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LONG-TERM FOLLOW-UP AFTER RISK-REDUCING MASTECTOMY AND IMMEDIATE BREAST RECONSTRUCTION – FROM A PATIENT, PARTNER, AND 3D PERSPECTIVE

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my grandparents

POPULAR SCIENCE SUMMARY OF THE THESIS

Breast cancer is the most common female cancer in Sweden, with 1–2 in 10 women estimated to be affected during their life-time. For some women, the risk of being affected with breast cancer is higher (7 in 10 women before age 80) because of changes in genes (mutations) inherited from a parent. *BRCA1* and *BRCA2* are examples of such mutations, where the changed genes can cause abnormal cell growth (cancer).

For individuals with confirmed high hereditary risk of breast cancer, tailored surveillance programmes involving more frequent clinical examinations and initiation of regular breast imaging at an earlier age is offered. As breast cancer risk is related to breast tissue mass, the removal of breast tissue (risk-reducing mastectomy) is an option. Because risk-reducing mastectomy often is performed when the women are relatively young, often otherwise healthy, and expected to live for many years after the surgery, it is of importance to follow the progress of various physical and psychological outcomes in the long-term.

In this thesis, four studies investigating women with high hereditary risk of breast cancer who underwent risk-reducing mastectomy and immediate breast reconstruction at Karolinska University Hospital, Stockholm, between 1997 and 2010 are presented. Through validated questionnaires, women and their partners were asked to evaluate aesthetic outcome, body image, sexuality, anxiety and depressive symptoms, and health-related quality of life up to 20 years after the risk-reducing surgery. In addition, we investigated a more objective method to assess the aesthetic outcome after breast reconstruction using three-dimensional surface imaging (3D-SI). Lastly, the 3D-SI measurements and the women's own evaluations regarding the aesthetic outcome were compared to test for associations between the 3D assessment and patient-reported outcomes.

Both the women (*n*=146) and participating partners (*n*=36) had low levels of anxiety and depressive symptoms, and their levels of health-related quality of life in the majority of cases were higher compared to age- and gender-matched levels in the normal Swedish population. Satisfaction with the aesthetic outcome after risk-reducing mastectomy and immediate breast reconstruction was generally high among the women. The women reported persisting problems with body image, which was confirmed but overestimated by their partners when the partners' perceptions of the women's evaluations were studied. Sex-related values were lower for women without previous breast cancer compared with women who had been diagnosed with and treated for breast cancer prior to the risk-reducing surgery. Measurements of breast symmetry and breast volume using 3D-SI of 58 women were found to have substantial to excellent reproducibility for measurements estimated by the same observer. The reproducibility was not as good of measurements by different observers, indicating that 3D-SI in its present form is not a great tool for assessment of the aesthetic outcome. There was no association between 3D-SI measurements and the women's own evaluations of the aesthetic outcome, implying that 3D-SI cannot replace the power of patient-reported outcomes.

The thesis includes (i) one of the longest prospective follow-ups investigating psychosocial outcomes in high-risk women after risk-reducing mastectomy and immediate breast reconstruction, (ii) one of few studies investigating the partners of these women, and (iii) a methodological and (iv) clinical study evaluating an objective method to assess aesthetic outcome in terms of breast symmetry and breast volume. The results from these studies could be of use during pre- and postoperative counselling for future women and partners.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bröstcancer är den vanligaste cancern bland kvinnor i Sverige, där cirka en till två av tio kvinnor riskerar att drabbas under en livstid. Risken är avsevärt högre för vissa kvinnor (cirka sju av tio före 80 års ålder) på grund av förändringar i arvsmassan (mutationer) som nedärvts från en förälder. *BRCA1* och *BRCA2* är exempel på sådana mutationer där förändringen i arvsmassan kan ge upphov till onormal celltillväxt (cancer).

För kvinnor med en bekräftad ökad ärftlig risk för bröstcancer erbjuds skräddarsydda kontrollprogram som omfattar tätare klinisk undersökning och regelbunden bröstavbildning med start i lägre ålder än den allmänna mammografiscreeningen. Eftersom risken för bröstcancer är relaterad till bröstvävnadsmassa är avlägsnandet av bröstvävnad (riskreducerande mastektomi) ett alternativ för att minska risken. Det är viktigt att följa hur kvinnor som genomgått riskreducerande mastektomi och omedelbar bröstrekonstruktion mår lång tid efter kirurgin eftersom de ofta är unga och i övrigt friska vid operationstillfället, och förväntas leva i många år efter operationen.

I denna avhandling presenteras fyra studier som omfattar kvinnor med ökad ärftlig risk för bröstcancer som genomgått riskreducerande mastektomi och omedelbar bröstrekonstruktion vid Karolinska universitetssjukhuset i Stockholm, mellan 1997 och 2010. Med hjälp av validerade frågeformulär har dessa kvinnor och deras partners besvarat frågor gällande estetiskt resultat, kroppsuppfattning, sexualitet, ångest och depressiva symptom, och hälsorelaterad livskvalitet upp till 20 år efter den riskreducerande operationen. Dessutom undersökte vi en ny analysmetod för att på ett mer objektivt sätt utvärdera det estetiska resultatet efter bröstrekonstruktion med hjälp av tredimensionell (3D) fotografering. Slutligen analyserade vi om 3D-utvärderingen överensstämde med kvinnornas egna uppfattningar av det estetiska resultatet.

Både kvinnorna (*n*=146) och deltagande partners (*n*=36) rapporterade låga nivåer av ångest och depressiva symptom, och att deras hälsorelaterade livskvalitet i de flesta fall var högre jämfört med ålders- och könsstandardiserade data från normalbefolkningen i Sverige. De flesta av kvinnorna var nöjda med det estetiska resultatet efter riskreducerande mastektomi och omedelbar bröstrekonstruktion. Vid långtidsuppföljningen observerades en bestående påverkan på kvinnornas kroppsuppfattning, där problemen bekräftades men överskattades av deras respektive partners. Sexrelaterade problem var lägre bland kvinnor som aldrig haft någon bröstcancer jämfört med kvinnor som hade haft bröstcancer innan de genomgick den riskreducerande kirurgin. Mätningar av 58 kvinnors bröstsymmetri och bröstvolymer med hjälp av 3D-analys visade betydande till utmärkt överensstämmelse mellan mätningar utförda av en och samma observatör. Överensstämmelsen var inte lika bra mellan två olika observatörers mätningar, vilket tyder på att 3D-analysmetoden i sin nuvarande form inte är tillräckligt bra för att användas som en standardiserad metod för utvärdering av det estetiska resultatet. Det fanns inget samband mellan 3D-mått och kvinnornas utvärdering av det estetiska resultatet, därför kan 3D-utvärdering inte ersätta patientrapporterade uppgifter vid mätning av patientnöjdhet av det estetiska resultatet.

Avhandlingen belyser (i) en av de längsta prospektiva uppföljningarna av psykosociala aspekter hos kvinnor med ärftlig förhöjd risk för bröstcancer som genomgått riskreducerande mastektomi och omedelbar bröstrekonstruktion, (ii) en studie som undersökt partners till dessa kvinnor, och (iii) en metodstudie följt av (iv) en applicerad klinisk studie som undersökt en objektiv mätmetod för skattning av det estetiska resultatet. Resultaten från dessa studier kan vara användbara vid pre- och postoperativa rådgivningssamtal för framtida kvinnor och deras partners.

ABSTRACT

BACKGROUND Breast cancer is the most common type of cancer among women. Approximately 5–10% of all breast cancer cases have an inherited pattern, and ~20% of all hereditary cases have an identifiable mutation. Through genetic counselling, individuals with an increased cancer risk can be identified and informed about appropriate management strategies. Risk-reducing mastectomy (RRM) and immediate breast reconstruction (IBR) is one of these options.

AIMS AND METHODS In a prospective study, women who underwent RRM and IBR between 1997 and 2010 at Karolinska University Hospital, Stockholm, were followed regarding the patient-reported outcome measures (PROMs) satisfaction with breast reconstruction (*EORTC breast reconstruction questionnaire module*), body image (*Body Image Scale*), sexuality (*Sexuality Activity Questionnaire*), anxiety and depressive symptoms (*Hospital Anxiety and Depression scale*), and health-related quality of life (HRQoL) (*Short Form-36 Health Survey*). This thesis presents the results from a long-term (6–20 years) follow-up of these women regarding aforementioned PROMs (**Paper I**), an investigation of the partners' perceptions (**Paper II**), an evaluation of the reproducibility of a three-dimensional surface imaging (3D-SI) technique (VECTRA XT 3D imaging system) (**Paper III**), and a comparison between the aesthetic evaluation using 3D-SI and PROMs (**Paper IV**).

RESULTS A total of 146 (73%) women responded to the questionnaires at the long-term assessment. Feelings regarding body image, sexuality, levels of anxiety and depressive symptoms, and HRQoL appeared to be relatively unchanged compared with their corresponding one-year postoperative evaluations regarding the psychosocial aspects. Body image problems were still prevalent at the long-term follow-up. Women without previous breast cancer reported lower levels of problems with sexuality than women with previous breast cancer (**Paper I**). A total of 36 (60%) couples were included. Women's evaluations regarding long-term psychosocial outcomes appeared to have been perceived by their partners, though the partners tended to overestimate the degree of body image problems. Both women and their partners scored higher on nearly all HRQoL domains compared with the age- and sex-adjusted normative population in Sweden (**Paper II**). A total of 64 women (80% of those who expressed interest to participate in 3D-SI) were 3D imaged and 348 images were analysed. The method used to assess breast symmetry in 3D surface images was found to have substantial to excellent intra-observer reproducibility and moderate to substantial inter-observer reproducibility. A relative parameter, volume-shape-symmetry (*VSS*), was proposed in order to facilitate the interpretation of breast symmetry measurements. It was found to have excellent intra-observer reproducibility and substantial inter-observer reproducibility (**Paper III**). Results of 58 3D surface images were compared to PROMs from the corresponding 58 women regarding aspects related to satisfaction of breast reconstruction and body image. The 3D-SI measurements did not show any statistically significant associations with the women's self-reported outcome measures (**Paper IV**).

CONCLUSIONS Long-term after RRM and IBR, both women and their partners reported low levels of anxiety and depressive symptoms and high levels of HRQoL. The women's body image problems were persistent and confirmed, but overestimated, by partners. 3D-SI measurements could potentially be used to evaluate and compare aesthetic outcomes of breast reconstructions from a more objective perspective. However, these measurements did not correspond to the women's own evaluations and should therefore not be used as a proxy for PROMs.

LIST OF SCIENTIFIC PAPERS

I. Lucy Bai, Brita Arver, Hemming Johansson, Kerstin Sandelin, Marie Wickman, Yvonne Brandberg. **Body image problems in women with and without breast cancer 6–20 years after bilateral risk-reducing surgery – A prospective follow-up study**.
Breast. 2019 Apr;44:120-127

II. Lucy Bai, Brita Arver, Hemming Johansson, Marie Wickman, Kerstin Sandelin, Yvonne Brandberg. **Partners' perceptions of women's satisfaction and body image long-term after risk-reducing mastectomy**.
Manuscript

III. Lucy Bai, Ola Lundström, Hemming Johansson, Farid Meybodi, Brita Arver, Kerstin Sandelin, Marie Wickman, Yvonne Brandberg. **Clinical Assessment of Breast Symmetry and Aesthetic Outcome: Can 3D Imaging Be the Gold Standard?**
Under revision in *Journal of Plastic Surgery and Hand Surgery* (July 2021)

IV. Lucy Bai, Kerstin Sandelin, Marie Wickman, Brita Arver, Ola Lundström, Hemming Johansson, Yvonne Brandberg. **Patient-reported Outcomes and 3-dimensional Surface Imaging after Risk-reducing Mastectomy and Immediate Breast Reconstruction**.
Plast Reconstr Surg Glob Open. 2021 May 21;9(5):e3561

CONTENTS

LIST OF ABBREVIATIONS

2D	Two-Dimensional
3D-SI	Three-Dimensional Surface Imaging
BCCT.core	Breast Cancer Conservative Treatment. cosmetic results
BIS	Body Image Scale
BMI	Body Mass Index
BOADICEA	Breast Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BRCA	Breast Cancer gene
CT	Computed Tomography
d_{RMS}	Distance between two surfaces as Root Mean Square, i.e., breast shape symmetry
DSM	Diagnostic and Statistical Manual of Mental Disorders
EORTC	European Organisation for Research and Treatment of Cancer
HAD	Hospital Anxiety and Depression scale
HRQoL	Health-Related Quality of Life
IBR	Immediate Breast Reconstruction
ICC	IntraClass Correlation
MRI	Magnetic Resonance Imaging
NAC	Nipple-Areola Complex
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
QLQ-BRR26 or QLQ-BRECON23	Quality of Life after Breast Reconstruction Questionnaire module
RRM	Risk-Reducing Mastectomy
RRSO	Risk-Reducing Salpingo-Oophorectomy
SAQ	Sexuality Activity Questionnaire
SD or σ	Standard Deviation
SF-36	Short Form-36 Health Survey
VAM	VECTRA Analysis Module®
VC or σ_x^2	Variance Component
VL	Volume of the Left breast
VR	Volume of the Right breast
VSS	Volume-Shape-Symmetry

1 BACKGROUND

1.1 HEREDITARY BREAST CANCER

Breast cancer is the most common type of cancer among women. A status report on the global cancer burden presented an estimation of around 2.1 million newly diagnosed breast cancer cases worldwide in 2018, where approximately 9000 were diagnosed in Sweden (Bray, Ferlay, and Soerjomataram 2018). Roughly 5–10% of all breast cancer cases have an inherited pattern, yet merely 20% of all hereditary cases have been able to be linked with an identifiable germline mutation (Shiovitz and Korde 2015; Stratton and Rahman 2008). Germline mutations are genetic changes present in all cells of the body inherited from a parent. Mutations can be inherited through an autosomal dominant pattern, where one copy of the mutation in each cell gives rise to an increased risk of developing cancer.

BRCA1 and *BRCA2* were two of the first autosomal dominant mutations identified in families with numerous breast cancer events (Hall et al. 1990; Wooster et al. 1995). The *BRCA* genes code for proteins involved in DNA repair. When these genes are altered, the transcribed proteins lose their ability to supress tumours, giving rise to uncontrolled cell growth and an increased risk of developing tumours. Together, these two mutations account for 2–5% of all breast cancer cases in the general population (World Cancer Research Fund/American Institute for Cancer Research 2018). In an international observational study of 19 581 *BRCA* mutation carriers identified between 1937 and 2011, 60–63% were diagnosed with breast and/or ovarian cancer (Rebbeck et al. 2015). Because of the high risk of developing both breast and ovarian cancer, the *BRCA* mutations are considered to be "high penetrance genes". The mean cumulative risk of breast cancer among the gene mutation carriers have been shown to range from 57–65% and 45–55% for *BRCA1* and *BRCA2* mutation carriers at age 70, respectively (Rousset-Jablonski and Gompel 2017). Corresponding risk figures for ovarian cancer have been shown to vary between 39–59% and 11–18% for *BRCA1* and *BRCA2* mutation carriers at age 70, respectively (Rousset-Jablonski and Gompel 2017).

Since the identification of the *BRCA* mutations, several other high (*PTEN*, *TP53, STK11,* and *CDH1*) and moderate/low (*CHECK2*, *PALB2*, and *ATM*) penetrance genes associated with an increased risk of breast cancer have been identified (Foulkes 2008; Rousset-Jablonski and Gompel 2017). Although the understanding of the human genome and techniques for genetic testing have evolved, the inheritance mechanism for several cases of breast cancer with clinical patterns of strong family history still remains unclear.

1.1.1 Surveillance and management options

The purpose of conducting cancer genetic investigations is to identify individuals with an increased cancer risk in order to recommend appropriate management strategies. Molecular genetic testing can be offered after genetic counselling to individuals that fulfil certain criteria for genetic testing based on guidelines proposed by experts, information and results from

databases, and international collaborations (Anon 2020; Paluch-Shimon et al. 2016). An individual's risk of being a mutation carrier, thereby having an increased risk of hereditary breast cancer, can be estimated on the basis of factors such as family history, genetic test results and/or tumour pathology (if known/relevant), as well as demographic data such as current age and/or age at breast or ovarian cancer diagnosis. These criteria are often incorporated into risk prediction models used to objectively and systematically identify individuals at risk. The Breast Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) or the Manchester guidelines are examples of such risk prediction models (Antoniou et al. 2004, 2008; Arver et al. 2011; Lee et al. 2013). These models can be of assistance in the choice of further appropriate recommendations for each specific case depending on their individual risk. For instance, *BRCA* mutation carriers are offered to undergo yearly magnetic resonance imaging (MRI) or ultrasound from the age of 25 and mammography from the age of 30 years in combination with clinical breast examination and monthly self-examinations (Paluch-Shimon et al. 2016). Ultrasound alternated with MRI every other year is offered to women with *TP53*-mutation from the age of 20 years because of the risks of ionizing radiation (Daly et al. 2017). The exact age interval of start and finish for surveillance of *BRCA* mutation carriers varies between European, American, British, and Canadian guidelines. Several meta-analysis have shown that the combination of mammography with MRI increases the sensitivity and yields earlier detection of lower grade tumours as the two modalities complement each other (Warner et al. 2008).

1.1.2 Risk-reducing breast surgery

For women with high risk of hereditary breast cancer, bilateral risk-reducing mastectomy (RRM) is an option that intends to reduce the risk of breast cancer by surgically removing visible breast tissue from which abnormal cell growth originates from. The former term "prophylactic mastectomy" is technically inaccurate and not recommended to be used anymore, since the breast cancer risk is not completely eliminated (Ghosh and Hartmann 2002). The decision to undergo such a surgery is often made after several months of consultations with physicians and psychologists to ensure that the individuals have been presented with the best available evidence-based information that covers both the pros and cons of RRM. They should fully understand its implications and be aware of the non-surgical options.

Due to ethical issues, it is impossible to investigate the breast cancer-specific survival with or without RRM through a randomised controlled trial. Therefore, the next best option is prospective cohort studies of a representative population of women with hereditary high risk of breast cancer, adjusted for confounding factors with an adequate follow-up period. A number of follow-up studies have shown that RRM in asymptomatic *BRCA1/2* mutation carriers decreases the incidence of breast cancer, and reduces the disease-specific mortality by up to approximately 90% (Domchek et al. 2010; Hartmann et al. 1999, 2001; Heemskerk-Gerritsen et al. 2013; Ingham et al. 2013; Kaas et al. 2010; Manning et al. 2015; Meijers-

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Heijboer et al. 2001; Peled et al. 2014; Yao et al. 2015). The incidence of occult cancer is reported to be less than 5% (Hartmann et al. 2001; Manning et al. 2015; Paluch-Shimon et al. 2016; Rebbeck et al. 2004; Yao et al. 2015). Because of the low incidence of occult carcinoma, axillary surgery by means of a sentinel node biopsy is not required (Eisemann and Spiegel 2018; Murphy et al. 2017; Murthy and Chamberlain 2013). RRM is therefore considered to be a safe option from an oncological perspective (Manning et al. 2015; Reynolds et al. 2011).

The risk of contralateral breast cancer is higher in mutation carriers with previous breast cancer who have a confirmed *BRCA1/2* gene mutation, compared to patients with sporadic breast cancer (Graeser, Engel, and Rhiem 2009; Kuchenbaecker et al. 2017; Svenska Bröstcancergruppens nationella riktlinjer n.d.). Therefore, the option to undergo a contralateral RRM should be discussed with breast cancer patients with a high-risk gene mutation. Several studies have reported a decreased incidence of breast cancer after contralateral RRM, but inconsistent results regarding the disease-specific survival because of multiple confounding factors such as the risk of recurrence/metastases from the previous breast cancer or synergistic effects after risk-reducing salpingo-oophorectomy (RRSO) (Evans et al. 2013; Ingham et al. 2013). For high-risk patients who have previously undergone a breast conserving cancer surgery, a complementary RRM of the affected breast can be offered. However, the possibility of achieving an equally symmetric aesthetic outcome as in a RRM for an asymptomatic woman is difficult due to previous scar tissue and local side effects caused by radiotherapy. It is debatable whether contralateral RRM for sporadic breast cancer patients will improve survival; for this reason, and because of the added psychological and physical morbidity, RRM is not recommended routinely to women with moderate risk of breast cancer (Eisemann and Spiegel 2018; Fayanju et al. 2014).

1.1.2.1 Total (simple) mastectomy

In a total (simple) mastectomy, the underneath muscles are kept intact. The incision is often horizontal and elliptical as it yields better aesthetic outcome. The breast tissue (as well as the nipple and areola) is then removed by dissection down to the pectoral muscles (**Figure 1**), extending from the infraclavicular border to right below the inframammary fold.

Rib

Superficial fascia

Deep layer

Superficial layer

Pectoralis major muscle

Suspensory ligament (Cooper's)

Pectoralis minor muscle

Lactiferous duct

Intercostal vessels and nerve

Intercostal muscle

Pleura

Fat (subcutaneous tissue)

Gland lobule
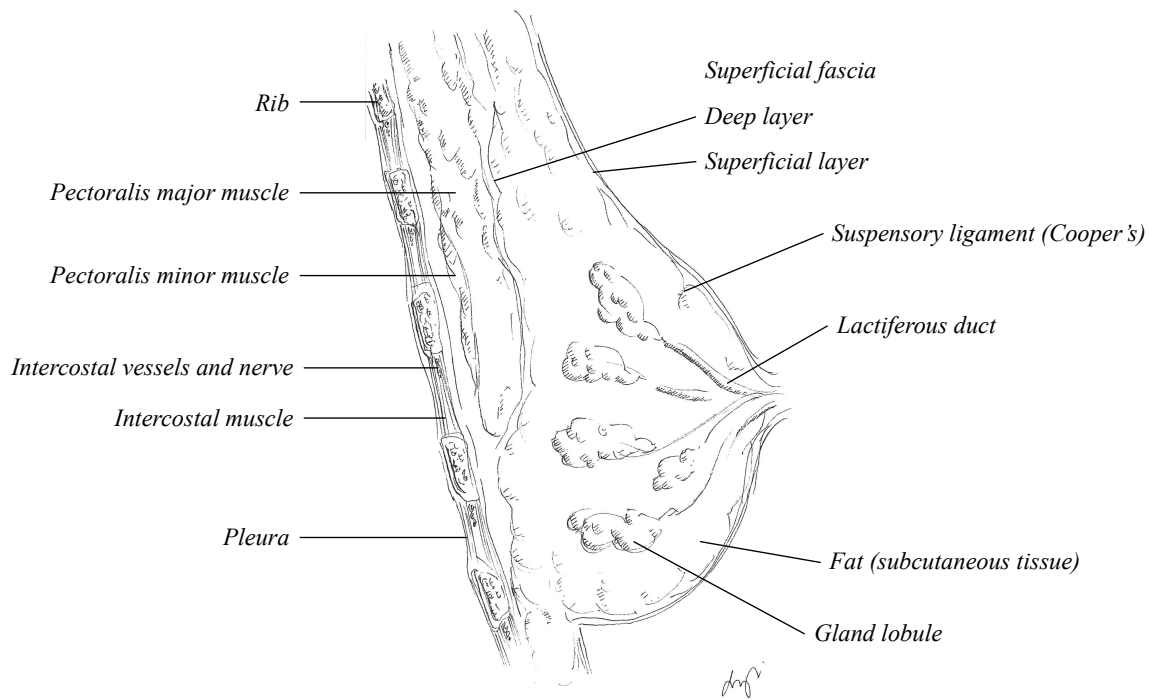
Figure 1 Anatomy of the breast

1.1.2.2 Nipple-sparing mastectomy

The nipple-sparing technique can be performed through several different incisions (**Figure 2**). A biopsy of the nipple base is collected for pathological analysis to ensure that no breast cancer is present in the nipple-areola complex (NAC) that is left in place. The size of skin reduction is adjusted depending on the initial breast volume, the remaining skin envelope after the removal of the breast tissue, and the woman's desired reconstructive results. If the tip of the nipple is aimed to be regrafted after full removal of the nipple, a biopsy of the nipple base is performed before it is regrafted at the end of the surgery. Tattooing of areolas around the regrafted nipple can be offered after the implant expansion is completed.

Figure 2 Different surgical techniques: (a) modified reduction mammaplasty incision in patients with large or ptotic breasts, (b) periareolar incision or (c) elliptical incision in women with small- to moderate-sized breasts
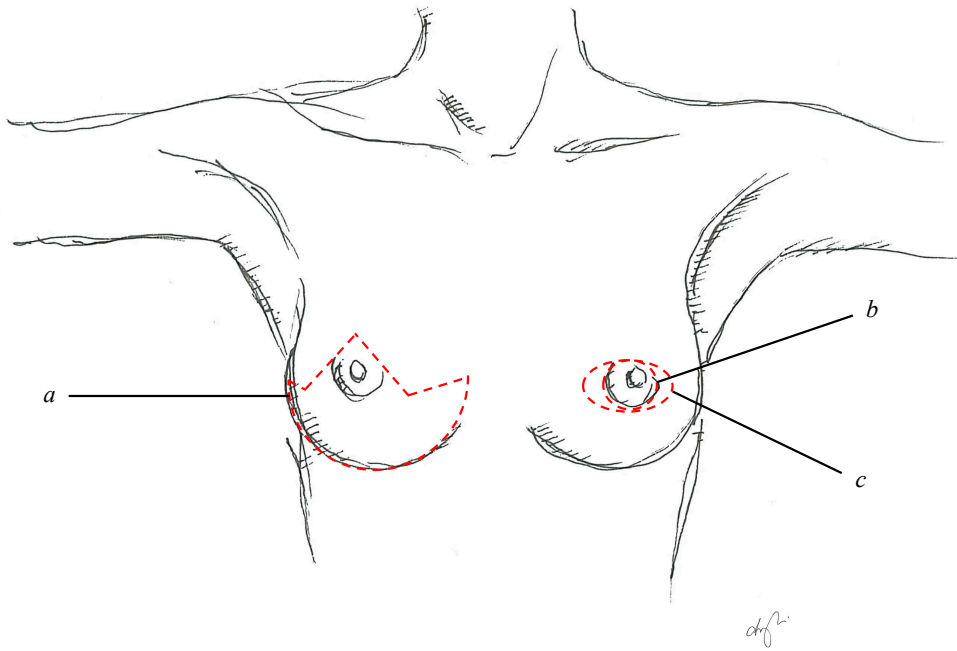
1.1.2.3   Reconstructive surgery

Reconstructive breast surgery is offered as an additional option to high-risk women who chose to undergo RRM. The option is discussed during the preoperative consultation, where the reconstructive plastic surgeon can show examples of and explain the pros and cons of different reconstructive techniques, present the option(s) that are most suitable for the woman based on her anatomical and health condition, and discuss the consequences related with and without breast reconstruction observed in follow-up studies.

The reconstruction can either be purely implant-based or involve autologous tissue. In Sweden, the most common implant-based reconstruction technique has since the 1990s been total submuscular placement, i.e., the implants are placed under and covered mainly by the pectoralis major muscle. Different implant shapes (anatomical or round) and materials (mainly silicone gel or saline) can be chosen depending on the quality of the surrounding tissue, breast volume and shape, preferences of the patient, and of the surgeon. Implants can have a prefilled fixed volume and form or be expandable. Expandable implants can be manufactured in different ways. For instance, permanent expander implants are filled with saline inside a silicone gel envelope, with filling ports that can be positioned subcutaneously at the chest wall. The filling ports are removed three to six months after the surgery when the desirable expansion/volume of the reconstructed breast is achieved.

