The Extent of Late-Term Impairments Among Danish Breast Cancer Survivors and the Treatment of Shoulder-Related Impairments

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Preface

The research presented in this PhD thesis was carried out during my time as a PhD-fellow at the Department of Physio- and Occupational Therapy, Vejle Hospital – University Hospital of Southern Denmark and Department of Regional Health Research, University of Southern Denmark between 2019-2025. This work focused on the nationwide extent of late-term impairments after primary breast cancer in Denmark and the treatment of shoulder related late-term impairments. The motivation for pursuing this area stems from my experience as a physiotherapist working with the target group. Figures 1, 2, 4, 5, 8, 11, and 12 included in this PhD thesis were created using images or vectors from Colourbox.com. Any adaption of figures or tables from the manuscripts that form the basis of this PhD thesis is explicitly highlighted.

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I am deeply grateful and honored to have collaborated with many highly skilled individuals who have supervised and inspired me over the past six years. Their support has enabled me to advance my academic expertise in clinical practice research, and fuelling my commitment to improving the treatment of late-term impairments among breast cancer survivors.

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Thirdly, I would like to send a huge acknowledgement to my statisticians: Associate Professor Lonny Stokholm for your exceptional knowledge in design, data management and statistical analyses within registry research. Your very structured approach and the way to simplify e.g. complex statistician language was really inspiring and something I will take with me in my academic career; and Professor Robin Christensen for your impressive expertise and great knowledge in designing, analysing and reporting of high quality research, including randomised trial designs. I really enjoyed your passion and your humorous support.

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Fifthly, a special thank you to the panel from the Patient and Relatives Council (PPR) from Vejle Hospital for your time to evaluate the questionnaire and provided indescribable important feedback; and thank you to the Shoulder Sector to perform the individual intervention treatment. Furthermore, thank you to the data manager from Open Patient data Explorative Network (OPEN) who assisted in setting up the questionnaire in the Research Electronic Data Capture (REDCap), and provided the computer generated randomisation list. Furthermore, I would like to send a huge acknowledge to all the Danish breast cancer survivors who spent their time to participate in the nationwide questionnaire, which gave unique and important knowledge on late-term impiarments.

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Finally, I want to express my deepest gratefulness to my nearest family, especially my amazing husband and our two beautiful little boys. Your love and immense support have been crucial in getting me where I am today.

Kim Michéle Feder, Physiotherapist, MScPH

Abbreviations

ALND	Axillary Lymph Node Dissection
AR	Absolut Risk
A-ROM	Active Range Of Motion
BCS	Breast-Conserving Surgery
BFI	The Brief Fatigue Inventory
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CPR	Danish Civil Person Registration
DNPR	Danish National Patient Registry
GPE	Global Perceived Effect
ICD10	International Classification of Diseases, 10th version
IQR	InterQuartile Range
ITT	Intention-To-Treat
LYMF-ICF-DK	The Lymphedema Functioning, Disability and Health
NRS	Numerical Rating Scale
OPEN	Open Patient data Explorative Network
OR	Odds ratio
P-ROM	Passive Range Of Motion
QuickDASH	The Quick Disabilities of Arm, Shoulder and Hand
REDCap	Research Electronic Data Capture
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan

SD	Standard Deviation
SE	Standard Error
SLNB	Sentinel Lymph Node Biopsy
SPADI	Shoulder Pain and Disability Index
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Table of Contents

Studies included in this PhD thesis

This PhD thesis is based on the following manuscripts of *Study I to IV*:

***Study I*. A nationwide cross-sectional survey study**

Feder KM, Ingwersen KG, Rahr HB, Egebæk HK, Stokholm L, Lautrup MD. *Specification of Self-Reported Late-Term Impairments 3-7 Years after Primary Breast Cancer Treatment: A Nationwide Cross-Sectional Study among Danish Breast Cancer Survivors.* J Cancer Surviv. 2025. DOI: https://doi.org/10.1007/s11764-025-01815-3

***Study II*. A national cohort study**

Feder KM, Stokholm L, Rahr HB, Ingwersen KG*/Lautrup MD*. *Risk Factors Associated with Self-Reported Late-Term Impairments 3-7 Years after Primary Breast Cancer Treatment: A Nationwide Cohort Study among Danish Breast Cancer Survivors*. *Shared last authors. Manuscript (submitted, under review at Journal of Cancer Survivorship). May 2025.

***Study III*. Protocol for a randomised controlled trial**

Feder KM, Rahr HB, Lautrup MD, Egebæk HK, Christensen R, Ingwersen KG. *Effectiveness of an Expert Assessment and Individualised Treatment Compared with a Minimal Home-Based Exercise Program in Women with Late-Term Shoulder Impairments after Primary Breast Cancer Surgery: Study Protocol for Randomised Controlled Trial.* Trials. 2022;23(1):701. DOI: https://doi.org/10.1186/s13063-022-06659-1

***Study IV*. Primary and secondary outcomes from the randomised controlled trial**

Feder KM, Lautrup MD, Nielsen SM, Egebæk HK, Rahr HB, Christensen R, Ingwersen KG. *Effectiveness of an Individualised Treatment Plan Compared with a Standard Exercise Programme in Women with Late-Term Shoulder Impairments after Primary Breast Cancer Treatment: A Randomised Controlled Trial*. Acta Oncologica. 2025;64:448-457. DOI: https://doi.org/10.2340/1651-226X.2025.42737

English Abstract

Introduction

Breast cancer is the most common cancer among women worldwide, with 2.3 million new cases in 2022. In Denmark, approximately 5,000 women are diagnosed annually, and due to mammography screening and improved both surgical and oncological treatments, the 5-year survival rate has reached 90%. This highlights the need to address breast cancer survivors' long-term quality of life (QoL) and late-term impairments such as shoulder impairment, lymphedema, fatigue, and chemotherapy-induced neuropathy, which affect up to 50% of survivors even up to 10 years post-treatment.

Nationwide data on the prevalence of late-term impairments and severity of these are unknown, since standard evaluation or treatment of late-term impairments in Danish hospitals is not routinely offered. Furthermore, it is unknown to what extent the Danish hospitals systematically take care of late-term impairments. Previous studies on late-term impairments have been small with selected samples, focused on specific surgical methods or single impairments. In fact, to date no comprehensively primary studies examined risks across multiple late-term impairments based on Danish standard treatments for breast cancer in a nationwide cohort study. Additionally, there is an evidence-based knowledge gap on shoulder rehabilitation strategies for breast cancer survivors. Given the diagnosis age of ≤62 years, with many still active in the workforce, improving shoulder management is essential for both patient well-being and societal benefits.

Aim and Objectives

The overall aim was to investigate the nationwide prevalence and severity of common self-reported late-term impairments, and the treatment of shoulder impairments. The specific study objectives were:

Study I. To describe characteristics of Danish women treated for primary breast cancer, the prevalence and severity of self-reported late-term impairments, and the registration of these impairments in the Danish National Patient Registry.
Study II. To investigate the association between Danish standard treatments for breast cancer and their risk of self-reported late-term impairments 3-7 years postoperatively.
Study III. To develop and describe a study protocol with explicit details for a randomised controlled trial that compared an individualised treatment with standardised home-based exercises based on a pamphlet in women with late-term shoulder impairments 3-7 years after primary breast cancer treatment.
Study IV. To assess the clinical effects on shoulder pain and disability symptoms of an expert assessment followed by an individualised treatment (Intervention Group; *IG*), compared with standardised home exercises based on a pamphlet (Control comparator Group; *CG*) in women with late-term shoulder impairments 3-7 years after primary breast cancer treatment.

Materials and Methods

Study I. A cohort of 9,927 women was invited to participate in a nationwide questionnaire focusing on late-term impairments such as shoulder impairment, lymphedema, fatigue, and chemotherapy-induced neuropathy. The severity of these late-term impairments was evaluated by using validated patient-reported scales. Clinical characteristics and diagnostic codes related to "late-term effects" were extracted from the Danish National Patient Registry.

Study II. A national cohort study of 5,729 women who underwent surgical treatment for primary breast cancer between 2015-2019 and completed a questionnaire addressing late-term impairments 3-7 years postoperatively; shoulder impairment, lymphedema, fatigue, and chemotherapy-induced neuropathy. The breast cancer treatments followed Danish standard treatments for surgery and radiotherapy, and were extracted from the Danish National Patient Registry. Logistic regression analyses, adjusted for

potential confounders, were used to analyse the data, complemented by absolute risk calculation.

Study III. A study protocol was designed and described for a stratified, assessor-blinded, parallel-group randomised controlled trial comparing an individualised treatment with standardised home exercises based on a pamphlet in women with late-term shoulder impairments 3-7 years post-treated. This study protocol included considerations on study design, setting and locations, inclusion and exclusion criteria, interventions, recruitment procedure, randomisation and allocation concealment, blinding, outcomes, data collection, data management, sample size and power consideration, and statistical methods.

Study IV. Participants were randomly assigned to receive either an individualised treatment based on an expert assessment or a 12 week standardised home-based exercise program based on a pamphlet. The primary outcome was the between-group difference of 8 points on change in the Shoulder Pain and Disability Index (SPADI) overall score (range 0 [best] to 100 [worst]) from baseline to 12 weeks follow-up. Data were analysed using a mixed model for repeated-measurements.

Results

Study I. The response rate was 60.9%, with 6,046 responders. On average, responders were 57 years old at the time of surgery, and 53.5% had a lower education level. Additionally, 62.7% were married, 56.7% had a Body Mass Index ≥25, and 54.4% reported one or more co-morbidities. Overall, 60.7% of responders reported late-term impairments related to their breast cancer treatment. The most commonly reported late-term impairments were shoulder impairment (75.3%), fatigue (56.9%), chemotherapy-induced neuropathy (49.6%), and lymphedema (26.3%). On average, 58.0% women reported their late-term impairments as moderate to severe on validated patient-reported scales. Despite the high self-reported rates, impairments were rarely recorded in the Danish National Patient Registry; lymphedema with 1.3%, fatigue with 0.2%, and both shoulder impairment and chemotherapy-induced neuropathy with 0.1%.

Study II. Compared to breast-conserving surgery (BCS) with SLNB and radiotherapy, neither mastectomy with sentinel lymph node biopsy (SLNB) without radiotherapy, nor BCS and SLNB without radiotherapy increased the odds ratio (OR) of late-term impairments. However, all other treatment combinations were associated with higher risk of self-reported late-term impairments: BCS with axillary lymph node dissection (ALND) and radiotherapy (ORadj 2.76, 95% CI: 2.25–3.39), mastectomy with SLNB and radiotherapy (ORadj 3.10, 95% CI: 2.48–3.88), and mastectomy with ALND and radiotherapy (ORadj 2.90, 95% CI: 2.02–4.15). Among all standard treatments for breast cancer, shoulder impairment consistently represented the late-term impairment with the highest absolute risk.

Study III. Not applicable (n/a)

Study IV. A nationwide questionnaire sent to 9,927 women yielded a 60.9% response rate (6,046 complete replies). Of these, 195 women met eligibility criteria, e.g. shoulder impairments, and consented to further contact. All 195 were contacted by the primary investigator, but 164 declined participation. Ultimately, 31 women were enrolled, randomised, and analysed: 16 in the individualised treatment group (∼*IG*) and 15 in the standardised home-based exercises group (∼*CG*).

The mean age among the 31 randomised participants was 56.0 years. In relation to the primary outcome there was no effect on SPADI overall score after 12 weeks, comparing the individualised treatment -10.5 and the standardised home-based exercises -14.4, corresponding to a between-group difference of -3.9 points ([95% CI -11.9 to 4.1; *P*=0.34]). Regarding the secondary outcomes, no significant differences were found at 12 weeks between *IG* and *CG* for SPADI pain (-3.5 points, 95% CI: -14.6 to 7.6, *P*=0.53) or SPADI function (-4.0 points, 95% CI: -11.0 to 3.1, *P*=0.26). However, some other secondary outcomes favoured CG, including GPE (-1.0 points, 95% CI: -1.8 to -0.2, *P*=0.01), A-ROM flexion (22.9°, 95% CI: 4.38 to 41.29, *P*=0.02), A-ROM abduction (40.5°, 95% CI: 6.77 to 74.23, *P*=0.02), and P-ROM abduction (44.5°, 95% CI: 5.91 to 83.09, *P*=0.02). No other significant differences were observed across active and passive movements or numeric rating scales (NRS). Clinical response (≥18 points SPADI overall

improvement) was observed in 31% of *IG* participants and 27% of *CG* participants.

Conclusion

Over 60% of Danish breast cancer survivors reported moderate to severe late-term impairments 3–7 years post-treatment, yet these were rarely recorded in the Danish National Patient Registry. This points to an underutilisation of specialized treatment or insufficient diagnostic coding, leaving breast cancer survivors may be overlooked by the Danish secondary healthcare. Therefore, increased focus should be on organizational structures within the Danish hospitals to facilitate timely detection and treatment of these late-term impairments. In order to assist physicians and therapists in this, it is important e.g. to differentiate the late-term impairments and understand the risks associated with Danish standard treatments.

The national cohort study revealed increased risk of self-reported late-term impairments among women who underwent mastectomy and SLNB with radiotherapy, mastectomy and ALND with radiotherapy, or BCS with ALND and radiotherapy, with shoulder impairment being the most common issue. Furthermore, shoulder impairment had the highest absolute risk across all standard treatment types. Surprisingly, only 13% of eligible women with shoulder impairment participated in the randomised trial, possibly due to reluctance to revisit their cancer experience, acceptance of impairment as inevitable, or busy schedules.

The randomised trial found no significant difference between individualised and standardised home-based exercises approaches based on SPADI overall scores after 12 weeks. However, secondary outcomes, including GPE, A-ROM flexion, A-ROM abduction, and P-ROM flexion, suggested potential benefits of the standardised home-based exercise approach. As the trial was underpowered, these results are inconclusive but could hold clinical relevance, supporting continued efforts to enhance shoulder rehabilitation for breast cancer survivors.

Dansk Resumé

Introduktion

Brystkræft er den mest almindelige kræftform blandt kvinder på verdensplan, med 2,3 millioner nye tilfælde i 2022. I Danmark diagnosticeres cirka 5.000 kvinder årligt, og takket være mammografiscreening og forbedrede kirurgiske og onkologiske behandlinger, er 5-års overlevelsesraten nået op på 90%. Dette understreger behovet for at fokusere på brystkræftoverleveres langsigtede livskvalitet og senfølger såsom skulder-dysfunktion, lymfødem, træthed og kemoterapi-induceret neuropati, der rammer op til 50% af overleverne, selv op til 10 år efter behandlingen.

Der mangler data om den nationale forekomst af senfølger og sværhedsgraden heraf, da evaluering eller behandling af senfølger ikke rutinemæssigt tilbydes på danske sygehuse. Desuden vides det ikke, i hvilket omfang danske sygehuse systematisk håndterer senfølger efter brystkræft. Tidligere undersøgelser om senfølger har været små med udvalgte stikprøver, fokuseret på specifikke kirurgiske metoder eller enkelte senfølger. Faktisk har ingen undersøgelser hidtil omfattende undersøgt risici på tværs af flere senfølger baseret på de danske behandlingsretningslinjer for brystkræft i et landsdækkende kohortestudie. Derudover mangler der evidensbaseret viden om rehabiliteringsstrategier for skulder-dysfunktion blandt brystkræft-overlevere. Med en alder ved brystkræftdiagnosen på ≤62 år, hvor mange stadig er aktive på arbejdsmarkedet, er det afgørende at forbedre skulderbehandling, for både patienternes velbefindende og ud fra et samfundsøkonomisk perspektiv.

Formål

Det overordnede formål var at undersøge den landsdækkende forekomst og sværhedsgrad af almindelige selvrapporterede senfølger samt behandlingen af skulder-dysfunktion. De specifikke formål var:

Studie I: At beskrive karakteristika for danske kvinder behandlet for primær brystkræft, undersøge forekomsten og sværhedsgrad af selvrapporterede senfølger samt registreringen af disse i Landspatientregisteret (LPR).
Studie II: At undersøge sammenhængen mellem danske standardbehandlinger af brystkræft og deres risiko for selvrapporterede senfølger 3-7 år postoperativt.
Studie III: At designe og beskrive en studieprotokol med eksplicitte detaljer for et randomiseret kontrolleret forsøg, der sammenlignede en individualiseret behandling med standardiserede hjemmeøvelser baseret på en pjece, til kvinder med senfølger i skuldrene 3-7 år efter primær brystkræftbehandling.
Studie IV: At vurdere de kliniske effekter på skuldersmerter og funktionsnedsættelser. En ekspertvurdering efterfulgt af en individualiseret behandlingsplan (~interventionsgruppen, *IG*) sammenlignet med standardiserede hjemmeøvelser baseret på en pjece (~kontrolgruppen, *CG*) til kvinder med senfølger i skuldrene 3-7 år efter primær brystkræftbehandling.

Materialer og Metoder

Studie I. En kohorte på 9.927 kvinder blev inviteret til at deltage i en landsdækkende spørgeskemaundersøgelse med fokus på senfølger såsom skulder-dysfunktion, lymfødem, træthed og kemoterapi-induceret neuropati. Sværhedsgraden af disse senfølger blev vurderet ved brug af validerede patientrapporterede spørgeskemaer. Kliniske karakteristika og diagnosekoder relateret til "senfølger" blev hentet fra LPR-registeret.

Studie II. Et nationalt kohortestudie som omfattede 5.729 kvinder, der blev kirurgisk behandlet for primær brystkræft mellem 2015-2019 og udfyldte et spørgeskema om senfølger 3-7 år postoperativt, herunder skulder-dysfunktion, lymfødem, træthed og kemoterapi-induceret neuropati. Behandlingerne fulgte danske retningslinjer for kirurgi og strålebehandling. Disse blev fundet i LPR-registeret. Data blev analyseret ved hjælp af logistiske regressionsanalyser justeret for potentielle confoundere. Derudover blev en absolut risiko beregning foretaget.

Studie III. En studieprotokol blev designet og beskrevet til et stratificeret, assessor-blinded, parallelt randomiseret kontrolleret forsøg, der sammenlignede individualiseret behandling med standardiserede hjemmeøvelser udleveret i en pjece til kvinder med senfølger i skuldrene 3-7 år efter brystkræftbehandling. Studieprotokollen omfattede overvejelser om studiedesign, setting og lokationer, inklusions- og eksklusionskriterier, interventioner, rekrutteringsprocedurer, randomisering og allokering, blinding, outcomes, dataindsamling, datastyring, stikprøvestørrelse, styrkeberegning samt statistiske metoder.

Studie IV. Deltagerne blev tilfældigt tildelt enten den individualiserede behandling baseret på en ekspertvurdering eller et 12-ugers standardiseret hjemmeøvelsesprogram baseret på en pjece. Det primære outcome var forskellen mellem grupperne på 8 point i ændring i Shoulder Pain and Disability Index (SPADI) samlede score (skala 0 [bedst] til 100 [værst]) fra baseline til 12 ugers opfølgning. Data blev analyseret ved hjælp af en mixed model for gentagne målinger.

Resultater

Studie I. Responsraten var 60,9% med 6.046 respondenter. Gennemsnitsalderen ved operationen var 57 år, og 53,5% havde et lavt uddannelsesniveau. Derudover var 62,7% gift, 56,7% havde et Body Mass Index på ≥25, og 54,4% rapporterede én eller flere komorbiditeter. Samlet set rapporterede 60,7% af respondenterne senfølger relateret til brystkræftbehandling. De hyppigst rapporterede senfølger var skulder-dysfunktion (75,3%), træthed (56,9%), kemoterapi-induceret neuropati (49,6%) og lymfødem (26,3%). Blandt disse rapporterede 58,0% deres senfølger som værende moderate eller alvorlige ud fra validerede patientrapporterede spørgeskemaer. Trods de høje selvrapporterede scoringer blev senfølger sjældent registreret i LPR-registeret: lymfødem (1,3%), træthed (0,2%), skulder-dysfunktion (0.1%) og kemoterapi-induceret neuropati (0,1%).

Studie II. Sammenlignet med brystbevarende kirurgi (BCS) og SLNB med strålebehandling, øger mastektomi og lymfeknude-biopsi (SLNB) uden strålebehandling eller BCS og SLNB uden strålebehandling ikke odds ratio (OR) for senfølger. Dog var alle andre behandlingskombinationer forbundet med højere risiko for selvrapporterede senfølger: BCS og aksilrømning (ALND) med strålebehandling (ORadj 2,76, 95% CI: 2,25–3,39), mastektomi og SLNB med strålebehandling (ORadj 3,10, 95% CI: 2,48–3,88), og mastektomi med ALND og strålebehandling (ORadj 2,90, 95% CI: 2,02–4,15). Blandt alle behandlingskombinationer var skulder-dysfunktion konsekvent den senfølge med den højeste absolutte risiko.

Studie III. Ikke relevant

Studie IV. Et landsdækkende spørgeskema sendt ud til 9.927 kvinder opnåede en responsrate på 60,9% (~6.046 fuldstændige svar). Af disse opfyldte 195 kvinder inklusionskriterierne, fx at opleve skulder-dysfunktion, og gav samtykke til yderligere at blive kontaktet. Alle 195 blev kontaktet via en telefonsamtale, men 164 afslog deltagelse. I alt blev 31 kvinder inkluderet, randomiseret, allokeret og analyseret: 16 kvinder i den individualiserede behandlingsgruppe (~*IG*) og 15 i gruppen for standardiserede hjemmeøvelser (~*CG*).

