Breast implants in reconstructive and aesthetic surgery

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Breast Implants in Reconstructive and Aesthetic Surgery
Studies on Self-Reported Health complaints and Quality of Life

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CHAPTERS

CHAPTER 1

General introduction, aims, and
outline of the thesis

GENERAL INTRODUCTION

Breast implant surgery is one of the most common surgical procedure performed by plastic surgeons worldwide.[1] Breast augmentations for cosmetic and reconstructive purposes have been described since 1895, using both autologous tissue (e.g. lipomas and omentum) and alloplastic materials (e.g. polyurethane and liquid silicone).[2] The development of the modern breast implants consisting of a shell with filling, as we know them today, started in 1962.[3] Despite the widespread use of silicone breast implants for both breast reconstruction and breast augmentation, there are still unresolved questions about the safety of these devices, which seem to have caused a lot of unrest in the Netherlands in recent years. The need of both patients and caregivers for answers has prompted this thesis.

Safety of silicone breast implants

The long-term safety of silicone breast implants has been under discussion ever since the introduction in the 1960's. Between 1992 and 2006, the use of silicone breast implants (SBI) was even banned by the FDA, due to safety concerns and its possible association with systemic diseases. When SBI were reintroduced to the market, the industry had to conduct follow-up studies on large groups of patients, but these showed no statistical association between silicone breast implants and systemic diseases, such as autoimmune disease or cancer.[4,5] Nevertheless, the topic has never completely disappeared from the radar. The discussion about the safety of silicone breast implants has received considerable attention in recent years, which has caused a lot of concern and anxiety among women with breast implants and among women considering breast implants.

A well-known example is the Poly Implant Prostheses (PIP) scandal in 2010, where implants had been fraudulently manufactured. These silicone breast implants had an inferior quality shell and lacked the shell barrier resulting in a high degree of permeability.[6,7] Together with the strong variation in shell thickness, this caused a huge increase in the probability of rupture. In addition, the implants were filled with industrial-grade silicone gel instead of medically approved gel, which erupted concern.[8,9] PIP implants were withdrawn from the market and patients were recalled to have the implants removed. Nevertheless, studies to date have shown similar long-term health effects of PIP implants to silicone implants from other manufacturers.[10-12]

Another disturbing finding over the past two decades has been the increase in the number of large-cell T-cell lymphomas seen in women with breast implants, especially textured implants.[13] Epidemiological research showed that women with breast implants indeed have a very small, but increased risk of developing breast implant associated anaplastic large cell lymphoma (BIA-ALCL). The cumulative risks of BIA-ALCL were 29 per million at age 50 and 82 per million at age 70.[14] Of the approximately 600 BIA-ALCL cases reported in total, the vast majority of patients achieved complete remission after adequate treatment.[15,16]

Although the association between breast implants and systemic disease has not been proven since the 1960s, there are still some women who report experiencing a pattern of distressing systemic symptoms of varying severity, including myalgia, arthralgia, fever, fatigue, dry eyes, and cognitive impairment. In 2011, Shoenfeld et al. proposed the existence of "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA syndrome) that could result from silicone incompatibility (table 1).[17] According to this theory, exposure to an adjuvant (e.g. silicone breast implants) leads to an increased (aberrant) autoimmune response in which both immunogenetic factors, such as pre-existing allergies, and environmental aspects, such as smoking, may play a role.[18,19]

Table 1. Criteria for the diagnosis of ASIA syndrome.

Major criteria	Minor criteria
Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations	The appearance of autoantibodies or antibodies directed at the suspected adjuvant
The appearance of "typical" clinical manifestations	Other clinical manifestation (i.e. irritable bowel syndrome)
Myalgia, myositis, or muscle weakness	Specific HLA (i.e. HLA DRB1, DLA DQB1)
Arthralgia and/or arthritis	Evolvement of an autoimmune disease (i.e. multiple sclerosis, systemic sclerosis)
Chronic fatigue, un-refreshing sleep, or sleep disturbances	
Neurological manifestations (especially associated with demyelination)	
Cognitive impairment, memory loss	
Pyrexia, dry mouth	
Removal of inciting agent induces improvement	
Typical biopsy of involved organs	

Recently, "breast implant illness" (BII) has been used as an umbrella term for this pattern of various non-specific symptoms that women attribute to their breast implants. Still little is known about the causes, risk factors, course, and treatment of BII for several reasons.[5,20] The evidence is based primarily on case reports, rather than on large cohort studies. These studies are largely subject to selection bias and the results of women with BII are not representative of common women with breast implants. In addition, there are no diagnostic tests for BII, and the reported symptoms mimic the symptoms of other conditions, such as fibromyalgia or irritable bowel syndrome.[21,22] This makes it difficult to determine the prevalence of BII. The literature mentions widely varying numbers, ranging from non-specific complaints in 2% to systemic complaints in 65% of women with silicone breast implants.[23,24]

Currently, the public awareness of BII in the Netherlands has increased significantly, both through TV shows and social media groups promoting a link between systemic symptoms and silicone breast implants. These media may play an important role in causing and amplifying worry and anxiety.[25,26] Nationwide, hospitals and clinics are facing an increase in calls from women concerned about the safety of their implants along with an increase in explant requests. Since 2017, breast implant removal has increased by more than 30%, as explantation improves the systemic complaints in about 75% of cases, according to the literature.[27,28]

The role of breast implants in reconstructive surgery

Not only do breast implants serve as an enlargement of the breasts for aesthetic needs, they also play an important role in reconstructing the breast following mastectomy. Breast cancer is the most prevalent cancer among women worldwide.[29] In the Netherlands, one in seven women develops breast cancer during a lifetime. Although the incidence of invasive breast cancer has nearly doubled in the past 30 years, population screening, early detection and improved treatment methods have improved the long-term survival of women with breast cancer.[30-33] Long-term goals and patient reported outcomes (PROs) have played an increasingly important role in the treatment of breast cancer patients and survivors.[34,35]

In recent years, more women have opted for unilateral or bilateral mastectomy for the treatment or prevention of breast cancer.[36,37] As a result of increased survival rates of breast cancer with more focus on survivorship for women who underwent a mastectomy, breast reconstruction rates have also increased over the last decades.[38] Breast reconstruction can support the restoration of body image, improve psychosocial well-being and improve QoL in women who have undergone a mastectomy.[39-41] However, not everyone opts for breast reconstruction. Although it is not fully elucidated why women do or do not opt for breast construction, many factors are known to play a role in the decision-making process.[42]

Women who opt for breast reconstruction are on average younger than women who opt out. Furthermore, higher educated women are more likely to opt for reconstruction than women with a lower educational level.[43] This is also related to the income of these women, although the latter seems to play less of a role in the Netherlands as breast reconstruction is reimbursed by the health insurance. In addition to demographic characteristics, sexuality plays an important role in the choice. Women undergoing breast reconstruction have been shown to be more sexually active. Psychological factors and personality traits also determine whether a woman will be more satisfied by undergoing breast reconstruction.[44] Moreover, research has shown that the information provided by a surgeon or plastic surgeon is one of the most decisive factors in the choice of whether or not to undergo breast reconstruction.[45] Appropriate counseling is necessary for a patient to make an informed decision about undergoing breast reconstruction.

At present, there are two main options for post-mastectomy breast reconstruction, namely implant-based breast reconstruction (IBBR) and autologous breast reconstruction (ABR). IBBR usually consists of a two-staged procedure in which a temporary tissue expander is placed and filled gradually, which is later replaced by a permanent silicone prosthesis. In autologous breast reconstruction, a vascularized flap is harvested elsewhere in the body and used to reconstruct the shape of the breast.[46] The most common type of autologous breast reconstruction is the Deep Inferior Epigastric Perforator (DIEP) flap reconstruction, in which vascularized skin and adipose tissue from the

abdomen is used for breast reconstruction.[47] In case that the abdomen is not a suitable donor site, flaps can be harvested from other parts of the body, such as the Lateral Thigh Perforator (LTP) flap.[48]

A third, emerging option is breast reconstruction by means of lipofilling, also known as autologous fat transfer (AFT). Research into its safety and (cost-) effectiveness is under way, but so far it shows promising results.[49,50] This type of breast reconstruction falls outside the scope of this thesis.
Both IBBR and ABR have their own advantages and disadvantages. For example, IBBR requires less invasive surgery with a shorter recovery time, but ABR can achieve a more natural look and feel. On the other hand, harvesting the tissue for autologous reconstruction creates additional scarring at the donor site, which is not the case with IBBR. Furthermore, ABR has been found to be more cost effective than implants, especially in women with a longer life expectancy, as the implants involve the risk of capsular contracture and implant rupture and will eventually need to be replaced.[51,52] As ABR is not feasible for everyone, due to the patient's surgical history or body type, physician's experience with the surgery, or medical expenses not covered by health insurance, implant-based reconstruction is therefore still the most widely used method to correct mastectomy deformity worldwide.[38] However, the uncertainty surrounding the safety of breast implants can cause doubt and fear among women who are faced with the choice of undergoing breast reconstruction. It is the duty of their plastic surgeon to adequately inform these women about the advantages and disadvantages of the different types of breast reconstruction and to provide them with correct information regarding BII. Closing knowledge gaps on this subject is therefore imperative, which is being worked on worldwide through scientific research.

Aims of this thesis

Patient-reported outcomes play an increasingly important role in breast surgery. In the current era in which patients have access to a lot of (online) information, and (social) media play an important role in the dissemination of (potentially biased) information, there is a need for clear, evidence-based advice.

The aim of this thesis was to provide an overview of long-term patient-reported outcomes of women who have undergone breast implant surgery, to

1. Support plastic surgeons, surgical oncologist, and other health care providers involved, in their advice when counseling a woman considering breast reconstruction or breast augmentation;

2. Provide women who have breast implants or are considering breast implants for either reconstructive or aesthetic purpose with evidence-based information regarding breast implant illness.

Outline of this thesis

In the first chapters, we take a closer look at the health complaints reported by women with breast implants and the QoL outcomes reported by these women. The following research questions are elaborated in these chapters:

- What is the prevalence of self-reported health complaints in women with breast implants compared to women without breast implants? **(Chapter 2)**

- What is the health-related QoL of women with breast implants compared to women without breast implants? **(Chapter 2)**

- Is there an improvement in health complaints after the removal of breast implants compared to preoperatively? And what is the effect of tertiary breast reconstruction on these symptoms? **(Chapter 3)**

- Is it possible to measure functional or structural brain alterations in women with suspected BII using 3T functional magnetic resonance imaging (fMRI)? **(Chapter 4)**

- How do BII patients score on somatization, distress, anxiety and depression, compared to asymptomatic women with breast implants? **(Chapter 4)**

- What role do personality characteristics play in the experience of physical complaints in women with breast implants? **(Chapter 5)**

In **chapters 6 to 9** we focus on the use of breast implants in breast reconstructive surgery.

- In **chapter 6**, we evaluate the influence of QoL and psychosocial well-being among women diagnosed with breast cancer, before the start of any treatment, on their decision whether or not to undergo reconstruction.

Chapter 7, 8, and 9 are dedicated to the following research questions regarding the long-term patient-reported outcomes of breast reconstruction and the occurrence of physical complaints in this population:

- Are women undergoing IBR more at risk of developing physical complaints than women undergoing ABR? And what is the long-term health-related QoL after IBR compared to ABR? **(Chapter 7)**

- Is long-term breast-related QoL after ABR better than after IBR? **(Chapter 8)**

- What is the effect of free flap breast reconstruction on satisfaction with the appearance of the donor site? What is the long-term body-related QoL after ABR and IBR? **(Chapter 8)**

- How do the aforementioned breast-related, body-related and health-related QoL after ABR compare to IBR in women who have undergone bilateral prophylactic mastectomy (BPM) due to an increased risk of breast cancer? **(Chapter 9)**

Chapter 10 provides a general discussion in which the results of this thesis are reviewed and future perspectives are discussed.

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CHAPTER 2

The Prevalence of Self-Reported
Health Complaints and Health-Related Quality
of Life in Women With Breast Implants

ABSTRACT

Background

Millions of women have silicone breast implants (SBI). Some report a pattern of systemic complaints, also referred to as ASIA syndrome. However, the association between these complaints and breast implants remains uncertain.

Objectives

This study aimed to evaluate the prevalence of complaints in women with breast implants and healthy controls, and to compare their health-related Quality of Life (HRQoL).

Methods

Four groups of subjects were requested to fill in a general and a diagnostic questionnaire, and the Short Form 36. Group 1 was recruited from the Dutch foundation for Breast Implant Illness (BII). Two groups were recruited from Dutch hospitals, where they were augmented or reconstructed with SBI (group 2) or saline-filled and hydrogel implants (group 3). A control group without breast implants was recruited from friends of subjects from group 2 and 3.

Results

In total, 238 women completed the questionnaires. ASIA manifestations appeared in the majority of the respondents (72.3-98.8%), with a latency period of 0-35 years. Adjusted for age, smoking, and comorbidities, typical symptoms only occurred significantly more frequent in group 1. The presence of a chronic disease was an independent predictor for ASIA syndrome. HRQoL was lower in women with SBI than in women without breast implants.

Conclusions

The adjusted prevalence of BII manifestations is not significantly higher in women with SBI compared to women without implants. The findings of this study suggest that results on BII are subject to selection bias. Further studies are needed to prove an association between self-reported complaints and SBI.

Introduction

In America alone, nearly 330,000 breast augmentation procedures were performed in 2018[1]. An estimated 3% of Dutch women between 20 and 70 years have breast implants[2]. Some of these women report a pattern of systemic health complaints with varying severity, such as myalgia, arthralgia, fever, fatigue, dry eyes and mouth, as well as cognitive impairment[3,4]. In 2011, Shoenfeld et al. introduced the ASIA syndrome: an autoimmune syndrome induced by adjuvants, e.g., breast implants[5]. Many studies have investigated the possible health effects of silicone breast implants (SBI); however, a clear association between breast implants and systemic diseases or autoimmune diseases remains uncertain[6-8]. The explanation of complaints in these patients is probably multifactorial. It is unclear whether these symptoms would have occurred if no implants were placed. However, in case where there is an association with implants, immunogenic factors such as preexisting allergies and environmental aspects such as smoking may play a role in the development of SBI-induced health complaints, also referred to as breast implant illness (BII)[9,10]. Interestingly, there is a remarkable overlap with fibromyalgia and it cannot be excluded that it concerns the same disease[11-13].

Studies on the prevalence of breast implant illness among women with SBI show different figures, varying from nonspecific complaints in 2%[14] to rheumatic symptoms after surgery in 37.4% of the cases[12], and the development of a pattern of systemic complaints in 65% of the women with SBI[15]. The Dutch Foundation for Women with Illness due to Breast Implants (Meldpunt Klachten Siliconen—MKS) indicates that in 2014 and 2015, around 150 women reported breast-associated complaints[16]. This, however, is a selected group and large epidemiological studies are lacking.

The main objective of this study was to evaluate the prevalence of clinical manifestations related to ASIA syndrome in four different cohorts. The first cohort is a group of women with self-reported complaints, recruited from the MKS. The second and third cohorts are groups of unselected women with respectively silicone or saline/hydrogel (Monobloc®, Laboratoires Arion, Mougins, France) breast implants. The fourth group is a control group of women without breast implants. In addition to the evaluation of typical complaints, the health-related quality of life (HRQoL) survey results were evaluated and compared between these groups.

Methods

Patient selection

Four groups of subjects were included in this retrospective cohort study. Group 1 consisted of women with SBI and self-reported complaints, recruited from the MKS. All women who were registered with MKS with address details were invited. Participants in groups 2 and 3 were women who had, based on surgery reports, breast augmentation or breast reconstruction in one of three hospitals in the Netherlands (Maastricht University Medical Center, Maastricht, Maxima Medical Center, Eindhoven, and St. Anna Hospital, Geldrop), between January 1997 and December 2004. This time span was chosen based on our previous study in which we found a median time between breast implantation and diagnosis of ASIA syndrome of 13 years[4]. All women who received SBI (group 2) or saline-filled/hydrogel implants (group 3) during this period were invited to participate in this study, provided that their address details were known. Any patient with silicone exposure before having an alternative implant was allocated to the silicone group (group 2). Patients in group 2 or 3 who also reported to the MKS were excluded from these groups as they were already allocated to group 1. A fourth—control group— consisting of healthy women without breast implants, was

recruited from close friends and family from responders of group 2 as they were most likely to be age-matched and to have a similar socioeconomic status. Having SBI and/or breast cancer, or a history of it, were exclusion criteria for the control group.

Written informed consent for participation in this study was obtained from all subjects. The study was approved by the local Medical Ethics board of the Maastricht University Medical Center, the Netherlands.

Questionnaires

All subjects were invited by post to complete a questionnaire after signing the informed consent form. The questionnaire consisted of a general questionnaire, the Dutch version of the 2010 American College of Rheumatology (ACR) Fibromyalgia Diagnostic Criteria, and the Dutch version of the Short Form 36 Health Survey (SF-36).

The general questionnaire contained items about the breast implants, health complaints, allergies, immune diseases, other chronic diseases, intoxications, and family history. The 2010 ACR Fibromyalgia Diagnostic Criteria is a validated questionnaire for the diagnosis of fibromyalgia and measurement of symptom severity. It consists of three sections: pain areas, symptom severity, and other symptoms. This questionnaire was used to examine the appearance of "typical" clinical manifestations of ASIA syndrome. A minimum of three symptoms was required for the diagnosis of ASIA: arthralgia and/or myalgia, chronic fatigue and/or cognitive impairment, and pyrexia and/or sicca complaints. Subsequently, symptom severity is scaled from 0 to 6 (number of typical symptoms). The Short Form 36 Health Survey (SF-36) is a 36-item survey for evaluating HRQoL on eight scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.

Paper questionnaires were distributed by the clinical researcher (MC). They were coded with a unique number in advance in order to anonymize obtained data (Appendix).

Statistical analyses

Symptoms were reported as count and percentages. Differences in percentages between groups were tested using Pearson's chi-square test. Multivariable logistic regression was performed to identify factors associated with typical clinical manifestations, and compute differences adjusted for potential confounding factors. The SF-36 outcomes were transformed into scores from 0 to 100, so that higher values indicate better functioning and health status. The Pearson correlation coefficient was used to measure linear correlation between age and HRQoL. One-way analysis of variance (ANOVA) was performed to determine whether mean differences between the outcomes of the four groups were significant. Subsequently, Games-Howell post-hoc tests were executed. All analyses were performed in IBM SPSS Statistics version 25, using an alpha level of 0.05 to determine significance.

Results
Patient characteristics and medical history

The survey yielded an overall response rate of 48%; 68% from the healthy control, 65% of the women from MKS, and 34% of the women from the hospital registries. In total, 238 women were included in this study. Eighty-five MKS-registered women (group 1), 83 women with—or with a history of—SBI (group 2), 13 women with saline-filled or Monobloc implants (group 3), and 57 healthy women from the control (group 4) completed the questionnaire. The mean age of the respondents per group was 52.7 (range 35–71), 57.1 (range 34–83), 50.2 (range 36–71), and 43.3 (range 19–75) years. Those in the healthy control group were significantly younger than women with silicone implants (p<0.001). In the self-reported (MKS) group, there was a trend toward more active smokers in comparison with the healthy control group (31.8% vs. 21.1%; p=0.081).

In the vast majority, breast implants were placed bilaterally (88.4%) and for cosmetic reasons (71.8%). In group 1, implants were placed between 1971 and 2011 (median 1999); in groups 2 and 3, implants were placed between 1972 and 2004 (median 1998). Of the women from the MKS, 86% reported that they underwent at least one revision, whereas for 68.7% of group 2 and 61.5% of group 3 a second surgery was needed. Surgeries were most frequently performed in group 1. Implant rupture and capsular contracture were mentioned as the main causes for revision. In groups 1, 2, and 3, 36.5%, 10.8%, and 7.7% of the women underwent explantation of the SBI respectively.

Comparison of the prevalence of comorbidities showed a significant difference between the four groups (Table 1). A significantly higher prevalence of chronic diseases (not specified), allergies, and irritable bowel syndrome (IBS) was found in women from the MKS compared to the control group; however, this was not found in women from groups 2 and 3. Chronic fatigue syndrome (CFS) was reported significantly more frequently in women with silicone breast implants, and fibromyalgia (FM) significantly more frequently in women with all types of breast implants, compared to women without breast implants.

Table 1. Prevalence of comorbidities.

	Group 1	Group 2	Group 3	Group 4	P value
Chronic disease, %	74.1*	44.6	53.8	31.6	<0.001
Allergy, %	56.5*	32.5	30.8	35.1	0.006
Fibromyalgia, %	27.1*	16.9*	23.1*	3.5	0.002
CFS, %	30.6*	10.8*	7.7	1.8	<0.001
IBS, %	44.7*	15.7	23.1	8.8	<0.001

CFS, chronic fatigue syndrome; IBS irritable bowel syndrome.
 *Prevalence is significantly higher compared to healthy controls.

Self-reported health complaints

One or more typical clinical ASIA manifestations appeared in 98.8%, 72.3%, 76.9%, and 78.9% of the respondents of groups 1, 2, 3, and 4 respectively (Figure 1). The mean time between implant placement and the development of symptoms in group 1 was 4.9 years (range 0–35). Women in groups 2 and 3 reported a latency period of 3.3 (range 0–10) and 7.8 (range 5–10) years, respectively.
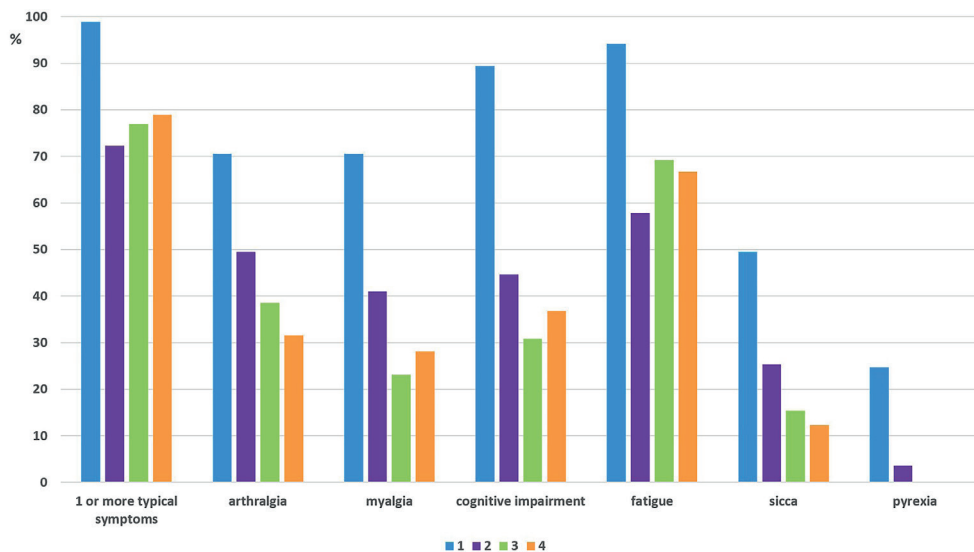
Figure 1. Prevalence (%) of typical clinical manifestations related to ASIA syndrome.

All symptoms were reported more frequently in group 1 than in the control group (p<0.001). In group 2, more women reported arthralgia (p=0.015) and sicca (p=0.038) than in the control group. Between group 3 and the control, there were no major differences in the prevalence of reported complaints. Significantly more women in groups 1 and 2 met the criteria for the clinical diagnosis of ASIA syndrome, as described earlier, compared to the control group. There were no significant differences in ASIA prevalence found based on the reason for implant placement (cosmetic vs. reconstructive) within groups 1 (83.6% vs. 93.4%, p=0.299), 2 (47.1% vs. 46.2%, p=0.940), and 3 (33.3% vs. 66.7%, p=0.523).

After adjusting for potential confounding variables (e.g., age, smoking, and comorbidities), only the prevalence of myalgia and cognitive impairment was significantly higher in group 1 than in the control group (Table 2). There was a significant difference between the prevalence of myalgia, fatigue, and cognitive impairment between groups 1 and 2. Furthermore, myalgia and cognitive impairment were more common in group 1 than in group 3. The adjusted prevalence of groups 2, 3, and 4 did not differ significantly. The prevalence of ASIA syndrome remained significantly higher in group 1 compared to the control group after adjusting for potential confounders. The adjusted ASIA prevalence in group 2 did not differ significantly from the control group.

Multivariable logistic regression that included age, smoking, and comorbidities (chronic disease, allergy, FM, CFS, and IBS) as independent variables showed that age was an independent predictor for arthralgia, that the presence of a chronic disease (not specified) was a predictor for arthralgia, fatigue, and sicca, and that fibromyalgia was a predictor for both arthralgia and myalgia. The presence of a chronic disease was the only independent predictor for the clinical diagnosis of ASIA syndrome (Table 3).

Table 2. Prevalence of self-reported manifestations related to ASIA syndrome.

	Group 1 (%)	Adjusted *P* value	Group 2 (%)	Adjusted *P* value	Group 3 (%)	Adjusted **P** value	Group 4 (%)
Arthralgia	70.6	0.315	49.4	0.910	38.5	0.449	31.6
Myalgia	70.6	0.009	41	0.494	23.1	0.320	28.1
Cognitive impairment	89.4	<0.001	44.6	0.492	30.8	0.919	36.8
Fatigue	94.1	0.183	67.8	0.375	69.2	0.569	66.7
Sicca	49.4	0.083	25.3	0.376	15.4	0.962	12.3
Pyrexia	24.7	* –	3.6	* –	0	* –	0
ASIA (≥3 symptoms)	84.7	0.003	46.2	0.700	38.5	0.931	28.1

Multivariable logistic regression analysis of self-reported symptoms in women with breast implants (group 1,2,3) compared with women without breast implants (group 4), adjusted for age, smoking, and comorbidities.
*Unable to estimate due to too few events.

Table 3. Predictors of typical clinical manifestations related to ASIA syndrome.

	Predictor	Adjusted P value
Arthralgia	Age	0.039
	Chronic disease*	0.039
	Fibromyalgia	0.006
Myalgia	Fibromyalgia	0.002
Fatigue	Chronic disease*	0.002
Sicca	Chronic disease*	0.003
ASIA (≥3 symptoms)	Chronic disease*	0.015

*Chronic diseases were not specified in the analysis. The presence of a chronic disease was scored binary.

SF-36

Patient-reported outcomes on health status measured by means of the SF-36 questionnaire were compared between all groups (Table 4). There was a statistically significant difference between the mean scores of the four groups on all subdomains (p<0.001). Post-hoc tests showed that women with silicone exposure (groups 1 and 2) scored significantly lower on all domains of the SF-36 compared to the healthy control group, except for "role emotional," where the mean difference between groups 2 and 4 did not reach statistical significance (p=0.159). No significant difference was found between the outcomes of group 3 and the healthy control group.

The Pearson correlation showed that physical functioning, role physical, general health, and bodily pain are associated with age (p<0.01). No correlation was found between age and role emotional, mental health and social functioning, and vitality.

Table 4. Mean SF-36 Scores per Group.

	Group 1	Group 2	Group 3	Group 4	P value
Physical functioning	59.3*	74.1*	82.7	92.5	<0.001
Role physical	26.2*	62.4*	75.0	86.3	<0.001
Role emotional	49.6*	77.6*	92.3	89.5	<0.001
Vitality	37.7*	59.1*	61.9	72.7	<0.001
Mental health	56.4*	73.9*	75.7	81.4	<0.001
Social functioning	43.9*	75.3*	84.7	90.0	<0.001
Pain	45.8*	66.0*	74.8	81.0	<0.001
General health	34.1*	58.3*	65.6	74.6	<0.001

*Mean difference is statistically significant compared to healthy controls.

Discussion

This retrospective cohort study aimed to evaluate the prevalence of clinical manifestations related to ASIA syndrome in women with breast implants, compared to women without breast implants. Furthermore, the HRQoL survey was evaluated and compared between these groups by means of the SF-36 questionnaire.

Three major outcomes arose from this study. Firstly, this study showed that the adjusted prevalence of clinical manifestations related to ASIA syndrome was only significantly higher in women who reported to the MKS. Secondly, age, fibromyalgia, and having a chronic disease were found to be independent predictors for the development of typical clinical symptoms. Thirdly, HRQoL was found to be significantly lower in women with silicone breast implants compared to women with no breast implants.

From the many case reports about breast implant illness, the signal has been that adverse effects may occur as a result of the use of silicone breast implants. Effects can be local, e.g., an inflammatory response to silicone leakage, or systemic. However, case reports do not form a basis for demonstrating an association between SBI and health complaints as there is selection bias, and outcomes are not generalizable. Besides, results are usually not compared with healthy controls without implants.

In the current study, we were able to compare the symptoms of women with all types of breast implants to women without breast implants. We found a pattern of unexplained systemic symptoms consisting of fatigue, arthralgia, myalgia, cognitive problems, sicca complaints, and pyrexia, often reported in previous studies[3,15,17] to be occurring more frequently in women with SBI compared to women without implants. Given the nonspecific nature of these complaints, it is crucial to compare the prevalence of these complaints with a control group, as these symptoms may occur independently from having breast implants. Our results showed that even in the general population, the prevalence of nonspecific complaints is high. Still, more women with SBI reported symptoms.

However, there may be confounders involved. In accordance with the findings of Maijers et al.[15] the majority of the women with self-reported complaints in our study reported allergies, almost half of the women had IBS, and there was a higher prevalence of fibromyalgia in women with breast implants. This high prevalence of fibromyalgia in women with SBI has been repeatedly noticed[3,11,18,19], although evidence has failed to support an association[20]. The complaints of women with SBI have a substantial overlap with the aforementioned functional disorders[21,22]. However, due to the retrospective design of this current study, it could not be verified whether these complaints were preexisting, were the result of a functional disorder, or can genuinely be attributed to the breast implants. Therefore, adjustments were made for comorbidities, as well as for age and smoking, which may also play a role in the development of similar complaints.

Interestingly, adjustment for potential confounders showed that the prevalence of clinical symptoms was only higher in the group of the self-reported women. The adjusted prevalence in women with SBI, recruited from the Dutch hospitals, did not differ from women without breast implants. This strongly suggests that results on the prevalence of health complaints in women with SBI are subject to selection bias. Women who registered at MKS do not accurately reflect the population of women with SBI; this group concerns a selection of women with the most severe complaints.

Moreover, age, fibromyalgia, and having chronic diseases were found to be independent predictors for the development of clinical manifestations related to ASIA syndrome. This means that the significantly older age and a more frequent occurrence of both fibromyalgia and chronic diseases in the MKS group have contributed to the development of typical complaints. This heterogeneity may cause a biased view on the development of health complaints due to silicone breast implants.

In contrast to earlier findings, another major outcome of this study was the decreased HRQoL in women with SBI. Previous studies showed an improvement in body image and QoL after breast augmentation surgery[23-26]. This, in particular, seems to concern a psychological benefit. Alderman et al. described a significantly improved QoL based on the subscales "satisfaction with breasts" and "psychosocial well-being" of the BREAST-Q25. Conversely, Coriddi et al. found a significant decrease in the "physical well-being" subscale in the short term[27]. In accordance with the results of Murphy et al., we observed statistically significant decreases in SF-36 scores of women with SBI[28]. When interpreting these results, the potential selection bias must be taken into account. We do not have the data of the non-responders. It is, however, plausible that these are the ones with a lower QoL, so the responders are not an accurate reflection of the invited group. Furthermore, age may have affected the QoL. Based on the Pearson correlation, however, only the physical domains of the SF36 are associated with age. The psychological well-being of women with SBI (groups 1 and 2) was found to be significantly lower, regardless of age. We are not certain, however, whether this developed as a result of the breast implants or was a preexisting problem. One of many hypotheses is that somatization plays an important role in the development and progression of symptoms and complaints in some women with silicone breast implants[22]. According to this, breast implant illness may be mediated by stress, personality characteristics, and social context. People who have a higher rate of physical or psychological stress seem more susceptible to somatization[29]. The higher prevalence of comorbidities that we found in women with SBI may be stress factors. Psychological initiation of dysfunction and intensification of symptoms, in combination with poor coping responses, may have led to the decreased HRQoL observed in the women with self-reported complaints[22]. We expect that, based on this hypothesis and the selection bias, the results of this study are an underestimate of the actual HRQoL of women with SBI. We feel that additional research into personality characteristics and psychological well-being of women seeking breast augmentation surgery can contribute to understanding breast implant illness.

