SUMMARY OF CHAPTERS

Capsular contracture is the leading complication after breast implant surgery. Formation of a capsule occurs around every foreign material as a normal foreign body reaction. However, in some cases this formation tends to overextend, leading to a thick and hard capsule; capsular contracture. According to literature the prevalence of capsular contracture ranges from 5-19% in aesthetic surgery and 19-25% in reconstructive surgery. Capsular contracture presents clinically with symptoms of pain, hardening, displacement and change of appearance of the breast. This often results in removal or replacement of the implants. Capsular contracture is clinically measured according the Baker score. According to this score, a Baker type I&II is a soft breast. Baker type III&IV is a hard, painful breast with implant deformation. Currently, the etiology of capsular contracture is still unknown. It is thought to be a multifactorial condition. The aim of the studies described in this thesis was to investigate the etiopathogenesis of capsular contracture. Doing so, we focused on the immunobiological factors as well as patient-, surgery- and implant-specific risk factors for the development of capsular contracture.

Chapter 2 provides an overview of the literature on the etiopathogenesis of capsular contracture. An important observation is the role of the immune system in capsular contracture. All studies investigating the role of the immune system found a chronic inflammation in capsular contracture. Another important theory is that bacteria peri-prosthetically play a role in the etiology of capsular contracture. Some studies found associations between the presence of bacteria peri-prosthetically and capsular contracture. The bacteria cultured most often were Staphylococcus spp.

The aim of part I was to investigate the role of bacteria on the etiopathogenesis of capsular contracture. Therefore the bacterial microbiota on breast capsules was investigated using a highly sensitive PCR-assay. Moreover, since it is unclear whether detected bacteria originate from the breast capsule, breast glandular tissue or skin contamination, bacterial microbiota in glandular tissue and breast skin were assessed. We also investigated if bacteria trigger the inflammatory response that is seen in capsular contracture.

In chapter 3 we investigated bacterial presence on contracted (n=22) and non-contracted (n=28) breast capsules, glandular tissue (n=10) of the breast and the breast skin (n=10) using a highly sensitive PCR-technique. We found low numbers of Staphylococcus spp. (4 species in 4 capsules) breast capsules. There was no difference in bacterial presence between
normal and contracted capsules. The skin of the breast harboured *Streptococcus spp.* and *Staphylococcus spp.* while the glandular tissue was sterile. The low numbers of bacteria found on the capsules might originate from skin contamination during capsule removal. Much higher numbers of bacteria would have been expected in the case of bacterial infection of the breast capsules. However, although the capsule is the most likely site of a potential bacterial low grade infection, it is also possible that bacteria inhibit other breast tissue or implant sites.

In chapter 4 we aimed to investigate if bacteria trigger the immune response that is seen in capsular contracture. Receptors on immune cells that recognize pathogens such as bacteria are Toll-like receptors (TLRs). In humans 10 TLRs have been identified so far. The same 50 samples as in chapter 3 were investigated for TLRs 1-10 expression. We found an expression of all TLRs in all Baker scores. TLR2 and TLR6 were more often present in contracted samples compared to uncontracted samples. These results suggest that bacteria do not trigger the immune response. We suggest that bacteria are not per se involved in the activation of an immune-cascade since it is expected that 11 years post implant surgery, bacteria should have been managed by the immune system, as has been confirmed in our sterile samples. Damage Associated Molecular Patterns (DAMPs), however, can be generated over a long period of time and might be involved in the pathway leading to capsular contracture.

Chapter 5 and addendum review the different patient-, surgery- and implant-specific risk factors for the development of capsular contracture. The different properties and insertion of biomaterials are of known influence on host immune response. We found five factors that were associated with capsular formation. These were longer duration of follow-up, breast reconstructive surgery in patients with a history of breast cancer, subglandular implant placement, postoperative hematoma, and a smooth implant surface. The aim of part 2 was therefore to investigate the risk factors for the development of capsular contracture.

Risk factors for the development of capsular contracture were investigated in a PIP cohort in Chapter 6, where 80 patients with a total of 152 breast implants that were explanted were analysed. Contracture was observed in 13.6% of the cases. This study showed that implant rupture resulted in a higher chance of contracture development (P = 0.044). This might be explained by the release of silicone outside the implant, which might cause an inflammatory reaction after silicone engulfment by macrophages or due to mechanical friction caused by the silicone that might cause an inflammatory reaction leading to contracture. The recall of PIP implants resulted in a wide range of patients removing their implants. This gave us
the opportunity to investigate the implant dynamics in relationship to clinical symptoms such as capsular contracture. **Chapter 6** is the first study to correlate implant behaviour with clinical findings. In 152 PIP implants pre- and post-operative volumes were calculated while the status was determined by the surgeon per-operatively. We found that gel bleed and implant rupture occurred in respectively 42 and 25% of the implants which is higher than breast implants on the market. Interestingly, intact implants showed post-operative volume increase as well as decrease. There was a correlation between gel bleeding and more post-operative implant volume increase \( (P \leq 0.05) \). Also there was a correlation found between capsular contracture and post-operative implant volume increase \( (P \leq 0.05) \).

The former observations in **Chapter 6** were further analysed in **Chapter 7** in a chemical study on three explanted PIP implants. This study found that all of the explanted implants had a yellow color. They also lacked a barrier layer in their envelopes. The implants also lacked vinyl containing components and did not contain high levels of cyclosiloxanes. They did, however, contain a high amount of water. The lack of a barrier layer was a major concern for patient safety as this can lead to higher bleeding rates.

Radiotherapy is an important risk factor for developing fibrous capsular contracture in breast reconstruction after breast cancer. It is unknown if capsular contracture is solely caused by tissue reactions or if the implant itself is also damaged by radiotherapy and the complications are caused by a combination of the two. In **Chapter 8 and addendum** we investigated if radiotherapy influences the mechanical properties of silicone breast implants in an ex-vivo setting. We investigated 32 ready-to-use silicone breast implants (Mentor and Silimed). Half of the implants of each brand were irradiated with 1x60 Gy, the other half were not irradiated. Tensile, mechanical hysteresis and rheology tests were performed and showed no differences between the irradiated and non-irradiated group. Our results suggest that irradiation of the breast tissue, perhaps in combination with breast implants, causes all irradiation-related problems.