Breast cancer surgery

Aspects of patient-reported outcomes and physical activity

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Do you know what I was, how I lived? You know
what despair is; then
winter should have meaning for you.

I did not expect to survive,
earth suppressing me. I didn´t expect
to waken again, to feel
in damp earth my body
able to respond again, remembering
after so long how to open again
in the cold light
of earliest spring--

afraid, yes, but among you again
crying yes risk joy

in the raw wind of the new world.

Louise Glück, Snowdrops

Till Hedvig och Sixten

*"*Everything we hear is an opinion, not a fact.
Everything we see is a perspective, not the truth."

Marcus Aurelius

Abstract

The aim of this thesis was to evaluate patient-reported outcomes (PROs) following breast cancer surgery using three different studies.

Paper I examined breast-conserving surgery through an inframammary fold incision using a retrospective cohort (n=27). We found the technique to be surgically safe with high levels of satisfaction with breast, evaluated using a patient-reported outcome instrument (BREAST-Q^{TM}).
Paper II compared an objective aesthetic evaluation of breast-conserving surgery using a computer software with long-term patient evaluation of quality of life in a retrospective cohort (n=216). A superior aesthetic rating was significantly correlated with higher patient-reported outcomes scores with BREAST-Q^{TM}.
Papers III-V describe results from PhysSURG-B, a randomized controlled trial of female patients with breast cancer (n=400) undergoing surgery, comparing an intervention of non-supervised physical activity with usual care. Endpoints were physical and mental recovery, readmissions, reoperations and complications, quality of life and sick leave, measured at 4 weeks or/and 12 months after surgery.
Paper III showed a high level of recovery and few complications after surgery. No significant improvement was seen regarding short-term recovery, complications, length of stay, readmissions or reoperations following the intervention compared with usual care.
Paper IV analysed quality of life, showing high and unchanged levels, with no significant differences seen between the study groups.
Paper V reported no significant differences regarding long-term recovery and sick leave between intervention and control groups. Predictive factors for sick leave were young age at diagnosis, adjuvant chemotherapy, lower FACT-B score and previous mental health problems.

In conclusion, breast cancer surgery is associated with a high level of recovery, few complications, and with a small impact on measures of short- and long-term quality of life. Predictive factors for sick leave could be identified for at-risk patients by using patient-reported outcomes and utilized for future tailored interventions.

Keywords: Breast cancer, Physical activity, Patient-reported outcomes

Sammanfattning på svenska

Bröstcancer är kvinnors vanligaste cancersjukdom. Behandlingen bygger på kirurgi av brösttumören samt av lymfkörtlar i armhålan, kompletterat med efterföljande tilläggsbehandling. Den kirurgiska behandling är vanligtvis en bröstbevarande operation där brösttumören opereras och omgivande bröst sparas. Vid samma operation tas den så kallade portvaktslymfkörteln från armhålan bort. I vissa fall kan hela bröstet behöva opereras bort (mastektomi) och ibland fler lymfkörtlar från armhålan (axillutrymning). Tilläggsbehandling består av strålning, endokrin terapi, cellgifter och antikroppsbehandling. Dessa behandlingar kombineras utifrån patientens förutsättningar, typ av tumör, lymfkörtelstatus och operationstyp. Onkoplastisk bröstkirurgi är kombinationen av plastikkirurgiska tekniker och en onkologiskt säker kirurgi. Syftet är att kunna ta bort tumören med god kosmetik och symmetri, vilket ibland kräver kontralateral operation.
För att utvärdera hur cancerbehandling påverkar patienternas liv är patientrapporterade utfallsmått ett komplement till mer traditionella kliniska mått, såsom komplikationer, vårdtid, återfall och överlevnad. Huvudsyftet med denna avhandling var att utvärdera patientrapporterade utfallsmått efter bröstcancerkirurgi genom tre olika studier.

Delarbete I redogör för den första retrospektiva kohortstudien (n=27), som beskriver en operationsteknik för bröstbevarande kirurgi med snittföring under bröstet. Patienterna utvärderades avseende komplikationer, otillräcklig kirurgisk marginal samt med det patientrapporterade utfallsmåttet ”Nöjdhet med bröst” som mått på estetiskt utfall, mätt med instrumentet BREAST-Q^{TM}. Jämfört med nationella och internationella data bedömdes operationsmetoden som säker och med god patientskattad kosmetik.

Delarbete II presenterar en prospektiv studie där kvinnor som gjort bröstbevarande kirurgi (n=216) vid 1-årsuppföljning utvärderades avseende estetiskt resultat. Fotografier analyserades med ett dataprogram (BCCT.core) och det objektiva resultatet jämfördes sedan med hur patienterna skattade ”Nöjdhet med bröst” och ”Psykosocialt välmående” med instrumentet BREAST-Q^{TM}. Det fanns en statistiskt signifikant koppling mellan bättre estetiskt resultat och högre skattning av livskvalitet över tid.

Delarbete III-V rapporterar resultat från den randomiserade multicenterstudien, PhysSURG-B, där kvinnliga patienter med bröstcancer (n=400) jämfördes utifrån om de fick en intervention med fysisk aktivitet eller sedvanlig vård. Interventionen bestod av ett individuellt samtal med fysioterapeut med syfte att patienten skulle öka sin fysiska aktivitet med 30 minuter dagligen, före och fyra veckor efter kirurgi. Utfallsmått var självrapporterad återhämtning, komplikationer, vårdtid, återinläggningar, reoperationer, samt livskvalitet och sjukskrivningsdagar. Patienterna fick svara på frågeformulär före kirurgi, samt fyra veckor och 12 månader efter kirurgi. Data hämtades också från journalsystem, det nationella kvalitetsregistret för bröstcancer samt från Försäkringskassan.

Interventionen med rekommenderad fysisk aktivitet kunde inte påvisa förbättrad återhämtning på kort eller lång sikt (*delarbete III och V*), och inte heller sågs någon signifikant effekt avseende komplikationer, vårdtid, återinläggningar, reoperationer (*delarbete III*), livskvalitet (*delarbete IV*) eller sjukskrivning (*delarbete V*). Bröstcancerkirurgi innebär kort vårdtid med få återinläggningar, reoperationer och komplikationer. Sjukskrivningstal, livskvalitet och återhämtning var signifikant sämre vid tilläggsbehandling med cellgifter, oavsett studiegrupp. Riskfaktorer för längre tids sjukskrivning var ung ålder och cytostatikabehandling, samt tidigare psykisk ohälsa och låg skattning med det patientrapporterande instrumentet FACT-B som mått på livskvalitet vid diagnos.

Att använda patientrapporterade utfallsmått adderar information vid planering och utvärdering av kirurgisk behandling av bröstcancer. Att rekommendera ökad fysisk aktivitet i samband med bröstcancerdiagnos påverkade inte återhämtningen och visar på behovet av ytterligare insatser för att åstadkomma effekt på utfallsmåtten. Kunskap om faktorer som påverkar återhämtning, livskvalitet och sjukskrivningsbehov negativt kan användas för att identifiera sårbara individer och skräddarsy interventioner för att motverka de ogynnsamma effekter som ses av behandling.

List of papers

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Heiman Ullmark J, Sahlin C, Hallberg H, Olofsson Bagge R

Breast-conserving surgery using an inframammary fold incision technique for breast cancer

Journal of Plastic Surgery and Hand Surgery 2017; 51(2):105-111

II. Dahlbäck C, Heiman Ullmark J, Rehn M, Ringberg A, Manjer J

Aesthetic result after breast-conserving therapy is associated with quality of life several years after treatment. Swedish women evaluated with BCCT.core and BREAST-Q™

Breast Cancer Research and Treatment 2017 Aug;164(3):679-687

III. Heiman J, Onerup A, Wessman C, Haglind E, Olofsson Bagge R

Recovery after breast cancer surgery following recommended pre and postoperative physical activity: (PhysSURG-B) randomized clinical trial

British Journal of Surgery 2021 Jan 27; 108(1):32-39

IV. Heiman J, Onerup A, Bock D, Haglind E, Olofsson Bagge R

The effect of non-supervised physical activity before and after breast cancer surgery on quality of life, results from a randomized controlled trial (PhysSURG-B)

Manuscript submitted

V. Heiman J, Pavia J, Bock D, Haglind E, Olofsson Bagge R

Recovery and sick leave at 12 months in the randomized controlled physical activity trial (PhysSURG-B) – factors predicting prolonged sick leave

Manuscript submitted

Content

Abbreviations

ALND	Axillary lymph node dissection
BAI	Becks Anxiety Inventory
BCCT.core	Breast Cancer Conservative Treatment. cosmetic result
BCS	Breast-conserving surgery
BCT	Breast-conserving treatment
BDI	Becks Depression Inventory
BMI	Body mass index
BPI-SF	Brief Pain Inventory-short form
BREAST-Q™	BREAST-Q™ questionnaire
CCI®	Comprehensive complication index
CRF	Clinical report form
DCIS	Ductal carcinoma in situ
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	EuroQol EQ-5D-3L instrument
EQ-VAS	EuroQol EQ-Visual analogue scale
EUSOMA	European Society of Breast Cancer Specialists
FACT-B	Functional Assessment of Cancer Therapy- Breast
FACT-G	Functional Assessment of Cancer Therapy- General
FYSS	Physical Activity in the Prevention and Treatment of Disease
GAPPA	Global Action Plan on Physical Activity
HRQoL	Health related quality of life
ICHOM	International Consortium for Health Outcomes Measurement
MDT	Multidisciplinary team conference
MET	Metabolic equivalent
NKBC	National quality register for breast cancer
OPB-pME	Oncoplastic breast surgery - partial mastectomy study
PhysSURG-B	Physical activity in relation to surgical operations- Breast cancer
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QALY	Quality-adjusted life year
QoL	Quality of life
RAND-36	The RAND-36-Item Health Survey
RCT	Randomized controlled trial
SENOMAC	Randomized study of patients with macrometastases in the sentinel node

SGPALS	Saltin-Grimby Physical Activity Level Scale
SLNB	Sentinel lymph node biopsy
SLN	Sentinel lymph node
SSORG	Scandinavian Surgical Outcomes Research Group
TNM	Tumor nodal metastasis
WHA	World Health Assembly
WHO	World Health Organization

1. Introduction

1.1 Breast cancer

Breast cancer is the most common malignancy among women worldwide and in Sweden, almost 8000 women are diagnosed each year (1). During the last decades, an annual increase in incidence of approximately 1.5% has been noted. At the same time, improved outcome due to early detection and advances in treatment have resulted in improved survival rates as seen in figure 1 (2).

All Swedish patients diagnosed with breast cancer are registered in the Swedish National Quality Register for Breast Cancer (NKBC). Data from the registry shows a relative 5-year survival rate of 92% and a 10-year survival rate of 86% (1, 2). Approximately 60% of breast cancers in Sweden are detected through a national screening program, inviting all women between 40 to 74 years for a mammogram every 18-24 months (3).

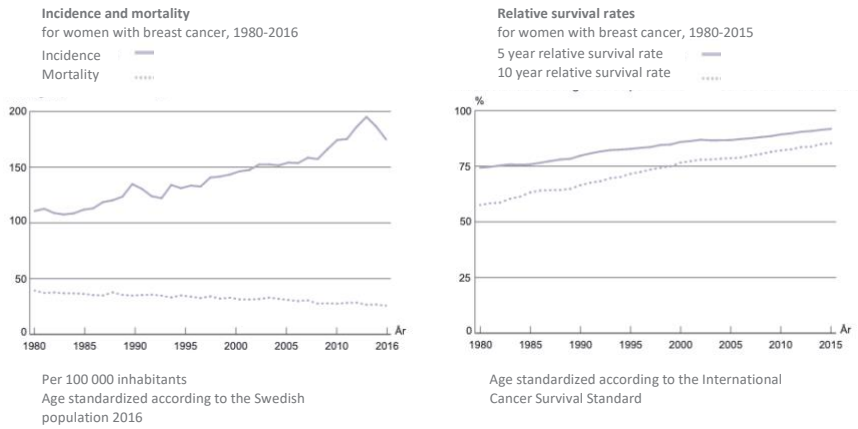

Figure 1. *Incidence and mortality of breast cancer in Sweden, 1980-2016 (Cancer i siffror 2018).*

Breast cancer is diagnosed through a process called triple-diagnostics: a clinical examination, imaging (mammography and ultrasound) and tissue examination. Every patient is given individual treatment recommendations during a multidisciplinary team conference (MDT), considering known patient characteristics such as age, previous treatment and comorbidity, as well as tumor

parameters such as size, localization, subtype, histological grade, Ki67 and hormone receptor (HR) expression of estrogen (ER), progesterone (PR), as well as epidermal growth factor 2 (ERBB2/HER2).

Treatment of early breast cancer is based on surgical tumor excision and axillary staging, with or without different combinations of adjuvant treatment: radiotherapy, chemotherapy including antibody treatment and endocrine therapy. The timeframe for primary breast cancer care in Sweden is guided by the national "Standardized Care Process" stipulating 28 days from referral for suspicion of breast cancer to the start of primary treatment ("Standardiserat vårdförlopp bröstcancer", issued by the Regional Cancer Centres 2019-11-21, accessed 2020-12-17).

Table 1. *TNM-classification and staging of breast cancer. Simplified and adapted from AJCC Cancer Staging Manual, Eight ed.*

STAGE	T- PRIMARY TUMOR		N – REGIONAL LYMPH NODES		M – DISTANT METASTASIS	
0	Tis	Ductal carcinoma in situ or Paget disease	N0	No positive nodes	M0	No distant metastasis
IA	T1	T size ≤ 20mm	N0		M0	
IIA	T0	No exidence of primary tumor	N1	1-3 positive axillary nodes	M0	
	T1		N1		M0	
	T2	T >20mm & ≤ 50mm	N0		M0	
IIB	T2		N1		M0	
	T3	T > 50mm	N0		M0	
IIIA	T0		N2	4-9 positive axillary nodes	M0	
	T1		N2		M0	
	T2		N2		M0	
	T3		N1/N2		M0	
IIIB	T4	T any size, extending direct to chest wall and/or skin	Any N		M0	
IIIC	Any T		N3	>10 positive nodes[1]	M0	
IV	Any T		Any N		M1	Distant metastasis[2]

T: maximum dimension of largest tumor
[1] Ipsilateral internal mammary, axillary or infra- or supraclavicular
[2] Clinical, radiographic or pathological >0.2mm

Breast cancer is staged according to the international TNM-classification, including tumor size (T), nodal involvement (N) and distant metastases (M) (4). A clinical staging (*c*TNM) is made prior to treatment based on clinical findings, and a pathologic staging is performed after surgery based on histopathologic examination of the specimen (*p*TNM). The TNM stage strongly correlates to prognosis and is used as a basis for adjuvant treatment recommendation.