Despite the lack of evidence for causality, women have requested removal of their implants due to extensive worrying. Studies reported subjective improvement of patient-reported complaints after explantation of the SBI[30-32]. A recent literature review showed that 75% of the patients with silicone-related complaints experienced relief of their complaints[33]. Although improved QoL was observed in more than 50% of the cases[34,35], correlating self-reported complaints to QoL remains difficult[35]. Also in this regard, a patient's psychological profile plays an important role[36]. To our knowledge, this is the first study into the prevalence of self-reported complaints in women with SBI compared to women without implants. However, we are aware that the design of our study may have several limitations. Due to selection bias, the outcomes of this study do not provide a representation of the total group of women with breast implants. Not only group 1, but also groups 2 and 3 are expected to contain women with more or more severe complaints than the general population with implants. Women with complaints are more likely to participate in this research than healthy women and may answer the questionnaires strategically, since they benefit from scientific research demonstrating the noxiousness of implants. This was reflected in the high response rate of group 1. Moreover, a retrospective survey research involves recall bias. Women

may inaccurately remember the exact course of complaints and therefore, it is not certain whether comorbidities developed before or after implant placement. Whenever women are convinced that their complaints are attributable to the implants, they may be reluctant to reconsider alternative causes. This can potentially exaggerate the association between the reported complaints and the breast implants. Furthermore, no data were available on preoperative QoL surveys. In order to correlate breast implants to a reduced QoL, knowledge of the preoperative physical and psychological status is required. Finally, the control group was not ideally matched. Although psychological well-being was not correlated to age, controls should properly match demographical characteristics in order to exclude potential confounders in future studies. This study shows no association between self-reported complaints and silicone breast implants based on this study, and confirmation by means of large prospectively controlled studies is necessary to establish causality.

Conclusions

The prevalence of self-reported health complaints related to ASIA syndrome, such as arthralgia, myalgia, chronic fatigue, cognitive impairment, pyrexia, and sicca complaints was not significantly higher in women with silicone breast implants in comparison with women without breast implants, when adjusted for age, smoking, and comorbidities. Fibromyalgia and chronic fatigue syndrome were significantly more common in women with silicone breast implants, and the presence of a chronic disease was found to be an independent predictor for ASIA syndrome. Furthermore, HRQoL was lower in women with silicone breast implants than in women without breast implants. The findings of this study suggest that results on breast implant illness are subject to selection bias. Further studies are needed to prove an association between self-reported complaints and silicone breast implants.

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2

CHAPTER 3

Self-Reported Health Complaints in Women
Undergoing Explantation of Breast Implants

ABSTRACT

Background

Concerns about the safety of silicone breast implants have existed for years, but a causal relationship between systemic complaints and SBI has not been proven. Nevertheless, women are worried and even request explantation.

Objectives

This study aimed to review the explantation procedures performed, focusing on patient-reported symptoms preoperatively, the effect of explantation, and the effect of breast reconstruction on these symptoms.

Methods

A retrospective chart review was performed for patients who had undergone explantation between 2010 and 2020 at Maastricht University Medical Center. Patients excluded were those who had undergone tissue expander (TE) removal, TE to implant exchange, and direct implant exchange.

Results

More than half of the patients undergoing explantation reported complaints, mostly pain. Some 15% reported suggested implant-related systemic complaints. Breast implant illness (BII) was found to be the fifth most common indication for explantation (11.2%). A history of either allergies or implant rupture resulted in higher odds ratios of having BII (OR=2.1 and 2.1, respectively). Subjective improvement of BII after explantation was reported in about 60%.

Conclusion

A relatively low prevalence of suggested BII exists among women undergoing explantation; one in nine procedures was performed for this reason. Allergy and implant rupture may increase the likelihood of having BII. About 60% of BII patients experienced an improvement in their complaints after implant removal. Autologous breast reconstruction appears a good alternative. Prospective studies into health complaints and quality of life should be performed to confirm the effectiveness of explantation as a therapy for BII.

Introduction

Following its introduction in the 1960s, millions of women received silicone breast implants (SBI) for cosmetic breast augmentation or breast reconstruction. The procedure is associated with risks of both aesthetic and clinical sequelae, such as malposition, capsular contraction, and pain[1]. Concerns have continued to grow about the impact of silicone particles potentially migrating through the body, and the development of systemic symptoms, which the literature refers to as breast implant illness (BII)[2]. Although the majority of women appear content with their implants, some report a pattern of systemic health complaints with varying severity, such as myalgia, arthralgia, fever, fatigue, dry eyes and mouth, as well as cognitive impairments[3,4]. However, the current literature has found insufficient evidence to associate these symptoms with SBI[5,6].

Despite the lack of evidence for an association between complaints and SBI, women are worried and request that their implants be removed. The few studies which have examined this population have shown subjective improvement in patient-reported complaints after SBI explantation[7-9]. Indeed, a recent literature review has calculated that 75% of patients with silicone-related complaints experienced at least temporary relief of their symptoms once their implants were removed[10].

Many studies have been conducted into the longevity and local complications of breast implants, predominantly infection, capsular contracture, and implant rupture[1,11,12]. However, little attention has been paid to those systemic complaints that precede explantation and the postoperative course of these complaints. Another underexposed topic is the effect of reconstruction after explantation in patients with self-reported complaints. Therefore, the aim of this study was to review all explantation procedures, where no implant was replaced, that had been performed in our center during the last ten years; the specific focus was on examining patient-reported symptoms preoperatively, the effect of explantation, and the effect of breast reconstruction on these symptoms.

Methods

Patient selection

A retrospective chart review was performed for patients who had undergone explantation of their breast implants between January 2010 and April 2020. Patients included were women of all ages, with silicone or saline filled breast implants for both cosmetic and reconstructive reasons, who had had their implants removed for any reason at Maastricht University Medical Center. The implants could have been inserted at other clinics. Patients excluded were those who had undergone tissue expander (TE) removal, TE to implant exchange, and direct implant exchange.

Data abstraction

A standardized abstraction form was used to abstract from the electronic medical records: demographic data (age, BMI, smoking, allergies, medical history, and cancer therapy), implant details (material, manufacturer, and volume), clinical data (clinical symptoms and reason for explantation), surgery dates, implant rupture, and breast reconstruction after explantation. Systemic symptoms, other than local pain, that women felt were connected to their breast implants were referred to as 'suggested breast implant illness'.

Data analysis

Data were analyzed using descriptive statistics. Characteristics of implants and prevalence of symptoms were reported as counts and percentages. Continuous variables were represented by mean, standard deviation, and range. The independent samples t test was performed to compare means between subgroups. Differences in percentages between groups were tested with Pearson's chi-square test or Fisher's exact test. Multivariable logistic regression was performed to identify factors associated with the occurrence of breast implant illness, adjusted for potential confounding factors. Results were quantified as odds ratio (OR) with 95% confidence interval (CI). All analyses were performed in IBM SPSS Statistics version 25 using an alpha level of 0.05 to determine significance.

This study was approved by the Ethics Committee at the Maastricht University Medical Center. Patient consent was not required.

Results

Patient and implant characteristics

One hundred and ninety-seven patients underwent an explantation procedure during this 10-year. Mean age was 52.0 (range 24-81) and mean BMI was 25.1 (range 17.3-44.6). Patient and implant characteristics are presented in Table 1. In total, 303 breast implants from 10 manufacturers were removed. Ninety procedures (45.7%) were unilateral, while in the other 107 cases (54.3%) implants were removed bilaterally. The average time from implant placement to explantation was 102.8 months (range 0-586), while total exposure to implants averaged 130.4 months (range 0-586).

Indications for explantation

The primary indications for explantation included: severe capsular contraction (14.7%); implant rupture (14.2%); pain in the absence of implant rupture or evident capsular contracture (13.2%); infection without exposure of the implant (13.2%); suggested implant-related systemic symptoms/BII (11.2%); unsatisfactory aesthetic result/asymmetry (9.1%); exposure of the breast implant as a result of infection or wound dehiscence (8.1%), breast cancer or prophylactic breast surgery (8.1%); seeking autologous breast reconstruction with no specific cause reported (4.6%); extensive worrying about the safety of silicone exposure (1.0%); other reasons (2.5%).

Self-reported complaints

Fifty-two percent of the women that underwent explantation reported complaints that they attributed to their implants. The most common complaint was local pain: present in 40.6% of all cases. Twenty-nine patients (14.7%) reported suggested BII. They experienced one or more systemic complaints, other than pain, that they related to the breast implants. The most commonly reported self-reported complaints were fatigue, arthralgia, and myalgia (Table 2). All women with suggested BII had silicone breast implants. In the medical history of these women, a high rate of psychological and functional comorbidities was found (see supplemental data for an overview of these 29 BII patients, their medical history, and their implant-related complaints). Women with BII were not significantly younger (mean age 50.6, range 29-68) than women without BII (mean age 52.3, range 24-81), nor did they have a significantly higher BMI (mean 25.4, range 17.7-39.7) than women without BII (mean 25.1, range 17.3-44.6). Neither the in situ duration of the removed implant nor the total duration of implant exposure was significantly different between the two groups. BII patients did

report allergies more often and their removed implants were found to be more often ruptured. A comparison of the characteristics of women with and without BII is presented in Table 3.

Multivariable logistic regression that included age, allergies, radiotherapy, chemotherapy, hormone therapy, and implant rupture as independent variables showed that none of these variables were significant independent susceptibility factors for breast implant illness, although some OR's may indicate potential clinical relevance (Table 4).

Table 1. Patient and implant characteristics.

Characteristic	
Total patients (n)	197
Total implants removed (n)	303
Age (mean±SD, range)	52.0±12.1 (24-81)
BMI (mean±SD, range)	25.1±4.7 (17.3-44.6)
Smoking (n, %)	51 (25.9)
Allergies (n, %)	81 (41.1)
Implant reasons	
Cosmetic (n, %)	67 (34.0)
Reconstruction (n, %)	130 (66.0)
Implant type (n, %)	
Silicone filled	172 (87.3)
Saline filled	13 (6.6)
Unknown	12 (6.3)
Implant manufacturer (n, %)	
Eurosilicone	91 (30.0)
Allergan	42 (13.9)
McGhan	29 (9.6)
Mentor	18 (5.9)
Polytech	9 (3.0)
Arion	7 (2.3)
CUI	3 (1.0)
Silimed	2 (0.7)
Rofil	2 (0.7)
Inamed	2 (0.7)
Unknown	98 (32.3)
Volume in cc (mean±SD, range)	372±144.3 (100-850)

Breast reconstruction after implant removal

After explantation, the majority of the women opted for breast shaping surgery without the use of implants. Autologous flap reconstruction (41.1%), mastopexy (10.7%), or lipofilling (2%) was performed. Some women opted for implants again within the study period (4.1%). Women opting for breast shaping or reconstructive surgery were slightly younger (51.4, range 24-73, vs. 52.9, range 27-81; p=0.435) and had a higher BMI (25.7 vs. 24.3; p=0.065) compared to women who did not.

Effect of explantation and breast reconstruction on complaints

In women with implant-related complaints, including pain, explanting the implants improved complaints in no less than 72.0% of the cases. Women with suggested BII experienced improvement of the systemic complaints in 58.6%; in 31.0% complaints were persistent. For three BII patients (10.3%), no follow-up of the systemic complaints was reported. In those women with suggested BII who underwent autologous breast reconstruction, improvement of systemic complaints occurred in 63.3%, 27.3% did not notice any improvement. For one BII patient with autologous breast reconstruction, no follow-up was reported. Women who did not experience improvement in their symptoms after explantation were slightly younger (48.8, range 29-65, vs 50.2, range 30-68), had a higher BMI (26.4 vs 25.3) and were exposed to implants longer (182.7 vs 133.2 months) than women who did experience improvement in symptoms. The differences were not statistically significant. Univariate analysis showed no associations between improvement of systemic complaints and the following variables: radiotherapy, chemotherapy, hormone therapy, immunotherapy, allergy, implant reason, previous implant exchange, implant rupture, autologous free flap reconstruction. A significant association was found with smoking: non-smokers more often experienced an improvement in complaints after explantation (p=0.034).

Pre- and postoperative examples of tertiary DIEP flap breast reconstructions are shown in Figures 1a through 3b.

Table 2. Self-reported complaints in women with suggested BII.

Complaint	N (%)
Fatigue	18 (62.1)
Arthralgia	15 (51.7)
Myalgia	10 (34.5)
Sicca	6 (20.7)
Skin problems/itch/rash	4 (13.8)
Cognitive impairment	5 (17.2)
Pyrexia/hyperhidrosis	5 (17.2)
Headaches	4 (13.8)
Neurologic deficit	3 (10.3)
Immune diseases	3 (10.3)
Hair loss	2 (6.9)
Vertigo	2 (6.0)
Others	7 (24.1)

Table 3. Comparison of characteristics of women with BII and without BII.

Characteristic	BII	No BII	P value
Total patients (n, %)	29 (14.7)	168 (85.3)	-
Total implants removed (n, %)	51 (168.)	252 (83.2)	-
Age (mean, SD)	50.6 (12.3)	52.3 (11.1)	0.475
BMI (mean, SD)	25.4 (47)	25.1 (4.7)	0.768
Smoking (n, %)	7 (24.1)	44 (27.3)	0.721
Allergies (n, %)	17 (58.6)	64 (38.3)	0.040
Breast cancer therapy (n, %)			
Radiation therapy	5 (17.2)	41 (25.6)	0.333
Chemotherapy	6 (27.3)	60 (39.5)	0.069
Hormone therapy	1 (3.6)	41 (27.0)	0.007
Immunotherapy	2 (7.1)	9 (5.9)	0.682
Implant reason			
Cosmetic (n, %)	13 (44.8)	54 (32.1)	0.183
Reconstruction (n, %)	16 (55.2)	114 (67.9)	
Implant type			
Silicone filled (n, %)	29 (100.0)	141 (91.6)	0.226
Saline filled (n, %)	0 (0.0)	13 (8.3)	
Previous implant exchange (n, %)	10 (34.5)	42 (25.0)	0.537
Implant rupture (n, %)	11 (40.7)	34 (207)	0.023
Time implant in situ (months, SD)	101.0 (58.6)	102.8 (103.8)	0.875
Total exposure to implants (months, SD)	146.5 (109.0)	127.5 (127.0)	0.450

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Table 4. Univariable and multivariable logistic regression analysis of factors associated with the occurrence of breast implant illness in women undergoing explantation.

Variables	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age	1.0 (1.0-1.0)	0.473	1.0 (0.9-1.0)	0.381
Allergy	2.3 (1.0-5.1)	0.044	2.1 (0.9-4.9)	0.109
Radiotherapy	0.6 (0.2-1.7)	0.337	0.6 (0.1-2.9)	0.545
Chemotherapy	0.4 (0.2-1.1)	0.075	0.9 (0.2-3.6)	0.933
Hormone therapy	0.1 (0.0-0.8)	0.026	0.2 (0.0-5.3)	0.098
Implant rupture	2.6 (1.1-6.2)	0.027	2.1 (0.8-5.3)	0.130
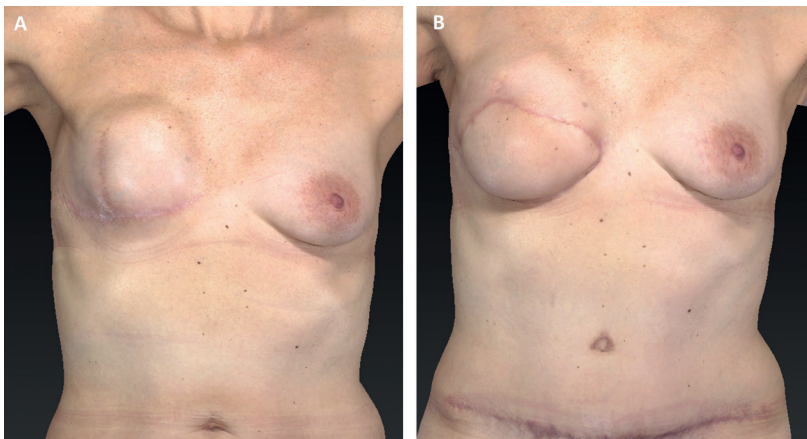
Figure 1. (A) Preoperative image of a 51-year-old female patient with a unilateral breast implant 1 year in situ. The patient reported a tight and unnatural feeling. (B) Postoperative image of the patient 4 months after unilateral tertiary DIEP reconstruction.
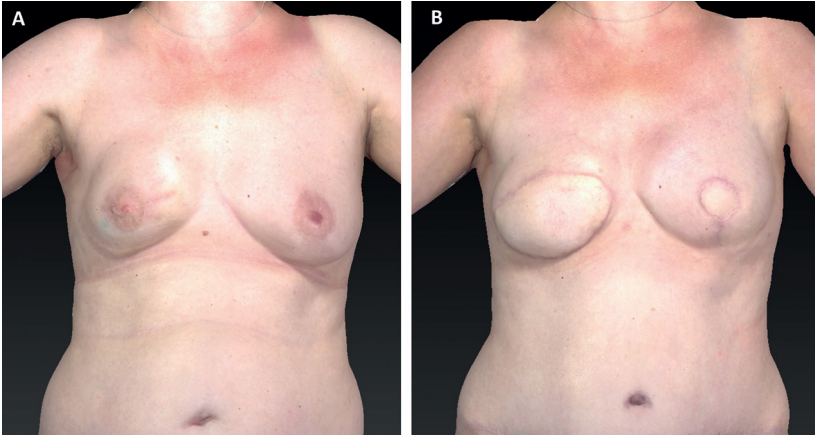
Figure 2. (A) Preoperative image of a 46-year-old female patient with a unilateral breast implant 1 year in situ. The patient reported severe capsular contracture and pain. (B) Postoperative image of the patient 7 months after unilateral tertiary DIEP reconstruction and contralateral primary DIEP reconstruction after prophylactic mastectomy (BRCA1 gene mutation).
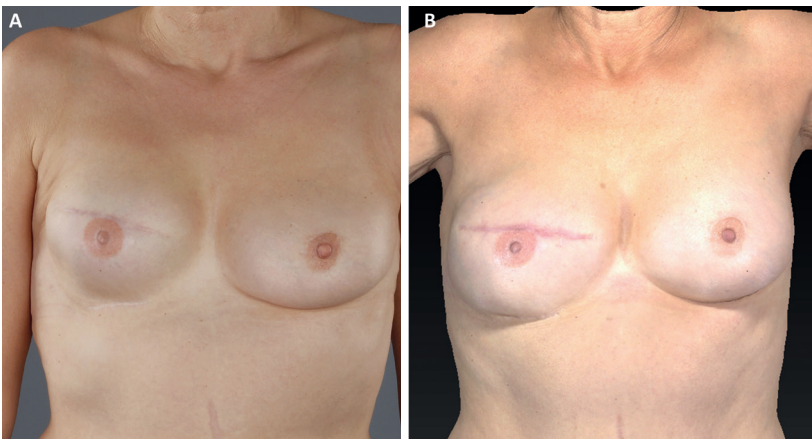
Figure 3. (A) Preoperative image of a 60-year-old female patient with a unilateral implant 6 years in situ. Suggested breast implant illness (fatighe, arthralgia, myalgia). (B) Postoperative image of the patient 16 months after unilateral tertiary DIEP reconstruction.

Discussion

It is known that breast implants for both cosmetic and reconstructive purposes eventually need to be replaced or removed, mostly due to aesthetic dissatisfaction or capsular contracture6,[12,13]. In daily practice, however, systemic complaints or concerns about the safety of silicone implants are increasingly being discussed by women as a reason for considering an explantation. In this study, we have reviewed all explantation procedures performed in our center during the preceding ten years in order to examine patient-reported symptoms preoperatively, the effect of explantation, and the effect of breast reconstruction on these symptoms.

In our study, more than half of the patients undergoing explantation reported complaints, with pain the most common symptom; one in seven patients reported suggested implant-related systemic complaints other than pain. Although an association has never been proven between these complaints and implants, suggested BII was found to be the fifth most common indication for explantation. Some 60% of all BII patients reported a subjective improvement of their implant-related complaints following removal of the implants and this proportion was even slightly higher in women who subsequently underwent flap reconstruction. This is in line with the results of our previously published systematic review[10]. Correspondingly, in the case reports published thereafter, 2 of the 3 cases experienced improvement after explantation[14-16].

Focusing on patients with the most severe complaints, we found several notable results. All of these patients had silicone breast implants and their implants were ruptured significantly more often than in other cases. Although in recent years mainly silicone implants have been placed in our center, it has been hypothesized that silicone elicits an allergy-like immune response. This may result in an autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome)[3,17]. Pre-existent allergies are thought to be a risk factor and were found more frequently in women with this syndrome[18]. In line with this thought, we found that allergies were significantly common in women with systemic complaints. By removing the adjuvant (SBI), the immune response should decrease[19]. Following explantation, over half of the patients in our study indeed experienced clinical improvement. One patient with ulcerative colitis was even able to discontinue the anti-inflammatory drug mesalazine after the implants had been removed, indicating a strong decrease in inflammation after explantation. However, those patients with the most severe systemic complaints are less likely to see their symptoms improve, suggesting that they might have developed a chronic immune response. Implant rupture and gel bleed may cause extracapsular migration of silicone-containing particles which are not completely removed when the implant is explanted. Consequently, according to this ASIA hypothesis, the immune response continues[20].

Another important finding in this BII subgroup was the high prevalence of functional and psychological conditions in their medical history. This finding corresponds to studies that have shown higher levels of significant psychological symptoms in women with breast implants and women requesting explantation, irrespective of whether these symptoms were a result of the implants[21-24]. A subset of these women may suffer from somatization disorder[22,25]. Furthermore, authors have hypothesized that BII is a functional somatic syndrome, comparable with fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome[26,27]. These syndromes have a lot of overlap in symptoms, making it difficult to distinguish between complaints caused by the implants and complaints that would also have occurred without implants, as a result of a functional syndrome. They are commonly associated with female gender, psychological factors, such as psychiatric comorbidity and health worry preoccupation[28,29]. The latter may be related to fear of harmful side effects of (silicone) breast implants, which is a significant factor in women requesting removal of their implants[22,30].

This fear may be stoked by the widespread (social) media attention the subject receives[31,32]. It may explain why women with saline-filled implants were spared the development of BII in this study. Removal of the implants can reduce anxiety, which potentially causes a relief of symptoms. Any symptom improvement after explantation in this group may therefore be partly explained by a placebo effect.

On the other hand, explantation may have a negative impact on body image and psychological well-being[21]. Therefore, alternative reconstructions should be proposed. Few studies have investigated the outcome of reconstruction after explantation. Autologous breast reconstruction after failed implant-based reconstruction was found to be safe and to improve quality of life[33,34]. Most women reported the advantage of have softer, more natural feeling breasts and less pain when they compared their autologous reconstruction with their implant-based reconstruction[34]. Importantly, reconstruction is only covered by the Dutch health insurance in oncological patients. The results could therefore be biased by selection. In addition, not all women are suitable for autologous reconstructions, since there needs to be sufficient tissue for transplantation[35]. This point is reflected in the higher BMI found in this subgroup.

Certain limitations need to be acknowledged, for example the study's retrospective design. It is undetermined whether some symptoms attributed to the implants preexisted the surgery of were a result thereof. The same applies to psychological and physical comorbidity. Only with a prospective design, starting before implantation, can this be determined. Further, during the chart review we were noticed with missing data regarding implant characteristics, operative reports, and the medical course of self-reported complaints. It has not been sufficiently reported whether capsules were partially or completely removed during explantation and therefore we cannot retrospectively determine this for all cases. This may have affected the clinical outcome. Systemic complaints were not systematically questioned, with limited information recorded in some medical charts, it is likely this led to an underreporting of implant-related complaints, rather than overreporting. Conversely, in those patients who requested explantation for the reason of suggested BII, a comprehensive documentation of both the symptoms and comorbidities was maintained. This approach of reporting encourages selection bias and should be considered when interpreting these results as well as other studies involving BII. Finally, there may be bias based on our patient population. Our center is a university hospital to which many patients with suggested BII are referred. As a result, the proportion of 'systemic complaints' as an indication for implant removal will probably be higher than in a private clinic, where cosmetic reasons, for example, may more often lead to implant removal.

Despite the attention the topic of breast implant attracts, this study has demonstrated that the number of explantation procedures related to this disease are relatively low. Capsular contracture, implant rupture, and pain are common indications for implant removal, however. In women experiencing systemic implant-related complaints, it is difficult to predict whether removal will lead to an improvement of the complaints or to what extent. Nonetheless, with the insights gained here, patients requesting explantation can be provided with more comprehensive information about the expected results. In order to provide patients with the best, evidence-based information about the effects of explantation in case of BII, long-term prospective studies must be conducted in which both physical and psychological symptoms are analyzed pre- and postoperatively. It is recommended that long-term outcomes be measured by means of quality of life questionnaires, as these can ultimately determine whether explantation will benefit patients with implant-related complaints.

Conclusions

A relatively low prevalence of suggested BII exists among women undergoing removal of their breast implant(s); one in nine explanation procedures was performed for this reason. Allergy and implant rupture may increase the likelihood of having BII. The clinical outcomes of explantation are promising: about 60% of BII patients experienced an improvement in their complaints. The same holds for women undergoing autologous breast reconstruction, which appears a good alternative. Prospective studies into health complaints and quality of life should be performed to confirm the effectiveness of explantation as a therapy for breast implant illness.

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Supplemental Table 1. Overview of the patients with suggested Breast Implant Illness.

Pt	Age	BMI	AII	RT	CT	HT	IT	Comorbidities	Reason	Type
1	56	26.4	-	-	-	-	-	Depression, anxiety disorder	Cos	Silicone
2	29	22.8	-	-	-	-	-	Borderline pd	Cos	
3	65	24.7	+	-	-	-	-	No (APS diagnose later)	Cos	Silicone
4	48	39.7	+	+	+	-	-	BRCA1 mutation, Breast cancer	Rec	Silicone
5	42	28.1	-	-	-	-	-	CFS	Cos	Silicone
6	67	34.0	-	-	-	-	-	CRPS, migraine	Cos	Silicone
7	41	19.7	+	-	-	-	-	Depression, functional complaints	Cos	Silicone
8	39	20.5	+	-	-	-	-	IBS	Cos	Silicone
9	42	24.0	-	-	-	-	-	DCIS, AF syndrome, Lyme	Rec	Silicone
10	58	22.5	-	-	-	-	-	DCIS	Rec	Silicone
11	51	25.7	+	-	-	-	-	Depression, FM, CFS, borderline ps	Cos	Silicone
12	45	21.7	+	-	-	-	-	History of drug abuse	Cos	Silicone
13	40	22.2	+	-	-	-	-	IBS	Cos	Silicone
14	60	21.0	+	-	+	-	+	Breast cancer	Rec	Silicone
15	42	24.5	-	-	-	-	-	BRCA2 mutation, prophylactic mastectomy	Rec	Silicone
16	68	32.3	-	-	-	-	-	BRCA1 mutation, prophylactic mastectomy	Rec	Silicone
17	54	23.5	+	-	-	-	-	FM, Lyme, DCIS	Rec	Silicone
18	34	22.6	-	-	-	-	-	Psoriasis, burn-out	Cos	Silicone
19	54	25.7	-	-	-	-	-	Immunodeficiency, Sjögren	Cos	Silicone
20	65	20.3	+	+	?	?	?	Breast cancer, psoriatic arthritis, lichen sclerosis	Rec	Silicone
21	57	23.7	-	+	+	-	-	BRCA1 mutation, breast cancer	Rec	Silicone
22	30	17.7	-	-	-	-	-	Ulcerative colitis	Cos	Silicone
23	47	30.1	-	-	-	-	-	Prophylactic mastectomy, bipolar disorder	Rec	Silicone
24	52	22.9	+	-	+	+	-	Myotonic dystrophy (Steinert), breast cancer	Rec	Silicone
25	57	29.6	+	-	+	-	-	Breast cancer	Rec	Silicone
26	61	25.5	+	-	-	-	-	FM, Sjögren, fibroadenomas	Rec	Silicone
27	61	28.6	+	+	-	-	-	BRCA mutation, breast cancer	Rec	Silicone
28	60	28.4	+	+	-	-	-	Breast cancer, arthrosis, COPD, diverticulitis	Rec	Silicone
29	41	27.1	+	-	+	-	-	BRCA mutation, breast cancer, asthma	Rec	Silicone

Supplemental Table 1. Continued.

Pt	Laterality	Exposure	Complaints	Improvement	Reconstruction
1	Bilateral	27y	Pain, paresthesia of the arm	Yes	Mastopexy
2	Bilateral	10y	Pain, fatigue, arthralgia	No	No
3	Bilateral	40y	Pain, fatigue, vertigo, APS	No	No
4	Bilateral	6y	Fatigue, amnesia, concentration disorder	No	Lipofilling
5	Unilateral	24y	Pain, fatigue	Yes	Mastopexy
6	Bilateral	28y	Fatigue, arthralgia	Yes	No
7	Bilateral	8y	Pain, fatigue, myalgia, immunological disease	Yes	Mastopexy + lipofilling
8	Bilateral	10y	Arthralgia, pyrexia, hyperhidrosis, sicca, hair loss, lymphadenopathy, cognitive impairments	No follow-up	No
9	Unilateral	1y	Pain, muscle weakness arm	Yes	No
10	Unilateral	2y	Skin problems (eczema)	No follow-up	DIEP
11	Bilateral	15y	Myalgia	No follow-up	No
12	Bilateral	15y	Lymphadenopathy, fatigue, arthralgia, pyrexia, sicca, amnesia	No	Mastopexy
13	Bilateral	13y	Pain, fatigue, arthralgia, myalgia, vertigo, malaise, sicca, pyrexia, cognitive impairments	Yes	No
14	Unilateral	11y	Fatigue, arthralgia, myalgia	Yes	DIEP
15	Bilateral	8y	Fatigue, arthralgia	Yes	No
16	Bilateral	11y	Myalgia	Yes	No
17	Unilateral	1y	Pain, arthralgia, hair loss, sleep disturbance, morning stiffness	Yes	DIEP
18	Bilateral	8y	Fatigue, arthralgia, myalgia	Yes	No
19	Bilateral	15y	Fatigue, arthralgia, sicca, swallowing problems, paresthesia, secondary Sjögren	No	No
20	Bilateral	12y	'Multiple systemic complaints', exacerbation skin problems	No follow-up	No
21	Bilateral	6y	Arthralgia	Yes	DIEP
22	Bilateral	7y	Pain, fatigue, sicca, headaches	Yes, discontinued mesalazine	No
23	Bilateral	11y	Pain, fatigue, arthralgia, myalgia, itching, rheumatic symptoms	Yes, but recurrence after years	DIEP
24	Bilateral	4y	Myalgia	Yes	DIEP
25	Bilateral	4y	Arthralgia, sicca, cognitive impairments, concentration problems	No	DIEP
26	Unilateral	27y	Fatigue, arthralgia, urticaria, itching	No	DIEP
27	Bilateral	5y	Fatigue, arthralgia, myalgia, pyrexia, headaches, shortness of breath	Yes	DIEP
28	Bilateral	13y	Walking disability (wheelchair dependent), bodily pain, fatigue	Yes, no longer wheelchair dependent	DIEP
29	Bilateral	9y	Fatigue, myalgia, hyperhidrosis	No	DIEP

CHAPTER 4

Neuroimaging in Breast Implant Illness:
An fMRI Pilot Study

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ABSTRACT

Background

Some women with breast implants report systemic and cognitive symptoms, known as breast implant illness (BII), which are very similar to those of fibromyalgia. Functional MRI has shown altered brain activity in fibromyalgia patients.

Objectives

In this pilot study, we investigated whether brain alterations could be observed in BII patients using fMRI.

Methods

Women aged 18 to 76 with silicone breast implants for cosmetic reasons were recruited through a Dutch online BII support organization (MKS) and through Maastricht University Medical Center. Twelve women with BII and twelve women without symptoms were included. Participants completed questionnaires regarding demographic characteristics, medical history, psychosocial complaints (4DSQ), cognitive failure (MSSE), pain intensity and pain-related disability (CPGS). Subsequently, brain images of all participants were obtained using resting-state fMRI (rs-fMRI) and Diffusion Tensor Imaging (DTI) at a 3 Tesla MRI scanner.