Gennemsnitsalderen blandt de 31 randomiserede deltagere var 56,0 år. I forhold til det primære outcome var der ingen effekt på SPADI overall score efter 12 uger, hvor den individualiserede behandling havde -10,5 og standardiserede hjemmeøvelser -14,4, svarende til en forskel mellem grupperne på -3,9 point ([95% CI -11,9 til 4,1; *P*=0,34]). Vedrørende de sekundære outcomes var der 12 uger efter ingen signifikante forskelle mellem *IG* og *CG* for SPADI-smerte (-3,5 point, 95% CI: -14,6 til 7,6, *P*=0,53) eller SPADI-funktion (-4,0 point, 95% CI: -11,0 til 3,1, *P*=0,26). Dog favoriserede nogle sekundære outcomes *CG*, som var GPE (-1,0 point, 95% CI: -1,8 til -0,2, *P*=0,01), A-ROM fleksion (22,9°, 95% CI: 4,38 til 41,29, *P*=0,02), A-ROM abduktion (40,5°, 95% CI: 6,77 til 74,23, *P*=0,02), og P-ROM abduktion (44,5°, 95% CI: 5,91 til 83,09, *P*=0,02). Ingen andre signifikante forskelle blev observeret for aktive og passive bevægelser eller på samtlige NRS-scoringer. Klinisk respons, som karakteriseres ved en individuel

forbedring med ≥18 point på SPADI´s samlet score, blev observeret hos 31% i *IG* og 27% i *CG*.

Konklusion

Over 60% af danske brystkræftoverlevere rapporterede moderate til alvorlige senfølger 3–7 år efter behandling. Disse blev sjældent registreret i LPR-registeret. Dette tyder på enten en manglende udnyttelse af specialiseret behandling eller utilstrækkelig registrering af relevante diagnosekoder, hvilket kan medføre, at brystkræftoverlevere overses i det danske sundhedsvæsen. Fremadrettet bør der være et øget fokus på organisatoriske strukturer på danske sygehuse for at fremme rettidig opsporing og behandling af disse senfølger. For at støtte læger og terapeuter er det vigtigt f.eks. at differentiere senfølger og forstå risici forbundet med standardiserede behandlingsretningslinjer i Danmark.

Den landsdækkende kohorteundersøgelse viste øget risiko for selvrapporterede senfølger blandt kvinder, der havde gennemgået mastektomi og SLNB med strålebehandling, mastektomi og ALND med strålebehandling eller BCS og ALND med strålebehandling. Skulder-dysfunktion var den mest almindelige senfølge og havde den højeste absolutte risiko på tværs af alle behandlingstyper. Overraskende deltog kun 13% af de kvalificerede kvinder med skulder-dysfunktion i det randomiserede kontrollerede forsøg, muligvis på grund af tilbageholdenhed over for at genbesøge deres kræftforløb, accept af ubehaget som uundgåeligt eller travle hverdage.

Det randomiserede forsøg fandt ingen signifikant forskel mellem individuel og standardiseret hjemmeøvelsestiltag baseret på SPADI overall score efter 12 uger. Dog viste sekundære resultater, såsom GPE, aktiv bevægelighed (A-ROM) ved fleksion og abduktion samt passiv bevægelighed (P-ROM) ved fleksion, potentielle fordele ved det standardiserede hjemmeøvelsestiltag. Da forsøget var underestimeret, er resultaterne inkonklusive, men de kan have klinisk relevans, hvilket understøtter fortsat indsats for at forbedre skulderrehabilitering for brystkræftoverlevere.

Introduction

Primary breast cancer

Primary breast cancer refers to the initial occurrence of malignant cells growth in the breast tissue. The condition often originates within the ducts (ductal carcinoma) and less often in the lobules (lobular carcinoma) (**Figure 1**).

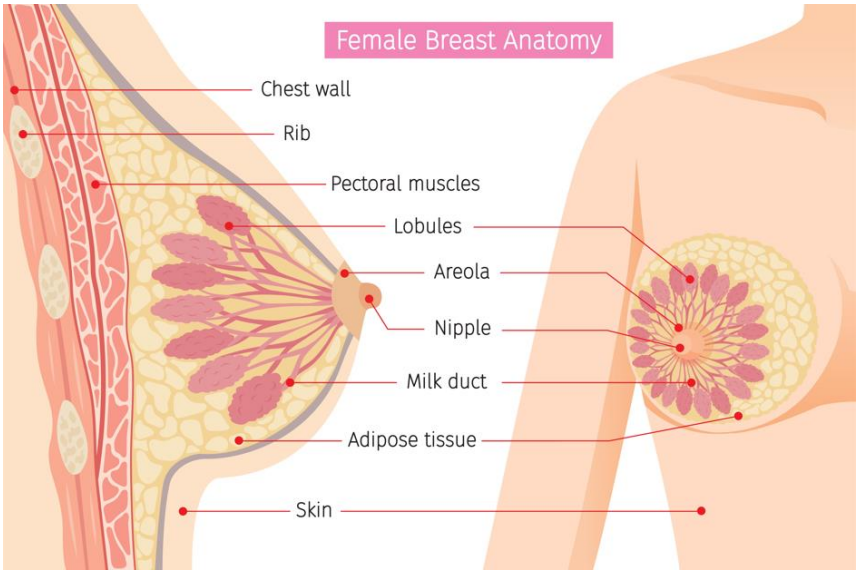


Figure 1. The female breast anatomy with area of ductal (milk duct) and lobular (lobules) carcinoma.

Table 1 gives a description of the pre-stage and types of breast cancer. The *Ductal Carcinoma In Situ (DCIS)* is a precursor to breast cancer, is non-invasive, and constitutes approximately 10%[1]. The *Invasive Ductal Carcinoma (IDC)* is the most common type of breast cancer with around 80%, followed by the *Invasive Lobular Carcinoma (ILC)* at almost 10%[1].

Over 80% of breast cancer is sensitive to the hormone estragon, *ER-positive*[2,3]. *HER2-positive* cases constitute around 10%[2]. *Triple negative* cases make up the remaining percentages of 10%[1-2]. This subtype

is more aggressive that lacks estragon, and HER2 receptors, and is treated accordingly[1,3]

Table 1. An overview of pre-stage and types of breast cancer

Type	Ductal Carcinoma In Situ (DCIS)	Invasive Ductal Carcinoma (IDC)	Invasive Lobular Carcinoma (ILC)
Percentage	**10%**	**80%**	**10%**
Description	A non-invasive form confined to the ducts of the breast, and is considered a pre-cursor to breast cancer	An invasive form of breast cancer originating in the milk ducts and invades surrounding breast tissue	An invasive form of breast cancer and starts in the milk-producing lobules
Receptor status		ER+ [a] or ER- in combination with HER2+[b] or HER-	ER+ [a] or ER- in combination with HER2+[b] or HER-

[a]Estrogen Receptor-positive is a form of breast cancer driven by the hormone estrogen[1,3].
[b]Human epidermal growth factor 2 positive is an invasive form of breast cancer driven by overexpression of the HER2 protein and tend to grow more quickly[1,3].

Epidemiology

Breast cancer is the most common cancer among women globally, with nearly 2.3 million new cases reported in 2022[4]. In Denmark around 5,000 women are diagnosed annually with breast cancer[5]. The age of a woman diagnoses with breast cancer is 62 years[1]. Half of the women are ≤62 years at the time of diagnosis[1], representing a large working-age population.

Risk factors

The risk factors of developing breast cancer includes genetic predispositions, hormonal influences (e.g. prolonged exposure to estrogen), and lifestyle factors (e.g. physical inactivity, obesity, alcohol consumption)[1,6].

Diagnosis and treatments

The diagnosis involves a combination of clinical examination, imaging (e.g. mammography, ultrasound and MR-scanning) and biopsy for histopathological confirmation[1].

Standard surgical treatment is breast-conserving surgery (BCS) or mastectomy (remove part or all of the breast) in combination with sentinel lymph node biopsy (SLNB) (removal of lymph node tissue for examination under a microscope) or axillary lymph node dissection (ALND) (remove lymph nodes in the armpit)[7]. The choice between BCS or mastectomy depends on the tumour size relative to the breast and its location. During breast cancer surgery, a SLNB is conducted to assess whether cancer has spread to the axillary lymph nodes. If cancer cells are found in the sentinel lymph node, it is likely, they have spread to other lymph nodes, can necessitating an ALND. The presence of cancer cells or micrometastases in the sentinel lymph node also determines the need for radiotherapy or not[8].

Oncological treatment strategies are dependent on the type (e.g. IDC), receptor status (e.g. ER-positive and HER2-status), tumor size, lymph node status, age, and menopause status[7-9]. Common oncological treatments include radiotherapy, chemotherapy, and endocrine therapy[8-9]. Endocrine therapies e.g Tamoxifen or Letrozole, can give musculoskeletal pain and accelerate bone density loss increasing the risk of osteoporosis and fractures[10-11]. Breast cancer survivors often receive Zoledronic acid to reduce the risk of breast cancer recurrence[11]. Furthermore, Zoledronic acid has a preventive effect against bone metastasis dissemination[11] and is also used as an osteoporosis treatment[12].

The Danish Breast Cancer Cooperative Group (DBCG)

The DBCG was founded in 1976 by the Danish Surgical Society to standardise and improve breast cancer diagnosis and treatment nationwide. Since its inception, DBCG has developed evidence-based treatments for diagnostics, surgery, radiotherapy, and systemic therapy. These standard treatments are continuously refined through randomised trials and quality-control studies[13].

Other treatments

Scarring, radiotherapy damages and axillary web syndrome are examples that can arise from surgical and oncological treatment for breast cancer. Early physiotherapy has a role in accommodate these issues and providing preventive rehabilitation against the development of late-term impairments[8]. A typical physiotherapeutic treatment includes manual treatments and specific upper limb exercises. Manual treatment therapy defines as techniques such as mobilise, stretching and manipulate tight tissue and joints, to improve tissue extensibility, and increase range of motion (ROM). Specific exercise therapy involves strength, resistance and cardio training, to restore musculoskeletal movement and function[8].

Prognosis

Due to early detection, advances in mammography screening, and improved surgical and oncological treatments[7,9], the 5-year survival rate for breast cancer in Denmark is 90%[14], while less than 25% experience breast cancer recurrence (local or disseminated breast cancer)[15]. The improved survival, emphasize the focus on these women´s long-term quality of life (QoL) and the growing importance addressing of late-term impairments after treatment.

Late-term impairments

Several studies have shown that surviving primary breast cancer often is related to physical late-term impairments such as shoulder impairment e.g. shoulder pain and functional disabilities[16-18], arm lymphedema[16-19], cancer-related fatigue[16,20-22] and chemotherapy-induced neuropathy[8,16,23]. These late-term impairments may persist for up to 10 years after treatment[16-17,23-25], and have a negative impact on QoL for breast cancer survivors including physical, psychological and social domains[22,24-28]. Physical impairments can e.g. affect reintegration into work[29] or disrupt a normal life in performing daily activities[17-18,26]. The physical late-term impairments typically were investigate in a selected sample, focused on a specific late-term impairment and compared with either a specific surgical treatment[16,19-20] such as ALND

versus SLNB on lymphedema or a specific patient related factor e.g. age or BMI.

With a background as a physiotherapist specialising in the musculoskeletal system, this PhD thesis focuses on four specific physical late-term impairments. Although a range of late-term impairments can occur after breast cancer treatment, these four were chosen because they are both prevalent and clinically relevant within physiotherapeutic practice[8]. Furthermore, they represent areas where physiotherapists have tools to address and potentially improve these impairments from a physiotherapy perspective.

The extent of late-term impairments

Persistent pain after breast cancer treatment, often occurs in the breast, armpit, shoulder or arm[8]. Persistent pain and functional disabilities of the upper limb affect up to 50%, up to 10 years post-treatment[8,16-17,19,23,27]. Additionally, both pain and decreased function has an impact on women's QoL[26,27], and hindering return to work of these women[29]. Arm lymphedema, resulting from lymph node dissection and radiotherapy develops gradually[19,30] and affects up to 17% of patients[16,19]. The prevalence of fatigue and chemotherapy-induced neuropathy are common in up to 30% of breast cancer survivors[8,16,21,23]. These late-term impairments require extensive physical and emotional rehabilitation to improve survivors' well-being[18,26].

Risk factors for late-term impairments

Late-term impairments following breast cancer treatment are influenced by various factors related to the type of surgical and oncological treatment and patient-related factors.

Surgical and oncological treatments

Surgical procedures such as mastectomy, especially in combination with ALND, pose a greater risk of impaired shoulder function, affected neuromuscular tissue and development of lymphedema[16]. ALND have been found to be significantly associated with lymphedema[16], as it disrupts the

lymphatic pathways, leading to chronic swelling and mobility problems[30]. Combinations of surgery and oncological treatment also increase the risk of chronic late-term impairments[8,16,20,31]. The combination of e.g. mastectomy with radiotherapy has been shown to increase the risk of lymphedema[16] and chronic shoulder dysfunction[31-33]. These impairments are due to muscle fibrosis, nerve damage or scarring[31-33].

Radiotherapy, chemotherapy and endocrine therapy are often given to reduce risk of recurrence and to improve long-term survival[7,9], but impairments are connected with these oncological treatments. Radiotherapy can cause muscle fibrosis, nerve damage, and vascular changes, contributing to shoulder stiffness and impairing muscle function, and chronic pain[31-33]. The extent of these effects often depends on the dose and area of treatment[32-33]. Chemotherapy has been found to influence fatigue[20,22] and chemotherapy-induced neuropathy[16], while endocrine therapy such as Tamoxifen and Letrozole is known to contribute to musculoskeletal conditions[10-11].

Patient-related factors

Marital status in relation to having a partner (were married) decreased the risk for fatigue[20-21]. Younger age (<50 years) revealed a significant association with persistent, more severe pain and chemotherapy-induced neuropathy[16,23], loss of muscle strength, decrease shoulder function[16] and fatigue[16,21]. On the other hand older age (≥50 years) was found with higher risk for lymphedema[19], ROM-deficit and functional decline[16]. A Body Mass Index (BMI) ≥25 was associated with increased risk for lymphedema[16,19], functional disabilities in the shoulder[16-17] e.g. decreased range of motion (ROM)[16], and fatigue[21]. Furthermore, comorbidities can exacerbate the severity of late-term impairments. Comorbidities were significantly associated with developing of lymphedema[16]. Among shoulder impairment, can e.g. rheumatoid arthritis influence the shoulder pain and functional disabilities[34]. Furthermore, psychological factors such as depression and anxiety[25,28] can intensify the perception of pain and fatigue, contributing to reduced QoL[21].

Rehabilitation of shoulder impairments

Early postoperative exercises improve upper limb impairments immediately after breast cancer treatment[35-37]. However, research has largely focused on arm lymphedema[16,19,38], leaving a considerable knowledge gap in understanding chronic shoulder impairments, which affect up to 50% of breast cancer survivors up to 10 years post-treatment[8,16-17,27]. Optimal rehabilitation strategies for this group remains unclear[18,36,39-40], despite their importance for the many survivors, with a diagnosis age of ≤62 years[1], who remain in the workforce.

The rehabilitation need are considered complex since they vary widely based on type of surgery, oncological treatments, postoperative complications and individual pathophysiological response, highlighting the importance of tailored approaches[18,36,39-40]. Yet, evidence-based treatments for advanced and individualised rehabilitation are lacking[18,29,36,39].

Standard evaluation or treatment of late-term impairments in Danish hospitals is not routinely offered to breast cancer survivors, resulting in a lack of knowledge about the extent, what type, frequency and what effect treatments have on late-term impairments among Danish breast cancer survivors. Late-term shoulder impairments in breast cancer survivors can to some extent, resemble ordinary shoulder impairments traditionally treated in Danish hospitals. In Denmark, patients with persistent non-cancer-related shoulder issues are typically referred to specialised orthopaedic departments for expert assessment and individualised treatment. To increase success of implementation of organisational pathways for referral and treatment, one can benefit from utilizing existing treatment options. Therefore, the interventions in this PhD project were based on existing treatments in Denmark.

Definition of late-term impairments in this PhD

All late-term impairments in this PhD thesis are self-reported and collected among women who were operated and treated for primary breast cancer between January 1, 2015 and December 31, 2019. This corresponded to experienced late-term impairments 3-7 years postoperatively. The question that was asked in relation to late-term impairments was the following:

Do you experience impairments after your breast cancer treatment (e.g. fatigue, swelling, pain, a feeling of tension or stiffness, tightness or sensory disturbance in the breast, shoulder or arm)?

If present, women indicated which of specific four dimensions they experience; shoulder impairment, lymphedema, fatigue and chemotherapy-induced neuropathy. Lastly, women identified their two most bothersome late-term impairments among the specific four dimensions, and these two impairments were the basis for the following PhD studies.

Self-reported shoulder impairment

The definition on self-reported shoulder impairment involves the impact on shoulder pain and functional disabilities, based on the question about experiencing pain or tightness/stiffness in the breast and shoulder area (due to e.g. scarring, radiotherapy or axillary web syndrome) (**Table 2**).

Self-reported lymphedema

The definition on self-reported lymphedema includes a chronic swelling in the arm and/or breast area, due to lymphatic system damage, and is based on the question about experiencing swelling or a feeling of heaviness (due to lymphedema) (**Table 2**).

Self-reported fatigue

The definition on self-reported fatigue focuses on cancer-related fatigue, and is based on the question about experiencing tiredness from their breast cancer treatment (**Table 2**).

Self-reported neuropathy

The definition on self-reported neuropathy involves chemotherapy-induced neuropathy affecting the peripheral nervous system, and is based on the question about experiencing sensory disturbance due chemotherapy (**Table 2**).

Table 2. An overview of the definition and the questions among self-reported late-term impairments included in this PhD thesis.

Self-reported late-term impairments	Definition	Questions in the questionnaire
Self-reported shoulder impairment	The impact on shoulder pain and functional disabilities	Do you experience pain or tightness/stiffness in the breast and shoulder area due to e.g. scarring, radiotherapy or axillary web syndrome?
Self-reported lymphedema	A chronic swelling in the arm and/or breast area, due to lymphatic system damage	Do you experience swelling or a feeling of heaviness due to lymphedema?
Self-reported fatigue	Cancer-related fatigue	Do you experience tiredness due to your breast cancer treatment?
Self-reported neuropathy	Chemotherapy-induced peripheral neuropathy	Do you experience sensory disturbance due chemotherapy (e.g. tingling, numbness and persistent pain)?

Rationale for this PhD thesis

The extent

Firstly, little is known about the nationwide prevalence and severity of self-reported late-term impairments, despite the high prevalence affecting up to 50%[8,16] of breast cancer survivors and persisting for up to 10 years post-treatment[16-17,23-25]. This raises the question of whether the four selected late-term impairments truly represent a significant problem in terms of severity. Additionally, it remains unclear to what extent Danish hospitals address these impairments, as routine evaluation or treatment for late-term impairments is not standard practice for breast cancer survivors in Denmark.

Risk factors

Secondly, previous research on late-term impairments has often focused on small, selective samples or specific surgical methods or oncological treatments related to a single late-term impairment[16,19-20], such as the association between ALND versus SLNB and lymphedema. To date, no population-based studies have comprehensively examined the risks of multiple physiotherapeutically relevant late-term impairments simultaneously. Furthermore, no studies have differentiated these four specific late-term impairments across standard guideline treatments for breast cancer in a national cohort. This gap highlights the need to identify specific high-risk groups to better prevent particular late-term impairments.

Treatment

Thirdly, optimal shoulder rehabilitation for breast cancer survivors remains uncertain[18,36,39-40], highlighting a considerable knowledge gap. With a diagnosis age of ≤62 years[1], many women remain active in the workforce[1], underscoring the need for evidence-based rehabilitation to enhance shoulder management and improve both individual and societal outcomes. This knowledge has motivated efforts to provide effective rehabilitation for women who have already developed severe shoulder impairments at a late stage, ensuring they receive needed support.

Aim and Objectives

The overall aim of this PhD thesis was to investigate the nationwide prevalence and severity of four common self-reported late-term impairments observed in physiotherapeutic practice, risk factors associated with self-reported late-term impairments, and the treatment of shoulder impairments. The specific objectives of the studies in this PhD thesis were:

Study I
To describe characteristics of Danish women treated for primary breast cancer, the prevalence and severity of self-reported late-term impairments, and the registration of these impairments in the Danish National Patient Registry.

Study II
To investigate the association between Danish standard treatments for breast cancer, and their risk of self-reported late-term impairments 3-7 years postoperatively.

Study III
To develop and describe a study protocol with explicit details for a randomised controlled trial that compared an individualised treatment with standardised home exercises based on a pamphlet in women with late-term shoulder impairments 3-7 years after primary breast cancer treatment.

Study IV
To assess the clinical effects on shoulder pain and disability symptoms of an expert assessment followed by an individualised treatment (Intervention Group; *IG*), compared with standardised home exercises based on a pamphlet (Control comparator Group; *CG*) in women with late-term shoulder impairments 3-7 years after primary breast cancer treatment.

