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## Safety & imaging of modern silicone breast implants

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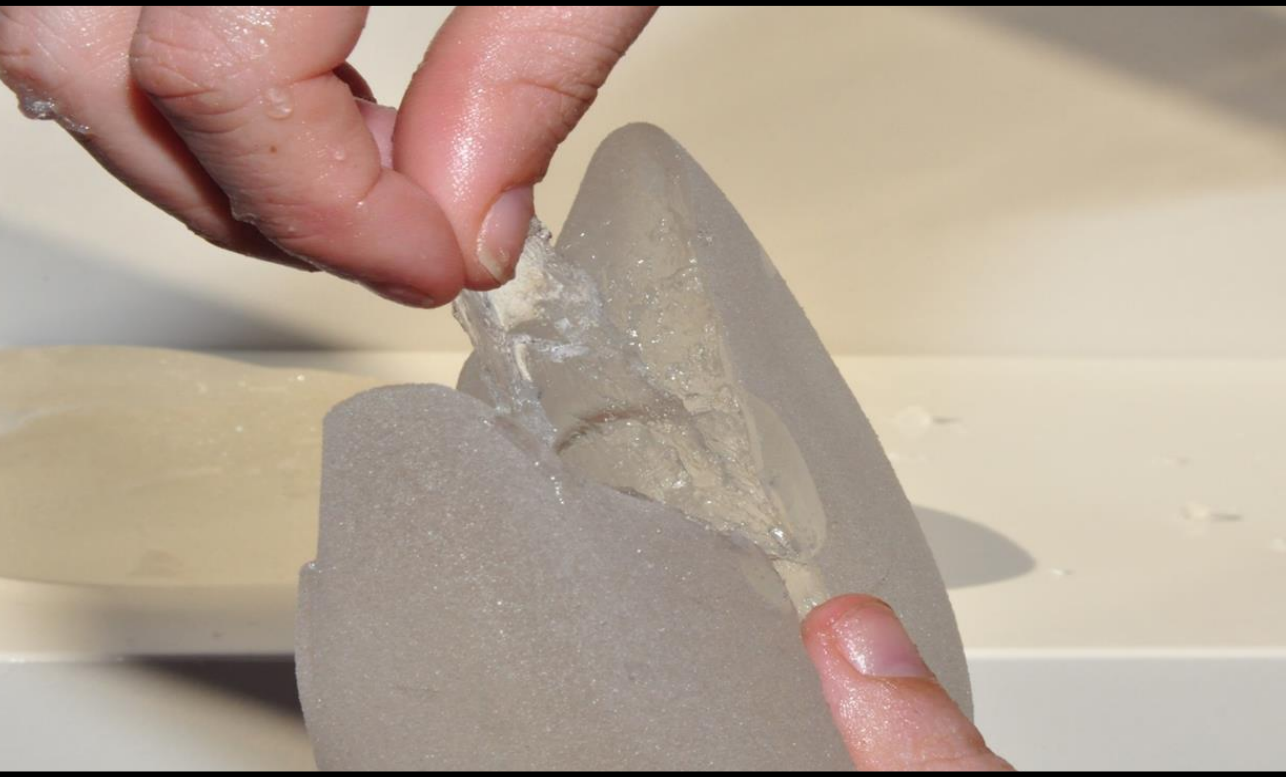
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# CHAPTER 1

General Introduction





# GENERAL INTRODUCTION

## BACKGROUND

Where would be a better place to start writing the introduction of this thesis than at the premises of a Dutch-German company, called Prescan®, a commercial MRI center where a customer, no longer called a patient, can get a self-prescribed and self-paid MRI. This is advertised as a preventive tool for the anxious customer, who wants to make sure his/her body is free of any (asymptomatic) pathology.<sup>1</sup> This fear was also true for hundreds of thousands of anxious women with silicone breast implants, who saw on news items and read in news magazines about dangerous implants that may rupture, causing chronic illness or even cancer.<sup>2-5</sup>

Anxiety, and especially mass anxiety, can force authorities to implement abrupt measures and decisions often before any scientific evidence for their viability is presented. Measures like these are used to control the situation and prevent further damage.<sup>6</sup> This is probably how the French minister of Health must have thought on December 23, 2011 when he announced the imperative recall and explanation advise of all women who had been implanted with silicone breast implants from the manufacturer Poly Implant Prothèse (PIP).<sup>7</sup>

Already for some time prior to this date, it was suggested that silicone implants from this manufacturer had a higher chance of rupture than other manufacturers.<sup>8,9</sup> Findings of substandard procedures during an inspection of the French health watchdog, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSPS), eventually led to closure of the company and a withdrawal from the European market on March 31<sup>st</sup> 2010. The director and founder Jean Claude Mass was recently sentenced to four years imprisonment for serious fraud by having used an inferior industrial grade silicone gel instead of authorized medical grade silicone gel in the breast implants they manufactured, which affected over 300.000 women in 65 countries.<sup>3</sup>

As in the rest of Europe also in the Netherlands PIP silicone breast implants have been on the market from the late 90's until 2010 and were used in approximately 3.000 women. The studies and articles described in this thesis were a direct result of the PIP recall in 2010. The department of Plastic, Reconstructive and Hand Surgery and the department of Internal Medicine of the VU Free University Medical Center in collaboration with the MRI Center Amsterdam and Medical Center Jan van Goyen took their responsibility to perform research on safety and imaging of modern silicone breast implants in the Netherlands.