Results

Eleven BII patients and 12 healthy controls were included for analysis. Baseline characteristics were similar in the two groups and the mean silicone exposure was 15 years. Patients scored significantly higher on both pain intensity and disability than controls. Patients scored worse on depression, somatization, distress, and anxiety compared to asymptomatic women. MMSE scores were normal. However, the analyses of both functional connectivity and structural integrity showed no significant differences between the two groups.

Conclusions

This pilot study showed no evidence of brain alterations in BII patients. However, patients scored significantly worse on psychosocial symptoms than controls. Psychological factors appear to play an important role in BII and should be further investigated.

Introduction

Some women with silicone breast implants (SBI) report systemic complaints, also referred to as breast implant illness (BII).[1-3] In addition to physical complaints, many of these patients report subjective cognitive failure, which is described as memory loss, concentration problems, and word-finding problems.[4] These non-specific symptoms of BII share many features with fibromyalgia, making the distinction difficult.[5, 6] However, the significant improvement following explantation in more than half of the patients seems to indicate the existence of two separate conditions.[7-9] The cause-effect relationship of SBI and systemic symptoms remains a subject of an ongoing debate and the prevalence of BII is still unknown.[10-13] The adjusted prevalence of symptoms was not found to be significantly higher in women with SBI than in women without SBI.[1] Additionally, no increased risk of subjective cognitive failure in SBI patients, when compared with controls, could be demonstrated.[4] There is no method to objectify the harmfulness of SBI and therefore no targeted therapy is available, except the permanent removal of the implants.[9] In the majority of cases, this treatment is not reimbursed by health insurance, as a result of which patients do not receive the desired help and do not feel taken seriously. On the other hand, women are at risk of undergoing unjustified medical interventions, which can have both physical and psychological consequences.[14, 15]

Objectifying complaints, such as pain, could contribute to recognition and point the way for treatment. One method that has been used to demonstrate chronic pain is neuroimaging, involving (functional) Magnetic Resonance Imaging (fMRI) of the brain's pain matrix.[16] This method may also visualize neurological correlates in women with BII.

Previous neuroimaging studies with chronic pain or fibromyalgia patients showed altered brain activity and structural changes in brain regions that are collectively referred to as the pain matrix[16-21]. These brain regions are known to be consistently activated during pain, such as the primary and secondary somatosensory cortex (S1 and S2), insular cortex (IC), anterior cingulate cortex (ACC), prefrontal cortex (PFC), and thalamus, and appear to play an important role in pain processing. Although the neurological underpinnings of BII are still ill-defined, Shoaib and Patten reported multiple white matter lesions as well as small ischemic lesions in women with SBI.[22, 23] The majority of these patients showed additional peripheral or neuromuscular pathologies, suggesting neurological involvement in BII. Given the clinical similarities to fibromyalgia, specific brain regions may also be affected in women with BII. To date, however, no fMRI results of BII patients have been reported in the literature. Therefore, we investigated whether brain alterations could be observed in BII patients, using resting-state fMRI (rs-fMRI) and Diffusion Tensor Imaging (DTI) at a 3 Tesla MRI scanner.

DTI is a commonly used non-invasive method to study white matter microstructures and white matter integrity[24]. Within clinical research it has shown valuable insights in various neurological and psychological disorders[25]. Water diffusion is traditionally modelled with a diffusion tensor model[26] which provides various diffusion parameters such as: mean diffusivity (MD) and fractional anisotropy (FA). Reductions in FA have been linked to myelin breakdown, to axonal degeneration or general decreases in white matter integrity[27, 28]. The aim of this pilot study was to examine whether alterations in these diffusion measures can be found in BII patients compared to women with SBI without health complaints.

Methods

Study population

Subjects were recruited between October 2020 and September 2021. Forty-five women were invited for they had previously participated in BII research and agreed to be invited again for participation. Fifty-one women signed up through the Silicone Breast Implants Organization (Meldpunt Klachten Siliconen, MKS), an online support organization for women with breast implants, that shared a call for participants. In addition, six women reported via the plastic surgery outpatient clinic of Maastricht University Medical Center (MUMC).

Inclusion criteria for the patient group were: women, age 18 to 76 year, cosmetic breast augmentation, SBI in situ, and suggested BII, including subjective cognitive impairment. The same inclusion criteria applied to the control group, except that they explicitly experienced no suggested BII and no cognitive impairment. Exclusion criteria for both groups were: diagnosis of chronic pain syndrome, fibromyalgia, chronic fatigue syndrome, cancer, or diabetes mellitus; history of cerebral vascular accident (CVA); use of antidepressants, anticonvulsants, opioids, or benzodiazepines; and (3T) MRI contraindications, such as metallic implants, permanent make-up, and claustrophobia.

The study protocol was approved by the Institutional Review Board at MUMC (METC19-089). All participants agreed to participate in this study and provided written informed consent.

Baseline characteristics and questionnaire data

Participants completed a set of questionnaires before undergoing the scan. A general questionnaire included items on demographic characteristics, medical history and implant-related complaints. The Four-Dimensional Symptom Questionnaire (4DSQ) is a 50-item questionnaire aimed at psychosocial complaints. The list distinguishes between non-specific distress complaints (score 0-32), depression (score 0-12), anxiety (score 0-24), and somatization (score 0-32).[29] The Chronic Pain Grade Scale (CPGS) is a multidimensional measure that assesses pain intensity (score 0-100) and pain-related disability (score 0-6) of chronic pain.[30] A Mini-Mental State Examination (MMSE) was administered to detect cognitive failure (score 0-30).

Statistical analyses of baseline data

Baseline data were analyzed with descriptive statistics. Continuous variables were reported as mean values and standard deviation (SD), and were compared using the independent samples t test. Categorical variables were reported as counts (%) and were compared using Pearson's chi square test or Fischer's exact test. Ordinal data were reported as counts (%) and were analyzed by the Mann-Whitney U test. A p value <0.05 was considered statistically significant. Baseline data analyses were performed in IBM SPSS Statistics[25].

MRI acquisition

Anatomical- (T1 weighted), diffusion- and functional MRI images were acquired using a 3T Siemens Prisma Trio whole body scanner (Siemens Medical System, Erlangen, Germany), equipped with a 32-channel head coil. The full MRI protocol is described in the Protocol, Supplement 1.

Data preprocessing and data quality assessment

Functional data were pre-processed using the BrainVoyager 22.2 package (Brain Innovation, Scannexus, Maastricht, The Netherlands), correcting for slice scan-time differences, 3D head motion using 3 translation and 3 rotation parameters. Subsequently, linear trends and low frequency temporal drifts were removed from the data using a high-pass filter, removing temporal frequencies below 0.01Hz. After the pre-processing, functional data were co-registered to the high-resolution anatomical volume and normalized to MNI space.

Diffusion-weighted images were pre-processed using FSL 6.0, correcting for susceptibility- and eddy-current distortions, as well as head motion.

Diffusion data analysis

The diffusion tensors were estimated from the corrected diffusion-weighted images using a linear fitting algorithm, after which FA and MD data was analyzed both on a whole-brain level as well as on the level of individual regions-of-interest (ROIs). These ROIs were defined using the John Hopkins JHU White-Matter Tractography and JHU ICBM-DTI-81 White Matter atlases.

Resting state data analysis

ROI definition

The nodes in the pain matrix were based on the paper of Kano et al., (2020)[31]. Regions were defined bilaterally, except for the periaqueductal grey (PAG), and were obtained from the Automated Anatomical Labeling (AAL) atlas32 and the Brodmann atlas.

Connectivity analysis on ROIs

Per participant, the connectivity for each ROI in the pain matrix with all other ROIs was computed. This resulted in a connectivity matrix per participant, which were averaged across all participants in both the BII group and the healthy control group. Subtraction of the control matrix from the BII matrix resulted in a difference matrix that indicates structural differences between groups in pain matrix functional connectivity.

Statistical significance of these difference scores was assessed through means of a permutation test. To control for false positives, all p-values were corrected using a false discovery rate (FDR) correction (q = 0.05).

Results

Baseline characteristics

Between November 2020 and October 2021, 23 participants underwent fMRI for this pilot-study (Figure 1). Eleven BII patients and 12 healthy controls were included for analysis. One participant in the BII group withdrew from the study due to claustrophobia and could therefore not be analyzed. Only cosmetic patients were included In the study. Baseline characteristics were similar in the two groups (Table 1). The mean age was 44 years (range 27-71, SD 12 years) and the mean BMI was 22.2 kg/m2 (range 18.1-25.3, SD 3.9). The average duration of silicone exposure was 15 years (4-43, SD 9 years).

Women in the patient group reported the following implant-related complaints: fatigue (n=11, 100%), cognitive failure (n=11, 100%), pain (n=10, 91%), gastro-intestinal complaints (n=10, 91%), myalgia (n=8, 73%), hair loss (n=8, 73%), sicca complaints (n=8, 73%), arthralgia (n=7, 64%), depression (n=7, 64%), skin problems (n=6, 55%), tinnitus (n=2, 18%), and fever (n=1, 9%). Participants in the control group reported that they had no implant-related complaints.
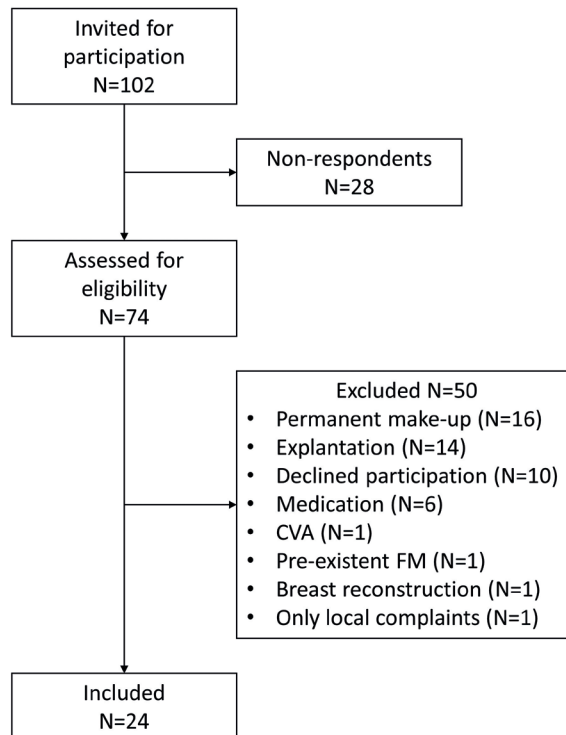
Figure 1. Flowchart of the subject recruitment and inclusion procedure.

Table 1. Baseline characteristics of BII patients and control group.

	BII (n=11)	Control (n=12)	P value	95% CI Lower	Upper
Age (mean, range, SD)	44.0 ±11.1	44.7±13.5	0.898	-11.404	10.070
BMI (mean, range, SD)	21.4±2.2	22.8±5.0	0.400	-4.7726	2.0120
Total silicone in situ, year (mean, range, SD)	15.8±5.0	15.2±12.0	0.865	-7.370	8.673
Education (n, %)			0.566	-	-
Secondary education or lower	0 (0)	1 (8)			
Middle-level vocational education	5 (45)	7 (58)			
Higher-level vocational education/college/university	5 (45)	1 (8)			
Academic/doctoral degree	1 (9)	3 (25)			
Smoking (n, %)			1.000	-	-
No	9 (82)	10 (83)			
1-10/day	2 (18)	1 (8)			
10-20/day	0 (0)	1 (8)			
>20/day	0 (0)	0 (0)			
Alcohol (n, %)			0.566	-	-
No	4 (36)	2 (17)			
1-4/week	5 (45)	0.027			
5-8/week	2 (18)	2 (17)			
>8/week	0 (0)	0 (0)			
Laterality (n, %)			0.478	-	-
Unilateral	1 (9)	0 (0)			
Bilateral	11 (91)	12 (100)			

The questionnaires revealed significant differences between the groups. Women in the BII group scored significantly higher on both chronic pain intensity (mean difference 42.7; 95% CI 22.6 to 62.7; P = .001) and pain disability (mean difference 2.0; 95% CI 0.6 to 3.4; P = .01) than controls. On the 4DSQ, BII patients scored significantly higher on the domains depression (mean difference 2.6; 95% CI 0.013 to 5.205; P = .049) and somatization (mean difference 8.8; 95% CI 3.657 to 13.834; P = .002). Patients scored (more than) twice as high on distress complaints (mean difference 8.4; 95% CI -0.361 to 17.107; P = .059) and anxiety (mean difference 2.3; 95% CI -2.378 to 6.905; P = .320) compared to the control group. With a minimal MMSE score of 29/30 in the BII group and 28/30 in the control group (mean difference 0.6; 95% CI 0.0725 to 1.2153; P = .029), no aberrant scores were identified. Questionnaire results were presented in Table 2.

Table 2. Questionnaire results of the MSSE, CPGS, and 4DSQ.

Variables	BII (n=11)	Control (n=12)	P value	95% CI lower	Upper
MMSE (mean, range, SD)	29.7±0.5	29.1±0.8	0.029	0.0725	1.2153
CPGS (mean, range, SD)					
Intensity	45.5±29.1	2.8±9.6	0.001	22.6301	62.7290
Disability	2.0±2.1	0.0±0.0	0.010	0.5908	3.4092
4DSQ (mean, range, SD)					
Distress	16.3±10.3	7.9±8.6	0.059	-0.361	17.107
Depression	2.9±3.8	0.3±0.7	0.049	0.013	5.205
Anxiety	4.4±6.1	2.1±3.7	0.320	-2.378	6.05
Somatisation	14.6±6.0	5.8±5.0	0.002	3.657	13.834

Functional connectivity results

The results of the connectivity analyses based on the resting state fMRI measurements are summarized in Figure 2. Despite clear network activity between the different nodes in the pain matrix, the analyses did not yield significant results between the two groups. Even before correcting for multiple comparisons, none of the correlation pairs were statistically significant. Still, an apparent difference in connectivity seems to exist between bilateral dorsolateral prefrontal cortex (DLPFC) and all other ROIs, in favor of the BII group. However, also when we averaged the connectivity between DLPFC and all other regions and tested this difference against the permutation distribution, no significant effect was found. Further investigation lead to the finding that this difference was attributable to a small anatomical deviation in the frontal regions of two control patients which overlapped with the DLPFC ROI. Connectivity between this region to all other regions in these two participants was negatively affected, explaining the difference between the groups.

Diffusion results

Whole brain group analyses did not reveal differences in FA or MD measures between the two groups. Clustered differences were found but none of these differences were statistically significant (Figure 3).

ROI-specific group differences

Additionally, regional-based group comparisons were performed. We examined the group differences within eight white matter tracts bilaterally and three commissural tracts (tracts that connect corresponding cortical regions in the two hemispheres[33]). For the bilateral tracts we first tested per ROI whether the DTI measures differed between hemispheres. For those ROIs showing hemispheric differences, the group comparisons were computed for the hemispheres separately. For those ROIs showing no differences, the DTI measures were averaged across the hemispheres for the estimation of the group differences.
ROI-based group comparisons did not reveal differences in FA and MD values between BII patients and asymptomatic women with SBI (Table 3 and Table 4). We found a significant difference within corpus callosum: in this region we found reduced FA values for patients with BII compared to women with SBI (mean difference = 0.012, P-value = 0.031). However, after correcting for the amount of ROI- comparisons, this difference did not reach the significance level.
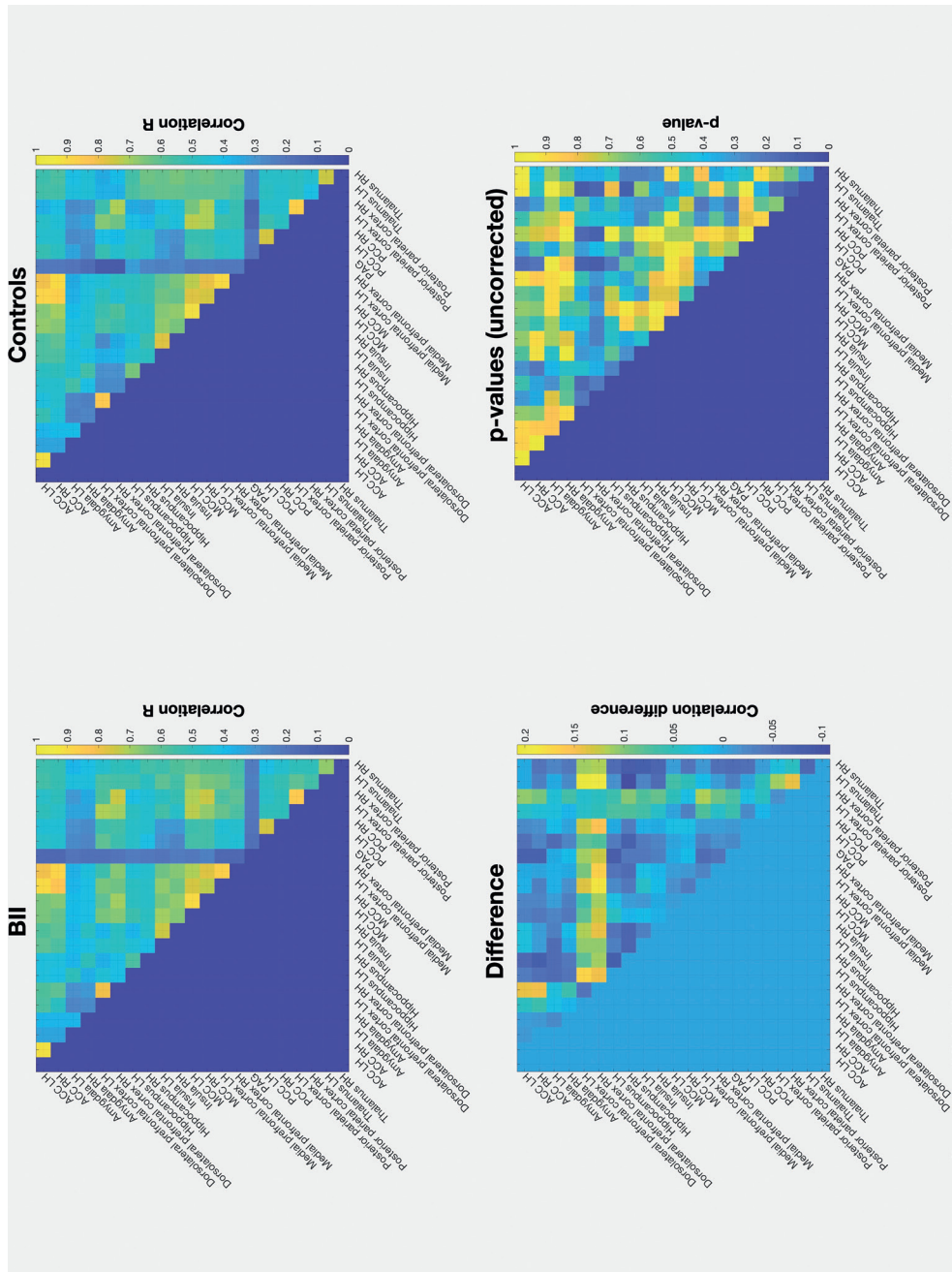
Figure 2. Functional connectivity results for the Bll group, control group, and difference between the groups.
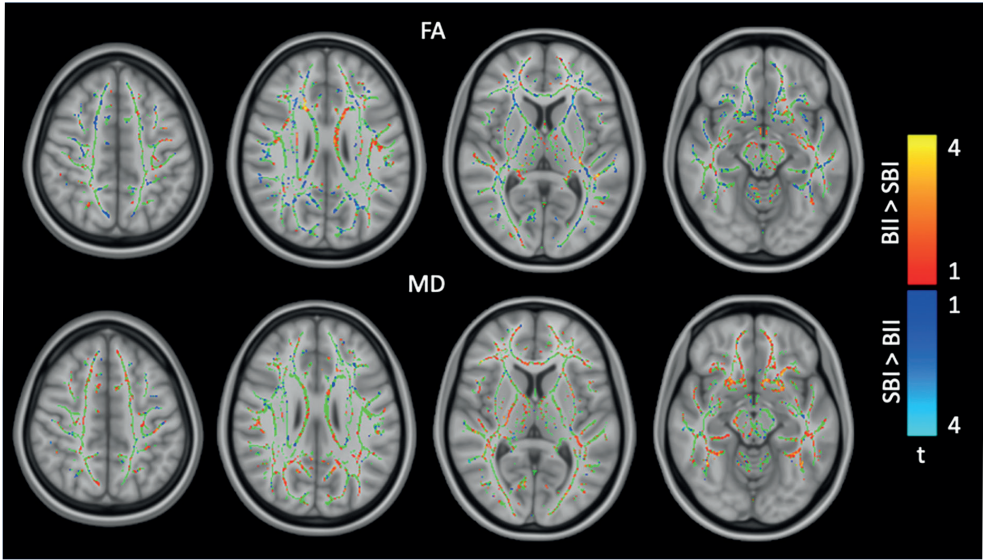
Figure 3. Group differences in DTI derived measures: fractional anisotropy (FA, upper part) and mean diffusivity (MD, lower part).

Table 3. ROI-specific group comparisons of fractional anisotropy (FA). Each row shows for the corresponding ROI the mean (sd) FA value for women with SBI without health complaints, mean (sd) for patients with BII, the difference score between the two groups and the uncorrected P-value of the difference score respectively.

ROI	$\bar{x}^{SBI} \pm s$	$\bar{x}^{SII} \pm s$	Difference	P value
Anterior thalamic radiation	0.437 ± 0.012	0.435 ± 0.009	0.002	0.660
Corticospinal tract LH	0.555 ± 0.018	0.557 ± 0.013	-0.002	0.742
Corticospinal tract RH	0.566 ± 0.016	0.571 ± 0.012	-0.006	0.360
Cingulum (cingulate partition) LH	0.598 ± 0.021	0.589 ± 0.022	0.009	0.355
Cingulum (cingulate partition) RH	0.525 ± 0.022	0.520 ± 0.034	0.005	0.710
Cingulum (hippocampal partition)	0.461 ± 0.014	0.450 ± 0.022	0.011	0.198
Inferior fronto-occipital fasciculus	0.496 ± 0.014	0.501 ± 0.022	-0.005	0.558
Inferior longitudinal fasciculus LH	0.465 ± 0.012	0.464 ± 0.019	0.001	0.877
Inferior longitudinal fasciculus RH	0.486 ± 0.013	0.477 ± 0.025	0.009	0.320
Superior longitudinal fasciculus LH	0.478 ± 0.013	0.477 ± 0.023	0.001	0.858
Superior longitudinal fasciculus RH	0.495 ± 0.016	0.502 ± 0.019	-0.006	0.410
Unicate fasciculus LH	0.471 ± 0.024	0.472 ± 0.020	-0.001	0.924
Unicate fasciculus RH	0.509 ± 0.020	0.0510 ± 0.015	-0.002	0.848
Corpus callosum	0.669 ± 0.012	0.658 ± 0.011	0.012	0.031
Forceps major	0.643 ± 0.016	0.643 ± 0.021	-0.000	0.956
Forceps minor	0.492 ± 0.014	0.491 ± 0.018	0.001	0.863

LH = left hemisphere, RH = right hemisphere.

Table 4. ROI-specific group comparisons of mean diffusivity (MD). Each row shows for the corresponding ROI the mean (sd) MD value for women with SBI without health complains, mean (sd) for patients with BII, the difference score between the two groups and the P- value of the difference score respectively.

ROI	$\bar{x}^{\,SBI} \pm s$ (e-03)	$\bar{x}^{\,SII} \pm s$ (e-03)	Difference (e-03)	P value
Anterior thalamic radiation LH	0.564 ± 0.027	0.568 ± 0.041	-0.003	0.826
Anterior thalamic radiation RH	0.569 ± 0.028	0.574 ± 0.047	-0.005	0.781
Corticospinal tract	0.543 ± 0.016	0.531 ± 0.033	0.012	0.312
Cingulum (cingulate partition) LH	0.597 ± 0.024	0.589 ± 0.045	0.008	0.624
Cingulum (cingulate partition) RH	0.614 ± 0.030	0.597 ± 0.039	0.017	0.285
Cingulum (hippocampal partition) LH	0.550 ± 0.031	0.521 ± 0.042	0.029	0.087
Cingulum (hippocampal partition) RH	0.570 ± 0.032	0.553 ± 0.042	0.018	0.284
Inferior fronto-occipital fasciculus	0.671 ± 0.019	0.666 ± 0.028	0.005	0.631
Inferior longitudinal fasciculus LH	0.686 ± 0.023	0.677 ± 0.032	0.009	0.441
Inferior longitudinal fasciculus RH	0.671 ± 0.019	0.666 ± 0.026	0.004	0.666
Superior longitudinal fasciculus LH	0.656 ± 0.015	0.655 ± 0.038	0.002	0.893
Superior longitudinal fasciculus RH	0.638 ± 0.014	0.635 ± 0.034	0.003	0.787
Unicate fasciculus	0.664 ± 0.021	0.650 ± 0.019	0.014	0.130
Corpus callosum	0.600 ± 0.022	0.590 ± 0.049	0.010	0.565
Forceps major	0.679 ± 0.021	0.664 ± 0.029	0.015	0.195
Forceps minor	0.672 ± 0.026	0.664 ± 0.026	0.008	0.477

LH = left hemisphere, RH = right hemisphere.

Discussion

The aim of this exploratory pilot study was to examine whether alterations in structural and functional measures can be found in brain regions involved in the pain matrix in BII patients compared to asymptomatic women with SBI, using 3T fMRI. The main findings of this study were that the analyses of both functional connectivity and structural integrity showed no significant differences between the two groups, despite the large clinical differences.

Women with BII report experiencing pain. Not only local pain to the chest, as in capsular contracture, but also widespread pain, as in fibromyalgia, has been reported in relation to breast implants.[1, 9] We found that both pain intensity and pain-related disability measured with the CPGS were significantly higher in BII patients than in controls. Previous MRI studies have led to the understanding that chronic pain patients display brain alterations regarding brain function and structure.[34, 35] In FM patients, both increased and decreased functional connectivity within the different pain-related brain regions have been found.[36] For example, reduced activity of the descending inhibitory pathways as well as reduced activity and connectivity within the ACC and thalamus have been found in FM patients compared with healthy volunteers in response to pressure stimulation.[37, 38] In addition, maladaptive cognitive and emotional factors in patients with chronic pain, such as pain catastrop-

hizing, anxiety, and depression, have been related to brain alteration in chronic pain patients.[18] In contrast, this first pilot study investigating brain regions involved in the pain matrix in women with breast implants demonstrated no differences between BII patients and asymptomatic women. Several reasons may underlie this outcome, such as methodological limitations (e.g. small sample size) or the lack of a neurological correlate.

Cognitive failure was reported as the most common symptom in BII patients alongside fatigue. This is consistent with the results of our previous study examining the prevalence of self-reported complaints in women with breast implants.[1] Cognitive disorders are often cited as major complaints by BII patients. These complaints are comparable to those of "fibrofog" in fibromyalgia patients: the experience of subjective cognitive failure.[39] Previous research showed that the prevalence and severity of subjective cognitive failure in unselected women with breast implants was comparable to that of healthy controls, that these cognitive complaints affect a selected patient group, and that there is no increased risk of cognitive failure among women with breast implants.[4] Fibromyalgia patients, on the other hand, scored significantly worse on the MMSE than healthy controls in several studies, indicating objective cognitive impairment in these patients.[40, 41] In our current study, we did not find lower MMSE scores in women with BII compared to asymptomatic women. Therefore, it could be suggested that the cognitive impairment related to BII is only of a subjective, rather than an objective nature. In addition, these findings make serious cognitive impairment with an underlying neurological cause more unlikely.

Although we did not find any significant differences between BII patients and controls using fMRI neuroimaging, large differences were found in the 4DSQ outcomes, a measure of psychological symptoms.[29] BII patients scored moderately to highly elevated on the distress scale, compared to controls. This score indicates the degree of subjective psychological suffering. According to the normative data, 17.5% of the general population experiences above-average distress (>10), while 63.6% of the BII patients in our study scored >10. In addition, 12.3% of the general population experiences above-average somatization, compared to 81.1% of the BII patients in our study. Women with BII also scored moderately to highly elevated on anxiety and depression.[42] These higher levels of anxiety in BII patients correspond to previous findings reported in the literature.[43] Therefore, psychological factors may play an important role in the perception of complaints in BII. The relationship between psychological or cognitive factors and persistent pain is well known. For example, a significant association between persistent postmastectomy pain and catastrophizing, somatization, and anxiety has been found, while demographic, surgical, medical, and treatment-related factors were not associated with persistent pain.[44] The same factors were found to be associated with persistent headache, low back pain, and temporomandibular pain.[45-47] The results of this current pilot study strongly suggest that distress, somatization, anxiety, and depression are significantly associated with the development of BII, regardless of other demographical and surgical characteristics.

Closely related to the above hypothesis is the nocebo effect. This effect is more likely to occur in people who are more anxious, experience more psychological distress, or have a history of medically unexplained symptoms.[48] As a result of the nocebo effect, people develop complaints due to negative expectations; the opposite of the placebo effect.[49] Learning mechanisms and classical conditioning underlie this effect, as does learning about the experience of others. In other words, negative effects can be induced by social context and modeling, such as negative media coverage, self-obtained information from the internet, or stories from other patients.[48] Women with breast implants can read other women's experiences on social media or watch TV documentaries, recog-

nizing the symptoms described. Subsequently, they may attribute their own systemic complaints, such as fatigue, to the breast implants.[50]

This exploratory pilot study had several limitations. Since we were the first to conduct a neuroimaging study on BII patients, we were unable to perform a power calculation. We used a small sample size in this study to make an initial exploration of brain function in women with breast implants. This may be the reason for the lack of statistical significance. However, significant differences were found in these small groups using the questionnaires. It is important to notice that various patient-related factors, such as the tendency to exaggerate, can influence the score upwards in individual cases, especially in BII. Due to the cross-sectional design of the study, a change over time could not be demonstrated. Longitudinal research with both preoperative and postoperative measurements could provide more insight into the effects of SBI on brain function. Furthermore,

we believe that comparing our results with the results of women without breast implants or (former) BII patients who have already undergone explantation of the prostheses would be a valuable follow-up to this study. We will therefore investigate this research question and publish the results in the near future.

Conclusion

This pilot study showed no evidence of brain alterations in BII patients. However, BII patients scored significantly higher on distress, somatization, anxiety, and depression than asymptomatic women with SBI. Psychological factors appear to play an important role in BII and should be further investigated.

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SUPPLEMENTAL MATERIAL

MRI protocol

MRI data acquisition

Anatomical- (T1 weighted), diffusion- and functional MRI images were acquired using a 3T Siemens Prisma Trio whole body scanner (Siemens Medical System, Erlangen, Germany), equipped with a 32-channel head coil. [T1-weighted images were acquired using an MPRAGE sequence at $1 \times 1 \times 1$ mm3 resolution (field of view = 256 x 256 x 192 mm3, echo time 4 ms, repetition time = 8600 ms, readout bandwidth = 320 Hz/pixel, GRAPPA acceleration factor = 2). Diffusion-weighted images were acquired using a spin-echo echo-planar imaging (SE-EPI) pulse sequence at $1.5 \times 1.5 \times 1.5$ mm3 resolution (83 slices with slice thickness = 1.5 mm, field of view = 204 x 204 mm2, matrix size = 136 x 136, echo time = 56.0 ms, repetition time = 10300 ms, number of averages = 1). Diffusion was measured at a b-value of 1000 s/mm2 along 30 noncollinear directions. Five non-diffusion weighted images (b = 0 s/mm2) were acquired for subsequent distortion correction, see preprocessing. Additionally, five reversed phase encoding images (b = 0 s/mm2) were acquired for subsequent susceptibility-induced distortion corrections, see preprocessing. T2*-weighted images were acquired using a clustered echo planar imaging sequence at 3.0×3.0 x 3.0 mm3 resolution (36 slices with slice thickness = 3.0 mm, field of view = 216 x 216 mm2, matrix size = 72 x 72, echo time = 30.0 ms, repetition time = 1000 ms, GRAPPA acceleration factor = 2).

Data preprocessing and data quality assessment

Functional MRI data were pre-processed using the BrainVoyager 22.2 package (Brain Innovation, Maastricht, The Netherlands), correcting for slice scan-time differences, 3D head motion using 3 translation and 3 rotation parameters. Subsequently, linear trends and low frequency temporal drifts were removed from the data using a high-pass filter, removing temporal frequencies below 0.01Hz. After the pre-processing, functional data were co-registered to the high-resolution anatomical volume and normalized to MNI space.

