en nu voor elkaar hebt, je prachtige huis in Weidum, samen met Jurrie.

Lieve pappie, leave heit. Ook jij hebt alles op de voet gevolgd, mij altijd gesteund en ik weet dat je heel trots bent dat het nu eindelijk zover is dat mijn boekje af is. Ik ben tegelijkertijd ook heel trots op jou en op het bedrijf op Bokkum zoals jij en Luciel dat nu voor elkaar hebben en de komende jaren nog zullen ontwikkelen. Je bent met ogenschijnlijk gemak een excellente paardenman, iets waar ik veel bewondering voor heb, en wat je heel bijzonder maakt. Hopelijk ga je vanaf dit jaar lekker genieten van je vrije tijd, die je zo verdiend hebt. Alout en ik genieten graag mee tijdens een fles bubbels en jouw favoriete eten hierbij!

JB en Jelle. Wat is het fijn om deze dag ook met jullie te vieren. Lieve broertjes, we zien elkaar niet zo vaak als ik zou willen (zeker niet sinds mijn afstuderen), maar ik weet dat ik altijd op jullie kan bouwen als er iets is, dat hebben we zeker de laatste jaren, zij het soms met wat horten en stoten, wel bewezen! Nu deze promotie achter de rug is heb ik weer meer tijd voor weekeinden in Friesland of een keer een vakantie in Zweden. Daar kijk ik nu al naar uit!

En dan nu als laatste jij, liefste Alout! Vanaf het begin van dit promotietraject ben je erbij geweest, en zonder jou had ik dit simpelweg niet kunnen doen. Er zijn zoveel dingen die je voor me over hebt en die ik (soms ook te veel) als vanzelfsprekend beschouw. Je hebt nooit geklaagd over de momenten die ik achter mijn laptop doorbracht in de avonden, weekenden en op vakantie, vaak op de bank, tegen jou aan liggend. Je bent getuige

geweest van alle mooie momenten tijdens dit onderzoek en het is mega lief hoe trots je altijd bent. Door jou is mijn leven leuker; jij zorgt ervoor dat we samen genieten van het leven, vaak samen met onze lieve vrienden en familie. Ik realiseer me dat door mijn passie en ambitie om plastisch chirurg te worden, ik jouw carrière heb beïnvloed, omdat je min of meer werd gedwongen in deze regio te blijven. Ik ben je heel erg dankbaar dat je me dat niet verwijt en ik ben tegelijkertijd ook heel trots op jou! Vanaf 2022 is er meer tijd voor ons, voor onze vrienden en familie, feestjes en vakanties, en voor wat dan ook ;)! Ik hou van jou!

CHAPTER

15

Scientific output

Publications

Published

1. Schreuder JA, Roelen CA, **de Boer M**, Brouwer S, Groothoff JW. Inter-physician agreement on the readiness of sick-listed employees to return to work. *Disabil Rehabil.* 2012;34(21):1814-9.
2. David P, Dagan A, **De Boer M**, Colaris MJL, Cohen Tervaert JW, Shoenfeld Y. Churg-Strauss Syndrome: Silicone Implant or Singulair (or could be both?). *Isr Med Assoc J.* 2016;18(3-4):168-70
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5. **De Boer M**, Qiu SS. Communications and Correspondence: Success of free flap anastomoses performed within the zone of trauma in acute lower limb reconstruction. *J Plast Reconstr Aesthet Surg.* 2016;69(10):1453-4
6. **de Boer M**, van der Sluis WB, MD, de Boer JP, Overbeek LIH, van Leeuwen FE, Rakhorst HA, van der Hulst RRWJ, Hijmering N, Bouman MB, de Jong D. Breast-Implant Associated Anaplastic Large Cell Lymphoma in a Transgender patient. *Aesth. Surg. J.* 2017;1;37(8):NP83-NP87
7. **de Boer M**, van Leeuwen FE, Hauptmann M, Overbeek LIH, de Boer JP, Hijmering NJ, Sernee A, Klazen CAH, Lobbes MBI, van der Hulst RRWJ, Rakhorst HA, de Jong D. Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast. *JAMA Oncol.* 2018;1;4(3):335-341
8. **de Boer M**, Hauptmann M, de Jong D, van Leeuwen FE, Rakhorst HA, van der Hulst RRWJ. Letter to the editor: response to "Macrotextured Breast Implants with Defined Steps to Minimize Bacterial Contamination around the Device: Experience in 42.000 implants. *Plast Reconstr Surg.* 2018;142(4):590e-591e
9. de Jong D, **de Boer M**, van Leeuwen FE: Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast - Reply. *Jama Oncol.* 2018;1;4(10):1435
10. Barbé E, **de Boer M**, de Jong D. A practical cytological approach to the diagnosis of breast-implant associated anaplastic large cell lymphoma. *Cytopathology.* 2019;30(4):363-369.
11. Becherer BE*, **de Boer M***, Spronk PER, Gijsbers AH, de Boer JP, van Leeuwen FE, Mureau MAM, van der Hulst RRWJ, de Jong D, Rakhorst HA. The Dutch Breast Implant Register (DBIR): Registration of Breast Implant - Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), a proof of concept. *Plast Reconstr Surg.* 2019;143(5):1298-1306

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13. Los-de Vries GT*, **de Boer M***, van Dijk E, Stathi P, Hijmering NJ, Roemer MGM, Mendeville M, Miedema DM, de Boer JP, Rakhorst HA, van Leeuwen FE, van der Hulst RRWJ, Ylstra B, de Jong D. Chromosome 20 loss is characteristic of breast implant-associated anaplastic large cell lymphoma 2020;17;136(25):2927-2932.
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(* Authors contributed equally)

In preparation

1. **de Boer M**, Heuts EM, de Jong D, van der Hulst RRWJ: Factors associated with the pathogenesis of Breast Implant Associated - Anaplastic Large Cell Lymphoma (BIA-ALCL): a review of the current literature.