Materials and Methods

Study I-IV in this PhD thesis are described in the following section. As the data is based on a national questionnaire survey, there is some overlap between the studies. **Figure 2** provides an overview of how the PhD projects are connected.

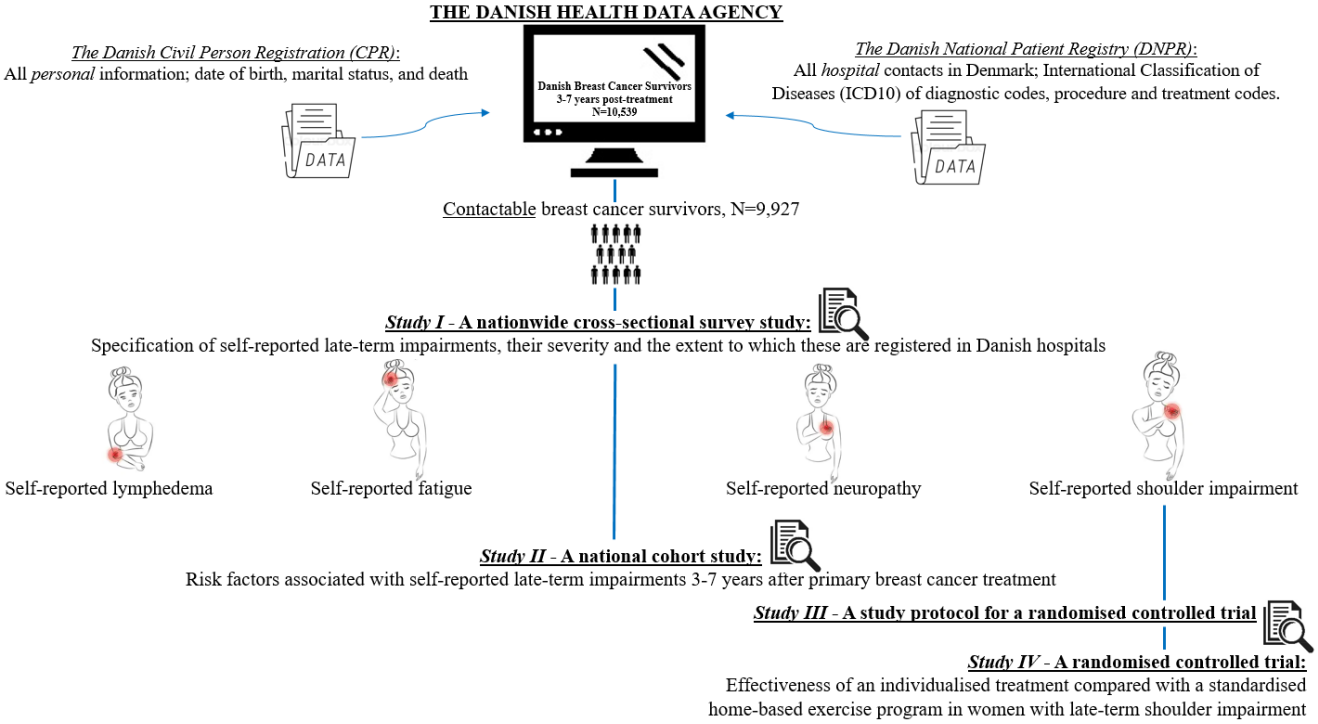


Figure 2. An overview of how the PhD projects are connected.

Ethics, study registration, and reporting

Relevant permission to conduct *Study I-IV* in this PhD thesis was obtained from The Health Research Ethics Committee of the Region of Southern Denmark *(*May 13, 2020, *Project-ID: S-20200021)* and from The Danish Data Protection Agency *(Journal-nr.: 19/16321)* according to The Danish Act on Processing of Personal Data*.* Approval to access and contact the study population was granted by The Danish Health Data Agency *(FSEID-00005599)(Study I).*

The Danish Health Data Agency provided and securely stored a full CPR- and DNPR extract containing relevant personal data and breast cancer treatment details *(FSEID-00005920)(Study I & II)*, and ensuring secure linkage with the collected questionnaire data for confidential processing. The questionnaire was hosted on a secure server by Open Patient Data Explorative Network (OPEN). All answers collected in *Study I* were handled with strict confidentiality and stored in a Research Electronic Data Capture (REDCap) database[41], while the management and analyses were performed on a secure server at the Danish Health Data Agency. To comply with data protection regulations, each participant was assigned a unique ID-number in the REDCap-database, ensuring pseudo-anonymity[42]. Furthermore, permission was obtained from The University of Texas MD Anderson Cancer Center[43], to use the Danish version of the validated patient-reported scale, the Brief Fatigue Inventory (BFI), in *Study I.*

All answers and measurements collected in *Study IV* were also also handled with strict confidentiality and stored in the REDCap database, OPEN[41]. Participants were assigned ID numbers in the REDCap database to ensure pseudo-anonymity, with personal data kept separate from main data for confidentiality. For analysis, encrypted data were uploaded to a password-protected server (Region of Southern Denmark) in compliance with data protection standards. Furthermore, *Study IV* was prospectively registered on ClinicalTrials.gov (March 11, 2022; NCT05277909)[44] to ensure transparency and minimize selective outcome reporting. The statistical analysis plan (SAP) (**Appendix 1**) were published

on ClinicalTrials.gov prior the initiating any analyses for Study IV (October 31, 2022)[44].

All procedures within this PhD thesis adhered to the ethical standards and principles for research involving human participants in accordance in The Helsinki Declaration[42]. All participants received information and provided written informed consent prior to enrolment, acknowledging that participation was voluntary and that they could withdraw their consent at any time without affecting their current or future treatment rights (**Appendix 2**).

Study I-IV were reported in agreement with relevant reporting guidelines, to accommodate the quality and transparency of health research[45]. *Study I & II* followed the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guideline[46], *Study III* the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[47] checklist, and *Study IV* the Consolidated Standards of Reporting Trials (CONSORT)[48].

Study population

The Danish Health Data Agency identified the study population, using data from the Civil Person Registration (CPR) system and the Danish National Patient Registry (DNPR). The CPR system provides *personal* details such as date of birth, marital status, and death[49]. The DNPR records all *hospital* contacts in Denmark, including diagnostic codes based on International Classification of Diseases; 10th version (ICD-10)[50,51], procedure and treatment codes[50]. Due the Danish secondary healthcare system is tax-funded, all healthcare services, including breast cancer treatments, must be registered in the DNPR whenever a woman interacts with Danish hospitals[50].

Female breast cancer patients were included in this study population if they had underwent surgery for primary breast cancer (ICD10 C50*), including breast-conserving surgery (BCS) or mastectomy, along with sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) between January 1, 2015, and December 31, 2019. Participants were required to be between 18 and 71 years old at the time of surgery.

Women were excluded if they had underwent bilateral breast cancer surgery, undergone primary or secondary breast reconstruction at any time, if the tumour was fixed to the thoracic/chest wall, if it had spread outside of the breast and/or armpit, or if the woman had cancer recurrence. **Figure 3** gives an overview of the inclusion and exclusion criteria with corresponded registry codes.

Figure 3. Inclusion and exclusion criteria with corresponded registry codes.

Setting

Women extracted by the Danish Health Data Agency were electronically invited to participate in a nationwide questionnaire survey on late-term impairments, including shoulder impairment, lymphedema, fatigue, and chemotherapy-induced neuropathy. All self-reported data were collected between 3 to 7 years after the primary breast cancer treatment. The questionnaire was sent out from Vejle Hospital, University Hospital of Southern Denmark, from March 3, 2022, to May 5, 2022. Reminders were sent on March 7 and March 11, 2022.

Since women still answered the questionnaire after the second reminder, the access to the questionnaire was finally ended on May 5, 2022. A total of 9,927 contactable women were invited to participate in a nationwide cross-sectional survey study (*Study I*), which will be described below. **Figure 4** provides an overview of the women's response rate.

Responders and non-responders

In this PhD thesis women were classified as responders when a complete or partly completed questionnaire returned. Non-responders were women who were invited but did not reply.

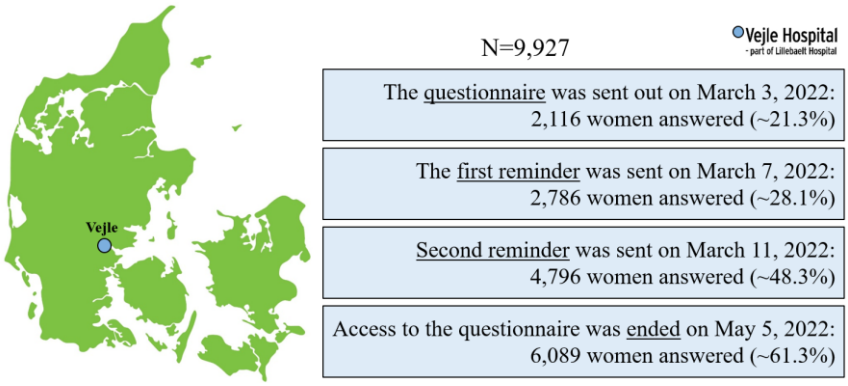


Figure 4. An overview of the period during which the questionnaire was sent out, along with the response rate expressed as a percentage.

Study I

Study I is a nationwide cross-sectional survey study of Danish breast cancer survivors, integrating data from high-quality Danish national registries[50,52]. A total of 9,927 women were invited to complete a questionnaire on late-term impairments, including shoulder impairment, lymphedema, fatigue, and chemotherapy-induced neuropathy. The severity was measured using validated patient-reported scales. Clinical characteristics of breast cancer survivors and diagnostic codes for "late-term effects" were extracted from the Danish National Patient Registry (**Figure 5**).

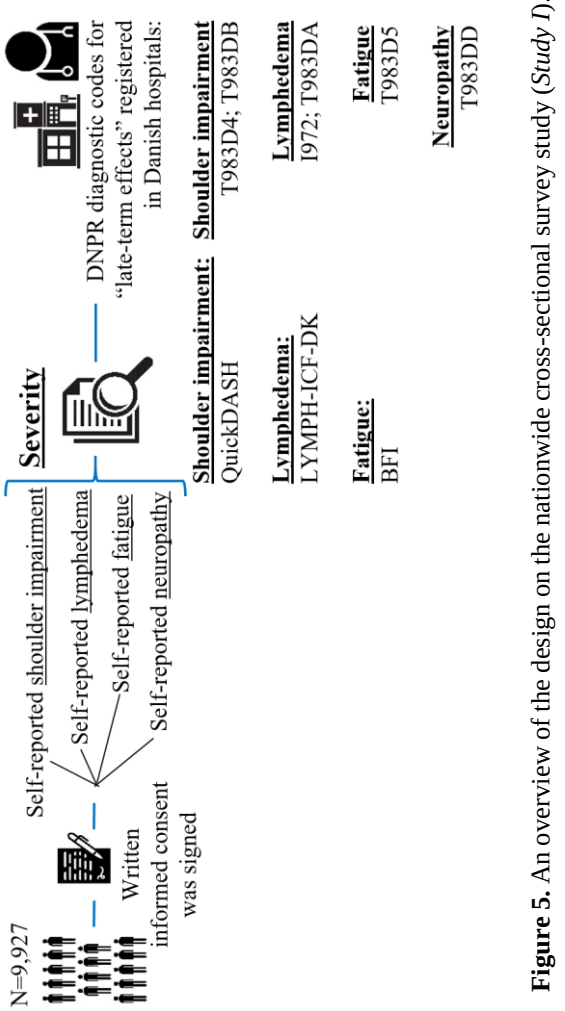


Figure 5. An overview of the design on the nationwide cross-sectional survey study (*Study I*).

Data source

The questionnaire

The self-administered questionnaire included questions on socio-demographics and breast cancer related late-term impairments in four dimensions: shoulder impairment, lymphedema, fatigue, and chemotherapy-induced neuropathy, incorporating validated patient-reported scales. The definition on the four late-term impairment dimensions are described at page 27-29.

The questionnaire was developed by a research group consisting of the primary investigator, the supervisors related to this PhD thesis, and experts within questionnaire development, breast surgeons and oncological physiotherapists. Furthermore, the research group thoroughly tested and reviewed the questionnaire to identify and correct any typographical errors, ensure proper functioning of automatic data validation, and verify the branching logic. Data validation and branching logic was e.g. ensured through limitations in questions with entering numeric values, and checkbox solutions. Following this, eight members of the Patient and Relatives Council (PPR) at Vejle Hospital, University Hospital of Southern Denmark, assessed the questionnaire's functionality, time requirements, and content. They specifically evaluated its suitability for individuals with a history of breast cancer, ensuring that no content could be perceived as insensitive. Feedback was provided both in writing and through follow-up discussions via phone or in person. Based on their input, the questionnaire was revised for clarity and enhanced with a more user-friendly layout.

In Denmark, every person has access to a secure digital mail account; e-Boks[53]. However, elderly citizens can be exempt to its use. The invitation to participate in this nationwide cross-sectional survey was sent via e-Boks and included a link to the questionnaire. Women without access to e-Boks were not invited. All women were required to actively click the "Yes"-box to agree to participate in this nationwide cross-sectional survey study before they may answer the questionnaire.

Variables

Register-based and self-reported characteristics

To obtain a broad view of the characteristics of Danish breast cancer survivors, both register-based and self-reported information were collected, and is listed in the table below (**Table 3**).

Table 3. Register-based and self-reported information collected during *Study I*.

Register-based characteristics	**Content**
Age at the time of surgery	Median with InterQuartile Range
Geographical place of treatment	The North Denmark Region Central Denmark Region Region of Southern Denmark Capital Region of Denmark Region Zealand
Type of surgical treatment	BCS, mastectomy, SLNB, ALND
Complications	Skin necrosis, wound infection, hematoma, seroma puncture
Type of oncological treatment	Chemotherapy, endocrine, radiotherapy
Received physiotherapy	During and after breast cancer treatment
Marital status	Single, married, divorced, widow
Self-reported characteristics	**Content**
Whether the affected arm was the dominant arm used in daily life	Yes/no
Highest attained educational level	Short, medium, long
Employment	Salaried, self-employed, sick leave, retired
Co-habitation status	Living alone, living together
Children	No children/pregnant for the first time, children living at home, children living on their own, children living at home and living on their own
Body Mass Index (BMI)	Calculated from height and weight (kg/m^2)

Alcohol consumption	0 units/week, 1-7 units/week, 8-14 units/week, ≥ 15 units/week
Smoking habits	Non smoker, previous smoker, current smoker
Co-morbidities	Allergy (not asthma), hypertension, cardiovascular disease, neurological disorder, chronic lung disease, diabetes (type 1 or 2), osteoporosis, migraine or frequent headaches, herniated disc, back/neck disorder, osteoarthritis, rheumatoid arthritis, multiple sclerosis, mental disorders and/or stress (less than 6 months), and mental disorders and/or stress (more than 6 months). The co-morbidity variable was classified by numbers of comorbidities (besides breast cancer) as 0, 1, 2, and 3+.
Pain medication due late-impairments	Yes/no, type and frequency
Women had to resigned from work due to shoulder late-term impairments	A follow-up question when a woman indicated that she experience shoulder impairment, and currently is not employed

Validated patient-reported scales

The Quick-Disabilities of Arm, Shoulder and Hand (QuickDASH), the Lymphedema Functioning, Disability and Health (LYMF-ICF-DK) and the Brief Fatigue Inventory (BFI) were used to assess the severity of self-reported shoulder impairment, lymphedema and fatigue. All women who participated in this nationwide cross-sectional survey study were required to answer the three validated patient-reported scales.

The QuickDASH is a validated and reliable, generic patient-reported questionnaire specific for assessing shoulder and other upper limb impairments over the past week[54-55]. It includes 11-items (3 for symptoms, 8 for function), scored on a Likert scale from 1 (no difficulty) to 5 (extreme

difficulty)[54-56]. Each item score is weighted equally, and the total score is calculated as a percentage, with higher scores indicating greater impairment[56]. Generally, there is no standard classification for the score division. For this study, QuickDASH scores were classified based on baseline averages among individuals with similar persistent shoulder impairments as this study population[57-58]: <20 (mild discomfort in the upper limb), ≥20-40 (moderate discomfort in the upper limb), and >40 (severe discomfort in the upper limb). In addition to being used to assess the degree of self-reported shoulder impairment, QuickDASH was also used to recruit participants for the randomised controlled trial described in the section *"Study IV; Participants"*, page 49.

The LYMF-ICF-DK questionnaire is a valid and reliable tool for assessing self-reported impairments in Danish breast cancer patients with arm lymphedema[59-60]. In this study, the first 7 questions (domain 1) from the LYMF-ICF-DK were used to evaluate the degree of lymphedema and its impact on physical function[60]. Other parts of the LYMF-ICF-DK were not included, due to overlap with the QuickDASH questionnaire. Scores range from 0 (not at all) to 10 (a lot), with a total percentage score calculated[59-60]. Based on World Health Organization (WHO) taxonomy, impairments were classified as: <25 (mild impairments in physical function), ≥25-50 (moderate impairments in physical function), and >50 (severe impairments in physical function)[59-60].

The Brief Fatigue Inventory (BFI) is a valid and reliable questionnaire for assessing cancer-related fatigue and its impact on daily functioning within the past 24 hours[43]. The BFI includes 9 questions rated on an 11-point scale (0 = no fatigue, 10 = most severe level of fatigue)[22,43]. Each item score is weighted equally, and the total score is summed into a percentage, with higher scores indicating greater fatigue, classified as: <40 (mild fatigue), ≥40-80 (moderate fatigue), and >80 (severe fatigue)[22,43].

Registration in the DNPR

Diagnostic codes for "late-term effects" registered in Danish hospitals were extracted from the DNPR. These included codes for shoulder impairment, lymphedema, fatigue and chemotherapy-induced neuropathy (**Table 4**).

Table 4. DNPR codes for "late-term effects", registered in Danish hospitals.

"Late-term effects"	**DNPR code**	**Definition**
Shoulder impairment	T983D4	Chronic pain after cancer treatment
	T983DB	Symptoms of musculoskeletal conditions after cancer treatment
Lymphedema	I972	Lymphedema after mastectomy
	T983DA	Lymphedema after cancer treatment
Fatigue	T983D5	Fatigue after cancer treatment
Neuropathy	T983DD	neuropathy after cancer treatment

Study II

Study II is a national cohort study of 5,729 women who underwent surgical treatment for primary breast cancer between 2015-2019 and completed a questionnaire on late-term impairments 3-7 years postoperatively; shoulder impairment, lymphedema, fatigue, and chemotherapy-induced neuropathy. Breast cancer treatments, adhering to Danish standard treatments for surgery and radiotherapy, were identified through the Danish National Patient Registry. Logistic regression analyses, adjusted for potential confounders, were used to analyse data, and supplemented with an absolute risk calculation (**Figure 6**).

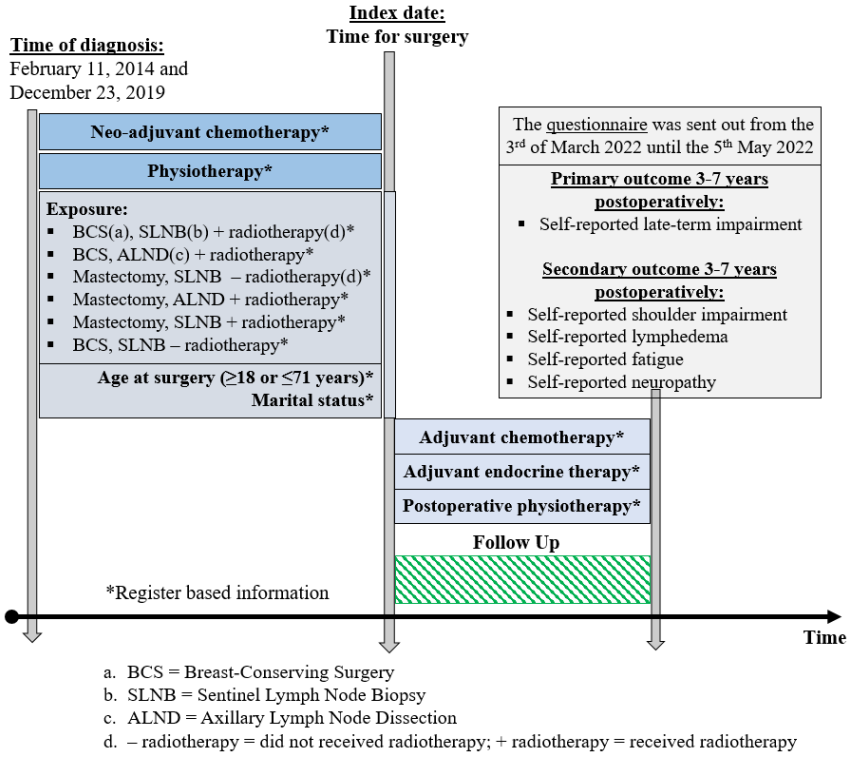


Figure 6. An overview of the design on the national cohort study (*Study II*).

Study population

The study population for this national cohort study was derived from the group identified by the Danish Health Data Agency (**Figure 3**, page 36). Women were eligible if they underwent breast cancer surgery; BCS or mastectomy with SLNB or ALND between January 1, 2015, and December 31, 2019, and were aged 18-71 at the time of surgery.

