

Anaplastic Large Cell Lymphoma in the breast in women with 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).