Scientific Meetings

1. Inspectie Gezondheidszorg & Jeugd; De Nederlandse situatie aangaande BIA-ALCL. Rapportage: huidige studies en uitkomsten. Period between 2016-2021.
2. IKNL-werkgroep mamma-tumoren Amsterdam. ALCL en mamma-prothesen; klinische en epidemiologische vragen. ALCL en mamma-prothesen; klinische en epidemiologische vragen. November 16, 2020, Amsterdam, Netherlands
3. JVPC Webinar. BII & BIA-ALCL: Risico analyse en management, zijn borstimplantaten veilig? October 31, 2020. Invited speaker.
4. Journal club webinar on BIA-ALCL of Journal of Plastic, Reconstructive and Aesthetic Surgery. Critical appraisal. May 15, 2020. London, United Kingdom. Invited speaker.
5. Webinar on BIA-ALCL. Interactive Plastic Surgery Network (IPSN). May 14, 2020. Mexico. Invited speaker
6. IKNL-werkgroep mamma-tumoren Amsterdam, ALCL en mamma-prothesen; klinische en epidemiologische vragen. November 12, 2019.
7. DICA Congres. De "Dutch Breast Implant Registry" (DBIR). Registratie van een zeldzame complicatie; Breast Implant Associated - Anaplastic Large Cell Lymphoma. Invited speaker. June 21, 2019, Amsterdam, Netherlands

8. 2018 meeting of the Dutch Association of Plastic Surgeons, Amsterdam, the Netherlands. De registratie van BIA-ALCL in DBIR; "proof of concept" op basis van PALGA. May 25, 2018
9. Innovations in Breast reconstruction Symposium. Catharina Hospital Eindhoven. Breast Implant-Associated Anaplastic Large Cell Lymphoma: An overview focussing on risks and causes. November 2017, Eindhoven, Netherlands. Invited speaker.
10. EURAPS meeting. Breast Implant Associated - Anaplastic Large Cell Lymphoma: relative and absolute risk assessment in the Netherlands, May 26, 2017, Pisa, Italy
11. (Poster) 2017 Science day Maastricht University Medical Center MUMC+. Relative and absolute risk assessment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) based on a population-based study over a 26-year period. May 10, 2017, Maastricht Netherlands.
12. 2016 meeting of the Dutch Association of Plastic Surgeons, Rotterdam, the Netherlands. ALCL in een axillaire lymfeklier bij een patiënte met een borstprothese. October 8, 2016.
13. 2016 meeting of the Dutch Association of Plastic Surgeons, Eindhoven, the Netherlands. De Nederlandse aanpak bij BIA-ALCL. Het algoritme en de studie. Aanbevelingen en een klinisch algoritme vanuit een Nederlands Expert Panel. May 20, 2016

Awards & grants

1. PALGA prijs 2017: Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL): Relative and absolute risk assessment based on a population-based study over a 26-year period
2. Jules Coenegracht stichting; wetenschapsfinanciering BIA-ALCL project MUMC+
3. RIVM Research project: Association of breast implants with auto-immune disorders, non-specific symptoms, allergic reactions and anaplastic large-cell lymphoma.

CHAPTER

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About the author

About the author

Mintsje de Boer was born the oldest of three siblings on April the 16th, 1992 in Nes, Friesland, The Netherlands. In June 2010 she graduated from the OSG Sevenwolden, Heerenveen, with a Gymnasium Diploma. Subsequently she started her medical training at Maastricht University, Maastricht, the Netherlands in 2010.

During her surgery internships she discovered her interest and enthusiasm for reconstructive surgery. She got involved in a research project on breast implant related health problems in Maastricht under supervision of prof. dr. René RWJ van der Hulst, at the Plastic, Reconstructive and Hand-Surgery department, Maastricht University Medical Center+, Maastricht (September 2014).

In December 2015, she helped to establish an independent multicenter and multidisciplinary research consortium on Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). This research consortium combines expertise of Pathology, Epidemiology, Hemato-oncology and Plastic Surgery, from the Amsterdam University Medical Center, location VU, the Dutch Cancer Institute, Amsterdam, Medical Spectrum Twente, Enschede, and the Maastricht University Medical Center+, Maastricht, respectively. The consortium is supported by the Dutch Society of Plastic Surgery (NVPC) and epidemiologists and database experts from Stichting PALGA (Pathological Anatomical National Automated Archive). Since januari 2016 this team has worked on clinico-epidemiological and biological studies to answer questions about BIA-ALCL. Beside research activities, the observed data and national trends are regularly communicated to health authorities (Inspectie Gezondheidszorg en Jeugd (IgJ), Rijksinstituut voor Volksgezondheid en Milieu (RIVM) and Ministerie van Volksgezondheid, Welzijn en Sport (VWS) and the consortium is involved in several (inter)national meetings and collaborative expert groups on the subject of breast implant use and safety.

After obtaining her medical degree in Juli 2016, she worked as a resident not in training at the Department of Plastic Surgery at the Maastricht University Medical Center+ and the VieCuri Hospital Venlo, while simultaneously continuing her PhD-program focussing on BIA-ALCL at the department of Plastic Surgery at MUMC and department of Pathology, Amsterdam UMC, location VU.

In February 2019, she started working as a resident at the Department of General Surgery at the VieCuri Hospital Venlo, as a part of her residency in Plastic Surgery. In December 2020 she continued her training to become a plastic and reconstructive surgeon at the Maastricht University Medical Center+.