Exclusion criteria included not adhering to Danish standard breast cancer treatments or not answer the question about late-term impairments in the nationwide cross-sectional survey.

Data source

The linkage of questionnaire data and the new DNPR-system

The Danish Health Data Agency undertook two tasks: 1) defining the study population for *Study I* (FSEID-00005599), and 2) storing a *full* CPR- and DNPR extract on their secure server with personal data and breast cancer treatment details for *Study I & II* (FSEID-00005920), while securely linking these to questionnaire data for confidential processing. By using the unique personal identifier, the Central Personal Registration number (CPR)[61], and the Personal Identity Code number (PNR-number)[62] allocated to each citizen in Denmark and serve as key, the Danish Health Data Agency could link data from the nationwide questionnaire with register data on an individual level.

During the inclusion period (2015–2019), the DNPR was updated and transitioned from LPR2 to a new system called LPR3[63]. To address potential data breaches, a *full* LPR extract with a view version was requested to ensure that updated reports among breast cancer treatments were continuously provided.

Variables

Primary and secondary outcomes; Self-reported information

The primary outcome for this national cohort study was self-reported late-term impairments 3-7 years postoperatively (yes/no). If present, the secondary outcomes were further classified into four specific dimensions: shoulder impairment (yes/no), lymphedema (yes/no), fatigue (yes/no) and chemotherapy-induced neuropathy (yes/no). How women who participated in the nationwide cross-sectional survey were asked about late-term impairments, how these impairments are defined, and that this PhD thesis is based on their two most bothersome late-term impairments is described in section "*Definition of late-term impairments in this PhD*", page 27-29.

Exposure; Register-based information

Exposure categories/groups were defined based on the Danish standard treatments for primary breast cancer as follows:

1) BCS and SLNB with radiotherapy
2) BCS and ALND with radiotherapy
3) Mastectomy and SLNB without radiotherapy
4) Mastectomy and ALND with radiotherapy
5) Mastectomy and SLNB with radiotherapy
6) BCS and SLNB without radiotherapy

The last two treatment groups were part of randomised controlled trials conducted during the inclusion period (2015–2019)[64-65]. One trial investigated whether clinically node-negative breast cancer patients with up to two macrometastases in their SLNB could avoid ALND by receiving expanded radiotherapy instead (*group 5*)[64]. The other trial explored whether radiotherapy could be safely omitted for selected low-risk breast cancer patients aged ≥60 years (*group 6*)[65]. These trials were initiated by the Danish Breast Cancer Cooperative Group (DBCG), which develops breast cancer standard treatments in Denmark and seeks to refine existing standards[13]. In total, six treatment groups were defined based on DNPR data with following procedure codes:

- BCS: KHAB40, KHAB40A
- Mastectomy: KHAC20, KHAC25
- SLNB: KPJD42C
- ALND: KPJD42, KPJD52
- Radiotherapy: BWGC5A, BWGC6, BWGC6B, BWGC7, BWGC7A

This study lacks registry data on lymph node metastases. As a result, some women in Group 1 may have received only breast radiotherapy, while others had extended breast and axillary radiotherapy. It is assumed all were treated according to the Danish guideline treatments for breast cancer. Based on this, about one quarter of women in Group 1 had lymph node metastases detected after SLNB. Of these, around two fifths (from January 2015 to October 2016) likely underwent ALND. During the SENOMAC trial's gradual implementation (from November 2016 to 2019), about half of the remaining three fifths of these women likely still underwent ALND, while the rest received extended breast and axillary radiotherapy instead of surgery. This reflects the trial's rollout at Aarhus University Hospital (November 2016), Rigshospitalet (December 2016), and other hospitals

from October 2017[66]. The trial investigates whether patients with up to two macrometastases in the SLNB can avoid ALND and receive extended radiotherapy to the breast and axilla instead[64,66-67]. Consequently, about 7.5% of Group 1 may have received extended breast and axillary radiotherapy without ALND.

Co-variates; Register-based information

The following potential confounders and effect modifiers were extracted from the DNPR and included as covariates:

- Age and marital status
- Type of oncological treatment
  - Chemotherapy (procedure code: BWHA)
  - Adjuvant endocrine therapy;
  Tamoxifen (procedure code: BWHC10)
  Letrozole (procedure code: BWHC12)
  Zoledronic acid (procedure code: BWHB40A)
- Physiotherapy (procedure codes: BTXY, BZFA, ZZ0175X, ZZ0175Y)

Age and marital status were extracted at the time of surgery. The age variable was categorised as above or below 55 years, as the average age of the study population at the time of surgery was 55. Additionally, marital status was divided into married/unmarried. Women who were single, divorced, or widowed were classified as "unmarried." Chemotherapy, endocrine therapy, and physiotherapy were cross-checked with the first registration code were given in the study population. When a registration code was assigned before the time of diagnosis (February 11, 2014), it was deleted, as it had no relation to their breast cancer treatment. When an endocrine therapy code was given before the time for surgery, is was deleted, for the same reason. When a physiotherapy registration code was assigned after 6 months from the time of surgery, it was deleted, as it did not necessarily relate to their breast cancer treatment (**Figure 6**).

Since this study did not focus on the timing of when a treatment was administered, but instead aimed to determine whether a woman respectively received chemotherapy (yes/no), endocrine

therapy (yes/no), or physiotherapy (yes/no), only the first occurring code was included. For the same reason, neo-adjuvant and adjuvant chemotherapy were combined into a single variable, as was the case with the physiotherapy variable. The variable for endocrine therapy included both Tamoxifen and Letrozole codes.

Age and marital status at the time of surgery were considered as potential confounders, since they are associated with the types of surgery (Danish standard treatments) and late-term impairments[16,19-21,23]. Sensitivity analyses were performed to control for these confounders. Chemotherapy, endocrine therapy, and physiotherapy were considered as potential effect modifiers, as they are covariates introduced as additional clinical treatments and have influence on late-term impairment[10-11,16,20,22,35-37]. Subgroup analyses were performed to control for effect modifiers.

Study III

Study III is the study protocol for a randomised controlled trial presented in *Study IV*, comparing an individualised treatment with standardised home exercises based on a pamphlet in women with late-term shoulder impairments 3-7 years post-treated. The protocol outlined details on the study design, setting, inclusion and exclusion criteria, interventions, recruitment process, randomisation and allocation concealment, blinding procedures, outcomes, data collection and management, sample size calculations, power considerations, and statistical analysis methods (**Appendix 3**).

Study IV

Study IV is a stratified, assessor-blinded, parallel-group randomised controlled trial with a 1:1 treatment allocation. Participants randomly assigned to either an individualised treatment based on an expert assessment or a 12-week standardised home exercise program based on a pamphlet. The primary outcome was the between-group difference of 8

points in change of the Shoulder Pain and Disability Index (SPADI) overall score (range 0 [best] to 100 [worst]) from baseline to 12 weeks follow-up. Data analysis was conducted using a mixed model for repeated-measurements.

Setting

This randomised controlled trial was conducted at Department of Physio- and Occupational Therapy and the Orthopaedic Department, Vejle Hospital in Denmark from the 4th of April to the 10th of October 2022.

Participants

In addition to the inclusion criteria already were set in *Study I*, e.g. underwent BCS or mastectomy for primary breast cancer between 2015 and 2019, further eligibility criteria included: 1) a score ≥ 15 on the QuickDASH[54]; 2) living within 75 km of Vejle Hospital, Denmark; and 3) providing written informed consent.

Exclusion criteria included: 1) severe lymphedema (an average score ≥ 70% on the first questionnaire on LYMPH-ICF-DK)[59], 2) previous surgery or fractures in the affected shoulder, 3) ongoing chemo-, endocrine- or radiotherapy, 4) co-morbidities affecting shoulder function (e.g. rheumatoid arthritis, stroke, multiple sclerosis), and 5) other reasons such as pregnancy or inability to comprehend information.

Enrolment procedures

As Danish hospitals do not routinely offer standard evaluation or treatment for late-term impairments, eligible participants were recruited from the nationwide cross-sectional survey (*Study I*) of women treated for breast cancer 3-7 years prior.

Women were automatically assessed for initial eligibility, based upon their survey responses. Eligible women (se inclusion and exclusion criteria opposite), were provided with information about the trial and could give informed consent by actively ticking a box in the survey, allowing to be contacted by phone for further details and potential recruitment to this randomised controlled trial (**Appendix 2**).

Eligible women were contacted based upon a randomised sequence, to minimise bias related to the order of survey responses. Interested participants received detailed electronic information about the trial, including the design and allocation to one of two interventions. The women were recommended taking at least 24 h to consider participation with a relative. Within 24–72 h, the primary investigator followed up by phone, and asked if they wish to participate in this study.

If participants agreed, a baseline assessment appointment was scheduled. A trained secretary at the Department of Physio- and Occupational Therapy handled recruitment to ensure an unbiased process. On the day of the baseline assessment, the secretary obtained written informed consent (**Appendix 2**), after which the primary investigator conducted the baseline assessment. The primary investigator performed also the 12-week follow-up. The secretary randomised then the participants, using the REDCap system to either the intervention group (*IG*) or the control group (*CG*). Randomisation occurred on the same day, with results revealed immediately or communicated via phone the following day.

For *IG* participants, the secretary referred them to the Shoulder Sector (the Orthopaedic Department) for further examination. *CG* participants received an exercise pamphlet. The secretary booked an appointment for follow-up measurements for all participants,12 weeks after the initiating intervention for (*IG*) or pamphlet distribution (*CG*). **Figure 8 & 9** show schematic overviews of the recruitment process and time-points for assessments, while **Figure 10** provides an overview of the different treatment start dates for *IG*.

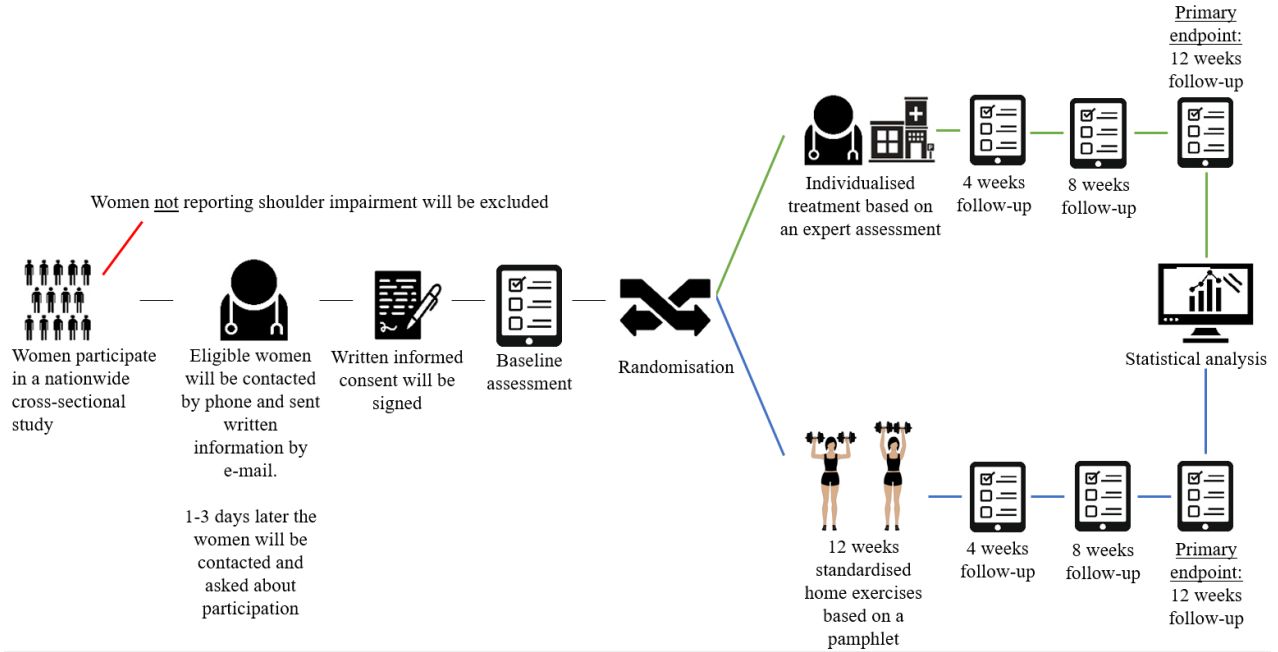


Figure 8. A schematic overview of the recruitment procedure and milestones in *Study IV*.
Intervention group (IG): Individualised treatment plan based on an expert assessment.
Control comparator group (CG): 12 weeks standardised home exercises based on a pamphlet.
Primary outcome: Shoulder Pain and Disability Index (SPADI) at 12 weeks follow-up.
This figure is adapted from the manuscript for *Study III*.

	Enrolment	Baseline	Allocation	Time-point of outcome assessment 4 weeks follow-up	8 weeks follow-up	12 weeks follow-up
ENROLMENT						
Eligibility screen	x					
Written informed consent	x					
Baseline measurements		x				
Allocation			x			
INTERVENTIONS						
Intervention group (*IG*)			→	→	→	
Control comparator group (*CG*)			→	→	→	
ASSESSMENTS:						
Primary Outcome						
1. SPADI overall score		x		x	x	x
Key Secondary Outcomes						
1. SPADI pain		x		x	x	x
2. SPADI function		x		x	x	x
3. Impression of the treatment´s success (GPE)				x	x	x
4. Maximum shoulder pain intensity		x		x	x	x
5. Shoulder pain during general activities		x		x	x	x
6. Shoulder pain at rest		x		x	x	x
7. Shoulder pain during sleep		x		x	x	x
8. Number of treatments received due to shoulder symptom during the trial						x
9. A-ROM in the affected shoulder (flexion/rotation/abduction)		x				x
10. P-ROM in the affected shoulder (flexion/rotation/abduction)		x				x
11. Shoulder pain assessment during flexion/rotation/abduction in the affected shoulder		x				x
12. SPADI clinical responder						x

Figure 9. Overview of the time-points for enrolment, interventions and assessments. This figure is adapted from the manuscript for *Study VI*.

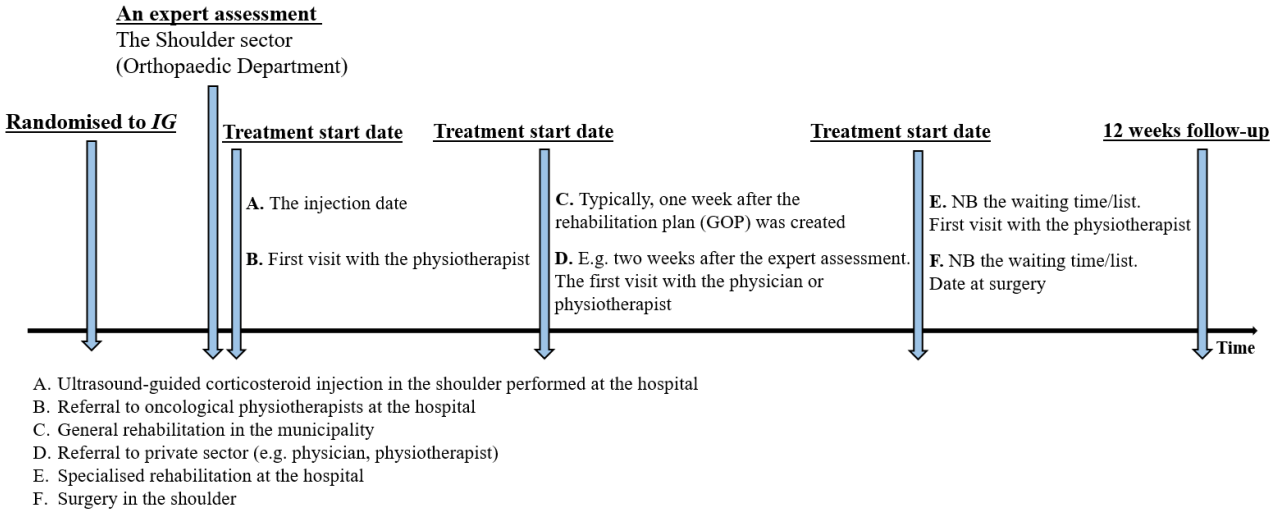


Figure 10. Fictional examples of the different start dates for initiating the treatment in *IG*.

Randomisation, allocation and blinding

Eligible participants were randomly assigned in permuted blocks of 2 to 6, with a 1:1 allocation, using a computer-generated randomisation list implemented in the REDCap system by an independent data manager. Participants were stratified into five groups based on surgery type and radiotherapy status:

1) BCS with SLNB + radiotherapy
2) BCS with SLNB − radiotherapy,
3) BCS with ALND + radiotherapy
4) Mastectomy with SLNB – radiotherapy
5) Mastectomy with ALND + radiotherapy

To ensure allocation concealment, the primary investigator and administrators were blinded to block sizes, as the randomisation code was securely stored in REDCap.

The primary investigator conducting baseline and follow-up assessments was blinded to group allocation. In connection with the 12-week follow-up assessment, the primary investigator was to determine and register in REDCap which group the participant was randomised, before this was revealed (**Appendix 4**). Baseline assessments occurred before randomisation, and participants were asked (both written and oral) not to disclose their assigned intervention during follow-ups to maintain blinding. Due to the study design, participants, the orthopaedic specialists who performed shoulder assessments, and the secretary involved in the interventions were aware of the treatment allocation. However, none of these individuals were involved in data analysis or manuscript preparation.

An independent biostatistician conducted the primary and secondary outcome analyses while remaining blinded to group allocation. Based on blinded results from the ITT-analyses, the trial group developed and signed a consensus statement with two blinded interpretations, publicly released on March 15, 2023 (**Appendix 5**), before unblinding the randomization code, following recommended blinded interpretation procedures[68]. Pre-specified sensitivity analyses and evaluations of serious adverse events (SAEs) were performed after unblinding.

Intervention

There is a lack of evidence-based knowledge regarding effective interventions for managing shoulder impairments as late-term effects of breast cancer treatment[18,36,39-40].

To increase the likelihood of successful implementation of organisational pathways for referral and treatment, it is advantageous to build on existing treatment structures. Therefore, the interventions in this study were based on established treatment pathways for shoulder impairments in Denmark, which are supported by extensive clinical experience.

In Denmark, patients with persistent shoulder complaints are typically referred to specialised orthopaedic departments, such as the one at Vejle Hospital, where they undergo a comprehensive assessment by shoulder experts. Based on this assessment, an individualised treatment plan is developed. This may include specific home-based exercise programs, supervised sessions at the hospital, municipality, or private clinics, corticosteroid injections, or surgical interventions.

Furthermore, exercises used in this study included only exercises that are part of standard physiotherapeutic practice at the hospital and are already routinely provided to the measurement group. This approach ensures the interventions are both clinically relevant and feasible for broader implementation.

The expert assessment of shoulder impairment followed by an individualised treatment (IG)

Participants randomised to the *IG* received an expert shoulder assessment by one of four specialists with 6+ years of experience in diagnosing shoulder impairments, at the Shoulder Sector, Vejle Hospital. Assessments included history, standard clinical shoulder tests[69-71], X-rays, and ultrasonography. Based on results, individualised treatment was decided through shared decision-making with the patient. Treatments typically included physiotherapy referrals (hospital, municipality, or private practice), ultrasound-guided corticosteroid injections, and/or load management advice. A typical physiotherapeutic treatment included manual therapy and

tailored shoulder exercises (e.g., strength, resistance, or cardio), with frequency and muscle focus individualised. IG participants were advised to avoid concurrent treatments during the intervention (**Figure 11**).

The standardised home exercise program based on a pamphlet (CG)
Participants in the *CG* received a pamphlet outlining a standardised home-based exercise program after randomisation (**Appendix 6**). The program included three warm-up exercises, three stretches for the breast and shoulder, one connective tissue displacement, and four rotator cuff strengthening exercises. Participants were advised to perform the mobility exercises (1 set of 5–10 repetitions), stretching exercises (1 set of 30 seconds), and connective tissue displacement (1 set for a few minutes) twice daily, with strength exercises (3 sets of 12 repetitions) once daily. Concomitant treatment was permitted for CG participants during the trial (**Figure 11**).

Both intervention strategies were expected to reduce shoulder pain and improve shoulder function. Participants randomised to *CG* had the opportunity of referral for individual treatment after the trial period, and the opposite for *IG* who had the option to receive the pamphlet.