For the participants in this thesis, immediate submuscular implant-based reconstruction was the technique of choice due to clinic preferences at the time (1997–2010). The implants were placed under the pectoralis major muscle, the serratus anterior muscle, and the fascia of the

rectus muscle for total muscle coverage (**Figure 3**). Most women received anatomically shaped or round permanent expandable implants with detachable filling ports, while a few were operated with permanent cohesive silicone gel implants with a fixed volume.
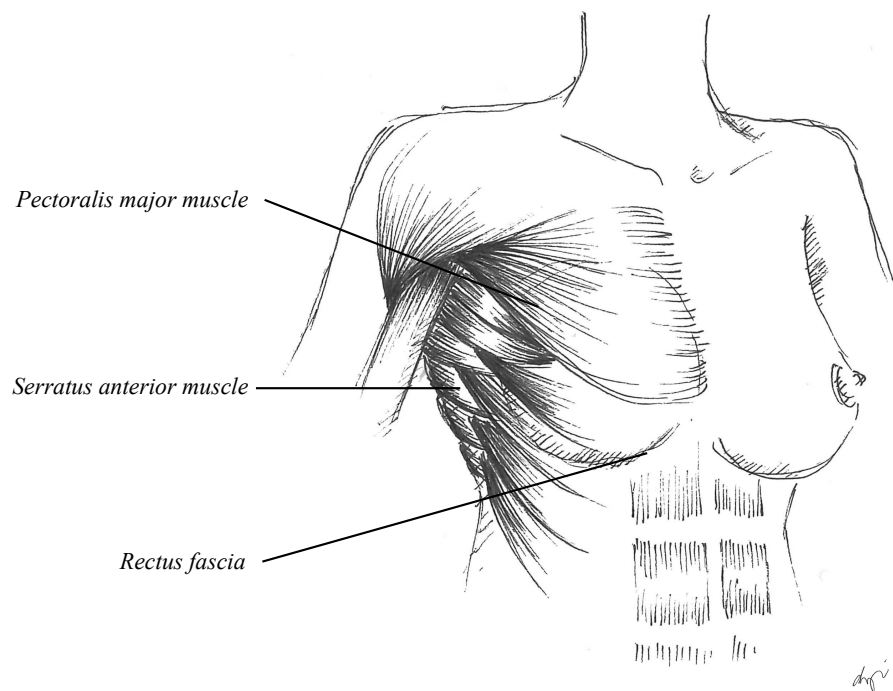
Pectoralis major muscle

Serratus anterior muscle

Rectus fascia

Figure 3 Total submuscular implant-based breast reconstruction

1.2   EVALUATION OF AESTHETIC OUTCOME

Many studies have investigated ways to evaluate aesthetic outcome of the female breasts, while other studies have explored the standard or ideal values of breast aesthetics. Limitations of these studies include variations in design and methods used, as well as different evaluators (ranging from plastic surgeons to lay persons with different experiences and backgrounds), which makes it difficult to draw conclusions from them. Therefore, more objective assessment methods have been studied. Skin discolouration, scars, placement of NAC, breast volume, symmetry, and ratio of specific landmarks are known important characteristics of breast aesthetics and most frequently used (Hauben et al. 2003; Loughry et al. 1987; Qiao et al. 1997; Smith et al. 1986; Sneeuw et al. 1992; Westreich 1997). Objective standardised determinants of breast aesthetics have thus far not been shown to correlate with subjective assessments and are therefore not widely used.

1.2.1   Objective evaluation of aesthetic outcome

In theory, an objective measurement diminishes the magnitude of systematic errors that comes with subjective evaluations depending on the observer. With an increasing diversity of breast surgical techniques, from breast conservation and oncoplastic surgery to post-

mastectomy reconstructions, the interest for an objective measurement method that allows for standardised comparisons of the aesthetic outcome has increased. If such a method can be tested and reproduced efficiently in the clinical setting, it allows surgeons to evaluate and compare their results over time in relation to different surgical techniques and effects of oncological treatment. Moreover, it could act as a tool to discuss possible patient–surgeon discrepancies in the evaluation of the aesthetic results.

Attempts to find objective assessment methods have continuously been explored and evaluated, from Archimedes principle of water displacement or thermoplastic casts, to computed tomography (CT) or MRI (Chae et al. 2014; Edsander-Nord et al. 1996; Rha, Choi, and Yoo 2014; Tezel and Numanoğlu 2000). Breast Cancer Conservative Treatment. cosmetic results (BCCT.core) is an example of a validated semiautomated photogrammetry[1] software developed in 2007, that categorises aesthetic outcome into four classes (excellent, good, fair, and poor), by using an anthropomorphic measurement[2] algorithm set to find the best subset and best relation between the following measures: observer-chosen specific reference marks on two-dimensional (2D) photographs, 14 asymmetry, 8 colour, and 8 scar features (Cardoso and Cardoso 2007). However, this type of assessment may miss important anatomical landmarks, as the information of a three-dimensional (3D) object is compromised when captured by 2D photography (Cardoso et al. 2007, 2015; Chang et al. 2015; Fitzal et al. 2007).

With improving technology, three-dimensional surface imaging (3D-SI) options have evolved from conventional cameras placed at different angles, thereby creating a perception of depth, to manufactured 3D cameras with tailored computer software programs enabling image rendering and analysis (Loughry et al. 1989). Compared to the 3D images obtained from CT and MRIs, 3D-SI is a non-invasive, quick, and safe biostereometric method[3] (Galdino et al. 2002; Losken et al. 2005). Consequently, the 3D-SI technique is predicted to have a great potential in oncoplastic surgery, with applications in the planning of surgical procedures, to patient education, and clinical research (Jacobs 2001; Kovacs et al. 2004; O'Connell et al. 2015).

The leading manufacturers of 3D-SI systems are either based on stereophotogrammetry, laser scans, 3D digital photography, or light digitalisation (Honrado and Larrabee 2004; Tzou et al. 2014). In the early 2000s, several studies investigated laser scan-based methods, with varying degrees of reproducibility of breast volume measurements (Cardoso et al. 2015; Eriksen et al. 2012; Galdino et al. 2002; Losken et al. 2005). It was, however, limited to high-income centres, with variable interest among academic institutions due to the lack of user experience,

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[1] Photogrammetry = calculating measurements from photographs
[2] Anthropomorphic measurements = measuring distances between a set of anatomical landmarks
[3] Biostereometric method or evaluation = anterior and lateral photographs of breasts, digitalised into computerised plotting device enabling breast volume determination through mathematically derived algorithms

local routines, and limited comparative studies with existing assessment methods that were commonly used at the time with good enough results to not be exchanged with a new technique (Cardoso et al. 2018).

During 2012–2020, the department of Medical Imaging at Karolinska University Hospital was equipped with the VECTRA XT 3D imaging system (Canfield Scientific, New Jersey, USA), that uses stereophotogrammetry technology to capture colour images in ultra-high resolution in approximately 3.5 milliseconds. With built-in lighting designed for clinical photography, the 3D imaging system does not require special lighting in the room to create true colour shadow-less images. Several computer software programmes have been developed for the imaging system, allowing for visualisation of expected surgical results with different breast implants (Breast Sculptor®) or data analysis of specific landmarks/surface areas (VECTRA Analysis Module® (VAM)) to name a few (Chae et al. 2016).

In a recent study evaluating breast images obtained through the VECTRA XT 3D imaging system, a ranking of factors affecting the aesthetic outcome was proposed, where breast shape (lower and upper pole) and height were found to be primary factors and ranked higher than breast size (volume) when evaluated by plastic surgeons (Sandberg et al. 2020). Another study specifically investigated measurements of breast volume acquired through VAM, showing promising results with high and better reproducibility than 3D breast volume measurements obtained from MRI (the previously most precise volume measuring method) (Killaars et al. 2020).

By copying and superimposing 3D surface images of the imaged torso, the distance between corresponding coordinates in the two surface images could be used to estimate the overall distance between them through root mean square (d_{RMS}) (Meybodi 2014). d_{RMS} is obtained by the square root of each distance squared, allowing both positive and negative surface differences (**Equation 1**, **Figure 4**). The closer d_{RMS} is to zero, the more symmetrical the compared breast surfaces (shapes) are.

$$d_{RMS} = \left(\frac{1}{n} \sum_{i=1}^{n} d_i^2 \right)^{\frac{1}{2}} = \text{mean distance between two surfaces}$$

$$d_i = \left(x_{i_{left}} - x_{i_{right}} \right)^2 + \left(y_{i_{left}} - y_{i_{right}} \right)^2 + \left(z_{i_{left}} - z_{i_{right}} \right)^2$$

Equation 1 Calculation of the distance between two surfaces (d_{RMS}), where d = distance between two corresponding points
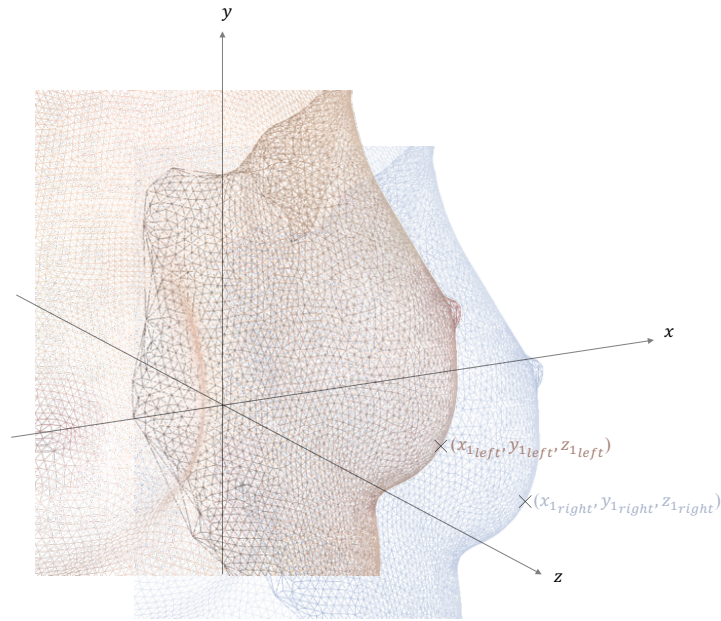
Figure 4 Schematic drawing of surface distances between two corresponding points in VECTRA Analysis Module®

The idea to use mathematics to describe and predict breast measurements in order to facilitate selection of the optimal surgical method is not new. For example, mathematical formulas using measurements of skeletal anatomical landmarks taken directly from a patient or a set of 2D photographs have been described in the 1990s as a method of predicting desired breast shape and volume changes (Brown, Cheng, and Kurtay 2000; Westreich 1997).

Today, there is a lack of an objective standardised method to evaluate breast symmetry. In addition, optical symmetry seems to play an important role psychosocially for patients (Chan et al. 2011; Neto et al. 2012). It was therefore of interest to use the mathematical properties of the surface image coordinates from 3D-SI to investigate this further.

1.2.2   Subjective evaluation of aesthetic outcome

Measurements of the "perfect" breast documented already in 1955 have commonly been used as standard values in aesthetic breast surgery, even though the selection of women might have been biased and not suitable for generalisation (Penn 1955). Since then, measurements of "normal" breasts have been investigated, where "normal values" between certain fixed anatomical landmarks were proposed (Smith et al. 1986; Westreich 1997). However, the perception of breast aesthetics is elusive due to cultural and ethnical differences, as well as varying personal preferences or trends at a specific time (Catanuto et al. 2019).

1.2.2.1 Questionnaires

Patient satisfaction of aesthetic outcome after breast reconstruction can be evaluated through self-reported questionnaires (Frost et al. 2000, 2005; Gahm, Jurell, et al. 2010; Keller et al. 2019). The development of a questionnaire is carried out in several phases (The EORTC Quality of Life Group & EORTC Quality of Life Unit 2002). Questionnaire items and scales must undergo detailed systematic scrutiny to ensure that the end product is relevant for the intended study sample, with as few conditional items as possible. Moreover, debriefing questionnaires and semi-structured interviews are performed in parallel to identify questions that might be perceived as upsetting, difficult to answer, or confusing. To ensure comparative possibilities, sociodemographic and clinical data should also be collected. By implementing the questionnaire in international settings, its utility can be expanded.

A number of different questionnaires have been developed to measure patient satisfaction of aesthetic outcome after breast reconstruction. A selection of examples is listed below:

> *BREAST-Q* was developed in 2009 by American, Canadian, and British clinicians to quantify the psychosocial, physical, and sexual well-being, pre- and postoperative satisfaction of the breast, overall outcome, and experience of the care, including a module targeting questions regarding breast reconstructions. It has been validated, and is translated into over 30 languages (Anon 2017; Pusic et al. 2009).

> The European Organisation for Research and Treatment of Cancer (EORTC) developed a questionnaire to measure the quality of life after breast reconstruction, *EORTC QLQ-BRECON23* (Winters et al. 2014, 2017). It has undergone Phase IV testing, and is considered a well-developed and valid instrument for patient-reported measurements of breast reconstruction after mastectomy (Davies et al. 2021).

> Another common approach is the use of *study specific questionnaires*, however, these are often not validated (Pusic et al. 2007).

1.2.2.2 Panels

Subjective evaluations can also be assessed by a panel consisting of laymen, experts/surgeons, or observers with mixed backgrounds. Measurements can be taken directly on the patient or evaluated using representative images. The panel can for instance use 2D photographs of the women's breasts to make their assessment following pre-selected measurable factors that have been considered to affect the breast aesthetics. However, subjective breast assessment by a panel often focuses on symmetry and distortion, rather than volume, and might lack accuracy and reproducibility (Haloua et al. 2013; Henseler et al. 2013; Yavuzer, Smirnes, and Jackson 2001).

Several studies have demonstrated that the perception of aesthetic outcome and body image is are evaluated differently by plastic surgeons and the patients themselves, with patients more often scoring higher satisfaction (Cohen et al. 2005; Hsia and Thomson 2003; Kuroda et al. 2016; Sneeuw et al. 1992; Visser et al. 2010). There is a knowledge gap regarding standardised objective methods to quantify determinants of aesthetic outcome to understand the impact of disproportion of the breast on a patient's quality of life. Furthermore, this method should ideally be compatible in the clinical setting and have high reproducibility.

1.3 ASSESSMENT OF PSYCHOSOCIAL OUTCOMES

Many women are relatively young and physically healthy at the time of making the decision to undergo bilateral RRM. Not only are there surgery-related risks such as bleeding, postoperative infections, reconstructive complications, and tissue necrosis, but, more so, the long-term effect of RRM and IBR constitutes an irreversible change of the body.

In order to assist the women in making an informed decision, it is of importance for the healthcare providers to be able to answer questions about the outcomes of women who have chosen to undergo RRM. This should be done not only in terms of breast cancer incidence, disease-specific mortality rates, and surgical aspects, but also in terms of aspects of the everyday lives that the women are expected to continue leading regardless of their choice. Patient-reported outcomes (PROs) are measurable outcomes of specific aspects evaluated by the patients themselves.

1.3.1 Satisfaction with breast reconstruction

The patient's own assessment of the aesthetic outcome is a key outcome measure in the assessment of satisfaction with the surgical results. From the retrospective studies, 6–32% reported unacceptable/dissatisfied results with the breast reconstruction (Borgen et al. 1998; Bresser et al. 2006; De La Peña-Salcedo, Soto-Miranda, and Lopez-Salguero 2012; Montgomery et al. 1999; Stefanek 1995), where higher satisfaction with the contralateral RRM has been shown to be associated with higher health-related quality of life (HRQoL) (Frost et al. 2011). Even so, the range of women who reported high/excellent satisfaction with the aesthetic results was 35–90%.

Results from prospective follow-up studies using validated questionnaires showed that more than 70% thought that the overall results corresponded to their expectations, and most of the women (over 80%) were satisfied with the size of their breasts. However, only acceptable levels of satisfaction with breast shape and NAC were reported, and around 50% thought that at least one breast was too hard when assessing implant reconstructions (Brandberg et al. 2012; Gahm, Jurell, et al. 2010).

1.3.2 Body image

In retrospective studies, around 30% reported that their body image was negatively affected after RRM, about 50% felt self-conscious about their appearance, and 20% reported dissatisfaction with their body and a worsened self-image (Frost et al. 2005, 2011; Hopwood et al. 2000; Metcalfe et al. 2004, 2005). Nevertheless, almost 50% reported no change in satisfaction with body image in another retrospective study (Frost et al. 2000).

From the prospective studies with validated questionnaires, similar results in the same direction were reported. Problems with body image seem to persist up to two years postoperatively, with over 50% reporting problems with their scars and appearance, although a slight improvement (but not to preoperative levels) was seen in one study at the 6–9 year follow-up (Brandberg et al. 2008; Gopie et al. 2013; den Heijer et al. 2012; Unukovych et al. 2012).

1.3.3 Sexuality

In retrospective studies using non-validated questionnaires, 23–44% reported an adverse change in their sexual relationship with over 70% feeling a negative change in their partner's perception (Bresser et al. 2006; Frost et al. 2000, 2005), where a diminished sense of sexuality and the results of their breast reconstruction were reasons that affected the sexuality (Montgomery et al. 1999). In retrospective studies with validated questionnaires, 15–55% reported that they felt less sexually attractive (Frost et al. 2011; Hopwood et al. 2000), and over 30% reported that their sexual lives were worsened (Metcalfe et al. 2004, 2005).

From prospective studies using validated questionnaires, women reported a decreased level of pleasure and sexual satisfaction postoperatively, significant negative changes in the sexual importance of the breasts and in the sexual enjoyment related to the breasts as almost 50% reported a total loss of sexual sensations in their breasts (Brandberg et al. 2008; Gahm, Wickman, and Brandberg 2010; Gopie et al. 2013). One study reported no statistical significant changes in the degree of sexual pleasure up to 18 months postoperatively (Hatcher, Fallowfield, and A'Hern 2001).

1.3.4 Anxiety and depressive symptoms

The majority of women have reported high satisfaction with the decision to undergo RRM (Boughey et al. 2015), with significantly lowered levels of breast cancer worry after RRM compared to preoperative baseline levels or levels of worry among women who chose surveillance. In contrast, studies have reported higher levels of anxiety and belief of developing breast cancer among those who opted for RRM.

In retrospective studies, less than 20% reported a negative impact on their levels of stress in life and emotional stability (Frost et al. 2005), 9–32% reported clinical levels of anxiety and

distress, while only 2% fulfilled the cut-off indicating potential clinical depression (Isern et al. 2008; Metcalfe et al. 2004, 2005).

In prospective follow-up studies, the levels of anxiety and depressive symptoms significantly decreased after the surgery (up to 18 months follow-up) (Brandberg et al. 2008; Hatcher et al. 2001). General and breast cancer-related distress were reduced, while body image problems after RRM increased (den Heijer et al. 2012).

1.3.5 Health-related quality of life

HRQoL measures assess the patient's subjective perceptions of aspects of HRQoL, such as physical-, emotional-, social-, and cognitive functioning. Few studies have used validated questionnaires for the assessment of HRQoL. One retrospective study used the Functional Assessment of Cancer Therapy questionnaire, where 61–76% of women who underwent RRM reported high contentment with quality of life (Geiger et al. 2006, 2007). This was similar to the levels of contentment reported by women who did not chose to undergo RRM. Another retrospective study used the Short Form-36 Health Survey Questionnaire (SF-36), where the women who underwent RRM and immediate breast reconstruction (IBR) reported higher scores in all domains except from mental health compared with the normative Swedish population (Isern et al. 2008). No negative impact on HRQoL was seen in prospective follow-up studies using the same questionnaire (up to two years postoperatively) (Brandberg et al. 2008; Elder et al. 2005; Gahm, Wickman, et al. 2010; Unukovych et al. 2012). General health was even seen to statistically significantly improve six months postoperatively (Gopie et al. 2013).

1.3.6 Partners' perspectives

Hereditary breast cancer and genetic testing involves the entire family and the emotional support from partners plays an important role in the women's coping mechanism (van Oostrom et al. 2007). The perception of partner support has been shown to be predictive of the women's cancer-specific distress up to two years post-genetic testing, with higher levels of distress among couples where partner support was insufficient (Manne et al. 2004; Wylie, Smith, and Botkin 2003). At the same time, partners have expressed anxiety and worry particularly when the women have tested positive for a cancer related mutation, which might affect partner support and communication (van Oostrom et al. 2007). Partner education regarding RRM and reconstruction possibilities has been suggested to alleviate partners' levels of concern (Metcalfe et al. 2002). The understudied field of partners to women with increased hereditary risk of breast cancer consists mainly of heterogenous and descriptive small studies (Lloyd et al. 2000; Metcalfe et al. 2002; Mireskandari et al. 2006), and few of prospective design (Manne et al. 2004), where psychological key aspects such as issues related to sexuality remain unexplored. In addition, the partners' levels of distress and

willingness to disclose personal intimate information might introduce selection bias of participating partners (Mauer et al. 2016).

Following RRM and IBR, body image problems and issues related with sexuality have been reported to increase among women compared with their preoperative reported levels (Gahm, Wickman, et al. 2010; Unukovych, Johansson, and Brandberg 2017). In comparison, in a small study, all men (*n*=11) reported unchanged levels of attractiveness to their partners after RRM and breast reconstruction (Mauer et al. 2016). Breast cancer patients themselves reported more negative perceptions of their body than their partners did (Mireskandari et al. 2006). Notably, partner's evaluation of the women's bodily appearance, and not the women's own evaluation have been described to be a statistical significant predictor for marriage adjustment (Ming 2002). Yet little is known about the partners' perception of the women's experiences after RRM and IBR. The method to investigate alternative information from the partners' perspective is a way to increase reliability and validity of the women's perspectives (Lloyd et al. 2000).

2 RESEARCH AIMS

I. To prospectively follow-up and investigate women's perceptions of the aesthetic outcome of their implant-based breast reconstruction, as well as body image, sexuality, anxiety and depressive symptoms, and health-related quality of life (HRQoL) 6 to 20 years after bilateral risk-reducing mastectomy (RRM) and immediate breast reconstruction (IBR) due to high risk of hereditary breast cancer.

    a. To compare the patient-reported outcomes (PROs) at the long-term assessment with the corresponding outcomes previously reported one-year post-RRM and IBR.

    b. To compare the long-term PROs reported by women without previous breast cancer to the corresponding outcomes reported by women who were diagnosed with breast cancer prior to their RRM and IBR.

II. To investigate partners' perceptions of the women's responses regarding body image, sexuality, and satisfaction with the aesthetic outcome long-term after RRM and IBR, and their own evaluations regarding HRQoL and anxiety and depressive symptoms.

    a. To compare the partners' perceptions of the women's responses with the women's self-reports.

    b. To compare the HRQoL and anxiety and depressive symptoms between the partners and the women.

    c. To compare the HRQoL of the study participants with age- and sex-adjusted normative data from the Swedish population.

III. To investigate if the VECTRA XT 3D imaging system could provide reproducible assessments of breast aesthetic outcome.

    a. To investigate the reproducibility of three-dimensional surface imaging (3D-SI) measurements (breast symmetry and volume) of women standing in two different postures estimated by two independent observers.

    b. To investigate the correlation between breast symmetry and volume difference.

    c. To propose and methodologically evaluate a new relative parameter: volume-shape-symmetry (VSS).

IV. To investigate the associations between PROs regarding satisfaction with the aesthetic outcome after RRM and IBR and 3D-SI measurements of reconstructive outcomes.

3 MATERIALS AND METHODS

3.1 STUDY POPULATION

In 1996, a multidisciplinary team constituted of clinical geneticists, oncologists, breast surgeons, reconstructive plastic surgeons, a gynaecologist, specialised nurses, and a psychologist was established at Karolinska University Hospital, Stockholm, in order to meet the increasing interest in risk-reducing mastectomy (RRM) for women with high hereditary risk of breast cancer. One year later, routine procedures had been implemented. The team met regularly to discuss all women who opted for RRM, including findings and results from consultations, examinations, and tests. Some of the women had a known family history of breast cancer with a confirmed mutation, and thus underwent genetic testing. Others did not have a relative with a confirmed mutation, but were offered to undergo RRM based on their pedigree. For some women, genetic testing was performed because they were diagnosed with breast or ovarian cancer, in addition to a family history of many breast cancer cases. Depending on their test results, estimated level of risk of developing breast cancer, and age, RRM and IBR were offered as a strategy of reducing the risk of developing breast cancer. The psychological impact in the short and long time of this risk-reducing procedure was unknown at the time. All women who underwent RRM between March 1997 and September 2010 were invited prior the surgery to partake in a prospective follow-up study specifically designed to investigate these women's HRQoL, anxiety and depressive symptoms, body image, sexuality, and satisfaction with the aesthetic outcome, before RRM, and 6, 12, and 24 months after the surgery. Both women with and without breast cancer prior to the risk-reducing surgery were invited.

Approximately 20 years after the first woman was enrolled in the prospective follow-up project, the PI (Yvonne Brandberg) was granted a new ethical approval to conduct a prospective long-term follow-up of the women that had previously participated in the project together with members from the original multidisciplinary clinical research team, and with Lucy Bai as their new PhD candidate. The aim was to investigate the long-term impact of RRM and IBR, since the women were relatively young at the time of surgery and were expected to live for many more years with the effects related to the surgery.

Data collection was initiated during November 2016, and continued until February 2018, summarised in detail in **Table 1**. For all papers, the inclusion criteria were that the women had participated in the previous follow-up studies at least once. The exclusion criteria were breast cancer or any other cancer diagnosis after the date of RRM (**Figure 5**). Demographic data of all participants are shown in **Table 2**.