1.2 Surgical treatment

Treatment of primary breast cancer is based on removing the tumor, using breast-conserving surgery or mastectomy. This is combined with surgery to axillary lymph nodes, either by sentinel lymph node biopsy alone or by axillary lymph node dissection.

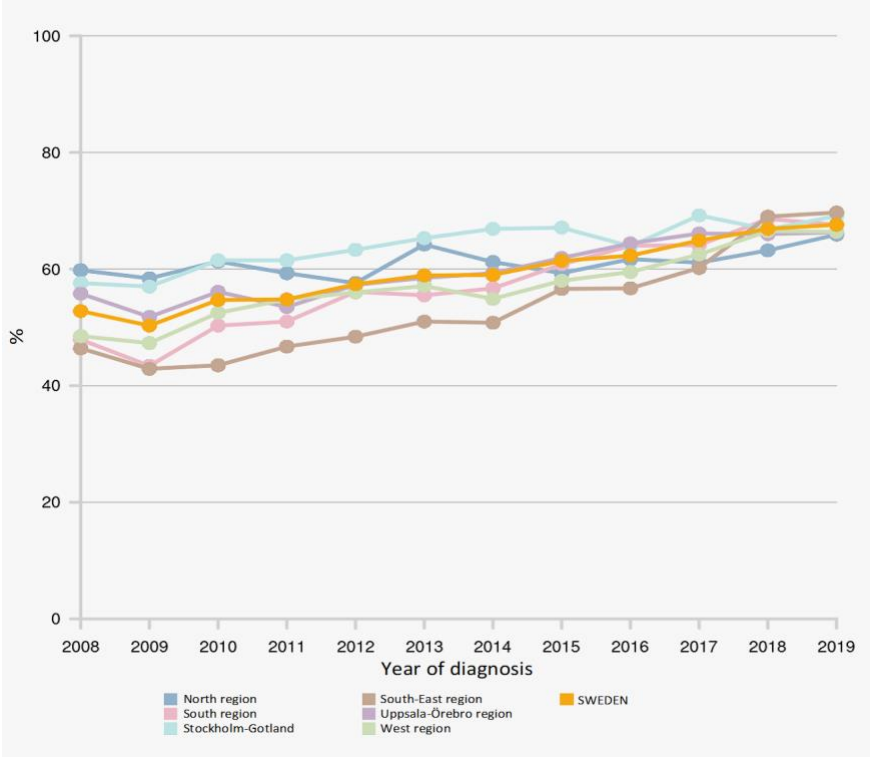

Figure 2 *Breast-conserving surgery among operated cases without distant metastasis at diagnosis, year 2008-2019. Data retrieved from National Quality Register for Breast Cancer 2021-01-12.*

The surgical management of the breast and axilla has undergone de-escalation during the last three decades. This evolution is the result of incorporating into clinical routine the combined findings from the American NSABP B-06 study by Fisher et al. (5) and the European study by Veronesi et al. (6), revealing comparable mortality rates for mastectomy and breast-conserving surgery. Advancements in surgical management has also been made possible thanks to the important studies on margin status following breast-conserving surgery by Morrow et al. (7). She found that there was no need for excessive free margin status, and the current international consensus (8) state that for invasive breast cancer "no ink on tumor" is sufficient margin, translated into that one tumor free cell layer is considered enough. By adapting surgical techniques from plastic surgery to overcome inadequate aesthetic results and allow larger resections, the field of oncoplastic breast surgery has emerged (9, 10).

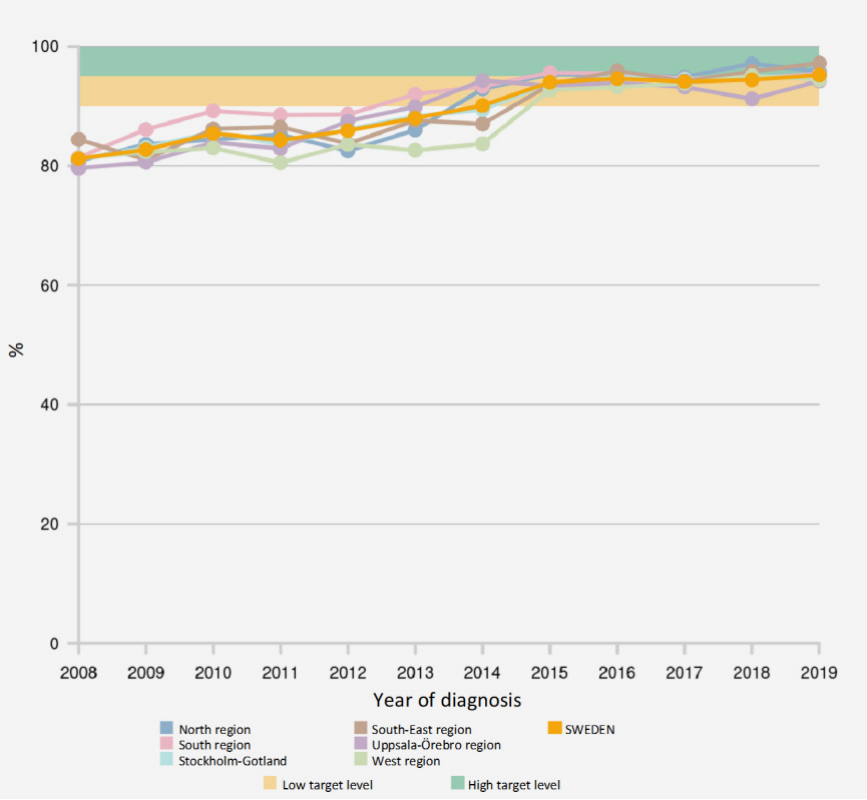

Figure 3 *Sentinel node biopsy among operated invasive cancers, clinically node negative and no distant metastases at diagnosis, years 2008-2019, including the defined national target levels. Data retrieved from National Quality Register for Breast Cancer 2021-01-12.*

The current standard for surgical management of early primary breast cancer is breast-conserving surgery and axillary staging with sentinel lymph node biopsy in patients with a clinically negative axilla (2, 11), as seen in figure 2 and figure 3.

1.2.1 Surgical treatment of the breast

Breast cancer surgery can be divided into two main categories. 1) breast-conserving surgery and 2) mastectomy. In Sweden, the combination of small tumor size (median 15mm, according to the National Quality Register for Breast Cancer 2019), current margin definition and the proficiency among breast surgeons regarding oncoplastic techniques makes breast-conserving surgery the suggested surgical option for most breast cancer patients (11, 12).

1.2.1.1 Breast-conserving surgery

Breast-conserving surgery is considered standard of care (8, 11). The level of breast-conserving surgery is used as a quality indicator in the National Quality Register for Breast Cancer and by the European Society of Breast Cancer Specialists (EUSOMA). The combination of breast-conserving surgery and radiotherapy to the remaining breast tissue is collectively known as breast-conserving therapy (BCT). This combined therapy is at least as oncologically safe as a mastectomy, with favorable qualities seen relating to body image, patient satisfaction and quality of life (3, 11). Today, almost seven out of ten primary breast cancers are removed using breast-conserving surgery (2), as seen in Figure 2.

Breast-conserving surgery can be performed with a wide range of surgical techniques ranging from simple radiating incisions over the tumor to extensive tissue- and skin excisions with remodeling of the breast shape. With the margin status consensus (7, 8, 13), there is no need for excision of overlying skin or underlying fascia if the tumor respects these anatomical boundaries, allowing the preferred incision to be guided by several other aspects, including location and size of the tumor, breast size, anticipated aesthetic result, risk for complications and the potential need of contralateral surgery for symmetry.

1.2.1.2 Mastectomy

Although advancements in surgical techniques have increased breast-conserving surgery, mastectomy is still the preferred option in some instances. Mastectomy is recommended when an adequate oncological excision is incompatible with a

satisfactory aesthetic result due to multicentricity or large tumors in relation to breast size, risk reduction for hereditary breast cancer, inflammatory breast cancer, inadequate margin status after re-excision, and when adjuvant radiotherapy is contraindicated or of the patient´s own choice (3, 11).

Modern mastectomies can be divided into three categories based upon the surgical approach. 1) simple mastectomy, removing breast tissue, skin and the nipple-areola complex 2) skin-sparing mastectomy, when the nipple-areola complex and glandular breast tissue is excised 3) skin- and nipple-sparing mastectomy. Mastectomy can be performed with reconstruction, either at the same time as the cancer surgery, or during a later stage.

1.2.1.3 Oncoplastic breast surgery

The definition of oncoplastic breast surgery encompasses both the conventional oncological tumor resection, together with ipsilateral surgical techniques to displace or replace breast tissue, and if needed to achieve optimal results, contralateral surgery for symmetry (9). Oncoplastic breast surgery utilizes the knowledge and techniques from plastic surgery and is applied when conventional breast-conserving surgery can be anticipated to generate inadequate aesthetic results. Oncoplastic breast surgery is considered as safe as conventional breast-conserving surgery regarding oncological outcome, as well as concerning the implicated risk of wound complications (14, 15).

Oncoplastic breast surgery makes larger excisions possible, and in addition to removing the tumor, the opportunity to improve symmetry, shape and nipple-areola complex placement using various techniques (10). There are two main concepts, volume displacement and volume replacement. For volume displacement the remaining breast tissue is used to close the excision defect by redistribution, level 1 is used for when less than 20% of breast volume is removed, and level 2 when 20-50% of the volume is lost. Volume replacement includes techniques of adding volume by using autologous tissue flaps, fat grafting or implants (9).

1.2.2 Surgical treatment of the axilla

Surgery to the axillary lymph nodes is done to 1) stage the disease and/or 2) to ensure disease control of lymph node metastases (N+). Both staging and treatment of the axillary lymph nodes was previously performed with axillary lymph node dissection, where at least 10 lymph nodes were to be removed from the axilla. The

current approach is to stage the axilla with sentinel lymph node biopsy for clinically node-negative patients (*c*N-) (*Figure 3*). The staging procedure is usually performed together with the primary breast surgery. For regional disease control of lymph node metastases, axillary lymph node dissection is still performed in patients with clinically positive node (s) (*c*N+), or if the sentinel node biopsy reveals macrometastasis (>2mm) (*p*N+) (16, 17).

With the benefit of reduced arm morbidity with less axillary treatment, the de-escalation of axillary surgery to improve survivorship for breast cancer patients is under further investigation. The landmark trial ACOSOG Z0011 did not show a survival benefit for completion axillary lymph node dissection after breast-conserving treatment (18) for women with 1-2 positive sentinel lymph nodes. An ongoing international multicenter randomized trial (SENOMAC) (19) compares the current axillary treatment standard for patients with positive sentinel lymph node(s), i.e. completion axillary lymph node dissection and irradiation, with axillary irradiation alone (18). Sentinel lymph node biopsy as treatment of lymph node metastasis (*c*N+) is under investigation using techniques to mark the affected nodes followed by a targeted axillary dissection. This can be valuable when the benefit of completion axillary lymph node dissection is unclear, for example if axillary downstaging is seen after neoadjuvant chemotherapy (*c*N+ into *yp*N-).

1.3 Adjuvant treatment

Adjuvant treatment is administered after surgery to prevent locoregional and distant recurrence in early breast cancer. Systemic treatment can also be given before surgery, then known as neoadjuvant or preoperative systemic treatment. After breast cancer surgery, the pathology report including tumor characteristics (see section 1.1) and axillary staging is assessed at a multidisciplinary therapy conference (MDT). Adjuvant treatment recommendations are based on these data compiled with information regarding patient factors and the surgical procedure performed (3, 11). Adjuvant treatments consist of locoregional radiation therapy, and the systemic treatments of chemotherapy, endocrine therapy and targeted therapy (anti-HER2 antibodies).

If breast-conserving surgery has been performed, additional *radiotherapy* is recommended with few exceptions, but after mastectomy only if tumor size >5 cm or if lymph node metastases are present. Radiation therapy to the remaining breast tissue is given in fractions for 5-15 days (up to 42.5 Gy). Radiation side-effects

are seen primarily in the radiated area, with skin reactions and long-term fibrosis of tissues, including the lung and heart (20).

Endocrine therapy is predominantly oral antiestrogens (Tamoxifen or Aromatase Inhibitors), that are recommended for patients with hormone receptor positive breast cancers for a standard duration of 5 (-10) years. Common side-effects of endocrine therapy are hot flashes, arthralgia and/or myalgia (21).

Chemotherapy is administered for high-risk tumors, such as the triple- negative subtype (HER2-, ER/PR -), locoregionally advanced tumors and as an adjunct to targeted anti-HER2 therapy for a treatment duration of 4.5 months. Cytotoxic chemotherapy regimens containing both anthracyclines and taxanes offer the greatest risk reduction and are recommended for patients with high-risk tumors, often combined with the alkylating agent cyclophosphamide. Short-term toxicity of chemotherapy is well-known and include nausea, neutropenia, asthenia, myalgia, edema, alopecia and sensory neuropathy (21). Long-term adverse effects are cognitive impairment, fatigue and persisting neuropathy that may result in delayed return-to-work (22, 23).

For HER2-positive tumors, the standard *anti-HER2 antibody treatment* (trastuzumab) duration is 12 months. Despite the targeted anti-HER2 therapy having few side effects by itself, it is administered together with a chemotherapy regimen.

All treatment options carry risks of unwanted toxic effects that impact the survivorship after breast cancer. The risk for impaired survivorship is balanced against the benefits of survival following an adjuvant treatment, that is based on the reduced risk of disease recurrence. Different gene expression assays are now recommended to assist in treatment decisions regarding benefit of adjuvant chemotherapy, primarily for hormone receptor positive and node negative disease (24, 25). As presented in the TailorX study, omitting chemotherapy for patients with low to intermediate risk score can be done without compromising oncological results (26, 27).

The standardized breast cancer care pathway, from diagnosis to treatment and follow-up is displayed in Figure 4. All patients undergo clinical and radiological evaluation 1 year after surgery.