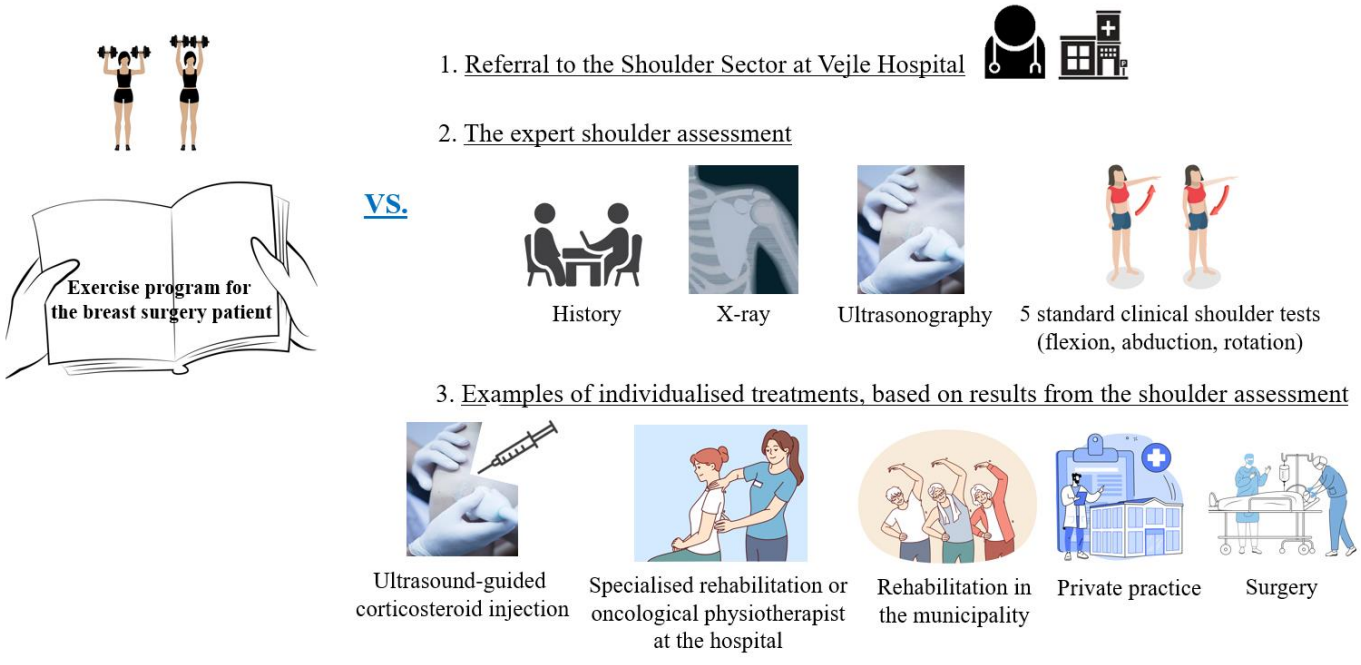


Figure 11. An overview of the two intervention groups.

Outcome

The primary outcome was the change in SPADI overall score, a composite measure of shoulder pain (questions 1-5) and function (questions 6-13) within the last week, ranging from 0 (best) to 100 (worst)[54,72]. SPADI is a valid, reliable[73-74] and specific tool for assessing shoulder impairments and suitable for repeated measures[75]. The primary endpoint was assessed at 12 weeks, with secondary endpoints at 4 and 8 weeks after initiating the treatment.

Key secondary outcomes included mean changes in SPADI pain and function scores (0–100, best to worst) at 0, 4, 8, and 12 weeks; global perceived effect (GPE)[76] (1=better, 2=unaltered, 3=worse) at 4, 8, and 12 weeks; and mean changes in maximum shoulder pain intensity, shoulder pain during general activities, rest, and sleep (Numeric Rating Scale (NRS): 0–10, best to worst)[77] over the previous 24 hours at 0, 4, 8, and 12 weeks. Additionally, changes in active and passive range of motion (A-/P-ROM) for flexion, internal/external rotation, and abduction (degrees, measured via the smartphone inclinometer GetMyROM)[78-82] and pain during these movements (NRS: 0–10) were assessed at 12 weeks.

Participants clinical response to treatment was defined as an improvement of ≥18 points in the SPADI score[75]. Details of how outcome measures were introduced and assessed are available in *Study III* (**Appendix 3)**.

Data collection

A test protocol with standardised guidelines and text for the physical baseline and follow-up assessments was prepared (**Figure 12**)(**Appendix 4**). Baseline characteristics and patient-reported outcomes were collected via online questionnaires. At baseline and the 12-week follow-up, participants completed questionnaires in an undisturbant room at Vejle Hospital. At 4- and 8-week follow-ups, participants received an email with a link to the questionnaires. If they did not respond within three days, a reminder email was sent, followed by a phone call within four days if there was still no response.

To prevent missing responses in patient-reported outcome questionnaires, the "Required Fields" option was activated. Data quality was ensured through answer validation and double data entry of physical performance data in REDCap.

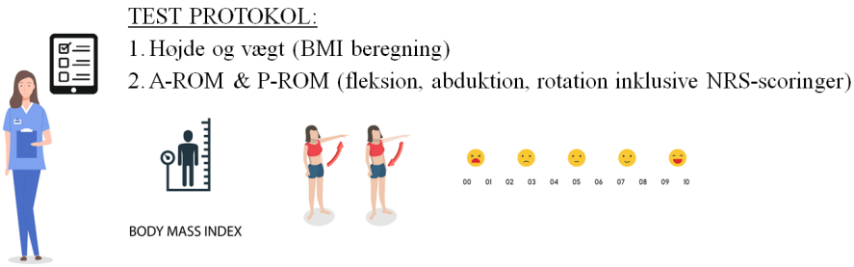


Figure 12. The primary investigator used a standardised test protocol.

Sample size

To ensure at least 85% statistical power at a two-sided significance level of α=0.05, with an anticipated SD of 15.41 SPADI points[83], a total sample size of 130 participants (~65 per group) was estimated to detect an 8-point difference between the groups on SPADI[75].

Statistical methods

All data management and statistics in relation to *Study I-IV* were conducted using STATA 18.5 (Statacorp, LP, College Station, Texas, USA) and SAS (SAS Insitute Inc., Cary, North Carolina, USA) software.

Study I

The primary investigator conducted all data management and performed all descriptive statistics in this cross-sectional survey study. Data were presented as counts and percentages for categorical variables, and as medians with Interquartile Range (IQR) for continuous variables. BMI-scores were set to missing if height or weight values exceeded 4.5 standard deviations (calculated for height/weight)[84]. For the QuickDASH, missing values were replaced with the mean for individual items if at least 10 of the

11 questions were answered[55-56]. Other missing values were reported in the tables, specifying the number of missing entries for each questionnaire.

Study II

The primary investigator conducted all data management and the statistical analyses in this national cohort study. Participants from the cross-sectional survey were categorised as either "Experiencing late-term impairments" or "No late-term impairments" based on their responses. The distribution of treatment codes and self-reported variables within these groups was analysed and presented as counts (with proportions) or medians with IQR. Missing data were reported in the table with the number of missing values indicated.

Associations between standard treatments and late-term impairments were assessed using logistic regression models adjusted for potential confounders, and were performed as complete case analyses[85]. Age at surgery, marital status, neoadjuvant or adjuvant chemotherapy, adjuvant endocrine therapy, and physiotherapy were included in the logistic regression models. Results were presented as Odds Ratios (ORs) with 95% Confidence Intervals (95% CI). Statistical significance was defined as *p*-values less than 0.05. BCS with SLNB and radiotherapy was chosen as the reference group, because it is the most commonly used standard treatment and regarded as relatively well-tolerated treatment in relation to developing late-term impairments[7].

Subgroup analyses were performed on covariates related to clinical treatment such as physiotherapy, chemotherapy, and endocrine therapy. The intention was to investigate whether a specific subgroup differed from the main results. The subgroup analyses were performed by categorising treatment such as physiotherapy into the six standard treatments, in order to assess whether physiotherapy influence the development of late-term impairments relative to each six standard treatments. Sensitivity analyses assessed the robustness of main findings by excluding age at surgery or marital status from the models one at a time.

An absolute risk calculation was performed to quantify the probability of late-term impairments associated with each of the Danish

standard treatments. This aimed to provide so as to inform patient counselling and support evidence-based decision-making in prevent treatment planning.

Study III

As this is the trial protocol, the statistical analyses is identical with *Study IV*, and is described in the section below.

Study IV

Independent biostatisticians, uninvolved in the development or conduct of the randomised controlled trial performed the statistical analyses blinded to treatment allocation in agreement with the publicly available SAP (**Appendix 1**).

The main analyses were based on the Intention-To-Treat (ITT) population, including all enrolled and randomised participants[48,86]. Continuous outcomes were analysed as changes from baseline using repeated measures mixed-effects linear models. These models included patient ID as a random effect and baseline score, treatment group (*IG* or *CC*), time points (baseline, 4, 8, and 12 weeks), type of Danish standard treatments based on surgery and radiotherapy, and treatment-time interactions as fixed effects (**Appendix 1**). Within-group changes from baseline are reported as least squares means (LS Means) with standard errors (SEs) or medians (IQR), depending on residual data distribution. The between-group differences are presented as Differences in LS Means with 95% Confidence Intervals (Difference in LSMeans 95% CI) or median differences with approximated 95% Cis[86].

Per the pre-specified SAP, participants were classified as having a clinical response if their SPADI change score was ≥18 points[75] (**Appendix 1**). For missing dichotomous endpoints, non-responder imputation was applied. Main analyses, based on the ITT population, used mixed-effects linear models assuming data were missing at random[86-88]. Sensitivity analyses on SPADI scores included a single-step non-responder imputation, replacing missing data with baseline values (baseline observation carried forward, BOCF)[89].

Results

The extent of self-reported late-term impairments (*Study I*)

Responders

The Danish Health Data Agency identified 10,539 eligible women for *Study I.* Of these, 612 were unreachable due to death, emigration, or lack of e-Boks access, leaving a contactable and invited study population of 9,927. Among them, 3,838 did not respond, and 43 were excluded for incomplete consent. A total of 6,046 women responded (60.9% response rate) and were included in *Study I* (**Figure 13**).

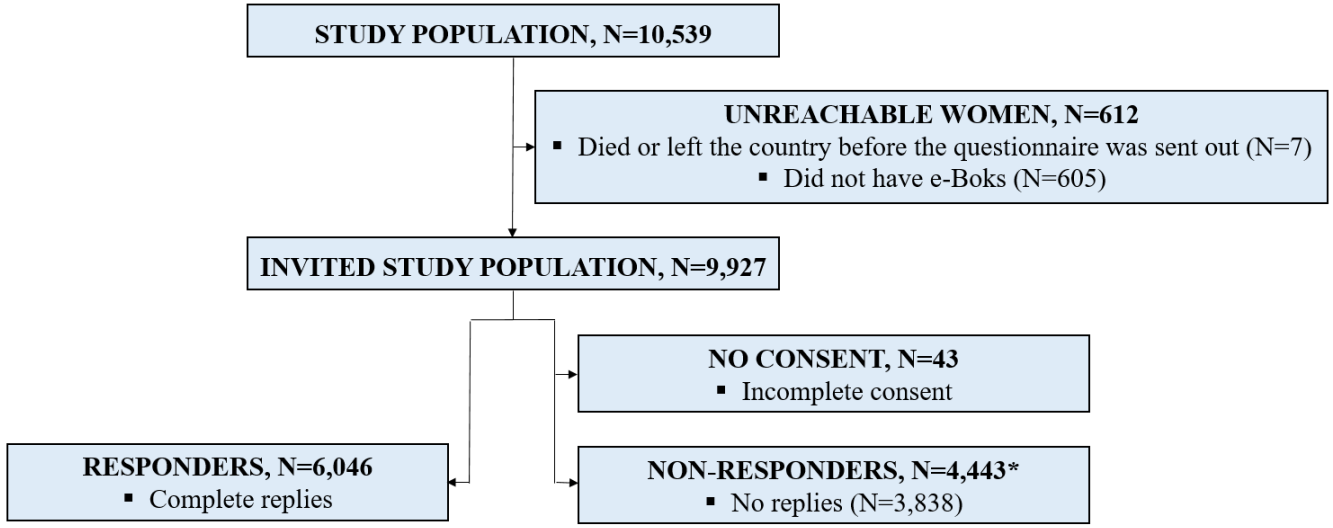


Figure 13. Flowchart of responders and non-responders among Danish breast cancer survivors.
*A total of 4,443 women are categorised as non-responders, as the Danish Health Authorities' secure server (FSEID-00005920) does not differentiate between those who did not respond and those without access to e-Boks. This figure is adapted from the manuscript for *Study I*.

Characteristics of Danish breast cancer survivors who responded the nationwide cross-sectional survey

The average age of responders at surgery was 57 years. Most were treated in the Capital Region (29.1%) or Central Denmark Region (23.3%) and underwent BCS with SLNB (52.0%) on the left (51.1%) or right (47.4%) side. About 15.1% transitioned from BCS to mastectomy. Complications after surgery occurred ≤1.1%, while 59.5% received chemotherapy, 87.2% received endocrine therapy, and 56.5% underwent physiotherapy (**Table 5**).

Most respondents had lower education levels (53.5%), were married (62.7%), retired (48.0%), and had children living independently (68.2%). Additionally, 56.7% had a BMI ≥25, 74.5% consumed 1-7 alcohol units per week, 51.9% were non-smokers, and 54.4% reported one or more co-morbidities (**Table 5**).

Table 5: Characteristics of responded women treated for primary breast cancer: clinical, socio-demographic, lifestyle and health information. This table is adapted from the manuscript for *Study I.*

Characteristics	
Clinical information	**Responders N=6,046**
Age at the time of surgery – median (IQR)[a] / n (%)	57.0 (45.1-68.9)
▪ ≥18-39 years	256 (4.2)
▪ 40-49 years	917 (15.2)
▪ 50-59 years	2,043 (33.8)
▪ 60-71 years	2,830 (46.8)
Geographical place of treatment– region, n (%)[a]	
▪ Capital Region of Denmark	1,759 (29.1)
▪ Region Zealand	999 (16.5)
▪ The North Denmark Region	645 (10.7)
▪ Central Denmark Region	1,410 (23.3)
▪ Region of Southern Denmark	1,233 (20.4)
Type of surgery and radiotherapy, n (%)[a]	
▪ BCS & SLNB + radiotherapy[b]	3,141(52.0)
▪ BCS & ALND + radiotherapy[b]	699 (11.6)
▪ Mastectomy & SLNB + radiotherapy[b]	691 (11.4)
▪ Mastectomy & SLNB – radiotherapy[b]	683 (11.3)
▪ Mastectomy & ALND + radiotherapy[b]	239 (4.0)
▪ BCS & SLNB – radiotherapy or BCS & ALND – radiotherapy[b]	432 (7.1)
▪ SLNB or ALND + radiotherapy, or only radiotherapy[b]	161 (2.7)
Occurred complications, n (%)[a]	
▪ Skin necrosis, n	<5 (n/a)[e]
▪ Wound infection, n	14 (0.2)
▪ Hematoma, n	18 (0.3)
▪ Seroma (≥5 seroma punctures), n	36 (0.6)
Received chemotherapy, n (%)a	3,596 (59.5)
Received endocrine therapy, n (%)a	5,272 (87.2)
Received physiotherapy, n (%)a	3,415 (56.5)

Socio-demographics	**Responders N=6,046**
Marital status, n (%)[a]	
▪ Single	786 (13.0)
▪ Married	3,791 (62.7)
▪ Divorced	1,003 (16.6)
▪ Widow	466 (7.7)
Highest attained education level, n (%)[c]	
▪ Short	3,232 (53.5)
▪ Medium	2,019 (33.4)
▪ Long	734 (12.1)
▪ *Missing*	*61 (1.0)*
Employment, n (%)[c]	
▪ Employed for wages or self-employed	2,577 (42.6)
▪ Sick leave	168 (2.8)
▪ Retired	2,902 (48.0)
▪ *Missing*	*399 (6.6)*
Co-habitation status, n (%)[c]	
▪ Living alone	1,674 (27.7)
▪ Living together	4,155 (68.7)
▪ *Missing*	*217 (3.6)*
Children, n (%)[c]	
▪ No children/pregnant for the first time	635 (10.5)
▪ Children living at home	757 (12.5)
▪ Children living on their own	4,123 (68.2)
▪ Children living at home and living on their own	420 (6.9)
▪ *Missing*	*111 (1.9)*

Lifestyle & health	**Responders N=6,046**
Body Mass Index (BMI) - kg/m^2, n (%)[c]	
▪ ≤ 18.5 (underweight)[d]	79 (1.3)
▪ 18.5-24.9 (normal weight)[d]	2,457 (40.6)
▪ 25.0-29.9 (pre-obesity)[d]	2,004 (33.1)
▪ 30.0-34.9 (obesity – class I)[d]	973 (16.1)
▪ 35.0-39.9 (obesity – class II)[d]	314 (5.2)
▪ ≥ 40 (obesity – class III)[d]	141 (2.3)
▪ *Missing*	*78 (1.3)*
Alcohol consumption, n (%)[c]	
▪ Drinking no alcohol	2,280 (37.7)
▪ 1-7 units per week	2,967 (49.1)
▪ 8-14 units per week	676 (11.2)
▪ ≥ 15 units per week	83 (1.4)
▪ *Missing*	*40 (0.6)*
Smoking habits, n (%)[c]	
▪ Non smoker	3,135 (51.9)
▪ Previous smoker	659 (10.9)
▪ Current smoker	2,231 (36.9)
▪ *Missing*	*21 (0.3)*
Co-morbidities, n (%)[c]	
▪ No co-morbidities	2,759 (45.6)
▪ 1	1,171 (19.4)
▪ 2	973 (16.1)
▪ 3+	1,143 (18.9)

[a] Register-based information.
[b] BCS = Breast-Conserving Surgery, SLNB = Sentinel Lymph Node Biopsy, ALND = Axillary Lymph Node Dissection, + radiotherapy = received radiotherapy, - radiotherapy = did not received radiotherapy.
[c] Self-reported information.
[d] WHO´s definition of BMI categorising[90].
[e] Not applicable.

Self-reported late-term impairments (the prevalence and severity) alongside DNPR diagnostic records

The median time from surgery to questionnaire completion was 4.6 years. Of the responders, 60.7% reported late-term impairments, with 54.6% noting that these were unrelated to their dominant arm (**Table 6**).

Among 3,667 women, the most common self-reported late-term impairments were shoulder impairment (75.3%), fatigue (56.9%), chemotherapy-induced neuropathy (49.6%), and lymphedema (26.3%). Shoulder impairment (53.1%) and fatigue (41.5%) were ranked as the most bothersome, followed by chemotherapy-induced neuropathy (24.6%) and lymphedema (14.7%). The most frequent combinations of bothersome impairments were shoulder impairment with fatigue (12.6%) or with chemotherapy-induced neuropathy (8.7%) (**Table 6**).

Of those reporting bothersome impairments, 50.3% with shoulder impairment had a QuickDASH score ≥20, indicating moderate to severe upper extremity impairments. For fatigue, 59.8% scored ≥40 on the BFI, reflecting moderate to severe fatigue, and 63.9% with lymphedema scored ≥25 on LYMPH-ICF-DK, showing moderate to severe physical function impairments (**Table 6**).

DNPR registrations for "late-term effects" were rare: lymphedema (1.3%), fatigue (0.2%), shoulder impairment (0.1%), and chemotherapy-induced neuropathy (0.1%) (**Table 6**). Among those with moderate to severe impairments, 35.3% reported using pain medication, with most taking prescription drugs 4-7 days per week (**Table 7**). Additionally, 13.6% of women aged 50-59 with shoulder impairment reported leaving work due to these impairments.

Table 6: Overview of nationwide prevalence and severity of common self-reported late-term impairments (overall and two most bothersome) and their DNPR registration. This table is adapted from the manuscript for *Study I.*

Responders	**N=6,046**
Self-reported late-term impairments, n (%)	
▪ Yes	3,667 (60.7)
▪ No	2,244 (37.1)
▪ *Missing*	*135 (2.2)*

Type of self-reported late-term impairments			**N=3,667**
	Overall[a] N=3,667	**Severe[b] N=3,667**	**DNPR-diagnosis[c] N=6,046**
Shoulder impairment, n (%)	**2,762 (75.3)**	**1,946 (53.1)**	**9 (0.1)[c]**
Quick DASH score, n (%)			
▪ *< 20 (mild discomfort in the upper extremities)*	*1,363 (49.3)*	*967 (49.7)*	
▪ *≥ 20-40 (moderate discomfort in the upper extremities)*	*812 (29.4)*	*536 (27.5)*	
▪ *> 40 (severe discomfort in the upper extremities)*	*587 (21.3)*	*443 (22.8)*	
Fatigue, n (%)	**2,085 (56.9)**	**1,520 (41.5)**	**10 (0.2)[c]**
BFI score, n (%)			
▪ *< 40 (mild fatigue)*	*846 (40.6)*	*612 (40.3)*	
▪ *≥ 40-80 (moderate fatigue)*	*1,049 (50.3)*	*781 (51.4)*	
▪ *> 80 (severe fatigue)*	*190 (9.1)*	*127 (8.4)*	
Neuropathy, n (%)	**1,818 (49.6)**	**902 (24.6)**	**7 (0.1)[c]**
▪ *No score*			
Lymphedema, n (%)	**965 (26.3)**	**538 (14.7)**	**78 (1.3)[c]**
LYMPH-ICF-DK score - domain 1, n (%)			
▪ *< 25 (mild impairments in physical function)*	*356 (36.9)*	*194 (36.1)*	
▪ *≥ 25-50 (moderate impairments in physical function)*	*308 (31.9)*	*160 (29.7)*	
▪ *> 50 (severe impairments in physical function)*	*301 (31.2)*	*184 (34.2)*	

Combinations of the two bothersome self-reported late-term impairments[d], n (%)					**N=3,667**
	Shoulder impairment	**Lymphedema**	**Neuropathy**	**Fatigue**	***Missing***
Shoulder impairment	974 (26.6)	193 (5.3)	318 (8.7)	461 (12.6)	
Lymphedema		160 (4.4)	66 (1.8)	119 (3.2)	
Neuropathy			281 (7.7)	237 (6.5)	
Fatigue				703 (19.2)	
Missing					*155 (4.2)*

[a] Represents overall self-reported late-term impairments, with women potentially included multiple times across the four listed impairment types.