## 1. SILICONE BREAST IMPLANTS USED IN PLASTIC & RECONSTRUCTIVE SURGERY

Silicone breast implants have been used for reconstruction or augmentation for over 50 years. They have come in many different types, generations and manufacturers since their introduction to the market in 1962.<sup>10</sup>

### 1.1 Silicone breast implant design

Innovations in design, shell and silicone gel consistency and structure have improved the product to a well-known, well integrated and accepted method for both women needing reconstruction after a mastectomy after breast cancer, as well as women with the desiring to increase their breast size for cosmetic reasons. All modern breast implants, also saline or cellulose filled implants typically consist of a silicone elastomer envelope or shell filled with either saline, cellulose or silicone gel. These envelopes vary in composition and characteristics of the elastomer, type of coating, number of layers and the type of barrier layer.<sup>11</sup>

In the case of silicone implants, the silicone gel inside the envelop is composed of synthetic polymers of silicone oxide with organic side chains (polydimethylsiloxane), which are formed into gels by lengthening the polymer chains and made more or less solid (often called high or moderate cohesive) by more or less cross-linking of the polymer chains.<sup>12</sup> Silicone gel in implants

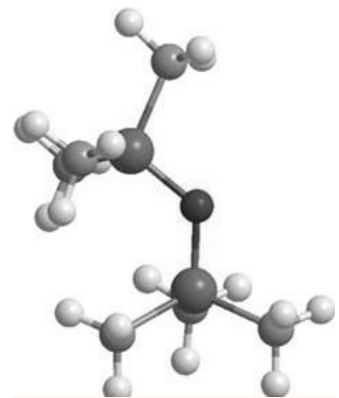


Figure 1 Chemistry of silicone

contains both low- and high-molecular-weight (respectively shorter or longer) polymers mixed together in various proportions. The low-molecular-weight silicone is not chemically attached to the main gel and can therefore diffuse into surrounding tissues (this occurrence is called gel bleed). A barrier layer in modern envelopes is designed to reduce this type of leakage. Cross-linked polymeric silicones are considered inert materials due to the durability and thermal stability of their chemical and elastic properties. Figure 1 shows the molecular composition of silicone gel.

In PIP implants the low bleed barrier was eliminated from its design in 2007 and high median low-molecular-weight silicone (D4 and D5) levels were found.<sup>13,14</sup>

### 1.2 Historical generations

The 1<sup>st</sup> generation implants were composed of a thick envelope typically filled with a thick silicone gel. Capsular contracture formed a major complication in these implants and therefore a 2<sup>nd</sup> generation was introduced with a thin, more fluid silicone gel, a thinner envelope and a smooth surface. Increased risk of rupture and gel bleed complicated this generation and led to the

development of the 3<sup>rd</sup> generation implants with a stronger “barrier coated” or “low bleed” envelope and again a thicker silicone gel. The so called 4<sup>th</sup> generation includes third generation technology with textured silicone surfaces and round as well as anatomic shapes. This textured surface reduced the incidence of capsular contracture dramatically.<sup>15,16</sup> The most modern 5<sup>th</sup> generation implants are implants in which the silicone gel is made more cohesive with more cross-linking and both high and moderate cohesive variants, for a more natural feel, better retention of shape and prevention of leakage of the silicone gel, even in case of rupture.<sup>17</sup> According to the manufacturer and development year PIP silicone breast implants would be classified as either 3<sup>rd</sup> or 4<sup>th</sup> generation implants. The different generations as described by Mathes<sup>18</sup> are included in Table 1.

Generation	Years	Shell	Gel	Surface	Shape
1 <sup>st</sup>	1962-1970	thick	thick	Dacron patches	teardrop
2 <sup>nd</sup>	1970-1982	thin	thin	smooth	round
3 <sup>rd</sup>	1982-present	thick & strong	thicker than 2 <sup>nd</sup>	smooth	round
4 <sup>th</sup>	1986-present	like 3 <sup>rd</sup>	like 3 <sup>rd</sup>	textured	round & anatomic
5 <sup>th</sup>	1993-present	like 3 <sup>rd</sup>	enhanced cohesive	textured	divers, round & anatomic