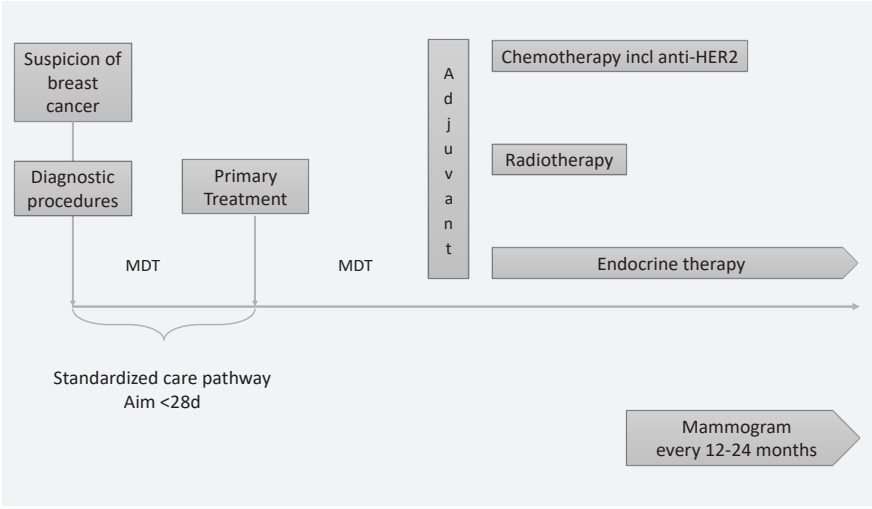

Figure 4 *Breast cancer diagnosis- and treatment pathway. Diagnostic procedures include clinical, imaging and pathological tissue examination. MDT: Multidisciplinary Team Conference*

1.4 Recovery

All surgical procedures induce a stress response in tissues, resulting in elevated oxygen demand followed by a phase of wound healing and postoperative recovery. Surgery-related recovery occurs within 3-6 weeks postoperatively, when patients are expected to experience resumed quality of life as well as returning to normal function (28). There is a lack of knowledge regarding recovery after breast cancer surgery and assessing 'functional recovery' is often limited to addressing specific symptoms related to treatment (29, 30). In enhanced recovery protocols for abdominal surgery, the concept 'functional recovery' is often transferred into 'length of hospital stay' as a goal for the health care given (31). Restoration of independence as an effect of functional recovery is central, since disabilities affecting daily activities can impact cancer patients more than prognosis (32), and arguably measuring recovery should be focused on the patient-centered process rather than proxy measures of the care utilized (29).

The word recovery is according to the Cambridge dictionary defined as "a return to a normal state of health, mind or strength" or "becoming well again after an illness or injury". Recovering after cancer diagnosis and treatment can be argued to be impossible, if it means regaining function and becoming the person you were before being diagnosed. The impact of surgery and adjuvant treatment mean that

many patients undergoing breast cancer treatment cannot regain their previous physical or health status (due to permanent loss of a breast or hormonal changes affecting reproductive abilities).

Recovery cannot be reduced into simply regaining lost function/s, but is rather an individual developmental process (33). Recovery beyond 'functional recovery of lost function' involves progression, finding new meaning and purpose, and depends on the focus and activity of each individual.

1.5 Survivorship

Increased survival rates as a result of early detection and improved treatment results have expanded the population of breast cancer survivors, now more than 100 000 women in Sweden (1). Patient-reported outcomes are essential for evaluating the impact of treatment on patients' life, their survivorship, and for proper management of breast cancer (34-36).

In addition to the well-established clinical outcomes traditionally used to evaluate surgical treatment, measurements of aesthetic and functional results, as well as patient satisfaction and quality of life, are now considered equally important when evaluating breast cancer care (34-36).

1.6 Evaluating treatment outcomes

Clinical outcomes of an objective nature have been the basis for developing and evaluating breast cancer treatment, such as re-excision rates, surgical complications, local recurrence rates, as well as overall- and disease-specific survival rates. The International Consortium for Health Outcomes Measurement (ICHOM) has agreed upon a standardized set of well-validated outcomes for improved breast cancer management including reoperations due to positive margin, complications using the Clavien-Dindo classification (37), and overall and breast cancer specific survival (38), as well as patient-reported outcomes considering symptoms and health-related quality of life.

1.6.1 Patient-reported outcomes

A patient-reported outcome (PRO) is a direct response regarding a specific situation where only the patient provides information (FDA 2009) (39). Patient-

reported outcomes provide a point of view otherwise lost and can be used to overcome the insufficiency of objective outcome measures of health, especially for comprehensive follow-up of survivors.

Patient-reported outcomes are now considered fundamental in the management of cancer care (35). There are no gold standard instruments for evaluating patient-reported outcomes in the management of breast cancer treatment, and several different instruments for assessment have been developed, generic as well as disease-specific ones. The International Consortium for Health Outcomes Measurement (ICHOM) has agreed upon a standard set of patient reported outcomes for assessing level of health in patients with breast cancer: anxiety and depression, pain, fatigue, body image, arm and breast symptoms, vasomotor symptoms, neuropathy, arthralgia, sexual dysfunction and health-related quality of life (38).

1.6.2 Quality of life

In 1948, the World Health Organization (WHO) defined health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (Preamble to the Constitution of WHO as adopted by the International Health Conference, New York, 19 June - 22 July 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of WHO, no. 2, p. 100) and entered into force on 7 April 1948).

Quality of life (QoL) is instead an extensive concept of "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" as defined by WHO (40). The distinction between health and QoL is important, though not easily elucidated. QoL is considered especially valuable to measure (34, 36) as a dimension of the life we live, and not necessarily confined by "health". The broadness of the concept makes measurements of QoL difficult to standardize, and different instruments use different definitions of QoL to further complicate the field of research.

1.6.3 Health-related quality of life

In the setting of health care and medical research, the concept health-related quality of life (HRQoL) is commonly used, encompassing the patient`s perceived health as a consequence of disease and/or treatment (41). HRQoL represents the patient´s subjective experience and functional aspects of a disease and/or

treatment. The concept is multidimensional and indirectly connected to disease compared to unidimensional symptom scores that are directly linked to a disease. HRQoL can be defined as the impact of an individual's health on the following dimensions of life: ability to function, physical well-being, mental well-being and social well-being. Health-related quality of life is measured using instruments that can be either generic (such as RAND-36 and EQ-5D) or disease- or treatment-specific (for example BREAST-Q^{TM} and FACT-B).

1.6.4 Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are tools or instruments used to measure patient-reported outcomes associated with healthcare and treatment. Measurements often include several dimensions that reflect different properties of the construct of measure, for example health-related quality of life. The different dimensions are referred to as scales or domains. Instrument scores can be profile-based for multiple domains of the construct, or preference-based, meaning that they produce a summated score for all domains (42).

1.6.4.1 RAND-36

RAND-36-Item Health Survey is distributed by RAND Corporation, USA and is analogous to Short Form Health Survey (SF-36). It is a measure for HRQoL based on 36 items, arranged into eight health domains: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain and general health. The impact that health, using the WHO definition, has on the individual´s life regarding functioning and perceived well-being concerning social, mental and physical aspects are considered for HRQoL (43).

1.6.4.2 EQ-5D-3L and EQ-VAS

The instrument was originally developed by the EuroQoL Group, Rotterdam, The Netherlands, to be a brief and generic measure of health status for comparing health outcomes, useful in cost-utility and quality-adjusted life year (QALY) analysis (44). The instrument consists of a health state classifier using five dimensions, each a single item, and a visual analogue scale (VAS) for current health. The EQ-VAS scale goes from 0 to 100, marked into units of ones and tens, and is accompanied with a box to record the rating. It has properties of a numerical rating scale but the fixed endpoints from 100 to 0 have descriptors as "best imaginable health" and "worst imaginable health". The EQ dimensions are

mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and each can be rated according to three levels (3L) (no problems, moderate and extreme problems). EQ-5D-3L is a preference-based measure and generates 243 (3^5) possible health profiles. To be used in health economic analysis, each health profile is assigned an index score from a value set from 0 (as bad as death) to 1 (equal to full health). A Swedish experience-based value set (45) and the UK hypothetical-based value set (46) are the most commonly used in Sweden (47).

1.6.4.3 BREAST-Q

BREAST-Q™ (Copyright© 2012, Memorial Sloan Kettering Cancer Center and The University of British Columbia) is a validated instrument with disease and treatment specific properties, developed for patients undergoing breast surgery (48). Since the launch in 2009, the instrument has increased the use of PROM in breast surgery and expanded the understanding of patient-reported outcomes and their use for patient management (49, 50). It is a multiscale instrument with six different modules: augmentation, reduction, mastectomy, reconstruction, reconstruction expectations and the breast-conserving therapy module. The breast-conserving therapy module was created using the six generic domains assessing satisfaction (with breasts, overall outcome and with care) and health-related quality of life scales (physical, psychosocial and sexual well-being), with the addition of "adverse effects of radiation" and focus on information by care professionals (51). By using the RASCH mathematical model (48, 51, 52), equal units have been produced linearly across the domains. Subscales can thus be presented and compared individually.

1.6.4.3 FACT-B

Functional Assessment of Cancer Therapy – Breast (FACT-B, Copyright © David Cella) was developed in 1997 (53) and is validated for patients with breast cancer. It is the most commonly used instrument for breast cancer regarding the patient-reported outcome of HRQoL (54, 55). The objective of the instrument is to measure multidimensional quality of life in patients with breast cancer. The instrument includes 37 items, arranged into five general domains: physical, social, emotional and functional well-being, as well as the breast cancer subscale. The 27 general items (FACT-G) are divided into physical, social, emotional, and functional well-being. The scope of the instrument is the last seven days. Individual responses skipped can be prorated using the mean value of the answers (56).

1.6.5 Evaluation of aesthetic result

Evaluation of aesthetic result after breast cancer surgery is important for proper surgical planning and improved patient decision-making. No golden standard method exists for assessment, but both self- and panel evaluation of photos are being used. Both methods have inherent difficulties, where self-ratings vary among study populations due to a vast number of confounding factors and panels show poor inter-observer agreement. The resulting evaluation is therefore difficult to use when comparing different studies in a research context.

Objective measures to evaluate cosmetic results have been developed to overcome these limitations, using different computer programs for patient photo assessment. The International Consortium for Health Outcomes Measurement (ICHOM) has no recommendation regarding objective aesthetic evaluation for breast cancer, neither has the European Society of Breast Cancer Specialists (EUSOMA) any designated quality indicators. The European Organization for Research and Treatment of Cancer (EORTC) recommend the combination of self- and panel assessment as well as objective measures, without further specification.

1.6.5.1 BCCT.core

The Breast Cancer Conservative Treatment. cosmetic results (BCCT.core) is a digital software that uses an algorithm to objectively assess the cosmetic outcome after breast-conserving surgery. It was developed by researchers in Portugal and introduced in 2007. It is semi-automatic, and require that the jugular notch, a calibration mark, the nipples and contour of the breasts are marked manually before the photo is subjected to a digital assessment. The final computerized result is based on differences between the breasts in symmetry, color and scar visibility and graded as “Excellent”, “Good, “Fair” or “Poor”.

1.6.6 Sick leave

The Swedish social insurance system is designed so that *sickness benefit* (economic compensation allowing sick leave) is granted for individuals, as part of the Swedish welfare system. After an initial period (from day 2- day 14) of sick pay covered by the employer, employees can receive sickness benefit from the Social Insurance Agency. Unemployed applicants receive sickness benefit from day 2 and individuals who are self-employed have the optional waiting period of 1-90 days.

Sickness benefit (one-quarter, half, three-quarters or full benefit) can be received according to the individuals reduced working capacity following illness. This is assessed with respect to the work capacity needed to perform their normal job for the initial 90 days. Thereafter, impaired work capacity is assessed in relation to any work by the same employer (<180 days), or to the whole labor market (>180 days). Sickness benefit can also be received when undergoing medical treatment or medical rehabilitation with the aim of preventing illness or shorten recovery.

The Swedish National Board of Health and Welfare offer guidelines on expected sick leave for primary breast cancer treatment (Table 6).

1.7 Physical activity

Physical activity is defined as "any bodily movement by skeletal muscle contraction that requires more than basal energy expenditure" (57). The association between lack of physical activity and increased risk for breast cancer is convincing (58, 59), with a reduced incidence seen in more physically active individuals (60). In observational studies, regular physical activity after breast cancer diagnosis is associated with decreased breast cancer specific and overall mortality (61-63). Physical activity has been associated with a reduced relative risk of mortality (64, 65) and (a small) improvement in quality of life (65).

Since lack of physical activity is a modifiable global risk factor for mortality, WHO issued "Global recommendations on physical activity for health" (Geneva 2010) with focus on the beneficial effects of physical activity on health and prevention of disease, such as reduced all-cause mortality and events of breast cancer. Adult individuals who achieve or surpass the guidelines for physical activity can still spend most waking hours sedentary (see definition below) with associated health risks (65, 66). To address this, the recommendations were updated into "WHO 2020 guidelines on physical activity and sedentary behavior" (67). The current recommendations state at least 150-300 min of aerobic moderate physical activity or at least 75 min of aerobic vigorous physical activity and muscle-strengthening activities for at least two days per week. In the updated version, limiting time spent sedentary is stressed and any duration of physical activity is accounted for, compared to previously when bouts of at least 10 coherent minutes of activity were needed to be taken into account.

Physical inactivity refers to insufficient amounts of physical activity to meet the recommendations (68). An estimated third of the world's population does not fulfil the physical activity guidelines (69) and physical inactivity is attributed 9% of the overall premature mortality globally (69, 70). Both physical inactivity and sedentary behavior (8.2 h/day; range 4.9–11.9 h/day) (66) are increasing in developed societies (71). Sedentary behavior is awake time spent sitting, reclining or lying down with little energy expenditure (72). To overcome the pandemic of physical inactivity (73) and inadequate adherence to the recommendations (69, 74), the World Health Assembly (WHA) approved the "Global Action Plan on Physical Activity (GAPPA) 2018-2030, More Active People for a Healthier World" with the goal of reducing physical inactivity by 15 % 2030 (75).

The Swedish Society of Medicine ratified recommendations for physical activity made by the Swedish Society of Exercise and Sports Medicine in 2011, in line with the WHO recommendations. The Swedish National Board of Health and Welfare are advising care professionals to promote physical activity for patients insufficiently active according to national guidelines (76). The American Heart Association statement "Routine Assessment and Promotion of Physical Activity in Healthcare Settings" (77), gives applied recommendations for healthcare providers regarding advocacy for increased physical activity among patients.