[b] Represents the two most bothersome self-reported late-term impairments per woman, with each woman included a maximum of two times.
[c] Refers to diagnostic codes for "late-term effects" recorded in the Danish secondary healthcare system (DNPR): For shoulder impairment= T983D4 (Chronic pain after cancer treatment) and T983DB (Symptoms of musculoskeletal conditions after cancer treatment); for lymphedema= I972 (Lymphedema after mastectomy) and T983DA (Lymphedema after cancer treatment); for fatigue= T983D5 (Fatigue after cancer treatment); and for neuropathy= T983DD (Neuropathy after cancer treatment). [d] Data distributed across individual women.

Table 7: Reported impacts of bothersome self-reported late-term impairments. This table is adapted from the manuscript for *Study I.*

	Shoulder impairment	Fatigue	Neuropathy	Lymphedema
	N=1,946	N=1,520	N=902	N=538
Pain medication due late-terms – yes, n(%)	**667 (34.3)**	**595 (39.1)**	**336 (37.3)**	**160 (29.7)**
▪ Prescription medicine	250 (37.5)	227 (38.2)	142 (42.3)	66 (41.2)
▪ Over the counter medicine	211 (31.6)	159 (26.7)	83 (24.7)	50 (31.2)
▪ Both	206 (30.9)	209 (35.1)	111 (33.0)	44 (27.5)
▪ 4-7 days per week	384 (57.6)	350 (58.8)	204 (60.7)	99 (61.9)
▪ 1-3 days per week	220 (33.0)	189 (31.8)	103 (30.7)	45 (28.1)
▪ Rarely	63 (9.4)	56 (9.4)	29 (8.6)	16 (10.0)

The risk of self-reported late-term impairments (*Study II*)

Study population

Out of 10,539 women who underwent surgery for primary breast cancer, 612 were excluded due to death, emigration, or lack of e-Boks access. Of the remaining 9,927 women invited to a nationwide cross-sectional survey, 3,838 did not respond, and 43 were excluded for incomplete consent, leaving 6,046 respondents (60.9% response rate). After excluding 191 women who did not receive standard treatment (BCS and ALND with radiotherapy; SLNB with radiotherapy; ALND with radiotherapy, or radiotherapy alone) and 126 who did not respond on late-term impairments, the final study population included 5,729 breast cancer survivors (**Figure 14**).

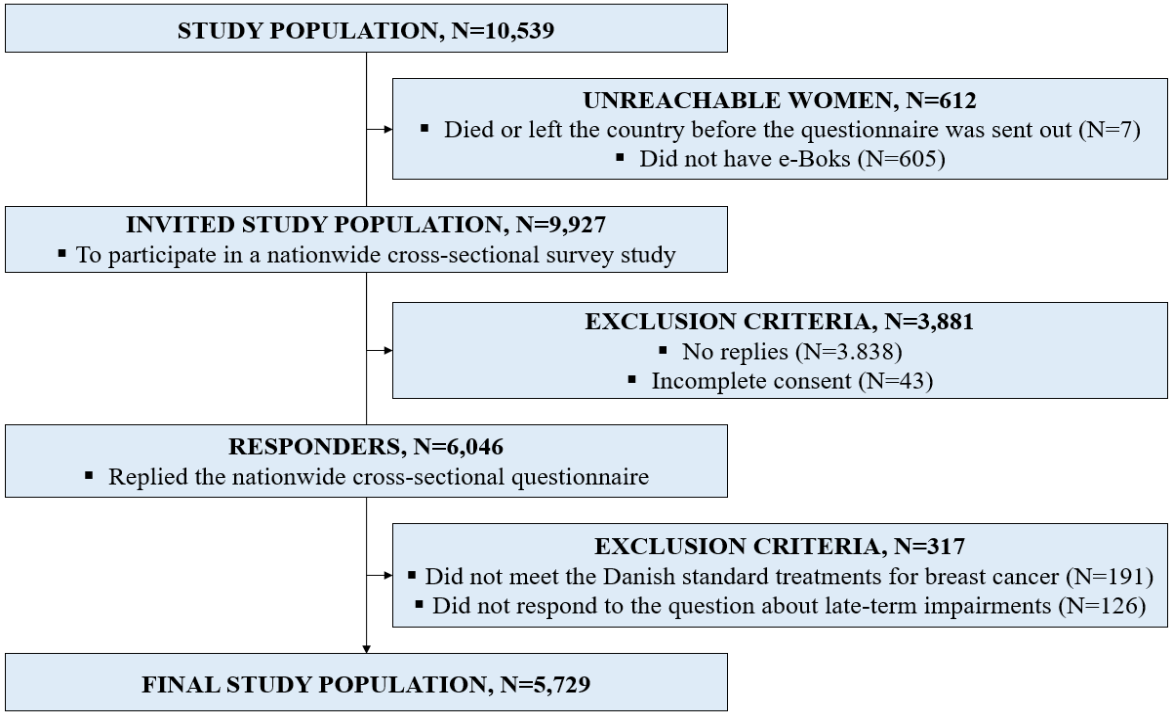


Figure 14. Flowchart over the final study population included in the national cohort study of Danish breast cancer survivors. This figure is adapted from the manuscript for *Study II*.

Characteristics of Danish Breast Cancer Survivors with presence or absence of self-reported late-term impairments

Women with *presence* of self-reported late-term impairments were, on average, 55 years old at surgery. The most common treatment was BCS and SLNB with radiotherapy (46.3%), followed by BCS and ALND with radiotherapy (15.0%) and mastectomy with SLNB and radiotherapy (16.3%). Most women received chemotherapy (69.2%) and physiotherapy (59.6%), were married (62.6%), employed (53.4%), had a BMI ≥25 (59.2%), and at least one co-morbidity (57.0%) (**Table 8**).

Women with *absence* of self-reported late-term impairments averaged 61 years at surgery. Most underwent BCS and SLNB with radiotherapy (65.8%) and were married (63.4%). Fewer in this group received chemotherapy (43.9%), were employed (33.1%), or had a BMI ≥25 (53.1%) (**Table 8**).

Table 8: Characteristics of Danish breast cancer survivors treated for primary breast cancer, categorised by *presence* or *absence* of self-reported late-term impairments (N=5,729). This table is adapted from the manuscript for *Study II*.

	Self-reported late-term impairments			
	Yes N=3,539	No N=2,190	Total N=5,729	*P*-value
Register-based information at the time of surgery				
Breast cancer-related information				
Age at the time of surgery – median (IQR)[a]				<0.001*
	55.5 (43.5-67.6)	61.0 (50.0-69.7)	57.6 (45.2-68.9)	
Geographical place of treatment – region, n (%)				0.40
▪ The North Denmark Region	376 (10.6)	199 (9.1)	575 (10.0)	
▪ Central Denmark Region	825 (23.3)	523 (23.9)	1,348 (23.5)	
▪ Region of Southern Denmark	702 (19.9)	465 (21.2)	1,167 (20.4)	
▪ Capital Region of Denmark	1,047 (29.6)	630 (28.8)	1,677 (29.3)	
▪ Region Zealand	589 (16.6)	373 (16.9)	962 (16.8)	
Type of surgery and radiotherapy (guideline treatments), n (%)				<0.001*
▪ BCS, SLNB + RT[b]	1,639 (46.3)	1,442 (65.8)	3,081 (53.8)	
▪ BCS, ALND + RT[b]	532 (15.0)	144 (6.6)	676 (11.8)	
▪ Mastectomy, SLNB – RT[b]	393 (11.1)	266 (12.2)	659 (11.5)	
▪ Mastectomy, ALND + RT[b]	196 (5.5)	40 (1.8)	236 (4.1)	
▪ Mastectomy, SLNB + RT[c]	577 (16.3)	114 (5.2)	691 (12.1)	
▪ BCS and SLNB – RT[c]	202 (5.7)	184 (8.4)	386 (6.7)	
Neoadjuvant or adjuvant chemotherapy – yes, n (%)				<0.001*
	2,448 (69.2)	961 (43.9)	3,409 (59.5)	
Adjuvant endocrine therapy – yes, n (%)				<0.001*
	3,170 (89.6)	1,831 (83.6)	5,001 (87.3)	
Physiotherapy – yes, n (%)				<0.001*
	2,108 (59.6)	1,116 (51.0)	3,224 (56.3)	
Marital status, n (%)				0.75
▪ Not married	1,325 (37.4)	802 (36.6)	2,127 (37.1)	
▪ Married	2,214 (62.6)	1,388 (63.4)	3,602 (62.9)	

Self-reported information 3-7 years postoperatively				
Time from surgery to receiving survey – median (IQR)[a]				<0.001*
	4.5 (2.5-6.6)	4.7 (2.7-6.6)	4.6 (2.6-6.6)	
Socio-demographics				
Highest level of education, n (%)				0.38
▪ Short (< 4 years)	1,877 (53.0)	1,183 (54.0)	3,060 (53.4)	
▪ Long (≥ 5 years)	1,634 (46.2)	981 (44.8)	2,615 (45.6)	
▪ *Missing*	*28 (0.8)*	*26 (1.2)*	*54 (0.9)*	
Employment, n (%)				<0.001*
▪ Retired	1,387 (39.2)	1,365 (62.3)	2,752 (48.0)	
▪ Employed	1,888 (53.4)	724 (33.1)	2,612 (45.6)	
▪ *Missing*	*264 (7.5)*	*101 (4.6)*	*365 (6.4)*	
Lifestyle and health				
Body Mass Index (BMI) - kg/m^2, n (%)[d]				<0.001*
▪ Not obese (≤ 24.9)	1,404 (39.7)	1,002 (45.7)	2,406 (42.0)	
▪ Obese (≥ 25.0)	2,095 (59.2)	1,162 (53.1)	3,257 (56.9)	
▪ *Missing*	*40 (1.1)*	*26 (1.2)*	*66 (1.2)*	
Alcohol consumption, n (%)[e]				<0.001*
▪ 0 unit/week	1,259 (35.6)	689 (31.5)	1,948 (34.0)	
▪ ≤ 7 units/week	1,910 (54.0)	1,145 (52.3)	3,055 (53.3)	
▪ > 7 units/week	370 (10.4)	356 (16.2)	726 (12.7)	
Smoking status, n (%)				0.025*
▪ Non-smoker	1,804 (51.0)	1,173 (53.6)	2,977 (52.0)	
▪ Previous smoker	1,364 (38.5)	765 (34.9)	2,129 (37.2)	
▪ Current smoker	371 (10.5)	252 (11.5)	623 (10.9)	
Co-morbidities, n (%)[f]				<0.001*
▪ No co-morbidities	1,524 (43.1)	1,091 (49.8)	2,615 (45.6)	
▪ 1	660 (18.7)	446 (20.4)	1,106 (19.3)	
▪ 2	582 (16.5)	338 (15.4)	920 (16.1)	
▪ 3+	773 (21.8)	315 (14.4)	1,088 (19.0)	

* Statistically significant estimate.

[a] IQR = Interquartile range.

[b] BCS = Breast-Conserving Surgery, SLNB = Sentinel Lymph Node Biopsy, ALND = Axillary Lymph Node Dissection, +/-RT = With (+) or without (-) radiotherapy.

[c] Women receiving this combination were part of a DBCG-led randomised controlled trial aimed at potentially supplementing Danish standard breast cancer treatments[64-65].

[d] Included Tamoxifen/Letrozole.

[e] Classified according to WHO's BMI categories[90].

[f] In the period the data were collected the Danish Health Authority recommended a maximum alcohol intake of 7 units per week for women aged 18+ to maintain low disease risk[91].

Risk factors for self-reported late-term impairments 3-7 years postoperatively

Compared to BCS and SLNB with radiotherapy (the reference group), neither mastectomy and SLNB without radiotherapy (ORadj 1.12, 95% CI: 0.94-1.34) nor BCS and SLNB without radiotherapy (ORadj 0.99, 95% CI: 0.79-1.24) showed increased risk of self-reported late-term impairments. All other standard treatments significantly increased risk: BCS and ALND with radiotherapy (ORadj 2.76, 95% CI: 2.25-3.39), mastectomy and SLNB with radiotherapy (ORadj 3.10, 95% CI: 2.48-3.88), and mastectomy with ALND and radiotherapy (ORadj 2.90, 95% CI: 2.02-4.15) (**Table 9**). For specific self-reported late-term impairments:

- **Shoulder impairment** risk increased with mastectomy and SLNB with radiotherapy (ORadj 2.49, 95% CI: 2.08-2.98), mastectomy with ALND and radiotherapy (ORadj 2.43, 95% CI: 1.84-3.20), and BCS and ALND with radiotherapy (ORadj 1.71, 95% CI: 1.43-2.05).

- **Lymphedema** risk was highest for BCS and ALND with radiotherapy (ORadj 10.74, 95% CI: 8.17-14.12), followed by mastectomy with ALND and radiotherapy (ORadj 7.94, 95% CI: 5.44-11.59), and mastectomy with SLNB and radiotherapy (ORadj 6.03, 95% CI: 4.49-8.11).

- **Chemotherapy-induced neuropathy** risk increased with BCS and ALND with radiotherapy (ORadj 1.67, 95% CI: 1.34-2.08), mastectomy and SLNB without radiotherapy (ORadj 1.46, 95% CI: 1.16-1.84), and mastectomy and SLNB with radiotherapy (ORadj 1.57, 95% CI: 1.25-1.96) (**Table 9**).

Subgroup analysis revealed higher risks in women who received physiotherapy (OR 1.68, 95% CI: 1.11-2.56) or chemotherapy (OR 2.95, 95% CI: 1.67-5.22) after mastectomy and SLNB with radiotherapy (**Appendix 7**). Sensitivity analyses on age and marital status did not change

the main results (**Appendix 8**). The absolute risk for self-reported late-term impairments was 61.8%, with shoulder impairment (33.0%) as the most frequent late-term impairment across all standard treatments. Absolute risks for shoulder impairment were highest in women underwent mastectomy and SLNB or ALND with radiotherapy (50.0%) followed by BCS and ALND with radiotherapy (39.6%) (**Table 10**).

Table 9: Odd ratio (OR) and 95% confidence intervals (95% CI) for *general* and *specific* self-reported late-term impairment among women with primary breast cancer, based on Danish standard treatments of surgery and radiotherapy (N=5,729). This table is adapted from the manuscript for *Study II.*

	Self-reported late-term impairment	
	Unadjusted	Adjusted[b]
	OR (95% CI)	OR (95% CI)
▪ BCS and SLNB with radiotherapy[a]	Reference	Reference
▪ BCS and ALND with radiotherapy[a]	3.25 (2.67-3.96)	2.76 (2.25-3.39)*
▪ Mastectomy, SLNB with radiotherapy[a]	4.45 (3.60-5.51)	3.10 (2.48-3.88)*
▪ Mastectomy, SLNB without radiotherapy[a]	1.30 (1.10-1.54)	1.12 (0.94-1.34)
▪ Mastectomy, ALND with radiotherapy[a]	4.31 (3.05-6.10)	2.90 (2.02-4.15)*
▪ BCS and SLNB without radiotherapy[a]	0.97 (0.78-1.19)	0.99 (0.79-1.24)

Self-reported shoulder impairment		Self-reported lymphedema		Self-reported fatigue		Self-reported neuropathy	
Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
1.71 (1.44-2.03)	1.71 (1.43-2.05)*	11.57 (8.91-15.01)	10.74 (8.17-14.12)*	1.13 (0.94-1.37)	0.87 (0.71-1.06)	2.08 (1.68-2.57)	1.67 (1.34-2.08)*
2.65 (2.24-3.14)	2.49 (2.08-2.98)*	7.11 (5.40-9.35)	6.03 (4.49-8.11)*	1.29 (1.07-1.55)	0.83 (0.69-1.01)	2.11 (1.71-2.60)	1.57 (1.25-1.96)*
1.12 (0.94-1.35)	1.10 (0.91-1.33)	1.18 (0.75-1.84)	1.08 (0.69-1.69)	1.13 (0.93-1.37)	0.94 (0.77-1.15)	1.66 (1.32-2.08)	1.46 (1.16-1.84)*
2.60 (1.99-3.40)	2.43 (1.84-3.20)*	9.27 (6.47-13.29)	7.94 (5.44-11.59)*	1.37 (1.03-1.83)	0.86 (0.64-1.17)	1.68 (1.19-2.38)	1.23 (0.86-1.76)
0.93 (0.73-1.19)	0.91 (0.71-1.16)	0.55 (0.25-1.19)	0.54 (0.25-1.17)	1.03 (0.81-1.32)	1.09 (0.85-1.41)	1.07 (0.78-1.48)	1.13 (0.81-1.56)

*The estimates with an asterisk are statistically significant values.
[a]BCS = Breast-Conserving Surgery, SLNB = Sentinel Lymph Node Biopsy, ALND = Axillary Lymph Node Dissection.
[b]Adjusted for age at surgery (reference = ≥ 55 years at surgery), marital status (reference = married), neo-adjuvant or adjuvant chemotherapy (reference = yes), adjuvant endocrine therapy (reference = yes), physiotherapy (reference = yes).

Table 10: Absolute risk (AR) expressed as a percentage (%) for *general* and *specific* self-reported late-term impairments among women with primary breast cancer, based on Danish standard treatments of surgery and radiotherapy (N=5,729). This table is adapted from the manuscript for *Study II*.

		Self-reported late-term impairments	
	Yes (N)	**Total (N)**	**Absolute Risk (%)**
Self-reported late-term impairments, n (%)	**N=3,539**	**N= 5,729**	**61.8**
BCS and SLNB with radiotherapy[a]	1,639	3,081	53.2
BCS and ALND with radiotherapy[a]	532	676	78.7
Mastectomy and SLNB with radiotherapy[a]	577	691	83.5
Mastectomy and SLNB without radiotherapy[a]	393	659	59.6
Mastectomy and ALND with radiotherapy[a]	196	236	83.1
BCS and SLNB without radiotherapy[a]	202	386	52.3
Self-reported shoulder impairment, n (%)	**N=1,892**	**5,729**	**33.0**
BCS and SLNB with radiotherapy[a]	856	3,081	27.8
BCS and ALND with radiotherapy[a]	268	676	39.6
Mastectomy and SLNB with radiotherapy[a]	349	691	50.5
Mastectomy and SLNB without radiotherapy[a]	199	659	30.2
Mastectomy and ALND with radiotherapy[a]	118	236	50.0
BCS and SLNB without radiotherapy[a]	102	386	26.4
Self-reported fatigue, n (%)	**N=1,472**	**5,729**	**25.7**
BCS and SLNB with radiotherapy[a]	747	3,081	24.2
BCS and ALND with radiotherapy[a]	180	676	26.6
Mastectomy and SLNB with radiotherapy[a]	202	691	29.2
Mastectomy and SLNB without radiotherapy[a]	175	659	26.6
Mastectomy and ALND with radiotherapy[a]	72	236	30.5
BCS and SLNB without radiotherapy[a]	96	386	24.9
Self-reported neuropathy, n (%)	**N=868**	**5,729**	**15.2**
BCS and SLNB with radiotherapy[a]	361	3,081	11.7
BCS and ALND with radiotherapy[a]	146	676	21.6
Mastectomy and SLNB with radiotherapy[a]	151	691	21.9
Mastectomy and SLNB without radiotherapy[a]	119	659	18.1
Mastectomy and ALND with radiotherapy[a]	43	236	18.2
BCS and SLNB without radiotherapy[a]	48	386	12.4
Self-reported lymphedema, n (%)	**N=510**	**5,729**	**8.9**
BCS and SLNB with radiotherapy[a]	100	3,081	3.2
BCS and ALND with radiotherapy[a]	189	676	28.0
Mastectomy and SLNB with radiotherapy[a]	133	691	19.2
Mastectomy and SLNB without radiotherapy[a]	25	659	3.8
Mastectomy and ALND with radiotherapy[a]	56	236	23.7
BCS and SLNB without radiotherapy[a]	7	386	1.8

[a] BCS = Breast-Conserving Surgery, SLNB = Sentinel Lymph Node Biopsy, ALND = Axillary Lymph Node Dissection.