Table 1 Overview of the study period and methods for **Paper I–IV**

Paper	I	II	III	IV
Study period of data collection	Mar 1997–May 2017	Nov 2016–Apr 2017	May 2017–Feb 2018	Nov 2016–Feb 2018
Study participants (*n*)	146	36 couples	58	58
Data collection	Questionnaire responses, clinical data from medical charts	Questionnaire responses, clinical data from medical charts, social information	3D surface images (58x3x2 images)	Questionnaire responses, clinical data from medical charts, 3D surface images (58 images)
Questionnaires	EORTC QLQ-BRR26, BIS, SAQ, HAD, SF-36	EORTC QLQ-BRR26, BIS, SAQ, HAD, SF-36		EORTC QLQ-BRECON23, BIS
Variables	Questionnaire items	Questionnaire items	VL, VR, d_{RMS}, VSS	VL, VR, d_{RMS}, VSS, questionnaire items
Statistical analysis	Paired *t*-test, unpaired comparisons by linear regression models	Paired *t*-test	Descriptive statistics, Bland-Altman plots, one-way and mixed-effects two-way ANOVA models	Descriptive statistics, Kruskal-Wallis test
Machines and software programmes	Stata/IC 14.2 for Mac, StataCorp, TX, USA	Stata/IC 14.2 for Mac, StataCorp, TX, USA	Stata/IC 14.2 for Mac, StataCorp, TX, USA. VECTRA XT 3D imaging system, Canfield Scientific, New Jersey, USA	Stata/IC 14.2 for Mac, StataCorp, TX, USA. VECTRA XT 3D imaging system, Canfield Scientific, New Jersey, USA

3D = Three-Dimensional

EORTC QLQ-BRR26 = European Organisation for Research and Treatment of Cancer Quality of Life after Breast Reconstruction Questionnaire

BIS = Body Image Scale

SAQ = Sexuality Activity Questionnaire

HAD = Hospital Anxiety and Depression scale

SF-36 = Short-Form-36 Health Survey

d_{RMS} = Distance between two surfaces as Root Mean Square, i.e., breast shape symmetry

VL = Volume of the Left breast

VR = Volume of the Right breast

VSS = Volume-shape-symmetry

TX = Texas

Figure 5 Flowchart of the study population for **Papers I–IV** (expandable spread)
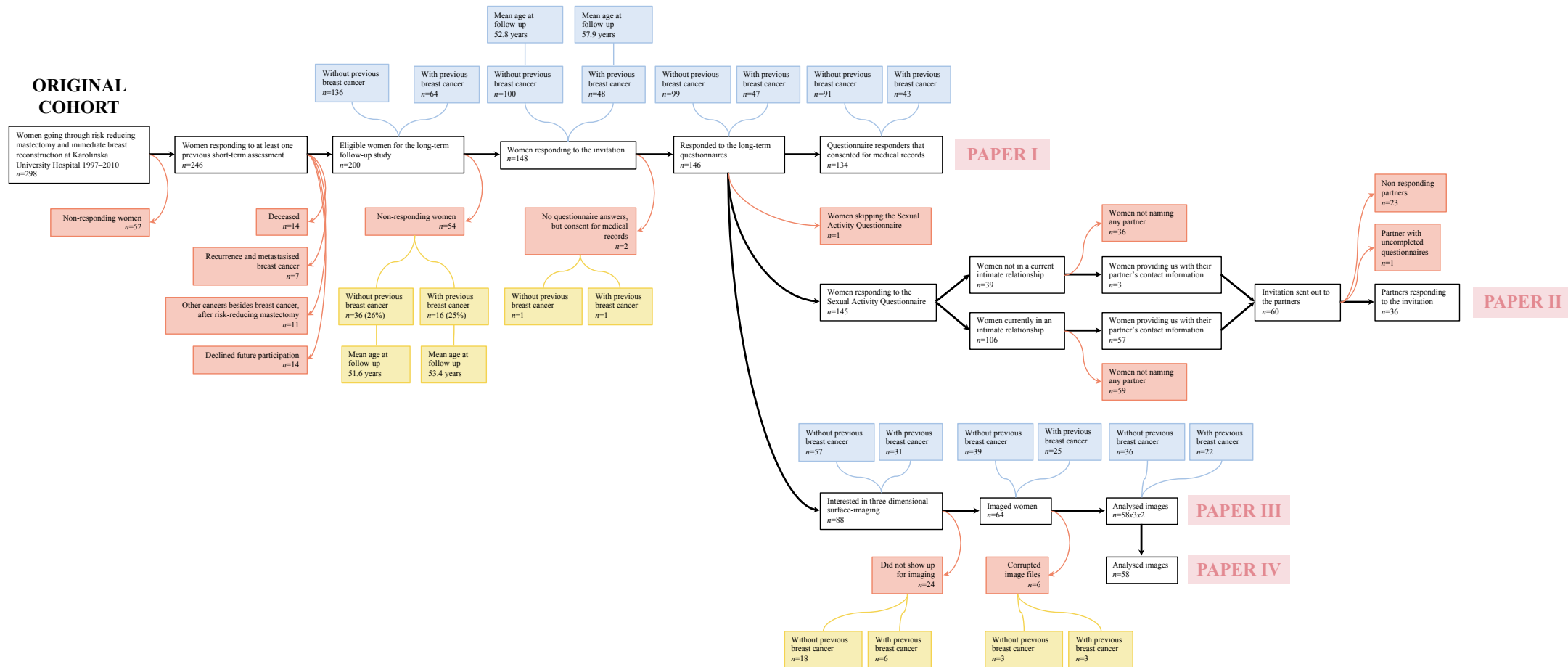
ORIGINAL COHORT

Women going through risk-reducing mastectomy and immediate breast reconstruction at Karolinska University Hospital 1997–2010
n=298

Women responding to at least one previous short-term assessment
n=246

Eligible women for the long-term follow-up study
n=200

Women responding to the invitation
n=148

Responded to the long-term questionnaires
n=146

Questionnaire responders that consented for medical records
n=134

PAPER I

Non-responding women
n=52

Deceased
n=14

Recurrence and metastasised breast cancer
n=7

Other cancers besides breast cancer, after risk-reducing mastectomy
n=11

Declined future participation
n=14

Without previous breast cancer
n=136

With previous breast cancer
n=64

Without previous breast cancer
n=100

With previous breast cancer
n=48

Without previous breast cancer
n=99

With previous breast cancer
n=47

Without previous breast cancer
n=91

With previous breast cancer
n=43

Mean age at follow-up 52.8 years

Mean age at follow-up 57.9 years

Non-responding women
n=54

Without previous breast cancer
n=36 (26%)

With previous breast cancer
n=16 (25%)

Mean age at follow-up 51.6 years

Mean age at follow-up 53.4 years

No questionnaire answers, but consent for medical records
n=2

Without previous breast cancer
n=1

With previous breast cancer
n=1

Women responding to the Sexual Activity Questionnaire
n=145

Women skipping the Sexual Activity Questionnaire
n=1

Women not in a current intimate relationship
n=39

Women currently in an intimate relationship
n=106

Women providing us with their partner's contact information
n=3

Women providing us with their partner's contact information
n=57

Women not naming any partner
n=36

Women not naming any partner
n=59

Invitation sent out to the partners
n=60

Partners responding to the invitation
n=36

PAPER II

Non-responding partners
n=23

Partner with uncompleted questionnaires
n=1

Interested in three-dimensional surface-imaging
n=88

Imaged women
n=64

Analysed images
n=58x3x2

PAPER III

Analysed images
n=58

PAPER IV

Without previous breast cancer
n=57

With previous breast cancer
n=31

Without previous breast cancer
n=39

With previous breast cancer
n=25

Without previous breast cancer
n=36

With previous breast cancer
n=22

Did not show up for imaging
n=24

Corrupted image files
n=6

Without previous breast cancer
n=18

With previous breast cancer
n=6

Without previous breast cancer
n=3

With previous breast cancer
n=3

Table 2 Demographic data of the participants in **Paper I–IV**

		Paper I		**Paper II**		**Paper III and IV**	
Variable		Cancer *n* (%)	No cancer *n* (%)	Women *n* (%)	Partners *n* (%)	Cancer *n* (%)	No cancer *n* (%)
Sex							
	Female	44 (100)	92 (100)	36 (100)	2 (6)	22 (100)	36 (100)
	Male				34 (94)		
Age at risk-reducing surgery (years)							
	Range	30–69	26–68	26–62		30–64	26–62
	Mean	47	41	40		48	42
	Median	45	39	37		47	41
Age at return of questionnaires (years)							
	Range	41–86	35–80	35–72	34–74	41–73	40–70
	Mean	58	53	51	53	59	54
	Median	56	52	49	51	58	54
Age at 3D-SI							
	Range					42–73	41–71
	Mean					60	55
	Median					58	54
***BRCA* mutation status**							
	BRCA1/BRCA2/BRCAX[*]	33 (75)	50 (54)	32 (89)		15 (68)	24 (67)
	No mutation or unknown	11 (25)	42 (46)	4 (11)		7 (32)	12 (33)
BMI							
	<18.5	2 (5)	4 (4)	3 (8)		2 (9)	2 (5.5)
	18.5–<25	31(70)	62 (67)	24 (67)		14(64)	23(64)
	25–<30	7 (15)	10 (11)	3 (8)		4 (18)	3 (8)
	≥30	2 (5)	6 (7)	0 (0)		1 (4.5)	2 (5.5)
	Missing	2 (5)	10 (11)	6 (17)		1 (4.5)	6 (17)
Bilateral risk-reducing salpingo-oophorectomy							
	Yes	28 (64)	52 (57)	20 (56)		13 (59)	22 (61)
	No	15 (34)	39 (42)	13 (36)		9 (41)	14 (39)
	Missing	1 (2)	1 (1)	3 (8)			
Type of breast cancer							
	None		92 (100)	25 (69)			36 (100)
	In situ	6 (14)		3 (8)		4 (18)	
	Invasive	35 (84)		7 (19)		17 (77)	
	Missing	1 (2)		1 (3)		1 (5)	
Type of breast surgery							
	Risk-reducing mastectomy[†]	42 (95)	89 (97)	36 (100)		22 (100)	36 (100)
	Immediate implant-based breast reconstruction	42 (95)	87 (95)	35 (97)		22 (100)	33 (92)
	Reduction/mastopexy	1 (2)	3 (3)				
	Missing			1 (3)			3 (8)
Radiotherapy							
	Yes	28 (64)		8 (73)[‡]		15 (68)	
	No	13 (29)		1 (9)[‡]		6 (27)	
	Missing	3 (7)		2 (18)[‡]		1 (5)	
Chemotherapy							
	Yes	28 (64)		7 (64)[‡]		15 (68)	
	No	13 (29)		2 (18)[‡]		5 (23)	
	Missing	3 (7)		2 (18)[‡]		2 (9)	
Endocrine therapy							
	Yes	22 (50)		4 (36)[‡]		11 (50)	
	No	18 (41)		4 (36)[‡]		7 (32)	
	Missing	4 (9)		3 (27)[‡]		4 (18)	
Reoperations after risk-reducing mastectomy							
	Planned[§]	29 (66)	48 (52)	12 (33)		8 (36)	16 (44)
	Unanticipated[¶]	15 (34)	40 (44)	22 (61)		14 (64)	17 (48)
	Missing		4 (4)	4 (11)			3 (8)

[*] *BRCAX* = women with breast cancer and/or ovarian cancer, screened negative for *BRCA1* and *BRCA2*, but with family history of breast cancer

[†] Number of women undergoing complementary/contralateral mastectomy after breast cancer surgery:

Paper I: *n*(breast conserving surgery)=20 (48%), *n*(mastectomy)=22 (52%)

Paper II: *n*(breast conserving surgery)=8 (73%), *n*(mastectomy)=2 (18%), *n*(missing)=1 (9%)

Paper IV: *n*(breast conserving surgery)=10 (45%), *n*(mastectomy)=12 (55%)

‡ In proportion to cancer cases only

§ Planned surgeries associated with risk-reducing mastectomy and immediate breast reconstruction, e.g., removal of filling port, nipple reconstruction

¶ Unanticipated surgeries after risk-reducing mastectomy and immediate breast reconstruction requiring general anaesthesia, e.g., implant-related issues, immediate postoperative complications, aesthetic concerns

3.2 PATIENT-REPORTED OUTCOME MEASURES

3.2.1 Data collection

3.2.1.1 Paper I

In total, 200 eligible women were identified and invited via post starting from November 2016. Each dispatch included an information letter explaining the purpose of the research project, an informed consent form, the questionnaires, an invitation to 3D surface imaging (3D-SI), an information letter about the purpose of the partner study with room for the women to fill out the contact information of their partners, and a pre-paid return envelope. One reminder letter that included all attachments was sent after one month if no answer had been obtained. The last reminder was sent in January 2017, and data collection of the questionnaires ended in May 2017.

3.2.1.2 Paper II

Partners were personally invited via post following the return envelopes from the women as the partners' contact information were provided to us by the women. Information about the purpose of the study, an informed consent form, instructions concerning how to respond to the attached questionnaires, and a pre-paid return envelope were included in the letter. One reminder letter that included all attachments was sent after one month if no answer had been obtained. The last reminder was sent in April 2017. Data collection of questionnaires ended in November 2017.

3.2.1.3 Paper IV

For the women participating in 3D-SI, responses from pre-selected items from their returned questionnaires were extracted for further analysis.

3.2.2 Instruments

Parts of the data in **Paper I**, **II**, and **IV** were composed of responses from the same set of questionnaires. In the invitation sent to the women and partners, instructions regarding how to respond to the questionnaires were attached. The questionnaires and types of responses are summarised in **Table 3**. Women were instructed to respond to the questionnaires from their own perspective long-term post-RRM and IBR. Notably, partners were instructed to respond to the same set of questionnaires (except from SF-36 and HAD) from their perception of the

women's evaluation of the investigated aspects. Partners were, however, instructed to respond from their own perspective for two of the questionnaires that covered HRQoL and anxiety and depressive symptoms.

Table 3 Summary of questionnaires and types of responses used in **Paper I**, **II**, and **IV**

Questionnaire	Women's own responses	Partners' perception of the women's responses	Partners' own responses
EORTC Breast Reconstruction Questionnaire (QLQ-BRR26 or QLQ-BRECON23)	Paper I, II, and IV	Paper II	
Body Image Scale (BIS)	Paper I, II, and IV	Paper II	
Sexuality Activity Questionnaire (SAQ)	Paper I and II	Paper II	
Hospital Anxiety and Depression scale (HAD)	Paper I and II		Paper II
Short Form Health Survey (SF-36)	Paper I and II		Paper II

EORTC = European Organisation for Research and Treatment of Cancer

3.2.2.1 EORTC QLQ-BRR26 or QLQ-BRECON23

The EORTC breast reconstruction questionnaire module (QLQ-BRR26 or QLQ-BRECON23) was developed to evaluate the aesthetic outcome after immediate or delayed breast reconstruction in breast cancer patients (The EORTC Quality of Life Group & EORTC Quality of Life Unit 2002; Winters et al. 2014, 2017). Six European centres from the United Kingdom, Italy, Belgium, Austria, and Sweden collected prospective and retrospective data through questionnaires and semi-structured interviews of a group of heterogenous cross-cultural breast cancer patients. Our research group was involved in the development of the first three phases of this questionnaire following EORTC guidelines.

The selection of items was performed following a predefined selection protocol, using provisional scaling and item-scale correlations. In phase III, several conditional items were excluded since they were not relevant for all patients in the study sample. This resulted in the provisional QLQ-BRR26, which constituted of 26 items categorised into three scales ("Sexuality", "Cosmetic outcome", and "Disease treatment/surgery-related symptoms"), where the Swedish translation was considered to be reliable and valid for usage (Thomson et al. 2013; Winters et al. 2014). Therefore, QLQ-BRR26 (the latest version at the time) was used.

Additional items were excluded in phase IV QLQ-BRECON23 due to high floor/ceiling effects, poor test-retest reliability, and week correlations in factor analysis. It was applied in the end of the project as it had been internationally validated (by 28 international centres) at that time (Winters et al. 2017).

The raw scores in the questionnaire are linearly transformed to a 0–100 scale, where a high scale score represents higher/better/healthier levels of functioning/quality of life, or a higher/worse level of symptoms/problems, and all items are scored 1 *"Not at all"*, 2 *"A little"*, 3 *"A lot"*, or 4 *"Very much"*.

3.2.2.2 BIS

The Body Image Scale (BIS) was developed in collaboration with the EORTC group, as body image was found to be an important aspect in the evaluation of quality of life in cancer patients (Hopwood et al. 2001). The consequences of cancer treatment and surgery cause major changes to the body, such as loss of parts of the body, scars, skin and tissue changes due to radiotherapy, hair loss due to chemotherapy, or fluctuations in body weight. With a patient-focused approach, BIS was designed to be suitable for assessment of patients with any cancer type or cancer treatment. Through interviews of breast cancer patients, literature review, and discussions with health professionals, a provisional scale in line with an affective-cognitive-behavioural model of body image disturbance was proposed to assess self-consciousness, physical and sexual attractiveness, femininity, satisfaction with body and scars, body integrity, and avoidance behaviour after surgery/treatment with reference to the past week. It was then tested on a larger scale of patients with newly diagnosed breast cancer, colorectal cancer, testicular cancer, cervical cancer, and lymphoma, 1- and 2-years postoperatively, post-radiotherapy, and/or post-chemotherapy. The patients were also interviewed to investigate any possible problems with completion, acceptance, and understanding of the items. For instance, positively phrased items (e.g., "I feel sexually attractive") were found to be uncomfortable/embarrassing to answer, and therefore changed to be negatively phrased. Finally, BIS underwent tests for scale structure, clinical validity, and reliability on a large group of breast cancer patients.

Time since primary surgery and patient age were found to affect the reported level of body image problems, where statistically significantly higher total BIS scores were reported at assessments ≥ 6 months compared to < 6 months postoperatively, and pre-menopausal patients scored significantly higher total BIS scores than post-menopausal patients, indicating that body image problems changed over time and that younger patients may have more body image worries (Hopwood et al. 2001). Consequently, the baseline assessment point chosen for the prospective longitudinal comparison in this study was one-year postoperatively (**Paper I**). In addition, adjustments were made for time since RRM and age at the long-term follow-up.

BIS consists of ten items, with scores 0 *"Not at all"*, 1 *"A little"*, 2 *"Quite a bit"*, and 3 *"Very much"* per item, generating a total BIS score of 0–30 points per patient. A higher total BIS score indicates more problems/symptoms/distress with one's body image. In 1997, it was translated to Swedish at Karolinska University Hospital. At the six-month follow-up for this study population, Cronbach's alpha was found to be 0.85. However, formal tests for validation and reliability has not been performed for the Swedish translation (Brandberg et al.

2008). For the prospective long-term follow-up in this thesis, women were instructed to respond to how they felt regarding their body image and changes that emerged after the surgery, i.e., not limited to specifically how they felt during the past week.

3.2.2.3 SAQ

The Sexuality Activity Questionnaire (SAQ) is also an important aspect in the evaluation of an individual's quality of life. SAQ was developed through assessments of the impact of long-term endocrine therapy (Tamoxifen) on sexual functioning of women with high hereditary risk of breast cancer compared with women in the general population without high hereditary breast cancer risk (Thirlaway, Fallowfield, and Cuzick 1996). It has undergone factor analysis, test-retest reliability, and discriminative validity (pre- vs post-menopausal women, with vs without hormone replacement therapy), with response rates/compliance equivalent to other standardised psychological questionnaires despite the sensitive/intimate nature of the questions (Thirlaway et al. 1996). No statistically significant differences were found between the high-risk vs general population regarding sexual activity, pleasure, or discomfort. Discomfort was found to statistically significantly increase with age while pleasure and frequency of sexual activity decreased. Based on these results in addition to the fact that bilateral risk-reducing oophorectomy alters oestrogen levels similarly as entering menopause, adjustments were made in **Paper I** for age at long-term follow-up and whether the women had undergone the gynaecological surgery.

The included version of SAQ is constituted of two sections. The first section investigates "Reasons for not being sexually active", with questions such as status of the current sex life, partner status, and possible reasons for the lack of an active sex life. The second section assesses the past month's sexual functioning through a ten-item scale that covers the aspects of "Pleasure" (desire, enjoyment, and satisfaction), "Discomfort" (dryness and pain), and "Sexual habit" (Thirlaway et al. 1996). Higher scores on the Likert-type scale represent higher pleasure (range 0–18) or more discomfort (range 0–6). A score below 0.33 represents a sexual habit that is less frequent than usual (single item, range 0–3). Though the Swedish translation has not been formally validated, the English version has been shown to be a valid and reliable questionnaire to assess women's sexual functioning (Thirlaway et al. 1996).

3.2.2.4 HAD

The Hospital Anxiety and Depression (HAD) scale was developed to detect and discriminate levels of anxiety and depressive symptoms among somatically ill patients at non-psychiatric clinics (Zigmond and Snaith 1983). This was because the use of the Diagnostic and Statistical Manual of Mental Disorders (DSM) for classification of mental disorders was too broad of a system to distinguish between a psychiatric disorder or the effects of a somatic illness (Snaith and Zigmond 1986). The purpose of the design of the HAD scale was also to create an instrument that was short, easy to complete in a hospital waiting room, and accepted by

patients. Only purely psychiatric symptoms are covered by the included items, since certain other symptoms, such as fatigue, may be difficult to determine if they originate from somatic or mental illness.

A heterogenous group of patients, with appointments at a general medical outpatient clinic, participated in the development of the instrument. They were asked to complete the questionnaire in the waiting room prior to their appointment with their clinician based on their feelings in the past week. They were also interviewed after their appointment by a psychiatrist who assessed their levels of anxiety and depressive symptoms without knowledge of their questionnaire responses. The correlation between the questionnaire responses and psychiatrist evaluations was statistically significant. The reliability and validity of the observed cut-offs that distinguished between the severity of the symptoms were good. For study participants without any symptoms of anxiety or depression, no statistically significant differences were found when compared with age- and sex-adjusted normative data (Zigmond and Snaith 1983).

The HAD scale consists of seven items regarding 'Anxiety' and seven items concerning 'Depressive symptoms' with a score of 0–3 per item, and a total score per scale ranging from 0–21. The interpretation of the total scores is based on the following cut-offs: < 8 = "within normal levels", 8 to 10 = "possible clinical case", and ≥ 11 = "clinical case". Since it was published in 1983 (Zigmond and Snaith 1983), it has been cited in over 39 000 articles. The Swedish translation of HAD has been validated against personal diaries in a sample of breast cancer patients (Arving, Glimelius, and Brandberg 2008).

3.2.2.5 SF-36

The Short Form Health Survey (SF-36) is a 36-item questionnaire developed to measure HRQoL. It was developed based on population studies in several diverse communities, and underwent extensive evaluations (including data completeness, scaling assumptions, reliability, and construct validity), which proved it to be a valid and reliable instrument, cited in over 38 000 articles.

It has been forward-backward translated and tested on individuals in the Swedish general population, which generated a useful dataset of normative data practical for comparative purposes (Sullivan et al. 1995; Sullivan and Karlsson 1994). The Swedish SF-36 version showed high internal consistency of items across subgroups and domains. The correlation of data between the Swedish version and the original American SF-36 version (McHorney et al. 1994) was good, with slightly poorer data quality for the oldest subgroup (≥75 years) due to a small sample size in that specific group.

SF-36 covers the eight domains: "Physical functioning", "Role physical", "Role emotional", "Bodily pain", "General health", "Social functioning", "Vitality", and "Mental health". The mean scores for each domain are transformed to a 0–100 scale, where a higher value represents higher functioning/better health.

3.3 THREE-DIMENSIONAL SURFACE IMAGING

3.3.1 Protocol development

Prior to the actual data collection, a pilot study was performed in 2017 with the help of two volunteers in order to test the machine and software, and to assess and improve the running schedule. The protocol was designed under the guidance from our collaborative partners Dr Meybodi and Dr Elder at the Breast Cancer Institute in Sydney. The aim to perform a methodological evaluation was initiated in the early planning stages of the 3D project since the 3D-SI method was relatively new. Moreover, we aimed to investigate and compare the data derived from two different postures of the same woman, as there were some varying publications and uncertainties regarding whether the type of posture might affect the data analysis.

An excerpt from the final running schedule that the medical photographer followed during 3D-SI reads as follows:

1. At the start of each day of data collection, a calibration of the 3D-SI setup is to be performed.
2. Collect and mark the participant's appointment letter with the date of 3D-SI.
3. Create a new folder in the 3D program and name it with the participant's identification number indicated on their appointment letter.
4. Instruct the participant to tie back their hair if needed, remove all jewellery, and undress to expose their upper torso. Attach a surgical drape to cover the participant's lower body to preserve anonymity.
5. Use surgical tape and a marking pen to mark out the following landmarks: the suprasternal notch (**Figure 6**), 7 cm to the left and rigth from the suprasternal notch on the clavicles (**Figure 7**), and the xiphoid process (**Figure 8**).

Figure 6 The suprasternal notch
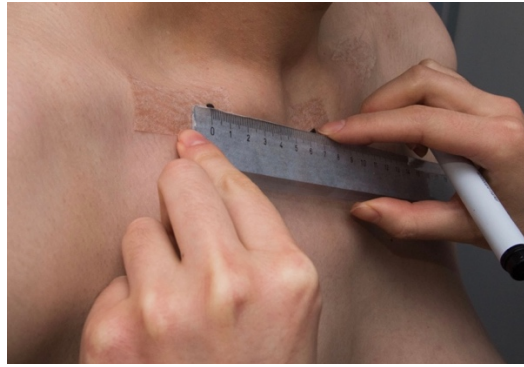
Figure 7 7 cm from the suprasternal notch on the clavicles (left and right)

Figure 8 The xiphoid process

6. Instruct the participant to abduct her arms to 45°, palms towards the floor and elbows fully extended.
7. Position the participant according to the gridlines in the camera and adjust the camera height if necessary.
8. Remind the participant to relax.
9. Capture the image.
10. Intruct the participant to place her hands on their hips, shoulders in resting position with elbows pointing outward, palms resting on iliac crest, the thumbs pointing towards the back.
11. Readjust the participant's position according to the grids.
12. Remind the participant to relax.
13. Capture the image.
14. Instruct the participant to relax their arms and shoulders before repeating step 6–13 two more times, obtaining in total three images per posture.

3.3.2 Observers

Reproducible data was one of our main goals. For this reason, the data analysis for **Paper III** and **Paper IV** were performed by two independent observers:

Observer 1: Lucy Bai (LB), medical intern, in charge of the planning stages and development of the 3D project, familiar with the 3D technique through observations of OL during data analysis of the 3D surface images of the pilot study volunteers

Observer 2: Ola Lundström (OL), medical photographer, 3D expert at the Department of Medical Imaging at Karolinska University Hospital, and contact person with Canfield Scientific.

Farid Meybodi (FM), breast surgeon, collaborative partner, and 3D expert at the Breast Cancer Institute, Sydney, Australia, was able to provide guidance through video calls with OL and LB, and in person during LB's research visit to Sydney.

3.3.3 Data collection

Invitations for 3D-SI were sent out from May to October 2017, with a maximum of ten women per designated day, dispersed over time until December 2017. A reminder was sent out between January and February 2018. The women were imaged using the VECTRA XT 3D imaging system (Canfield Scientific, New Jersey, USA) at the Department of Medical Imaging, Karolinska University Hospital, Stockholm. The data collection of 3D surface images continued until the end of February 2018. All images were coded to a key (Patient ID) to preserve anonymity during data analysis.

3.3.4 Data analysis

The images were independently analysed in VAM by the two observers. Observer 1 analysed the first image of each woman in the study population, followed by the second image of each woman, i.e., all rows in column B, then column C etc. (**Figure 9**), while observer 2 analysed all images of the same woman consecutively, i.e., columns B to G for an entire row before moving on to the images of the next woman.

	A	B	C	D	E	F	G
1	PATID		Arms at 45°			Hands on hips	
2	1	Image 1	Image 2	Image 3	Image 1	Image 2	Image 3
3	2	Image 1					
4	3	Image 1					
5	4	Image 1					
6	5	Image 1					

Figure 9 Order of data analysis for observer 1 (blue) and 2 (orange)

3.3.4.1 Three-dimensional surface imaging (3D-SI) measurements

In the VECTRA XT 3D imaging system experiments, the raw data are the surface coordinates of the left and right breasts. The surface can be written mathematically as $z = f(x, y)$, where x and y are coordinates parallel to the base plane of the breasts and z is the

height of the breasts (*normal to the $x - y$ plane*). From this surface function the volumes of the two breasts can be computed. In order to quantity the difference between the two breasts, a standard technique is to compute the Root Mean Square (d_{RMS}) of the height of the left and right breasts at the corresponding (x, y) coordinates. This parameter has a physical meaning of the mean difference between the heights of the two breasts, and is a way to describe the symmetry of the breasts' shape. The dimension of this quantity is a length. The absolute value of this length is not always easy to judge, i.e., whether this value is large or small.

The protocol with instructions for image analysis in VAM to measure shape symmetry (d_{RMS}) and the breast volumes of the left (VL) and the right breast (VR) were as follows:

1. Crop out the face and clothes, saving just the surface area of the upper torso.
2. In an anterior-posterior view (**Figure 10**), apply the 3D coordinate axis grids and adjust the surface image so that the vertical skin marks (suprasternal notch and xiphoid process) of the midline are aligned where $x = 0$.
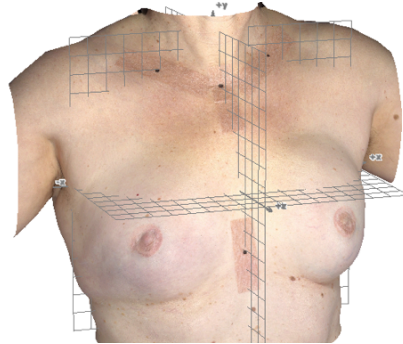
Figure 10 Three-dimensional surface image of an upper torso in anterior-posterior view, with vertical skin marks of the midline adjusted where $x = 0$

3. Change the point of perspective to a cranio-caudal view (**Figure 11**). Adjust the marks on the clavicles and right and left shoulders so that they are aligned where $y = 0$.
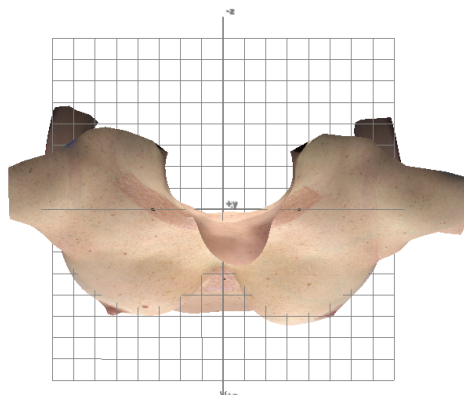
Figure 11 Three-dimensional surface image of an upper torso in cranio-caudal view, with horizontal skin marks aligned where $y = 0$

4. Select the tool *'paint area selection'* and start marking out the breast area of interest 2 cm below the suprasternal notch, including the areas of the left and right breasts

reaching the anterior axillary line, and the area 2 cm below the inframammary fold. Now the selected area should be turquoise (**Figure 12**).
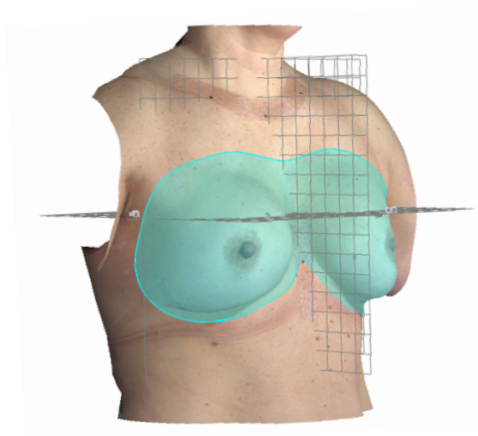
Figure 12 Three-dimensional surface image of an upper torso in oblique view, with the breast area of interest (turquoise) selected

5. Copy and reflect the breast surface area in the x-plane. A mirror surface image has now been created and aligned with the original surface image where $x = 0$.