Different ways to improve physical activity level was reviewed in the Lancet 2012, confirming that counseling has a small to moderate positive effect on physical activity levels (78). Assessing and promoting physical activity through the healthcare system could motivate and enhance physical activity (70, 77, 79-81), and there is a global call to incorporate evidence-based physical activity strategies to combat the physical inactivity pandemic (73). In Sweden, the book Physical Activity in the Prevention and Treatment of Disease (FYSS) provides evidence-based guidance about the role of physical activity for common health issues (82).

1.7.1 Measuring physical activity

To measure physical activity, objective and subjective tools can be used, none, however, reflects all the multifactorial aspects of physical activity. The gold standard to measure energy expenditure is through the "doubly labelled water-method" (83-85), but being elaborate, expensive and tedious it is an unsuitable method for clinical practice and larger clinical studies.

Cardiorespiratory fitness is the body's capacity to transport oxygen to working muscles, measured as maximum oxygen consumption (VO_2-peak). It is considered to have the highest predictive value of the different physical activity entities (64), but cost and resource consumption limit its use. However, the rate of aerobic energy expenditure in ml O_2 x kg^{-1} x min^{-1} is used to describe the absolute intensity of different physical activities in metabolic equivalents (METs). 1 MET equals 3,5ml O_2 x kg^{-1} x min^{-1}. Sedentary behavior equals 1-1.5 METs, whereas physical activity with light intensity equals 1.6-2.9, moderate intensity 3-5.9, and vigorous intensity $\geq$ 6 (86).

Self-reported questionnaires are commonly used to assess physical activity in epidemiological studies and have shown associations with health outcomes (87, 88). The Saltin-Grimby Physical Activity Level Scale (SGPALS), developed in the 1960s (89), is a single-item instrument with a four-level descriptive rating scale of mean physical activity level during the past week. SGPALS has been validated against doubly labelled water and correlates to energy expenditure. Being a simple tool and reported to correlate with health outcomes, its use is supported in clinical practice (90, 91).

1.8 Prehabilitation

The appealing expressions "Fit 4 Surgery", "Fit to Fight" and "Better in, better out" describe the intent of surgical prehabilitation. The idea is to improve outcome by the optimization of a patient's capacities *before* the surgical injury (Figure 5). The preoperative period is considered a "window of opportunity" for lifestyle changes (92), and the physician-patient interphase can be referred to as "teachable moments" (93). The time between diagnosis and surgery (or other treatment modalities) is the period available for proactive actions.

Prehabilitation is defined as a coherent multimodal process of care to assess and address modifiable risk factors prior to surgery, with the purpose of increasing resilience to the surgical trauma. This includes baseline assessment of functional capacity, identification of impairments, and interventions to improve the patient's functional, nutritional, medical and psychological reserve (94). The aim is to improve treatment outcome by expanding the functional reserve and taking actions to avoid or to overcome complications. Assessment of the patient's needs should be undertaken before initiation of cancer treatment (95, 96). Before

surgery, recommendations regarding reduced alcohol intake and tobacco use are aspects of prehabilitation implemented in the Swedish health care system (76).

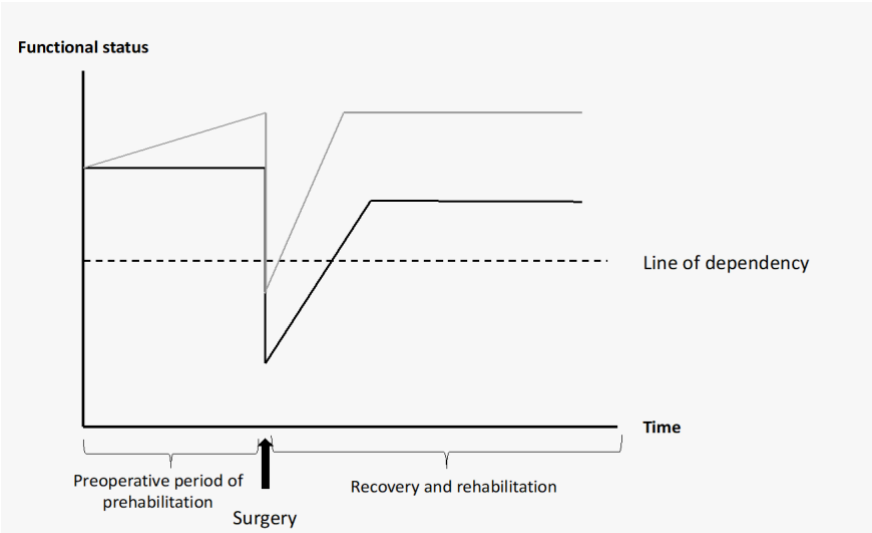

Figure 5 *The concept of prehabilitation and recovery. Simplified and adapted from Tew GA et al., Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. Anaesthesia 2018;73:750–68*

During and after adjuvant therapy for breast cancer, interventions with physical activity have improved cardiorespiratory fitness, quality of life and reduced fatigue (97-101). In a cohort of patients operated for breast cancer, regular physical activity resulted in increased levels of physical recovery at 3 weeks after surgery compared to physically inactive patients (102). A systematic review by Lahart et al., 2018 described the effects of physical activity after adjuvant therapy for women with breast cancer, calling for caution when interpreting effects regarding breast cancer-related and all-cause mortality or breast cancer recurrence (103). In a Cochrane review from 2010 evaluating exercise interventions, the focus was on upper-limb functioning following breast cancer treatment, and none of the included studies had a prehabilitation intervention (104).

Preoperative physical activity is considered safe (105), however very little data is available regarding prehabilitation and outcome after breast cancer surgery and treatment. Two studies on the feasibility of prehabilitation in breast cancer have been published (106, 107), and there is an ongoing randomized trial (IMPROVE-B, NCT:03498157) that has not yet presented results.

2. Aims

The overall objective of this thesis was to evaluate patient-reported outcomes in relation to breast cancer surgery, and the effect of a non-supervised physical activity intervention using the PhysSURG-B trial. The specific aims for the individual studies were

1. To evaluate a surgical technique for breast-conserving surgery regarding feasibility, safety and outcome, using a patient-reported outcome measure (BREAST-Q^{TM}).

2. To assess the correlation between aesthetic result according to the computer program BCCT.core and long-term health-related quality of life using the BREAST-Q^{TM} instrument for breast-conserving surgery.

3. To compare a physical activity intervention before and after breast cancer surgery with usual care in the PhysSURG-B trial. Primary outcome was patient-reported short-term recovery, and surgical complications, readmissions and reoperations within 90 days.

4. To longitudinally evaluate health-related quality of life in the PhysSURG-B trial between the intervention and control group at baseline, 4 weeks and 12 months after surgery.

5. To assess long-term recovery in the PhysSURG-B trial and explore predictive factors for prolonged sick leave.

3. Patients and methods

3.1 Summary of included studies

Table 2. *Papers included in the thesis and their respective study design.*

PAPER	DESIGN	POPULATION	INCLUSION YEARS	TRIAL
I	Retrospective observational cohort	Breast cancer *n*=27	2011	
II	Prospective observational cohort	Breast cancer n=216	2008-2012	OPB-pME
III	Prospective randomized controlled trial	Breast cancer *n* =400	2016-2018	PhysSURG-B
IV	Prospective randomized controlled trial	Breast cancer *n* =354	2016-2018	PhysSURG-B
V	Prospective randomized controlled trial	Breast cancer *n* =354	2016-2018	PhysSURG-B

OPB-pME: Oncoplastic Breast surgery-partial mastectomy
PhysSURG-B: Physical Activity in relation to surgical operations- Breast cancer

3.2 Paper I

3.2.1 Study design

An observational cohort of 27 female patients was studied retrospectively regarding surgical outcomes. The observational study has limitations regarding patient selection, lack of control and conclusions about causality. However, for rare occurrences this may be the only manageable approach and, in this instance, the only way to evaluate the results for a patient cohort already treated. Initial assumptions regarding feasibility and safety of a new procedure can be judged in

this retrospective manner, before conducting prospective studies to draw further conclusions.

3.2.2 Selection and inclusion of patients

All patients undergoing surgery using an inframammary fold incision during 2011 were identified from medical records at a single centre in western Sweden. Patients with suspected breast cancer after triple diagnosis were chosen for the procedure at a multidisciplinary board meeting, based on tumor characteristics and location. Data from the National Quality Register for Breast Cancer (NKBC) from year 2012 was used for comparison.

3.2.3 Data collection and follow-up

Patients were routinely followed in the clinic for 24 months, including radiological examination annually. Surgical complications were retrieved from medical documentation within the hospital.

3.2.4 Outcome measures

Margin status and reoperations were used to evaluate the surgical technique in combination with patient satisfaction as a measure of aesthetic result using the "Satisfaction with breast" from the postoperative BREAST-Q^{TM} questionnaire, Breast Conserving Therapy (BCT) module. Analysis followed the instructions by the provider MAPI Research Trust, and the result was converted into a Rasch score between 0-100, allowing for individual scales to be used separately. There was no normative data for these Rasch-scores available. Complications were defined and limited to surgery, infection (Grade II according to Clavien-Dindo) and seroma (Grade I according to Clavien-Dindo) within 30 days after surgery.

3.3 Paper II

3.3.1 Study design

The Oncoplastic Breast surgery-partial mastectomy study (OPB-pME) was an observational prospective cohort study of patients undergoing breast cancer surgery. The observational design has limitations (see 3.2.1) however the prospective nature can offer reduced selection bias if all eligible patients are included.

3.3.2 Selection and inclusion of patients

Patients offered breast-conserving surgery due to suspected breast cancer after triple diagnostics were included in a study database at a single center in southern Sweden, between 2008 and 2012. The database showed a 78% coverage when compared to the National Quality Register for breast cancer (NKBC). A total of 165 patients were not registered in the database for unknown reasons, these non-participants were slightly older (median 63 vs 60 years) and had a greater percentage of tumors staged T0, Tis or TX. Patient-reported outcomes were evaluated using BREAST-Q^{TM} questionnaires posted to the patients included in the study database during 2015.

3.3.3 Data collection and follow-up

The preoperative examination was made by the attending surgeon, and the study drop-outs at this point were mainly because of having a mastectomy (n=112/121), see Paper II, fig 1. At the one-year follow-up visit after completed radiotherapy treatment, breast measurements and photographs were taken by a nurse. A substantial number (37%, n=198/532) were lost to follow-up, predominantly due to lack of invitation (66%, n=131/198) as a result of limited resources in the out-patient clinic. This loss is considered at random, at least by the comparable baseline characteristics seen between the groups (paper II, Table 1).
BREAST-Q^{TM} questionnaire return rate was 76%, which is considered acceptable for follow-up mailed questionnaires (median time from surgery of 5.5 years). Among those lost to follow-up, the majority (84%, n=118/141), did not complete their questionnaires, reasons unknown.

3.3.4 Outcome measures

A total of 216 patients were available for evaluation both regarding aesthetic outcome at one year after treatment and long-term (health-related) quality of life. A high number of patients (93%, n=310/334) had photos available for subsequent BCCT.core evaluation. The digital software evaluation with BCCT.core was preceded by the placement of manual marks using measurement recalculations. Photographs were taken with a Nikon® Coolpix S200 (Nikon® Europe, Amsterdam, The Netherlands).

Patient-reported outcomes were evaluated using the postoperative BREAST-Q^{TM} questionnaire, Breast Conserving Therapy (BCT) module, domains “Satisfaction with breast” and “Psychosocial well-being”.

3.3.5 Statistical methods

The association between BCCT.core grades and baseline factors and treatment, was analyzed using a *chi*-2 test (statistical significance $p<0.05$). This examines whether the variables are independent, i.e have no relationship, or are dependent, i.e., have a relationship. Alternative methods could have been Pearsons *Chi-2-test* or Fisher's exact test, the latter being a non-parametric model. Association between BCCT.core scores and median Q-scores for each domain was analyzed using a *logistic regression model*. Both BCCT.core grades and Q-scores were dichotomized to allow this analysis, with the intrinsic effect that distribution in data is lost for the benefit of analysis and interpretation. Adjusted analyses were made for age and the statistically significant factors found associated with BCCT.core ranking.

3.4 Paper III-V

3.4.1 Trial design

The PhysSURG-B (Physical activity in relation to surgical operation - breast cancer) trial was a prospective open-label randomized controlled trial of the effect of a physical activity intervention on complications and recovery after breast cancer surgery. The trial had a multicentre design and was planned and organized during 2015 within the framework of the Scandinavian Surgical Outcomes Research Group (SSORG), Sahlgrenska University Hospital and Sahlgrenska Academy at the University of Gothenburg, Sweden. The aim was to evaluate the effect of prehabilitation by a physical activity intervention before planned surgery for three different patient groups: in breast cancer, in colorectal cancer (PhysSURG-C) and for bariatric (PABOS) surgery. The PhysSURG-B multicentre trial was performed at one large university hospital, one teaching hospital and one local hospital within western Sweden.

Randomized controlled trials (RCTs) are appropriate for examining causal relationships between a treatment or intervention and an outcome. The process of randomization must be appropriate in order to deduce inference correctly. Proper assessment of the sample selection is crucial in order to apply the results on the population of interest, known as external validity. CONSORT guidelines are used to evaluate the quality of randomized controlled trials (108). PhysSURG-B was designed as a pragmatic interventional trial, to evaluate the effect of the

intervention under authentic clinical conditions, making a real-world implementation feasible.

Statisticians were involved in designing the PhysSURG-B trial, contributing to design, considerations about sample size and interim analysis, and in constructing a pre-specified statistical analysis plan. They performed the advanced analyses and participated during data analysis and interpretation.

3.4.2 Selection and inclusion of patients

Inclusion commenced Nov 2016 and was completed by Dec 2018. A screening log was kept, and non-participants were registered with information regarding age and reason, if known. The inclusion rate was monitored continuously and efforts were made to reduce inclusion bias and limit inclusion time. Screening for inclusion was made by a research nurse and the study information was given by the consultant surgeon at the outpatient clinic when the patient was told about her diagnosis. Randomization used permutated blocks with fixed size, stratified for study site, to reduce selection bias based on randomization. See Figure 6 for the trial timeline. An interim analysis (see paper III, Statistical analysis) was used for sample size estimation.

3.4.3 Intervention

The intervention of added non-supervised physical activity started preoperatively and extended 4 weeks beyond surgery (described in paper 3, section Procedures) (see Figure 6 below).