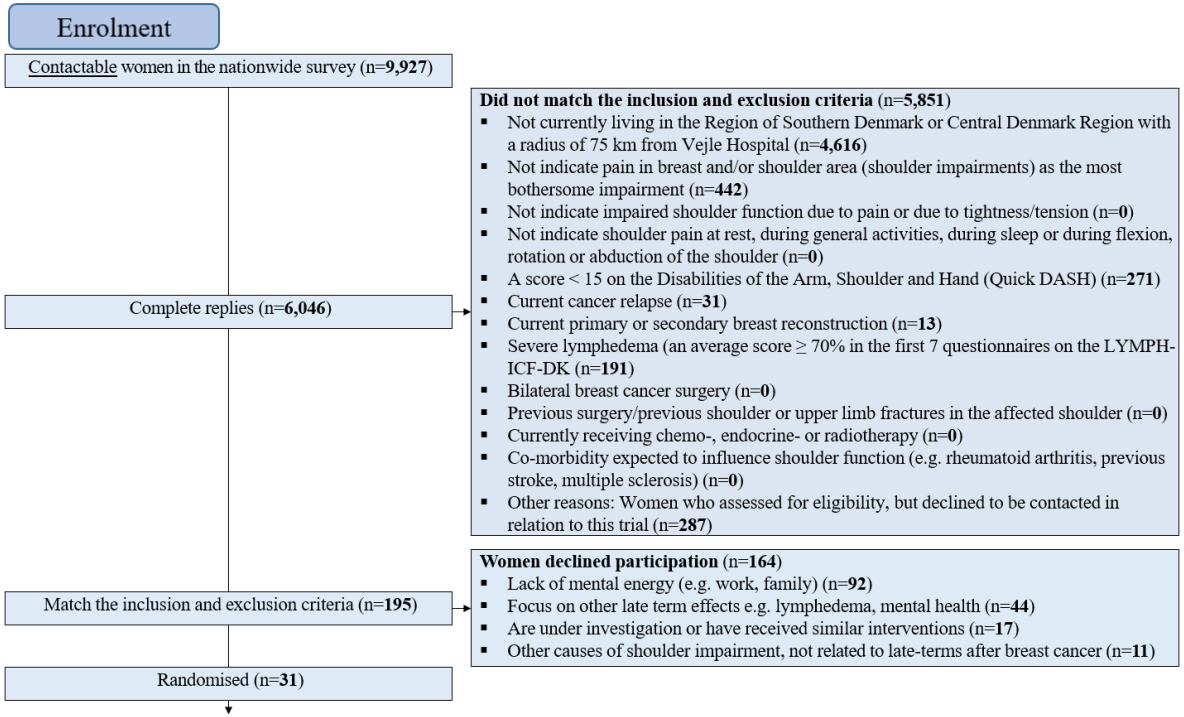
Treatments of shoulder impairments (*Study IV*)

Characteristics of the participants who experience shoulder impairment

From the nationwide cross-sectional survey of 9,927 women (60.9% response rate; 6,046 complete replies), 195 eligible women consented to be contacted for trial participation. All were contacted by the primary investigator, but 164 declined (**Figure 15**). A total of 31 women were enrolled and randomised (*IG*: n=16, *CG*: n=15). Baseline characteristics[48] for the participants are in **Table 11**.

All baseline data were collected. At 4 and 8 weeks, six (*IG*=3; *CG*=3) and six (*IG*=5; CG=1) women, respectively, did not respond, mainly due to summer holidays or lack of mental energy. One withdrew at 8 weeks due to cancer recurrence. At 12 weeks, all completed the questionnaire, but four (*IG*=3; *CG*=1) not participate in the physical tests (**Figure 15**). No crossover and no woman received concomitant treatments during the trial.

Women allocated to *IG* typically received an ultrasound-guided corticosteroid injection with physiotherapeutic exercises at hospital, or were referred to private practice physiotherapist. Five declined private physiotherapy due to self-payment (**Table 12**).


Enrolment
Contactable women in the nationwide survey (n=9,927)
Complete replies (n=6,046)
Match the inclusion and exclusion criteria (n=195)
Randomised (n=31)
Did not match the inclusion and exclusion criteria (n=5,851)
Not currently living in the Region of Southern Denmark or Central Denmark Region with a radius of 75 km from Vejle Hospital (n=4,616)
Not indicate pain in breast and/or shoulder area (shoulder impairments) as the most bothersome impairment (n=442)
Not indicate impaired shoulder function due to pain or due to tightness/tension (n=0)
Not indicate shoulder pain at rest, during general activities, during sleep or during flexion, rotation or abduction of the shoulder (n=0)
A score < 15 on the Disabilities of the Arm, Shoulder and Hand (Quick DASH) (n=271)
Current cancer relapse (n=31)
Current primary or secondary breast reconstruction (n=13)
Severe lymphedema (an average score ≥ 70% in the first 7 questionnaires on the LYMPH-ICF-DK (n=191)
Bilateral breast cancer surgery (n=0)
Previous surgery/previous shoulder or upper limb fractures in the affected shoulder (n=0)
Currently receiving chemo-, endocrine- or radiotherapy (n=0)
Co-morbidity expected to influence shoulder function (e.g. rheumatoid arthritis, previous stroke, multiple sclerosis) (n=0)
Other reasons: Women who assessed for eligibility, but declined to be contacted in relation to this trial (n=287)
Women declined participation (n=164)
Lack of mental energy (e.g. work, family) (n=92)
Focus on other late term effects e.g. lymphedema, mental health (n=44)
Are under investigation or have received similar interventions (n=17)
Other causes of shoulder impairment, not related to late-terms after breast cancer (n=11)

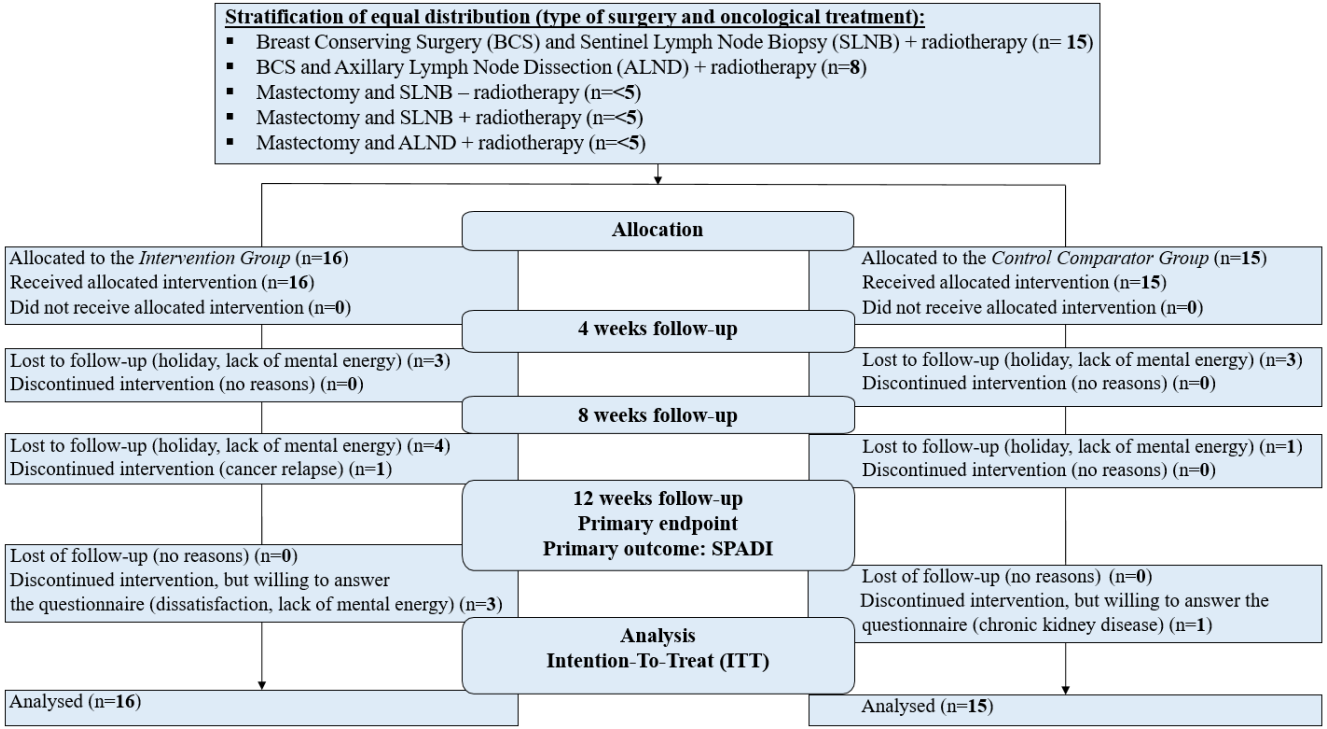


Figure 15: Flow of participants in this randomised controlled trial. Intervention group; *IG* = Individualised treatment. Control comparator group; *CG* = standardised home-based exercise program. This table is adapted from the manuscript for *Study IV*.

Table 11: Baseline characteristics of the ITT population*. This table is adapted from the manuscript for *Study IV*.

	Intervention group (IG) **(N=16)**	***Control comparator group (CG)*** **(N=15)**	**Total Combined (N=31)**
General characteristics			
Age — years	54.4 (10.9)	57.6 (9.8)	56.0 (10.3)
Height — cm	165.5 (4.3)	164.3 (6.2)	164.9 (5.2)
Weight — kg	78.2 (14.4)	77.9 (15.0)	78.0 (14.5)
Body Mass Index — kg/m^2	28.5 (5.1)	28.9 (5.6)	28.7 (5.2)
Alcohol Consumption:			
0 units per week — no. (%)	6 (37.5)	6 (40.0)	12 (38.7)
1-7 units per week — no. (%)	10 (62.5)	9 (60.0)	19 (61.3)
8-14 units per week — no. (%)	0 (0)	0 (0)	0 (0)
≥15 units per week — no. (%)	0 (0)	0 (0)	0 (0)
Smoking Habits:			
Smoker — no. (%)	0 (0)	0 (0)	0 (0)
Current smoker — no. (%)	6 (37.5)	8 (53.3)	14 (45.2)
Not a smoker — no. (%)	10 (62.5)	7 (46.7)	17 (54.8)
Highest Education level:			
Short — no. (%)	10 (62.5)	10 (66.7)	20 (64.5)
Long — no. (%)	6 (37.5)	5 (33.3)	11 (35.5)
Employment:			
Employed or self-employed – no. (%)	11 (68.7)	7 (46.7)	18 (58.0)
Sick leave — no. (%)	0 (0)	0 (0)	0 (0)
Retired — no. (%)	5 (31.3)	8 (53.3)	13 (42.0)
Index shoulder:			
Right side — no. (%)	9 (56.3)	7 (46.7)	16 (51.6)
Left side — no. (%)	7 (43.7)	8 (53.3)	15 (48.4)
Dominant side affected:			
Yes — no. (%)	9 (56.3)	6 (40.0)	15 (48.4)
No — no. (%)	7 (43.7)	9 (60.0)	16 (51.6)
Mean duration shoulder symptoms – months	5.6 (1.1)	5.7 (1.6)	5.7 (1.4)

Outcome measures			
SPADI[a] overall score – 0 to 100	45.7 (19.4)	47.6 (16.2)	46.6 (17.7)
SPADI[a] shoulder pain – 0 to 100	53.4 (19.5)	58.4 (12.7)	55.8 (16.5)
SPADI[a] shoulder function – 0 to 100	38.0 (21.7)	36.8 (23.4)	37.5 (22.2)
NRS max shoulder pain intensity – 0 to 10	6.4 (1.5)	6.4 (1.3)	6.4 (1.4)
NRS shoulder pain during general activities	4.6 (2.6)	4.2 (1.7)	4.4 (2.2)
NRS shoulder pain at rest – 0 to 10	3.8 (2.6)	3.7 (1.7)	3.7 (2.2)
NRS shoulder pain during sleep – 0 to 10	4.0 (2.9)	4.5 (2.8)	4.2 (2.8)
A-ROM in the affected shoulder — degree			
Flexion	118.2 (18.1)	124.1 (18.5)	121.1 (18.2)
Internal rotation	53.4 (19.0)	66.3 (15.6)	59.6 (18.3)
External rotation	36.0 (16.1)	51.3 (22.1)	43.4 (20.4)
Abduction	83.9 (31.2)	107.2 (30.0)	95.2 (32.4)
NRS active shoulder pain during — 0 to 10			
Flexion	4.3 (2.4)	3.9 (1.8)	4.1 (2.1)
Internal rotation	4.1 (2.5)	2.3 (2.0)	3.3 (2.4)
External rotation	4.6 (2.7)	3.9 (2.4)	4.3 (2.6)
Abduction	4.8 (2.5)	4.6 (1.6)	4.7 (2.1)
P-ROM in the affected shoulder — degree			
Flexion	110.0 (21.9)	117.6 (16.0)	113.7 (19.3)
Internal rotation	53.5 (25.1)	68.9 (17.9)	60.9 (22.9)
External rotation	34.0 (22.0)	48.7 (26.5)	41.1 (25.0)
Abduction	78.2 (29.5)	98.9 (32.3)	88.2 (32.1)
NRS passive shoulder pain during — 0 to 10			
Flexion	4.5 (2.2)	3.9 (1.8)	4.2 (2.0)
Internal rotation	4.1 (2.6)	2.3 (2.1)	3.2 (2.5)
External rotation	4.8 (2.9)	4.0 (2.6)	4.4 (2.7)
Abduction	4.8 (2.4)	4.8 (2.1)	4.8 (2.2)

*Values are reported as means and standard deviations (SDs) unless otherwise stated

[a] SPADI ranges from 0 (best) to 100 (worst), with lower scores indicating better disease status.

Table 12: An overview of participants allocated to *IG* and their received treatments (N=16). This table is adapted from the manuscript for *Study IV*.

Description of treatments received in *IG*
Ultrasound-guided corticosteroid injection in the shoulder (performed at the Shoulder Sector, Orthopaedic Department, Vejle Hospital) **Physiotherapy at Vejle Hospital** (strength training with weights/machines, elastic bands; self-training after following instructions from a physiotherapist) **Follow-up** (physical or telephone)
Ultrasound-guided corticosteroid injection in the shoulder (performed at the Shoulder Sector, Orthopaedic Department, Vejle Hospital) **Physiotherapy at Vejle Hospital** (strength training with weights/machines, elastic bands; self-training after following instructions from a physiotherapist) **Follow-up** (physical or telephone) **Physiotherapist in private practice** (massage)
Ultrasound-guided corticosteroid injection in the shoulder & follow-up (performed at the Shoulder Sector, Orthopaedic Department, Vejle Hospital) **Masseuse in private practice** (massage)
Physiotherapy at Vejle Hospital (mobility training and stretching) **Follow-up** (physical or telephone)
Referral to another professional in the municipality (performed at the Shoulder Sector, Orthopaedic Department, Vejle Hospital) **Physiotherapy in the municipality** (strength training with weights/machines, elastic bands; self-training after following instructions from a physiotherapist, mobility training and stretching, tape)
Referral to another professional in the private practice; self-payment (performed at the Shoulder Sector, Orthopaedic Department, Vejle Hospital) **Physiotherapist in private practice** (group training)
Referral to another professional in the private practice; self-payment (performed at the Shoulder Sector, Orthopaedic Department, Vejle Hospital)

Primary outcome

Mean SPADI overall score change from baseline to 12 weeks was -10.5 (SE 2.8) in *IG* and -14.4 (SE 2.9) in *CG*. The between-group difference was -3.9 points (95% CI -11.9 to 4.1; *p*-value=0.34). Since the difference was ≤8 points[75], this indicated no differences between the two groups (**Table 13**).

Key secondary outcomes

At 12 weeks, no significant differences were found between *IG* and *CG* for SPADI pain -3.5 points (95% CI -14.6 to 7.6; *p*-value=0.53) or SPADI function -4.0 points (95% CI -11.0 to 3.1; *p*-value=0.26). However, *CG* showed significantly greater improvement in GPE (impression of the treatment success) compared to *IG*, with a median between-group difference of -1.0 points (95% CI -1.8 to -0.2; *p*-value=0.01). No significant differences were found between *IG* and *CG* for all pain NRS measurements (**Table 13**). Compared with *IG, CG* showed significantly greater improvements in A-ROM flexion 22.9° (95% CI 4.38 to 41.29; *p*-value =0.02), A-ROM abduction 40.5° (95% CI 6.77 to 74.23; *p*-value=0.02), and P-ROM abduction 44.5° (95% CI 5.91 to 83.09; *p*-value=0.02). No other active or passive movement significant differences were found, as well as for all NRS measurements (**Table 13**).

Treatment response

Although the mean change favoured *CG*, 31% of women in *IG* and 27% in *CG* showed a clinical response (≥18 points improvement in SPADI)[75], resulting in a risk ratio difference of 0.9 (0.27/0.31) (**Table 13**). **Table 14** shows treatment response for individual patients in both groups.

Serious adverse events (SAE´s)

Two serious adverse events requiring hospitalisation[92] were recorded: breast cancer recurrence in *IG* and chronic kidney disease in *CG*. The woman with chronic kidney disease completed the trial treatment in this trial.

Sensitivity analyses

Due to the small sample size and challenges in examining robustness, sensitivity analyses were performed only on SPADI overall scores at 12 weeks using single-step non-responder imputation. The results were consistent with the primary analysis (**Table 15**).

Table 13: Primary and Key Secondary Outcomes at 12 weeks in the ITT population*. This table is adapted from the manuscript for *Study IV*.

Outcome	***12 weeks after initiating the treatment***		***Between-Group Difference in Mean Improvement***	
	Intervention group (IG)	*Control comparator group (CG)*	*Difference in LSMeans (95%CI)*	*P-Value*
	LS Means (SE)	LS Means (SE)		
Primary endpoint				
Change SPADI overall score[a] (0-100)	-10.5 (2.8)	-14.4 (2.9)	-3.9 (-11.9 to 4.1)	0.34
Key secondary outcome measures				
Change SPADI pain[a] (0-100)	-13.2 (3.9)	-16.7 (3.9)	-3.5 (-14.6 to 7.6)	0.53
Change SPADI function[a] (0-100)	-7.8 (2.5)	-11.8 (2.5)	-4.0 (-11.0 to 3.1)	0.26
GPE; treatment success (median[b])	2.0 [2.0;2.0]	1.0 [1.0;2.0]	-1.0 (-1.8 to -0.2)	0.01
Change NRS max shoulder pain intensity (0-10)	5.1 (0.4)	4.8 (0.4)	-0.3 (-1.4 to 0.8)	0.56
Change NRS shoulder pain during general activities	3.5 (0.4)	3.4 (0.4)	-0.1 (-1.2 to 1.1)	0.91
Change NRS shoulder pain at rest (0-10)	2.4 (0.4)	2.0 (0.4)	-0.4 (-1.5 to 0.8)	0.56
Change NRS shoulder pain during sleep (0-10)	3.5 (0.4)	2.7 (0.5)	-0.8 (-2.1 to 0.4)	0.19
Number of treatments due to shoulder pain (median[b])	0.0 [0.0;0.0]	0.0 [0.0;0.0]	0.0 (0.0 to 0.0)	0.00
A-ROM in the affected shoulder (degree):				
Flexion (median[b])	124.8 [107.17;141.67]	147.7 [132.67;154.33]	22.9 (4.38 to 41.29)	0.02
Internal rotation (median[b])	79.5 [62.17;85.83]	73.3 [62.33;85.67]	-6.2 (-20.48 to 8.15)	0.40
External rotation (median[b])	51.5 [36.33;65.33]	60.5 [45.00;74.67]	9.0 (-4.49 to 22.49)	0.19
Abduction (median[b])	101.8 [90.33;114.50]	142.3 [113.00;144.67]	40.5 (6.77 to 74.23)	0.02
Active NRS shoulder pain assessment during (0-10):				
Flexion (median[b])	3.5 [2.0;4.0]	2.0 [1.0;6.0]	-1.5 (-3.8 to 0.8)	0.19
Internal rotation (median[b])	1.0 [0.5;2.5]	1.5 [0.0;3.0]	0.5 (-0.8 to 1.8)	0.45
External rotation (median[b])	2.0 [1.0;4.5]	2.0 [0.0;5.0]	0.0 (0.0 to 0.0)	0.35
Abduction (median[b])	4.5 [2.0;5.5]	2.5 [1.0;5.0]	-2.0 (-5.0 to 1.0)	0.20
P-ROM in the affected shoulder (degree):				
Flexion (median[b])	117.7 [94.83;136.83]	136.0 [129.33;145.67]	18.3 (-0.43 to 37.09)	0.06
Internal rotation (median[b])	78.7 [65.17;84.17]	74.8 [59.67;87.33]	-3.9 (-12.20 to 4.53)	0.37
External rotation (median[b])	51.0 [33.67;69.17]	62.7 [45.00;75.00]	11.7 (-6.10 to 29.43)	0.20
Abduction (median[b])	93.7 [82.67;109.33]	138.2 [99.67;141.67]	44.5 (5.91 to 83.09)	0.02
Passive NRS shoulder pain assessment during (0-10):				
Flexion (median[b])	2.0 [2.0;5.0]	2.0 [1.0;6.0]	0.0 (0.0 to 0.0)	0.32
Internal rotation (median[b])	1.0 [0.5;2.5]	1.5 [0.0;3.0]	0.5 (-0.7 to 1.7)	0.41
External rotation (median[b])	2.0 [1.5;4.5]	2.0 [0.0;5.0]	0.0 (0.0 to 0.0)	0.32
Abduction (median[b])	4.5 [2.0;5.5]	2.5 [1.0;5.0]	-2.0 (-5.1 to 1.1)	0.21
Response to Treatment				
Change SPADI clinical response[c] no. (%)	31%	27%	0.9[d] (0.27/0.31)	

*All analyses were based on the ITT population: Using a mixed model for repeated measurements (with a mixed-effects linear-models approach for missing data); Estimates will be least squares means (LSMeans) and standard

errors (SE) with the difference between groups reported with 95% confidence intervals (95% CI).
[a] SPADI ranges from 0 (best) to 100 (worst), with lower scores indicating better disease status.
[b] Median (IQR;InterQuartile Range) and median differences with 95% CI reported for these outcomes
[c] Patients classified as having a clinical response if the SPADI change score improves by ≥18 points.
[d] Risk ratio (RR) difference reported for these outcome.