Diffusion-weighted images were pre-processed using FSL 6.0, correcting for susceptibility- and eddy-current distortions, as well as head motion. The susceptibility induced off-resonance field was estimated from the spin-echo EPI images acquired with different phase-encode directions[1]. This field was passed to "eddy", a tool that combined it with estimating gross subject movement and eddy current-induced distortions[2]. The quality of the dataset was assessed using the eddy QC tools[3]. Slices with signal loss caused by subject movement coinciding with the diffusion encoding were detected and replaced by predictions made by a Gaussian Process[4]. Intra-volume subject movement was corrected using slice-to-volume alignment[5] and changes to the susceptibility-induced distortions caused by subject movement were estimated[6]. The quality of the data of single participants was evaluated with respect to the quality of the data of all participants within this study. None of the participants had data quality that fell within the lower ranks on various assessment parameters, and therefore none of the participants were excluded from subsequent analyses.

Diffusion data analysis

The diffusion tensors were estimated from the corrected diffusion-weighted images using a linear fitting algorithm, after which FA and MD data was analyzed both on a whole-brain level as well as on the level of individual regions-of-interest (ROIs). These ROIs were defined using the John Hopkins JHU White-Matter Tractography and JHU ICBM-DTI-81 White Matter atlases.

Resting state fMRI analysis

ROI definition
We based the nodes in the pain matrix on the paper of Kano et al., (2020)[7], focusing on the thalamus, insulae, anterior cingulate cortex, medial cingulate cortex, posterior cingulate cortex, amygdala, hippocampus, medial prefrontal cortex, hippocampus, periaqueductal gray [PAG], dorsolateral prefrontal cortex, and posterior parietal cortex. Regions were defined bilaterally, except for the PAG, and were obtained from the AAL atlas[8] and the Brodmann atlas, both available in MRIcron. For the PAG we used a sphere of 6 mm radius around the MNI coordinate 0,–28,–8.[12]

Connectivity analysis on ROIs
For each participant, for each ROI in the pain matrix, we averaged the time course across voxels and computer the Pearson correlation coefficient between this averaged time course with all other ROIs' time courses in a pair wise fashion. This resulted in a connectivity matrix per participant, which was averaged across all participants in both the ASIA group and the healthy control group. By subtracting the control matrix from the ASIA matrix, we ended up with a difference matrix that indicates structural differences between groups in pain matrix functional connectivity.

We assessed statistical significance of these difference scores through means of a permutation test. For each of the permutation iterations, we shuffled the group labels across participants before computing the average connectivity matrices for the two (arbitrary) groups, after which we computed the difference matrix. By repeating this procedure 10,000, we built a distribution of difference scores under the null hypothesis. By ranking the connectivity difference between each pair of ROIs against the null distribution, we can compute the p-value for each ROI pair. To control for false positives, all p-values were corrected using a false discovery rate (FDR) correction (q = 0.05).

Calculations of the diffusion measures: FA and MD and statistical analyses of whole brain group comparisons

The diffusion tensors were estimated from the corrected diffusion-weighted images using a linear fitting algorithm "dtifit", implemented in FSL. Voxel wise statistical analysis of the FA and MD data was carried out using Tract-Based Spatial Statistics (TBSS)[9] as part of FSL. All subjects' FA images were aligned to a standard MNI 152 space using nonlinear registration. A group-averaged FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA image was then projected onto this skeleton. The nonlinear warps and skeleton projections estimated on the FA images were also applied to the MD images. On the skeletonized FA or MD data permutation-based statistics were carried out (using randomize of FSL; 5000 permutations) using group as a between-subjects factor. P-values were corrected by means of the Threshold-Free Cluster Enhancement (TFCE) option[10] and family-wise error rate (a = 0.05) was used to correct for multiple-comparisons.

Definition of white matter regions-of-interest (ROIs) for diffusion analyses

Additional group comparisons were based on atlas-based regions-of-interest (ROIs) analyses. For each participant the following bilateral white matter tracts were defined based on the Johns Hopkins University (JHU) White-Matter Tractography Atlas[11]: anterior thalamic radiation, corticospinal tract, cingulum (cingulate and hippocampal partitions), inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus and unicate fasciculus. We additionally defined the following commissural tracts based on JHU White-Matter Tractography Atlas or JHU ICBM-DTI-81 White Matter Labels[11]: corpus callosum (body partition) and forceps' (major and minor). The group centers of the ROIs were defined based on the mean FA skeleton, defined in the previous step and subsequent statistical analyses were computed on these group centers.

Statistical analysis of ROI-specific diffusion group comparisons

We tested for statistical significance of the group differences using two-tailed permutation testing. For the bilateral tracts we first tested for hemispheric differences between corresponding ROIs. For each diffusion measure (FA or MD) we tested whether the scores differed between the left and right hemispheres of each ROI, using Python-based toolbox: netneurotools (https://netneurotools.readthedocs.io/en/stable/index.html). The test statistic was the group-averaged difference between the two hemispheres and the null distribution was obtained with approximated Monte Carlo simulations (10.000 permutations). The P-value of the test statistic was computed as the proportion of the null distribution that yielded a group difference equal to or more extreme than the observed one ($a_{corrected}$ = 0.05, corrected for the number of ROIs [N=8]). When no hemispheric difference was found the diffusion measures were averaged across the hemispheres for that specific ROI. When a hemispheric difference was found the group differences were computed for the hemispheres separately.

Group differences were computed for each diffusion measure and each ROI separately. The test static was the group-averaged difference score and the null distribution was obtained by randomly permuting (10.000 permutations) the group labels across the participants and recalculating the group-averaged difference score. The P-value of the test statistic for the group differences was also computed as the proportion of the null distribution that yielded a group difference equal to or more extreme than the observed one ($a_{corrected}$ = 0.05, corrected for the number of ROIs [N = 16 for FA and for MD]).

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CHAPTER 5

The Influence of Personality on Health Complaints and Quality of Life in Women With Breast Implants

ABSTRACT

Background

A causal relation between systemic symptoms and breast implants is not establised. Psychological factors, such as personality and psychological distress, are strongly associated with the development of medically unexplained symptoms. It could be hypothesized that psychological factors may be related to the development of breast implant illness (BII).

Objectives

This study was conducted to evaluate the correlation between self-reported health complaints, health- and breast-related Quality of Life (QoL), and personality, in women with cosmetic breast implants.

Methods

Women who attended the plastic surgery outpatient clinic of Maastricht University Medical Center between October 2020 and October 2021 for reasons related to their implants and women recruited for one of our BII-studies during this period were invited to this study. Only women who underwent cosmetic breast augmentation were eligible. Participants completed a physical complaints score form and BREAST-Q, SF-36, EPQ-RSS questionnaires via an online survey.

Results

In total, 201 women completed the questionnaires. Extroversion and social desirability were predominant personality traits in women with breast implants, followed by neuroticism. Relatively high levels of neuroticism were found compared to normative data. Neuroticism correlated significantly with health status and breast-related QoL. Health related QoL had the strongest correlation with neuroticism (b= -3.94, b= -4.86 p <.001).

Conclusion

Personality can play a role in the development of complaints. High levels of neuroticism are seen in cosmetic surgery patients and are negatively correlated with subjective health and patient-reported outcomes in women with breast implants. Therefore, neuroticism may be a factor in the development of BII.

Introduction

Since the introduction in the 1960s, silicone breast implants (SBI) have been hypothesized to be associated with systemic disease. This is referred to as breast implant illness (BII). While many studies have explored this hypothesis, they have failed to show a relation between non-specific symptoms such as fatigue, myalgia, arthralgia, cognitive impairment, and SBI.[1] Psychological factors, such as personality and high levels of psychological distress, are strongly associated with the development of medically unexplained symptoms in general.[2] Furthermore, female gender and reporting of various physical complaints appear to be risk factors for the development of unexplained (functional) syndromes.[3] Risk factors for the development of BII have only been elucidated to a limited extent. However, it has been suggested that BII is a functional somatic syndrome, similar to fibromyalgia.[4] From that perspective, the patient's psychological profile may play an important role in understanding and treating breast implant illness.

It is known that women who opt for breast surgery differ in demographic, medical, and psychological characteristics from other women.[5,6] Several studies Some authors suggest that women who undergo cosmetic breast augmentation are more likely to have a history of depression, anxiety and neurotic personality.[7-9] Some authors have even suggested an increased suicide risk among these women. Several studies show an up to 2 to 3 fold increase in the risk on suicide among these women.[10-16] Although Joiner suggests that this is to be expected given the difference in demographic and personality features and when these differences are taken into account the suicide risk is even relatively low.[17]

Negative body image and low self-esteem are strongly correlated to psychological stress and may be an explanation for the high rate of psychiatric problems in cosmetic surgery candidates.[18] Moreover, body image is related to personality. Neuroticism, in particular, is associated with negative body perception. Individuals who score highly on this personality trait are more likely to experience more negative emotions.[19] For example, neuroticism was found to be associated with greater breast size dissatisfaction, which in turn has negative consequences for the psychological and physical well-being of women.[20]

In addition, personality dimensions play an important role in outcomes including satisfaction with surgical results, subjective well-being, quality of life (QoL), and even illnesses.[5,19,21] Therefore, it could be hypothesized that psychological factors, such as personality traits, may be related to the development of BII. The objective of this study was to evaluate the correlation between self-reported health complaints, health- and breast-related QoL, and personality, in women with cosmetic breast implants.

Methods

Study population

This cross-sectional survey was conducted in October and November 2021. All women who had visited the plastic surgery outpatient clinic of Maastricht University Medical Center (MUMC+) between October 2020 and October 2021 for reasons related to their breast implants were invited to participate. Furthermore, all women who had responded to the invitations of other BII-studies performed by our research group during the same period were invited to participate in this survey. In addition, the invitation was published on the platform of the Dutch Foundation for Women with Illness due to Breast Implants (Meldpunt Klachten Siliconen). Only women, aged over 18 years, who underwent breast augmentation for cosmetic reasons were eligible, also if they had undergone explantation surgery. Male gender was an exclusion criterium. All subjects signed an online informed consent form.

This study was reviewed and approved by the medical ethics review committee of AZM/Maastricht University (METC 2020-2324).

Data collection

Patients were invited to participate in this study by means of an invitation letter by mail or email. They were able to confirm their interest by sending an email to the coordinating researcher, from whom they then received a link to the online questionnaire (Qualtrics, Provo, UT, USA). Participants They were requested to complete the questionnaire within 3 weeks and a reminder was sent after 2 weeks. The online survey was anonymous and consisted of items on demographics, medical history, physical complaints, health-related QoL (SF-36), breast-related QoL (BREAST-Q; augmentation module), and personality traits (EPQ).

Sum of Physical Complaints

For the evaluation of the physical complaints related to BII, patients were asked to score 8 commonly reported ailments.[22] This questionnaire was not validated but based on the most reported complaints. The query was provided in Dutch and translated into understandable language. For the following physical complaints, a score was given on a Likert-scale from 0-5: fatigue, myalgia, arthralgia, skin problems, sicca, fever, cognitive impairment, and hair loss. Subsequently a sum of the above-mentioned scores was made resulting in a minimum score of 0 and a maximum score of 40, with a higher score indicating an increase in burden due to physical complaints.

Short Form-36

The Short Form-36 (SF-36) health survey is a validated questionnaire consisting of 36 items measuring health status and its related QoL.[23] It comprises 8 domains: physical functioning, the impact of the health status, pain, general health, vitality, social functioning, the impact of the mental health, and mental health. The sum of these 8 domains results in two summarized measures: physical health component and mental health component. For this study the two summarizing domains were used for statistical analysis. Scores range from 0 to 100 with higher scores indicating a better health status.

BREAST-Q

The BREAST-Q is patient-reported outcome measure (PROM) for health-related quality of life (HR-QoL) and patient satisfaction. The questionnaire is developed for different types of breast surgery, such as mastectomy, reconstruction, and augmentation. The two main domains of the BREAST-Q are the Quality of Life domain, consisting of three subdomains (physical well-being, sexual well-being, and psychosocial well-being), and the satisfaction domain again consisting of three subdomains (satisfaction with breasts, satisfaction with outcome, and satisfaction with care).[24]

Eysenck Personality Questionnaire

A short version of the Eysenck Personality Questionnaire (EPQ-RSS) was used as a tool for measuring the most important dimensions of personality. The 48 questions result in four domains of personality: psychoticism, extroversion, neuroticism and social desirability[25]. A higher score indicates a stronger correlation with the personality domain. The Dutch version of the questionnaire was used.[26]

Statistical analysis

All data were statistically evaluated for normality of distribution. Patient demographics were analyzed with descriptive statistics and were reported as mean values and standard deviation. Categorical variables were reported as total and percentage. Associations between personality and physical complaints, breast-related and health-related QoL were tested with Pearson's correlation. The correlations were corrected for potential confounders (age, body mass index (BMI), allergies and relationship status, using multivariable linear regression.

All analysis were performed in SPSS statistics version 28 and a P-value smaller than 0.05 was interpreted as statistically significant.

Results

Baseline characteristics

A total of 201 women were included in this study. The mean age was 46. 2 years (range 21-75) and the average BMI 24.3 kg/m2 (range 17.7 - 43.4). 80 women (39.8%) had their implants removed. Baseline characteristics of the subjects are presented in Table 1.

Physical complaints, health-related QoL, breast-related QoL, and personality traits

Table 2 shows the mean scores on the physical complaint score, SF36, BREAST-Q, and EPQ. Extroversion is the most prominent personality trait in this sample followed by social desirability and neuroticism (7.1±3.2, 7.0±2.5, 6.7±3.5). Psychoticism had the lowest mean score (2.5 ±1.5). For breast related QoL the mean scores on physical wellbeing and psychosocial wellbeing were 55.2 ±32.7 and 60.2 ±19.9. The mean scores on the individual symptoms that resulted in the physical complaint score are shown in figure 1. The physical component of the SF-36 had a mean score of 51.9 ±27.8 and the mental component score had a mean of 53.3 ±26.6.

Table 1. Baseline patient demographics.

	(n=201)
Age, mean (SD)	46.2 ±12.8
Body Mass Index, mean (SD)	24.3 ±4.4
Smoking	
No, n (%	155 (77.1)
Yes, n (%)	45 (22.4)
Allergies	
Yes, n (%)	86 (42.8)
No, n (%	115 (57.2)
Relationship status	
Yes, n (%)	145 (72.1)
No, n (%	56 (27.9)
Educational level n, (%)	
Elementary education	18 (8.9)
Secondary/middle level vocational education	120 (59.7)
Higher level vocational	52 (25.9)
Academic/doctoral degree	11 (5.5)
Occupation	
Yes, n (%)	119 (59.2)
No, n (%	82 (40.8)
Implants removed	
Yes, n (%)	80 (39.8)
No, n (%	121 (60.2)
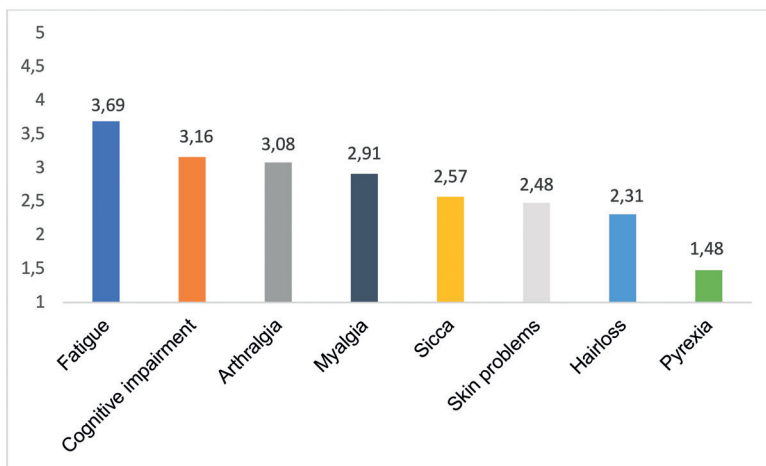
Figure 1. Mean scores of induvidual health symptoms. The sum of these scores gives the physical complaints score.

Correlation between personality traits and health

Figure 2 shows the association between personality traits and physical complaints, health-related QoL, and breast-related QoL, determined with Pearson correlation. A correlation between neuroticism and all outcomes was found with Pearson correlation, except the physical wellbeing scale of the BREAST-Q, (r= 0.47, -0.50, -0.67,-0.27, -0.50, -0.37, -0.35, -0.23, p <.05). Additionally, a correlation between extroversion and most outcomes was found. Table 3 presents the associations between personality traits and physical complaints, health-related QoL, and breast-related QoL, determined with multivariable linear regression correcting for age, BMI, allergies, and relationship status, determined with multivariable linear regression. Most correlations persist after correction.

Table 2. Mean scores of physical complaints, health-related QoL, breast-related QoL, and personality traits.

	(n=201)
Physical complaints[1]	21.7 ±7.4
SF-36[2]	
Physical complaints	66.6 ±27.2
Limitation by physical status	40.0 ±43.8
Limitation by emotional status	56.7 ±45.4
Fatigue	40.4 ±25.7
Emotional wellbeing	60.2 ±22.0
Social functioning	55.7 ±30.3
Pain	56.8 ±28.9
General Health	43.8 ±25.9
Physical component score	51.9 ±27.8
Mental component score	53.3 ±26.6
Breast-Q	
Satisfaction with breast	60.2 ±21.4
Psychosocial wellbeing	60.2 ±19.9
Physical wellbeing	55.2 ±32.7
Sexual wellbeing	54.1 ±22.3
Satisfaction with outcome	62.2 ±25.9
Information given by doctor	50.1 ±14.9
EPQ[3]	
Psychoticism	2.5 ±1.5
Extroversion	7.1 ±3.2
Neuroticism	6.7 ±3.5
Social Desirability	7.0 ±2.5

Outcomes presented as mean, SD.
[1]Total score of physical complaints (range 0-40); higher score indicating a higher burden due to physical complaints.
[2]SF-36, Short Form-36 (range 0-100).
[3]EPQ, Eysenck Personality Questionnaire.

Neuroticism is correlated with all outcome measures except the physical wellbeing scale of the Breast-Q. Higher levels of neuroticism correlate with more physical complaints (b= 0.89 p <.001) and higher levels of neuroticism correlate with lower scores on SF36 and BREASTQ, indicating lower physical health-related QoL (b= -3.94, p <.001), mental health-related QoL (b= -4.86 p <.001), and most breast-related QoL scales. Additionally, higher psychoticism levels are associated with lower satisfaction with outcome (b= -3.52, p <.05) and the idea of having been given less information (b= -1.82, p <.05). The highest impact of extroversion is on both the physical and mental part of health related QoL (b= 2.64, 2.20, p <.001).

Table 3. Regression coefficients between personality traits and health- and breast-related outcomes.

EPQ dimensions[1]	Psychoticism	Extroversion	Neuroticism	Social Desirability
Physical complaints	0.40 (-0.33 – 1.13)	-0.45* (-0.79 – -0.10)	0.89* (0.59 – 1.20)	-0.32 (-0.79 – 0.15)
SF-36[2], Physical Component	-2.05 (-4.80 – 0.69)	2.64* (1.37 – 3.91)	-3.94* (-5.04 – -2.84)	0.60 (-1.19 – 2.39)
SF-36[2], Mental Component	-1.19 (-3.80 – 1.42)	2.20* (0.98 – 3.42)	-4.86* (-5.77 – -3.95)	1.83* (-1.78 – 3.50)
Breast-Q				
Satisfaction with breast	0.26 (-1.90 – 2.41)	1.10* (0.06 – 2.13)	-1.49* (-2.45 – -0.53)	0.16 (-1.24 – 1.56)
Psychosocial wellbeing	0.40 (-1.56 – 2.36)	1.33* (0.40 – 2.25)	-2.69* (-3.48 – -1.91)	0.99 (-0.27 – 2.25)
Physical wellbeing	-0.19 (-3.42 – 2.58)	-0.12 (-1.70 – 1.45)	-1.20 (-2.66 – 0.26)	-1.41 (-3.50 – -0.67)
Sexual wellbeing	-0.91 (-3.10 – 1.29)	1.53* (0.49 – 2.56)	-2.31* (-3.25 – -1.38)	1.00 (-0.41 – 2.42)
Satisfaction with outcome	-3.52* (-6.92 – -0.12)	1.71* (-1.07 – 1.69)	-2.17* (-3.66 – -0.68)	-1.73* (-4.07 – -0.62)
Information given by doctor	-1.82* (-3.31 – -0.34)	0.76* (0.04 – 1.48)	-0.88* (-1.55 – -0.21)	0.51 (-0.46 – 1.49)

*p-value < 0.05
[1]EPQ, Eysenck Personality Questionnaire
[2]SF-36, Short Form-36
Correlation coefficients calculated with multivariable linear regression correcting for BMI, age, allergies, and relationship status.

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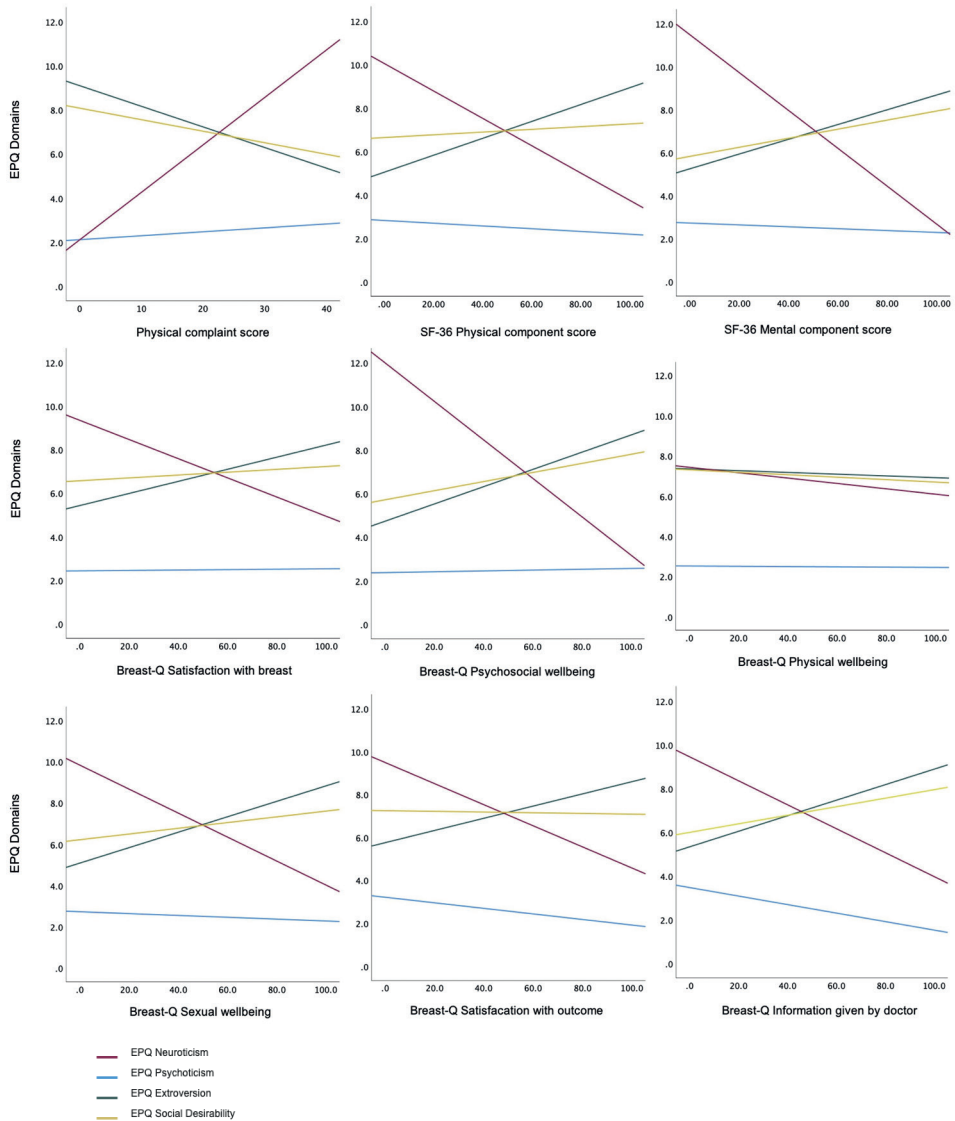
Figure 2. Correlation plots for EPQ domains and all outcomes. The y axis presents all 4 domains of the EPQ questionnaire. (A) Physical complaint score; (B) SF-36 physical component score; (C) SF-36 mental component score; (D) BREAST-Q satisfaction with breast; (E) BREAST-Q psychosocial well-being; (F) BREAST-Q physical well-being; (G) BREAST-Q sexual well-being; (H) BREAST-Q satisfaction with outcome; and (I) BREAST-Q information given by doctor. EPQ, Eysenck Personality Questionnaire; SF-36, Short Form-36.

Discussion

Personality plays an important role in satisfaction with outcomes, subjective well-being and QoL. However, the role of personality factors in QoL after breast implant surgery and breast implant-related illness is still unknown. This cross-sectional study aimed to evaluate the association between self-reported health complaints, health- and breast-related QoL, and personality traits, in women with cosmetic breast implants.

First, we analyzed the personality profile of women with cosmetic breast implants. We found that extroversion and social desirability were predominant traits, followed by neuroticism. Psychoticism was the least characteristic feature of these women's personalities. This order of traits is similar to that of the EPQ-RSS normative data (control group with 64.3% women, and a mean age of 47.5).[26] However, in our study we found significantly higher levels of neuroticism than the levels described in normative data (mean 6.7 vs. 4.1), while the means of other traits were close to match (psychoticism 2.5 vs. 2.3; extroversion 7.1 vs 7.2; social desirability 7.0 vs 6.6). These results may be explained by the fact that personality is correlated with body image.[19,27] For example, neuroticism has a positive association with body dissatisfaction, whereas extraversion has a negative association with body dissatisfaction. As a consequence, people who are more neurotic are more likely to undergo cosmetic surgery. Indeed, higher levels of neuroticism in women undergoing cosmetic surgery, including breast augmentation, were found in previous studies and in this current study.[28] Only cosmetic patients were included in our study, as personality may distinguish cosmetic patients from reconstructive patients. Breast augmentation patients deliberately opted for surgery to improve their appearance, driven by low self-esteem or other personal reasons, while breast cancer patients are involuntarily faced with the choice of restoring the shape of the breast through breast reconstructive surgery after losing their breast, regardless of their psychological profile.[7,29] In other words, reconstructive patients can be considered a random sample of society or control group, assuming that personality has not changed as a result of the disease or treatments. Previous research on personality of breast cancer survivors showed no association between neuroticism and breast cancer risk.[30] Nor could a significant difference in neuroticism and extraversion between breast cancer survivors and controls be found.[31] Nevertheless, low neuroticism and high levels of extroversion also appear to be protective factors associated with mental health in people with cancer.[32] Still, we feel that these two groups should be studied separately in terms of personality traits and related outcomes, such as satisfaction with outcomes and QoL. Second, neuroticism was found to be significantly correlated with the severity of physical complaints and both health-related and breast-related QoL in women with breast implants. The mean BREAST-Q scores in this study were lower than the normative data (control group with a mean age of 54 and a mean BMI 24 kg/m2) for both psychosocial well-being (60.2 vs. 66) and physical well-being (55.2 vs. 86).[33] Higher levels of neuroticism were associated with worse health status. This finding is consistent with the existing literature on neuroticism. Neuroticism is related to the tendency to experience negative emotions, a greater tendency to fear and see the world as a dangerous place and is also linked to maladaptive coping.[34,35] This results in worse physical and mental health outcomes.[36] For example, neuroticism has been associated with a higher risk of chronic pain as well as functional somatic syndromes and fibromyalgia.[37-39] Neuroticism was positively associated with higher symptom severity, as well as higher levels of anxiety, depression, stress, and worse mental QoL in fibromyalgia patients.[37] Since the symptom complex of BII is very similar to that of fibromyalgia and we found this correlation between neuroticism and subjective health in women with breast implants as well, we hypothesize that neuroticism may be a factor in the development of BII.[40]

A factor that may be closely related to neuroticism and the development of health complaints in women with breast implants is the nocebo effect. The nocebo effect means that people develop complaints due to negative expectations; the opposite of the placebo effect.[41] Some characteristics are known to be associated with the nocebo effect, for example anxiousness, psychological distress, and history of medically unexplained symptoms.[42] These characteristics are more common in people who are high in neuroticism as well as in women with BII.[43] It is therefore not inconceivable that, due to this nocebo effect, these women experience more negative health effects than would normally be expected when using breast implants. The negative expectations can be reinforced by media attention or via social media groups.[44] Women may seek information through these sources if they feel they are insufficiently informed about the risks of breast implants.[45] In our study, women reported low scores on the subscale 'information given by doctor', which was significantly negatively correlated with neuroticism and psychoticism. Therefore, these women will be more likely to seek their information elsewhere, which also puts them at risk of receiving misinformation.

There are a number of limitations in the current study. This study included a relatively small sample size due to the recruitment method used. Also, the lack of a control group is a significant limitation which was only partially relieved by the comparison with normative data. Therefore, a control group with similar demographics should be added in future studies. Furthermore, a form of selection bias may have occurred because women with negative experiences may be more likely to participate in scientific research and express their dissatisfaction. As a result, outcomes can be more negative than reality, as evidenced by the BREAST-Q scores. Results related to physical discomfort could also be affected negatively by physical complaints directly related to the implant, such as capsular contraction or pain. This information was not collected, which resulted in another limitation for this study. Finally, it is not verifiable that participants completed the questionnaire about personality traits completely truthfully. Since these are very personal questions, there may be a tendency to fill in more desirable answers. This will most likely mean that the outcomes of neuroticism and psychoticism are an underestimate of reality and that the effect of these characteristics on patient-reported outcomes is stronger than this study suggests. This study shows a possible influence of personality on the development of breast implant related systemic symptoms. Due to the study design no causal relationships can yet be established. Therefore, future studies should elaborate on this theory by prospectively collecting data from an unselected group of women undergoing breast augmentation, regarding pre- and postoperative levels of personality traits, health complaints, and satisfaction with surgical outcomes. Comparing these results with reconstruction patients as well as a control group without breast implants would be valuable to gain more insight into the difference in personality between these groups.

Conclusion

Although some women report health problems related to breast implants, little is known about their origin and risk factors. Psychological factors, such as personality, can play a role in the development of complaints. High levels of neuroticism are seen in cosmetic surgery patients and are significantly negatively correlated with subjective health and patient-reported outcomes in women with breast implants. Therefore, neuroticism may be a factor in the development of breast implant associated illness. Furthermore, the nocebo effect can cause complaints due to negative expectations, fed by (social) media. Large prospective comparative studies should be conducted to further investigate the effect of psychological factors on the development of BII.

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CHAPTER 6

Psychosocial well-being at time of diagnosis of breast cancer affects the decision whether or not to undergo breast reconstruction

ABSTRACT

Objectives

Numerous studies have shown that breast reconstruction after mastectomy improves QoL in breast cancer survivors. However, still about half of the patients does not opt for reconstruction. In order to accommodate suitable counseling, we should elucidate the factors that play a role in the decision-making process. This study aimed to evaluate the influence of QoL, among women diagnosed with breast cancer before the start of any treatment, on their decision whether or not to undergo breast reconstruction.

Materials and Methods

BREAST-Q surveys were provided to breast cancer patients at the specialized breast care outpatient clinic after their first consultation with a surgical oncologist, between June 2017 and March 2019. The Q-scores of the subdomains physical well-being, psychosocial well-being, sexual well-being, and satisfaction with breasts of patients that underwent mastectomy were statistically analyzed.

Results

Sixty-seven patients, undergoing mastectomy, completed the questionnaire. Fifty-four percent received reconstructive surgery. Mean age of patients seeking breast reconstruction was significantly lower than patients who did not opt for a reconstruction (53.5 vs. 63.7). Mean follow-up after mastectomy was 18.1 months. Except for satisfaction with breasts, mean Q-scores were higher in the group of patients who did not choose for reconstructive surgery. Psychosocial well-being was significantly higher in the non-reconstruction group (p = 0.012).

Conclusions

Psychosocial well-being at time of diagnosis of breast cancer was significantly higher in patients refraining from breast reconstructive surgery after mastectomy. Psychosocial characteristics might be essential for the decision-making process as well. Further prospective research should evaluate this.