Supervised interventions are known to have higher adherence but have the drawback of possibly not reaching vulnerable patient groups resulting in a selection bias (109). Our intervention was designed based on the 2010 WHO guidelines and the 2011 Swedish National Board of Health and Welfare guidelines, recommending at least 150 minutes of aerobic moderate-intensity physical activity evenly spread out during the week and in bouts of at least 10 minutes. The added physical activity in the intervention should correspond to a medium-intensity activity according to the Borg´s Rating of Perceived Exertion Scale (110), and be performed during at least 10 consecutive minutes. The type of physical activity was agreed upon during the consultation with the physiotherapist and could be altered during the intervention period.

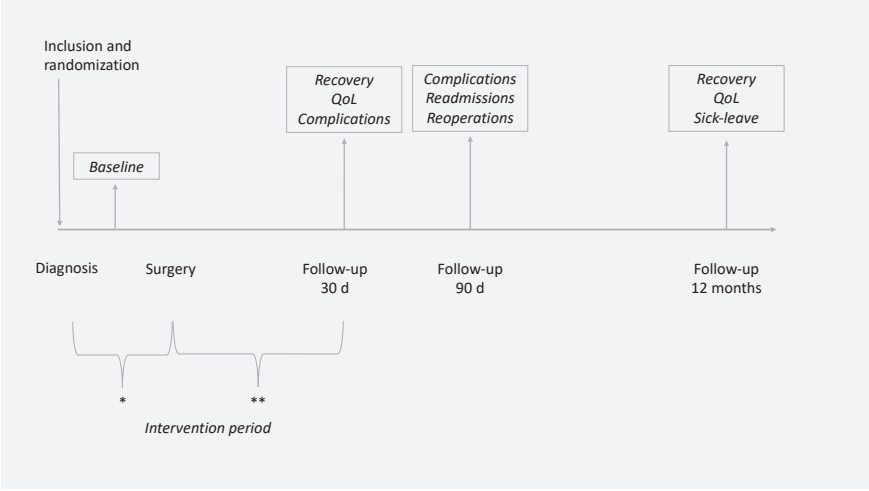

Figure 6. *Timeline for baseline evaluation and outcome follow-up in the PhysSURG-B Trial*
**Intervention before surgery: Individual consultation with physiotherapist, 30 min of physical activity daily. Physical activity diary. Follow–up telephone call.*
*** Intervention after surgery: 30 min of physical activity daily. Physical activity diary. Follow–up telephone call.*

The physical activity diary, where participants could mark an "X" for each day of added physical activity according to the intervention, was used, not primarily for physical activity assessment but as an adjunct to increase adherence. The physical activity diary was used for additional per-protocol analysis, made as an explanatory attempt to describe the effect of the actually performed intervention.

3.4.4 Control

The control group received usual care and were unmasked to study group allocation due to the nature of the intervention.

3.4.5 Blinding

Participants were not able to be blinded. Since breast cancer surgery is predominantly day surgery, and the intervention was non-supervised and home-based, blinding of health care personnel involved in the routine care of the patient before, during or after surgery was considered unwarranted and was not undertaken.

3.4.5 Data collection and follow-up

Outcome variables were collected using study specific patient questionnaires and electronic clinical report forms (eCRFs) by three research nurses (see Figure 6, Table 3). Digital answers to the patient questionnaires were possible, but none of the participants at the time of the study opted for this possibility.

A high return rate of 83-90% for the questionnaires was seen, crucial for evaluation of patient-reported outcomes. Follow-up questionnaires were sent by mail following a telephone call, and reminders were also sent by mail, all efforts made to minimize attrition (see Results section 4.2.3). All data collection was separated from the care-giving hospital to reduce appraisal bias (see Results section 4.3).

Data regarding tumour characteristics was retrieved from the Swedish National Quality Register for Breast Cancer (NKBC), which shows an excellent 99% coverage for 2016-2019 compared to the Swedish Cancer Register.

From the Swedish Social Insurance Agency's database (Store), data regarding sickness benefit was retrieved from 2016-11-01 to 2020-02-28. Since assessment of sickness benefit (based on qualifying income) only takes place when you apply for a benefit, the Swedish social insurance system is estimated to cover 91% of the (female) population (according to Social Insurance in Figures 2019, data from 2018).

***Table 3**. Data collection during the PhysSURG-B trial*

	TIMEPOINT				
ASSESSMENTS	Baseline	Surgery	Surgery +30 d	Surgery +90 d	Surgery + 12 m
Physical activity diary	*Intervention group*				
Clinical report forms			X	X	X
ASA classification		X			
Length of stay		X			
Complications			X	X	X
Reoperations			X	X	X
Readmittances			X	X	X
Adjuvant treatment					X
Study specific questionnaires	X		X		X
Demography, smoking	X				X
Comorbidities	X				X
Sense of Coherence	X				
Previous sick leave[1]	X				
Physical activity level[2]	X		X		X
Alcohol use[3]	X		X		X
Becks Anxiety Inventory	X		X		X
Becks Depression Inventory	X		X		X
BPI-SF[4]	X		X		X
HRQoL instruments[5]	X		X		X
Physical recovery			X		X
Mental recovery			X		X
Registry data					
Tumour characteristics[6]			X		
Sickness benefit days[7]					X

[1] *<12 months preceding baseline*
[2] *Saltin-Grimby Physical Activity Level Scale (SGPALS)*
[3] *Alcohol Use Disorders Identification Test- Consumption (AUDIT-C)*
[4] *Brief Pain Inventory-Short Form*
[5] *Functional Assessment of Cancer Therapy- Breast (FACT-B), EuroQol EQ-VAS, The RAND-36-Item Health Survey (RAND-36)*
[6] *National Quality Register for Breast Cancer*
[7] *Swedish Social Insurance Agency*

3.5 Outcome measures

***Table 4**. Papers I-V and their corresponding study outcomes and measurement*

PAPER	SETTING	STATISTICAL METHOD	OUTCOME	MEASUREMENT	FOLLOW-UP[1]
I	Retrospective analysis *n=27*		Reoperations Complications Recurrence Mortality PRO[2]	 BREAST-Q™ RASCH-score	30 days 30 days 35 months* 35 months* 35 months*
II	Prospective analysis *n=216*	Logistic regression	Aesthetic outcome HRQoL[3]	BCCT.core BREAST-Q™ Q-score	16 months* 66 months*
III	Prospective randomized analysis *n=400*	Poisson regression	PRO: Short-term recovery[4] Complications Length of stay Reoperations Readmissions	Study Specific Question Clavien-Dindo classification, CCI® 	4 weeks 30 and 90 days 90 days 90 days
IV	Prospective randomized analysis *n=354*	Ordinal logistic regression	HRQoL	FACT-B score, EQ-VAS, RAND-36	4 weeks and 12 months
V	Prospective randomized analysis *n=354*	Ordinal logistic regression Random Forest	PRO: Long-term recovery[4] Sick leave days Predictive factors	Study Specific Question Swedish Social Insurance Agency Study Specific Questionnaire	12 months 12 months 12 months

[1] *time (median*) after primary breast surgery*
[2] *"Satisfaction with Breast" domain in postoperative BCT module*
[3] *"Satisfaction with Breast" and "Psychosocial well-being" domains in postoperative BCT module*
[4] *Self-reported mental and physical recovery*

3.5.1 Classification of surgical complications

The Clavien-Dindo classification is a well-established system where surgical complications are graded based on treatment required (37). All complications within a postoperative timeframe (30 days) should be registered to minimize the subjective interpretation needed to classify complications as related to surgery or not. The highest grade of linked events is to be accounted for and independent complications should be graded separately (37). The grading system works well to expose the magnitude of individual complications but is inadequate to fully demonstrate the total burden of morbidity.

Patients with more than one complication are underrated, and comparisons between several complications of low grade with a single high-grade complication are challenging. A serious attempt to handle such problems is the use of a comprehensive complication index (CCI®), which integrates the severity of all complications (111). The total burden of morbidity is calculated using weights (wC) for each complication (see figure 7) with the resulting sum ranging from from 0 (no complications) to 100 (death). A grade V complication always result in CCI® 100.

***Table 5**. Clavien-Dindo classification of surgical complications. Adapted and simplified (5)*

	DESCRIPTION
GRADE I	Any deviation from expected postoperative path *E.g. Seroma treated bedside*
GRADE II	Pharmacological treatment (other than accepted for grade I) *E.g. Antibiotics, blood transfusion*
GRADE III	Surgical or radiological intervention a: local anaesthesia b: general anaesthesia
GRADE IV	Life-threatening complication a: single organ dysfunction b: multiorgan dysfunction
GRADE V	Death

Complications were recorded in clinical report forms by one of three research nurses and graded together with the same surgeon (Jenny Heiman), using a template for any deviations from the standard postoperative course. This was done to ensure corresponding grading with minimal difference in interpretation.

However, difficulties remain. Patients are routinely offered drop-in visits at the outpatient clinic after surgery, based on their own perceived needs. Seroma drainage can be done at the outpatient clinic or by radiological intervention, with a grade of either I or IIIa. This decision is made by the individual nurse or surgeon, arguably not solely based on clinical presentation but also influenced by workload and access to radiological intervention. Temporary drainage at the out-patient clinic were given grade I, but if drainage was ultrasound-guided and/or a drain left in the surgical wound it was given a grade IIIa, since conducted by the radiologist.

$$CCI^{®} = \frac{\sqrt{(wC_1 + wC_2 \ldots + wC_x)}}{2}$$

	WEIGHT OF COMPLICATION	CCI® SINGLE VALUE
GRADE I	300	8.7
GRADE II	1750	20.9
GRADE IIIA	2750	26.2
GRADE IIIB	4550	33.7
GRADE IVA	7200	42.4
GRADE IVB	8550	46.2

Figure 7 *CCI® calculator and weights of complication (wC) according to corresponding Clavien-Dindo grade*

3.5.2 Recovery

Measuring recovery can range from objective ratings of functional capacity or abilities, length of stay and sick leave to patient-reported outcomes. We used both objective outcome measures and the patient-reported outcome of recovery (primary outcome). This was assessed as "To what extent do you feel physically/mentally recovered after surgery?", with physical and mental recovery measured separately. A self-rated recovery utilizes each individual's own applied definition of recovery and a patient-reported outcome in this form can be expected to be less prone to appraisal bias than if asked by the operating surgeon. Our primary analysis was unadjusted, and the supporting adjusted analysis was made to evaluate sensitivity. For the 12-month outcome, we adjusted our model for adjuvant chemotherapy, since this was distributed in an unbalanced fashion between the study groups.

3.5.2.1 Length of stay

Breast cancer surgery is generally day surgery and the need for overnight hospital stay is normally unrelated to the type of surgical procedure (except for extensive reconstructive surgery), but is instead based on patient frailty and expectations. The need for overnight stay is usually assessed at the time of surgical planning and preparation at the outpatient clinic. For these reasons the length of hospital stay as days is a difficult endpoint for breast cancer surgery.

3.5.2.2 Sick leave

At discharge, all patients of working age undergoing breast cancer surgery were offered sick leave according to clinical routine, usually 4 weeks (+- 2 weeks)

following surgery. Equivalents to full days of sickness benefit (100%) were calculated if partial days were registered and referred to as net days on sick leave < 12 months after surgery. The national database reports each sickness benefit case with a diagnose code according to ICD-10-SE (International Statistical Classification of Diseases and Related Health Problems), but this may change during the progression of the disease and hence throughout an ongoing case of sickness benefit. This makes reasons for being sick (diagnosis) not necessarily the same as the reasons for sick leave, the latter also influenced by a number of individual factors (age, gender, socioeconomic and demographic status) and factors related to the workplace as reported by The Swedish Council on Technology Assessment in Health Care (www.sbu.se/167).
We separated sick leave (equal to sickness benefit) from permanent sick leave (sickness compensation) and excluded parental leave benefit to refine sick leave days as a result of the current diagnosis of breast cancer. The result is a quantitative assessment of sick leave days in the whole trial cohort; however, no conclusions can be drawn regarding the reasons for sick leave.

Table 6 *Recommendations[1] regarding sick leave for breast cancer diagnosis and treatment (C50, D05, Z853, ICD-10-SE). Time period and extent of sick leave.*

	TIME PERIOD		PERCENTAGE
	Sentinel lymph node biopsy	*Axillary lymph node dissection*	
Breast-conserving surgery[2]	Postop 3-6 weeks	Postop 4-8 weeks	100%
Mastectomy[2]	Postop 4-8 weeks	Postop 4-8 weeks	100%
Radiotherapy	Treatment 3-5 weeks		Partial
Chemotherapy	Treatment 4-5 months Post-treatment 2-4 months (12 months)		100% 100%
Anti-Her2 treatment	Treatment 12 months		Partial
Endocrine therapy	Treatment 5-10 years		0%

[1]*Adapted from Försäkringsmedicinskt beslutsstöd https://roi.socialstyrelsen.se/fmb/brostcancer/632, accessed 210113*
[2]*Primary surgery without complications*

3.5.3 Patient-reported outcome measures

Patient-reported outcomes were measured using several validated instruments. How well an instrument matches the latent variable it claims to be measuring (for example HRQoL) is the *construct validity* of a measurement. *Content validity* refers to how well it covers all the different aspects of the variable of interest (i.e

HRQoL). The scores of a measure should also correlate to other known variables expected to be associated to the latent variable, having so-called *criterion validity*. *Reliability* refers to the ability of repeated testing to achieve the same results, and with unchanged status ensure *repeatability*, with minimal random variability. If a measure has good *test-retest reliability* it would yield the same score over time for a construct, given that this construct is constant. All items in a multi-item measure are supposed to reflect the same underlying construct to yield a high *internal consistency* across the individual items, measured as Cronbach's alpha (>0.8). Ideally, an instrument is *sensitive* to differences between patients or groups, as well as longitudinal changes within the same patient over time, the latter known as *responsiveness*.

To interpret small statistically significant differences in health-related quality of life with assumed low clinical importance, minimally important differences (MIDs) or minimal clinically important differences (MCIDs) are used. The definition is "the smallest difference in score that patients perceive important, either beneficial or harmful, and which would lead the clinician to consider a change in management" (112). Minimally important differences can also be useful in defining the appropriate sample size for clinical trials where health-related quality of life is the primary endpoint (113).

3.5.4 Health-related quality of life instruments

We have used the well validated RAND-36 (i.e., SF-36) and EQ-5D-3L and EQ-VAS for measuring generic health-related quality of life, as well as a single-item question of general QoL (paper IV, V).

The *RAND-36* assesses eight health domains for the past 4 weeks. A single item assesses change in perceived health during the last 12 months (42). Two summary scores (physical and mental health) are sometimes used but the Swedish scoring manual advices against using summary scores, and we used a recommended spider diagram to visualize outcome. Minimal clinically important differences is in the range of 3-5 points difference (114). RAND-36 is widely used in studies and offer a basis for comparison of results between different patient groups.