Table 14: SPADI change scores for individual participants in *IG* and *CG*. This table is adapted from the manuscript for *Study IV*.

Surgery/oncological treatment	*SPADI-score* [a]		*Change in SPADI-score* [a]	
	Baseline	12 weeks follow-up	SPADI-change	SPADI clinical response (≥ 18 points) [b]
Intervention Group (*IG*)				***31%***
Breast Conserving Surgery and Sentinel Lymph Node Biopsy + radiotherapy				
	16.25	19.00	+2.75 (aggravation)[c]	-
	44.13	18.5	-25.63 (improvement)[c]	Improvement
	85.63	86.00	+0.37 (aggravation)[c]	-
	49.50	16.63	-32.87 (improvement)[c]	Improvement
	44.88	38.88	-6.00 (improvement)[c]	-
	38.75	54.50	+15.75 (aggravation)[c]	-
	64.63	75.38	+10.75 (aggravation)[c]	-
	16.13	16.50	+0.37 (aggravation)[c]	-
Breast Conserving Surgery and Axillary Lymph Node Dissection + radiotherapy				
Mastectomy and Sentinel Lymph Node Biopsy – radiotherapy				
Mastectomy and Axillary Lymph Node Dissection + radiotherapy				
	69.13	50.25	-18.88 (improvement)[c]	
	29.63	27.63	-2.00 (improvement)[c]	
	68.25	51.00	-17.25 (improvement)[c]	
	47.50	31.75	-15.75 (improvement)[c]	-
	36.88	9.75	-27.13 (improvement)[c]	Improvement
	46.88	23.75	-23.13 (improvement)[c]	Improvement
	23.38	7.50	-15.88 (improvement)[c]	-

Control comparator Group (*CG*)				***27%***
Breast Conserving Surgery and Sentinel Lymph Node Biopsy + radiotherapy				
	37.25	21.00	-16.25 (improvement)[c]	-
	55.25	11.50	-43.75 (improvement)[c]	Improvement
	24.75	14.00	-10.75 (improvement)[c]	-
	45.38	2.88	-42.50 (improvement)[c]	Improvement
	48.50	32.25	-16.25 (improvement)[c]	-
	52.88	57.75	+4.87 (aggravation)[c]	-
	35.38	19.00	-16.38 (improvement)[c]	-
Breast Conserving Surgery and Axillary Lymph Node Dissection + radiotherapy *Mastectomy and Axillary Lymph Node Dissection + radiotherapy*				
	71.75	65.13	-6.62 (improvement)[c]	-
	68.25	67.38	+0.87 (aggravation)[c]	-
	73.75	54.38	-19.37 (improvement)[c]	Improvement
	34.88	17.75	-17.13 (improvement)[c]	-
	26.00	12.88	-13.12 (improvement)[c]	-
	33.13	38.63	+5.50 (aggravation)[c]	-
	63.50	67.88	+4.38 (aggravation)[c]	-
	43.63	15.13	-28.50 (improvement)[c]	Improvement

[a] SPADI ranges from 0 (best) to 100 (worst), with lower scores indicating better disease status
[b] Participants were classified as having a clinical response if the SPADI change score improved by ≥18 points, and reported as no. (%)
[c] Values are reported as + (aggravation) or – (improvement)

Table 15: Sensitivity Analysis at 12 weeks in the ITT population using a single-step non-responder (BOCF) imputation. This table is adapted from the manuscript for *Study IV*.

Outcome	***12 weeks after initiating the treatment***		***Between-Group Difference in Mean Improvement***	
	Intervention group (IG)	*Control comparator group (CG)*	*Difference in LSMeans (95%CI)[b]*	*P-Value*
	LS Means (SE)†	LS Means (SE)†		
Primary endpoint				
Change SPADI overall score[a] (0-100)	-9.6 (2.7)	-14.5 (2.8)	-4.8 (-12.5 to 2.9)	0.22
Key secondary outcome measures				
Change SPADI pain[a] (0-100)	-12.2 (3.7)	-17.0 (3.8)	-4.7 (-15.4 to 6.0)	0.38
Change SPADI function[a] (0-100)	-7.2 (2.3)	-11.9 (2.4)	-4.7 (-11.3 to 1.9)	0.16

[a] SPADI ranges from 0 (best) to 100 (worst), with lower scores indicating better disease status
[b] Estimates are least squares means (LSMeans) and standard errors (SE) with the difference between groups reported with 95% confidence intervals (CI)

Discussion

Summery of main findings

The extent of self-reported late-term impairments

Over 60% of Danish breast cancer survivors reported late-term impairments 3–7 years post-treatment, with most experiencing moderate to severe symptoms on validated patient-reported scales. These impairments affected medication use, and among women with shoulder impairments, also reduced work ability. However, these impairments were recorded in the DNPR for only a small percentage of survivors. This suggests either an underutilisation of specialized treatment by these women, or a negligence of registration of the relevant diagnostic codes in the Danish secondary healthcare.

Risk factors associated to develop late-term impairments

Women *with* self-reported late-term impairments were, on average, 56 years old at the time of surgery, typically employed, had a BMI ≥25, and at least one comorbidity.

Over 60% of breast cancer survivors reported late-term impairments, with significant risk differences across the standard treatments. Shoulder impairment was the most common complaint, affecting 33% of survivors. Women who underwent mastectomy and SLNB with radiotherapy or mastectomy and ALND with radiotherapy had the highest risk of shoulder impairment, followed by those treated with BCS and ALND with radiotherapy. Additionally, women who underwent mastectomy and SLNB with radiotherapy and received chemotherapy had an increased risk of self-reported late-term impairments compared to those who did not.

Treatments for late-term shoulder impairment

This was the first trial comparing individualised treatment and standardised home-based exercises for late-term shoulder impairments after breast cancer treatment. No significant difference in SPADI overall scores was found at 12 weeks (*p-value*=0.34). Some key secondary

outcomes favoured *CG* (GPE, A-ROM flexion/abduction, P-ROM flexion), but due to the trial's limited power, the risk of type II error remains high, making conclusions uncertain.

Interpretation of findings and comparison with previous studies

This PhD thesis examined physical late-term impairments among Danish breast cancer survivors: shoulder impairments, lymphedema, fatigue, and chemotherapy-induced neuropathy. Several key themes emerged across the PhD studies:

- High prevalence of self-reported late-term impairments
- Inadequate clinical registration and follow-up
- Socioeconomic and health-related vulnerability
- Variation in risk depending on treatment type
- Low participation in rehabilitation
- Limited evidence and unclear efficacy of interventions
- A healthcare system not routinely yet adapted to the complex needs of late-term survivors

These findings raise questions about how post-treatment care is conceptualised and delivered.

Shoulder impairments: common, multifactorial, and underprioritised

A consistent finding across the PhD studies is the persistent prevalence of shoulder impairments, reported years after treatment regardless of guideline treatments (e.g., mastectomy, ALND, SLNB, radiotherapy). This confirms previous research indicating that shoulder pain, reduced range of motion (ROM), and stiffness are common, multifactorial, and long-lasting conditions among breast cancer survivors[16,18,29,31-33,36,39]. Despite this, shoulder impairments only receive minor clinical attention, as follow-up care in Danish hospitals focused on recurrence detection[7,9], creating a gap in addressing late-term rehabilitation needs.

The relative burden and visibility of shoulder impairments may vary, and it remains unclear whether they are deprioritised in favour

of other late-term effects, such as psychological distress and lymphedema, or if they in general are underrecognised by clinicians and patients alike, as they may be perceived as a natural consequence of ageing and breast cancer treatment. Shoulder impairments are common in the general population, with an annual incidence of 1.2%[93], especially among people of working age[93-94]. These consequences may be particularly relevant for women with primary breast cancer, who are doubly exposed to both surgical treatment and radiotherapy, highlighting the urgent need for targeted prevention.

The DBCG guidelines recommend systematic assessment of locoregional late-term impairments[95-96], however detection and documentation in practice remain inconsistent[97]. Findings from the 2023 Danish Barometer study by Kræftens Bekæmpelse further underscore this gap, showing that many survivors report late-term impairments that are not adequately acknowledged during routine follow-up visits[98]. This distortion likely stems from a combination of multiple factors: a historical emphasis on cancer recurrence detection[7,9], lack of evidence for rehabilitation interventions of complex late-term impairments[18,26,29,36,39-40], and the fact that late-term impairments often fall outside routinely oncologists' core expertise.

Importantly, this PhD thesis indicated that simple, home-based exercises in a pamphlet potentially could provide functional improvement (ROM) after 3–7 years. It suggests that effective rehabilitation interventions do not have the need to be resource-intensive, provided they are timely and accessible. Vulnerable subgroups and barriers such as out-of-pocket costs, as reported by five participants in study IV declining treatment in the intervention group, indicate systemic inequalities in access that must be addressed[99]. This reflects findings from the Barometerundersøgelsen 2023, where patients reported that co-payment and unclear referral pathways were common barriers to receiving necessary rehabilitation services[98]. Existing literature also highlight the need for individualised treatment approaches[16,18,29,31-33,36,39]. Due to their multifactorial causes (e.g., scar tissue, surgery, radiotherapy) addressing shoulder impairments effectively requires interdisciplinary coordination involving physiotherapists, and the primary healthcare system. While this

may increase short-term healthcare costs, it holds the potential to reduce long-term burdens, such as increased morbidity, medication use, and workforce withdrawal[25-29,100].

Missed opportunities for early intervention

Only 13% of eligible women engaged in Study IV. This raises concerns about intervention timing, perceived relevance, and accessibility, especially for socioeconomically vulnerable groups. In summary, late-term impairments may not be addressed with a timely, structured, or sufficiently individualised response in the current Danish healthcare model. This aligns with existing literature pointing out weak systematic structures and underscore the need for greater efforts from healthcare professionals and policymakers to develop effective rehabilitation interventions[16,25,29,36,39-40]. The recently published Cancer Plan V (Kræftplan V) also calls for stronger, more equitable survivorship care, especially for those with physical or psychological sequelae[97].

Early physiotherapy has shown effectiveness in improving shoulder function within the first year post-treatment[35-37], yet this PhD-thesis highlights a missed opportunity: by the time rehabilitation is offered, impairments may already be entrenched. This raises an important question about timing: Should shoulder rehabilitation begin earlier as a preventive measure, perhaps immediately after completed treatment? Also, this PhD thesis identified a distinct high-risk subgroup of breast cancer survivors who may particularly benefit from targeted, preventive rehabilitation strategies[16,31-33]. These women, who self-reported persistent late-term impairments, were on average 56 years old at the time of surgery, commonly employed, and had a BMI ≥25 as well as at least one comorbidity. Their treatment patterns further indicated elevated risk when they underwent mastectomy with SLNB and radiotherapy, or mastectomy with ALND or BCS with ALND - both in combination with radiotherapy. Additionally, the risk increased when the women also received chemotherapy.

Study II found an association between physiotherapy and higher impairment risk, likely due to selection bias[101], since resourceful

women or those with severe symptoms are more likely to be referred[98]. Without structured screening tools, patients with milder symptoms may go unnoticed until symptoms worsen. The Barometer study corroborates this, noting women often lack knowledge about symptom development and where to seek help[98]. The DBCG guidelines for postoperative rehabilitation and prevention of upper limb late-term impairments advocates for early and risk-adapted rehabilitation[96]. Kræftplan V further recommends referring women with mild impairments to municipal services while reserving hospital-based rehabilitation for more severe cases[97].

Clinical practice, systemic challenges, and future directions

Currently, the lack of diagnostic coding and structured follow-up for late-term impairments in secondary healthcare hampers both clinical monitoring and research development. To better support women experiencing late-term impairments, new initiatives could be implemented, including:

- Improved diagnostic coding for late-term impairments for clinical practice for monitoring and research purposes
- Development and integration of screening tools to help physicians identify patients in need of rehabilitation
- A broader implementation of the digital platform developed by the Danish Center and Clinic for Late-effects (DCCL)[102] within routine care pathways.
- Developing and testing effective rehabilitation interventions.

Kræftplan V emphasizes the importance of anchoring tools in real-world clinical practice to ensure early detection and timely referral[97]. This PhD thesis contributes comprehensive, nationwide evidence linking guideline-based treatments for breast cancer with the risk of developing specific late-term impairments. Such insights can help healthcare providers—such as physicians and physiotherapists—guide early interventions, potentially reducing the burden of impairments and improving survivors' quality of life.

Looking ahead, future research should investigate:

- Optimal timing for initiating rehabilitation
- Identify vulnerable subgroups and tailored rehabilitation needs
- Factors influencing patient engagement and adherence
- Systemic reforms to integrate late-term survivorship care into standard practice in Danish hospitals.

A fundamental shift is needed, both in clinical mindset and system design, to treat breast cancer not just as an acute condition, but as a chronic survivorship journey, requiring ongoing support, also for those with physical impairments. National strategies, such as Kræftplan V and DBCG's clinical guidelines, provide a solid framework but could be strengthened through greater accountability, funding, and education across all levels of the healthcare system[95,97].

Limitations and strengths

Study I

A limitation of this nationwide cross-sectional survey study is the risk of selection bias[101]. The 'healthy participant effect' may have influenced results, as resourceful women are more likely to participate[98]. Additionally, the 605 women without e-Boks, often older or sicker, were excluded, potentially could underestimate the self-reported late-term impairments. However, this further highlights the need for a structured system to identify affected breast cancer survivors.

However, this study is among the few assessing self-reported late-term impairments in Danish breast cancer survivors 3-7 years post-operatively. Its strengths include a large nationwide cohort (6,046 participants), a high response rate (>60%), and minimal missing data (<5%). Another strength is that the self-administered questionnaire was specifically designed for Danish breast cancer survivors, incorporating validated scales (QuickDASH, LYMF-ICF-DK, BFI)[43,55-56,59] and tested by an expert group and the PPR-panel from Vejle Hospital. Additionally, linking survey data with high-quality registry data from DNPR[50] through the unique Danish CPR system[49] ensured the data completeness and accuracy.

Study II

This study had some limitations. First, the study population consisted of women who voluntarily participated in a nationwide cross-sectional survey, which may introduce selection bias and affect the generalizability of the findings[101]. Participants may be women with more significant late-term impairments, and the fact that this group receive physiotherapy could mistakenly suggest physiotherapy has no effect on late-term impairments. Second, due to the register-based nature of the study, information are limited to the data available in the registers. Data on certain factors like BMI and other relevant associated risk factors were not available. To address this limitation, the nationwide questionnaire collected data on these factors (e.g. height and weight to calculate BMI, alcohol consumption, and comorbidities), knowing that self-reported lifestyle data can be sensitive and often misreported, resulting in information bias[101]. Third, a potential limitation is the lack of detailed radiotherapy data, as axillary radiotherapy can contribute to shoulder impairments[31-33]. However, Group 1 in this study, representing about 7.5% of the total population of breast cancer survivors who received BCS and SLNB with radiotherapy, is small, so any impact on results is likely minimal and would probably reinforce the study findings. Shoulder impairments are associated to ALND, especially with radiotherapy, and to a lesser extent mastectomy[16,31]. The SENOMAC trial further showed that Danish patients receiving only extended radiotherapy without ALND reported fewer shoulder-related issues[103].

A major strength of the study is the use of a substantial nationwide cohort of breast cancer survivors. Additionally, it is considered a strength that survey data were linked with high-quality registry data from DNPR[50], via Denmark's unique CPR system[49,61]. Since Danish hospitals are tax-funded, all healthcare services for breast cancer patients are recorded in the DNPR[50,52]. This ensure comprehensive and accurate data for all women treated for breast cancer, minimise selection bias and improve the study's validity.

Study IV

This randomised controlled trial had some limitations. Only 31 of the expected 130 women (~13%) were included, making the study statistically underpowered with a high risk of type II error. This limits its ability to detect meaningful differences between interventions. The low recruitment rate also raises concerns about selection bias[101]. Potentially more resourceful women can cope better with home-based exercises, than less resourceful women who need of more individualised support. As a result, findings may not be generalizable to the broader patient population, emphasizing the need for more representative future studies. Nonetheless, this trial evaluated a complex intervention as a whole.

On the other hand, this trial was the first to compare individualised treatment with standardised home-based exercises for late-term shoulder impairments after breast cancer, addressing a research gap. It also had several key methodological strengths, including a publication of a detailed study protocol and a SAP, blinded outcome assessment, independent biostatistical analysis, and pre-unblinding result interpretation, enhancing the transparency and its credibility.

Ontological considerations

While this PhD thesis has primarily adopted a biomedical and epidemiological perspective, emphasising measurable outcomes, population-level associations, and structured data, this approach does come with ontological limitations. Late-term impairments are inherently complex, situated within personal, social, and healthcare contexts[18,22,24-28,36,39] that may not be fully captured through surveys, registries, or clinical endpoints alone. For example, how women perceive, manage, and prioritise late-term impairments can vary greatly and may be shaped by individual narratives, access to care, or societal expectations. These dimensions are less visible in quantitative frameworks[104]. Nonetheless, given the complexity of breast cancer survivorship and the need for scalable solutions within a hospital system, the chosen methodology has been relevant and appropriate for the aims of this PhD thesis. It has provided robust, generalizable evidence to inform clinical practice.

However, future research could benefit from integrating complementary qualitative or mixed-method approaches[104] to explore how late-term impairments are experienced and managed in everyday life, or to identify which rehabilitation interventions are most relevant and motivating; particularly those that align with women's busy daily routines. Such approaches could offer a richer, more nuanced understanding[104] that extends beyond what quantitative measures alone can reveal.

Conclusion

Over 60% of Danish breast cancer survivors reported late-term impairments 3-7 years postoperatively. Most of them experienced moderate to severe impairments, which affected medication use, and among women with shoulder impairments also reduced work ability. Despite the high self-reported rates, these impairments were recorded in the DNPR for only a small percentage of survivors, suggesting that they may be overlooked in Danish secondary healthcare.

To support physicians and physiotherapists, it is important to differentiate late-term impairments and understand the risks associated with Danish standard treatments. The nationwide cohort study revealed that Danish breast cancer survivors *with* self-reported late-term impairments had an average age of 56 years at time of surgery. Typically, they were employed, had a BMI ≥25, and reported at least one comorbidity. Surgically, they underwent BCS with ALND and radiotherapy, or mastectomy with SLNB or mastectomy with ALND, both combined with radiotherapy. The majority also received chemotherapy. Shoulder impairment was the most common complaint among the four dimensions of self-reported late-term impairments, and occurred across all standard treatments.

The randomised controlled trial found that an expert assessment followed by individualised treatment had no superior clinical effect over standardised home-based exercises on shoulder pain and disability symptoms among women with late-term impairments 3–7 years after primary breast cancer treatment. However, secondary key outcomes, such as GPE, A-ROM in flexion and abduction, and P-ROM in flexion, indicated potential benefits of the standardised home-based exercise intervention. As the trial was underpowered, these results are inconclusive but could hold clinical relevance, reinforcing the need for ongoing improvements in shoulder rehabilitation for breast cancer survivors.

Perspectives and implications

The PhD thesis revealed a high rate of self-reported late-term impairments among Danish breast cancer survivors, yet these conditions were rarely recorded in the DNPR. Whether due to underutilisation of specialised treatment or a failure to register the appropriate diagnosis codes in clinical practice, these women risk being overlooked in the secondary healthcare system. Greater attention should therefore be given to improving organizational structures within Danish hospitals to ensure timely detection and management of late-term impairments.

A potential strategy could be to expand the current cancer care pathway ("Kræftpakken") to implement screening procedures for late-term impairments and preventive rehabilitation for high-risk subgroups, rather than the general rehabilitation recommendation. Particularly younger women who underwent BCS with ALND, mastectomy with SLNB or mastectomy with ALND, all of them combined with radiotherapy, and also received chemotherapy, as identified in this PhD thesis. Understanding the association between Danish guideline treatments for breast cancer, and their risk of self-reported late-term impairments can support physicians and physiotherapists in tailoring preventive rehabilitation efforts. Future research should prioritize the development of predictive tools and treatment trials aimed at reducing late-term consequences for breast cancer survivors. In addition a stronger focus on using correct “late-term effect” diagnosis codes in clinical practice, will provide a more comprehensive data set and thus a deeper understanding of the problem.

Only 13% of eligible participants joined the intervention trial, possibly due to reluctance to revisit their illness, acceptance of shoulder impairment as a natural consequence of treatment, or skepticism about treatment effectiveness. Others may have resumed busy lives or avoided further trials after previous long follow-ups. Future research should address these barriers more in greater depth, to identify which rehabilitation interventions are most relevant and motivating; particularly those that align with women's busy daily routines.

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Appendices

Appendix 10. *Study II*. A national cohort study, p. 120

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Appendix 11. *Study IV*. Primary and secondary outcomes from the randomised controlled trial, p. 143

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