### 1.3 Prevalence

Breast augmentation has become one of the most popular cosmetic plastic surgery procedures in the US since the reintroduction to the market of silicone breast implants in 2006.<sup>19</sup> The use of silicone breast implants in cosmetic surgery is increasing and furthermore the number of women who choose for a breast reconstruction technique which includes the implantation of silicone breast implants is increasing. In 2012, 286.274 breast augmentations with silicone breast implants were performed in the US alone and 64.114 silicone implants were used at breast reconstructive surgery.<sup>20</sup>

It is difficult to say how many women worldwide have silicone breast implants. The U.S. Food and Drug Administration (FDA) estimates the number of silicone breast recipients to be 5 to 10 million worldwide,<sup>21</sup> of which 3 to 5 million probably in the US alone and with increasing numbers in countries like Brazil and China. Most of these millions of women have breast implants to increase the size of healthy breasts (80%) and a significant number (a bit less than 20%) for reconstruction after mastectomy.<sup>22</sup> A small minority of these women have silicone breast implants because of congenital deformity like in Poland syndrome or as part of transgender surgery.

The exact total number of women in the Netherlands with silicone breast implants is unknown. Manufacturers guess that approximately 18.000 silicone breast implants are sold in the Netherlands yearly and that more than 80.000 women have silicone breast implants in situ at the moment of writing.

## 2. LOCAL COMPLICATIONS & ADVERSE EFFECTS

Although silicone breast implants currently used in plastic and reconstructive surgery as explained are very different from their predecessors, health and safety issues are still a much discussed subject. There are both local and systemic complaints and signs related to silicone breast implants, some of which require revision surgery.<sup>23</sup> Local complications are well described and less debated than systemic complications are. Within the first 6 years, in one third of women after primary implantation of silicone breast implants local complications will lead to revision surgery.<sup>24,25</sup> Table 2 shows all local complications that occur in at least 1% of breast implant patients as formulated by the FDA.<sup>26</sup> In this paragraph the most frequently reported local complications are summarized.

### 2.1 Rupture

Silicone breast implants do not last a life long and do rupture after some years, which in most women will lead to additional procedures such as revision surgery and replacement of the ruptured implants.<sup>27,28</sup> Authors predict most modern implants to rupture after being 7 to 15 years in situ.<sup>29,30</sup> Rupture of implants can be caused by e.g. trauma or closed capsulotomy, but will in most cases be caused by normal wear and tear of the elastomer envelope.

The rupture rate or prevalence of rupture is very difficult to assess. Prevalence of rupture studies in the past have used different methods (MRI screening or explantation study), different patient populations (after augmentation or reconstruction), varied implant types (older studies included double lumen, at times even saline implants), varied generations and manufacturers. Therefore it is

**Table 2. Type of local complication that occur in at least 1% of breast implant patients as mentioned by the FDA website in alphabetic order**

Asymmetry
Breast feeding difficulties
Breast pain
Breast tissue atrophy
Calcification
Capsular contracture
Chest wall deformity
Delayed wound healing
Deflation of the breast implant
Extrusion
Hematoma
Iatrogenic injury or damage
Implant displacement or malposition
Implant palpability
Implant removal
Implant visibility
Implant wrinkling or rippling
Infection, including toxic shock syndrome
Inflammation or irritation
Lymphedema or lymphadenopathy
Necrosis
Nipple or breast changes
Ptosis
Redness or bruising
Reoperation
Rupture of the breast implant
Scarring
Seroma
Skin rash
Unsatisfactory appearance

extremely difficult to compare these studies. Furthermore, the definition of rupture varies among different researchers from true tear to pin-hole sized ruptures, including gelbleed or not in their “ruptured cases.”<sup>31,32</sup>

The cumulative prevalence of rupture varied strongly throughout the years that silicone breast implants have been in use and the overall cumulative rupture prevalence went down with the newer 4<sup>th</sup> and 5<sup>th</sup> generation moderate to high cohesive silicone gel filled implants. Most large explantation studies on rupture prevalence in the past included selected symptomatic women with implants from the 1<sup>st</sup> to 3<sup>rd</sup> generation and therefore reported quite high 10-12 year cumulative prevalence of rupture varying from 34% up to 69%.<sup>33-39</sup> Marotta et al. reviewed 35 studies and calculated the 10 year cumulative failure rate to be 50%.<sup>25</sup> In these explantation studies however the 2<sup>nd</sup> generation implants were often overrepresented and they had proven to rupture two to three times more easily than the other generations.<sup>35,37</sup> The last 15 years, research on prevalence of rupture shifted from explantation studies to MRI based studies and the incidence of rupture for 3<sup>rd</sup> generation implants was calculated to be 2.3 ruptures per 100 implant years.<sup>40</sup> Innovations in the strength of the shell and the consistency of the silicone gel may have reduced the frequency of rupture. A study on 3<sup>rd</sup> generation implants found 8% (15% when reconstructions patients were included) cumulative rupture rate after 11 years.<sup>41</sup> Recent studies on 4<sup>th</sup> generation implants have reported a cumulative prevalence of rupture of 1.1 to 3.8% after 6 years, based on spontaneous reporting.<sup>42,43</sup>