The *EQ-VAS* measures an individual's overall health of the day using a standardized vertical 20 cm visual analogue scale. Minimal clinically important difference for EQ-VAS has been proposed at 8 points (115). The instrument is well validated regarding content and construct validity, has acceptable test-retest reliability and responsiveness (41, 116, 117).

The BREAST- Q™ and FACT-B were used for disease-specific measures (paper I, II and IV, V). The *BREAST- Q™*, being developed for breast surgery, was chosen for evaluation of aspects regrading surgical techniques and specific surgery-related outcomes (paper I and II). The BREAST-Q™ questionnaire translation process of the Breast-conserving Therapy - module was managed by Jenny Heiman, with permission granted by Dr Andrea Pusic. The translation process followed the "Linguistic validation of a patient reported outcomes measure" from the MAPI Research Trust (Lyon, France), described in Paper II, Methods. The BREAST-Q™ questionnaire scales were used individually as data was transformed into a Q-score, ranging from 0-100, higher scores indicating better outcome (48).

FACT-B is the most commonly used instrument for patient-reported outcome (PRO) related to breast cancer treatment (54, 118). FACT-B was developed for the use in clinical oncological trials, as well as in clinical practice, with emphasis on patients' values and brevity and therefore was chosen in the large, randomized trial (paper IV, V), where used in combination with other patient-reported outcome measures. The alpha coefficient (internal consistency) for the FACT-B total score is high (alpha 0.90), subscale alpha coefficients ranging from 0.63 to 0.86. Evidence supports test-retest reliability, as well as convergent, divergent, and known groups validity and sensitivity to change (53, 55). FACT-B response alternatives from 0 (not at all) to 4 (very much) for all scales were scored according to a manual, so that a high score equals better quality of life and a total FACT-B score was derived. A total score was calculated if all the subscales had valid scores, and an overall item response rate greater than 80%. A subscale score was prorated for missing items if more than 50% of the items are answered. In a breast cancer population, a minimal important difference of 7-8 points for FACT-B has been used (119).

3.5.5 Measuring physical activity

Physical activity level was assessed using Saltin- Grimby Physical Activity Level Score (SGPALS) (89) and further objective measures were not employed in order to keep the intervention simple. The four-level item responses were regrouped into, inactive, low and moderate/high intensity according to practice before analysis, since the high intensity group is usually 2-4%. Change from baseline to 4 weeks was calculated in both study groups to account for adherence to the intervention and to assess the degree of contamination of the control group. As SGPALS was not designed for measuring change, the results were not used as a factor for outcome analysis, but rather as an explanatory supporting analysis.

3.6 Statistical analysis

For the randomized trial, our statistical analyses were intention-to-treat, meaning that all participants were analysed as randomized, regardless of conducting the intervention or not. This was due to the pragmatic nature of our trial, where we wanted to examine if a recommendation of non-supervised added physical activity increased recovery, not if physical activity was undertaken per se. To take into account the low *adherence* to the intervention in the PhysSURG-B trial, an additional per-protocol analysis of the subgroup who fulfilled the intervention as intended (registered in the physical activity diary) was conducted for explanatory purposes.

3.6.1 Statistical models

In order to test a research hypothesis, statistical models and hypothesis testing is used. The aim of a statistical model is to characterize the variability (variance) in data and to quantify the contribution of each of the components specified in the model (independent variables or predictors such as an intervention) to the total variability in outcome. This is called Analysis of Variance (ANOVA). By estimating the individual predictor's contribution to outcome, we can evaluate which have the most explanatory power. This forms a basis for estimation and statistical testing of our scientific hypotheses. The models also state the element of variation at random (the residual factor that cannot be explained) and the resulting uncertainty or accuracy of the statistical estimate.

3.6.1.1 Generalized linear models

Generalized linear models perform multivariable analyses using regression analysis. The models are used to make predictions about data and evaluate treatment effects. Assumptions about probability distributions (parametric or non-parametric) regarding expected outcome and randomness in data (unknown variables) have to be met for the model that is being used. If the requirements for the model is met, it can quantify the relationship between a dependent variable (Y) and (one or) multiple independent variables (X_1-X_X). A statistical statement regarding the uncertainty of the model prediction is used, for example the correlation coefficient, p-value or confidence intervals (CI). We used 95% confidence intervals, meaning that with the statistical model used, 95% of the true values within the data were compatible within this range. The width of the confidence intervals depends on the number of observations and the dispersion of the parameters true value.

The simplest *linear regression analysis* uses the assumption that the distribution of variables contributing to the outcome and the probability distribution for randomness in data are linked in a linear fashion, normally distributed and continuous. To account for several factors simultaneously, a *multiple or multivariable regression analysis* is appropriate to estimate the relationship between sets of variables (multivariable) and outcome. Logistic regression estimates the probability that a binary outcome occurs, as used in paper II.

The primary outcome analysis of recovery at 4 weeks (paper III) used a modified *Poisson regression analysis* with robust error variance (120). The answering options (0, 25, 50, 75, 100% recovered) were dichotomized into 0-50% and 75-100% recovery prior to analysis. Dichotomization creates binary outcome and enhances interpretation regarding benefit of the intervention vs the control group. Effect sizes were presented as a relative risk (RR) of being 75-100% recovered, >1 favoring the intervention and <1 favoring control. Due to high levels of recovery (see Figure 8), the scale steps 0%, 25%, 50%, 75%, 100% seemed insensitive to change at the high level of recovery seen in our patient group. An additional dichotomization for 0-75% vs 100% recovered was made to counteract this ceiling phenomenon (see paper III, Figure 2). An alternative model could have been a log-binominal model or an ordinal model, see below.
As the recovery answering alternatives were an ordinal scale with five scale steps, dichotomization between the answering alternatives involves interference with the scale. This means that the scale is subjected to interpretation when the cut-off is placed, and that you risk losing the real threshold level. For a continuous variable, you also lose data regarding a dose-response relationship. To overcome this, analysis of HRQoL (paper IV) and recovery at 12 months (paper V) was done using an *ordinal logistic regression model.* The relationship between the two study groups were quantified and displayed as odds ratios (OR) of higher recovery ratings. OR >1 in favour of higher recovery ratings in the intervention group, and OR <1 favouring control.

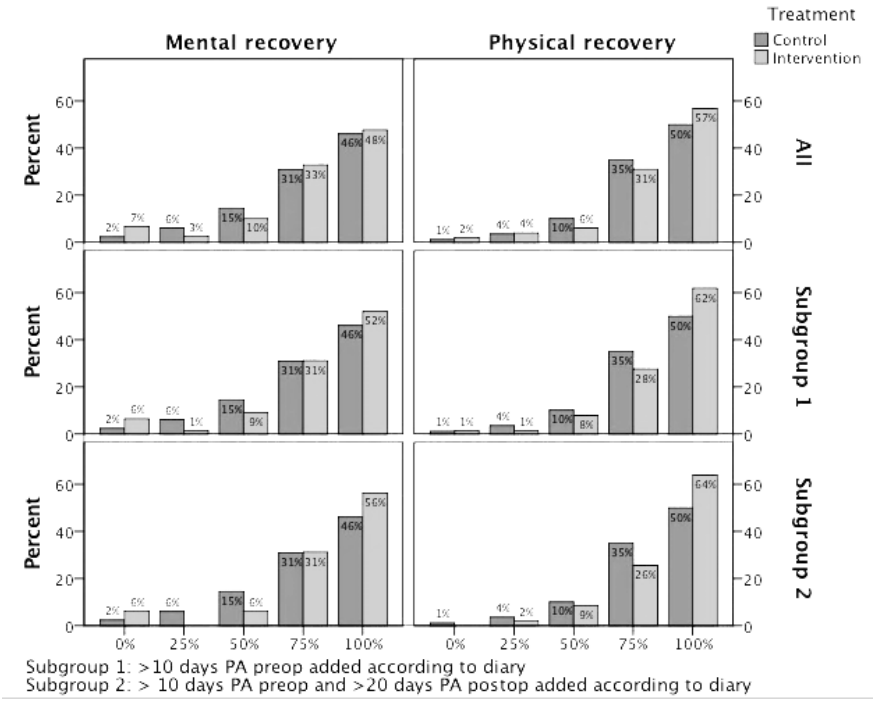

Figure 8. *Recovery at 4 weeks postoperatively, distribution of participants (%) from 0-100% recovered*

3.6.1.2 Random forest

A decision tree is a statistical model that divides a dataset by using a tree-like structure and assigns a predicted value to each subset of observations, represented in the leaves. Decision trees are easy to build, easy to use and easy to interpret, but display inaccuracy. A *random forest* is an ensemble method that outputs the majority vote of a large number of constructed trees and involves machine learning. The main objective for using a random forest, rather than a tree, is to increase accuracy and reduce variance. The forests also display better predictive performance (121).

Regression trees were constructed for the outcome (more) sick leave days. Predictive variables were ranked by the model depending on how significant their impact was on the outcome variable (of sick leave). Ranking the importance of variables was done by assessing the prediction errors. An increased prediction

error when the variable was excluded from the model, indicates that it is a variable of higher importance to the outcome. The variables identified by the model can be used to predict outcome for a new patient with the accuracy of the prediction error. The number of variables included in the random forest model (we used 25) should be less than the number of observations (n=113), see paper V.

3.6.2 Statistical significance

A statistically significant result does not necessarily offer a true (clinical) implication, neither is a non-significant result less true if effect size seen is considered important (122). You need to take into account what is a reasonable sample size in comparison to the expected point estimate. With a large enough sample size, anything can be proven statistically significant, however, this indicates that the effect size (of for example the intervention) is small and the clinical significance debatable. On the other hand, above threshold changes in minimal important differences for patient-reported outcome instruments are considered clinically significant, and regardless of statistical significance ($p>0.05$) they are important to detect.

3.7 Methodological considerations

Every trial cohort is a sample of the target population which your scientific question concern. In other words, you want a large enough sample size (external validity) to achieve statistical power, but you want a homogenous group to reduce outcome variability and confounders (internal validity) and a design to answer your research question (with the help of statistical methods).

How you design a trial is based on the research question that you want answered. To do so, you create a *null hypothesis (H0)* considering the relationship in outcome between the study groups, that you test regarding statistical significance.

3.7.1 Trial design and sample size

PhysSURG-B was a superiority trial, designed to detect differences between intervention and control. The statistical null hypothesis stated that the true effect of the intervention (intervention vs control) was zero and the alternative hypothesis (H1) that the difference was non-zero. Rejecting the null hypothesis would mean that we state a difference between the groups. Statistical significance includes a generally accepted insecurity level regarding the results being found by chance, known as a *type I error*. At a set *significance level,* usually at 5%, we

would reject the null hypothesis if $p < 0.05$. This means that we accept a 5% risk of falsely rejecting a true null hypothesis due to random variability among the groups.

Not being able to reject the null hypothesis (H0) with accepted statistical significance might be due to inadequate power. The difference between the groups we wish to reveal (for H1) is dependent on the statistical power. You need enough observations, i.e., a large enough *sample size* to achieve statistical power. With a statistical power (usually set at 80%), in 80/100 cases you can detect an expected difference in outcome (if present) and reject the null hypothesis. In 20/100, when an alternative hypothesis (H1) is true (that there is a true difference), you fail to reject the null hypothesis, a *type II error*.

An initial trial sample size was calculated for the primary outcome of physical recovery (paper III) but not for the secondary outcomes (paper IV-V). For details see Paper III, Statistical analysis. For the primary outcome of self-reported recovery, a minimal important difference was unknown at the start of the study, so making assumptions about sample size was impossible. The point estimate (9% difference noted between the study groups in the interim analysis) was the estimated effect size to be detected if present, with 80% desired power, however, the underlying rate of physical activity in the population was not fully anticipated. Taking into account the uncertainty of the estimate and a 10% dropout frequency, a target of 400 study participants was set based on the interim analysis.

High external validity is needed to ensure that you have a representative study population (sample) to be able to transfer the findings to the general breast cancer population (target). A highly controlled setting (ideal circumstances, stratified groups, supervised intervention) would yield a high *internal validity* at the expense of lower *external validity*. That is, we would be confident that we eliminated all alternative explanations to the tested relationship between the intervention and outcome, but we would have no prospect of generalizing our results to apply to patients with breast cancer in the actual clinical setting. *External validity* is susceptible to influence if there is a change in behavior solely because of study participation (known as the Hawthorne effect).

Internal validity is tampered with when the outcome is influenced by an unpredicted change in the study conditions over the course of time, the baseline test itself, selection bias, attrition due to the intervention itself, regression towards the mean, change in how outcome is measured and/or group interaction.

Regression to the mean is a known phenomenon associated with repeated longitudinal testing. This means that extreme values tend to become less extreme with repeated measurement. There is also a relationship between the baseline value and the size of the change possible, however, this can be handled statistically (paper IV).

3.7.2 Retrospective study design

A retrospective study evaluates a specified outcome and exposures in a defined cohort. The limitations of a retrospective design can be seen in paper I, where we can expect a substantial selection bias, a limited sample size, lack of a control group and the resulting level of evidence is poor. The conclusions to be drawn from this study are few. Margin status was chosen to be the most useful outcome for evaluating a new surgical technique for breast-conserving surgery, where the ability to achieve radical surgery was a surrogate marker for oncological safety.

If a particular variable or outcome is rare, retrospective case-control studies are useful since a prospective randomized trial for such an outcome would need an unreasonable inclusion time to yield an adequate study size. Retrospective studies also have a role in "screening", as their findings can entail more thoroughly designed larger prospective trials needed for testing a new surgical treatment.

3.7.2 Prospective study design

Prospective studies have less confounding and bias, compared to retrospective studies. The prospectively collected OPB-pME study database (paper II) was considered regarding selection bias by comparing the cohort with the Swedish National Quality Register for Breast Cancer (NKBC). The database included almost 80% of the possible patients and these were slightly younger and had more invasive tumors. The majority who were lost to follow-up were due to lack of resources in the outpatient clinic. For the patient-reported outcome evaluation, actions were made to reduce attrition, however, most lost to follow-up were due to uncompleted questionnaires. Further evaluations were made to appraise if the analyzed cohort differed regarding patient and tumor characteristics compared to the initial cohort (Paper II, Figure 1 and Table 1).

Timing of the aesthetic evaluation can be discussed, however, 12 months after completed adjuvant radiotherapy is considered appropriate as results have been shown to become stable at this time (123).