6. Calculate the d_{RMS} of the selected breasts areas of interest and not the d_{RMS} for the surface area of the whole upper torso. Make sure to select and compare the images by the distance of selected regions of the breast surfaces, as shown in **Figure 13**.

7. The distance between the corresponding coordinates in the two breast surfaces can now be observed in terms of an absolute value of d_{RMS} (as the distance statistics in **Figure 13**) and visually with colour gradients (**Figure 14**).
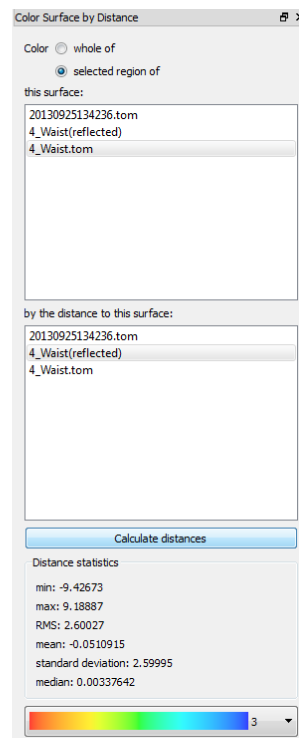
Figure 13 Calculation of d_{RMS} in VECTRA Analysis Module® through the selection of the breast area of interest in the original image compared with the breast area of interest in the copied and reflected image
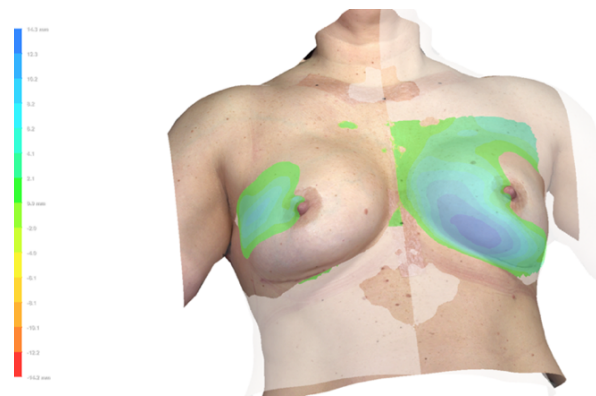
Figure 14 Two overlapping three-dimensional surface images (one original and one copied and reflected) of an upper torso. Colour gradients indicate the difference in distance between two corresponding coordinates in the two breast surface areas

8. Go back to the original surface layer with the marked out breast area of interest. To estimate the volume of one breast at a time, deselect half of the breast area of interest using the *'lasso tool'* and the vertical midline of the torso as the border.

9. An interpolated virtual chest wall is created as a new surface layer (**Figure 15**).
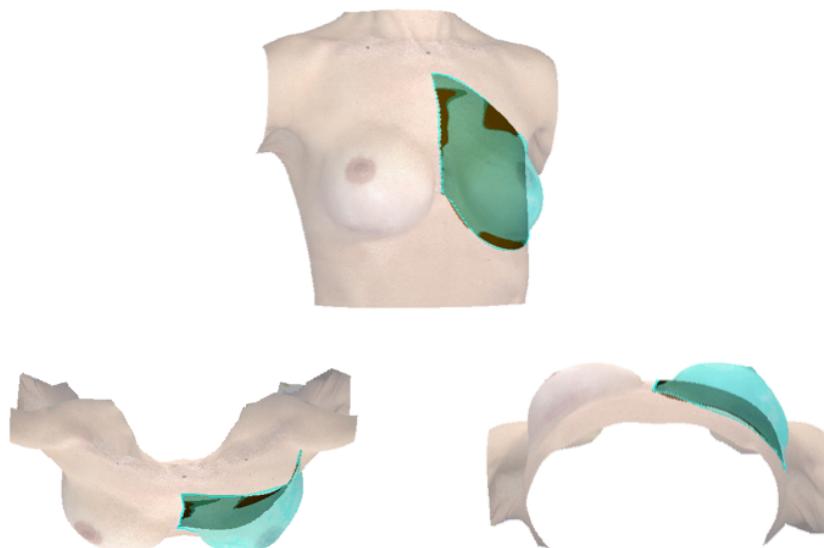
Figure 15 Volume measurement of the left breast in VECTRA Analysis Module® through estimation of the enclosed volume between the breast surface area of interest (turquoise) and an interpolated virtual chest wall (brown)

10. The volume (VL or VR expressed in cm^3) enclosed between the virtual chest wall and the surface area of the breast can now be measured in VAM as seen in **Figure 16**.
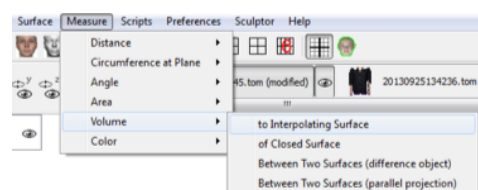
Figure 16 Print screen of the program used for measurements of volume in VECTRA Analysis Module®

In order to judge the d_{RMS} value, it is important to compare this quantity with a length of the breasts. Since the volume (cm³) of the breasts is measured it is possible to estimate a length of breasts. Possible choice of a length includes:

(a) The width of a breast in the x direction

(b) The width of a breast in the y direction

(c) The mean height of the mean breast (in the z direction)

(d) The distance between the centers of the two breasts

(e) An equivalent length of the breasts

Given that the volume and the d_{RMS} values are the only data available from the experiments, choice (e) is the only feasible option. Since the shape of the breasts is complex, the length of the breasts can only be determined by simplifying the shape of the breasts to certain ideal shapes, for example, a half oval or a hemisphere. A half oval or any other shapes than a hemisphere involves two or more lengths to define; thus, we used the relationship of a hemisphere to assume a 'characteristic diameter' (d_b) of the breast as a comparative measure to d_{RMS}, i.e., not a true diameter or length of the breast's footprint. In reality, the breasts could be more flat/elliptical (not an ideal hemisphere), then the diameter of the footprint would be larger than d_b while the height of the breast would be smaller than d_b. Thus, d_b is a length in between the height of the breasts and the diameter of the footprint. This makes the proposed characteristic diameter representable as a measure of the size of the breasts.

Both d_{RMS} and the diameters are lengths, and they have the same unit of a length (mm, cm, or m). If not, the unit must be converted to the same one. The ratio between d_{RMS} and the mean diameters of the two hemispherical breasts is thus a non-dimensional quantity that represents the relative difference between the two quantities. The relative value of d_{RMS} was named volume-shape-symmetry (VSS):

$$\bar{V}_{one\ breast} = \frac{\pi}{12} d_b{}^3 \approx \frac{VL + VR}{2}$$

$$d_b = \left(\frac{12\bar{V}_{one\ breast}}{\pi} \right)^{\frac{1}{3}} \approx \left(\frac{6}{\pi}(VL + VR) \right)^{\frac{1}{3}}$$

$$VSS = 1 - \frac{d_{RMS}}{d_b} = \text{volume shape symmetry factor}$$

Equation 2 The mathematical deduction of volume-shape-symmetry (VSS)

VSS is 1 minus the ratio between the d_{RMS} and the mean diameter of the two hemispherical breasts. $VSS = 1$ means that the two breasts are identical; $VSS = 0$ means that the difference between the two breasts is 100% (the difference between the two breasts is nearly the size of the breasts). A schematic illustration of the parameters is presented in **Figure 17**.
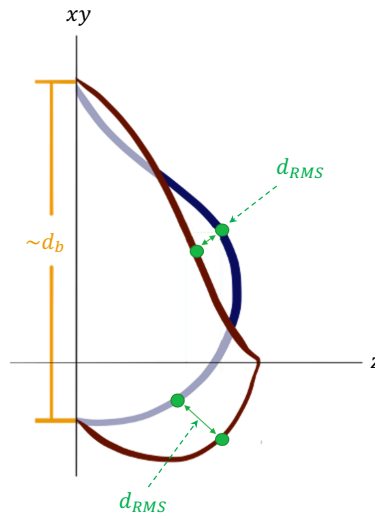
Figure 17 Schematic illustration of the mean distance between the two breast surfaces (d_{RMS}) and the characteristic diameter (d_b) of the left (blue) and the right (brown) breast obtained in the VECTRA Analysis Module®

For **Paper IV**, the 3D-SI measurements were compared to patient-reported outcome measures (PROMs) that evaluated the same aspects of the aesthetic outcome (**Table 4**). Only the 3D-SI measurements obtained from the first image per woman (imaged with their hands resting on the hips) analysed by the same observer (OL) were included.

Table 4 Three-dimensional surface imaging (3D-SI) measurements and their corresponding patient-reported outcome measures from preselected questionnaire items in European Organisation for Research and Treatment of Cancer Quality of Life after Breast Reconstruction Questionnaire module

3D-SI measurement		Unit	Range	Interpretation	Questionnaire item
Shape symmetry	d_{RMS}	mm	0–∞	0 = Perfect shape symmetry	How satisfied are you with the **shape** of the breasts?
					How satisfied are you with the **symmetry** of the breasts?
Volume of the left breast	VL	cm³	0–∞	Estimation of breast volume	How satisfied are you with the **size** of the left breast?
Volume of the right breast	VR	cm³	0–∞	Estimation of breast volume	How satisfied are you with the **size** of the left breast?
Volume-shape-symmetry	VSS		0–1	1 = Perfect volume-shape-symmetry	How satisfied are you with the **shape** of the breasts?
					How satisfied are you with the **symmetry** of the breasts?
					How satisfied have you been with the **overall results** of your breast reconstruction?

d_{RMS} = Distance between two surfaces as Root Mean Square, i.e., breast shape symmetry

VL = Volume of the Left breast

VR = Volume of the Right breast

VSS = Volume-shape-symmetry

3.4 STATISTICAL METHODS

All analyses were performed in Stata/IC 14.2 for Mac, StataCorp, Texas, USA. The statistical level of significance was set to 0.05, *p*-values were two-sided and referred to Wald tests.

3.4.1 Paper I

Paired *t*-tests were used to investigate differences in scores between the one-year and long-term assessment points. Linear regression adjusted for scores one year post-RRM, time since RRM, age at long-term follow-up, mutation status, bilateral RRSO, and body mass index (BMI; kg/m²) were used for unpaired comparisons of scores between women without and with previous breast cancer prior to RRM and IBR. Mean differences were presented with 95% confidence intervals.

3.4.2 Paper II

Paired *t*-tests were used to investigate the differences in responses between the women and their partners. The mean paired differences were presented together with 95% confidence intervals.

3.4.3 Paper III

Descriptive statistics were presented as means, standard deviations (SD or σ), range (min-max), and variance components (VC or σ_x^2). The intra- and inter-observer reproducibility were estimated using one-way ANOVA models and mixed-effects two-way ANOVA models. Bland-Altman plots with 95% limits of agreement were used to illustrate graphical results of mean values of the repeated measurements from three 3D surface images per woman per posture. The correlation between breast symmetry and volume difference ($\Delta V = |VL - VR|$), and VSS and volume ratio ($V_{rat} = \frac{|VL-VR|}{VL+VR}$) was estimated using the non-parametric Spearman rank-order correlation test respectively, yielding a correlation coefficient (ρ) with a statistical significance level of 0.05.

3.4.4 Paper IV

Descriptive statistics of categorical data were presented as counts and percentages, while continuous data were presented as medians and range. The test for associations between the categorical data (PROMs categorised as the response options for the items) and the continuous data (3D-SI measurements) were performed using the non-parametric Kruskal-Wallis test.

3.4.5 Comparison with normative data

Interpretation of total scores can be challenging. Therefore, comparisons were made with published reference values when possible. For SF-36, large population data from the general population in Sweden (Sullivan and Karlsson 1994) were used for comparative purposes in **Paper II**. In addition, the normative data were categorised for sex and age.

3.4.6 Proportions of dichotomised grouped results

Another way to interpret the results in a more clinically relevant presentation was to present the proportions of the women's responses for each item, dichotomised into "Not at all" vs "Any extent". This method was used to present the results from BIS in **Paper I** and **II**.

3.4.7 Minimal clinically important differences

The comparative design of long-term scores versus scores from the one-year assessment, and group differences of women without and with previous breast cancer prior to RRM and IBR were calculated for statistically significant differences. However, such differences are not always easy to interpret. Thus, the concept of minimal clinically important differences were also investigated to facilitate the interpretation of such results (Osoba et al. 1998). Small perceived changes in physical, emotional, and social functioning have previously been established to correspond to changes of magnitudes of 5–9 points in a quality-of-life questionnaire, while moderate and large changes correspond to 10–19 and greater than 20 points, respectively.

3.4.8 Evaluation of a new method

Often in the field of Medical Sciences, old theories and believes evolve, change, or are even proven wrong as we are enlightened with more knowledge. One aspect that needs to be made clear is whether or not the new method correlates with the present conventional one(s), and if so, how well they agree with each other.

For instance, it has been described that the minimum difference of breast volume detectable by the human eye is around 50 cm^3 (Sigurdson and Kirkland 2006). In a recent study, the usage of 3D-SI as a tool to estimate breast volumes was investigated. They found that the mean relative difference of the volume estimated by two observers was 5.78% of breast volumes up to 1000 cm^3 (O'Connell et al. 2018), i.e., 57.8 cm^3. Naturally, one could wonder if this new method has the potential to be used and have a meaningful role in clinical practice, and if there would be enough evidence to prove or strengthen that it is "good enough" to be used. Besides the fact of whether the new method is more or less superior than the conventional one in terms of time- and cost-efficiency, one should also evaluate if the use of the new method can generate identical results independent of the user (reproducibility). In order to do so, a couple of fundamental statistical terms ought to be understood:

3.4.8.1 Reproducibility

Reproducibility assesses the variability of measurements from the same patient, made under changing circumstances such as different methods (different arm positionings or skin markings versus anatomical structures) or evaluated by different observers (LB or OL) (Bartlett and Frost 2008). However, bias might be present between observers, and their measurements might have different SDs. The term reproducibility is used as an umbrella term for the following concepts:

3.4.8.1.1 Reliability

Reliability is used for discriminative purposes. Intraclass correlation (ICC) is the reliability parameter. When $ICC = 1$, there are zero measurement errors. When all variability in the measurements occur because of measurement errors, $ICC = 0$. ICC is dimensionless, which makes it possible to compare measurement methods given on different scales or metrics. It can be used to find the meaning of scores and to assess minimally important changes that are clinically relevant through comparison of two different instruments (de Vet et al. 2006). However, ICC is only an estimate and should be presented with a 95% CI as we have done in **Paper III**. Reliability is dependent on the heterogeneity of the population and the magnitude of measurement errors. It is of importance to present the estimates of inter- and intra-patient SD (repeatability) in addition to the ICC estimate.

The presence of changing bias can be assessed if at least two measurements have been made with each method on each patient (Bland and Altman 1986). Measurements made by different observers can vary systematically because of bias between the observers, or because of different measurement error.

In the case of **Paper III** in this thesis, the reproducibility of the method of 3D-SI was investigated by two observers and more than two measurements on each patient with each method of arm positioning were made. This allowed the repeatability and reliability to be estimated for each method. The cut-offs for the interpretation of levels of reliability for different ICC values used in **Paper III** are presented in **Table 5** (Killaars et al. 2020; Landis and Koch 1977).

Table 5 The interpretation of levels of reliability for different intraclass coefficient (ICC) values

Intraclass coefficient (ICC)	Level of reliability
0.00–0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Substantial
0.81–1.00	Excellent to perfect

The intra-observer reliability for each observer was estimated as $\frac{\sigma^2_{patient}}{\sigma^2_{patient}+\sigma^2_{error}}$ in a one-way ANOVA model, and as $\frac{\sigma^2_{patient}+\sigma^2_{observer}}{\sigma^2_{patient}+\sigma^2_{observer}+\sigma^2_{error}}$ in a mixed-effects two-way ANOVA model. The inter-observer reliability was estimated as $\frac{\sigma^2_{patient}}{\sigma^2_{patient}+\sigma^2_{observer}+\sigma^2_{error}}$ using a mixed effects two-way ANOVA model (Bartlett and Frost 2008).

3.4.8.1.2 Agreement

Agreement is used to evaluate how close two measurements performed on the same patient are. Differences between measurements could be due to bias between observers or variability in the measurement procedures. The differences between measurements are often expressed with 95% limits of agreement. Since reliability is a dimensionless parameter, the variability of the true value can be related to the variability of the measurement error of the observed measurements (Koo and Li 2016). The bias between measurements will then be ignored, thus agreement between the measurements of the same patient will depend only on the intra-patient SD. It measures the measurement error.

The agreement between measurements from the same woman made by observer 1 and observer 2 in **Paper III** were estimated using 95% Bland-Altman limits, which were calculated as mean differences (bias) between the observers $\pm 1.96 \times \sqrt{2} \times \sqrt{(\sigma^2_{observer} + \sigma^2_{error})}$, where the VC were estimated using a mixed-effects two-way ANOVA model with a random patient effect and fixed observer effect (Gerke et al. 2016).

3.4.8.1.2.1 _Repeatability_

Repeatability refers to the variability of repeated measurements from the same patient done under identical circumstances, i.e., using the same instrument or method (same 3D camera, same arm positioning, same markings), and performed by the same observer or evaluator (Bartlett and Frost 2008). Agreement can be estimated using the repeatability coefficient (RC) for measurements by the same observer. Variability under these ideal conditions is dependent on measurement error of the process.

The limits of agreement in **Paper III** were deduced based on the premises of repeated measurements. Using a one-way ANOVA model with a random patient effect, the σ^2_{error} and RC were estimated as $1.96 \times \sqrt{2} \times \sqrt{\sigma^2_{error}}$ (Bartlett and Frost 2008).

3.4.8.2   How to interpret Bland-Altman plots

A scatter plot is often used to illustrate the correlation between two types of measurements. For instance, using unpublished graphs from **Paper III** as an example, the estimated breast volumes obtained through analysis of 3D surface images by two independent observers seem have a positive correlation as seen in **Figure 18**.
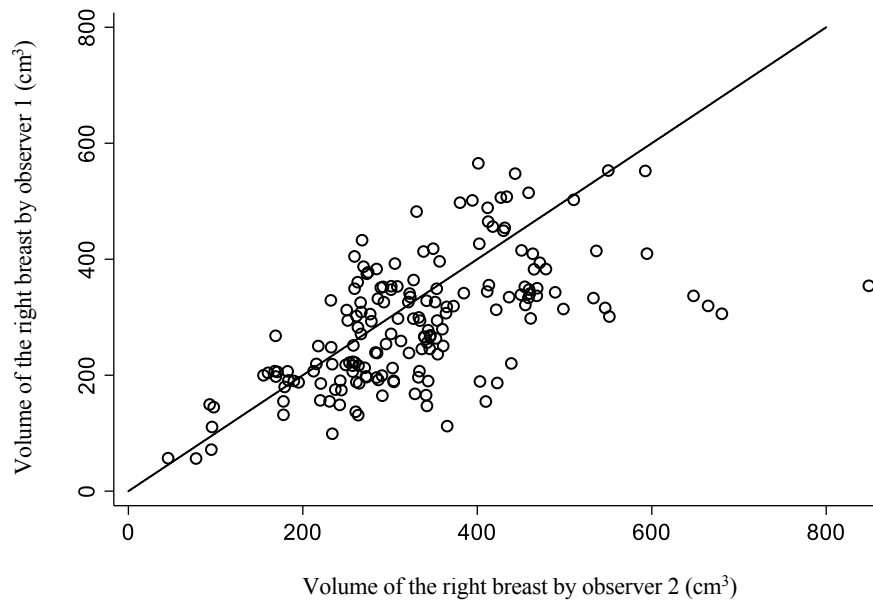
Figure 18 Scatter plot of estimated breast volume measurements of the right breast by observer 1 (*y*-axis) and observer 2 (*x*-axis) obtained through analysis of three-dimensional surface images of 58 women posing with their hands on their hips

But what does this really tell us about the reproducibility of the 3D analysis method? How can we tell if the breast volume measurements estimated by different observers following the same instructions yield reproducible data?

An informative visual way to do this is to illustrate the difference between two measurements of the same object (measured using two different methods, by two different observers, or where the object is posing in two different postures), and to plot it against the average measurement of the paired underlying value. This type of visualisation of data was first proposed by Bland and Altman (Bland and Altman 1986), and thus referred to as a Bland-Altman plot. It gives an overview of the agreement between two methods, which cannot be seen in a scatter plot even though the correlation may seem good. In addition, the plot allows for detection of the systematic error (bias) between the measurements, potential outliers, and calculations of the mean and SD, as seen in **Figure 19** where the same data as plotted in **Figure 18** is presented in a Bland-Altman plot instead. Because the plotted agreement measurements are related to the underlying value of the measurement, this graphical representation also allows for identification of variations in agreement depending on the size of the measurement. For instance, the agreement is more spread out for larger average breast

volumes compared to smaller average breast volumes (highlighted using the coloured triangle in **Figure 19**).
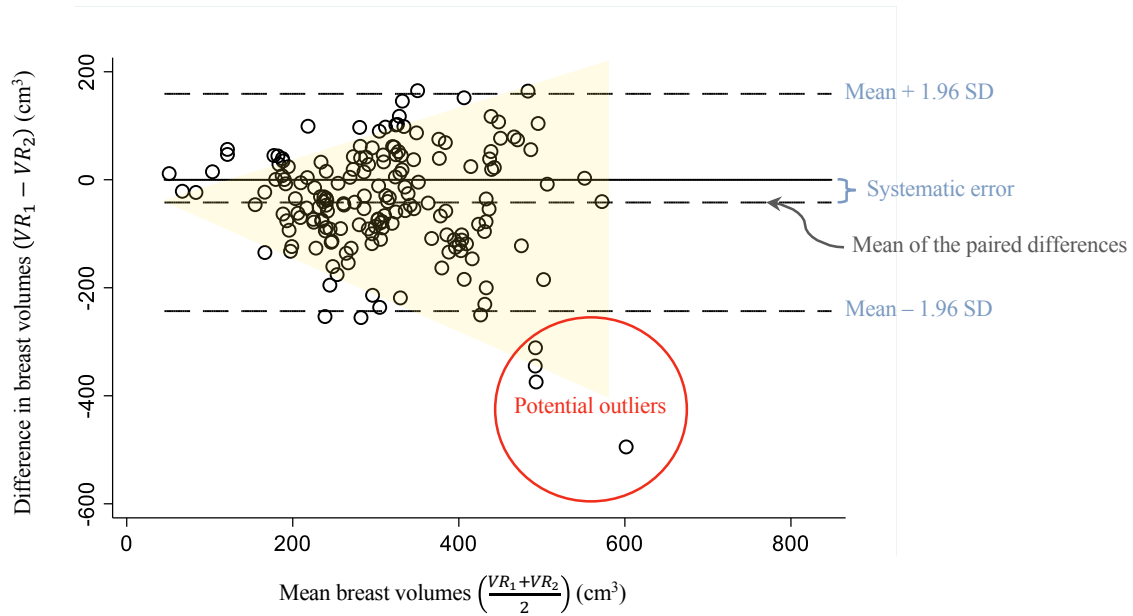
Figure 19 Bland-Altman plot of estimated breast volumes of the right breast by observer 1 (VR_1) and observer 2 (VR_2) through analysis of 3D surface images of 58 women obtained through analysis of 3D surface images of 58 women posing with their hands on their hips

The upper and lower horizontal dashed lines mark the estimated upper and lower 95% limits of agreement, which are estimated from the mean of two values measured of the same object $\pm\ 1.96 \times$ SD, assuming that the SD is uniform. The zone between the limits of agreement is expected to contain 95% of the differences between two measurements of paired future measurements.

4 RESULTS

4.1 PATIENT-REPORTED OUTCOME MEASURES

In total, 146 women (73%) and a total of 36 partners (60%) responded to the long-term questionnaires, see the study overview flow chart of **Paper I–IV** in **Figure 5**. Ninety-five per cent of all participants underwent IBR (**Table 2**). The results are presented according to the responses to each of the questionnaires.

4.1.1 Satisfaction with breast reconstruction

No comparison with any previous assessment could be performed, as this questionnaire was used for the first time in the long-term follow-up in **Paper I**. There were no differences between women with and without previous cancer for most variables, with two exceptions (**Table 6**). Women without previous breast cancer had statistically significantly lower levels of "Disease treatment/surgery related symptoms" (*p*=0.006) and higher satisfaction with "Sexuality" (*p*=0.031) after adjustment for confounding factors, compared to women with previous breast cancer. Clinically significant differences were also noted for these two subscales (small and moderate), as well as for "Satisfaction with reconstructed nipple" (moderate).

Table 6 Satisfaction with the breast reconstruction (EORTC QLQ-BRR26): mean and standard deviation (SD) for all women responding at the long-term assessment; unadjusted and adjusted mean differences (MD) between women with and without previous breast cancer (from **Paper I**)

Parameter	Long-term assessment		Unadjusted mean difference		Adjusted* mean difference	
	Cancer (*n*=34–47) Mean (SD)	No cancer (*n*=84–99) Mean (SD)	MD (95% CI) (*n*=141–146)	*p*	MD (95% CI) (*n*=99–120)	*p*
Disease treatment/surgery related symptoms	13.1 (2.8)	4.5 (1.1)	8.6^S (3.6 to 13.5)	0.001	8.7^S (2.6 to 14.8)	0.006
Problems finding a well-fitting bra	31.9 (5.7)	31.3 (3.6)	0.6 (-12.1 to 13.4)	0.922	-3.3 (-18.3 to 11.8)	0.666
Sexuality	45.3 (4.6)	28.8 (2.5)	16.6^M (6.9 to 26.2)	0.001	12.8^M (1.2 to 24.5)	0.031
Cosmetic outcome breast	59.0 (3.6)	64.3 (2.5)	-5.3 (-14.1 to 3.4)	0.228	-3.4 (-13.2 to 6.4)	0.491
Cosmetic outcome donor site†	15.0 (4.9)	11.9 (4.4)	3.1 (-11.7 to 17.9)	0.651	15.5^M (-115.2 to 146.2)	0.373
Satisfaction with reconstructed nipple	31.9 (4.1)	45.0 (3.1)	-13.2^M (-24.2 to -2.1)	0.020	-19.1^M (-21.6 to 1.4)	0.086
Problems with losing the nipple‡	29.6 (6.7)	30.6 (8.7)	-0.9 (-25.2 to 23.3)	0.937	8.7^S (-28.7 to 46)	0.600

Range 0–100, where higher scores indicate higher satisfaction for 'Satisfaction with reconstructed nipple' and 'Cosmetic outcome of breast', and vice versa for the rest of the measures.