Introduction

Breast cancer is the most frequent cancer affecting women worldwide. Implementation of population based screening programs and improvement in treatment options have resulted in an increased number of long-term breast cancer survivors[1-4]. The higher survival rate of breast cancer has caused a shift of focus from breast cancer survival to quality of life after breast cancer. As a consequence, Quality of Life (QoL) and patient-reported outcomes measures (PROMs) have become increasingly important in the field of breast cancer.

There has been an increase in both immediate and delayed breast reconstruction rates over the past decades[5, 6], of which numerous studies have demonstrated a positive effect on quality of life[7-9]. Still, about half of the patients does not opt for breast reconstruction[10]. Reasons why women do or do not opt for a reconstruction remain largely unclear. Besides demographic characteristics, tumor stage, and surgeon's counseling, there is literature suggesting that the patient's psychological profile and the need for psychological wholeness might be associated with the choice for or against reconstruction, however, these influences have been scarcely described[11-16]. In order to accommodate suitable counseling, we should elucidate the factors that play a role in their decision-making process about breast reconstructive options.

This study aimed to compare psychological well-being, physical well-being, sexual well-being and satisfaction with breasts subscales of the BREAST-Q questionnaire among women diagnosed with breast cancer, before the start of any treatment, to evaluate the influence of Quality of Life (QoL) and breast-related satisfaction on their decision about reconstructive options.

Materials and methods

Patient selection

This retrospective, cross-sectional study on prospectively collected BREAST-Q surveys analyzes patient-reported outcomes of breast-related satisfaction and QoL in breast cancer patients before oncological surgery was performed. Patients with diagnosis of breast cancer were referred to the specialized breast care outpatient clinic after their first consultation with a surgical oncologist at the Maastricht University Medical Center. They were requested to complete the BREAST-Q questionnaire. For this study, all patients who filled out their survey between June 2017 and March 2019 were included.

Questionnaire

The BREAST-Q is a validated questionnaire that quantifies breast-related satisfaction and quality of life from the patient's perspective and is developed for both cosmetic and reconstructive breast-surgery, pre and postoperative. This patient-reported outcome measure (PROM) consists of two domains with each three subdomains, namely physical well-being, psychosocial well-being and sexual well-being in the Quality of Life domain, and satisfaction with breasts, satisfaction with outcome and satisfaction with care in the Satisfaction domain. Each item is scaled from 0 (worst) to 100 (best)[17, 18].

Statistical analysis

Data from the questionnaires were extracted and the Q-score program was used to transform the scores. The Q-scores of patients that underwent mastectomy were used for statistical analyses. Independent-samples T Tests were performed to determine the significance of differences between the mean outcomes of the groups with and without reconstruction. Dichotomous variables were analyzed by means of Pearson's Chi-square test. All analyses were performed in SPSS Statistics 25 using an alpha level of 0.05 to determine significance.

Results

Patient characteristics

In total, 152 women filled out the BREAST-Q. Mean age of patients undergoing mastectomy was 58.2 (range 36-83) and mean body mass index (BMI) was 26.0 (range 16-37). Mean age of patients choosing for breast reconstruction after mastectomy was significantly lower than patients who did not seek reconstructive surgery. Incidence of radiotherapy, chemotherapy, hormone therapy, and immunotherapy did not significantly differ between the reconstruction and non-reconstruction group (table 1). There were no statistically significant differences in tumor characteristics between the two groups (table 2). Mean follow-up after mastectomy was 18.1 months (range 9-28).

Table 1. Patient characteristics of mastectomy group.

	Total (n = 67)	Reconstruction (n = 36)	No reconstruction (n = 31)	P value
Age (mean ± SD)	58.2 ± 10.4	53.5 ± 8.7	63.7 ± 9.6	<0.001
BMI (mean ± SD)	26.0 ± 4.2	25.9 ± 3.9	26.2 ± 4.7	0.748
DM (n, %)	3 (4.5)	0 (0)	3 (9.7)	0.056
Smoking (n, %)	6 (9.0)	1 (2.8)	5 (16.1)	0.056
Radiotherapy (n, %)	23 (34.3)	12 (33.3)	11 (35.5)	0.853
Chemotherapy (n, %)	30 (44.8)	19 (52.8)	11 (35.5)	0.360
Neo-adjuvant (n, %)	17 (25.4)	11 (30.6)	6 (19.4)	
Adjuvant (n, %)	13 (19.4)	8 (22.2)	5 (16.1)	
Hormone therapy (n, %)	40 (59.7)	23 (63.9)	17 (54.8)	0.451
Immunotherapy (n, %)	5 (7.5)	3 (8.3)	2 (6.5)	0.770

Surgical procedures

Mastectomy was performed in 67 subjects (44.1%), while 85 subjects (55.9%) underwent breast-conserving surgery. In 36.5% of breast-conserving surgery, oncoplastic surgery was performed. Fifteen procedures were bilateral (9.9%), of which nine were prophylactic mastectomies on one side. Fifty-four percent of the mastectomy group underwent reconstructive surgery. Primary breast reconstruction was performed in 32 patients and secondary reconstruction in 4 patients. A schematic overview of the surgical procedures performed was given in figure 1.

Table 2. Tumor characteristics of mastectomy group.

		Total (n = 67)	Reconstruction (n = 36)	No reconstruction (n = 31)	P value
Histology	DCIS	10 (14.9)	5 (13.9)	5 (16.1)	0.303
	IDC/NST	42 (62.7)	23 (63.9)	19 (61.3)	
	LCIS	1 (1.5)	1 (2.8)	0 (0)	
	ILC	11 (16.4)	7 (19.4)	4 (12.0)	
	Other	11 (16.4)	0 (0)	3 (9.7)	
T	In situ	9 (13.4)	5 (13.9)	4 (12.9)	0.516
	1	33 (49.3)	20 (55.6)	13 (41.9)	
	2	21 (31.1)	10 (27.8)	11 (35.5)	
	3	4 (6.0)	1 (2.8)	3 (9.7)	
N	0	48 (71.6)	26 (72.2)	22 (71.0)	0.263
	1	16 (23.9)	10 (27.8)	6 (19.4)	
	2	2 (3.0)	0 (0)	2 (6.5)	
	3	1 (1.5)	0 (0)	1 (3.2)	
M	0	65 (97.0)	35 (97.2)	30 (96.8)	0.914
	1	2 (3.0)	1 (2.8)	1 (3.2)	
B&R	NA	2 (3.0)	1 (2.9)	1 (3.2)	0.633
	1	6 (9.0)	2 (5.6)	4 (12.9)	
	2	40 (59.7)	21 (58.3)	19 (61.3)	
	3	19 (28.4)	12 (33.3)	7 (22.6)	

Patient-reported outcomes

All participants who underwent mastectomy (n = 67) completed the subdomain 'physical well-being', 65 completed the subdomain 'psychosocial well-being', and 66 completed 'satisfaction with breasts'. Twenty-two patients (32.8%) did not complete the subdomain 'sexual well-being'. In three of the four subdomains, the mean Q-scores were higher in the group of patients who did not choose for reconstructive surgery (table 3). Psychosocial well-being was significantly higher in the non-reconstruction group (p = 0.012), while the differences in the subdomains 'physical-'and 'sexual well-being', and 'satisfaction with breasts' did not reach statistical significance.

Table 3. Patient-reported outcomes measured by the BREAST-Q.

	Reconstruction		Reconstruction		
	N	Mean score ± SD	N	Mean score ± SD	P value
Psychosocial well-being	35	58.9 ± 15.05	30	68.8 ± 15.7	0.012
Physical well-being	36	73.0 ± 14.6	31	78.6 ± 14.5	0.123
Sexual well-being	25	57.0 ±19.7	22	60.6 ± 21.4	0.552
Satisfaction with breasts	36	62.4 ± 18.3	30	58.5 ± 18.6	0.397
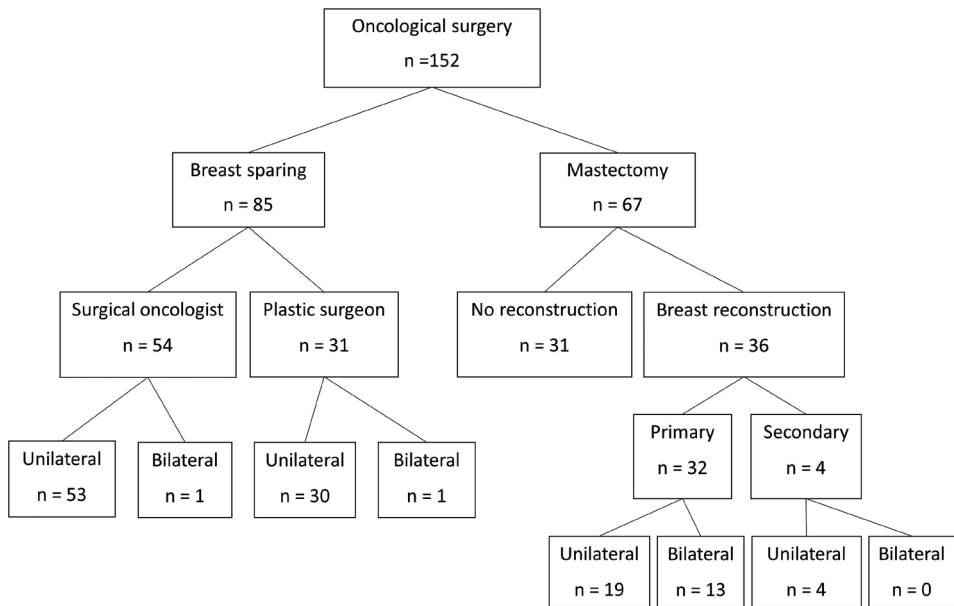
Figure 1. Surgical procedures.

Discussion

This study aimed to evaluate if the quality of life of newly diagnosed breast cancer patients affects their decision whether or not to have a breast reconstruction. For this, the BREAST-Q subscales psychological well-being, physical well-being, sexual well-being, and satisfaction with breasts were used. Questionnaires were provided to the patients at time of diagnosis, before the start of any treatment. We hypothesized that quality of life at time of diagnosis influences the decision regarding breast reconstructive surgery.

In our cohort, we found that women who did not have the wish for breast reconstruction scored significantly higher on psychosocial well-being in comparison with women who did choose for breast reconstruction. Thus, we observed that this domain of the quality of life was significantly reduced at time of diagnosis in women eventually seeking breast reconstruction.

Several studies on determinants associated with patient's choice of breast reconstruction after mastectomy have been published. These have shown that demographic factors play a substantial role in predicting the use of reconstruction. In accordance to the results of our study, age was repeatedly proven significantly lower in reconstructed patients than in patients with mastectomy only[12-15]. Reaby et al. and Shameem et al. found that women sometimes reported themselves too old to consider reconstruction[12, 19]. Next to age, this even might be related to generations. Furthermore, literature showed that women who opted for breast reconstruction had a higher level of education and a higher yearly income. They were more likely to be Caucasian, to be married and to have under-aged children[12, 13, 15, 19]. However, in this study, financial aspects did not play a role in the decision-making process since all Dutch patients have basic health insurance which fully reimburses breast reconstruction.

Other factors that may influence the choice for or against breast reconstruction are sexual well-being and body image. The surgery process in breast cancer treatment has great impact on body image, intimacy and sexual life[20]. A breast reconstruction, on the other hand, appears to improve sexual functioning. Women seeking breast reconstruction were sexually more conscious, had been more interested in sex and were more sexually active than patients without breast reconstruction[11, 16]. Furthermore, significantly more women who opted for breast reconstruction rated body image and sexuality important than those women who did not seek reconstruction[15]. Lee et al. found that women preferring reconstruction found breast shape with or without clothes more important than women who did not seek reconstruction[21]. Nonetheless, our study did not show a significant difference in sexual well-being between the two groups at baseline, although the non-reconstruction group scored slightly higher. However, women in the non-reconstruction group were less satisfied with their breasts, which suggests that breast shape is not directly related to sexual well-being. Imaginably, this might be related to age.

Interestingly, it has been described that some women may feel that breast reconstruction is not essential for their physical or emotional well-being[19]. In that case, offering reconstructive surgery might not necessarily result in an improvement in quality of life. Wehrens et al. postulated that quality of life is only improved in those women specifically asking for a breast reconstruction; a personality-based request[11]. Future studies on personality traits and psychosocial characteristics are therefore required in order to predict someone's preferences in regard to breast reconstruction as well as the expected outcomes.

Along with all of these personal factors, the information provided by the surgeon can be decisive in making a choice. Ananian et al. found that the surgeon's counseling was the most important factor in the decision-making process in half of the women[15]. Dobke et al. showed that plastic surgeons not only influence the choice for breast reconstruction, but also influence the choice for the entire breast cancer treatment process[22]. Due to the design of our study we were unable to evaluate the extend of this factor on the patients' decision-making process. Quantification of the quality of the information patients receive from their surgeon should preferably be included in subsequent studies.

In this study, we have been able to identify a group of consecutive breast cancer patients who has prospectively reported their quality of life at the moment of breast cancer diagnosis. Baseline differences within the two post mastectomy groups were theoretically not a consequence of the study design. However, there were certain limitations while exploring the aim of the study. By requesting all consecutive patients to complete the questionnaire, selection bias was limited. However, since not all patients gave informed consent, a limited number of subjects was included in this study and some selection bias did occur. The effect of this bias is difficult to determine, although it might give an overestimation of the quality of life of patients. Due to the retrospective design of our study, limited predictors could be analyzed as they were not collected in the survey. Besides, we did not adjust for confounders that potentially have played a role in the decision-making process, such as medical contra-indications for reconstructive surgery and the influence of the surgeon's counselling[16, 22, 23]. Furthermore, because of a relatively limited follow-up period, it cannot be said that a woman in the non-reconstruction group will yet undergo a breast reconstruction at a later stage. For instance, women first want to be assured that they are oncologically healthy before they would like to consider reconstructive options. Herein, psychological profile might play an essential

role. This would therefore indicate a basis for further prospective research which should look into the role of psychological determinants.

Conclusion

In our study we found that psychosocial well-being at time of diagnosis of breast cancer was significantly higher in women refraining from breast reconstructive surgery after mastectomy. Other subdomains of Quality of life and breast-related satisfaction measured using the BREAST-Q were similar between women seeking breast reconstructive surgery and those who did not. Although age was significantly lower in women who underwent breast reconstruction, psychosocial characteristics of the breast cancer patient might be essential for the decision-making process as well. Therefore, we feel that further research evaluating these predictors should be performed in a prospectively designed study.

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6

CHAPTER 7

Long-term health status and systemic complaints following implant-based, autologous, or tertiary breast reconstruction

SUMMARY

Breast reconstruction rates have increased over the past few years. At the same time, there is concern about the safety of silicone and the development of systemic complaints as a result of breast implants. In this multicenter, cross-sectional study, self-reported systemic health complaints and health-related Quality of Life (HRQoL) of women who underwent implant-based (IBBR) or autologous breast reconstruction (ABR) between 2015 and 2018 were compared. Patient-reported outcomes of 329 women were analyzed (103 IBBR, 202 ABR, and 24 tertiary ABR). Systemic health complaints occurred equally in women after implant-based, autologous, and salvage autologous breast reconstruction. The severity of the complaints was not significantly different between groups. Multivariable logistic regression demonstrated that age, BMI, and chemotherapy, in particular, were independent predictors of common systemic symptoms, but that the type of reconstruction was not. Multivariable linear regression showed no significant differences in HRQoL between women with implant-based and autologous breast reconstruction. In conclusion, long-term HRQoL outcomes in women who underwent implant reconstruction are comparable to those who underwent autologous breast reconstruction. Based on this study, there are no indications that women undergoing implant-based breast reconstruction have an increased risk of developing systemic complaints compared to women undergoing autologous breast reconstruction.

Introduction

Breast cancer is the most common cancer in women. In the Netherlands, 1 in 7 women will develop breast cancer in their lifetime.[1] As a result of early detection and better treatments the survival rates continue to improve.[2] In recent years, more women have opted for (bilateral) mastectomy for breast cancer treatment or prophylaxis.[3] Breast reconstruction rates have increased, with the largest increase in the number of implant-based reconstructions (IBBR). Breast reconstruction can help restore body image and improve psychosocial well-being and Quality of Life (QoL).[4-7]

Patient-reported outcome measures are increasingly used to evaluate outcomes of different reconstructive methods.[8] Short and long-term studies showed that autologous breast reconstruction (ABR) results in a significantly higher satisfaction with breasts and outcomes when compared to IBBR.[9-11] Nevertheless, ABR is not feasible for everyone, due to the patient's body type, physician's medical expertise, or medical expenses not covered by insurance.[12,13] Implant reconstruction is still the most widely used method to correct mastectomy deformity worldwide.[14,15]

The use of silicone breast implants (SBI), however, has caused concern among women because of some evidence of an association between SBI and systemic health problems.[16,17] This is mainly based on case reports, rather than on large cohort studies.[18] The literature on breast implant illness mainly concerns women with cosmetic augmentation; long-term data on women with breast reconstruction is scarce. However, it is imperative for these patients to know whether systemic health risks are associated with each reconstructive method when making a choice. Therefore, the aim of this study was to compare self-reported systemic health complaints and long-term health-related quality of life (HRQoL) of women with implant-based breast reconstruction to women who underwent autologous breast reconstruction, to assess whether there is an association between type of breast reconstruction and health complaints.

Materials and Methods

Patient Selection

A multicenter, cross-sectional study was performed in Maastricht University Medical Center and Zuyderland Medical Center between November and December 2020. Women aged 18 years and older with a history of mastectomy who underwent implant-based or autologous breast reconstruction in one of both centers between January 2015 and December 2018 were included. The following exclusion criteria were used in selecting subjects for this study: bilateral reconstruction with implant reconstruction on one side and autologous reconstruction on the other side or a mixed timing, total breast reconstruction with fat grafting, currently no breast reconstruction after previously failed reconstruction, or currently distant metastases. Informed consent was obtained from all participants. The study was approved by the local Ethical Committee of both participating centers (METC2020-2232; METCZ20200113). The manuscript was written according to the STROBE guidelines.[19]

Data collection

Women were invited by means of a mail or an email containing a URL which led to the online survey (Qualtrics, Provo, UT, USA), as well as contact information to request a paper version of the questionnaire. A one-time reminder was sent to non-responders after three weeks. Demographic information, medical history, surgical and reconstructive treatment, patient-reported health complaints, and patient-reported outcomes on HRQoL were obtained from the questionnaire. More detailed medical information, such as tumor staging, was obtained from medical records.

The presence of health complaints was assessed by means of a study-specific question. Participants were asked to indicate to what extent they suffered from 11 common systemic complaints that have been suggested to be related to breast implant illness on a Likert scale from 0 (never) to 5 (always). Scores greater than 2 (more than rarely) were considered relevant for determining prevalence. The 36-Item Short Form (SF-36) was used to assess HRQoL. This validated questionnaire consists of eight scales: physical functioning, role physical, role emotional, vitality, mental health, social functioning, bodily pain, and general health.

Statistical analysis

Statistical analyses were performed in IBM SPSS Statistics version 25. Baseline demographics of women who underwent implant reconstruction versus autologous reconstruction were analyzed as follows. Continuous variables were presented as mean and standard deviation (SD) and the independent samples t-test was used to compare patient characteristics between reconstruction types. Categorical variables were presented as count and percentage (%) and compared using Pearson's chi-square test or Fisher's Exact test. Ordinal data (i.e. tumor stage and symptom severity) was compared using the Mann-Whitney U test. Tertiary (autologous salvage) breast reconstruction (TBR) was considered a separated group in the analyses.

SF-36 outcomes were transformed into scores from 0-100 with higher scores meaning better HRQoL. Mean differences in SF-scores were adjusted for potential confounders by means of multivariable linear regression analysis. Independent variables in the regression model were selected a priori (i.e. chemotherapy) and by applying backward stepwise model selection based on Wald-tests (i.e. BMI, smoking, tumor classification (N stage), radiotherapy, hormone therapy, reconstruction timing, follow-up duration after reconstruction and reconstruction type).

Multivariable logistic regression was performed to compute differences in symptom prevalence adjusted for potential confounding variables, and to identify independent predictors of health complaints after implant or autologous reconstruction. Variables in this model were selected a priori on the basis of an expected association with systemic complaints (i.e. age, BMI, smoking, allergies, chronic disease, chemotherapy, radiotherapy, hormone therapy, immunotherapy, reconstruction type).

P values less than 0.05 were considered statistically significant.

Results

Patient selection and demographics

During the study period, 913 women had undergone postmastectomy breast reconstruction, of which 887 women were still alive at the time of the survey. Of these, 444 women (50.1%) responded and agreed to participate (Figure 1). Based on the eligibility criteria, 61 responders were excluded from participation, as were

54 responders who returned the questionnaire empty or nearly empty. Participants who had left three or more domains of the SF-36 blank were omitted from the analysis. This left 329 reconstruction patients eligible for the analysis: 103 underwent implant reconstruction (31%), 202 underwent autologous reconstruction (61%), and 24 underwent tertiary autologous breast reconstruction after failed implant reconstruction (7%). The mean follow-up duration after reconstruction was 46.6 ± 15.1 months.

Participants had a mean age of 55.5 ± 9.9 years and a mean BMI of 25.7 ± 4.1. Women with autologous reconstruction were on average slightly, but not significantly, younger (p = 0.233) and had a higher BMI (p<0.001) than women with implant reconstruction and were significantly more often non-smokers (p<0.001). They had on average a higher lymph node stage (N) at time of diagnosis and underwent significantly more often radiotherapy (p<0.001) and hormone therapy (p=0.040). Baseline demographics of IBBR and ABR patients are presented in Table 1.

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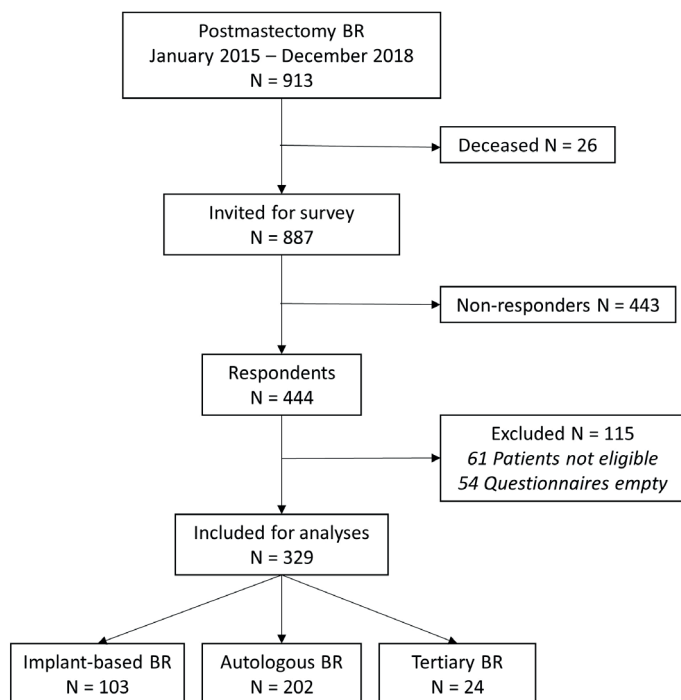
Figure 1. Flowchart of the patient selection.

Complications

Women with autologous breast reconstruction reported having slightly more complications during their reconstruction process than women with implant reconstruction (37% vs. 30%; p=0.223). Complications following implant reconstruction more often led to reoperation compared to autologous reconstruction (Table 1).

Tertiary autologous breast reconstruction

Twenty-four women underwent tertiary autologous breast reconstruction after failed implant-based breast reconstruction. Their mean age was 55.7 ± 8.6 year and mean BMI was 25.8 ± 3.9. The mean follow-up after tertiary breast reconstruction was 41.2 months. The majority of the cases involved bilateral reconstruction. Two patients were smokers, 11 reported having allergies, and six reported having chronic diseases. Nine patients underwent chemotherapy, eight radiotherapy, ten hormone therapy, and one immunotherapy. A total of seven reasons for implant reconstruction failure were reported, mostly in combinations: capsular contracture (24%), pain (24%), aesthetically disappointing outcome (17%), physical complaints/breast implant illness (12%), infection (9%), implant rupture (9%), and implant extrusion (3%).

Self-reported systemic health complaints

Systemic health complaints were reported by women with IBBR, ABR, and TBR. The most common complaint per group was fatigue (61, 61, and 71%, respectively). Pyrexia was the least common complaint in all groups and occurred more than rarely in one ABR patient and two TBR patients (Figure 2). After adjusting for potential confounders, no statistically significant differences in symptom prevalence were found between IBR and ABR, nor between ABR and TBR. The severity of almost all symptoms ranged from 1 (never) to 5 (always) in all groups and was distributed equally across all groups, with the exception of skin problems (ABR-TBR: p=0.025). The mode and quartiles (Q1 and Q3) of symptom severity are presented in Table 2.
Multivariable logistic regression analysis yielded several independent predictors for the development of particular systemic complaints after breast reconstruction. These are presented in Table 3.

Health related Quality of Life

Patient-reported health status outcomes of women with IBBR and ABR were compared. Women with implant reconstruction scored slightly higher on average in all domains of the SF-36, with the exception of bodily pain (p=0.771). Vitality was significantly lower in women with ABR (p=0.048). Adjusted for potential confounders, no statistically significant differences between the mean SF-36 scores of women with IBBR and women with ABR were found (Table 4). Mean SF-36 scores of women with TBR were compare to the mean outcomes of women with ABR. TBR patients reported on average higher scores on physical functioning, physical role, emotional role, and vitality, while ABR scored better on mental health, social functioning, bodily pain, and general health. None of these mean differences were statistically significant (Table 5).
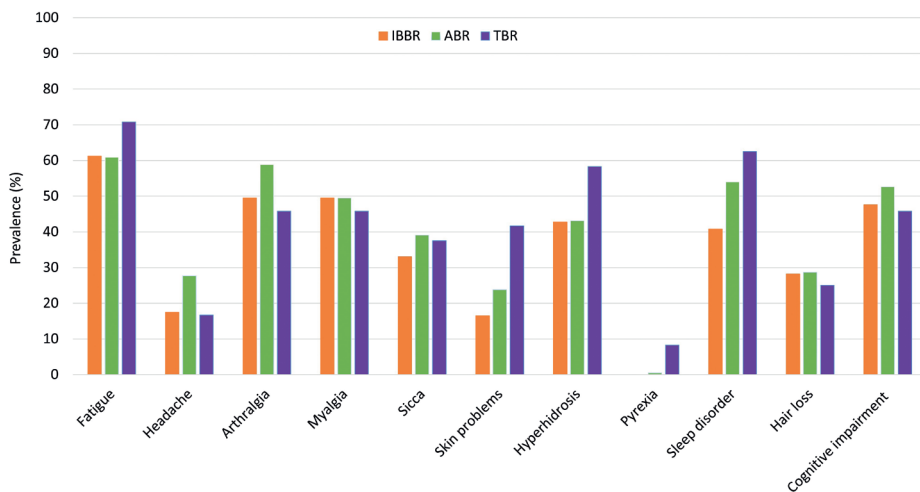
Figure 2. Prevalence of self-reported health complaints in IBBR, ABR, and TBR patients. The prevalence of systemic complaints was expressed as the percentage of patients who reported a score >2 (more than rarely).

Table 3. Independent predictors of health complaints after breast reconstruction.

Symptom	Predictor(s)
Fatigue	Age, BMI, chemotherapy, immunotherapy
Headache	Chronic disease
Arthralgia	Chronic disease, hormone therapy
Myalgia	BMI, chronic disease
Sicca	Age, allergies, chronic disease, chemotherapy
Skin problems	BMI
Hyperhidrosis/night	Allergies
Sweats	
Pyrexia	–
Sleep disorder	–
Hair loss	Age, chemotherapy
Cognitive impairment	Chemotherapy

Variables included in the multivariable logistic regression analysis: age, BMI, smoking, allergies, chronic disease, chemotherapy, radiotherapy, hormone therapy, immunotherapy, reconstruction type.

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Table 4. Unadjusted and adjusted differences in SF-36 domain scores between IBBR and ABR patients.

Symptom	IBBR n=103	ABR n=202	Unadjusted difference (95% CI)	P value	Adjusted difference (95% CI)	P value
Physical functioning	81.2 ± 20.7	80.9 ± 19.4	-0.2 (-4.9-4.5)	0.935	0.3 (-6.2-6.7)	0.926
Role physical	73.9 ± 39.1	72.5 ± 38.7	-1.3 (-10.6-7.9)	0.776	-0.7 (-14.4-12.9)	0.916
Role emotional	88.2 ± 27.7	81.5 ± 35.2	-6.7 (-14.5-1.2)	0.095	-8.8 (-20.5-2.9)	0.139
Vitality	65.4 ± 19.1	60.6 ± 20.3	-4.8 (-9.5-0.0)	0.048	-4.2 (-10.7-2.3)	0.204
Mental health	76.0 ± 16.2	76.1 ± 15.7	-0.1 (-3.-3.9)	0.979	0.7 (-4.4-5.8)	0.794
Social functioning	83.1 ± 20.5	79.8 ± 22.5	-3.4 (-8.6-1.8)	0.204	-3.8 (-11.2-3.6)	0.310
Bodily pain	72.6 ± 23.1	73.4 ± 22.7	0.8 (-4.6-6.2)	0.771	0.9 (-6.9-8.8)	0.813
General health	68.1 ± 19.6	67.0 ± 22.2	-1.1 (-6.2-4.0)	0.671	-1.3 (-8.2-5.6)	0.717

Independent variables computed in this model: BMI, smoking, tumor classification (N stage), chemotherapy, radiotherapy, hormone therapy, reconstruction type, reconstruction timing, follow-up duration after reconstruction.

Table 5. Unadjusted and adjusted differences in SF-36 domain scores between ABR and TBR patients.

Dependent variable	ABR (n=205)	TBR (n=24)	Unadjusted difference (95% CI)	P value	Adjusted difference (95% CI)	P value
Physical functioning	81.0 ± 19.4	82.0 ± 22.0	1.0 (-7.4-9.4)	0.809	5.0 (-5.5-15.5)	0.349
Role physical	72.5 ± 38.7	77.1 ± 35.3	4.6 (-11.8-20.9)	0.583	10.6 (-11.7-32.8)	0.350
Role emotional	81.5 ± 35.2	87.5 ± 30.8	6.0 (-8.8-20.8)	0.426	6.3 (-14.2-26.6)	0.546
Vitality	60.6 ± 20.3	61.7 ± 14.1	1.1 (-7.3-9.5)	0.800	3.4 (-7.3-14.2)	0.527
Mental health	76.1 ± 15.7	72.3 ± 10.9	-3.8 (-10.3-2.7)	0.255	-4.2 (-12.6-4.1)	0.319
Social functioning	79.8 ± 22.5	76.6 ± 25.6	-3.2 (-12.9-6.5)	0.517	-4.7 (-17.6-8.2)	0.474
Bodily pain	73.4 ± 22.7	69.2 ± 23.7	-4.2 (-13.9-5.5)	0.392	-0.6 (-12.9-11.7)	0.918
General health	67.0 ± 22.2	63.5 ± 18.9	-3.5 (-12.8-5.9)	0.466	-4.2 (-15.8-7.5)	0.480

Independent variables computed in this model: BMI, smoking, tumor classification (N stage), chemotherapy, radiotherapy, hormone therapy, failed implant reconstruction, follow-up duration after reconstruction.

Discussion

In this study, patient-reported systemic symptoms and HRQoL in women who underwent implant-based reconstruction were compared to women who underwent autologous breast reconstruction to assess whether women are at risk of developing breast implant illness following implant reconstruction.

We found that both women with IBBR and ABR reported systemic complaints, more than half of the women experienced fatigue more than rarely. Arthralgia, myalgia and sleeping problems were also common in about half of the women. These figures are roughly consistent with our previous findings in women with breast implants.[20] No significant difference in prevalence between the two reconstruction methods could be demonstrated with this present study. Previous studies comparing symptoms in women with cosmetic augmentation to women with breast reduction were unable to identify distinctive group symptoms as well.[21,22] To our knowledge, this is the first study to compare systemic health complaints following implant-based and autologous breast reconstruction.