3.7.3 Randomized controlled trial

A randomized trial evaluates outcomes and correlates them to other factors, such as an intervention. Random allocation to different interventions or treatments is used. This design provides the highest grade of research evidence according to the GRADE system (Grading of Recommendations, Assessment, Development and Evaluations) (124).

In 2016, a pilot study within the PhysSURG-B trial, including 20 patients in each arm, tested the clinical and administrative capacity that was needed to perform the trial. The results from this pilot were transferred into an improved version of the study protocol. The main changes were to enhance adherence to the physical activity intervention and minimize contamination of physical activity in the control group, the diary was simplified and used solely in the intervention group, in an effort to improve the external validity of the trial.

With a randomized group allocation, the study groups are ideally similar in every aspect apart from the intervention/treatment studied, and selection bias and confounders that could influence the results are minimized, however we cannot fully account for inclusion bias before randomization. I consider our external validity to be good when considering the participants' data regarding tumour size, type and treatment factors compared to the national quality register data. We made efforts during the phase of inclusion to invite all patients eligible for participation to reduce selection bias. Our screening-log revealed that there are two principally very different groups, who were not approached or declined participation; they were either very physically active and/or didn't have the time to get involved with the study, or they considered themselves too frail due to comorbidity, indicative of possible inclusion bias of patients with the highest and lowest functional capacity.

To increase validity, we minimized selection and sampling bias using a randomized design, kept a screening log and made efforts to ensure a high inclusion rate to limit the study period. We had broad inclusion criteria of female patients with breast cancer, and excluded patients not primarily treated with surgery (subjected to neoadjuvant treatment or palliative care). We used a pragmatic intervention to lessen attrition and limited the timepoints for evaluation. The Hawthorne effect was in part neutralized by randomization, but since neither of the groups could be blinded to the intervention, the control group might have increased their physical activity as well, just by study participation. The written

study information was kept general in order to minimize this sort of control group contamination.

3.8 Ethical considerations

In accordance with the WMA declaration of Helsinki (125) all studies were reviewed by Ethical Review Boards. The PhysSURG-B trial was registered at clinicaltrials.gov for public access before recruitment started. Blinding an intervention such as physical activity vs a sham intervention is impossible when adhering to the ethical standards of fully informed participation. The aspect of contamination of the control group is therefore in part inevitable due to the nature of the intervention.

During our study planning we considered whether our intervention could pose harm, physically or mentally, to a group of patients diagnosed with a potentially life-threatening disease. Given that we did not recommend a specific activity but adhered to the national and international recommendations regarding physical activity we deemed our intervention to be safe and ethically sound.

Using patient-reported outcome measures in Swedish meant that we excluded patients who were not competent in the Swedish language, which must be considered in the ethical context and a weakness when interpreting external validity of the results.

4. Results

4.1 Summary of results

***Table** 7. Summary of study findings and implications for the included papers I-V.*

PAPER	AIM	FINDINGS	IMPLICATIONS
I	Evaluate the inframammary fold incision technique	Positive margins 16.7% Complications 11.1%	Inframammary fold incision is feasible
	Translate BREAST-Q™	"Satisfaction with breast": score 72.5	BREAST-Q™ BCT module can be used for PRO-evaluation in Swedish
II	Does BCCT.core aesthetic evaluation correlate to long-term HRQoL measured with BREAST-Q™?	Good or excellent aesthetic results had higher BREAST-Q™ Q-scores: "Satisfaction with breast" median score 66 (OR 3.4; CI 1.7-6.8) "Psychosocial well-being" median score 82 (OR 2.2; CI 1.1-4.2)	BCCT.core evaluation is an objective measure of patient photos regarding aesthetic outcome. A higher aesthetic evaluation correlates to better HRQoL 5.5 years after surgery. Including aesthetic results in treatment planning and evaluation is of importance for improving outcome.
III	Does non-supervised physical activity improve recovery at 4 weeks after surgery?	Physical recovery* RR 1.14 (95% CI 0.92-1.40) Mental recovery * RR 1.03 (95% CI 0.82-1.31)	Non-supervised physical activity did not improve short-term recovery, complication, LoS, reoperations or readmissions.
	Complications, LoS, reoperations, readmissions?	CCI* 4.2 (I) vs 4.7 (C) LoS days 1.1 (I) vs 1.2 (C) Reoperations 4% (I) vs 4% (C) Readmissions 8% (I) vs 5% (C)	Breast cancer surgery has low levels of complications and high levels of recovery.
IV	Does non-supervised physical activity improve QoL 4 weeks and 12 months after surgery?	*FACT-B* (4w;12m): OR 0.98 (ns); OR 0.88 (ns) Chemo (4w; 12 m): OR 0.42 (95% CI 0.26-0.67); 0.475 (95% CI 0.30-0.75). *EQ-VAS* (4w; 12m): OR 1.16 (ns); OR 0.82 (ns) Chemo (4w; 12m) OR 0.56 (95% CI 0.35-0.87); OR 0.656 (ns)	Non-supervised physical activity did not improve short-term or long-term quality of life. Breast cancer patients show high and stable levels of quality of life. Adjuvant chemotherapy significantly lowered quality of life scores.
V	Does non-supervised physical activity improve recovery or sick-leave at 12 months after surgery?	Physical recovery* OR 1.10 (95% CI 0.69-1.75) Mental recovery* OR 0.97 (95% CI 0.62-1.53) Sick-leave OR 1.21 (95% CI 0.64-1.66)	Non-supervised physical activity did not improve long-term recovery or sick-leave. Adjuvant chemotherapy significantly decreased levels of recovery and increased sick-leave days.
	Can predictive factors for sick-leave be identified at baseline?	See Paper V, Figure 4a	Baseline factors can be identified that predict prolonged sick-leave.

**Crude values according to intention-to-treat for full recovery CCI®: comprehensive complication index, HRQoL: health-related quality of life, LoS: length of stay. QoL: quality of life*

4.2 Interpreting results

4.2.1 Study design

When interpreting results, it is crucial to acknowledge the limitations of the used study design. All group-based research designs imply that the group label (here breast cancer) is a sufficient categorization to make recommendations regarding the target population. It involves the assumption that results are representative for a larger population than the one being studied and that study results can be generalized by using *inferential statistics* (126).

For non-randomized observational data, the distribution between groups regarding known factors are presented in descriptive tables (table 1, paper I and II). An even distribution is the base for the external validity of the statistical estimations regarding correlations made between groups or factors, but unknown confounding factors cannot be accounted for. This study design limits the ability to state conclusions regarding causal relationships.

Using prospective randomized controlled trials (RCTs) yield high level of evidence compared to retrospective studies, suffering high risk of selection and inclusion bias. However, for an RCT it is important to assess the quality of the inclusion and randomization process and the following generalizability as a result of the external validity. With randomization you reduce the factors that in a non-random fashion influence group allocation and outcome. *Confounders* are variables with a relationship to the outcome, and that you fail to eliminate or control for, and hence they can affect outcome. Randomization is done to make (all) confounding variables randomly dispersed between the different study groups. If balance between the groups is achieved for known variables of importance (tabulated as descriptive statistics), it is also presumed to be true for possible unknown confounders. Block randomization which we used was performed to reduce the confounding site-related variation (127). The groups were well balanced in the PhysSURG-B trial, except for adjuvant chemotherapy, unknown at the time of randomization. This was handled by adjusting for chemotherapy. The results of the PhysSURG-B outcomes were interpreted with the assumption that a properly conducted randomization process was done, which made valid comparisons between the study groups regarding outcomes possible.

Interpretation of results also have to account for sources of error (bias) commonly found in clinical research (128)

4.2.2 Screening and inclusion

A screening-log was used to monitor the quality of inclusion to avoid *selection bias* and *inclusion bias* in the RCT. Our inclusion criteria mandated being able to understand and read Swedish, which have implications regarding representation of non-Swedish speaking women in the studied population. The internal validity was considered high, with a short inclusion time at three different sites within the same region. The screening-log for non-participation revealed a large number of individual reasons for not participating. Out of 1260 patients screened for inclusion, 263 were not approached with study information due to the following reasons: resource shortage in the outpatient clinic, crisis reaction following cancer diagnosis, or that patients expressed other commitments. Among the 309 women who were asked but declined participation, the reasons could be grouped into: lacked energy or time to engage in the study, stated being very physically active already or expressed that their comorbidities were a hindrance. Due to short lead-times to fulfill the standardized care pathway timeframe and the preoperative phase of the intervention, the study inclusion had to be managed at the first clinical visit after the diagnostic procedures were completed. Hence, study inclusion and randomization were done at the same time as patients received their cancer diagnosis. This was problematic, both regarding time management for the attending surgeon and for the patient being able to take the information into proper consideration.

4.2.3 Follow-up

For longitudinal analysis of patient-reported outcomes, there is no gold standard for acceptable attrition rate (missing values). A rule of thumb says that 5% attrition have minimal effect on the validity of the analysis, whereas 20% attrition would cause problems (41). Unequal loss of participants (attrition bias) in different study arms of an RCT or in the analyzed cohort compared to the possible cohort including those lost to follow-up in a non-randomized study (127) has to be considered. Missing at random yields lost study power, while non-random loss results in bias regarding treatment or intervention effects. Problems in achieving statistical power, due to a resulting smaller sample size following missing at random, was possibly seen in our RCT. Non-random loss constitutes a threat to both the internal and external validity and cannot be managed by an increased sample size, since it is a systematic error, known as *attrition bias*. It can result from unacceptable treatment (or intervention) effects, difficulties to comply with the intervention or death. It must be handled by limiting dropouts, keeping track of the ones who decline to participate and methods to deal with missing data.

When possible, reasons for dropout or withdrawn consent were asked for and noted, though this was not compulsory since participation and withdrawal were at the participant's own discretion. In the OPB-pME study, the large portion of missing at one-year follow-up were due to lack of resources in the outpatient-clinic (considered a random loss).

In PhysSURG-B, no participants were lost due to administrative functions, such as moved or having lost contact with. Lost to follow-up due to death did not pose a problem in the PhysSURG-B study, one patient in each study group died within the 12 months follow-up period. The reasons for withdrawn consent, when known, fell into two main categories: the questionnaires were too tiresome, or participants didn´t have the energy to fully engage in the study with everything that happened simultaneously. There were more patients lost in the intervention group during the onset and active intervention period, possibly indicating that they could not commit to the intervention, rather than the questionnaires being overwhelming. The majority of patients who withdrew their consent did so before, or at the very beginning of the intervention, perhaps reflective that the anticipation of, rather than the actual physical activity itself, was a hindrance. The uneven attrition seen could have resulted in the remaining intervention group being a more resourceful group and could impact their response to patient-reported outcomes such as health-related quality of life and give a false positive result. However, over the course of the trial, attrition was considered low and numerical group differences in attrition rates diminished.

The outcome analyzed, the patient group studied and follow-up time must be considered when deciding on acceptable attrition rates. Efforts to minimize loss to follow-up included using our locally well-established practice of administration and handling of study questionnaires. Although labour intensive, actions to increase the return rate of questionnaires is a key factor in the proper evaluation of patient-reported outcomes. In the OPB-pME trial, an informative letter was sent together with the questionnaire and two mail notices were used to improve return rate. We considered the rate of 76% acceptable in this setting of in median 5.5 years since study inclusion. For PhysSURG-B, a practice that used a phone call preceding questionnaires being sent by mail and two reminders by mail for non-responders was used. Return rates were 90 % (baseline) 86% at 4 weeks after surgery, and 84 % for the 12 months questionnaires, and no difference in return rate were seen between the study groups. This is a high return rate, equivalent for both study groups, supporting that results can be considered representative.

For patient-reported outcomes imputation is sometimes recommended, since missing single responses are common and not conducting imputation would mean losing the ability to utilize available data. Multiple imputation techniques are often used. We decided not to perform imputation for the primary outcome, since this could tamper with the integrity of the results, and we considered our missing manageable. The complete case method was used with list-wise deletion of cases with missing values.

4.2.4 Intervention

Keeping the integrity of the given intervention during the trial is a key factor. One physiotherapist conducted the intervention at Sahlgrenska University Hospital and was also responsible for instructing the physiotherapists at the other sites to ensure that the instructions and interventions were as similar, reliable and reproducible as possible.

Blinding the intervention in a randomized controlled trial will provide the highest level of validity in clinical research (127). This will reduce the risk of non-random error in the assessment of exposure to the intervention or the outcome, called measurement bias. Blinding is obviously not possible with this type of intervention, but we made efforts to minimize the contamination of the control group regarding details of the intervention.

Lack of intervention adherence, despite of being comparable to other reports of physical activity interventions in a breast cancer population (109), led us to conduct an additional per-protocol analysis.

In keeping with the national recommendations to the population, our intervention aiming at the whole populace of patients with breast cancer, was limited to individual counselling, a physical activity diary as a co-adjuvant and two follow-up telephone calls to improve the participants' physical activity level. The self-reported instrument Saltin-Grimby Physical Activity Level Scale (SGPALS) revealed a slight difference in change from baseline between the study groups at 4 weeks. We had no objective measurement of physical activity type, level or intensity in our study, but ranking physical activity level using SGPALS have shown good correlation to objective accelerometry measures (90). Further objective measurement of physical activity level was considered difficult to manage within the short period of time before surgery (according to the national aim for lead-time of 14 days from diagnosis until surgery), and objective monitoring of both groups was considered influencing behavior to a larger extent

and thus decided against. Self-reported measurements are known to influence behavior to a lesser extent than objective tools, but have the disadvantage of *recall bias*, *social desirability bias* and tendency to over-report (*acquiescence bias*) (87, 88, 129).

4.3 Outcomes

The translation and use of patient-reported outcome measures gave insight into the process of developing valid questionnaires for the extensive topic of health-related quality of life. It also brought attention to limitations in current breast cancer research regarding patient-reported outcomes and standardized measures. In addition, patient-reported instruments have intrinsic sources of error (*response bias*) to be taken into consideration for outcome analysis.

Response shift is the change in the respondent´s internal frame of judgement regarding the construct studied. This means that measuring the same construct (for example health-related quality of life) at different timepoints gives different results. This is the result of a change in internal standard (scale recalibration), or how an individual values the importance of the measure (reprioritization), or that the meaning of the whole construct health-related quality of life has changed (reconceptualization). Response shift can result from the influence of a (cancer) diagnosis, treatment, personal growth, knowledge etc. For example, if you have perfect health you may consider health-related quality of life differently compared with when you have a potentially deadly disease (130). We did not consider response shift a problem in the randomized group setting.