* Adjusted for age at long-term follow-up, time since risk-reducing surgery, mutation, bilateral risk-reducing salpingo-oophorectomy, and body mass index (kg/m^2)

† Too few observations: *n*=9–12

‡ Too few observations: *n*=16–21

^{S} Small and ^{M} moderate clinical significant differences (Osoba et al. 1998)

In **Paper II**, the partners were asked to respond to the same set of questions – from their perception of the women's responses. When the partners' perceived levels of satisfaction with results of breast reconstruction were compared with the women's own responses, the women

had scored statistically significantly higher levels of satisfaction in the subscale "Cosmetic outcome of the breasts" (*p*=0.036). No other subscales differed between the partners and women's responses.

In **Paper IV**, only the PROMs that corresponded to a 3D-SI measurement were studied. Women without previous breast cancer appeared to rate satisfaction with breast symmetry lower than their scoring of the other aesthetic outcome variables. Those with previous breast cancer scored somewhat lower degrees of satisfaction with breast symmetry and shape compared with their reported levels of satisfaction with the breast size and overall result.

4.1.2 Body image

The reported levels of body image problems in **Paper I** were relatively unchanged at the long-term follow-up compared with the responses collected at the one-year assessment (**Figure 20** and **Figure 21**). More than 40% of the women without previous breast cancer reported problems in the following categories: "Dissatisfied with the scar(s)", "Less sexually attractive", "Less feminine", and "Less physically attractive". Among the women with previous breast cancer, more than 40% reported persisting problems with most variables with the exception of three categories: "Avoid people", "Difficulties to see oneself naked", and "Self-consciousness". The only statistically significantly improved level of body image was found for "Self-consciousness" among the women without previous breast cancer (*p*=0.026, **Figure 20**).
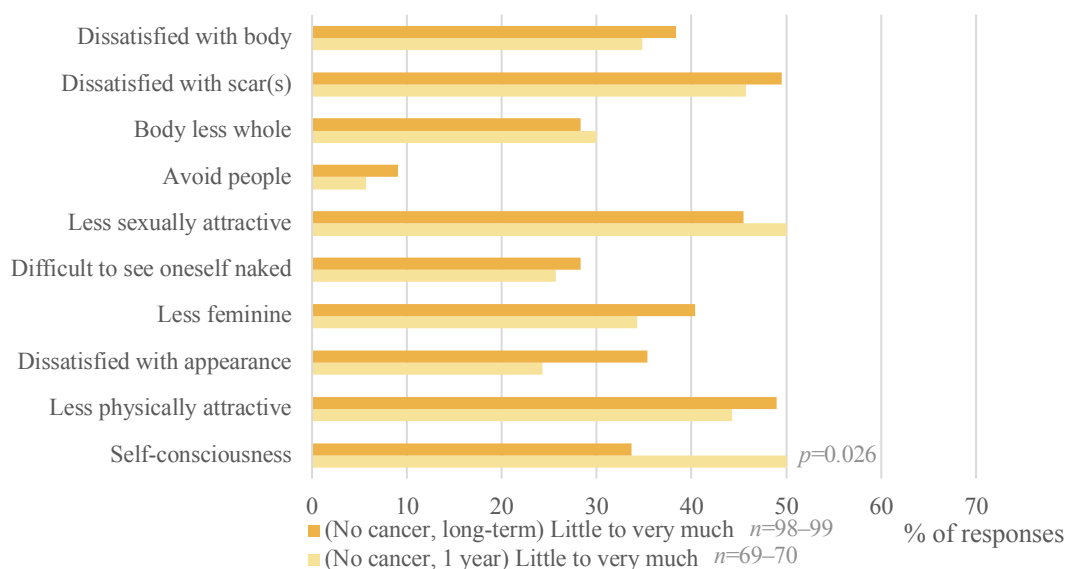
Figure 20 Proportion of women without previous breast cancer reporting 'little' to 'very much'-body image problems at the one year and long-term assessment after the risk-reducing breast surgery with immediate breast reconstruction (from **Paper I**)
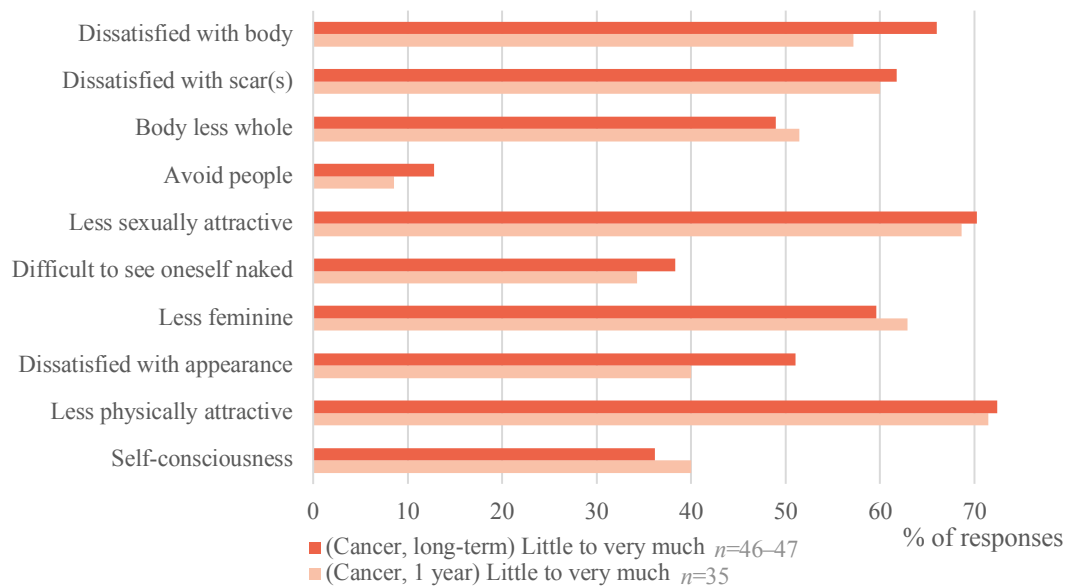
Figure 21 Proportion of women with previous breast cancer reporting 'little' to 'very much'-body image problems at the one year and long-term assessment after the risk-reducing breast surgery with immediate breast reconstruction (from **Paper I**)

In **Paper II**, the three main body image problems reported by the women themselves were also the three main issues perceived by their partners: "Less sexually attractive", "Dissatisfied with the body", and "Less physically attractive". The women reported statistically significantly lower levels of body image problems than what their partners had perceived in terms of the total BIS score (p=0.042), specifically for the items "Dissatisfied with body" (p=0.041) and "Body less whole" (p=0.009).

4.1.3 Sexuality

The proportion of women without previous breast cancer who reported that they had a "current active sex life" had decreased from 76% (n=52) at the one-year assessment, to 61% (n=57) at the long-term follow-up (**Paper I**). Corresponding figures for women with previous breast cancer were 63% (n=22) at the one-year assessment to 43% (n=20) at the long-term follow-up. For the latter group, the proportion of women who reported "Discomfort" had statistically significantly increased since the one-year assessment (p=0.016). On the other hand, a statistically significant increase in "Sexual habit" was observed among the group of women without previous breast cancer (p=0.031). No statistically significant differences between the groups were observed when the reported long-term outcomes were adjusted for confounding factors.

Partners' perceptions of the women's responses concerning "Pleasure", "Discomfort", and "Habit" and the women's own responses did not differ statistically significantly (**Paper II**). Five out of 15 couples indicated the same reason as to why they did not have a "current active sex life".

4.1.4 Anxiety and depressive symptoms

There was a statistically significant increase in depressive symptoms over time among women without previous breast cancer (*p*=0.042, **Paper I**). However, none of the groups reported mean scores that indicated anxiety or depressive symptoms of clinical or possible clinical relevance at the one-year or long-term assessment.

Partners reported their own levels of anxiety and depressive symptoms, all within normal levels. There were neither any statistically significant differences between the partners and the women (**Paper II**), or when comparing the long-term responses of women without and with previous breast cancer (**Paper I**).

4.1.5 Health-related quality of life

A statistically significant decrease in "General health" was reported by both women without and with previous breast cancer when the one-year post-op and long-term outcomes were compared (*p*=0.042 and 0.018, respectively (**Table 7**, **Paper I**)). No other differences were found between the one-year and the long-term follow-up.

Table 7 Long-term changes in health-related quality of life (SF-36) compared with one year after risk-reducing surgery among women with and without previous breast cancer who responded on both occasions (excerpt from **Paper I**)

		Difference over time Women responding at both assessments							
		Cancer				No cancer			
	Variable	One year Mean (SD)	Long-term Mean (SD)	Difference (95% CI)	*p*	One year Mean (SD)	Long-term Mean (SD)	Difference (95% CI)	*p*
	Number of women	31–35				65–70			
	Physical Functioning*	87 (20)	85 (21)	-3 (-10 to 5)	0.510	92 (13)	92 (16)	-1 (-5 to 3)	0.726
	General health†	82 (19)	74 (24)	-9 (-16 to -2)	0.018	84 (19)	79 (23)	-5 (-11 to 0)	0.042
	Vitality†	66 (25)	63 (24)	-3 (-12 to 6)	0.531	68 (22)	65 (23)	-2 (-8 to 3)	0.320
	Mental health‡	79 (18)	77 (17)	-2 (-8 to 5)	0.645	83 (18)	79 (18)	-4 (-8 to 1)	0.094
	Role–Physical*	79 (38)	85 (34)	5 (-3 to 14)	0.223	87 (30)	85 (32)	-2 (-11 to 7)	0.691
	Role–Emotional‡	85 (27)	82 (34)	-3 (-16 to 10)	0.620	86 (30)	85 (30)	-1 (-9 to 7)	0.851
	Social functioning‡	91 (18)	87 (22)	-4 (-12 to 4)	0.344	93 (19)	88 (22)	-5 (-10 to 1)	0.091
	Bodily pain*	76 (24)	76 (25)	0 (-9 to 9)	0.978	83 (23)	83 (24)	1 (-7 to 8)	0.882

Health-related quality of life (vertical label, left column)

SF-36 [range 0–100, higher scores indicate better well-being]:

* Physical health

† Overall representation of both physical and mental health. Both scales are bipolar. The median of Vitality or General Health implies absence of fatigue or no negative values of health in general, respectively

‡ Mental health, where Mental Health is a bipolar scale. Mid-values imply an absence of either anxiety/depressive symptoms or psychosocial impairment. 100 indicates best possible well-being

SD = standard deviation

CI = confidence interval

Both the women and the partners reported higher levels of HRQoL on most subscales compared with the age- and sex-adjusted normative SF-36 data from the Swedish population (**Figure 22**, **Paper II**). The participating women in **Paper II** reported clinically significantly poorer "General health" (a small clinical significant difference), "Physical role" (small

difference), "Social functioning" (small difference), and "Emotional role" (moderate difference) compared to their partners.
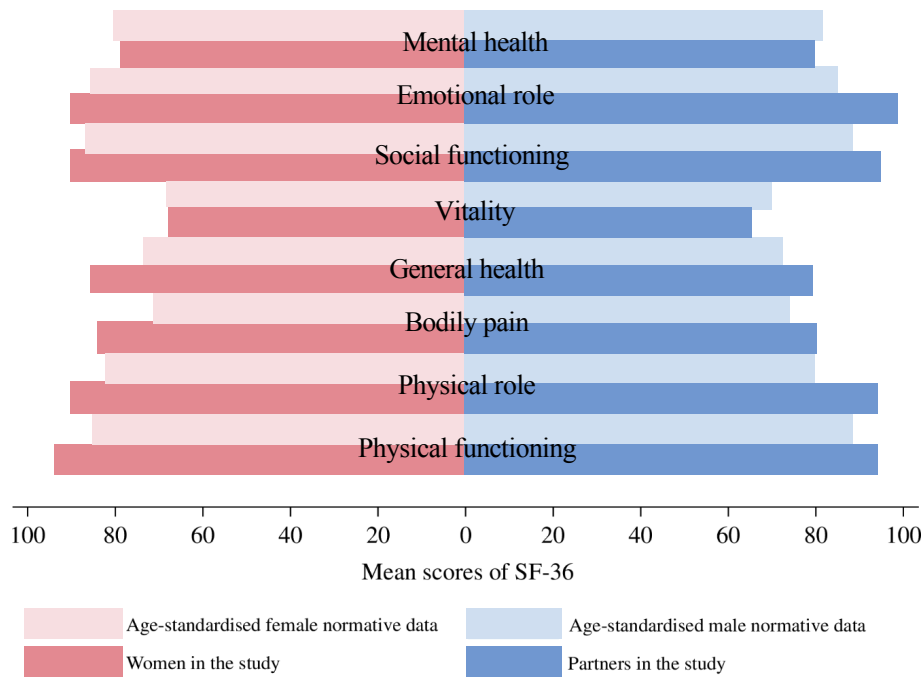
Figure 22 Mean scores of the eight domains of health-related quality of life (SF-36) for partners and women, and the age- and sex-adjusted normative data for each domain (from **Paper II**)

4.2   THREE-DIMENSIONAL SURFACE IMAGING

The participation rate for **Paper III** and **IV** was 73% (*n*=64 out of 88 interested). However, the image files of six women were corrupted/damaged, and therefore had to be excluded from further analysis.

4.2.1   Reproducibility of raw data

The reproducibility of results generated from data analysis of d_{RMS}, breast volumes, and VSS were investigated in **Paper III**. The intra-observer reproducibility of d_{RMS} measurements were substantial for observer 1 and perfect to excellent for observer 2, while the intra-observer reproducibility of breast volume measurements was perfect to excellent for both observers (**Table 8**). The inter-observer reproducibility of the 3D-SI measurements was moderate–substantial, with a systematic underestimation throughout the measurements by observer 1 when compared with the measurements by observer 2. For measurements by both observers, the inter-posture reproducibility was found to be substantial for d_{RMS}, and substantial–excellent to perfect for breast volume (data not shown). The correlation between breast symmetry and volume difference, and VSS and volume ratio, respectively, was not statistically significant.

Table 8 Estimates of agreement and reliability of the mean distance between the breast surfaces, d_{RMS}, the left breast volume, V_L, and the right breast volume, V_R, in two different postures, 45° arm abduction and hands placed on hips (from **Paper III**)

	$d_{RMS,45}$ (mm)	$d_{RMS,hip}$ (mm)	$V_{L,45}$ (cm³)	$V_{L,hip}$ (cm³)	$V_{R,45}$ (cm³)	$V_{R,hip}$ (cm³)
One-way random effects ANOVA:						
Observer 1						
Mean (SD)	7.1 (2.9)	7.1 (2.8)	282 (102)	281 (90)	281 (110)	289 (107)
Range	2.2 to 15.7	2.4 to 16.4	102 to 580	81 to 526	62 to 644	56 to 565
$\sigma^2_{patient}$	5.99	5.79	9352	6700	11284	10214
σ^2_{error}	2.17	1.83	1217	1408	922	1283
Repeatability coefficient (95% CI)	4.1 (3.6 to 4.6)	3.8 (3.3 to 4.3)	97 (85 to 110)	104 (91 to 118)	84 (74 to 96)	99 (87 to 113)
Intra-observer reliability (95% CI)	0.73 (0.63 to 0.82)	0.76 (0.66 to 0.84)	0.88 (0.83 to 0.92)	0.83 (0.75 to 0.88)	0.92 (0.89 to 0.95)	0.89 (0.83 to 0.93)
Observer 2						
Mean (SD)	8.0 (3.4)	8.2 (3.3)	337 (129)	346 (139)	323 (116)	331 (120)
Range	2.3 to 19.6	2.5 to 19.2	47 to 685	22 to 830	79 to 766	46 to 849
$\sigma^2_{patient}$	9.76	9.44	15271	18485	12534	12954
σ^2_{error}	1.61	1.73	1674	1068	1015	1521
Repeatability coefficient (95% CI)	3.5 (3.1 to 4.0)	3.6 (3.2 to 4.1)	113 (100 to 129)	91 (80 to 103)	88 (78 to 100)	108 (95 to 123)
Intra-observer reliability (95% CI)	0.86 (0.79 to 0.91)	0.85 (0.77 to 0.90)	0.90 (0.85 to 0.94)	0.95 (0.92 to 0.96)	0.93 (0.89 to 0.95)	0.89 (0.84 to 0.93)
Two-way mixed effects ANOVA:						
$\sigma^2_{patient}$	6.18	5.66	9132	8478	6910	7757
$\sigma^2_{observer}$	1.70	1.96	3180	4115	4999	3827
σ^2_{error}	1.89	1.78	1445	1238	968	1402
Bias (95% CI)	-0.9 (-1.5 to -0.3)	-1.1 (-1.7 to -0.5)	-55 (-77 to -32)	-65 (-89 to -40)	-42 (-69 to -15)	-42 (-66 to -18)
95% limits of agreement	-6.2 to 4.3	-6.5 to 4.3	-243 to 134	-268 to 138	-256 to 172	-242 to 158
Intra-observer reliability (95% CI)	0.81 (0.74 to 0.86)	0.81 (0.74 to 0.86)	0.89 (0.85 to 0.93)	0.91 (0.88 to 0.94)	0.92 (0.90 to 0.95)	0.89 (0.85 to 0.92)
Inter-observer reliability (95% CI)	0.63 (0.50 to 0.75)	0.60 (0.46 to 0.73)	0.66 (0.53 to 0.78)	0.61 (0.46 to 0.75)	0.54 (0.37 to 0.70)	0.60 (0.44 to 0.73)

SD = standard deviation
σ^2_x = variance component of x
CI = confidence interval

4.2.2 Introduction of a new parameter

The intra-observer reproducibility was excellent to perfect for both observer 1 and observer 2 independent of in which posture the 3D surface images were captured (**Table 9**). Because of the systematic underestimation of raw data measurements by observer 1, the inter-observer reproducibility of *VSS* was substantial (**Paper III**). The variability between the two observers' *VSS* measurements was larger for women with less symmetrical breasts (lower *VSS* values).

Table 9 Estimates of volume-shape-symmetry (VSS) agreement and reliability, based on raw data measurements from the three-dimensional surface images presented for two postures (arms at 45° and hands placed on hips) (from **Paper III**)

	VSS_{45}		VSS_{hip}	
	Observer 1	Observer 2	Observer 1	Observer 2
Mean (SD)	0.929 (0.029)	0.923 (0.034)	0.930 (0.028)	0.923 (0.032)
Range	0.828 to 0.975	0.806 to 0.977	0.820 to 0.977	0.788 to 0.980
One-way random effects ANOVA:				
$\sigma^2_{patient}$	0.0006	0.0010	0.0006	0.0009
σ^2_{error}	0.0002	0.0001	0.0002	0.0002
Repeatability coefficient (95% CI)	0.041 (0.036 to 0.046)	0.033 (0.029 to 0.038)	0.038 (0.034 to 0.043)	0.035 (0.030 to 0.039)
Intra-observer reliability (95% CI)	0.74 (0.63 to 0.83)	0.87 (0.81 to 0.92)	0.76 (0.66 to 0.84)	0.85 (0.78 to 0.90)
Two-way mixed effects ANOVA:				
$\sigma^2_{patient}$	0.0006		0.0006	
$\sigma^2_{Observer}$	0.0002		0.0002	
σ^2_{error}	0.0002		0.0002	
Bias (95% CI)	0.006 (-0.0004 to 0.012)		0.007 (0.001 to 0.013)	
95% limits of agreement	-0.046 to 0.060		-0.037 to 0.050	
Intra-observer reliability (95% CI)	0.82 (0.75 to 0.87)		0.81 (0.75 to 0.86)	
Inter-observer reliability (95% CI)	0.62 (0.48 to 0.74)		0.61 (0.47 to 0.73)	

SD = standard deviation
σ^2_x = variance component of x
CI = confidence interval

4.2.3 *In vivo* magnitudes

Among the 58 3D surface imaged women, 36 women did not have previous breast cancer prior to the RRM while 22 women did. The median age at 3D-SI for women without and with previous breast cancer was 54 and 58 years, respectively. Additional clinical and demographic data can be found in **Table 2**. 3D surface images with specified 3D-SI measurements of four women are presented in **Figure 23**.

Estimated volume-shape-symmetry (VSS) values ranged from 0.788 to 0.980, where the highest value, i.e., the most symmetrical reconstructed breasts in terms of volume and shape, was obtained from a 3D surface image of a woman without previous breast cancer.
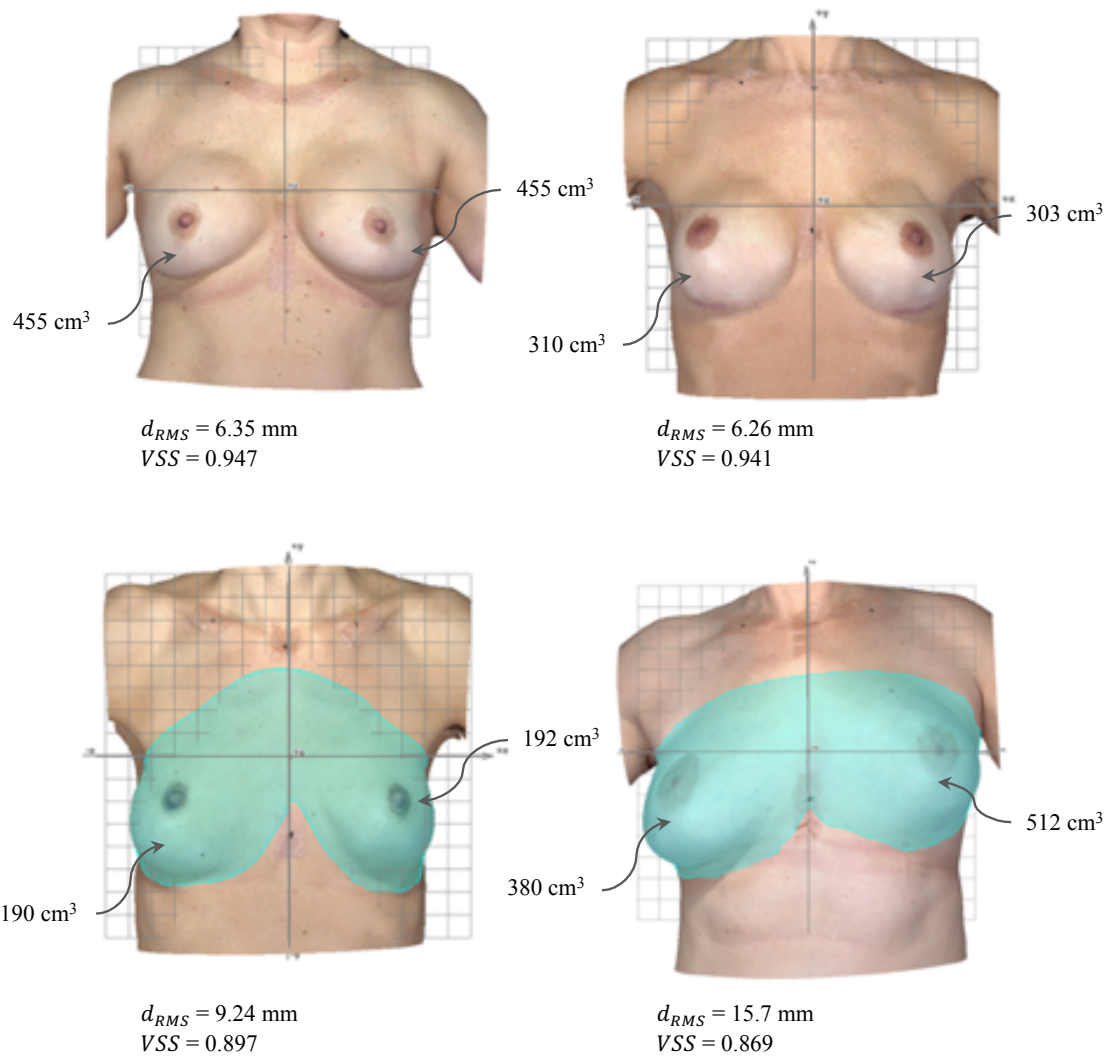
Figure 23 Three-dimensional surface images of four women with varying aesthetic outcome. The snapshots are captured during image analysis in VECTRA Analysis Module®. The bottom two breast surface areas (turquoise) are marked out for shape symmetry calculations (from **Paper IV**)

4.2.4 Association with patient-reported outcome measures

Neither the raw data nor relative parameter *VSS* of 3D-SI measurements had any statistically significant associations with the corresponding PROMs. Thus, the 3D-SI measurements did not capture the patient reports.

5 DISCUSSION

In summary, the major findings of this thesis were that among women with a high hereditary risk of breast cancer who underwent RRM and IBR 6 to 20 years ago, feelings regarding body image, levels of anxiety and depressive symptoms, sexuality, and HRQoL appeared to remain relatively unchanged compared with their corresponding one-year postoperative evaluations. Problems with body image were still relatively prevalent at the long-term follow-up. Women with previous breast cancer reported more problems with sexuality at the long-term follow-up than those without a previous diagnosis. Women's own evaluations regarding long-term psychosocial outcomes appeared to have been perceived by their partners. Partners tended, however, to overestimate the degree of body image problems reported by the women themselves. Moreover, both women and their partners reported higher levels on almost all investigated HRQoL aspects compared with the age- and sex-adjusted normative population in Sweden long-term after RRM and IBR. When long-term breast reconstructive outcomes were evaluated from a 3D-SI perspective, this, in theory, more objective method yielded moderate–excellent to perfect reproducible measurements that could be used to describe aspects related to the aesthetic outcome of the breasts. Nevertheless, based on the data collected in this thesis, 3D-SI measurements did not appear to be a statistically significantly associated to women's self-reported outcome measures related to the satisfaction of their breast reconstruction and body image.

5.1 SATISFACTION WITH BREAST RECONSTRUCTION

Since EORTC QLQ-BRR26 (phase III) and QLQ-BRECON23 (phase IV) were only recently developed and internationally validated (Winters et al. 2014, 2017), no data from the one-year assessment were available for comparison with the long-term results in **Paper I**. Furthermore, apart from another validation study of a translated version of QLQ-BRECON23 (Bok et al. 2020), there is to date only one other published study that has used QLQ-BRR26 (Lohmander et al. 2020). Nevertheless, the results from our study measured through these validated questions were in line with, and can be supported by, other studies on breast cancer patients undergoing mastectomy and IBR using similar questionnaires.

The observed statistically and clinically significant differences between the groups of women without and with previous breast cancer were in most cases related to cancer treatment or surgery-related symptoms. For women without previous breast cancer, issues such as arm numbness/fullness related to consequences of axillary dissection, or unilateral problems such as capsular contracture, implant rupture, deformity, and/or pain related to previous breast cancer radiotherapy are not relevant as they underwent bilateral RRM and IBR. These breast cancer treatment or surgery-related symptoms have all been seen to persist or develop many years post-treatment or surgery for breast cancer patients (Berbers et al. 2014; Krag et al. 1998; Quinn et al. 2016). Nonetheless, because of a low response rate for two of the seven subscales and the lack of other published comparable data as of today, generalisability of the results should be drawn with caution.

Among the participating couples in **Paper II**, partners seemed to have perceived the major issues related with the long-term outcomes of RRM and IBR as their responses were coherent with the most prevalent ones reported by the women themselves. Similarly in another study (*n*=11 couples), a strong positive correlation was found between breast cancer patients and their partners' responses regarding each party's own satisfaction with the aesthetic outcome of the breast reconstruction after a mastectomy (Cimaroli, Logiudice, and Doren 2020). However, further conclusions or comparisons with other studies are difficult to draw because of the small sample size and small quantity of published studies investigating partners' perceptions of women's satisfaction with the aesthetic outcome after RRM and IBR. Moreover, the satisfaction with the aesthetic outcome is a multifaceted matter. For instance, differences in personal experiences related to the loss of their own breasts may affect body image and expectations with the reconstructive outcome more or less depending on their physical and psychological starting point.