HRQoL measured with the SF-36 was not significantly different between women two years after implant and autologous reconstruction. This matches previous findings in the literature regarding the health status following different reconstruction methods.[23,24] While autologous breast reconstruction has been repeatedly shown to result in a better breast-related QoL and outcome satisfaction compared to implant reconstruction, this does not automatically mean that it yields better overall health outcomes.[7,8,25] The higher complication rate after autologous reconstruction may adversely affect patient-reported outcomes in terms of HRQoL. Nevertheless, implant reconstruction has a higher rate of reconstruction failure.[26,27]

In this study, we found several local (e.g. capsular contraction and pain) and systemic (e.g. systemic health complaints) causes of implant reconstruction failure reported by women with tertiary breast reconstruction. We previously showed that about half of the symptomatic women with breast implants experienced an improvement in their systemic symptoms after explanting the implants.[28,29] Tertiary (salvage) autologous breast reconstruction is considered a good alternative to failed implant reconstruction.[30-33] The women with the most severe physical complaints may have had their implants removed and opted for a different reconstruction method. Therefore, we included tertiary reconstruction in our analysis to reduce the chance of bias. However, this subgroup did not report significantly more complaints or a lower QoL than other women with autologous breast reconstruction, suggesting that complaints are not more common within this subgroup or that complaints have improved after tertiary reconstruction.

Although many studies have investigated the association between SBI and systemic disease, a causal relationship could not be established.[18,34] Selection bias continues to distort study results as recruitment of subjects is aimed at symptomatic patients.[16,20] In addition, there is a high risk of confounding when investigating systemic complaints. Both women who underwent breast augmentation and women who underwent breast reconstruction differ from the general population, in either patient characteristics and medical history.[35] Factors, such as age and fibromyalgia, may be involved in the development of complaints.[20] In reconstructive cases, we found that age, BMI, and chemotherapy, in particular, were independent predictors of common systemic symptoms, but that the type of reconstruction was not. Given the well-established long-term side effects of cancer treatments, this was not an unexpected outcome.[36-38]

We are aware that this study may have certain limitations. The study design causes a lack of preoperative data on physical complaints and QoL. Baseline data may positively or negatively affect postoperative outcomes and is therefore an important variable in interpreting long-term patient-reported outcomes. In this study, we used a generic questionnaire, the SF-36, to determine HRQoL. Although surgery-specific questionnaires, such as the BREAST-Q, are increasingly being used, we found it important for this study to assess the health status in general. Therefore, we considered health-related QoL separately from breast-related QoL. Research into implant-related disease and systemic complaints is often at high risk of both selection and recall bias. We cannot rule out that the included participants are not an unbiased representation of the patient population. Women who are willing to participate in research may be exceptionally satisfied or dissatisfied with the surgery results and the outcomes of this study can therefore be an over- or underestimation of reality.

Conclusion

Systemic complaints are common in women who underwent breast reconstruction and may be a result of aging, BMI, and cancer treatment. Long-term HRQoL outcomes in women who underwent implant reconstruction are comparable to those who underwent autologous breast reconstruction. Based on this study, there are no indications that women undergoing implant-based breast reconstruction have an increased risk of developing systemic complaints compared to women undergoing autologous breast reconstruction.

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SHORT COMMUNICATION

Introduction

Breast reconstruction rates have increased over the past years. It helps restore body image and improve Quality of Life (QoL).[1] However, there are concerns about the potential association between silicone breast implants and systemic symptoms.[2] Literature on breast implant illness (BII) among reconstructive patients is scarce, while it is essential for these women to know whether any health risks are associated with each reconstructive method. Therefore, the aim of our study was to compare systemic symptoms and health-related QoL of IBBR patients with autologous breast reconstruction (ABR) patients, to assess whether there is an association between the type of breast reconstruction and health complaints.

Patients and methods

We performed a multicenter, cross-sectional study in Maastricht University Medical Center and Zuyderland Medical Center in November and December 2020. Women who underwent IBBR or ABR between 2015 and 2018 were invited to an online questionnaire (paper version available), containing items on demographics, medical/surgical history, health complaints, and health-related QoL (SF-36). More detailed medical information, e.g. tumor staging, was obtained from medical records. IBBR involved two-stage reconstruction with subpectoral placement of a tissue expander followed by the definitive prosthesis. ABR included free flap reconstruction, e.g. DIEP flap or LTP flap. Full reconstruction by autologous fat transfer was excluded. Mean differences in SF36-scores were adjusted for potential confounders with multivariable linear regression analysis. Multivariable logistic regression was performed to compute differences in symptom prevalence adjusted for potential confounding variables, and to identify independent predictors of health complaints.

Results

Fifty percent of the 887 women alive responded, but after excluding non-eligible patients or inadequate responses we were able to analyze 329 responses (103 IBBR; 202 ABR; 24 tertiary ABR). The mean follow-up duration after reconstruction was 46.6±15.1 months. Participants had a mean age of 55.5±9.9 years and a mean BMI of 25.7±4.1. Women after ABR had a higher BMI (p<0.001) than women after IBBR and were more often non-smokers (p<0.001). They were found to have a relatively higher lymph node (N) stage (p=0.001) and underwent more often radiotherapy (p<0.001), hormone therapy (p=0.040), and delayed reconstruction (p<0.001). The complication rate was similar between IBBR and ABR (Table 1).

Twenty-four women underwent tertiary autologous breast reconstruction (TBR) after failed IBBR for the following reasons: capsular contracture (24%), pain (24%), aesthetically disappointing outcome (17%), physical complaints/BII (12%), infection (9%), implant rupture (9%), and implant extrusion (3%). Systemic health complaints occurred equally following IBBR, ABR, and TBR. The most common complaint per group was fatigue (61, 61, and 71%, respectively). No significant differences in adjusted symptom prevalence were found between IBR and ABR, nor between ABR and TBR (Figure 1*). The severity of almost all symptoms ranged from 1 (never) to 5 (always) in all groups and was distributed equally across all groups, with the exception of skin problems (Table 2). Logistic regression showed that, in particular, age, BMI and chemotherapy were independent pre-

dictors of common systemic symptoms, but the type of reconstruction was not (Table 3). Adjusted for possible confounders, no significant differences in mean SF-36 scores were found between IBBR and ABR, nor between ABR and TBR.

Discussion

This study showed no significant difference in the prevalence of self-reported health complaints, nor in health-related QoL in women 2-5 years after IBBR or (tertiary) ABR.

While ABR has been repeatedly shown to result in better breast-related QoL compared to IBBR, it does not automatically result in superior physical outcomes.[1] ABR requires more extensive surgery and is associated with higher complication rates. Yet, IBBR has a higher rate of reconstruction failure.[3] In addition, BII is increasingly an indication for explantation which may lead to improvement of complaints in about 75% of the cases.[4] Selection bias and confounding factors, however, distort the results in research into BII. Age, menopause and fibromyalgia, among others, may play a role in the development of complaints.[2] In reconstructive cases, the side-effects of cancer treatment might be confused with implant-related complaints. ABR is considered a good alternative to failed implant reconstruction.[5] Therefore, we included tertiary ABR in the analyses, as these may be the cases with the most severe physical complaints. Nevertheless, our results suggest that either complaints within this subgroup are not more frequent or that they improve after tertiary reconstruction.

We are aware that our study was limited by the cross-sectional design, the limited number of patients included and the potential selection bias that occurred. More confounding variables may be involved, which we did not control for. Participants may have been exceptionally satisfied or dissatisfied with their result and therefore the outcomes of this study should be appraised carefully.

Conclusion

Long-term health-related QoL after IBBR and after ABR is similar. In this study, no association was found between IBBR and an increased risk of systemic complaints. However, known predictors of physical symptoms in breast cancer survivors play a role in both groups.

Figure 1 in short communication correlates with figure 2 in manuscript.
Tables 1,2, and 3 of short communication correlate with tables 1,2, and 3 in manuscript.

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CHAPTER 8

Breast-related and body-related quality of life
following autologous breast reconstruction
is superior to implant-based breast
reconstruction - A long-term follow-up study

ABSTRACT

Introduction

The better survival rates after breast cancer allow for setting of long-term goals, such as Quality of Life (QoL) and aesthetic outcomes following breast reconstruction. Studies find a higher breast-related QoL and greater satisfaction with breasts following autologous breast reconstruction (ABR) compared to implant-based breast reconstruction (IBR). However, aesthetic results from donor sites can influence body image. This concern is little addressed in the literature. Therefore, the aim of this study was to compare the long-term breast-related and body-related QoL of women who underwent ABR to women who underwent IBR.

Material and methods

A multicenter, cross-sectional survey was conducted between November and December 2020 among women who underwent postmastectomy breast reconstruction between January 2015 and December 2018. A general questionnaire, the BREAST-Q, and the BODY-Q were used to collect data. Multivariable linear regression was performed to adjust differences in Q-scores for potential confounders.

Results

In total, 336 patients were included (112 IBR, 224 ABR). Autologous reconstruction resulted in significantly higher mean scores in all subdomains of the BREAST-Q. On the BODY-Q, IBR scored significantly higher on scars, while ABR scored moderately to significantly higher on all other scales. Despite a lower mean score on Hips & outer thighs in women with Lateral Thigh Perforator (LTP) flap reconstruction, no negative influence on body image was found in these women.

Conclusions

Long-term breast-related and body-related outcomes of ABR are superior to IBR. Donor site aesthetic does not adversely affect body image in women who underwent free flap breast reconstruction.

Introduction

In the Netherlands, one in seven women develops breast cancer during lifetime[1,2]. It is the most common cancer in women. The five-year survival rate continues to rise as a result of improved early detection and treatment.[1] This allows for setting of long-term goals, such as improving Quality of Life (QoL) and aesthetic outcomes.[3] As a result, breast reconstruction has become increasingly important in the therapeutic course after breast cancer. Furthermore, breast reconstruction can contribute to the restoration of QoL and body image in women undergoing prophylactic mastectomy because of familial risk of breast cancer.[4,5]

The two main options for post-mastectomy breast reconstruction are implant-based breast reconstruction (IBR) and autologous breast reconstruction (ABR).[6] Both types have their advantages and disadvantages.[7] For example, IBR requires a less invasive operation with a shorter recovery time, but ABR can achieve a more natural feeling, even more with the upcoming nerve coaptation for recovery of sensation.[8-10] Autologous breast reconstruction is more cost-effective than implants, especially in women with a longer life expectancy.[11-13]

Studies using patient-reported outcome measures (PROMs) found a higher breast-related QoL and greater satisfaction with breasts following ABR compared to IBR.[14-16] However, donor site morbidity and aesthetic outcomes are major concerns in ABR, which are relatively little addressed in the existing literature.[17-19] In addition to satisfaction with breasts, aesthetic outcomes of donor sites may also play an important role in the subjective perception of the body. The concept of body image is becoming increasingly important in psycho-oncology, as an impaired body image due to breast cancer treatments can have long-term negative effects on psychological well-being and QoL in breast cancer survivors.[20-22] Assessment of body image in a broader sense could therefore be a valuable addition to the commonly used breast-related outcome measures, such as the BREAST-Q.[23,24] Women faced with a choice to undergo breast reconstruction should be adequately informed regarding both breast-related and body-related outcomes.

Little is known in the literature about the long-term (> 2 years) breast-related and donor site-related patient-reported outcomes after ABR; IBR patients and a short follow-up duration often predominate.[16,25] Having completed cancer treatment for a longer period of time may allow women to view their breast reconstruction differently, conceivably more critically than in the short term. Therefore, the aim of this study was to compare the long-term breast-related and body-related QoL of women who have undergone ABR to women who have undergone IBR, reported two to five years after the reconstruction procedure.

Material and methods

Study population

This multicenter, cross-sectional survey was conducted between November and December 2020. Women 18 years or older who underwent a postmastectomy breast reconstruction in either Maastricht University Medical Centre (MUMC+) or Zuyderland Medical Centre between January 2015 and December 2018 were invited to participate. Women who underwent immediate or delayed IBR or ABR were eligible. Exclusion criteria were: bilateral reconstruction with unilateral IBR and contralateral ABR or a mixed timing, tertiary breast reconstruction (after failed reconstruction or unsatisfactory results), breast reconstruction by autologous fat transfer (AFT), currently no breast

reconstruction after previously failed reconstruction, or currently distant metastases. All participants signed an online informed consent form. The study was approved by the Medical Ethics Committees of Maastricht University Medical Center (METC2020-2232) and Zuyderland MC (MET-CZ20200113).

Data collection

Patients were invited to participate in this study by means of an invitation letter by (e-)mail, including a personal link to the online questionnaire (Qualtrics, Provo, UT, USA). They were requested to complete the questionnaire within four weeks if they wanted to participate. A reminder was sent after 3 weeks to those who did not respond. A paper version was available on request.

Questionnaires

The online survey consisted of items on patient demographics, medical history, breast reconstruction, and the following patient-reported outcome measures (PROMs). The BREAST-Q Version 1.0 (Dutch), Reconstruction module (postoperative scales), was used to assess breast-related satisfaction and QoL. This validated questionnaire consists of six domains: satisfaction with breasts, psychosocial well-being, sexual well-being, physical well-being chest, physical well-being abdomen and satisfaction with outcome. The BODY-Q was used to measure satisfaction with the appearance of specific body parts that can be donor sites in ABR. The following scales of the BODY-Q were analyzed: abdomen, body, buttocks, hips & outer thighs, scars, and body image.
Additional medical information, such as tumor staging, was obtained from the electronic medical records.

Statistical analysis

Baseline demographics were analyzed with descriptive statistics. Continuous variables were reported as mean values, standard deviation (SD), and range, and were compared between IBR and ABR using the independent-samples t-test, categorical variables were reported as counts (%) and were compared using Pearson's chi square test. The Mann-Whitney U test was used to compare ordinal data. BREAST-Q and BODY-Q scores were transformed using the Q-score software into scores from 0-100 with 0 meaning 'worst' and 100 meaning 'best'.

Multivariable linear regression analysis was performed to adjust differences between IBR and ABR on Q-scores for confounding variables. For BREAST-Q results, we selected confounding variables a priori (i.e., age and pTx stage) and using backward stepwise elimination based on the Wald test (i.e., educational level, smoking, BMI, cup size, Nx staging, radiotherapy, hormone therapy, reconstruction timing, and follow-up duration). Next, we added an interaction between reconstruction type and timing to the model. In case of a significant interaction, indicating that the difference between IBR and ABR differed between immediate and delayed reconstructions, the model was subsequently analyzed stratified by reconstruction timing (immediate and delayed). For BODY-Q results, a priori selected confounders (age, BMI, smoking, reconstruction type, follow-up duration after reconstruction) were used to adjust between-group differences. The regression analysis was repeated for specific flap procedures in order to further analyze the influence of the donor site appearance on the body-related quality of life.

A p value ≤ 0.05 was considered statistically significant. All analyses were performed in IBM SPSS Statistics 25.

Results

Patient demographics and clinical characteristics

Between January 2015 and December 2018, 913 women underwent postmastectomy breast re-construction. Of those women, 26 deceased. The survey yielded a response rate of 50.1% (444 of 887 patients). Eighty-five respondents were excluded based on the eligibility criteria, and 23 questionnaires were returned blank or mostly empty. In total, 336 patients were eligible for analysis, of which 224 women underwent autologous breast reconstruction (66.7%) and 112 women underwent two-staged IBR (33.3%). Of the 224 ABR patients, 191 (85.3%) underwent deep inferior epigastric perforator (DIEP) flap reconstruction, 30 (13.4%) underwent lateral thigh perforator (LTP) flap reconstruction, two women underwent both a DIEP reconstruction on one side and an LTP reconstruction on the other (0.9%), and one woman (0.4%) underwent a stacked hemi-abdominal extended perforator (SHAEP) flap reconstruction (Figure 1).

The mean age of all included women was 55.5 years (SD 9.8, range 28-82) and mean BMI was 25.7 (SD 4.2, range 18.2-43.9). The mean follow-up after breast reconstruction was 46.7 months (SD 14.8, range 23-76). Patient characteristics per reconstruction type are presented in Table 1. On average, women with ABR had a higher BMI, a larger bra cup size, were less likely to be active smokers, and had a higher educational level compared to women with IBR. Women with IBR had on average a lower lymph node staging (N stage) at diagnosis, underwent radiotherapy relatively less often but more often hormone therapy. Implant-based reconstruction was performed relatively more often immediately than delayed, compared to autologous breast reconstruction.

Breast-related Quality of Life

Unadjusted and adjusted mean BREAST-Q scores for both IBR and ABR patients are presented in Table 2. Women who underwent ABR reported higher satisfaction with breast and outcome, as well as higher physical, psychosocial, and sexual well-being, compared to IBR patients. However, the subdomains psychosocial well-being (unadjusted between-group difference: 4.4, p=0.068) and sexual well-being (unadjusted between-group difference: 5.0, p=0.078) were not statistically significant. Adjusted for potential confounders, linear regression showed significantly higher mean scores in all subdomains of the BREAST-Q in ABR patients.

When an interaction between reconstruction type and timing was added as an independent variable to the regression model for breast-related QoL scores, the interaction effect was significant. Therefore, the regression analyses were stratified by immediate and delayed reconstruction (Table 3). Stratification of the breast-related outcomes showed that the effect of the reconstruction type on satisfaction with breast was greater in patients that underwent delayed reconstruction. In immediate breast reconstruction, however, the effect of the reconstruction type on satisfaction with outcome was greater.

Body-related Quality of Life

Compared to IBR patients, ABR patients scored a higher mean outcome on the BODY-Q scales Abdomen and Buttocks, but scored lower on Hips & outer thighs, Body, and Scars. The latter showed a significant difference in favor of IBR patients (unadjusted between-group difference: 6.5, p=0.008). On Body image, both groups scored nearly the same mean score (mean difference: 0.2, p=0.950). Multivariable regression analysis showed statistically significant mean differences on

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Abdomen in favor of the ABR patients and on Scars in favor of the IBR patients. The adjusted mean difference on Body image, however, did not reach statistical significance (mean difference: 2.3, p=0.469). The outcomes of the regression analyses for BODY-Q scores are presented in Table 4.
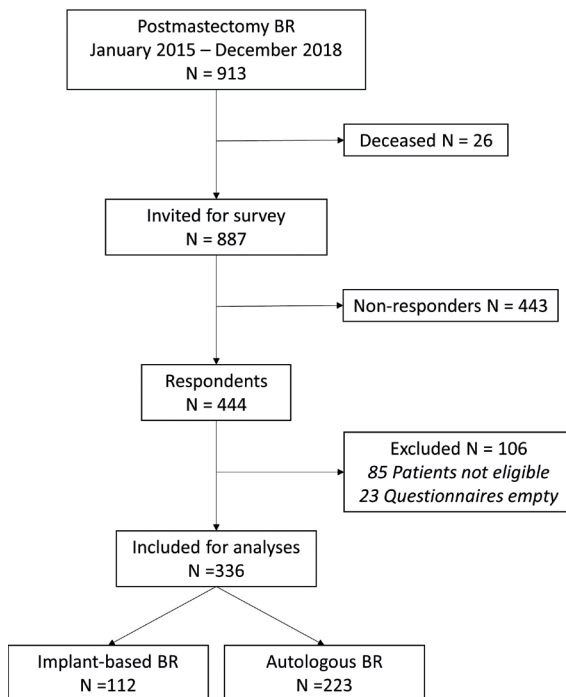
Figure 1. Flowchart of patient inclusion.

Influence of specific donor site appearance

Women who underwent DIEP flap reconstruction (n=191) had a mean age of 55.9 years (SD 8.5, range 33-78) and a mean BMI of 26.7 (SD 4.2, range 18.7-43.9). They scored on average 6.7 points higher on Abdomen (p=0.053) and 6.4 points lower on Scars (p=0.012) of the BODY-Q, compared to IBR patients. Mean scores on Body and Body image were nearly equal in both groups (mean difference: 0.3, p=0.919). Adjusted for potential confounders, DIEP flap patients scored significantly higher on both Abdomen (p=<0.001) and Body (p=0.028), and significantly lower on Scars (p=0.043) compared with IBR patients.

Women who underwent LTP flap reconstruction (n =30) had a mean age of 49.9 years (SD 9.9, range 30-70) and a mean BMI of 24.2 (SD 3.4, range 19.6-34.7). On average, they reported a significantly lower outcome on Hips & outer thighs (mean difference: -20.4, p<0.001) compared to IBR patients. Also on all other BODY-Q scales, LTP patients scored a lower mean outcome, although these differences were not statistically significant. Adjusted for potential confounders, mean scores of Hips & outer thighs (p<0.001) and Scars (p=0.037) were significantly lower in LTP patients compared to IBR patients, other scales did not differ significantly. Outcomes of the univariable and multivariable regression analyses for BODY-Q scores of DIEP and LTP patients are presented in Table 5.

Table 1. Patient characteristics by reconstruction type.

Characteristic	IBR (n = 112)	ABR (n = 224)	P value
Age (mean ± SD)	56.4 ± 11.3	55.0 ± 8.9	0.256
Body Mass Index (mean ± SD)	24.2 ± 3.9	26.3 ± 4.2	<0.001
Breast cup size preoperatively (n, %)			<0.001
AA	2 (1.8)	0 (0)	
A	12 (10.7	9 (4)	
B	49 (43.8)	61 (27.2)	
C	16 (14.3)	64 (28.6)	
D	20 (17.9)	55 (24.6)	
E	11 (9.8)	24 (10.7)	
>E	2 (1.8)	10 (4.5)	
Smoking (n, %)			<0.001
Yes	21 (18.8)	10 (4.5)	
No	91 (81.3)	214 (95.5)	
Allergies (n, %)			0.146
Yes	28 (25.0)	73 (32.6)	
No	84 (75.0)	150 (67.0)	
Chronic disease, self-reported (n, %)			0.569
Yes	24 (21.4)	54 (24.1)	
No	88 (78.6)	169 (75.4)	
Relationship (n, %)			0.775
Yes	88 (78.6)	179 (79.9)	
No	24 (21.4)	45 (20.1)	
Children (n, %)			0.190
Yes	95 (84.8)	201 (89.7)	
No	17 (15.2)	23 (10.3)	
Educational level			0.001
1 – No education	0 (0)	0 (0)	
2 – Elementary education	5 (4.5)	1 (0.4)	
3 – Secondary education	24 (21.4)	25 (11.2)	
4 – Middle-level vocational education/	43 (38.4)	95 (42.4)	
5 – Higher-level vocational education/ college/university	36 (32.1)	77 (34.4)	
6 - Academic/doctoral degree	3 (2.7)	25 (11.2)	
Reconstruction timing (n, %)			<0.001
Primary	88 (78.6)	121 (54.0)	
Secondary	24 (21.4)	103 (46.0)	
Laterality (n, %)			0.938
Unilateral BR	62 (55.4)	125 (55.8)	
Bilateral BR	50 (44.6)	99 (44.2)	

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Table 1. Continued.

Characteristic	IBR (n = 112)	ABR (n = 224)	P value
Complications (n, %)			0.173
Yes	32 (28.6)	82 (36.6)	
No	78 (69.6)	142 (63.4)	
Follow-up duration after reconstruction in months (mean ±SD)	51.5 ± 14.3	44.3 ± 14.6	<0.001
Mastectomy indication			0.790
Invasive carcinoma	82 (73.2)	170 (75.9)	
In situ carcinoma/non-cancerous pathology	17 (15.2)	28 (12.5)	
Bilateral prophylactic mastectomy	13 (11.6)	26 (11.6)	
Tumor stage at diagnosis[1]			
T			0.822
1	43 (38.4)	82 (36.6)	
2	28 (25.0)	82 (36.6)	
3	5 (4.5)	8 (3.6)	
N			<0.001
0	63 (56.3)	92 (41.1)	
1	12 (10.7)	51 (22.8)	
2	1 (0.9)	8 (3.6)	
3	0 (0)	4 (1.8)	
M			1.000
0	81 (100)	168 (100)	
Bloom & Richardson[1]			0.876
Grade 1	15 (18.3)	26 (15.3)	
Grade 2	35 (42.7)	71 (41.8)	
Grade 3	17 (20.7)	32 (18.8)	
Chemotherapy (%)			0.151
Yes	54 (48.2)	126 (56.3)	
No	58 (51.8)	97 (43.3)	
Radiotherapy (%)			0.001
Yes	20 (17.9)	81 (36.2)	
No	92 (82.1)	142 (63.4)	
Hormone therapy (n, %)			0.040
Yes	40 (35.7)	106 (47.3)	
No	72 (64.3)	117 (52.2)	
Immunotherapy (n, %)			0.643
Yes	14 (12.5)	32 (14.3)	
No	98 (87.5)	191 (85.3)	

[1]Only invasive tumors included

Table 2. Regression model for BREAST-Q scores in IBR vs. ABR patients.

Dependent variable	IBR (n=112)	ABR (n=224)	Unadjusted difference (95% CI)	P value	Adjusted difference (95% CI)	P value
Satisfaction with breast	55.5 ± 18.4	68.3 ± 19.4	12.8 (8.4-17.2)	<0.001	14.7 (8.3-21.0)	<0.001
Satisfaction with outcome	60.0 ± 20.8	70.9 ± 21.6	10.9 (6.0-15.7)	<0.001	14.9 (8.0-21.9)	<0.001
Psychosocial well-being	68.8 ± 21.2	73.2 ± 20.3	4.4 (-0.3-9.1)	0.068	7.6 (1.0-14.2)	0.024
Sexual well-being	52.9 ± 24.6	57.8 ± 22.7	5.0 (-0.6-10.5)	0.078	9.4 (1.6-17.2)	0.019
Physical well-being	64.2 ± 17.6	68.7 ± 17.2	4.5 (0.5-8.4)	0.027	6.2 (0.8-11.7)	0.026

Independent variables computed in this model: age, BMI, cup size preoperatively, smoking, educational level, tumor classification (T stage, N stage), radiotherapy, hormone therapy, reconstruction type, reconstruction timing, follow-up duration after reconstruction.

Table 3. Regression model for BREAST-Q scores, stratified by reconstruction timing.

Dependent variable	Immediate reconstruction (n=209)		Delayed reconstruction (n=127)	
	Unadjusted difference (95% CI)	P value	Adjusted difference (95% CI)	P value
Satisfaction with breast	14.1 (6.7-21.4)	<0.001	19.8 (6.7-32.9)	0.003
Satisfaction with outcome	19.3 (11.7-26.9)	<0.001	10.7 (-4.0-25.4)	0.150
Psychosocial well-being	9.2 (1.7-16.8)	0.017	9.5 (-4.4-23.3)	0.177
Sexual well-being	8.8 (-0.1-17.7)	0.051	11.5 (-5.3-28.4)	0.177
Physical well-being	9.3 (2.8-15.8)	0.005	0.6 (-10.4-11.5)	0.920

Independent variables computed in this model: age, BMI, cup size preoperatively, smoking, educational level, tumor classification (T stage, N stage), radiotherapy, hormone therapy, reconstruction type, reconstruction timing, follow-up duration after reconstruction.

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Table 4. Regression model for BODY-Q scores in IBR vs. ABR patients.

Dependent variable	IBR (n=112)	ABR (n=224)	Unadjusted difference (95% CI)	P value	Adjusted difference (95% CI)	P value
Abdomen	59.8 ± 28.7	65.9 ± 28.2	6.1 (-0.5-12.8)	0.070	11.4 (4.6-18.1)	0.001
Buttocks	64.7 ± 24.0	65.3 ± 27.1	0.6 (-5.5-6.7)	0.843	3.4 (-3.0-9.9)	0.296
Hips & outer thighs	66.7 ± 25.0	62.5 ± 26.6	-4.3 (-10.3-1.8)	0.169	0.4 (-6.0-6.7)	0.912
Body	62.0 ± 20.9	60.9 ± 23.7	-1,1 (-6.5-4.2)	0.676	4.6 (-0.4-9.7)	0.086
Scars	78.8 ± 19.6	72.3 ± 20.8	-6.5 (-11.3—-1.7)	0.008	-6.0 (-11.1—-0.8)	0.023
Body image	61.5 ± 27.2	61.7 ± 26.9	0.2 (-6.0-6.4)	0.950	2.3 (-3.9-8.5)	0.469

Independent variables computed in this model: age, BMI, smoking, reconstruction type, follow-up duration after reconstruction.

Table 5. Regression model for BODY-Q scores in IBR vs. DIEP patients and LTP patients

Dependent variable	IBR (n=112)	DIEP[a] (n=224)	Unadjusted difference (95% CI)	P value	Adjusted difference (95% CI)	P value	LTP[b] (n=30)	Unadjusted difference (95% CI)	P value	Adjusted difference (95% CI)	P value
Abdomen	59.8 ± 28.7	66.5 ± 28.2	6.7 (-0.1-13.5)	0.053	13.9 (6.5-20.5)	<0.001	58.4 ± 28.2	-1.3 (-14.4-11.7)	0.839	-0.3 (-6.0-5.4)	0.921
Buttocks	64.7 ± 24.0	66.0 ± 27.2	1.3 (-4.0-7.6)	0.672	5.1 (-1.6-11.8)	0.139	59.7 ± 27.0	-5.0 (-15.5-5.5)	0.351	-3.6 (-8.8-1.7)	0.184
Hips & outer thighs	66.7 ± 25.0	65.1 ± 26.1	-1.6 (-7.8-4.5)	0.603	5.1 (-1.3-11.5)	0.119	46.3 ± 24.5	-20.4 (-30.6—10.3)	<0.001	-9.7 (-14.8-4.6)	<0.001
Body	62.0 ± 20.9	61.2 ± 23.9	-0.8 (-6.2-4.7)	0.787	5.9 (0.6-11.2)	0.028	56.3 ± 22.4	-5.6 (-15.1-3.8)	0.239	-2.1 (-6.2-2.1)	0.328
Scars	78.8 ± 19.6	72.4 ± 21.3	-6.4 (-11.4—1.4)	0.012	-5.6 (-11.0—0.2)	0.043	71.0 ± 18.1	-7.9 (-15.8-0.0)	0.051	-4.3 (-8.4—0.3)	0.037
Body image	61.5 ± 27.2	61.8 ± 26.7	0.3 (-6.1-6.7)	0.919	3.0 (-3.5-9.4)	0.366	58.0 ± 28.5	-3.5 (-14.7-7.7)	0.537	-2.2 (-7.5-3.2)	0.419

Independent variables computed in this model: age, BMI, smoking, reconstruction type, follow-up duration after reconstruction.
[a]DIEP Deep Inferior Epigastric Perforator flap, [b]LTP Lateral Thigh Perforator flap.

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Discussion

This study compared the long-term breast-related and body-related QoL of women with autologous breast reconstruction (ABR) to women with implant-based breast reconstruction (IBR), reported two to five years after the reconstruction procedure.

We found that ABR patients reported higher mean long-term outcomes for breast-related QoL when compared with IBR patients. Following ABR, women scored significantly higher satisfaction with breasts, satisfaction with outcome, physical well-being, psychosocial well-being, and sexual well-being than following IBR, after adjusted for potential confounders. These results are consistent with previous findings in the literature and further support the hypothesis that ABR results in a better breast-related QoL, both in the short and long term.[14,15,25]

Literature suggests that the difference between IBR and ABR outcomes increases in the longer term in favor of ABR, partly because of the development of ptosis in the ABR, resulting in a more natural appearance of the breast.[14,26] There are certain drawbacks to IBR, such as the risk of capsular contracture and implant rupture, which will eventually lead to the implants having to be replaced.[27,28] In addition, the negative media attention that breast implants have received in recent years can negatively influence patient-reported outcomes. Worrying statements in journalism, such as in 'The implant files', contribute to unrest among women with breast implants.[29-31] In very few cases, the use of breast implants can lead to breast implant illness.[32-34] Removal of the implants improves health complaints in half of the patients.[35] A tertiary ABR could offer a solution for these women.[36]

The second purpose of this study was to measure the influence of donor sites on body-related QoL. Body image concerns are common among breast cancer survivors, as breast cancer treatments can profoundly affect physical appearance temporarily (e.g. hair loss, weight fluctuation) or permanently (e.g. loss of a breast, lymphedema).[37,38] Protective factors such as a strong romantic relationship or postmenopausal age may explain why some women suffer less from a distorted self-perception than others.[39,40] Different, but not all types of psychosocial interventions on body image outcomes were shown to be effective with varying effect sizes.[41-43] Breast reconstruction aims to mitigate body image distress by restoring the appearance of the breast. Research showed that body image improved significantly after breast reconstruction, regardless of the type of reconstruction.[44,45] However, women who underwent delayed reconstruction after mastectomy showed higher levels of body dissatisfaction.[46] We considered the use of free flaps for breast reconstruction as a potential risk factor for body image distortion due to visible scarring and changes in body shape. Therefore, we used the BODY-Q to measure satisfaction with the appearance of specific body parts that function as donor sites for ABR. Our results show that women who underwent ABR report worse outcomes with regard to Hips & outer thighs, Body, and Scars, compared to women who underwent IBR. Nevertheless, no significant difference in body image was reported between the two groups. Hence, it might be concluded that donor site appearance does not materially affect body image.