Appraisal is the psychological process involved that link evaluation of a situation with emotions. Assessment and rating of QoL items is subjected to appraisal to an individual's self-fulfilling prophecy.
When subjected to a choice, the respondent's wish to give a socially desirable answer and a tendency to select a positive, favorable or expected option can result in *acquiescence bias*. This form of response bias can be influenced by personality, cultural aspects, situation and time (130). Appraisal and acquiescence bias can be lessened by separating the roles of participant and observer as we did by using study questionnaires to be filled out at home and sent in to an administrative function separated from the care provider (126)..

For common patient-reported outcomes appraisal and acquiescence bias can be expected equal in the study groups, but options related by the individual to the intervention can display study group discrepancies.

In addition to patient-reported outcomes, data from medical records was used. Margin status, length of stay, complications, reoperations and readmissions were such clinical outcomes. For these outcomes, loss can be controlled for to a larger extent. To ensure that convergent interpretations were made when needed, one research nurse at each site was in charge of data collection according to a template, and monitoring and evaluation was conducted by a single surgeon (Jenny Heiman) for the PhysSURG-B.

With knowledge about potential confounders, you can identify an uneven factor distribution between randomly assigned groups. For example, adjuvant treatment with chemotherapy, directly correlated to outcomes sick leave days, showed a difference between the randomly assigned study groups. As a *sensitivity analysis* we adjusted for factors assumed to affect outcome, such as adjuvant treatment, age, type of surgery and physical activity level at baseline in PhysSURG-B and age, BMI, tumour size and radiotherapy in OPB-pME, showing that the results were robust as they were concordant with the crude analyses.

5. Discussion

The results from the included papers in this thesis shed light on the added information provided by patient-reported outcomes. To improve our choice of proper surgical methods in regard to the best achieved outcome for the individual in front of us, treatment evaluation must encompass all elements of importance, and it should also include different measures to represent as many aspects as possible of the result that patients experience and live with.

The results from the randomized trial could not support a recommendation of non-supervised physical activity as a way to improve outcome after breast cancer surgery. Breast cancer patients have a high level of recovery and robust quality of life, and breast surgery was associated with few complications, reoperations and readmissions (paper I-IV). New surgical techniques, such as the inframammary fold incision may offer ways to improve aesthetic results (paper I), which was shown to correlate to long-term health-related quality of life (paper II). As our results conformed with previous knowledge, that adjuvant chemotherapy was associated with significantly lower levels of recovery and increased sick leave (paper IV, V), indicating that this and other subgroups of susceptible patients should be the focus for future interventions in order to improve breast cancer care.

5.1 Outcome measures

Breast cancer diagnosis today is no longer equal to a deadly outcome, but instead results in a survivorship, bearing resemblance to a chronic disease. The complete evaluation of treatment can therefore not be restricted to the time around the diagnosis and immediate care given. Patient-reported outcomes should ideally be evaluated continuously over the course of life.

The use of appropriate and validated instruments is thought to be the groundwork for reliable responses and a good response rate for patient-reported outcomes. Limiting measurements used is a way to value patients' time and effort and restricts the selective reporting bias seen when only the ones that show superior effects or statistical significance for the intervention are chosen. In hindsight, we could have selected fewer instruments and questions that turned out difficult to interpret or redundant as they were examining the same construct.

The challenge for the future is how to properly conduct assessments regarding breast cancer treatment and how to take adequate action following this information to improve outcome. Meta-analysis would be the approach for highest level of evidence before implementing new treatment strategies and changing guidelines for clinical practice. To be able to take patient-reported outcomes into account, the first step is to determine a standardized set of outcome variables (clinical and patient-reported) to be measured and to determine the timing for their evaluation. The next step is to evaluate the results correctly using the proper statistical methods and to draw accurate conclusions. These conclusions can then be turned into suitable actions, either for the individual patient or to improve the care of future patients. After we conducted our studies, the SPIRIT-PRO Extension (Standard Protocol Items: Recommendations for Interventional Trials - Patient-reported outcomes), have been published in JAMA 2018, as a result of an international, consensus-based effort to give PRO-specific recommendations for trial protocols (131). The variable set for outcome analysis should be dynamic and ideally subjected to continuous evaluation and modification.

Many patient-reported instruments are developed using psychometric methods based on assumptions that scales are to be estimates of a *true score.* They also assume that the observed score conveys information about the latent variable of interest (for example QoL), and that there is a consistent relationship between them. However, the assumption that quality of life (*and* scores) is consistent and comparable across individuals and over time is debatable. Ideally, with longitudinal measurement, you must take into account the intrinsic processes of differences in appraisal and response shift regarding the actual construct. For assessment of non-observable characteristics or concepts, there cannot be a 'true' measure because they are not observable (126)*;* instead they are multidimensional and the true score is likely contingent over time (130).

Convergent validity and inter-rater reliability are considered low for many patient-reported outcomes, but the whole purpose of many patient-reported outcomes (such as HRQoL or recovery) is to tap into the subjective experience otherwise undetected and not to establish a link to observed performance (criterion validity) (130). In essence, patient-reported outcomes are the purest form of data about the patient's health, satisfaction, quality of life or applied functional status (39).

To determine whether a change in health status is meaningful and desirable, a result of significant difference in outcome (for example a MID) must to be put into the context of the duration of that change and the cost of achieving the

outcome. This information is not usually encompassed within the patient-reported outcome measure or instruments. It needs to be discussed with knowledge about the bigger perspective of clinical management, resource consumption and implication for the individual patients and society at large. That interventions with positive effects on recovery are of individual importance and essential in the aspects of patient care are intuitive. In addition, for a large patient group such as breast cancer survivors, even small differences in, for example, recovery can have big implications when combined for a large number of patients.

Recovery is a complex evolving journey into survivorship, and the progress relies on the individual's ability to see opportunities. In other words, being recovered does not necessarily imply that you are free of symptoms or impairments, but rather that you have developed a way of handling them in order to lead a fulfilling life. Recovery is a matter of regaining command over your life, control over symptoms and difficulties (33). The use of different outcome measures of recovery in this thesis are intended to reflect the different entities of this broad concept: patient-reported recovery, aesthetic outcome, length of stay, complication load, health-related quality of life and sick leave. The different measures of outcome can be regarded as pieces of a puzzle, where all pieces are equally important for completing the picture.

5.2 When and how to improve outcome

The survival rates for breast cancer have reached high levels, reflecting a highly successful adaption of research knowledge into advancements in clinical care. The medical evolution experienced during the last half century has been remarkable. Impressive technical advancements, a fast-growing research body and improved professional comprehension have facilitated more elaborate procedures and advanced treatments, traditionally delivered to passive recipients. The effect of treatment on the disease has been extensively evaluated using set outcomes, but the effect of treatment on the patient has rarely been considered, other than as adverse events. The objective to evaluate patient-reported outcomes to grasp the actual impact of treatment on the individual is a landmark of medical evolution. As of last year (2020), patient-reported outcomes are included in the Swedish Quality Register for Breast Cancer (NKBC) to mark the tilt in the medical paradigm.

Hand-in hand with the idea of evaluating long-term patient-reported outcome on life goes identifying risk factors and adapting our (surgical) treatment strategies to alleviate or avoid detrimental patient outcome. The aim to optimize the patient's status before surgery, as opposed to managing treatment side-effects, is revolutionary within the medical field from a historic viewpoint.

Increased physical activity is a world-wide ambition at the population level. Physical activity prehabilitation as a tool to improve outcome for patients undergoing cancer treatment is of increasing interest. In a meta-analysis of physical activity during adjuvant treatment, improvements were seen for fatigue, cardiorespiratory fitness, emotional-, physical- and social function, as well as anxiety and health-related quality of life. However, many of the included studies displayed heterogeneity and bias, which the authors acknowledge as they call for caution when interpreting the results, especially regarding oncological outcome (103). A systematic review by Yang et al. revealed benefits of prehabilitation on upper extremity recovery after breast cancer surgery (30) but apart from this there is a lack of knowledge.

All preoperative interventions are challenging, as the target is to start treatment for breast cancer within 28 days of referral due to suspicion, with 14 days allocated to diagnostic procedures and 14 days are set aside for planning and starting treatment. Oncological considerations were not primarily the reason for the standardized care pathways, but rather a political will to diminish regional differences in diagnostics and treatment for cancer patients within Sweden. Still, improved fitness has been seen after just 2 weeks of intervention (132). Self-managed interventions (home-based) are less researched but were preferred by one third in a recent study (92). Advantages include flexibility, lower costs and the possibility to engage a larger group with otherwise limited access. Drawbacks are lack of adherence and missing peer- and/or staff support, though a systematic review revealed comparable results when home-based and center-based interventions for cardiac rehabilitation were compared (133).

From our results where a prehabilitation intervention with physical activity did not significantly impact any of the outcomes studied, together with the limited research to support this (103), we believe that non-supervised physical activity used as a single intervention in this patient group as a whole is insufficient for improved outcome. In the future perspective, prehabilitation should be considered as a structured person-centered possibility for combined interventions. Ideally it supports patients to regain control, independence and to improve their outcome.

5.2 Designing future studies

With increased incidence of breast cancer and improved survival rates, the number of women survivors is growing. To fully comprehend the magnitude of treatment impact on survivorship, understanding based on well-designed studies assessing relevant clinical outcomes including patient-reported outcomes is essential. This will assist professionals and supply patients with correct information for transparent and informed decision-making in a real-life setting.

In the light of the limited health resources available, conducting clinically relevant and applied studies to expand our knowledge into real action, becomes increasingly important. The PhysSURG-B was a large pragmatic trial, with a simple intervention reflecting the national and international recommendations considering physical activity given to all members of society (134). If effective, the intervention could be applicable and suitable for the majority of patients in everyday clinical practice with a minimal economic burden. Previous studies have shown that perceived short-term benefits yield higher motivation, confidence and priority among patients to actually increase their physical activity compared to long-term benefits (92). Short-term outcomes important during treatment combined with those for survivorship, as well as the modest intervention, were chosen with this in mind.

The drive to produce significant and positive results can easily interfere with research integrity. During the review process of publishing our negative results (Paper III-V) we received many suggestions on how we could adjust our protocol to achieve the desired (positive) results. More extensive supervised interventions, adding objective forms of measurement, or additional per-protocol analysis including responders in the control group were suggested. These explorative proposals to make results conform with the hypothesis are a threat to basic research values. The intention should be to explore your posed research question, not to design studies or interventions to obtain the sought-after results. These proposed adaptions of our protocol could possibly have given us a significant result but would not have answered the question of whether a recommended physical activity intervention (commonly used to advocate increased physical activity on both population and patient group level) had an effect. Interventions that are only manageable in selected cohorts of motivated patients, or within the setting of a study, have limited use and the aim should be to produce research results valid in a real-life context.

The future of breast cancer care is possibly "precision medicine", with individually tailored treatment pathways, but little is published about what patients actually want or need, and how to evaluate these outcomes properly. When we have this information, we can use the knowledge to carefully select the suitable patient for the appropriate surgical procedure in a well-timed manner. In addition, we can add interventions to overcome factors predictive of demanding future problems following the treatment period, in order to optimize the care for each patient.

Multimodal targeted interventions are probably more effective since risk behaviors tend to be clustered (92). Multiple approaches that are timely and efficient can tackle pooled problems and possibly achieve synergistic effects on outcome (105) but are more difficult to study. In a research framework it is difficult to expose the treatment integrity for complex packages of interventions, and how to evaluate these combined interventions is debatable (126). These interventions must be paired with the correct set of preferably standardized outcome variables to enable clinical follow-up and research.

Furthermore, to assure individuals access to these future bespoke care pathways in a resource demanding scenery is presumed challenging. A proposed strategy can be found in Macmillan Cancer Support where they postulate a general "risk screening" of patients undergoing treatment. The interventions are then added in a step-wise manner, starting with basic recommendations to all, and successively escalating the interventions to target groups with higher risk levels for complications and worsened outcome (135). From our results, we can add to this that mere recommendations are unlikely to achieve the desirable result and should be combined with other efforts.

We, as medical professionals and researchers within the field of breast cancer care, are experiencing a paradigm shift with the attention turned to patient-experienced outcomes after treatment as the real objective for guiding breast cancer care and future research. As the former US Secretary of Defense Robert McNamara reportedly said:

"The challenge is to make the important measurable,
not the measurable important".

6. Conclusion

Patient-reported outcomes add information when evaluating breast cancer treatment. An objective evaluation of aesthetic results after breast-conserving surgery using a digital tool correlated to long-term health-related quality of life. To improve future surgical treatment this knowledge can be used to aid in surgical planning and development of new surgical techniques.

Modern breast cancer surgery is associated with few complications, a high level of recovery, and low impact on short-term and long-term health-related quality of life.

Recommending non-supervised aerobic physical activity before and after breast cancer surgery did not improve clinical or patient-reported outcomes in the setting of a large, randomized trial.

Previous mental health problems and low FACT-B score at baseline in combination with younger age and adjuvant chemotherapy were predictors for prolonged recovery measured as sick leave after breast cancer treatment.

7. Future perspective

Based on previous knowledge and in keeping with our findings regarding the harmful effect of chemotherapy, improved selection of patients who truly benefit from chemotherapy is expected to have the largest beneficial impact for improving future survivorship after breast cancer treatment. In addition, with proper screening of individuals at risk who are subjected to adjuvant chemotherapy, tailored targeted multimodal supportive interventions should be possible.

Predictive factors could be used to identify patients with anticipated prolonged recovery and/or sick leave or reduced health-related quality of life. To identify vulnerable patients, in addition to knowledge about age and adjuvant chemotherapy, we suggest asking patients about previous mental health problems and identifying patients with anticipated poor aesthetic outcome.

To validate our predictive model for sick leave, a randomized setting is needed, where a prehabilitation program compared to usual care in the group of patients anticipated to experience the greatest benefit could be investigated. Mobile or web-based applications, tracking devices for physical activity and on-demand endorsement from health-care providers can be used to improve outreach (71), adherence and hopefully outcome.

A harmonized set of key outcomes and measurements that reflects both the treatment given and the effect on the patients´ lives should be included in clinical breast cancer evaluation and trials to ensure high-quality output. Future comprehensive care of breast cancer patients is anticipated to involve individually tailored treatment based on identified risk factors. Patient-reported outcomes of importance to the individual's narrative should be a cornerstone for all cancer treatment evaluation.

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"Who knows what women can be when they are finally free to be themselves".
Betty Friedan

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