5.2 BODY IMAGE

The degree of body image problems reported in the long-term follow-up were of similar degree to the problems reported at the one-year assessment point*, i.e.,* body image problems seemed to persist in the long-term after RRM and IBR. In our long-term follow-up, the number of unanticipated surgeries after RRM and IBR requiring general anaesthesia, e.g., implant-related issues, immediate postoperative complications, or aesthetic concerns, were *n*=40 (44%) and *n*=15 (34%) for women without and with previous breast cancer in **Paper I**, respectively.

In a previously published two-year follow-up of women after RRM and IBR, more problems with body image were reported among women who had undergone reoperations compared with women who had not (Unukovych et al. 2016). Possible explanations might be that women with less satisfactory aesthetic outcomes underwent additional corrective surgeries, or because the additional surgery caused less satisfactory aesthetic outcomes. Nevertheless, short-term findings with similar body image problems after RRM as observed in our long-term follow-up have been reported (Gahm et al. 2013; Gahm, Wickman, et al. 2010; Gopie et al. 2013; Hopwood et al. 2000).

In addition, decreased feelings of femininity and impaired body image have been reported as the most common issues in a large systematic review investigating effects of RRM on breast cancer incidence and mortality, physical morbidity, and psychosocial outcomes (Lostumbo et al. 2004). However, only three out of 22 studies were prospective cohort studies, which meant that the impact of recall bias is debatable. Nevertheless, similar findings were observed in our prospective long-term follow-up and were supported by the partners' perceptions in **Paper II**, where the most common issues reported by both women and partners were problems with sexual and physical attractiveness and satisfaction with the body post-surgery. Since mismatched expected versus actual aesthetic outcomes have been seen to be associated

with regret (Lee et al. 2018), women opting for RRM should be informed about the risk of these persisting problems that this thesis has highlighted.

5.3 SEXUALITY

Both EORTC QLQ-BRR26/BRECON23 and SAQ cover several aspects related to sexuality. In our long-term follow-up, the group of women without previous breast cancer reported lower levels of sexuality-related problems compared with the group of women with previous breast cancer prior to RRM and IBR. Although women in both groups had undergone bilateral surgery, a moderate clinically significant difference between the groups was found. This difference may have been the result of hormonal changes due to anti-cancer treatment for breast cancer in addition to contraindications for hormone replacement therapy after bilateral RRSO. More than 50% of the women in both groups had undergone this procedure because of the high risk of hereditary breast and ovarian cancer. However, only women without previous breast cancer were safely offered hormone replacement therapy, which for instance might have yielded differences in the levels of vaginal dryness between the groups (Couzi, Helzlsouer, and Fetting 1995; Johansen et al. 2016; Panjari, Bell, and Davis 2011). The levels of sexual discomfort measured in SAQ were lower in the group without previous breast cancer, possible due to differences in the vaginal mucosa between the groups.

The women's evaluations regarding aspects related to sexuality long-term after RRM and IBR were confirmed by their partners, who seemed to have accurately perceived the women's feelings, as their responses did not show any statistically or clinically significant differences from the women's own responses. The average relationship length among the participating couples was 21 years. Despite the longevity of the average relationships, only a minority of the couples selected matching responses to the questions regarding reasons for not having a "current active sex life". In previous literature, no strong correlations have been found between relationship length and accuracy in estimation of sexual satisfaction. Quality of partner support has, on the other hand, been found to be a predictor for sexual well-being and satisfaction after mastectomy and implant based breast reconstruction (Grift et al. 2020). However, absence of support from a partner, in combination with long-term side-effects of surgery such as loss of skin sensation, or vaginal dryness due to hormonal changes as an effect of breast cancer treatment, might not resolve without clinical counselling. Therefore, the possible effects of RRM and IBR on sexual aspects should be a discussion point (pre- and postoperatively) with both women and their partners, in order to offer suitable treatments such as sexual counselling.

5.4 ANXIETY AND DEPRESSIVE SYMPTOMS

Among women with a high hereditary risk of breast cancer, the levels of anxiety and depressive symptoms were found to be persistent and relatively low at the long-term follow-

up compared with the corresponding levels one-year post-RRM. Among *BRCA1/2* carriers, anxiety has been found to be associated with the women's perception of breast cancer risk itself and related to her decision to undergo RRM, with a decrease in psychological morbidity after RRM (Hatcher et al. 2001).

Preoperative levels of anxiety and depressive symptoms have been previously studied by our research group. The results demonstrated that women without previous breast cancer prior to RRM and IBR had equivalent levels of anxiety and depressive symptoms to those in women from the general population. Likewise, women with previous breast cancer prior to RRM and IBR had similar levels to those in breast cancer patients without known hereditary risk (Brandberg et al. 2004). Moreover, in another study based on the same cohort of women as in this thesis, anxiety decreased six months and one year post-RRM and IBR, while the levels of depressive symptoms remained low and relatively unchanged when compared to the preoperative levels (Brandberg et al. 2008).

To this date, there are few studies that have prospectively investigated long-term psychological problems after RRM (den Heijer et al. 2012; Heiniger et al. 2015). In one of the studies, the reported levels of anxiety and depressive symptoms were statistically significantly lower at six months post-RRM compared with preoperative levels, as well as at the long-term follow-up (6–9 years) compared with the six-month reports (den Heijer et al. 2012). One explanation as to why we did not find a statistically significant decrease in anxiety and depressive symptoms might be because our selected baseline for comparison was one year post-RRM. During the first postoperative year, planned revisits to the plastic surgeon associated with filling of expanders and/or removal of filling ports might have had time to be completed, in addition to leaving the women more time to mentally adjust to their postoperative condition. Based on the findings in **Paper I**, the women's adapted levels of anxiety and depressive symptoms one-year post-RRM seemed to be persistent up to 20 years.

5.5   HEALTH-RELATED QUALITY OF LIFE

Among the women in our cohort, as previously reported, levels of HRQoL did not differ before, or six months, or one year after RRM (Brandberg et al. 2008). In **Paper I**, these levels of HRQoL were found to be persistent in the long-term for all SF-36 subscales except for "General health", demonstrating that undergoing RRM and IBR did not seem to affect these women's HRQoL. The decrease in "General health" in our study did not differ depending on if the women had not or had had breast cancer prior to RRM and IBR. A possible explanation for the lower level of "General health" in the long-term follow-up could simply be the natural process of aging.

Other studies with commensurate follow-up periods of approximately six years observed an improved and possibly increased quality of life over time in high-risk women after RRM compared with prior surgery, and that adaptation among the women who had undergone RRM was higher compared to those who had decided to not undergo RRM (Hooker et al.

2014a; Shapira et al. 2018). Similarly, the HRQoL among the women in our study were higher than the normative levels of HRQoL among age-adjusted Swedish women. However, anxiety prior to RRM has not been found to be a predictor of quality of life post-surgery (Hooker et al. 2014b).

Differences between characteristics of the participants in this thesis and the general population may introduce a bias. For instance, previous research showed that women at an outpatient oncogenetic clinic for women with hereditary breast cancer appeared to have higher socioeconomic status compared with the general population of women in the same geographical district (Wachenfeldt et al. 2009). This implies that women who attend genetic counselling clinics, such as the women in our thesis, may have a higher socioeconomic status than the general population. If higher socioeconomic status is also related to higher levels of HRQoL, it may be a potential confounding factor that could explain the higher levels of HRQoL among the women in our study sample compared to the normative population. However, in our study we do not have data of the participants' socioeconomic status and could therefore not adjust for it in our models.

There is a lack of comparative results of partners of women with high risk of hereditary breast cancer. In a study on partners of breast cancer survivors, partners of older breast cancer survivors (diagnosis at 55–70 years) reported greater quality of life compared to partners of younger breast cancer survivors (diagnosis at ≤ 45 years), where the latter group also reported lower marital satisfaction (Cohee et al. 2018). Higher quality of marital status and better information given to partners have been described to benefit the psychological and emotional well-being both of partners and breast cancer patients in another study (Rowland and Metcalfe 2014). In **Paper II**, the median age of women when they underwent RRM and IBR was 37 years (range 26–62). However, further subgroup analysis for differences between women without or with previous breast cancer prior to RRM and IBR stratified on age could not be performed due to the small sample size.

In another study, the psychological adaptation after testing positive for hereditary breast cancer and undergoing RRM was good both among women and their partners, with a positive correlation between the women's and their partners' levels of adaptation (Shapira et al. 2018). This could possibly explain the levels of HRQoL among partners in our study, which did not differ from the women's levels of HRQoL in our study, in addition to also being higher than the levels of HRQoL among the age- and sex-adjusted Swedish normative population.

5.6 THREE-DIMENSIONAL SURFACE IMAGING

Because the method of using measurements from 3D-SI to describe breast shape symmetry in terms of d_{RMS} is relatively new, the interpretation of the obtained 3D-SI measurements has been challenging. For this reason, examples of 3D surface images were presented in this thesis with their corresponding 3D-SI measurements in order to assist the reader in the interpretation of the values (**Figure 23**). Although 3D-SI was introduced in the early 2000s,

the most common method for evaluation of the aesthetic outcome is still based on 2D images and/or panel assessment.

In **Paper IV**, no statistically significant associations between 3D-SI measurements and PROMs were found. The heterogeneity of study designs and populations in similar studies make it difficult to generalise this conclusion. For example, no correlation was found between PROMs and volume symmetry measurements in a study using a BREAST-Q and 3D laser scans of women who had undergone unilateral or bilateral, immediate or delayed breast reconstruction using different surgical techniques (Yip et al. 2015). At the same time, another study found statistically significant, though weak, correlations between 3D-SI measurements and PROMs, evaluated using BREAST-Q and the same 3D-SI system as we used (O'Connell et al. 2017). They also found a strong association between mean values of 3D-SI measurements and a consensus score of the aesthetic outcome based on the majority of the opinions from a panel consisting of two breast surgeons, one clinical oncologist, and one breast care nurse who used the four-point Harvard cosmesis scale.

Reasons to why we did not find statistically significant associations between 3D-SI and PROMs in contrast to previous findings (O'Connell et al. 2017) could be because of differences in the aesthetic outcomes of the reconstructed breasts between the two studies. The median shape symmetry (d_{RMS}) in our study was 6.98 for women without and 8.49 for women with previous breast cancer, with a range of 2.98 to 19.2 for the entire cohort, while the median shape symmetry in the study using the same 3D-SI system was 5.9 with a range of 4.2 to 8.0. In other words, the women in our study had estimated shape symmetries that differed up to almost twice as little and twice as much as the women in their study when comparing the left and the right side of the breast areas of interest. Moreover, the satisfaction with the aesthetic outcome of the breast reconstruction might be influenced by and differ depending on the women's medical histories and personal experiences, causing them to have different levels of vulnerability and expectations of the surgery. The women in our study had all undergone RRM and IBR due to a high hereditary risk of breast cancer up to 20 years ago, while the women in the study from O'Connell et al. were breast cancer patients that were 3D surface imaged approximately three years after their unilateral surgery.

In conclusion, women's subjective evaluations of the aesthetic outcome cannot be measured by 3D-SI measurements, although objective measures might be of use to assess the aesthetic outcome in terms of breast volume, shape, and symmetry.

5.7 METHODOLOGICAL CONSIDERATIONS

One of the strengths of this thesis is the addition of findings to this field from a long-term perspective among women with a high risk of hereditary breast cancer who had undergone RRM and IBR 6 to 20 years ago. **Paper I** is, to the best of our knowledge, one of the longest prospective long-term follow-up studies investigating the psychosocial outcomes among these women, and has a large sample size (*n*=146) compared to similar international studies.

The response rate (73%) for the questionnaires was high considering the long-term aspect. In addition, several different validated questionnaires were used, specifically tailored to measure the different aspects investigated. Apart from the advantages of being a relatively time- and cost-efficient method to collect a large amount of data, validated questionnaires also yield reliable results comparable with findings from other studies. Furthermore, the prospective design reduces the risk of recall bias.

One weakness of using questionnaires is the risk of collecting responses possibly affected by social desirability, as the PI/main PhD supervisor (Yvonne Brandberg) and the co-supervisors (Brita Arver, Kerstin Sandelin, and Marie Wickman Chantereau) have been involved with the women's treatments prior to, during, and/or after the women's RRM and IBR. Nevertheless, in order to decrease this impact on the women's responses, information about the procedure of data collection and analysis were distinctively provided in the information letter attached with the questionnaires. We ensured that neither the psychologist, oncologist, nor the surgeons would have access to the participants' identifiable data by assigning a key to replace their social security number and name. Similarly, the partners were also linked to the key.

Since the original project was designed and initiated in 1997, included questionnaires were chosen at that time and have been consistently used throughout the prospective follow-up studies. Though it could be argued that the questionnaires are old or outdated, a major strength of the study design is ensuring comparative measurements at the different assessment points by using the same questionnaires. Moreover, several published articles in 2021 still use questionnaires such as BIS, SAQ, HAD, and SF-36, which indicates the solidity of the design of these questionnaires that still yields valid and reliable measurements.

In contrast to the participation rate in **Paper I**, the participation rate for 3D-SI was relatively low, with 88 of 200 eligible women expressing interest in 3D-SI and only 64 women actually participating. In addition to this, a weakness of the imaging system was that the images of six women became corrupted/damaged, forcing us to exclude them from the analysis. However, the number of women who voluntarily participated for 3D-SI could be interpreted as relatively good when put into context, since the participation was time consuming and required women to physically come to the Department of Medical Imaging at Karolinska University Hospital. The sample size is also sufficient to perform a solid evaluation of the reproducibility of the 3D-SI method since the total number of images analysed by each observer was 348. Another aspect regarding the sample size for **Paper III** and **IV** was the absence of a power analysis. However, as the design was based on the fact that all of the eligible women for **Paper I** were invited for 3D-SI, the reached sample size was dependent on the number of women who were interested in 3D-SI in that specific group, i.e., no power analysis was applicable based on the premises of the design.

The sample size of partners in **Paper II** was even smaller (*n*=36) and dependent on the number of women with an actual current partner who were willing to share their partner's contact information with us. Evidently, though assumptions could be drawn based on the number of women who responded to the question of whether or not they were in a current

intimate relationship in SAQ (*n*=106 with and *n*=39 without a current intimate relationship, *n*=1 who skipped the question), the true number of existing partners was unknown to us.

A strength of this study was the innovative study design of using the exact same set of validated questionnaires for the partners. More specifically, the partners were instructed to respond to the questions from their perception of the women's responses as a way to investigate and evaluate the authenticity of the women's own replies – which for instance might have been coloured by the effect of social desirability as mentioned earlier. However, because of the small sample size, the results may only give an indication of tendencies observed among couples and should be generalised with caution. Nevertheless, women and partners could benefit from our results by being informed during the pre- and postoperative consultations about possible long-term issues.

The limitation of the study design of asking the women to provide us with their partners' contact information and contacting the partners separately was at the same time one of its strengths. It ensured the partners' and women's privacy relative to each other and provided them with the choice to opt in or out without having their status of participation known by the other. Another strength related to the ethical deliberations within our studies was that the women were given the opportunity to consent to each section of data collection. This provided the women an opportunity to participate in the studies to the extent that they felt comfortable with. For instance, 146 women completed the questionnaires, whereas 136 women consented to data collection from medical records, and 88 women showed interest in 3D-SI. Thanks to our prospective and longitudinal study design, the missing clinical data of women who did not want to share their current medical records could be replaced with pre-existing information from the research group's established database instead of having to exclude these women from the study completely.

5.7.1 Three-dimensional surface imaging

As the method of using 3D-SI as a more objective tool for assessment of the aesthetic outcome was relatively novel and unused at Karolinska University Hospital, it was naturally of interest to investigate the reproducibility of the method prior to any further comparisons with other more common and recognised methods for evaluation of the aesthetic outcome.

The average time between questionnaire responses and 3D-SI was 11 (min–max 5 to 23) months. This was because we encountered some issues prior to the initiation of data collection from 3D-SI. The creation of 3D surfaces of the images captured was incomplete for some of the participants in our pilot study. As seen in **Figure 24**, areas of the imaged surface appeared to have missing data (surface coordinates), which made it impossible to perform further analysis on the image. We hoped to find a solution to this problem, such as to interpolate the surface area of the missing data. The Canfield Scientific technical support argued that the problem might have occurred because of the positioning of the patient in front of the camera. However, our medical photographer did not find this reason plausible as the

issue with missing data occurred at random. In addition, the software did not have a tool for interpolation of surface coordinates at the time. In the end, the technical support concluded that the problem might be related to the ratio between the breast and abdominal volumes, i.e., ptotic breasts in combination with a more prominent abdomen might yield loss of surface area information. A software update without any improvements regarding the problem with the missing data led to a further delay in the initiation of data collection from 3D-SI.
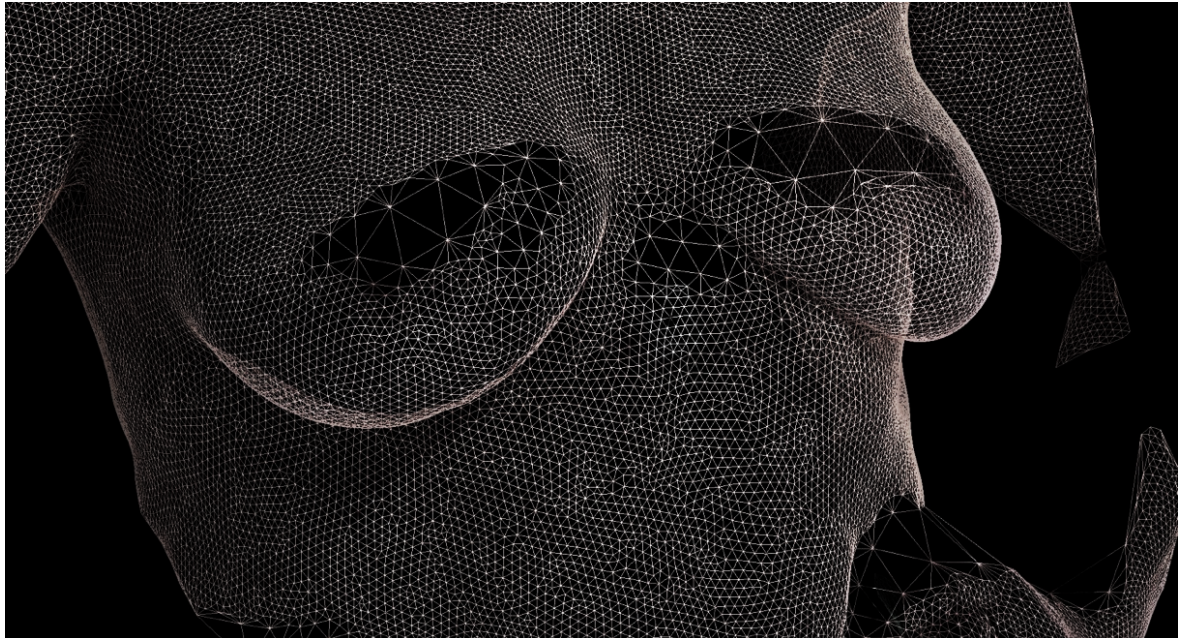
Figure 24 Example of missing data (surface coordinates) in a three-dimensional surface image in VECTRA Analysis Module ®

After an internal discussion, we came to the conclusion that the number of potential study participants with a body constitution that would not yield areas of missing data would be enough for our data collection to commence. Our solution to minimise the issue with missing data was to add an additional step in the protocol, which was to troubleshoot the captured 3D surface image in real time while still having the study participant in the room ready to be imaged again if missing data was found. A calibration of the VECTRA XT 3D imaging system was performed prior to patient arrival to ensure that the relationship between the cameras and other apparatuses was comprehended by the system.

In the end, none of the participating women had a body constitution (ptotic breasts) that caused the same problem as we encountered in the pilot study. Furthermore, although there were a couple of months between the points of assessment, the probability of the women changing their personal opinion regarding their satisfaction with the aesthetic outcome long-term after their breast reconstruction and their body image was considered relatively small. The discrepancy in months ought to have minimal impact on the results when put in relation to the time since RRM and IBR.

One of the strengths of the 3D-SI method was the time-efficient procedure of capturing an image (generated in a couple of milliseconds), equivalent to the conventional 2D photography once the photographer had been introduced to the system. In addition, 3D-SI

provided more information and perspectives of the portrayed object compared with a 2D image, which could be an advantage during panel evaluation of the aesthetic outcome. The quantity of captured information in a 3D image gives rise to a higher level of overview of the aesthetic outcome of the breasts. This makes 3D-SI a powerful tool to investigate details in order to, for instance, determine an aesthetic rank list of relative contributions of different factors of the female breasts affecting the overall impression of the aesthetic outcome (Sandberg et al. 2020). Primary factors of female breast aesthetics seem to be the shape of the lower and upper pole, as well as the height of the breast, since these factors were very strongly correlated with the overall breast aesthetic score when rated by ten Scandinavian plastic surgeons using the VECTRA XT 3D imaging system (Sandberg et al. 2020). The results from their study could be useful for surgeons when planning breast surgeries in order to achieve an optimal aesthetic outcome. However, these abovementioned factors were not individually investigated in our studies, as we studied the breast areas of interest which related to the same information, but from a broader perspective.

Data analysis of the 3D surface images was also reasonably user-friendly once the observers were familiarised with the toolbars in VAM. The analysis of 348 images took approximately 120 hours for each observer to complete. A weakness with the method was that although it is an objective method in theory, the observers performing the analysis could be more or less subjective during image analysis. This may lead to systematic errors that could alter the estimated 3D-SI measurements. Though skin markings and borders of the breast area of interest had been predefined, small differences in the placement of the 3D surface image in relation to the coordinate grid could give rise to different superimposed breast surface images which would affect the calculations of d_{RMS} and/or breast volumes. The intra-observer reproducibility was better than the agreement between the observers, i.e., the observers themselves seemed to be consistent with their own technique of data analysis. In addition, estimations and evaluations could have been affected by the so-called observer-expectancy effect. Differences between users and clinical experiences might be the reason for the demonstrated moderate–substantial inter-observer reproducibility, where inexperienced observers' agreement of the assessment of aesthetic results has previously been shown to be significantly lower compared to experienced observers' level of agreement (Cardoso et al. 2005). Furthermore, it can be argued that conclusions based on measurement error studies with only two observers are not strong enough to be generally applied. Therefore, future studies aiming to generalise the results should have an adequate number of observers and correction of observer drift by periodic retraining or refreshing of the analysis procedure to ensure that the observers understand the guidelines in the same manner. However, given our design where the observers independently performed the analysis, the evaluation of the reproducibility of the method could be considered more valid and thereby a strength of this thesis.

Another strength of this thesis is that we introduced a new parameter, VSS, in order to interpret d_{RMS}. Its usefulness was strengthened by the fact that we did not find any statistically significant correlations between VSS and volume ratio, i.e., breast volume seems

to be independent of d_{RMS} and VSS, indicating that volume measurements on its own do not give information about the breasts' shape symmetry. Thus, d_{RMS} is of importance to take into consideration in the evaluation of breast aesthetic outcomes using 3D-SI measurements. Since the absolute value of d_{RMS} is difficult to judge on its own, the introduction of a relative value (VSS) was motivated. Moreover, VSS was found to have excellent to perfect intra-observer reproducibility. However, more studies are needed to investigate its clinical applicability.

5.8 ETHICAL CONSIDERATIONS

Prior to RRM, performed between 1997 and 2010, all women were invited to participate in the primary project designed to investigate the psychological reactions related to the surgery with a follow-up time of up to 24 months. Participating women agreed to respond to several questionnaires with the possibility of withdrawing their participation at any time or of declining further participation. Because of the lack of prospective long-term follow-up studies, a new ethical application was filed and approved by the Regional Ethics Committee in Stockholm in 2016, which granted us permission to conduct the follow-up studies included in this thesis.

The first ethical dilemma was associated with the re-establishment of contact with the study participants. When the invitation with information about the long-term follow-up study was sent to the women 6 to 20 years post-RRM they might have felt uncomfortable, reminded of their increased risk of breast cancer, or of the treatments they had undergone in conjunction to the RRM. Even so, an interest to participate in the study could be due to the fact that they have an inherited increased risk of developing breast cancer and potentially that other family members (for instance their daughters) might have to face the same choice of whether or not to undergo RRM and IBR in the future. All the women were given the opportunity to contact us in case of questions concerning the long-term follow-up. Merely a few women contacted us, only to ask some practical questions related to the questionnaires.

The second ethical dilemma was our interest to investigate the partners of the women. They had not been involved in our previous studies. We asked the women to send us the name and address of their partners, in order to send the partners a personal invitation and an information letter with the questionnaires attached. The questionnaires covered several intimate questions. We also asked the partners to respond to some of the questionnaires from their perceptions of how the women had responded to those questions. To ask the partners to formulate and share such perceptions could be interpreted as a disloyal act. In addition, the questions might have evoked distress in the partners regarding the high hereditary risk of breast cancer of their partner (and potentially their children). However, because of the lack of studies about the partners' perceptions and feelings, the benefit of investigating this further with the aim of improving the information to future couples facing the same dilemma was considered to outweigh the risk of doing any harm.

The third ethical dilemma was that we also invited the women for 3D-SI in order to document and analyse the long-term aesthetic outcome of the reconstructed breasts. The women did not benefit from participating. Obviously, the women had to be unclothed on the upper body in order for the medical photographer to capture a 3D image of their reconstructed breasts. This might have made some women feel embarrassed or uneasy, especially if they were unsatisfied with the reconstructions or had a negative body image. We ensured that all participating women were met with respect and together with at least another colleague (medical photographer or LB) in a room with no windows. Skin marks were not drawn directly on their skin but on surgical tape in order to be easily removed by the women themselves after the appointment. All women were instructed to remove their jewellery and tie back their hair prior to 3D-SI to minimise the risk of identification. Their lower bodies were covered with surgical drapes, and the images were cropped so that their faces were not included, in order to ensure anonymity during the data analysis.

The fourth and final ethical dilemma concerns the permission for us to read the women's complete medical records. We specifically subdivided each section of the informed consent statement attached in the information letter in order to give the women the chance to opt out of specific sections instead of completely declining their participation on the basis of not wanting to partake in a certain section. This choice seemed to be welcomed by the participants, as there were several cases where the women responded to the questionnaires but did not wish to participate in the 3D-SI study or share their complete medical records.

6 CONCLUSIONS

Low levels of anxiety and depressive symptoms, and high levels of HRQoL were observed up to 20 years after RRM and IBR in women with a high hereditary risk of breast cancer, and remained relatively unchanged compared with levels reported at a one-year assessment. Although body image problems appeared to persist at the long-term follow-up in both women without and with previous breast cancer, an improved level of self-consciousness was observed among the women without previous breast cancer.

Differences in the satisfaction with the long-term outcomes of the breast reconstruction were observed between the groups of women without and with previous breast cancer prior to RRM and IBR. These differences were mostly related to the effects of previous breast cancer surgery and/or treatment(s), such as symptoms connected to axillary dissections, consequences of radiotherapy, or side-effects of endocrine therapy. The proportion of women who reported having a "current active sex life" decreased in both groups. For women with previous breast cancer, an increase in sexual discomfort was found. Differences over time observed for both groups of women at the long-term follow-up regarding general health and sexuality may primarily be related to the inevitable effects of aging.

Most of the women in this cohort lived in long-lasting relationships. Even though the choice to undergo RRM and IBR is personal, partners of women with a high hereditary risk of breast cancer will more or less be part of the journey. Long-term effects on body image after RRM and IBR were confirmed but overestimated by partners to these women. Furthermore, both partners and women demonstrated similarly low levels of anxiety and depressive symptoms, and high levels of HRQoL compared with the age- and sex-adjusted normative data in Sweden.

Usage of the 3D-SI method for evaluation of aesthetic outcomes of breast reconstructions in terms of breast symmetry and breast volume had substantial–perfect to excellent reproducibility when analysed by the same observer. The posture in which the 3D surface image was captured did not seem to compromise the reproducibility of data measurements either. No strong statistically significant correlations were found between breast symmetry and breast volume differences, nor between VSS and volume ratio. Despite a substantial inter-observer reproducibility, VSS showed excellent to perfect reproducibility for both observers independent of posture.