A remarkable outcome of this study is the higher satisfaction with the abdomen reported by women who underwent DIEP flap ABR compared to women who underwent IBR. One hypothesis is that DIEP flap harvest in women with a higher BMI on average results in a flatter stomach, as this procedure has close similarities to abdominoplasty.[47,48] Previous research demonstrated equal satisfaction with the aesthetic outcome after these two surgeries.[49]

Contrarily, previous studies showed a deterioration in abdominal well-being among women undergoing ABR as assessed with the BREAST-Q.[14,50] However, while the BREAST-Q mainly concendergoing ABR as assessed with the BREAST-Q.[14,50] However, while the BREAST-Q mainly concentrates on the *functional* donor site morbidity, the BODY-Q focuses more on the *appearance* of the abdomen.[51] Apparently those are two different outcomes.

Whenever the abdomen is not a suitable donor site, the LTP flap can be harvested from the lateral thigh.[52,53] Compared to women who underwent IBR, women who underwent an LTP reconstruction scored moderately to significantly lower on all body-related scales. We found a striking mean score difference on Hips & outer thighs, something not seen in DIEP patients or ABR patients in general. While DIEP flap harvest appears to have a positive effect on donor site appearance and body image, this effect does not appear to apply to thigh flap harvest. Surgical refinements have been implemented over time to reduce donor site deformations, including liposuction and lipofilling. This allows better results, even longer after reconstruction.[52] Nevertheless, Body and Body Image scores after LTP reconstruction suggest that, by the aesthetically satisfying outcomes of the breast, women are overall satisfied with the outcome of the surgery.

This study has certain strengths and limitations. We believe this was the first study to compare body-related patient-reported outcomes of women with different reconstruction types. However, usage of the BODY-Q was originally validated for patients after massive weight loss and post-bariatric surgery. Nevertheless, the scales of this questionnaire concern the appearance of body parts that could serve as donor sites for microsurgical free flaps.[54] The BODY-Q items are easily answered by all women, while the Abdomen scale of the BREAST-Q is only intended for abdominal flaps. The BODY-Q enabled the assessment of other donor sites and included a body image scale, which could be considered a comprehensive outcome.

Using an online questionnaire to collect results may involve participation bias. It cannot be ruled out that women who were more satisfied with their outcome were more likely to participate. Furthermore, women may be excluded because their reconstruction failed. This may have resulted in the omission of the worst outcomes from the analysis. Moreover, we explicitly adjusted for radiotherapy in the multivariable models as we acknowledge this may be a very important confounding factor. Furthermore, the sample size of specific flaps, e.g. the LTP flap, was small, leading to a low statistical power for this subgroup analysis. Body-related outcomes of rarely used flaps could not be determined from this study because of the small sample size. Finally, the cross-sectional study design prevented us from following up the outcomes over time. Baseline QoL is a potential confounder for long-term outcomes, which could not be adjusted for in this study. This should be taken into account when interpreting the results. Furthermore, the effectiveness of breast reconstruction on improving body image after mastectomy cannot be demonstrated with this design. We hypothesize that breast reconstruction reduces body image distress and that, in combination with personalized psychological interventions earlier in breast cancer treatment, it can reduce psychological symptoms in the adaptation to breast cancer.

Our study was conducted in a hospital that provides specialist care in autologous breast reconstruction. Clinical and aesthetic outcomes are closely related to the surgical experience of the plastic surgeon. We are aware that ABR in general or certain flaps, such as the LTP flap, cannot be offered to all patients. Although technical expertise in flap surgery is constantly improving, breast reconstruction remains patient-specific: some types of reconstruction may be better suited to one

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patient than another. When counseling a patient considering breast reconstruction, all reconstructive options and their pros and cons should be discussed. In addition to surgery time, complication risks, and recovery time, this also includes long-term breast-related outcomes and body-related outcomes.

Conclusions

Long-term breast-related and body-related results of ABR are superior to IBR. Aesthetic results of the donor site do not adversely affect body image in women undergoing ABR. Contrarily, women who underwent ABR are significantly more satisfied with the abdomen than women who underwent IBR. While LTP flap harvest affects the appearance of the hips and outer thighs, it does not negatively affect body image. The results of this study contribute to the tailor-made approach to breast reconstruction.

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CHAPTER 9

Patient-reported outcomes following bilateral prophylactic mastectomy and immediate breast reconstruction: comparing implant-based with a utologous breast reconstruction

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ABSTRACT

Background

Since the number of breast cancer genetic gene testing is increasing, more women opt for bilateral prophylactic mastectomy (BPM) followed by breast reconstruction. However, little is known about the differences in Quality of Life (QoL) after various reconstructive surgeries in this population. In this study, the long-term breast-related, body-related, and health-related QoL between immediate implant-based breast reconstruction (IBBR) and autologous breast reconstruction (ABR) were compared, in women who underwent BPM.

Methods

In this cross-sectional study, women who underwent postmastectomy breast reconstruction between January 2015 and December 2018 were invited for an online questionnaire, in which the BREAST-Q, the BODY-Q and the SF-36 were included. Women who underwent BPM and immediate breast reconstruction were included for analysis. Multivariable linear regression analysis was performed to adjust mean differences in patient-reported outcomes between IBBR and ABR for potential confounders.

Results

Of the included women (n=47), 33 underwent ABR and 14 women underwent IBBR following BPM. BREAST-Q scores were in favor of the ABR group before and after adjustment, with statistically significance on Satisfaction with breasts (mean difference 15.8, p=0.019) and Physical well-being (mean difference 13.5, p=0.033). None of the mean differences in BODY-Q and SF-36 scores between groups, before and after adjustment, were statistically significant.

Conclusion

This study suggests there is a higher Satisfaction with breasts and Physical well-being in women who underwent immediate ABR compared to those who underwent immediate IBBR after BPM. However, these data should be interpreted carefully as a result of selection bias and a small sample size.

Introduction

Breast cancer is the most common cancer in women. Five to ten percent of all breast cancer cases are hereditary, with BRCA1 and BRCA2 germline gene mutations being accountable for approximately 30% of these cases.[1, 2] Multigene panel testing is increasingly adopted in individuals with an increased risk of hereditary breast cancer. As a result, the number of detected gene mutations is growing.[3]

There are several risk-reducing options for women with a high risk of breast cancer. They can choose intensive breast surveillance to detect breast cancer at an early stage or they can opt for the prophylactic removal of all breast tissue by undergoing a bilateral prophylactic mastectomy (BPM), which reduces the risk of breast cancer by up to 100%. Both options lead to comparable survival rates at age 65 of 98-100%.[4] While risk-reducing surgery can reduce the fear of cancer, removing healthy breasts is a radical choice with potential surgical complications and altered body image as a result.[5-7] Studies have shown that breast reconstruction can restore body image and Quality of Life (QoL) after mastectomy.[8-11] It has its positive effects on sexual and psychosocial wellbeing. Therefore, a rising number of women opt for breast reconstructive surgery after mastectomy.[12, 13]

In order to facilitate decision-making whether or not to undergo BPM and breast reconstruction, women must be informed about the benefits and drawbacks of the different options. Short-term complication rates as well as long-term QoL outcomes should be an important part of patient counseling. However, little is known about the long-term QoL outcomes in this specific population in terms of physical, psychosocial, and sexual well-being, as well as satisfaction with their choice, satisfaction with breasts, and satisfaction with body image. Studies showed mixed results, were based on small sample sizes, and used non-validated or generic questionnaires.[14] This results in a paucity of high-quality data on long-term QoL in women with a high risk of breast cancer. Therefore, more research using validated patient-reported outcomes measures (PROMs) is required.

The aim of this study was to evaluate long-term breast-related, body-related, and health-related QoL in women who underwent BPM and immediate breast reconstruction, and to compare implant-based breast reconstruction (IBBR) to autologous breast reconstruction (ABR).

Materials & Methods

Patient selection and data collection

Patient demographics, medical history, and patient-reported outcomes of all women who underwent postmastectomy breast reconstruction in either Maastricht University Medical Centre (MUMC+) or Zuyderland Medical Centre between January 2015 and December 2018 were collected through an online survey. Women aged 18 years or older who underwent IBBR or ABR following BPM were included for analysis. Exclusion criteria were unilateral mastectomy, unilateral reconstruction, delayed reconstruction, mixed reconstruction methods, tertiary breast reconstruction after previously failed reconstruction, and currently distant metastases. Women received a personal URL to get access to the online questionnaire (Qualtrics, Provo, UT, USA). A paper version of the questionnaire was available on request. Non-responders received one reminder after three weeks. Medical history, including diagnoses, treatments, and complications, was obtained from the electronic medical record. The manuscript was written according to the STROBE guidelines.[15]

Patient-Reported Outcome Measures

The following postoperative scales of the BREAST-Q reconstruction module (Dutch, version 1.0) were used to measure breast-related QoL: Satisfaction with breasts, Satisfaction with outcome, Psychosocial well-being, Sexual well-being, and Physical well-being. Additionally, a study-specific question about satisfaction with reconstruction with the following three answer options was used: I am satisfied with my breast reconstruction (1), I would choose a different reconstruction method (2), I would no longer opt for breast reconstruction (3).

The BODY-Q was used to assess body image and satisfaction with certain body parts: Body, Abdomen, Buttocks, Hips and Outer Thighs, Scars, and Body Image.

The Short Form 36 (SF-36) was used to measure Health-Related Quality of Life (HRQoL). This PROM consists of eight domains, being Physical functioning, Physical role functioning, Emotional role functioning, Social role functioning, Bodily pain, General mental health, Vitality, and General health perceptions.

Statistical analysis

Patient characteristics were analyzed with descriptive statistics. Q-scores were converted into outcomes from 0 (worst) to 100 (best) with the Q-score software. SF-36 outcomes were transformed into scores from 0-100 with higher scores meaning better HRQoL. Continuous variables were represented as mean and standard deviation (SD). Categorical variables were represented as counts and percentages (%).

The independent-samples t-test was used to compare the mean outcomes of continuous variables, categorical variables were compared using the Pearson's chi-square test or the Fisher's exact test, and ordinal data were compared using the Mann-Whitney U test. Multivariable linear regression was performed to adjust mean differences in patient-reported outcomes between IBBR and ABR for potential confounders. Independent variables were determined a priori, based on literature and professional experience. For the BREAST-Q model, the following variables were selected: age, BMI, smoking, and mastectomy type. For the BODY-Q model, variables selected were age, BMI, smoking, and salpingo-oophorectomy. The outcomes of the SF-36 were adjusted for the following independent variables: age, BMI, active smoker, allergies, chronic illness, mastectomy type, and salpingo-oophorectomy.

A p-value ≤ 0.05 was considered statistically significant. All analyses were performed in IBM SPSS Statistics version 25.

Results

Patient characteristics

Of the 887 living women who underwent breast reconstruction during the study period, 444 responded. Of these, 63 women underwent BPM. Sixteen women did not meet the eligible criteria and were therefore excluded from the analyses. Of the included women (n=47), 33 underwent ABR and 14 women underwent IBBR following BPM (figure 1). The mean age of ABR patients (mean 42.6±8.3) was significantly higher (p=0.002) than IBBR patients (mean 33.0±10.7). Mean BMI was 26.3±4.4 in the ABR group compared to 23.5±4.6 in the IBBR group (p=0.057). Five women under-

went BPM because of a familial increased risk of breast cancer, without a genetic mutation being detected. In one case a CHEK2 mutation was diagnosed. In the remaining cases, a BRCA1 and/or BRCA2 germline gene mutation was the reason for BPM. More than half of the women in the ABR group also underwent salpingo-oophorectomy compared to 21% in the IBBR group (p= 0.052). Median follow-up was 39.0 and 39.5 months in the ABR and IBBR group, respectively (p = 0.630). Patient demographics are presented in Table 1.
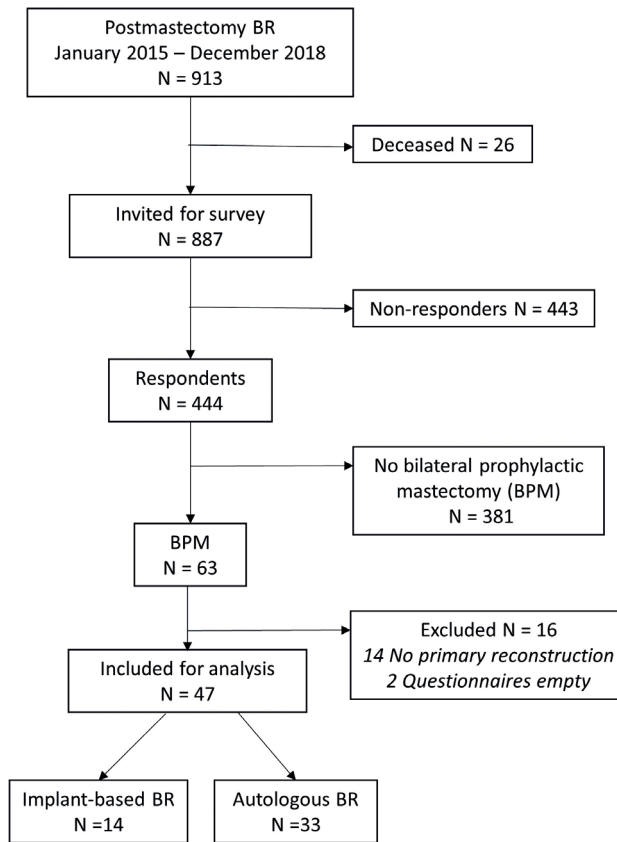
Figure 1. Flowchart of patient inclusion.

Complications

Complications that occurred within 3 months of breast reconstruction are described in Table 2. Minor complications of the breast occurred in nine patients after ABR and three patients after IBBR. Infection was significantly more common after IBBR than after ABR (p = 0.026).

Minor donor site complications occurred in eight ABR cases, with infection being the most common complication (n = 4). Major complications occurred in four IBBR and two ABR cases (p=1.000). Six cases of ABR required an unplanned reoperation, compared to two cases of IBR (p=1.000).

Table 1. Patient characteristics of women who underwent BPM and immediate breast reconstruction.

Characteristics	ABR (n=33)	IBBR (n=14)	P value
Age; mean±SD (range)	42.6±8.3 (25–64)	33.0±10.7 (22–61)	0.002
BMI; mean±SD (range)	26.3±4.4 (19.6–43.8)	23.5±4.6 (18.2–37.0)	0.057
Active smoker, n(%)	1 (3.0)	3 (21.4)	0.073
Allergies, n(%)	15 (45.5)	4 (28.6)	0.343
Genetic mutation, n(%)			0.456
No diagnosed mutation	3 (9.4)	2 (14.3)	
BRCA1	15 (46.9)	5 (35.7)	
BRCA2	13 (40.6)	7 (50.0)	
CHEK2	1 (3.1)	0	
Chronic disease, n(%)	6 (18.2)	1 (7.1)	0.413
Cardiovascular disease	0	0	
Diabetes	0	0	
Lung disease	2 (6.1)	0	
Joint disease	1 (3.0)	0	
Thyroid disease	2 (6.1)	0	
Skin disease	1 (3.0)	0	
Fibromyalgia	1 (3.0)	0	
Irritable bowel syndrome	0	1 (7.1)	
Salpingo-oophorectomy, n(%)	18 (54.5	3 (21.4)	0.052
Education, n(%)			0.631
Secondary school	3 (9.4)	1 (7.1)	
Middle vocational education	13 (40.6)	3 (21.4)	
Higher vocational education	9 (28.1)	9 (64.3)	
Academic/doctoral	7 (21.9)	1 (7.1)	
Employed, n(%)	29 (87.9)	10 (71.4)	0.215
Mastectomy type, n(%)			0.106
Skin-sparing	28 (87.5)	9 (64.3)	
Nipple-sparing	4 (12.5)	5 (35.7)	
Follow-up in months; median (range)	39.0 (11–69)	39.5 (19–71)	0.630

Patient-reported outcomes

BREAST-Q
Women who underwent ABR reported higher scores on all BREAST-Q domains. After adjusting for potential confounders, statistically significantly higher scores were found on Satisfaction with breasts (mean difference 15.8, p=0.019) and Physical well-being (mean difference 13.5, p=0.033) in the ABR group.

BODY-Q
Women who underwent IBBR scored higher on all BODY-Q domains. After adjusting for potential confounders, only the mean scores of Hips and Outer thighs and Scars were higher in IBBR patients. None of these mean differences were statistically significant.

SF-36
 Women in the ABR group reported higher scores in all domains of the SF-36 except for Social Functioning and Mental Health. After adjusting for potential confounders, women in the ABR group scored slightly, but not statistically significant, higher on all SF-36 domains.

Patient satisfaction
When asked whether, in retrospect, women were satisfied with their breast reconstruction choice, 29 of the ABR patients compared to 9 of the IBBR patients answered positively. The remaining women, being four of the ABR patients and five of the IBBR patients, would have chosen another reconstruction method. However, there were no major differences in complications between these groups (p=0.810). In both groups, none of the women would not opt for breast reconstruction again. However, this difference in satisfaction with reconstruction was not statistically significant (p = 0.102). Table 3 provides an overview of all PROMs.

Table 2. Complication rates within 3 months after BPM and immediate reconstruction.

Complication	ABR (n=33)	IBBR (n=14)	P value
Minor complication of the breast	9 (27.3)	3 (21.4)	0.725
Infection	0	3 (21.4)	0.026
Hematoma	2 (6.5)	0	1.000
Seroma	0	0	
Fat necrosis	2 (4.4)	0	1.000
Wound dehiscence	4 (12.9)	0	0.294
Superficial skin necrosis	5 (16.1)	0	0.305
Minor complication of the donor-site	8 (24.2)	-	
Infection	4 (12.9)	-	
Hematoma	0	-	
Seroma	2 (6.5)	-	
Wound dehiscence	2 (6.5)	-	
Superficial skin necrosis	1 (3.2)	-	
Major complication	4 (12.9)	2 (14.3)	1.000
Total flap loss	0	-	
Venous congestion	4 (12.9)	-	
Implant removal	-	2 (14.3)	
Reoperation	6 (18.2)	2 (14.3)	1.000
Venous congestion	4 (12.9)	-	
Infection	0	1 (7.1)	0.311
Hematoma	2 (6.5)	0	1.000
Partial necrosis	1 (3.2)	0	1.000
Implant extrusion	-	1 (7.1)	

Table 3. Patient-reported outcomes following ABR vs. IBBR.

PROM	ABR (n=33)	IBBR (n=14)	Unadjusted mean difference (95% CI)	Unadjusted p-value	Unadjusted mean difference (95% CI)	Unadjusted p-value
BREAST-Q; mean±SD	67.8±14.5	57.3±21.0	10.5(-.3–21.3)	0.056	15.8(2.8–28.8)	0.019
Satisfaction with breasts	67.5±16.4	58.1±16.6	9.3(-1.3–20.0)	0.084	8.1(-.5–20.8)	0.201
Satisfaction with outcome	68.8±18.4	68.8±18.4	6.4(-6.5–19.3)	0.321	7.5(-7.8–22.8)	0.328
Psychological well-being	74.1±15.1	63.6±15.6	10.4(.6–20.3)	0.038	13.5(1.1–25.8)	0.033
Physical well-being	67.8±14.5	57.3±21.0	10.5(-.3–21.3)	0.056	15.8(2.8–28.8)	0.019
Sexual well-being	53.9±19.2	50.4±29.6	3.5(-11.6–18.7)	0.639	5.5(-13.8–24.5)	0.574
BODY-Q; mean±SD						
Body	57.7±20.5	61.7±22.4	-4.0(-17.8–9.8)	0.563	4.1(-12.6–20.7)	0.624
Abdomen	63.2±22.9	63.6±24.7	-.4(-15.8–15.0)	0.959	11.8(-5.4–28.9)	0.173
Buttocks	64.0±24.8	64.1±15.7	-.1(-14.7–14.5)	0.988	5.6(-12.4–23.5)	0.534
Hips and Outer Thighs	54.5±26.4	64.1±22.6	-.1(-14.7–14.5)	0.242	-5.9(-25.8–14.1)	0.556
Scars	67.7±20.2	78.5±20.9	-10.8(-24.1–-2.4)	0.105	-5.5(-21.5–10.5)	0.490
Body Image	55.5±25.4	59.1±22.8	-3.6(-19.5–12.3)	0.105	6.5(-12.2–25.2)	0.490
SF-36; mean±SD						
Physical Functioning	90.3±16.2	88.5±13.4	1.9(-8.5–12.2)	0.717	3.4(-8.6–15.4)	0.566
Role-Physical	87.5±26.9	73.1±37.4	14.4(-5.9–34.8)	0.160	11.7(-14.6–38.0)	0.372
Role-Emotional	88.9±29.5	84.6±29.2	4.3(-15.4–24.0)	0.664	15.7(-8.4–39.9)	0.195
Vitality	63.5±16.1	61.5±18.4	2.0(-9.3–13.2)	0.727	6.9(-7.1–20.9)	0.324
Social Functioning	83.8±22.1	85.6±18.3	-1.8(-15.9–12.3)	0.795	2.2(-15.0–19.4)	0.798
Bodily Pain	82.4±19.5	71.3±24.7	11.8(-3.1–25.3)	0.123	13.7(-2.9–30.4)	0.102
General Health	74.7±21.7	69.6±20.9	5.1(-9.3–19.4)	0.482	7.6(-8.5–23.6)	0.346
Mental Heath	72.5±15.8	72.9±20.1	-4.0(-11.9–11.1)	0.946	5.5(-8.1–19.2)	0.414

Independent variables computed in the model for BREAST-Q: age, BMI, smoking, and mastectomy type; BODY-Q: age, BMI, smoking, and salpingo-oophorectomy; SF-36: age, BMI, smoking, allergies, chronic illness, mastectomy type, and salpingo-oophorectomy.

Discussion

The aim of this study was to evaluate breast-related, body-related, and health-related QoL in women who underwent BPM and immediate breast reconstruction, and to compare IBBR to ABR.

Our study showed that women who underwent ABR reported higher BREAST-Q scores than the IBBR group, with significantly higher satisfaction with breasts and physical well-being. The adjusted mean difference in satisfaction with breasts suggests that several confounders in the model, such as age and BMI, do affect this domain. These findings contrast with those of a descriptive study by Metcalfe et al, which reported no difference in satisfaction between IBBR and ABR among 37 women with BPM and breast reconstruction. However, a study specific questionnaire was used and the results can therefore not compared directly to our results.[16] In a cross-sectional retrospective study by Moberg et al., women after BPM were significantly less satisfied with breast and outcomes after IBBR (n=157) than after ABR (n=18). In addition, the ABR group reported higher scores in all BREAST-Q domains, with the exception of sexual well-being, which is largely consistent with our results.[17] Toyserkani et al. were the first to compare BREAST-Q data between ABR and IBBR in a systematic review and meta-analysis, which included nine studies. They too found higher satisfaction with breasts and better overall outcome in the ABR group, but physical well-being was similar in both groups.[18] The latter contradicts our results, but can be explained by the differences in baseline characteristics, such as prophylactic or curative mastectomy, radiotherapy, unilateral procedures, and reconstruction timing, which may influence breast reconstruction outcomes according to previous studies. We hypothesize that the more natural-feeling and -looking breast, as well as the natural aging of the breast achieved by using the ABR technique, contribute to the better patient-reported outcomes.[19]

The lower BODY-Q scores reported by women who underwent ABR may be explained by the additional scarring resulting from flap harvesting, e.g. from the abdomen, which may negatively impact body-related QoL. However, after adjusting for potential confounders, only the mean Hips and Outer Thighs scores and Scars scores were higher in IBBR patients. The similarities between abdominoplasty and DIEP flap harvest may cause better abdominal and body outcomes in ABR patients. [20] Nevertheless, the mean differences in BODY-Q outcomes between the two groups were not statistically significant.

Health-related QoL was similar in both groups in our study. This is in line with the previously mentioned findings of Moberg et al.[17] Complications can be a confounding variable for health-related outcomes. With the exception of infection, no significant difference in complications was found between the two methods and is therefore unlikely to have influenced the HRQOL outcomes of this study. In terms of HRQoL it can be suggested that one technique is not superior to another.

This study had several limitations. The study was nonrandomized, suggesting it is likely that women were not all eligible for both types of breast reconstruction. In addition, no preoperative patient reported outcome data was available. Psychosocial factors such as family members with breast cancer and / or fear of breast cancer may play an important role in the QoL outcomes of this population. No adjustments could be made for these elements. Another limitation of this study is the small sample size and the low significance level, which both does not benefit the generalizability.

Major strengths of this study include the wide range of questionnaires administered and a strong statistical model in which specific covariates for adjustment were chosen carefully based on li-

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terature search and clinical experience. However, more large-scale, comparative research using validated PROMs is needed to collect high-quality data on QoL in women who underwent BPM and breast reconstruction.

Conclusion

This study suggests that there is a higher Satisfaction with breasts and Physical well-being in women who underwent immediate ABR compared to IBBR after BPM. However, the results should be interpreted carefully due to possible selection bias and the limitations inherent in the cross-sectional design. Further research with a larger sample size is needed to elaborate on the findings of this study and to provide recommendations for clinical practice.

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CHAPTER 10

General discussion

GENERAL DISCUSSION

Breast augmentation is one of the most performed aesthetic surgical procedure worldwide, with 1.8 million procedures in 2019.[1] Additionally, implant-based reconstruction is the most commonly used method to correct postmastectomy deformity of the breast. At the same time, there are concerns about the safety of silicone breast implants (SBI). It is known that the use of breast implants is associated with a risk of local complications. Large-scale research has recently shown that after 7 years, 12% of primary augmentations and 25% of primary reconstructions have undergone reoperation, most commonly for capsular contracture or aesthetic dissatisfaction.[2] In addition to the local complications, in recent years there seem to be an increasing number of reports of systemic complaints.

Some women with SBI report a pattern of systemic complaints that includes fatigue, arthralgia, myalgia, sicca, as well as cognitive failure, referred to as breast implant illness (BII).[3-5] It is attracting the attention of media, plastic surgeons, and researchers worldwide, but so far no scientific research demonstrates a causal relationship between silicones and systemic complaints. Moreover, the extent of BII remains unknown: it is the stories of symptomatic women that come to light in case reports and media reports, but it is not clear what proportion of women with breast implants experience implant-related symptoms. Uncertainty about the safety of breast implants can create doubts and fears among women who are faced with the choice of breast reconstruction and can complicate the decision-making process. The goal of this thesis was to provide women with evidence based-information about the long-term patient-reported outcomes and breast implant-related symptoms, and to support plastic surgeons and other breast cancer specialists in their advice to these women, either regarding cosmetic or reconstructive surgery. In this chapter, the outcomes of our studies will be critically discussed and placed in a broader perspective.

Health complaints in women with breast implants

In **chapter 2**, we examined the prevalence of self-reported complaints among women with breast implants. Given the non-specific nature of these complaints, it is critical to investigate this prevalence in both women with implants and in a control group, as these symptoms can occur independently of having breast implants. The symptoms attributed to BII appear to be common in the general population: nearly 80% of controls in this study reported one or more systemic symptoms. All symptoms were more common in women who reported to 'Meldpunt Klachten Siliconen' (MKS), but adjustment for confounders negated this difference. Therefore, these results strongly suggest that selection is involved and that multiple confounding variables play an important role in BII. However, both a higher prevalence of allergies and fibromyalgia were found among women with breast implants and self-reported symptoms. This was consistent with previous studies.[6-8] A literature review by Lipworth et al. highlighted that epidemiological research could not support an association between breast implants and subsequent fibromyalgia.[9] The non-specific nature of these complaints as well as the overlap with other functional disorders, such as chronic fatigue and irritable bowel syndrome, complicate distinguishing a syndrome.[10, 11] Most importantly, longitudinal studies are needed to determine whether the symptoms pre-existed or were a result of the implants. It therefore remains difficult to determine what the extent of breast implant illness really is.

Still, fear of harmful effects from using implants may deter women from undergoing breast surgery or encourage women to reverse their surgery. Recently, there has been an increasing demand for implant removal due to patient concerns about the safety of their implants or the risk of systemic

disease.[12] Studies showed that explantation of the silicone breast improves silicone-related complaints in 75 % of the patients.[13] In chapter 3 we investigated how many explants had taken place in the past 10 years in the MUMC+ and for what reason. More than half of the 197 patients undergoing explantation reported implant-related complaints and 15% experienced symptoms other than pain. Although no independent predictors of symptom onset were found in the analyses, the odds ratios of allergy and implant rupture may be clinically relevant.[6] Another notable finding of this study was the high prevalence of psychological and functional comorbidities in women with suggested BII. Dush proposed a hypothesis that somatization plays an important role in the development and worsening of symptoms and complaints in some women with SBI.[11] According to his hypothesis, BII may be mediated by stress, personality traits, and social context. People with a higher level of physical or psychological stress seem to be more prone to somatization. It is known that psychological well-being and coping styles are strongly related to physical complaints and functional syndromes.[10, 11] The high prevalence of comorbidities that we found in women with SBIs in **chapter 2 and 3** may thus act as stressors mediating implant-related complaints. In **chapters 4 and 5** we further elaborated on the role of psychological factors and personality characteristics in the experience of physical complaints in women with breast implants.

The study described in **chapter 4** was the first pilot study to investigate structural and functional brain alterations using 3T fMRI. Previous neuroimaging studies with chronic pain or fibromyalgia patients showed altered brain activity and structural changes in brain regions that are known to be consistently activated during pain. The demonstration of neurological correlates in BII patients could have contributed to recognition and lead the way for treatment of BII. The pain questionnaire administered in this study showed significantly more pain intensity and disability in BII patients than in asymptomatic women with breast implants. However, the analyses of functional connectivity and structural integrity showed no significant differences between symptomatic and asymptomatic women with breast implants. It was also striking that 100% of the BII patients experienced cognitive failure, but that they scored no worse on the MMSE. Therefore, it could be suggested that the cognitive impairment related to BII is only of a subjective, rather than an objective nature. In addition, these findings make serious cognitive impairment with an underlying neurological cause more unlikely. Previous research on cognitive functioning in BII showed that BII patients indeed experience subjective cognitive failure, but that the prevalence and severity of subjective cognitive failure in a general population of women with breast implants was comparable to that of healthy controls.[14] Thus, subjective cognitive failure appear to affect only a selected group of women and there is no evidence for an overall increased risk of cognitive failure in women with breast implants. Furthermore, significantly higher levels of distress, somatization, anxiety, and depression were found in BII patients compared to asymptomatic women with breast implants. This strongly suggests that psychological factors are indeed associated with the development of BII, as described in Dush's hypothesis mentioned earlier.[11]

In **chapter 5**, the correlation between personality traits, self-reported health complaints, and patient-reported outcomes in women with breast implants was further elucidated. Women undergoing breast augmentation showed high levels of neuroticism, a personality trait that is associated with the tendency to experience negative emotions, with a greater tendency to fear, and with maladaptive coping.[15, 16] Neuroticism is also known to be correlated with body dissatisfaction and the likelihood of undergoing cosmetic surgery.[17] Neuroticism was found to be significantly correlated with the severity of physical complaints and both health-related and breast-related QoL in women with breast implants. Previous literature showed a positive association of neuroticism with

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higher symptom severity, as well as higher levels of anxiety, depression, stress, and worse mental QoL in fibromyalgia patients.[18] Based on the results fount in our study, we hypothesize that neuroticism may play a role in the development of breast implant-associated illness.[19]

Another hypothesis for the increase in the number of complaints, which is closely related to the findings on psychological factors described in chapters 2 to 5, is the nocebo effect. The nocebo effect means that people develop complaints due to negative expectations; the opposite of the placebo effect.[20] This is usually seen in the context of a treatment response. Learning mechanisms and classical conditioning play roles in these effects, as does learning about the experience of others. Research has shown that social context and modeling can induce side effects. Negative reports in the media, information obtained on the internet or stories heard directly from women with symptoms can play a key role.[21]

Women with breast implants may be reading stories from other women on the Internet or watching TV documentaries and recognize the symptoms described in themselves. Subsequently, they attribute their own systemic complaints, such as fatigue or muscle aches, to the implants. The role of social media should not be underestimated in this context. Patient support groups on Facebook connect women with similar concerns and provide emotional support to women with BII.[22] However, research showed that these Facebook groups led to increased anxiety and symptom awareness and that women who frequented the page were more preoccupied with health issues than other women.[23]

Some characteristics are known to be associated with the nocebo effect. It is, for example, more likely to occur in people who are more anxious, experience more psychological distress, or have a history of medically unexplained symptoms.[21] Characteristics that also fit with neuroticism. Based on our studies, these characteristics appear to be common in BII patients.