Rupture rates do not only vary between generations, but also between manufacturers.<sup>29</sup> Most recent studies on prevalence of rupture are therefore studies based on single generation and single manufacturer implants, often sponsored by these manufacturers. In 2012 studies from the 3 FDA approved manufacturers reported cumulative prevalence of rupture of 1,8%, 3,8% and 2,1% in modern 4<sup>th</sup> and 5<sup>th</sup> generation silicone implants of the manufacturers Sientra®, Allergan® and Mentor® after 5 to 6 years.<sup>44-46</sup> The ten years results of these prospective studies are yet to be expected, but preliminary results of the CORE studies of Allergan® and Mentor® show estimated 10 year cumulative MRI diagnosed ruptures after primary augmentation in Allergan® silicone implants to be 10.1% (95% CI, 7.4-13.7) and 8-year cumulative MRI diagnosed ruptures in Mentor® implants to be 13.6% (95% CI, 7.6-23.6).<sup>47</sup> Patients who have silicone implants due to reconstructive reasons after breast cancer have a much higher chance of rupture, up to 27.2% and 14.0% respectively in the 2 previous studies at 10 and 8 year. As a matter of fact, the frequency of all local complications tends to be higher after reconstruction compared to augmentation.<sup>48</sup>

Another problem concerning the estimation of the prevalence of rupture is that most studies are not free of selection bias, because often only symptomatic women are included in the studies. Most implant ruptures of modern silicone breast implants however do not produce symptoms and/or signs and are called ‘silent’ ruptures.<sup>29,49</sup> Implant rupture can be either intracapsular or extracapsular, the latter causing more complaints, as free silicone gel spreads outside the fibrous capsule that forms around an implant. It is still unclear whether implant rupture without complaints requires replacement surgery.<sup>32,38,50,51</sup>



## 2.2 Gel bleed

Implant rupture is not the only way by which silicone may escape to the surrounding breast tissue as the low-molecular-chain polymers may diffuse, or “bleed”, through the silicone elastomer envelope, even in the absence of a true tear.<sup>52,53</sup> A study showed this diffusion of silicone gel fluid to amount to 300mg per year, depending on age and manufacturer of the implant<sup>54</sup>. At explantations, surgeons describe a gel like greasy fluid often to be present around the implant. This was assumed to lead to lymphadenopathy and even to general systemic complaints.<sup>55-57</sup> Gel bleed has been described since 1970, but its exact prevalence remains unclear. Some reported 20% percent<sup>32</sup> of severe gel bleed at explantations and include severe gel bleed into the category of ruptured implants.<sup>33,38</sup> Others accept some form of gel bleed as normal occurrence in silicone breast implants after some time<sup>58,59</sup> or consider gel bleed as a “possible rupture” category.<sup>60</sup> The clinical significance of moderate to severe gelbleed is not fully agreed upon until today.<sup>32,51,61</sup>

## 2.3 Capsular Contracture

The most frequently described local complication of silicone breast implants is capsular contracture.<sup>47,62-64</sup> In every woman after the implantation, a fibrous capsule is formed around the implants. This is also the case in saline implants or as a matter of fact around any foreign device implanted in the human body and is thus considered a normal result of a foreign body inflammatory response.<sup>65,66</sup> Already in the 1970’s the first cases of capsular contracture were reported. This condition causes pain, hard breast consistency, and disfigurement.<sup>67</sup> A clinical measurement for the severity of capsular contraction is the Baker score, which is shown in Table 3.<sup>68</sup>

<b>Table 3. Baker score of severity of Capsular Contraction</b>	
<b>Baker Score</b>	<b>Symptoms &amp; Signs</b>
1	Non palpable capsule and soft
2	Minimal hardness, not visible
3	Moderate hardness, visible disfiguring
4	Hard, painful, cold breasts
<i>Clinically Baker score 1 and 2 are considered normal capsule formation and only Baker score 3 and 4 as a complication, that might warrant treatment</i>	

Innovations in the design of the shell were aimed to target this important local adverse effect of silicone breast implants. Textured implants have been shown to have lower capsular contracture rates than smooth surfaced silicone breast implants (2.5-8% versus 58-81% ).<sup>15,69,70</sup> Some authors argued that the presence of silicone leakage or gel bleed contributes to the thickening of the fibrous capsule and the amount of contracture and disfigurement,<sup>71</sup> whereas others have argued that immunologic and inflammatory processes<sup>72,73</sup> or even the presence of periprosthetic bacterial contamination or a ‘biofilm’ are of influence.<sup>74-77</sup> Perioperative measures like the use of antibiotics or antiseptic washing were introduced in the hope that this might prevent severe capsular contracture, but had only limited effect.<sup>78,79</sup>

The prevalence of capsular contracture varies largely and depends greatly on type and generation of implants, which resulted in percentages varying from 10% to 62% in the past.<sup>67,80</sup> In more recent studies on FDA approved manufacturers of modern cohesive silicone breast implants, capsular contracture rates of 5.6% to 14.8% are mentioned.<sup>42,43,81,82</sup> Figure 2 shows a woman with silicone breast implants with on the left side grade 4 capsular contracture.