Finally, even though 3D-SI measurements could potentially be used to evaluate and compare aesthetic outcomes of breast reconstructions from a more objective perspective, the 3D-SI measurements did not correspond to the women's own evaluations of the reconstructions or their body images.

7 FUTURE PERSPECTIVES

The following issues may be of importance in future research:

Many women who have undergone breast reconstructions with implants may experience problems with unnatural-looking breasts, especially when aging. Continuous improvements of surgical techniques are therefore warranted. Different placements of implants on the chest wall as well as development of the implants themselves (e.g., material, form, softness, and surface texture) have been introduced since the women in our studies underwent surgery. Currently, Karolinska University Hospital is involved in an international multicentre study investigating whether pre-pectoral placement of breast implants is favourable in terms of quality of life and aesthetic outcome.

There is still a lack of randomised studies on RRM with different reconstructive techniques evaluating aesthetic outcome, body image, sexuality, and HRQoL from a short- and long-term perspective.

Recently, the trend to "go flat" has been a hot topic, where some women opt for RRM without breast reconstruction. A future study investigating women undergoing RRM without IBR and following them prospectively regarding body image, satisfaction after the operation, sexuality, and HRQoL would be of interest.

The use of 3D-SI to evaluate the aesthetic outcome cannot replace the power of PROMs when measuring patient satisfaction. However, objective measurement methods have the potential to be further improved and investigated in order to better correspond to the women's subjective evaluations.

There is a paradox in performing RRM on healthy individuals without cancer versus breast conserving techniques for patients with sporadic breast cancer. Future research should aim at improving methods to identify women with hereditary breast cancer who will develop the disease. Next-generation sequencing may improve the identification of women who need RRM and relieve others from feeling obliged to undergo the surgery.

Prophylactic medication for women with hereditary risk of breast cancer should be developed and tested. In these studies, prospective assessments of cancer worry, sexuality, body image, and HRQoL should be included, and compared with operated women.

Most of the women in this study were of Swedish origin. Cultural and ethnical aspects should be considered in counselling pre- and post-operatively. Follow-up studies of women with different cultural and ethnical backgrounds is important and a field for future research.

8 ACKNOWLEDGEMENTS

9 REFERENCES

Anon. 2017. "BREAST-Q Version 2.0 User's Guide." (July 2012):1–27. Retrieved September 7, 2020 (http://qportfolio.org/wp-content/uploads/2020/02/BREAST-Q-USERS-GUIDE-V2.pdf).

Anon. 2020. "Nationellt Vårdprogram Bröstcancer. Regionala Cancercentrum." Retrieved March 8, 2021 (https://kunskapsbanken.cancercentrum.se/globalassets/cancerdiagnoser/brost/vardprogram/nationellt-vardprogram-brostcancer.pdf).

Antoniou, A. C., A. P. Cunningham, J. Peto, D. G. Evans, F. Lalloo, S. A. Narod, H. A. Risch, and J. E. Eyfjord. 2008. "The BOADICEA Model of Genetic Susceptibility to Breast and Ovarian Cancers : Updates and Extensions." *British Journal of Cancer* (March):1457–66.

Antoniou, A. C., P. P. D. Pharoah, P. Smith, and D. F. Easton. 2004. "The BOADICEA Model of Genetic Susceptibility to Breast and Ovarian Cancer." *British Journal of Cancer* 1580–90.

Arver, Brita, Karin Isaksson, Hans Atterhem, Annika Baan, Leif Bergkvist, Yvonne Brandberg, Hans Ehrencrona, Monica Emanuelsson, Henrik Hellborg, Karin Henriksson, Per Karlsson, Niklas Loman, Jonas Lundberg, Anita Ringberg, Marie Stenmark Askmalm, Marie Wickman, and Kerstin Sandelin. 2011. "Bilateral Prophylactic Mastectomy in Swedish Women at High Risk of Breast Cancer: A National Survey." *Annals of Surgery* 253(6):1147–54.

Arving, Cecilia, Bengt Glimelius, and Yvonne Brandberg. 2008. "Four Weeks of Daily Assessments of Anxiety, Depression and Activity Compared to a Point Assessment with the Hospital Anxiety and Depression Scale." *Quality of Life Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation* 17(1):95–104.

Bartlett, J. W. and C. Frost. 2008. "Reliability , Repeatability and Reproducibility : Analysis of Measurement Errors in Continuous Variables." (December 2007):466–75.

Berbers, Judith, Angela Van Baardwijk, Ruud Houben, Esther Heuts, Marjolein Smidt, Kristien Keymeulen, Maud Bessems, Stefania Tuinder, and Liesbeth J. Boersma. 2014. "'Reconstruction: Before or after Postmastectomy Radiotherapy?' A Systematic Review of the Literature." *European Journal of Cancer* 50(16):2752–62.

Bland, J. Martin and Douglas G. Altman. 1986. "Statistical Methods for Assessing Agreement between Two Methods of Clinical Measurement." *Lancet* 327(8476):307–10.

Bok, Soo Kyung, Youngshin Song, Ancho Lim, Hyunsuk Choi, Hyunkyung Shin, and Sohyun Jin. 2020. "Korean Translation and Psychometric Evaluation of Korean Version EORTC QLQ-BRECON23." *International Journal of Environmental Research and Public Health* 17(24):1–10.

Borgen, Patrick I., Arnold D. K. Hill, Katherine N. Tran, Kimberly J. Van Zee, Mary J. Massie, David Payne, and Carina G. Biggs. 1998. "Patient Regrets after Bilateral Prophylactic Mastectomy." *Annals of Surgical Oncology* 5(7):603–6.

Boughey, Judy C., Tanya L. Hoskin, Lynn C. Hartmann, Joanne L. Johnson, Steven R. Jacobson, Amy C. Degnim, and Marlene H. Frost. 2015. "Impact of Reconstruction and Reoperation on Long-Term Patient-Reported Satisfaction After Contralateral Prophylactic Mastectomy." *Annals of Surgical Oncology* 22(2):401–8.

Brandberg, Y., B. Arver, H. Johansson, M. Wickman, K. Sandelin, and A. Liljegren. 2012. "Less Correspondence between Expectations before and Cosmetic Results after Risk-Reducing Mastectomy in Women Who Are Mutation Carriers: A Prospective Study." *European Journal of Surgical Oncology : The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 38(1):38–43.

Brandberg, Y., B. Arver, A. Lindblom, K. Sandelin, M. Wickman, and P. Hall. 2004. "Preoperative Psychological Reactions and Quality of Life among Women with an Increased Risk of Breast Cancer Who Are Considering a Prophylactic Mastectomy." *European Journal of Cancer* 40(3):365–74.

Brandberg, Yvonne, Kerstin Sandelin, Staffan Erikson, Göran Jurell, Annelie Liljegren, Annika Lindblom, Ann Lindén, Anna Von Wachenfeldt, Marie Wickman, and Brita Arver. 2008. "Psychological Reactions, Quality of Life, and Body Image after Bilateral Prophylactic Mastectomy in Women at High Risk for

Breast Cancer: A Prospective 1-Year Follow-up Study." *Journal of Clinical Oncology* 26(24):3943–49.

Bray, Freddie, Jacques Ferlay, and Isabelle Soerjomataram. 2018. "Global Cancer Statistics 2018 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." 394–424.

Bresser, P. J. C., Caroline Seynaeve, Arthur R. Van Gool, Cecile T. Brekelmans, Hanne Meijers-Heijboer, Albert N. Van Geel, Marian B. Menke-Pluijmers, Hugo J. Duivenvoorden, J. G. M. Klijn, and Aad Tibben. 2006. "Satisfaction with Prophylactic Mastectomy and Breast Reconstruction in Genetically Predisposed Women." *Plastic and Reconstructive Surgery* 117(6):1675–82.

Brown, Robert W., Y. C. Cheng, and M. Kurtay. 2000. "A Formula for Surgical Modifications of the Breast." *Plastic and Reconstructive Surgery* 106(6):1342–1345.

Cardoso, Jaime S. and Maria J. Cardoso. 2007. "Towards an Intelligent Medical System for the Aesthetic Evaluation of Breast Cancer Conservative Treatment." *Artificial Intelligence in Medicine* 40(2):115–26.

Cardoso, Maria João, Jaime Santos Cardoso, Hélder P. Oliveira, and Pedro Gouveia. 2015. "The Breast Cancer Conservative Treatment . Cosmetic Results – BCCT . Core – Software for Objective Assessment of Esthetic Outcome in Breast Cancer Conservative Treatment : A Narrative Review." *Computer Methods and Programs in Biomedicine* 126:154–59.

Cardoso, Maria João, Jamie Cardoso, Natália Amaral, Isabel Azevedo, Lise Barreau, Mario Bernado, David Christie, Susy Costa, Florian Fitzal, José L. Fuogo, Maria João Cardoso, Jamie Cardoso, Natália Amaral, Isabel Azevedo, Lise Barreau, Mario Bernado, David Christie, Susy Costa, Florian Fitzal, José L. Fuogo, Maria João JCardoso, Jamie Cardoso, Natália Amaral, Isabel Azevedo, Lise Barreau, Mario Bernado, David Christie, Susy Costa, Florian Fitzal, José L. Fuogo, Maria João JCardoso, Jamie Cardoso, Natália Amaral, Isabel Azevedo, Lise Barreau, Mario Bernado, David Christie, Susy Costa, Florian Fitzal, José L. Fuogo, Jørgen Johansen, Douglas Macmillan, Maria Piera Mano, Lea Regolo, José Rosa, Luís Teixeira, and Conny Vrieling. 2007. "Turning Subjective into Objective : The BCCT . Core Software for Evaluation of Cosmetic Results in Breast Cancer Conservative Treatment." *Breast* 16:456–61.

Cardoso, Maria João, Cristina Ana Santos, Jaime Cardoso, Henrique Barros, and Manuel Cardoso de Oliveira. 2005. "Choosing Observers for Evaluation of Aesthetic Results in Breast Cancer Conservative Treatment." *The Breast* 61(3):879–81.

Cardoso, MJ, C. Vrieling, JS Cardoso, HP Oliveira, NR Williams, Dixon JM, and Project Delphi Panel PICTURE, Project Clinical Trial Team PICTURE. 2018. "The Value of 3D Images in the Aesthetic Evaluation of Breast Cancer Conservative Treatment. Results from a Prospective Multicentric Clinical Trial." *Breast* 41:19–24.

Catanuto, Giuseppe, Wafa Taher, Nicola Rocco, Francesca Catalano, Dario Allegra, Filippo Luigi Maria Milotta, Filippo Stanco, Giovanni Gallo, and Maurizio Bruno Nava. 2019. "Breast Shape Analysis with Curvature Estimates and Principal Component Analysis for Cosmetic and Reconstructive Breast Surgery." *Aesthetic Surgery Journal* 39(2):164–73.

Chae, Michael P., David J. Hunter-Smith, Robert T. Spychal, @bullet Warren, Matthew Rozen, Warren Matthew Rozen, @bullet Warren, and Matthew Rozen. 2014. "3D Volumetric Analysis for Planning Breast Reconstructive Surgery." *Breast Cancer Research and Treatment* 146(2):457–60.

Chae, Michael P., Warren Matthew Rozen, Robert T. Spychal, and David J. Hunter-Smith. 2016. "Breast Volumetric Analysis for Aesthetic Planning in Breast Reconstruction: A Literature Review of Techniques." *Gland Surgery* 5(2):212–26.

Chan, Woanyi, Bhagwat Mathur, Diana Slade-Sharman, and Venkat Ramakrishnan. 2011. "Developmental Breast Asymmetry." *Breast Journal* 17(4):391–98.

Chang, Jessica B., Kevin H. Small, Mihye Choi, and Nolan S. Karp. 2015. "Three-Dimensional Surface Imaging in Plastic Surgery: Foundation, Practical Applications, and Beyond." *Plastic and Reconstructive Surgery* 135(5):1295–1304.

Cimaroli, Sawyer, John A. Logiudice, and Erin L. Doren. 2020. "Exploring the Role of Partner Satisfaction in Predicting Patient Satisfaction Regarding Post-Mastectomy Breast Reconstruction." *Plastic and Reconstructive Surgery - Global Open* 1–4.

Cohee, Andrea A., Silvia M. Bigatti, Cleveland G. Shields, Shelley A. Johns, Timothy Stump, Patrick O.

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Monahan, and Victoria L. Champion. 2018. "Quality of Life in Partners of Young and Old Breast Cancer Survivors." *Cancer Nursing* 00(0):1–7.

Cohen, Michael, Bradley Evanoff, Laura T. George, and Keith E. Brandt. 2005. "A Subjective Rating Scale for Evaluating the Appearance Outcome of Autologous Breast Reconstruction." *Plastic and Reconstructive Surgery* 116(2):440–49.

Couzi, R. J., K. J. Helzlsouer, and J. H. Fetting. 1995. "Prevalence of Menopausal Symptoms among Women with a History of Breast Cancer and Attitudes toward Estrogen Replacement Therapy." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 13(11):2737–44.

Daly, Mary B., Robert Pilarski, Jennifer E. Axilbund, Michael Berry, Saundra S. Buys, Beth Crawford, Meagan Farmer, Susan Friedman, Judy E. Garber, Seema Khan, Catherine Klein, Wendy Kohlmann, Allison Kurian, Jennifer K. Litton, Lisa Madlensky, P. Kelly Marcom, Sofia D. Merajver, Kenneth Offit, Tuya Pal, Huma Rana, Gwen Reiser, Mark E. Robson, Kristen Mahoney Shannon, Elizabeth Swisher, Nicoleta C. Voian, Jeffrey N. Weitzel, Alison Whelan, Myra J. Wick, Georgia L. Wiesner, Mary Dwyer, Rashmi Kumar, and Susan Darlow. 2017. "Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017." *Journal of the National Comprehensive Cancer Network* 15(1):9–20.

Davies, C. F., R. Macefield, K. Avery, and J. M. Blazeby. 2021. "Patient-Reported Outcome Measures for Post-Mastectomy Breast Reconstruction : A Systematic Review of Development and Measurement Properties." *Annals of Surgical Oncology* 28(1):386–404.

Domchek, Susan M., Fergus J. Couch, Tara M. Friebel, Christian F. Singer, D. Gareth Evans, Henry T. Lynch, Claudine Isaacs, Judy E. Garber, Susan L. Neuhausen, Ellen Matloff, Nadine Tung, Jeffrey N. Weitzel, Mary B. Daly, Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Claudine Isaacs, Garber JE, Neuhausen SL, Ellen Matloff, Rosalind Eeles, Gabriella Pichert, Van t'veer L, Nadine Tung, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Gail Tomlinson, Laura Van t'veer, Nadine Tung, Jeffrey N. Weitzel, Fergus J. Couch, Wendy S. Rubinstein, Patricia A. Ganz, Mary B. Daly, Olufunmilayo I. Olopade, Gail Tomlinson, Joellen Schildkraut, Joanne L. Blum, and Timothy R. Rebbeck. 2010. "Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers with Cancer Risk and Mortality." *JAMA : The Journal of the American Medical Association* 304(9):967–75.

Edsander-Nord, Åsa, Marie Wickman, Göran Jurell, Marie Wickman, and Goran Jurell. 1996. "Surgery and Hand Surgery Measurement of Breast Volume with Thermoplastic Casts A." *Scand J Plast REconstr Surg Hand Surg* 30(2):129–32.

Eisemann, Bradley S. and Aldona J. Spiegel. 2018. "Risk-Reducing Mastectomy and Breast Reconstruction Indications and Evidence for Current Management Strategies." *Clinics in Plastic Surgery* 45(1):129–36.

Elder, Elisabeth Edstrom, Yvonne Brandberg, Tina Björklund, Richard Rylander, Jakob Lagergren, Göran Jurell, Marie Wickman, and Kerstin Sandelin. 2005. "Quality of Life and Patient Satisfaction in Breast Cancer Patients after Immediate Breast Reconstruction: A Prospective Study." *Breast* 14(3):201–8.

Eriksen, Catharina, Emelie Nordstrand Lindgren, Jan Frisell, and Birgit Stark. 2012. "A Prospective Randomized Study Comparing Two Different Expander Approaches in Implant-Based Breast Reconstruction." *Plastic and Reconstructive Surgery* 130(2):254–64.

Evans, D. Gareth R., Sarah L. Ingham, Andrew Baildam, Gary L. Ross, Fiona Lalloo, Iain Buchan, and Anthony Howell. 2013. "Contralateral Mastectomy Improves Survival in Women with BRCA1/2-Associated Breast Cancer." *Breast Cancer Research and Treatment* 140(1):135–42.

Fayanju, Oluwadamilola Motunaryo, Carolyn R. T. Stoll, Susan Fowler, Graham A. Colditz, and Julie A. Margenthaler. 2014. "Contralateral Prophylactic Mastectomy After Unilateral Breast Cancer A Systematic Review and Meta-Analysis." *Annals of Surgery* 260(6):1000–1010.

Fitzal, F., W. Krois, H. Trischler, L. Wutzel, O. Riedl, U. Kühbelböck, B. Wintersteiner, M. J. Cardoso, P. Dubsky, M. Gnant, R. Jakesz, and T. Wild. 2007. "The Use of a Breast Symmetry Index for Objective Evaluation of Breast Cosmesis." *The Breast* 16(4):429–35.

Foulkes, William D. 2008. "Inherited Susceptibility to Common Cancers." *New England Journal of Medicine* 359(20):2143–53.

Frost, M. H., D. J. Schaid, T. A. Sellers, J. M. Slezak, P. G. Arnold, J. E. Woods, P. M. Petty, J. L. Johnson, D. L. Sitta, S. K. McDonnell, T. A. Rummans, R. B. Jenkins, J. A. Sloan, and L. C. Hartmann. 2000. "Long-

Term Satisfaction and Psychological and Social Function Following Bilateral Prophylactic Mastectomy." *Jama* 284(3):319–24.

Frost, Marlene H., Tanya L. Hoskin, Lynn C. Hartmann, Amy C. Degnim, Joanne L. Johnson, and Judy C. Boughey. 2011. "Contralateral Prophylactic Mastectomy: Long-Term Consistency of Satisfaction and Adverse Effects and the Significance of Informed Decision-Making, Quality of Life, and Personality Traits." *Annals of Surgical Oncology* 18(11):3110–16.

Frost, Marlene H., Jeffrey M. Slezak, Nho V. Tran, Constance I. Williams, Joanne L. Johnson, John E. Woods, Paul M. Petty, John H. Donohue, Clive S. Grant, Jeff A. Sloan, Thomas A. Sellers, and Lynn C. Hartmann. 2005. "Satisfaction after Contralateral Prophylactic Mastectomy: The Significance of Mastectomy Type, Reconstructive Complications, and Body Appearance." *Journal of Clinical Oncology* 23(31):7849–56.

Gahm, Jessica, Per Hansson, Yvonne Brandberg, and Marie Wickman. 2013. "Breast Sensibility after Bilateral Risk-Reducing Mastectomy and Immediate Breast Reconstruction: A Prospective Study." *Journal of Plastic, Reconstructive & Aesthetic Surgery : JPRAS* 66(11):1521–27.

Gahm, Jessica, Göran Jurell, Åsa Edsander-Nord, and Marie Wickman. 2010. "Patient Satisfaction with Aesthetic Outcome after Bilateral Prophylactic Mastectomy and Immediate Reconstruction with Implants." *Journal of Plastic, Reconstructive and Aesthetic Surgery* 63(2):332–38.

Gahm, Jessica, Marie Wickman, and Yvonne Brandberg. 2010. "Bilateral Prophylactic Mastectomy in Women with Inherited Risk of Breast Cancer – Prevalence of Pain and Discomfort, Impact on Sexuality, Quality of Life and Feelings of Regret Two Years after Surgery." *Breast (Edinburgh, Scotland)* 19(6):462–69.

Galdino, Greg M., Maurice Nahabedian, Michael Chiaramonte, Jason Z. Geng, Stanley Klatsky, and Paul Manson. 2002. "Clinical Applications of Three-Dimensional Photography in Breast Surgery." *Plast Reconstr Surg* 110(1):58–70.

Geiger, Ann M., Larissa Nekhlyudov, Lisa J. Herrinton, Sharon J. Rolnick, Sarah M. Greene, Carmen N. West, Emily L. Harris, Joann G. Elmore, Andrea Altschuler, In Liu A. Liu, Suzanne W. Fletcher, and Karen M. Emmons. 2007. "Quality of Life after Bilateral Prophylactic Mastectomy." *Annals of Surgical Oncology* 14(2):686–94.

Geiger, Ann M., Carmen N. West, Larissa Nekhlyudov, Lisa J. Herrinton, In-Liu A. Liu, Andrea Altschuler, Sharon J. Rolnick, Emily L. Harris, Sarah M. Greene, Joann G. Elmore, Karen M. Emmons, and Suzanne W. Fletcher. 2006. "Contentment With Quality of Life Among Breast Cancer Survivors With and Without Contralateral Prophylactic Mastectomy." *Journal of Clinical Oncologyn* 24(9):1350–56.

Gerke, Oke, Mie Holm Vilstrup, Eivind Antonsen Segtnan, Ulrich Halekoh, and Poul Flemming Høilund-carlsen. 2016. "How to Assess Intra- and Inter-Observer Agreement with Quantitative PET Using Variance Component Analysis : A Proposal for Standardisation." *BMC Medical Imaging* 1–9.

Ghosh, Karthik and Lynn C. Hartmann. 2002. "Current Status of Prophylactic Mastectomy." *Oncology* 16(10):1319–1332.

Gopie, Jessica P., Marc A. M. Mureau, Caroline Seynaeve, Moniek M. Ter Kuile, Marian B. E. Menke-Pluymers, Reinier Timman, and Aad Tibben. 2013. "Body Image Issues after Bilateral Prophylactic Mastectomy with Breast Reconstruction in Healthy Women at Risk for Hereditary Breast Cancer." *Familial Cancer* 12(3):479–87.

Graeser, Monika, Christoph Engel, and Kerstin Rhiem. 2009. "Contralateral Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers." *J Clin Oncol* 27(35):5887–92.

Grift, Tim C. Van De, Rieky E. G. Dikmans, Marc A. M. Mureau, Vera N. Negenborn, Mark-bram Bouman, and Margriet G. Mullender. 2020. "Predictors of Women ' s Sexual Outcomes after Implant-Based Breast Reconstruction." (April):1272–79.

Hall, JM, MK Lee, B. Newman, JE Morrow, LA Anderson, B. Huey, and MC King. 1990. "Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21." *Science* 250(4988):1684–89.

Haloua, Max H., Nicole M. a Krekel, Henri a H. Winters, Derek H. F. Rietveld, Sybren Meijer, Frank W. Bloemers, and Monique P. van den Tol. 2013. "A Systematic Review of Oncoplastic Breast-Conserving Surgery: Current Weaknesses and Future Prospects." *Annals of Surgery* 257(4):609–20.

Hartmann, L. C., D. J. Schaid, J. E. Woods, T. P. Crotty, J. L. Myers, P. G. Arnold, P. M. Petty, T. A. Sellers, J. L. Johnson, S. K. McDonnell, M. H. Frost, and R. B. Jenkins. 1999. "Efficacy of Bilateral Prophylactic Mastectomy in Women with a Family History of Breast Cancer." *The New England Journal of Medicine* 340(2):77–84.

Hartmann, Lynn C., A. Thomas, Daniel J. Schaid, S. Thomas, Cheryl L. Soderberg, L. Sitta, Marlene H. Frost, S. Clive, John H. Donohue, E. John, Shannon K. Mcdonnell, Catherine Walsh Vockley, Fergus J. Couch, and Robert B. Jenkins. 2001. *Efficacy of Bilateral Prophylactic Mastectomy in BRCA1 and BRCA2 Gene Mutation Carriers*. Vol. 93.

Hatcher, Mal Bebbington, Lesley Fallowfield, and Roger A'Hern. 2001. "The Psychosocial Impact of Bilateral Prophylactic." *BMJ* 322(January):1–6.

Hauben, Daniel J., Neta Adler, Ram Silfen, and Dan Regev. 2003. "Breast – Areola – Nipple Proportion." *Annals of Plastic Surgery* 50(5):510–13.

Heemskerk-Gerritsen, B. A. M., M. B. E. Menke-Pluijmers, A. Jager, M. M. A. Tilanus-Linthorst, L. B. Koppert, I. M. A. Obdeijn, C. H. M. van Deurzen, J. M. Collée, C. Seynaeve, and M. J. Hooning. 2013. "Substantial Breast Cancer Risk Reduction and Potential Survival Benefit after Bilateral Mastectomy When Compared with Surveillance in Healthy BRCA1 and BRCA2 Mutation Carriers: A Prospective Analysis." *Annals of Oncology* 24(8):2029–35.

den Heijer, Mariska, Caroline Seynaeve, Reinier Timman, Hugo J. Duivenvoorden, Kathleen Vanheusden, Madeleine Tilanus-Linthorst, Marian B. E. Menke-Pluijmers, and Aad Tibben. 2012. "Body Image and Psychological Distress after Prophylactic Mastectomy and Breast Reconstruction in Genetically Predisposed Women: A Prospective Long-Term Follow-up Study." *European Journal of Cancer* 48(9):1263–68.

Heiniger, Louise, Phyllis N. Butow, Joseph Coll, Tracey Bullen, Judy Wilson, Brandi Baylock, Bettina Meiser, and Melanie A. Price. 2015. "Long-Term Outcomes of Risk-Reducing Surgery in Unaffected Women at Increased Familial Risk of Breast and/or Ovarian Cancer." *Familial Cancer* 14(1):105–15.

Henseler, Helga, Joanna Smith, Adrian Bowman, Balvinder S. Khambay, Xiangyang Ju, Ashraf Ayoub, and Arup K. Ray. 2013. "Subjective versus Objective Assessment of Breast Reconstruction." *Journal of Plastic, Reconstructive and Aesthetic Surgery* 66(5).

Honrado, Carlo P. and Wayne F. Larrabee. 2004. "Update in Three-Dimensional Imaging in Facial Plastic Surgery." *Current Opinion in Otolaryngology and Head and Neck Surgery* 12(4):327–31.

Hooker, Gillian W., Lesley King, Lauren Vanhusen, Kristi Graves, Beth N. Peshkin, Claudine Isaacs, Kathryn L. Taylor, Elizabeth Poggi, and Marc D. Schwartz. 2014a. "Long-Term Satisfaction and Quality of Life Following Risk Reducing Surgery in BRCA1 / 2 Mutation Carriers." *Hereditary Cancer in Clinical Practice* 12(9):1–8.

Hooker, Gillian W., Lesley King, Lauren Vanhusen, Kristi Graves, Beth N. Peshkin, Claudine Isaacs, Kathryn L. Taylor, Elizabeth Poggi, and Marc D. Schwartz. 2014b. "Long-Term Satisfaction and Quality of Life Following Risk Reducing Surgery in BRCA1 / 2 Mutation Carriers." *Hereditary Cancer in Clinical Practice* 12(1):1–8.

Hopwood, P., I. Fletcher, A. Lee, and S. Al Ghazal. 2001. "A Body Image Scale for Use with Cancer Patients." *European Journal of Cancer (Oxford, England : 1990)* 37(2):189–97.

Hopwood, Penelope, Andrew Lee, Andrew Shenton, Andrew Baildam, Anne Brain, Fiona Lalloo, Gareth Evans, and Anthony Howell. 2000. "Clinical Follow-up after Bilateral Risk Reducing ('prophylactic') Mastectomy: Mental Health and Body Image Outcomes." *Psycho-Oncology* 9(6):462–72.

Hsia, Henry C. and J. Grant Thomson. 2003. "Differences in Breast Shape Preferences between Plastic Surgeons and Patients Seeking Breast Augmentation." *Plastic and Reconstructive Surgery* 112(1):312–20.