Furthermore, a negative doctor-patient relationship also appears to have an important influence on the reporting of symptoms.[24] Patients who experience their doctor as empathetic not only report fewer (serious) complaints, but also objectively show better physical outcomes. Our study participants with self-reported BII often felt that doctors did not take their complaints seriously and that they felt left without answers. Women felt insufficiently warned by their plastic surgeons about the potential risks of breast implants and believed this information could have influenced their decision. They experienced their participation in scientific research as an opportunity to share their story. In a recent qualitative study, women who had experienced negative physical or psychological effects following breast implant surgery revealed negative experiences in their interaction with healthcare professionals.[25] They too indicated that they did not feel believed and that they did not feel taken seriously. According to the theory about the nocebo effect, this may have negatively affected the experience and reporting of physical complaints. Yet, the recently updated FDA guidelines stress breast-implant patient communication by recommending manufacturers include comprehensive information in their product packaging about potential risks, implant rupture screening recommendations, and a patient decision checklist.[26]

Patient-reported outcomes of implant-based breast reconstruction

As described in chapters 3 to 5, psychological factors play an important role in body image, the choice for breast augmentation, and the experience of physical complaints. In **chapter 6**, we aimed to investigate the influence of psychological factors on breast reconstruction choice in breast cancer patients. This study showed that psychological well-being has a significant influence on the desire to restore the shape of the breast in this population. We found that women who underwent reconstructive surgery scored significantly lower on psychosocial well-being at the time of breast cancer diagnosis than women who did not undergo reconstruction. These women may expect that losing their breasts will be psychologically difficult and that breast reconstruction will provide some relief from the anxiety. Another factor that significantly influences the decision-making process for breast reconstruction is age; younger women are more likely to undergo reconstruction, and so are women who are married and sexually active.[27, 28] Fingeret et al. developed a theoretical framework to illustrate associations between patient satisfaction, body image and quality of life for women undergoing breast reconstruction. Herein, patient demographics, such as age and marital status, medical factors, such as BMI and previous (cosmetic) breast surgery, as well as psychosocial factors, are considered key 'premorbid' variables that can influence patient-reported outcomes.[29] It is emphasized that personality traits are an important factor in predicting QoL outcomes, as they are related to coping styles that determine how someone adapts to certain life events and processes this emotionally. Thus, psychosocial characteristics also play a key role in the decision-making process as well as in predicting patient-reported outcomes of breast reconstruction.

As discussed in chapter 6, breast reconstruction decision-making is influenced by many internal and external factors. Concerns about the safety of silicone breast implants may interfere with this choice. Patients who do not trust the use of breast implants may be inclined to opt for autologous breast reconstruction or even forgo reconstruction. In **chapter 7**, it was investigated whether women after implant-based breast reconstruction (IBR) had an increased risk of developing BII symptoms compared to women after autologous breast reconstruction (ABR). In this study, the prevalence of 11 common systemic symptoms in women who underwent IBR was compared with the prevalence in women who underwent ABR. As in BII, fatigue was the most frequently reported complaint by women in this study (over 60%). However, no significant difference was found in the prevalence of symptoms associated with BII between both reconstruction groups and the reported symptom severity was equally distributed within the groups. Even women undergoing tertiary autologous reconstruction after failed IBR did not report significantly more or more severe complaints, while these women were expected to have the worst complaints. In addition, no significant differences in HRQoL between women with IBR and ABR could be demonstrated. Several independent predictors for the onset of specific symptoms were defined, such as age, BMI, and chemotherapy, but the type of reconstruction was none. These results are in line with previous studies examining HRQoL after different breast reconstruction methods and they indicate that the reported symptoms are not a direct result of breast implants.[30, 31] Especially in reconstructive cases, confounding factors must be extensively analyzed and make it almost impossible to distinguish between comorbidities or side effects and breast implant illness.

In chapters 6 and 7, several factors that may influence the choice for reconstruction, such as psychological well-being and health-related QoL, were discussed. In addition, the aesthetic results of a reconstruction contribute to the patient's choice. Patient-reported outcomes related to satisfaction and body image are highly relevant in the field of breast surgery considering that the main goal of breast reconstruction is to recreate the appearance of the breast that is satisfactory to the

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patient. In **chapter 8**, we compared the long-term patient-reported outcomes of IBR with ABR. In agreement with the existing literature, we found greater satisfaction with breast and better breast-related QoL after ABR than after IBR. This benefit of ABR has been described repeatedly in the literature, presumably because of the more natural look and feel of the autologous reconstructed breast. In addition, these breasts age more naturally compared to an implant-based reconstruction, which only increases the benefit over time.[32, 33]

While many studies have been conducted on the breast-related outcomes of ABR compared to IBR, the effect of donor sites of ABR on patient-reported outcomes has received little attention. Free flap harvesting may be considered a potential risk factor for body image distortion in women undergoing ABR. In **chapter 8**, we evaluated the aesthetic outcomes and overall body image, in addition to breast-related outcomes, of breast reconstruction. Body-related QoL was measured using the BODY-Q, as the scales of this questionnaire relate to body parts that could serve as donor sites for microsurgical free flaps. While the Abdomen scale of the BREAST-Q focuses on functional donor site morbidity, the BODY-Q focuses on aesthetic outcomes. Notably, women who underwent DIEP flap reconstruction scored significantly higher on 'Abdomen; as well as on 'Body' than the IBR group. So, rather than being a risk factor for body image deterioration, the DIEP flap harvesting appears to have a positive effect on abdominal satisfaction. Since a DIEP flap breast reconstruction is usually indicated in women with a higher BMI and this procedure has strong similarities with abdominoplasty, it results in a flatter abdomen.[34, 35] This positive effect was not observed following LTP reconstruction: the LTP group scored significantly lower on 'Hips and outer thighs' compared to the IBR group.[36] Also the aesthetic outcomes of the scars were rated worse by the ABR group (both DIEP and LTP flap) than by the IBR group. Nevertheless, no significant difference in 'Body image' was observed between ABR (DIEP nor LTP) and IBR, suggesting that the appearance of the donor site does not considerably deteriorate body image.

In **chapter 9**, we performed subgroup analyses of the patient-reported outcomes in women who underwent bilateral prophylactic mastectomy (BPM) followed by immediate breast reconstruction. As a result of advances in genetic testing, more and more women with an increased risk of breast cancer are opting for BPM followed by breast reconstruction. However, little literature is available on patient-reported outcomes after breast surgery in this population.[37] Women who underwent ABR reported significantly greater satisfaction with breasts and better physical well-being than women who underwent IBR. In previous literature, Metcalfe et al. reported that type of reconstruction was not associated with satisfaction with cosmetic outcomes after BPM-reconstruction, but that self-reported postoperative complications had a significant negative effect on these outcomes.[38] In our study, major complications as a result of the reconstruction were equally common in both groups. Furthermore, reconstruction techniques have probably improved over the years and data from dated studies should therefore be critically examined. It should also be noted that older studies have not yet used the BREAST-Q and that the results of different questionnaires cannot simply be compared. More recently, Moberg et al. found BREAST-Q results that were broadly consistent with our results, namely that women undergoing BPM were significantly more satisfied with breasts and outcomes after ABR than after IBR.[39] Satisfaction with the result may also be related to body image. Hatcher et al. found that women who had a positive body image before BPM showed no deterioration postoperatively.[40] Furthermore, Metcalfe et al. described a correlation between satisfaction and age, which is related to body consciousness after mastectomy at a younger age.[41] We found that body image outcomes were similar in both groups. Nevertheless, the results presented in chapter 9 should be interpreted with caution given the small study population.

Limitations and future perspectives

Certain factors make BII a difficult subject to comprehend and obstruct the path to scientific consensus. While conducting the studies described in this thesis, we faced some of these factors.

Avoiding selection bias is arguably the greatest challenge in BII research. Selection has so far made it impossible to give a true representation of the magnitude of the BII problem. It is the stories of women who are having severe symptoms that come to light. Participants in most BII research seem not representative of the total group of women with implants. Those who do not suffer from symptoms do not feel compelled to proclaim how satisfied they are with their breasts. It has therefore proved difficult to recruit a large and unselected sample of subjects. In addition, the division in opinions and beliefs about breast implant illness causes a feeling of misunderstanding in symptomatic women. This can lead to suspicion and dissuade women from participating in research, especially when it comes to measures of mental health. In future research, however, efforts should be made to further elucidate psychological causes and consequences of breast implant illness.

Furthermore, the vague nature of the symptoms reported by women with breast implants makes it difficult to distinguish a syndrome. Confounding is a major limitation in BII research, including ours. For example, symptoms can be the result of chemotherapy or hormone therapy, or be due to menopause or smoking. Moreover, due to a lack of prospective data collection in combination with recall bias, we cannot be sure that complaints have arisen since the implant surgery and did not already exist pre-operatively.

The lack of longitudinal data has been the result of inadequate registration and follow-up of implant surgery during the past decades. A systematic, prospective registration and evaluation of breast implant outcomes, correlating preoperative symptoms and morbidity with postoperative health outcomes, is therefore required.

By using national registers, such as the Dutch Breast Implant Registry (DBIR), which has been registering patient characteristics, surgical procedures and breast implants since 2015, a better estimate can be made of the prevalence of complications and systemic symptoms, while the effect of selection bias is reduced. The comprehensive prospective registration of physical and mental health, based on measurements with validated questionnaires, of women undergoing breast surgery would ideally be added to this.

Whether future research will demonstrate a causal relationship between complaints and silicone remains uncertain. It may, however, be possible to draw up a profile of women who are more likely to develop complaints on the basis of (psycho)medical history. Special attention should be paid to patient experiences, beliefs, and behaviors in order to predict patient-reported outcomes. Furthermore, we propose to physicians to take individual complaints and concerns seriously and to inform patients about the current evidence about systemic complaints. Knowledge of the findings presented in this thesis may improve the plastic surgeon's ability to counsel women on breast reconstruction decisions.

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CHAPTER 11

Summary

Summary in Dutch - Nederlandse samenvatting

SUMMARY

Women undergoing a mastectomy face the choice of whether or not to undergo breast reconstruction. Many personal and external factors play a role in the choice not to undergo breast reconstruction, to undergo an implant-based reconstruction or to undergo an autologous reconstruction. For example, there is a lot of public awareness about the safety of silicone breast implants and the development of systemic complaints, also known as breast implant illness (BII). This causes fear and worry in women who currently have or are considering breast implants. In addition to reconstructive cases, this also concerns women who have undergone or are considering undergoing cosmetic augmentation. There has been an increase in the number of requests for explantation in recent years. However, little is known about the prevalence, risk factors, and management of BII. More research on this topic is needed to adequately counsel women considering breast implants for breast reconstruction or augmentation. Furthermore, long-term breast- and body-related outcomes are important determinants in making a choice for reconstruction. This thesis aimed to provide an overview of long-term patient-reported outcomes of women who have undergone breast implant surgery, compared to women who have not, such as healthy controls or women with a different type of breast reconstruction.

Chapter 2 describes a study in which we evaluated the prevalence of self-reported complaints in women with breast implants. Also health-related quality of life was compared between women with and without breast implants in this study. Women with silicone or saline breast implants who had or had not registered with complaints at the Dutch foundation for breast implant illness (MKS) were compared with a control group without breast implants. Almost all of the 238 women reported systemic complaints, only women from MKS had significantly more physical complaints than all other groups. Age, fibromyalgia and chronic diseases were identified as independent predictors for the development of multiple systemic complaints. Furthermore, health-related quality of life was significantly lower in women with silicone breast implants than in women without implants. However, selection bias seems to play a major role in this and other studies on breast implant illness. This study demonstrates that systemic symptoms are common in both women with and without breast implants and that selection bias in many studies is likely to bias the true extend of breast implant illness among women with silicone breast implants.

In the study described in **chapter 3**, we investigated the course of physical complaints in women who had their breast implants removed, by means of a retrospective chart review. Patients who had undergone an explantation in Maastricht UMC+ between 2010 and 2020 were included. More than half of the patients reported complaints, mostly pain. Capsular contracture was the most common primary indication for explantation. Breast implant illness (BII) was suggested in 14.7% of the cases. After removing the breast implants, more than half noticed an improvement in complaints. Allergy and implant rupture caused an increase in the likelihood of BII. Also striking was the high prevalence of psychological and functional disorders in women with BII. This study confirms that the removal of the implants leads to an improvement of complaints in the majority of BII cases.

Chapter 4 describes an exploratory pilot study investigating whether changes in structural and functional measures could be found in brain regions involved in the pain matrix in women with BII compared to asymptomatic women with SBI, using 3T fMRI. Twelve women in both groups were included. The main findings of this study were that the analyses of both functional and structural measures showed no significant differences between the two groups, despite the large clinical dif-

ferences in self-reported symptoms. However, large differences were found in the level of anxiety, distress, somatization, and depression, suggesting that these psychological factors are associated with the development of breast implant illness. These women may as well be more sensitive to the nocebo effect, in which negative expectations contribute to the development of complaints. The results of this study prompted further research into the role of personality in breast implant illness, as described in chapter 5.

Chapter 5 describes the evaluation of the association between self-reported health complaints, health- and breast-related QoL, and personality traits, in women who underwent breast augmentation. The health status, breast-related QoL, as well as the personality traits of 201 breast augmentation patients were analyzed. Levels of neuroticism were significantly different between augmentation patients and normative data. Neuroticism was found to be significantly negatively correlated with subjective health and breast-related QoL in women with breast implants. Therefore, personality may be a factor in the development of breast implant-associated illness.

The aim of the study described in **chapter 6** was to study the influence of a woman's quality of life at the time of breast cancer diagnosis on the decision whether or not to undergo breast reconstruction after mastectomy. This cross-sectional study included 67 women, 54% of whom ultimately decided to undergo breast reconstruction. Those undergoing breast reconstruction were significantly younger and slightly more satisfied with their breasts preoperatively. Preoperative psychosocial well-being was significantly higher in women who did not undergo breast reconstruction than women who did undergo reconstruction. The results of this study suggest that psychosocial characteristics are essential for the decision-making process in breast reconstruction.

Chapter 7 describes a study we performed in order to investigate whether there is a difference in the prevalence of self-reported complaints between women undergoing different types of breast reconstruction. Furthermore, we compared health-related quality of life after implant-based breast reconstruction with autologous breast reconstruction. In this multicenter study, 329 women were included, of whom 103 underwent implant-based reconstruction, 202 autologous reconstruction and 24 tertiary reconstruction. We found no significant differences in the prevalence and severity of health complaints in the different groups, resulting in an equal health-related quality of life. Based on this study, there is no evidence that women undergoing implant-based breast reconstruction have an increased risk of developing health problems compared to women undergoing autologous breast reconstruction.

The study described in **chapter 8** measured breast-related and body-related quality of life 2 to 5 years after breast reconstruction. The outcomes of 336 women showed that breast-related quality of life was significantly higher after autologous breast reconstruction than after implant-based breast reconstruction and that donor site appearance did not negatively affect body image. In fact, women who underwent DIEP flap reconstruction were significantly more satisfied with their abdomen than women who underwent implant-based reconstruction. This study indicates that autologous breast reconstruction is superior to implant-based reconstruction in both breast-related and body-related outcomes.

In **chapter 9**, long-term outcomes regarding breast-related, body-related and health-related quality of life are investigated in a specific group of women who underwent breast reconstruction after bilateral prophylactic mastectomy. This risk-reducing procedure has a major impact on the body

image and psychosocial well-being of these (often young and disease-free) women. Forty-seven women who underwent implant-based or autologous breast reconstruction were included. Satisfaction with breasts and physical well-being following autologous breast reconstruction was significantly higher than following implant-based reconstruction. Women who underwent implant-based breast reconstruction scored a slightly higher body-related quality of life and a minimally lower health-related quality of life. However, these differences were not significant. This study indicates that, also in women undergoing bilateral prophylactic mastectomy, autologous breast reconstruction results in higher breast-related quality of life than implant-based breast reconstruction.

SUMMARY IN DUTCH - NEDERLANDSE SAMENVATTING

Vrouwen die een borstamputatie ondergaan, staan voor de keuze om al dan niet een borstreconstructie te ondergaan. Veel persoonlijke en externe factoren spelen een rol bij de keuze om géén borstreconstructie, een reconstructie met implantaten (prothesen) of een reconstructie met eigen weefsel te ondergaan. Er is momenteel bijvoorbeeld veel publieke aandacht voor de veiligheid van siliconen borstimplantaten en het ontstaan van systemische klachten, ook wel borstimplantaat-gerelateerde ziekte of 'Breast implant illness' (BII) genoemd. Dit kan het maken van een keuze lastig maken. Er is echter weinig bekend over hoe vaak het voorkomt, mogelijke risicofactoren en de behandeling van BII. Meer onderzoek over dit onderwerp is nodig om vrouwen die borstimplantaten overwegen of vrouwen die zich zorgen maken over hun borstimplantaten adequaat te adviseren. Verder spelen borst- en lichaam-gerelateerde uitkomsten op de lange termijn een belangrijke rol in het maken van een keuze voor reconstructie. Dit proefschrift had tot doel een overzicht te geven van lange termijnuitkomsten, gerapporteerd door vrouwen die een operatie met borstimplantaten hebben ondergaan, in vergelijking met vrouwen die niet zo een operatie hebben ondergaan, zoals gezonde controles of vrouwen met een ander type borstreconstructie.

Het doel van de studie beschreven in **hoofdstuk 2** was om het voorkomen van zelf-gerapporteerde klachten bij vrouwen met borstimplantaten te evalueren. Daarnaast werd de gezondheid-gerelateerde kwaliteit van leven vergeleken tussen vrouwen met en zonder borstimplantaten. In dit onderzoek werden vrouwen met siliconen of zoutoplossing-gevulde borstimplantaten die zich wel of niet met klachten hadden aangemeld bij het Meldpunt Klachten Siliconen (MKS) vergeleken met een controlegroep zonder borstimplantaten. Bijna alle 238 vrouwen rapporteerden systemische klachten, alleen vrouwen van MKS hadden significant meer lichamelijke klachten dan alle andere groepen. Leeftijd, fibromyalgie en chronische ziekten werden geïdentificeerd als onafhankelijke voorspellers voor het ontstaan van meerdere systemische klachten. Bovendien was de gezondheid-gerelateerde kwaliteit van leven significant lager bij vrouwen met siliconen borstimplantaten dan bij vrouwen zonder implantaten. Selectiebias lijkt een grote rol te spelen in dit onderzoek en andere onderzoeken naar borstimplantaat-gerelateerde ziekte. Deze studie toont aan dat systemische symptomen vaak voorkomen bij zowel vrouwen met als zonder borstimplantaten en dat selectiebias in veel onderzoeken waarschijnlijk de ware omvang van borstimplantaat-gerelateerde ziekte bij vrouwen met siliconen borstimplantaten vertekent.

In **hoofdstuk 3** onderzochten we het beloop van lichamelijke klachten bij vrouwen bij wie de borstimplantaten werden verwijderd, door middel van een retrospectief (terugblikkend) dossieronderzoek. Patiënten die tussen 2010 en 2020 een verwijdering van borstimplantaten ondergingen in het Maastricht UMC+ werden geïncludeerd. Meer dan de helft van de patiënten meldde klachten, voornamelijk pijn. Kapselcontractuur was de meest voorkomende primaire indicatie voor verwijdering van de implantaten. Borstimplantaatziekte (BII) werd in 14,7% van de gevallen gesuggereerd. Na verwijdering merkte meer dan de helft een verbetering van de klachten op. Allergie en implantaatruptuur veroorzaakten een toename van de kans op BII. Opvallend was ook het veel voorkomen van psychische en functionele stoornissen bij vrouwen met BII. Dit onderzoek bevestigt dat het verwijderen van de implantaten in de meeste gevallen van BII leidt tot een verbetering van de klachten.

Hoofdstuk 4 beschrijft een verkennende proefstudie waarin wordt onderzocht of veranderingen in structurele en functionele metingen kunnen worden gevonden in hersengebieden die betrokken zijn bij pijn, bij vrouwen met borstimplantaatziekte in vergelijking met vrouwen met borstimplantaten zonder klachten, met behulp van 3T fMRI. Twaalf vrouwen in beide groepen werden geïncludeerd. De belangrijkste bevindingen van deze studie waren dat de analyses van zowel functionele als structurele metingen geen significante verschillen lieten zien tussen de twee groepen, ondanks de grote klinische verschillen in de gerapporteerde symptomen. Er werden echter wel grote verschillen gevonden in het niveau van angst, angst, somatisatie en depressie, wat suggereert dat deze psychologische factoren verband houden met de ontwikkeling van borstimplantaatziekte. Deze vrouwen zijn mogelijk ook gevoeliger voor het nocebo-effect, waarbij negatieve verwachtingen bijdragen aan het ontstaan van klachten. De resultaten van deze studie waren aanleiding voor verder onderzoek naar de rol van persoonlijkheid bij ziekte van borstimplantaten, zoals beschreven in hoofdstuk 5.

In **hoofdstuk 5** wordt het verband tussen zelf-gerapporteerde gezondheidsklachten, gezondheid- en borst-gerelateerde kwaliteit van leven en persoonlijkheidskenmerken onderzocht, in vrouwen die een borstvergroting hebben ondergaan. De gezondheidsstatus, borst-gerelateerde kwaliteit van leven en de persoonlijkheidskenmerken van 201 patiënten werden hiervoor geanalyseerd. De mate van neuroticisme was significant verschillend tussen vrouwen met een borstvergroting en normatieve gegevens. Neuroticisme bleek significant negatief te correleren met de subjectieve gezondheid en de borst-gerelateerde kwaliteit van leven bij vrouwen met borstimplantaten. Mogelijk speelt persoonlijkheid daarom een rol bij de ontwikkeling van borstimplantaat-gerelateerde ziekten.

Het doel van de studie beschreven in **hoofdstuk 6** was het bestuderen van de invloed van de kwaliteit van leven van een vrouw op het moment dat zij de diagnose borstkanker krijgt, op de beslissing om al dan niet een borstreconstructie te ondergaan na de borstamputatie. Deze cross-sectionele studie omvatte 67 vrouwen, van wie 54% uiteindelijk besloot een borstreconstructie te ondergaan. Vrouwen die een borstreconstructie ondergingen waren significant jonger en waren iets meer tevreden met hun borsten, vóór de borstamputatie. Het psychosociaal welbevinden was significant hoger bij vrouwen die géén borstreconstructie ondergingen dan bij vrouwen die wel een reconstructie ondergingen. De resultaten van dit onderzoek suggereren dat psychosociale kenmerken essentieel zijn voor het besluitvormingsproces rondom een borstreconstructie.

Hoofdstuk 7 beschrijft een studie waarin werd onderzocht of er een verschil is in het voorkomen van zelf-gerapporteerde klachten tussen vrouwen met verschillende soorten borstreconstructies. Daarnaast werd de gezondheid-gerelateerde kwaliteit van leven tussen vrouwen met een reconstructie met borstimplantaten vergeleken met vrouwen met een reconstructie met eigen weefsel. In deze multicenter studie werden 329 vrouwen geïncludeerd, waarvan 103 met implantaten, 202 met een reconstructie met eigen weefsel en 24 vrouwen die een reconstructie met eigen weefsel ondergingen nadat eerder een reconstructie met implantaten had gefaald (tertiaire reconstructie). We vonden geen significante verschillen in het voorkomen of in de ernst van gezondheidsklachten in de verschillende groepen, resulterend in een gelijke gezondheid-gerelateerde kwaliteit van leven. Op basis van deze studie is er geen bewijs dat vrouwen die een borstreconstructie met implantaten ondergaan een verhoogd risico hebben op het ontwikkelen van gezondheidsproblemen in vergelijking met vrouwen die een borstreconstructie met eigen weefsel ondergaan.

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De studie beschreven in **hoofdstuk 8** onderzocht de borst-gerelateerde en lichaam-gerelateerde kwaliteit van leven 2 tot 5 jaar na de borstreconstructie. De uitkomsten van 336 vrouwen toonden aan dat de borst-gerelateerde kwaliteit van leven significant hoger was na borstreconstructie met eigen weefsel dan na borstreconstructie met borstimplantaten en dat het uiterlijk van de donorplaats geen negatief effect had op het lichaamsbeeld. Vrouwen die een DIEP-lapreconstructie ondergingen, waren zelfs significant meer tevreden met hun buik dan vrouwen die een reconstructie met borstimplantaten ondergingen. Deze studie geeft aan dat borstreconstructie met eigen weefsel superieur is aan borstreconstructie met borstimplantaten, zowel in borst- als lichaam-gerelateerde uitkomsten.

Hoofdstuk 9 beschrijft een studie naar de lange termijn kwaliteit van leven gerelateerd aan borst, lichaam en gezondheid in een specifieke groep vrouwen die beiderzijdse preventieve borstamputatie onderging. Deze risico verlagende ingreep heeft een grote impact op het lichaamsbeeld en het psychosociaal welzijn van deze (vaak jonge en ziektevrije) vrouwen. Zevenenveertig vrouwen die een beiderzijdse preventieve borstamputatie en borstreconstructie ondergingen werden geïncludeerd. De tevredenheid met borsten en fysiek welzijn na reconstructie met eigen weefsel was significant hoger dan na reconstructie met implantaten. Vrouwen die een reconstructie met implantaten ondergingen hadden een iets hogere lichaam-gerelateerde en een iets lagere gezondheid-gerelateerde kwaliteit van leven. Deze verschillen waren echter niet significant. Deze studie laat zien dat, ook bij vrouwen die een beiderzijdse preventieve borstamputatie ondergaan, een reconstructie met eigen weefsel resulteert in een hogere borst-gerelateerde kwaliteit van leven dan reconstructie met implantaten

CHAPTER 12

Impact paragraph

IMPACT PARAGRAPH

The goal of cosmetic surgery is to improve and reshape body structures to improve a person's appearance, self-esteem and confidence. In women who are dissatisfied with their breasts, the breasts can be augmented. In addition to aesthetic breast surgery on healthy women, there are women who have lost their breasts as a result of breast cancer treatment. In these women, breast reconstructive surgery can help restore their physical appearance and improve the quality of life. Breast implants are commonly used for both cosmetic and reconstructive breast surgery. However, questions about the safety of silicone breast implants are causing doubt and uncertainty among a growing number of women.

There is a lot of media attention for the safety of breast implants. The development of systemic complaints as a result of breast implants, also known as breast implant illness, is a much-discussed topic. In the Netherlands for instance breast implant illness has been the focus of the Dutch television program Radar. Furthermore, the documentary 'Moordtieten', which discusses the possible, rare and serious side effects of breast implants, received a lot of publicity. As a result of all this (social) media attention, women are inundated with stories of women who experience systemic physical complaints, such as fatigue, muscle complaints and cognitive problems. However, the actual relationship of these complaints with breast implants is not evidence-based. Media coverage of breast implants is often disproportionately focused on potential dangers. As breast implants are used on a large-scale worldwide, many women may be at risk. Maastricht research showed that more than 3% of adult women in the Netherlands have one or two breast implants. For all these women, solid scientific support about safety issues of implants is crucial. This dissertation contributes to that knowledge. The results of the studies described in this thesis provide patients and healthcare providers with evidence-based information.

This thesis shows that systemic symptoms are common in both women with and without breast implants and that selection bias in many studies likely skews the true extend of breast implant illness. Contrary to what the media has suggested, it has not been proven that systemic symptoms are more common in women with breast implants than in women without breast implants. However, in about 50% of the BII cases, an improvement in physical complaints is observed with the removal of implants, which is in line with previous research into explantation. It is unclear what role the placebo effect plays in this symptom improvement.

The results of this thesis provide new insights into the role of psychosocial characteristics in the development and experience of physical complaints in women with breast implants. Several studies in the literature have shown a relationship between psychological well-being and physical complaints. This relationship may also exist in women with breast implants. In our brain imaging study, no neurological abnormalities could be detected by means of fMRI examination and cognitive questionnaires. So, we found no evidence of brain damage from breast implants, as suggested by others. Instead, high levels of anxiety, fear, somatization and depression may make women more susceptible to experiencing physical symptoms. Furthermore, women may experience symptoms as a result of the nocebo effect, which is influenced by social media and social modelling. By means of scientific information, incorrect information on social media can be refuted and experiences can be placed in the right context.

With regard to the application of breast implants in oncology, women undergoing breast reconstruction may be disturbed by negative and incorrect information when choosing a particular reconstruction method. The decision-making process depends on many internal and external factors and requires proper counseling by the plastic surgeon and other medical specialists of the breast cancer team. However, this consideration should not include unproven side effects. Based on this thesis, women can be reassured that an implant reconstruction does not carry a higher risk of systemic physical complaints than an autologous breast reconstruction. No significant differences in the prevalence and severity of health complaints were found between the two reconstruction methods, resulting in an equal health-related quality of life. However, breast-related and body-related outcomes were higher in women undergoing autologous breast reconstruction. This is widely confirmed in the literature.

The results of this thesis are relevant for medical professionals in the field of breast reconstruction and cosmetic breast augmentation, such as plastic surgeons and surgical oncologists, so that they can counsel patients based on the latest evidence. Furthermore, this thesis is of interest to those who currently have breast implants or are considering breast implants, as the results provide insight into patient-reported outcomes after breast implant surgery or breast implant removal.

While this thesis may not be sufficient to answer all the major issues surrounding breast implant illness, it is a step in the right direction. More large-scale prospective studies are required in order to elucidate the association between breast implants and health complaints. A systematic, prospective registration such as the Dutch Breast Implant Registry (DBIR) allows a better estimate of the prevalence of complications and side effects, without selection bias. Ideally, this would include extensive prospective registration of physical and mental health. Whether future research will demonstrate a causal relationship between complaints and silicone remains to be seen. It may become possible to draw up a profile of women with a greater chance of developing complaints on the basis of (psycho)medical history. Physicians should take complaints and concerns seriously and should properly inform patients about the current evidence on the relationship with systemic complaints. This thesis can help plastic surgeons and other medical professionals to advise women on breast implant decisions.

CHAPTER 13

Appendices

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'Wat is belangrijker,' vroeg Grote Panda, 'de reis of de bestemming?'
'Het gezelschap,' zei Kleine Draak.

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Breast implant surgery

Berben, J. A., **Miseré, R. M. L**., Schop, S. J. & van der Hulst, R. R. W. J. (2022). The Influence of Personality on Health Complaints and Quality of Life in Women With Breast Implants. Aesthetic Surgery Journal. https://doi.org/10.1093/asj/sjac247

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ABOUT THE AUTHOR

Renée Miseré was born on November 19, 1993 in Brunssum, The Netherlands. After completing the Atheneum at the Sintermeerten College in Heerlen in 2012, she moved to Maastricht where she studied Health Sciences and successfully completed her propaedeutic year. In 2013 she passed the decentralized selection procedure and started her Bachelor of Medicine at Maastricht University. During the second year, she had the opportunity to take an elective course in Oncology at the University of Ferrara, Italy. In 2016 she obtained her bachelor's degree in Medicine cum laude. During her masters she went to Kampala, Uganda, for a surgical internship. At the end of her studies, she completed an elective plastic surgery internship at Zuyderland medical center, followed by a 36-week internship at the plastic surgery department of Maastricht University Medical Center (MUMC+), where research and clinical work alternated. During this last internship she researched both lymphedema and facial paralysis, about which she wrote several articles and presented at national and international conferences. After obtaining her master's degree in 2019, she worked as a PhD candidate at the plastic surgery department of the MUMC+, where she researched physical complaints and quality of life in women with breast implants. Since January 2022 she has been working as resident not in training (ANIOS) at the plastic surgery department of Zuyderland Medical Center, VieCuri Medical Center and MUMC+ respectively.

"HORA EST"