**Figure 2.** Photograph shows left sided grade 4 capsular contracture

## 2.4 Hematoma and infection

Every operation can lead to post-operative hematoma, seroma or infection, but these are relatively rare after primary breast augmentation as they occur in 1-3% of all cases.<sup>62,83,84</sup> Preventative measurements are a bandage or an elastic firm bra, worn during the first weeks after implantation or perioperative antibiotics and sterility improving measures. Some cases of late hematoma have been described.<sup>85,86</sup>

## 2.5 Breast pain or sensibility loss

Breast pain is often associated with severe capsular contracture, but is also seen in women without capsular contracture.<sup>87</sup> The pain may be very local and occur only shortly after surgery, but may also be chronic in up to 18% of women.<sup>26,88</sup> Sensibility loss of the nipple and areola occurs in approximately 15%-26% of breast augmentation patients.<sup>89,90</sup>

## 2.6 Unsatisfying aesthetic result

Both round and anatomic cohesive silicone gel implants<sup>76</sup> give highly predictable results and most recent studies report a high degree of patient satisfaction with rates of 70% up to an incredible 99%.<sup>44-46,91-98</sup> Despite the high patients satisfaction rates published by plastic and reconstructive surgeons, authors blame unsatisfying aesthetic results for most revision surgeries.<sup>99</sup> At times breast reconstruction or augmentation can have disfiguring outcomes. The FDA includes terms like asymmetry, distorted form, consistency, size, malrotation, implants placed too high, too low, extruding, bulging etc., all to describe an unsatisfying aesthetic result after silicone breast implant surgery.<sup>26</sup>

### 3. SYSTEMIC COMPLICATIONS & ADVERSE EFFECTS

Systemic complaints and adverse effects of silicone breast implants have been a subject of debate since the first case reports.<sup>100</sup> Generally accepted systemic effects of ruptured or leaking implants have been lymphadenopathy and silicone granulomas.<sup>77</sup> Less accepted, but frequently reported complaints are rheumatic complaints such as arthralgia, myalgia, morning stiffness, but also complaints like chronic fatigue, flue like symptoms, dermatologic symptoms (rashes) and cognitive problems.<sup>24</sup>

#### 3.1 Lymphadenopathy and granulomas

The first articles of local silicone migration into the surrounding breast tissue were soon followed by studies on inflammatory reactions in regional lymph nodes.<sup>101</sup> Migration of silicone into the surrounding breast tissue evokes a nonspecific foreign body reaction, resulting in typical macrophage invasion, giant cell formation, and eventually scarring.<sup>101-103</sup> Silicone lymphadenopathy is a deposition of the silicone in one or more lymph nodes due to lymphatic drainage and can be seen as a normal response to a foreign body.<sup>104</sup> Lymphadenopathy might lead to systemic problems,<sup>105,106</sup> which was the case in a very recent report of a woman with idiopathic pericarditis after bilateral silicone implant rupture, which resolved after explantation.<sup>107</sup>

#### 3.2 Autoimmune diseases, complex of systemic complaints

The link between silicone breast implants and autoimmune disease was often suggested, never proven, but the dispute also never completely resided in large epidemiologic trials. In 1979, 10 years after the first local complications were reported, the first article on alleged implant induced connective tissue disease was published.<sup>108</sup> From the early 80's until 1992 numerous case reports and case series described women with silicone breast implants and a variety of systemic problems, often autoimmune diseases, such as (systemic) lupus erythematosus, connective tissue disease (undifferentiated, mixed, atypical), rheumatoid arthritis, Sjögren's syndrome, scleroderma, inflammatory oligoarthritis or polyarthritis, adult onset Still's disease and diffuse myalgia's.<sup>55,56,109-117</sup> In 1992, at the American College of Rheumatology meeting, a review of in total 750 women with silicone breast implants showed most patients to report nonspecific systemic symptoms of myalgia, arthralgia and fatigue and more than 130 women had proven connective tissue diseases.<sup>118-127</sup> These women had their implants for an average of 8.9 years and 32% of these women also developed capsular contraction and 36% lymphadenopathy besides their systemic complaints.<sup>12</sup>