Ingham, Sarah L., Matthew Sperrin, Andrew Baildam, Gary L. Ross, Richard Clayton, Fiona Lalloo, Iain Buchan, Anthony Howell, and D. Gareth R. Evans. 2013. "Risk-Reducing Surgery Increases Survival in BRCA1/2 Mutation Carriers Unaffected at Time of Family Referral." *Breast Cancer Research and Treatment* 142(3):611–18.

Isern, A. E., I. Tengrup, N. Loman, H. Olsson, and A. Ringberg. 2008. "Aesthetic Outcome, Patient Satisfaction,

and Health-Related Quality of Life in Women at High Risk Undergoing Prophylactic Mastectomy and Immediate Breast Reconstruction." *Journal of Plastic, Reconstructive and Aesthetic Surgery* 61(10):1177–87.

Jacobs, R. A. 2001. "Three-Dimensional Photography." *Plastic and Reconstructive Surgery* 107(1):276–77.

Johansen, Nora, Astrid H. Liavaag, Tom G. Tanbo, Alv A. Dahl, Are H. Pripp, and Trond M. Michelsen. 2016. "Sexual Activity and Functioning after Risk-Reducing Salpingo-Oophorectomy: Impact of Hormone Replacement Therapy." *Gynecologic Oncology* 140:101–6.

Kaas, Reinoutje, Senno Verhoef, Jelle Wesseling, Matti A. Rookus, Hester S. A. Oldenburg, Marie Jeanne Vrancken Peeters, and Emiel J. T. Rutgers. 2010. "Prophylactic Mastectomy in BRCA1 and BRCA2 Mutation Carriers: Very Low Risk for Subsequent Breast Cancer." *Annals of Surgery* 251(3):488–92.

Keller, Katja, Cornelia Meisel, Nannette Grübling, Andrea Petzold, Pauline Wimberger, and Karin Kast. 2019. "Patient-Reported Satisfaction after Prophylactic Operations of the Breast." *Breast Care* 14(4):217–23.

Killaars, Renee C., Myriam L. G. Preu, Nathalie J. P. De Vos, and René R. W. J. Van Der Hulst. 2020. "Original Article Clinical Assessment of Breast Volume : Can 3D Imaging Be the Gold Standard ?" *Plastic and Reconstructive Surgery - Global Open* 8(11):1–8.

Koo, Terry K. and Mae Y. Li. 2016. "A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research." *Journal of Chiropractic Medicine* 15(2):155–63.

Kovacs, Laszlo, Alexander Zimmermann, Nikolaos A. Papadopulos, and Edgar Biemer. 2004. "Re: Factors Determining Shape and Symmetry in Immediate Breast Reconstruction." *Annals of Plastic Surgery* 53(2):192–94.

Krag, David, Donald Weaver, Takamaru Ashikaga, Frederick Moffat, V. Suzanne Klimberg, Craig Shriver, Sheldon Feldman, Roberto Kusminsky, Michele Gadd, Joseph Kuhn, Seth Harlow, Peter Beitsch, Pat Whitworth, Roger Foster, and Kambiz Dowlatshahi. 1998. "The Sentinel Node in Breast Cancer — A Multicenter Validation Study." *New England Journal of Medicine* 339(14):941–46.

Kuchenbaecker, Karoline B., John L. Hopper, Daniel R. Barnes, Kelly-anne Phillips, Thea M. Mooij, Sarah Jervis, Flora E. Van Leeuwen, Roger L. Milne, Nadine Andrieu, David E. Goldgar, Mary Beth Terry, Matti A. Rookus, Douglas F. Easton, Antonis C. Antoniou, and Brca Cohort Consortium. 2017. "Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers." *JAMA* 317(23):2402–16.

Kuroda, Flavia, Cicero Urban, Gustavo Zucca-Matthes, Vilmar Marques De Oliveira, Gabriel Hubner Arana, Marco Iera, Mario Rietjens, Gabriela Santos, Caroline Spagnol, and Rubens Silveira De Lima. 2016. "Evaluation of Aesthetic and Quality-of-Life Results after Immediate Breast Reconstruction with Definitive Form-Stable Anatomical Implants." *Plastic and Reconstructive Surgery* 137(2):278e-286e.

De La Peña-Salcedo, Jose Abel, Miguel Angel Soto-Miranda, and Jose Fernando Lopez-Salguero. 2012. "Prophylactic Mastectomy: Is It Worth It?" *Aesthetic Plastic Surgery* 36(1):140–48.

Landis, JR and GG Koch. 1977. "The Measurement of Observer Agreement for Categorical Data." *Biometrics* 33:159–174.

Lee, A. J., A. P. Cunningham, K. B. Kuchenbaecker, N. Mavaddat, D. F. Easton, and A. C. Antoniou. 2013. "BOADICEA Breast Cancer Risk Prediction Model : Updates to Cancer Incidences , Tumour Pathology and Web Interface." *British Journal of Cancer* 110(2):535–45.

Lee, Clara Nan-hi, Michael Patrick Pignone, Allison M. Deal, Lillian Blizard, Caprice Hunt, Ruth Huh, Yuen-Jong Liu, and Peter Anthony Ubel. 2018. "Accuracy of Predictions of Patients With Breast Cancer of Future Well-Being After Immediate Breast Reconstruction." *JAMA Surgery* 43212:e176112.

Lloyd, S. M., M. Watson, G. Oaker, N. Sacks, U. Querci Della Rovere, and G. Gui. 2000. "Understanding the Experience of Prophylactic Bilateral Mastectomy: A Qualitative Study of Ten Women." *Psycho-Oncology* 9(6):473–85.

Lohmander, F., J. Lagergren, H. Johansson, P. G. Roy, J. Frisell, and Y. Brandberg. 2020. "Quality of Life and Patient Satisfaction after Implant-Based Breast Reconstruction with or without Acellular Dermal Matrix: Randomized Clinical Trial." *BJS Open* 4(5):811–20.

Losken, Albert, Hisham Seify, Donald D. Denson, Alfredo A. Paredes, and Grant W. Carlson. 2005. "Validating Three-Dimensional Imaging of the Breast." *Annals of Plastic Surgery* 54(5):471–76.

Lostumbo, L., Carbine N. E., J. Wallace, J. Ezzo, and K. Dickersin. 2004. "Prophylactic Mastectomy for the Prevention of Breast Cancer." *Cochrane Database of Systematic Reviews* (4).

Loughry, C., D. B. Sheffer, T. E. Price, R. L. Einsporn, R. G. Bartfai, W. M. Morek, and N. M. Meli. 1989. "Breast Volume Measurement of 598 Women Using Biostereometric Analysis." *Plastic and Reconstructive Surgery* 22(5):380–85.

Loughry, C. W., D. B. Sheffer, T. E. Price, M. J. Lackney, R. G. Bartfai, and W. M. Morek. 1987. "Breast Volume Measurement of 248 Women Using Biostereometric Analysis." *Plastic and Reconstructive Surgery* 80(4):553–558.

Manne, Sharon, Janet Audrain, Marc Schwartz, David Main, Clinton Finch, and Caryn Lerman. 2004. "Associations between Relationship Support and Psychological Reactions of Participants and Partners to BRCA1 and BRCA2 Testing in a Clinic-Based Sample." *Annals of Behavioral Medicine* 28(3):211–25.

Manning, A. T., C. Wood, A. Eaton, M. Stempel, D. Capko, A. Pusic, M. Morrow, and V. Sacchini. 2015. "Nipple-Sparing Mastectomy in Patients with BRCA1/2 Mutations and Variants of Uncertain Significance." *British Journal of Surgery* 102(11):1354–59.

Mauer, Caitlin, Sara Spencer, Jeffery Dungan, and Karen Hurley. 2016. "Exploration of Male Attitudes on Partnerships and Sexuality with Female BRCA1/2 Mutation Carriers." *Journal of Genetic Counseling* 25(2):290–97.

McHorney, CA, JE Jr Ware, JF Lu, and CD Sherbourne. 1994. "The MOS 36-Item Short-Form Health Survey (SF-36): III. Tests of Data Quality, Scaling Assumptions, and Reliability across Diverse Patient Groups." *Med Care* 32(1):40–66.

Meijers-Heijboer, H., B. van Geel, W. L. van Putten, S. C. Henzen-Logmans, C. Seynaeve, M. B. Menke-Pluymers, C. C. Bartels, L. C. Verhoog, A. M. van den Ouweland, M. F. Niermeijer, C. T. Brekelmans, and J. G. Klijn. 2001. "Breast Cancer after Prophylactic Bilateral Mastectomy in Women with a BRCA1 or BRCA2 Mutation." *The New England Journal of Medicine* 345(3):159–64.

Metcalfe, KA, A. Liede, M. Trinkaus, D. Hanna, and SA Narod. 2002. "Evaluation of the Needs of Spouses of Female Carriers of Mutations in BRCA1 and BRCA2." *Clinical Genetics* 62(6):464–69.

Metcalfe, Kelly A., Mary Jane Esplen, Vivek Goel, and Steven A. Narod. 2004. "Psychosocial Functioning in Women Who Have Undergone Bilateral Prophylactic Mastectomy." *Psycho-Oncology* 13(1):14–25.

Metcalfe, Kelly A., Mary Jane Esplen, Vivek Goel, and Steven A. Narod. 2005. "Predictors of Quality of Life in Women with a Bilateral Prophylactic Mastectomy." *Breast Journal* 11(1):65–69.

Meybodi, Farid Aghaee. 2014. "3D Photography in Assessment of Breast Symmetry and Correlation with Other Subjective and Objective Methods." University of Sydney.

Ming, V. Mak Wai. 2002. "Psychological Predictors of Marital Adjustment in Breast Cancer Patients." *Psychology, Health & Medicine* 7(1):37–51.

Mireskandari, Shab, Bettina Meiser, Kerry Sherman, Beverley J. Warner, Lesley Andrews, and Katherine M. Tucker. 2006. "Evaluation of the Needs and Concerns of Partners of Women at High Risk of Developing Breast/Ovarian Cancer." *Psycho-Oncology* 15(2):96–108.

Montgomery, Leslie L., Katherine N. Tran, Melissa C. Heelan, Kimberly J. Van Zee, Mary Jane Massie, David K. Payne, and Patrick I. Borgen. 1999. "Issues of Regret in Women with Contralateral Prophylactic Mastectomies." *Annals of Surgical Oncology* 6(6):546–52.

Murphy, Brittany L., Amy E. Glasgow, Gary L. Keeney, Elizabeth B. Habermann, and Judy C. Boughey. 2017. "Selective Use of Sentinel Lymph Node Surgery in Patients Undergoing Prophylactic Mastectomy Using Intraoperative Pathology." *Annals of Surgical Oncology* 24(10):3032–37.

Murthy, Vijayashree and Ronald S. Chamberlain. 2013. "Prophylactic Mastectomy in Patients at High Risk: Is There a Role for Sentinel Lymph Node Biopsy?" *Clinical Breast Cancer* 13(3):180–87.

Neto, Miguel Sabino, Luiz Eduardo Felipe Abla, Ana Lucia Lemos, Élvio Bueno Garcia, Mariana Junqueira Reis Enout, Nádia Canale Cabral, and Lydia Masako Ferreira. 2012. "The Impact of Surgical Treatment on the Self-Esteem of Patients with Breast Hypertrophy, Hypomastia, or Breast Asymmetry." *Aesthetic Plastic Surgery* 36(1):223–25.

O'Connell, Rachel L., Komel Khabra, Jeffrey C. Bamber, Nandita DeSouza, Farid Meybodi, Peter A. Barry, and Jennifer E. Rusby. 2018. "Validation of the Vectra XT Three-Dimensional Imaging System for Measuring Breast Volume and Symmetry Following Oncological Reconstruction." *Breast Cancer Research and Treatment* 171(2):391–98.

O'Connell, Rachel L., Rosa Di Micco, Komel Khabra, Lisa Wolf, Nandita DeSouza, Nicola Roche, Peter A. Barry, Anna M. Kirby, and Jennifer E. Rusby. 2017. "The Potential Role of Three-Dimensional Surface Imaging as a Tool to Evaluate Aesthetic Outcome after Breast Conserving Therapy (BCT)." *Breast Cancer Research and Treatment* 164(2):385–93.

O'Connell, Rachel L., Roger J. G. Stevens, Paul A. Harris, and Jennifer E. Rusby. 2015. "Review of Three-Dimensional (3D) Surface Imaging for Oncoplastic, Reconstructive and Aesthetic Breast Surgery." *The Breast* 24(4):331–42.

van Oostrom, I., H. Meijers-heijboer, H. J. Duivenvoorden, A. H. J. T. Bröcker-vriends, C. J. Van Asperen, R. H. Sijmons, C. Seynaeve, A. R. Van Gool, E. Klijn, and A. Tibben. 2007. "Family System Characteristics and Psychological Adjustment to Cancer Susceptibility Genetic Testing: A Prospective Study." *Clinical Genetics* 71(1):35–42.

Osoba, D., G. Rodrigues, J. Myles, B. Zee, and J. Pater. 1998. "Interpreting the Significance of Changes in Health-Realted Quality-of-Life Scores." *Journal of Clinical Oncology* 16(1):139–44.

Paluch-Shimon, S., F. Cardoso, C. Sessa, J. Balmana, M. J. Cardoso, F. Gilbert, E. Senkus, and on behalf of the ESMO Guidelines Committee. 2016. "Prevention and Screening in BRCA Mutation Carriers and Other Breast/Ovarian Hereditary Cancer Syndromes: ESMO Clinical Practice Guidelines for Cancer Prevention and Screening." *Annals of Oncology* 27(Supplement 5):v103–10.

Panjari, Mary, Robin J. Bell, and Susan R. Davis. 2011. "Sexual Function after Breast Cancer." *Journal of Sexual Medicine* 8(1):294–302.

Peled, Anne Warren, Chetan S. Irwin, E. Shelley Hwang, Cheryl A. Ewing, Michael Alvarado, and Laura J. Esserman. 2014. "Total Skin-Sparing Mastectomy in BRCA Mutation Carriers." *Annals of Surgical Oncology* 21(1):37–41.

Penn, J. 1955. "Breast Reduction." *British Journal of Plastic Surgery* 7(4):357–71.

Pusic, Andrea L., Constance M. Chen, Stefan Cano, Anne Klassen, Colleen McCarthy, E. Dale Collins, and Peter G. Cordeiro. 2007. "Measuring Quality of Life in Cosmetic and Reconstructive Breast Surgery: A Systematic Review of Patient-Reported Outcomes Instruments." *Plastic and Reconstructive Surgery* 120(4):823–37.

Pusic, Andrea L., Anne F. Klassen, Amie M. Scott, Jennifer A. Klok, Peter G. Cordeiro, and Stefan J. Cano. 2009. "Development of a New Patient-Reported Outcome Measure for Breast Surgery: The BREAST-Q." *Plastic and Reconstructive Surgery* 124(2):345–53.

Qiao, Qun, D. Ph, Gang Zhou, and Yi-chun Ling. 1997. "Breast Volume Measurement in Young Chine.Pdf." *Aesth* 21(5):362–68.

Quinn, Tam T., George S. Miller, Marie Rostek, Miguel S. Cabalag, Warren M. Rozen, and David J. Hunter-Smith. 2016. "Prosthetic Breast Reconstruction: Indications and Update." *Gland Surgery* 5(2):174–86.

Rebbeck, Timothy R., Tara Friebel, Henry T. Lynch, Susan L. Neuhausen, Laura Van't Veer, Judy E. Garber, Gareth R. Evans, Steven A. Narod, Claudine Isaacs, Ellen Matloff, Mary B. Daly, Olufunmilayo I. Olopade, and Barbara L. Weber. 2004. "Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: The PROSE Study Group." *Journal of Clinical Oncology* 22(6):1055–62.

Rebbeck, Timothy R., Nandita Mitra, Fei Wan, Olga M. Sinilnikova, Sue Healey, Lesley Mcguffog, Sylvie Mazoyer, Georgia Chenevix-trench, Douglas F. Easton, Antonis C. Antoniou, and Katherine L. Nathanson. 2015. "Association of Type and Location of BRCA1 and BRCA2 Mutations With Risk of

Breast and Ovarian Cancer." *JAMA* 313(13):1347–61.

Reynolds, Carol, Jennifer A. Davidson, Noralane M. Lindor, Katrina N. Glazebrook, James W. Jakub, Amy C. Degnim, Nicole P. Sandhu, Molly F. Walsh, Lynn C. Hartmann, and Judy C. Boughey. 2011. "Prophylactic and Therapeutic Mastectomy in BRCA Mutation Carriers: Can the Nipple Be Preserved?" *Annals of Surgical Oncology* 18(11):3102–9.

Rha, Eun Young, Ik Kyun Choi, and Gyeol Yoo. 2014. "Accuracy of the Method for Estimating Breast Volume on Three-Dimensional Simulated Magnetic Resonance Imaging Scans in Breast Reconstruction." *Plast Reconstr Surg.* 133:14–20.

Rousset-Jablonski, Christine and Anne Gompel. 2017. "Screening for Familial Cancer Risk: Focus on Breast Cancer." *Maturitas* 105(July):69–77.

Rowland, Emma and Alison Metcalfe. 2014. "A Systematic Review of Men's Experiences of Their Partner's Mastectomy: Coping with Altered Bodies." *Psycho-Oncology* 23(9):963–74.

Sandberg, Lars Johan, Kim A. Tønseth, Kristine Kloster-Jensen, Jun Liu, Charee Robe, Gregory Reece, Elisabeth H. Hansen, Karin Berntsen, Martin Halle, Åsa Edsander-Nord, Anna Höckerstedt, Susanna Kauhanen, Christian Sneistrup, Tyge Tindholdt, Hans Petter Gullestad, Gudjon Leifur Gunnarsson, Erik Berg, and Jesse Creed Selber. 2020. "An Aesthetic Factor Priority List of the Female Breast in Scandinavian Subjects." *Plastic and Reconstructive Surgery - Global Open* 1–8.

Shapira, Rachel, Erin Turbitt, Lori H. Erby, Barbara B. Biesecker, William M. P. Klein, and Gillian W. Hooker. 2018. "Adaptation of Couples Living with a High Risk of Breast / Ovarian Cancer and the Association with Risk-Reducing Surgery." *Familial Cancer* 17(4):485–93.

Shiovitz, Stacey and L. A. Korde. 2015. "Genetics of Breast Cancer: A Topic in Evolution." *Annals of Oncology* 26(7):1291–99.

Sigurdson, Leif J. and Susan A. Kirkland. 2006. "Breast Volume Determination in Breast Hypertrophy: An Accurate Method Using Two Anthropomorphic Measurements." *The Breast* 118(2):313–20.

Smith, D. J., W. E. Palin, V. L. Katch, and J. E. Bennett. 1986. "Breast Volume and Anthropomorphic Measurements: Normal Values." *Plastic and Reconstructive Surgery* 78(3):331–35.

Snaith, R. P. and A. S. Zigmond. 1986. "The Hospital Anxiety and Depression Scale." *Br Med J (Clin Res Ed)* 292:1986.

Sneeuw, K. C., N. K. Aaronson, J. R. Yarnold, M. Broderick, J. Regan, G. Ross, and A. Goddard. 1992. "Cosmetic and Functional Outcomes of Breast Conserving Treatment for Early Stage Breast Cancer. 1. Comparison of Patients' Ratings, Observers' Ratings, and Objective Assessments." *Radiotherapy and Oncology* 25(3):153–159.

Stefanek, M. E. 1995. "Bilateral Prophylactic Mastectomy: Issues and Concerns." *Journal of the National Cancer Institute. Monographs* (17):37–42.

Stratton, Michael R. and Nazneen Rahman. 2008. "The Emerging Landscape of Breast Cancer Susceptibility." 40(1):17–22.

Sullivan, Marianne and Jan Karlsson. 1994. *Swedish Manual and Interpretation Guide [Swedish]*. International Quality of Life Assessment (IQLA) Project Health Care Research Unit Medical Faculty Gothenburg University and Sahlgrenska Hospital.

Sullivan, Marianne, Jan Karlsson, J. E. Jr Ware, and John E. Ware Jr. 1995. "The Swedish SF-36 Health Survey-I. Evaluation of Data Quality, Scaling Assumptions, Reliability and Construct Validity across General Populations in Sweden." *Social Science and Medicine* 41(10):1349–58.

Svenska Bröstcancergruppens nationella riktlinjer. n.d. "Utredning, Uppföljning Och Omhändertagande Av Personer Med Misstänkt Ärftligt Ökad Risk För Bröst- Och Äggstockscancer." Retrieved May 19, 2019 (https://sfmg.se/download/riktlinjer/Cancergenetik/Riktlinjer arftlig brost aggstockscancer 2011.pdf).

Tezel, Erdem and Ayhan Numanoğlu. 2000. "Practical Do-It-Yourself Device for Accurate Volume Measurement of Breast." *Plastic and Reconstructive Surgery* 105(3):1019–23.

The EORTC Quality of Life Group & EORTC Quality of Life Unit, . 2002. *Guidelines for Assessing Quality of Life in EORTC Clinical Trials*.

Thirlaway, K., L. Fallowfield, and J. Cuzick. 1996. "The Sexual Activity Questionnaire: A Measure of Women's Sexual Functioning." *Quality of Life Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation* 5(1):81–90.

Thomson, H. J., Z. E. Winters, Y. Brandberg, F. Didier, J. M. Blazeby, and J. Mills. 2013. "The Early Development Phases of a European Organisation for Research and Treatment of Cancer (EORTC) Module to Assess Patient Reported Outcomes (PROs) in Women Undergoing Breast Reconstruction." *European Journal of Cancer* 49(5):1018–26.

Tzou, Chieh-han John, Nicole M. Artner, Igor Pona, Alina Hold, Eva Placheta, Walter G. Kropatsch, and Manfred Frey. 2014. "Comparison of Three-Dimensional Surface- Imaging Systems *." *British Journal of Plastic Surgery* 67(4):489–97.

Unukovych, Dmytro, Hemming Johansson, and Yvonne Brandberg. 2017. "Preoperative Psychosocial Characteristics May Predict Body Image and Sexuality Two Years after Risk-Reducing Mastectomy: A Prospective Study." *Gland Surg* 6(1):64–72.

Unukovych, Dmytro, Kerstin Sandelin, Annelie Liljegren, Brita Arver, Marie Wickman, Hemming Johansson, and Yvonne Brandberg. 2012. "Contralateral Prophylactic Mastectomy in Breast Cancer Patients with a Family History: A Prospective 2-Years Follow-up Study of Health Related Quality of Life, Sexuality and Body Image." *European Journal of Cancer (Oxford, England : 1990)* 48(17):3150–56.

Unukovych, Dmytro, Marie Wickman, Kerstin Sandelin, Brita Arver, Hemming Johansson, and Yvonne Brandberg. 2016. "Associations between Reoperations and Psychological Factors after Contralateral Risk-Reducing Mastectomy : A Two-Year Follow-Up Study." 2016.

de Vet, Henrica C. W., Caroline B. Terwee, Dirk L. Knol, and Lex M. Bouter. 2006. "When to Use Agreement versus Reliability Measures." 59:1033–39.

Visser, Noortje J., Tim H. C. Damen, Reinier Timman, Stefan O. P. Hofer, and Marc A. M. Mureau. 2010. "Surgical Results, Aesthetic Outcome, and Patient Satisfaction after Microsurgical Autologous Breast Reconstruction Following Failed Implant Reconstruction." *Plastic and Reconstructive Surgery* 126(1):26–36.

Wachenfeldt, Anna Von, Yvonne Brandberg, Hemming Johansson, and Tommy Fornander. 2009. "Socioeconomic Status and Quality of Life of Women with Family History of Breast Cancer Attending an Oncogenetic Counseling Clinic – a Comparison with General Population." *Acta Oncologica* (48):85–92.

Warner, Ellen, Hans Messersmith, Petrina Causer, Andrea Eisen, Rene Shumak, and Donald Plewes. 2008. "Systematic Review: Using Magnetic Resonance Imaging to Screen Women at High Risk for Breast Cancer." *Annals of Internal Medicine* 148(9):671–79.

Westreich, Melvyn. 1997. "Anthropomorphic Breast Measurement: Protocol and Results in 50 Women with Aesthetically Perfect Breasts and Clinical Application." *Plastic and Reconstructive Surgery* 100(2):468–79.

Winters, Z. E., M. Afzal, C. Rutherford, B. Holzner, G. Rumpold, R. A. da Costa Vieira, S. Hartup, K. Flitcroft, V. Bjelic-Radisic, A. Oberguggenburger, M. Panouilleres, M. Mani, G. Catanuto, M. Douek, J. Kokan, P. Sinai, and M. T. King. 2017. "International Validation of the European Organisation for Research and Treatment of Cancer QLQ-BRECON23 Quality-of-Life Questionnaire for Women Undergoing Breast Reconstruction." *British Journal of Surgery* 30.

Winters, Z. E., V. Balta, H. J. Thomson, Y. Brandberg, A. Oberguggenberger, Y. Sinove, D. Unukovych, M. Nava, K. Sandelin, H. Johansson, J. Dobbeleir, P. Blondeel, N. Bruno, G. Catanuto, and R. Llewellyn-Bennett. 2014. "Phase III Development of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Module for Women Undergoing Breast Reconstruction." *The British Journal of Surgery* 101(4):371–82.

Wooster, Richard, Graham Bignell, Jonathan Lancaster, Sally Swift, Sheila Seal, Jonathan Mangion, Nadine Collins, Simon Gregory, Curtis Gumbs, Gos Micklem, Rita Barfoot, Rifat Hamoudi, Sandeep Patel, Catherine Rices, Patrick Biggs, Yasmin Hashim, Amanda Smith, Frances Connor, Adalgeir Arason, Julius Gudmundsson, David Ficenec, David Kelsell, Tonin Ford DeborahPatricia, D. Timothy Bishop, Nigel K.

Spurr, Bruce A. J. Ponder, Rosalind Eeles, Julian Peto, Peter Devilee, Cees Cornelisse, Henry Lynch, Steven Narod, Gilbert Lenoir, Valdgardur Egilsson, Rosa Bjork Barkadottir, Douglas F. Easton, David R. Bentley, P. Andrew Futreal, Alan Ashworth, and Michael R. Stratton. 1995. "Identification of the Breast Cancer Susceptibility Gene BRCA2." *Nature* 378(6559):789–92.

World Cancer Research Fund/American Institute for Cancer Research. 2018. *Continuous Update Project Expert Report: Diet, Nutrition, Physical Activity and Breast Cancer.*

Wylie, Jean E., Ken R. Smith, and Jeffrey R. Botkin. 2003. "Effects of Spouses on Distress Experienced by BRCA1 Mutation Carriers over Time." *American Journal of Medical Genetics - Seminars in Medical Genetics* 119 C(1):35–44.

Yao, Katharine, Erik Liederbach, Rong Tang, Lan Lei, Tomasz Czechura, Mark Sisco, Michael Howard, Peter J. Hulick, David J. Winchester, Suzanne B. Coopey, and Barbara L. Smith. 2015. "Nipple-Sparing Mastectomy in BRCA1/2 Mutation Carriers: An Interim Analysis and Review of the Literature." *Annals of Surgical Oncology* 22(2):370–76.

Yavuzer, Reha, Stefani Smirnes, and Ian T. Jackson. 2001. "Guidelines for Standard Photography in Plastic Surgery." *Annals of Plastic Surgery* 46(3):293–300.

Yip, Jia Miin, David I. Watson, Marika Tiggemann, Shawn Hsia, Andrea E. Smallman, and Nicola R. Dean. 2015. "Determinants of Breast Reconstruction Outcome: How Important Is Volume Symmetry?" *Journal of Plastic, Reconstructive & Aesthetic Surgery* 68(5):679–85.

Zigmond, A. S. and R. P. Snaith. 1983. "The Hospital Anxiety and Depression Scale." *Acta Psychiatrica Scandinavica* 67(6):361–70.