Since the US moratorium on silicone breast implants in 1992 most epidemiologic studies failed to demonstrate any increase in risk of connective tissue diseases, other systemic diseases or patterns of symptoms in women with silicone breast implants.<sup>128-132</sup> A review focusing on silicone implant

rupture and connective tissue disease found little scientific basis for any association between implants rupture with well-defined or atypical connective tissue diseases.<sup>133</sup> Although no relation was found with implant rupture in the 5 studies evaluated, in one study a large proportion of women with silicone implants was reported with vague systemic symptoms like cognitive problems (34%), joint and muscle symptoms (26% and 20% respectively) and fatigue (17%),<sup>134</sup> while another study included in this review suggested certain common characteristics among women with silicone breast implants and fibromyalgia, whose main symptoms also include joint and muscle pain and fatigue.<sup>135</sup> Two other studies in the same review saw rupture associated with neurasthenia/neuropathy.<sup>136,137</sup>

Although silicone breast implants have not been convincingly proven to cause any autoimmune condition, a small proportion of women with silicone breast implants do complain of vague systemic symptoms that mimic autoimmune diseases and improve after removal of their implants.<sup>138</sup> The relation between these symptoms and local complications like capsular contraction was never well explored.

### 3.3 Cancer & ALCL

Silicone breast implants are frequently used as reconstruction method after mastectomy for breast cancer or after preventive mastectomy in women who have a high risk of developing breast cancer. A significant group of women with silicone breast implants therefore had a history of breast cancer prior to their implantation and one can imagine how worrisome an alleged carcinogenic effect of silicone breast implants would be for them. Fortunately, the risk of breast cancer after silicone breast implantation has been assessed in several studies and no increased risk was found.<sup>139-144</sup> One of the studies even suggested that women with silicone breast implants would have a lower risk of breast cancer than the general population.<sup>145</sup>

Although there is general consensus that silicone breast implants do not cause breast cancer, concerns remain on their influence on breast cancer detection. An implant, because it is radio-opaque, might hide tumors on mammograms, which hinders detection of breast cancer at an early stage.<sup>146-149</sup> Fortunately, MRI offers the twofold advantage of being more sensitive and specific for the detection of breast cancer as well as not being hindered by the silicone implants. A very recent systemic review and meta-analysis found that women with cosmetic breast implants who develop breast cancer have an increased risk of being diagnosed in a non-localized stage of breast cancer than women without implants. Cosmetic breast augmentation might therefore adversely affect the survival of women who are diagnosed as having breast cancer.<sup>150</sup>

As yet no relationship has been proven between the occurrence of most malignancies and silicone breast implants. Recent investigation showed no association between silicone breast implants and breast cancer, multiple myeloma, lymphoma, leukemia, lung cancer, cancer of the GI tract, cancer of the genitals, kidney or bladder cancer, or cancer of the nervous system.<sup>151-155</sup>

Lymphomas of the breast are rare and Anaplastic Large Cell Lymphoma (ALCL) is a very rare type of lymphoma, or cancer of the immune system, characterized by abnormal growth of T-lymphocytes. Due to publication of case reports<sup>156</sup> the FDA identified 34 cases of ALCL in breast implant recipients<sup>157,158</sup> and concluded in May 2010, the same year of the PIP recall, that there may be a very small risk of developing ALCL in the scar capsule adjacent to breast implants. In the cases reported, the median time from breast implantation to the diagnosis of ALCL was 8 years and the tumor was found in the immediate surroundings of the breast implant.<sup>47</sup> No specific type (silicone or saline) nor specific generation or manufacturer was linked to this type of lymphoma.<sup>158</sup> Globally 130 cases of ALCL related to breast implants have been reported.<sup>159</sup> Still, because of unfortunate timing of the report of a French woman who died from ALCL, the same day the PIP recall was announced, a huge health scare affected many women with silicone breast implants, often unaware of the name of their implants manufacturer.

#### 4. DIAGNOSING IMPLANT RUPTURE

Because implant rupture can lead to complaints, the diagnosis of intact or ruptured implants is of importance. Especially when a large group of women is worried and uncertain about possible threats to their health due to uncertified PIP implants.

##### 4.1 Physical examination

The easiest and cheapest way to diagnose complications and especially rupture in silicone breast implants would be a physical examination by the consulted plastic and reconstructive surgeon. Unfortunately, the accuracy of physical examination in the detection of implant rupture in modern silicone breast implants is quite low, with a sensitivity of 25% and a specificity of 89%.<sup>160</sup> Although it is difficult to predict implant rupture based solely on physical examination, there is still a place for it in the consultation room. The physical examination of the breast is needed to classify capsular contracture according to the Baker score and the palpation of the axillary lymph nodes is paramount to find possible lymphadenopathy, which might need additional examination.

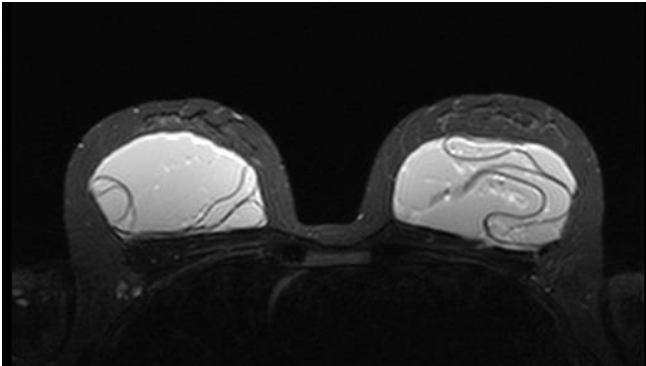
##### 4.2 MRI screening

MRI is widely accepted as the best imaging modality to diagnose rupture of silicone breast implants.<sup>160,161</sup> A meta-analysis in 2001 found an overall sensitivity of 78% (95% CI, 71%-83%) and a specificity of 91% (95% CI, 86%-94%).<sup>162</sup> More recent studies found a higher accuracy with a sensitivity of 89% and a

**Table 4. Signs at MRI screening indicative of implant rupture**

Signs
linguine sign
subcapsular line
teardrop sign
noose or key-hole sign
extracapsular silicone
train rail sign

specificity of 97%.<sup>60</sup> The first clinical experience with MRI screening of silicone breast implants was reported in 1991-1992.<sup>163-165</sup> MRI techniques have changed in time and the accuracy of the detection of implant rupture has been improved<sup>164</sup>. Presently the most frequently used pulse sequences are a series of STIR (Short TI Inversion Recovery) image acquisitions with selective suppression of silicone and water and the use of a dedicated breast coil<sup>166</sup>.



**Figure 3.** Example of intracapsular rupture with a linguine sign

The reading of MR images requires experience and well defined diagnostic criteria.<sup>167-169</sup> Different signs and criteria for implant rupture in silicone breast implants have been validated in radiologic literature and the most known and validated signs are mentioned in Table 4.<sup>59,160</sup> Figure 3 shows an example of intracapsular ruptures with linguine signs on both sides.

The FDA has since the reintroduction of silicone breast implants to the US home market advised women with silicone breast implants to undergo MRI three years after implantation and every two years after that.<sup>19</sup> Some authors have questioned the usefulness of MRI as serial screening instrument to detect asymptomatic rupture in women with silicone implants and questioned if it will lead to a reduction of patient morbidity.<sup>170,171</sup>

### 4.3 Other imaging modalities

Mammograms are considered the least sensitive imaging modality to detect implant rupture in women with silicone breast implants with a sensitivity of 11-69%.<sup>166,172-175</sup> A recent study calculated sensitivity to be 68% and specificity to be 81%.<sup>176</sup> Furthermore, if an implant is already ruptured, the pressure from a mammogram could cause silicone gel from the implant to leak outside of the capsule.<sup>28</sup> Some authors even claimed the mammography procedure to be responsible for ruptures by itself.<sup>177</sup>

Ultrasound is judged by some to be a good and cheaper alternative imaging method to diagnose implant rupture in silicone breast implants.<sup>178-180</sup> Others find it to be too operator dependent and inferior to MRI.<sup>172</sup> Criteria for implant rupture are 1. echogenicity or snowstorm pattern outside the implant lumen, 2. visualization of the collapsed shell or abnormal heterogeneity of the implant fluid and 3. presence of silicone outside the implant lumen.<sup>181</sup> A recent study found the sensitivity to be 77% and the specificity to be 69%.<sup>176</sup>

## 5. PIP RECALL & START OF STUDY

### 5.1 PIP recall in the Netherlands

The use of unauthorized non-medical grade silicone gel and substandard manufacturing processes led to the closure of the French company PIP in 2009. Since March 2010 the commercial distribution of PIP implants has been prohibited in Europe, but general recommendations of implant removal were announced only much later that year by the French government.<sup>2</sup> In Europe, not all governments and health authorities followed the French example from the start and in the UK even until today the reimbursement of patients who want replacement of their fraudulent implants remains unclear.<sup>182-184</sup>

Also in the Netherlands, the initial advice of the Health Care Inspectorate (IGZ) was to replace or explant ruptured PIP implants only. This is why plastic surgeons at Medical Center Jan van Goyen in Amsterdam recalled all PIP implanted patients and performed MRI screening to identify silent ruptures. At the start of our studies early 2011, only PIP implants in women of whom at least one of their implants appeared ruptured were operated. Later that same year, after the 23th of December 2011, while already following a cohort of 112 women with 224 implants, this advice changed and in the Netherlands, like in France, and explantation of all PIP silicone breast implants was required.<sup>185</sup> This is how our retrospective cohort study with 10 year follow-up time became a prospective MRI screening study and eventually an explantation study with a follow-up of 3 more years.

### 5.2 Impact on patients and health resources

With approximately 400.000 PIP implants sold worldwide<sup>186</sup> and the media attention that accompanied the whole affair, the PIP scandal caused immense anxiety among women with breast implants and additionally led to huge costs.<sup>187</sup> In the UK a study reported the extra National Health Service (NHS) costs in a single facility treating almost 80 women to be £32,501.68 (of British pounds).<sup>187</sup> Since the recall of PIP implants in 2010 other authors have published their experiences and the impact the recall had on their daily practices.<sup>187-190</sup>

The timing of the announcement of the French government to advocate the removal of all PIP implants, following the announcement of the death of a women with PIP implants from ALCL, was used in the media to link PIP implants directly to cancer. A lot of women are unaware of the brand name of their silicone breast implants and this blunt media coverage has let also women with silicone breast implants other than PIP to present to their plastic surgeons, GP's and other specialists with questions concerning health risks and diagnostic means.<sup>191</sup> As Sir Keogh explained in the NHS report in the PIP matter, *"anxiety is in itself a genuine health issue and may well increase the risk of other health problems"<sup>14</sup>*. We therefore identified a need to research the consequences and outcomes of the PIP recall for patients, medical specialists and regulators.

## AIM & OUTLINE OF THIS THESIS

The aim of the studies described in this thesis is assisting those previously mentioned hundreds of thousands of anxious women with silicone breast implants and providing timely and compelling data on the complications and means to detect these complications. The PIP recall is used to study safety and imaging in modern silicone breast implants.

During our studies we at times became painfully aware of the influence of media on health behavior and public opinion concerning silicone breast implants; this is why in **Chapter 2** we address this issue. We provide a historical overview of silicone breast implants in medical literature as an introduction to our studies on safety and imaging of these medical devices. We illustrate the history of silicone breast implants by a review of medical literature found in PubMed and examples of lay media on the same topic. We explore these two forms of publication and their influence on each other. This chapter will place the PIP recall and the medical publication spike in 2012 in perspective of other literature spikes concerning silicone breast implants.

The media attention caused by the recent PIP crisis drove anxious women with silicone breast implants and unexplained symptoms to consult different physicians. To assist these women, who often felt ignored by their plastic surgeons, the Netherlands Association of Internal Medicine (NIV) and the Netherlands Society of Plastic Surgery, Hand Surgery, Aesthetic and Reconstructive Surgery (NVPC) implemented a special outpatient clinic at the VU Free University Medical Center. So far this clinic has been visited by more than 150 patients and in **Chapter 3** we describe our preliminary findings regarding the first 80 patients in a descriptive cohort study.

The women who attended the special outpatient clinic did not necessarily have PIP implants. Still our aim is to study the impact and clinical consequences of PIP implants used in the Netherlands. To do so we will first quantify the problem: how many women did have ruptured PIP implants? Since there was no published data on the prevalence of rupture in PIP implants, we present our first retrospective cohort study. **Chapter 4** describes the first results on prevalence of rupture by MRI screening of the first 112 women with PIP implants at Medical Center Jan van Goyen in Amsterdam. We aim to research the number of symptomatic and asymptomatic ruptures in PIP implant recipients and place the prevalence of rupture in perspective of rupture prevalence in implants of other manufacturers.

In **Chapter 5** we aim to examine the clinical and diagnostic consequences of implant rupture in women with PIP implants in comparison to women with implants of other manufacturers. Only women who had at least one ruptured implant underwent revision surgery. Due to our results on the prevalence of rupture in PIP implants and those of other researchers the advice of the health authorities in Europe changed to explantation of all PIP implants. Within one year after our first two studies almost all women underwent revision surgery.



**Chapter 6** describes all explantation results of our prospective cohort study and assesses the cumulative 10-year prevalence of rupture at explantation compared with the MRI screening results in women with PIP implants. Our study aims to provide insight into the accuracy of MRI screening in mostly asymptomatic women in a day to day clinical setting.

Because of the somehow disappointing accuracy of MRI in our study and the use of a variety of terms and jargon used in literature on the status of silicone breast implants, a new method for MRI reporting was developed by the authors to improve communication between plastic surgeon and radiologist. This classification system called SI-RADS is further explained in **Chapter 7**.

In **Chapter 8** this new protocol is used to evaluate the accuracy and inter- and intraobserver variability of MRI screening in modern silicone breast implants. This chapter together with Chapter 6 contributes to international knowledge on accuracy of MRI screening of modern last generations' silicone breast implants and the consistency of this accuracy in non-selected, mostly asymptomatic women. No study until now was able to compare MRI evaluation of intact implants with explantation results. The PIP recall gave us the unique opportunity to do so. These studies have added value in the ongoing debate on the effectiveness and appropriateness of the FDA advice for regular MRI screening of asymptomatic women with silicone breast implants.

**Chapter 9** provides a general discussion of the studies presented in this thesis and their relevance to patients, doctors and authorities. We discuss the effects of media, the evidence based health risks, consequences of PIP implants and new insights in MRI screening of modern silicone breast implants. Future perspectives will focus on new ideas on the link between local and systemic complications in women with silicone breast implants, ways to improve imaging techniques, suggested interesting future study domains and final recommendations.

**Chapter 10** gives an English and Dutch summary of this thesis on safety and imaging of modern silicone breast implants.

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