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PhD thesis

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Early recovery and chronic sequelae after treatment for breast cancer

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List of abbreviations

ALND	Axillary lymph node dissection
BCS	Breast conserving surgery
BRT	Breast radiotherapy, loco-regional radiotherapy to the residual breast tissue
CEF	Cyclofosphamide, epirubicin, and fluorouracil (chemotherapy)
DASAIM	Danish Society of Anaesthesiology and Intensive Care Medicine
DBCG	Danish Breast Cancer Cooperative Group
EMLA	Eutectic mixture of local anaesthetics
ICN	Intercosto brachial neuralgia
PACU	Post-anaesthetic care unit
PMPS	Post-mastectomy pain syndrome
PONV	Postoperative nausea and vomiting
PVB	Paravertebral block
SLND	Sentinel lymph node dissection
TIVA	Total intravenous anaesthesia
VAS	Visual analogue pain score
5HT3-antagonist	5-hydroxytryptamine-3 receptor antagonist, anti-emetic drug

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Preface

Most breast cancer research has a natural focus on the treatment and survival of breast cancer patients.

The aim of this thesis is to deal with: 1) treatment-related discomfort in the early recovery phase and 2) the physical chronic sequelae affecting patients treated for breast cancer.

In order to improve treatment-related discomfort in the early recovery phase a multimodal opioid-sparing evidence-based regimen for prevention of PONV and pain was introduced at the Department of Breast Surgery at Rigshospitalet. The purpose was to implement current knowledge regarding prevention of pain and PONV to the benefit of the patients and subsequently to facilitate the introduction of a short stay practice in the department. The two studies adherent to the implementation of the regimen were designed to explore the level of treatment-related discomfort after the introduction of the regimen at the post-anesthetic care unit (PACU), exploring why patients stayed at the unit (Article I) and controlling for the most common side effects and eventual discomfort at the ward (Article II).

In order to uncover treatment-related physical chronic sequelae after treatment for breast cancer, a questionnaire was designed and sent out nation wide. The questionnaire focused on frequencies and severity of pain, sensory disturbances, lymphedema and functional impairment in different treatment groups defined by modern treatment standards. Furthermore, the impact of different treatment modalities on pain and sensory disturbances as well as lymphedema and functional impairment was assessed in multivariate analyses. Pain and sensory disturbances, and lymphedema and functional impairment are reported in Articles III and IV respectively.

Thus the thesis is based on four articles:

- I **Dealing with:** Why patients are at the PACU after breast cancer surgery.
- II **Dealing with:** Frequency and severity of pain and PONV after the implementation of a multimodal opioid-sparing regimen in breast cancer surgery controlling for eventual side effects of the regimen.
- III **Dealing with:** Prevalence and severity of and factors associated with pain and sensory disturbances after treatment for breast cancer.
- IV **Dealing with:** Prevalence and severity of and factors associated with lymphedema and functional impairment after treatment for breast cancer.

Aim of the Thesis

The aim of the thesis is divided in two:

1. Optimising early recovery after surgery for breast cancer, facilitating the introduction of a short stay practice in breast cancer surgery (Article I and II).
2. Describing the prevalence and severity of and factors associated with chronic pain, sensory disturbances, lymphedema and impairment of function in the late recovery phase (Article III and IV).

Articles on which this PhD thesis is based

Part 1.

- I Gartner R, Callesen T, Kroman N, Kehlet H. Recovery at the post anaesthetic care unit after breast cancer surgery.
Dan Med Bull 2010;57:A4137.
- II Gartner R, Callesen T, Kroman N, Kehlet H. Multimodal prevention of pain, nausea and vomiting after breast cancer surgery.
Minerva Anesthesiologica, 2010;76:805-13.

Part 2.

- III Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery.
JAMA 2009;302:1985-92.
- IV Gartner R, Jensen MB, Kronborg Lise, Ewertz M, Kehlet H, Kroman N. Self-reported arm-lymphedema and functional impairment after breast cancer treatment - A nationwide study of prevalence and associated factors.
The Breast 2010;19:506-515.

English summary

Breast cancer is the most common cancer among women in the Western world. Today more than 45,000 women are living in Denmark after treatment for breast cancer and more than 4,000 new breast cancer cases are diagnosed every year.

According to the literature, postoperative pain, nausea and vomiting cause substantial problems in postoperative care, thus compromising early recovery. The population of women treated for breast cancer is growing due to increased incidence and higher survival rates. Accordingly physical problems such as persistent pain, sensory disturbances, lymphedema and functional impairment are affecting an increasing number of women with longer general life expectations.

The studies on which this thesis is based were aimed at 1) optimising the early recovery after surgery for breast cancer and 2) describing the prevalence of, and factors associated with, physical problems in the late recovery phase.

1. Early recovery after surgery for breast cancer.

In an attempt to improve early recovery, an evidence-based multimodal opioid-sparing regimen for preventing pain and postoperative nausea and vomiting (PONV) was introduced. Effects on pain and PONV, as well as major side effects, were recorded for 36 hours postoperatively. Additionally, the pathway of the patients through the postoperative anaesthetic care unit was monitored in order to examine why the patients were at the unit and which factors prolonged their stay.

The postoperative pathway of the patients was changed in accordance with the findings, discharging 70% of the patients directly to the ward and reducing mean hospitalisation from 3.6 days to 1.2 days.

2. Chronic sequelae after breast cancer surgery and adjuvant treatment

In order to determine the prevalence of, and factors associated with, chronic physical problems, a nationwide questionnaire study was undertaken. Patients following modern standardised treatment, according to the Danish Breast Cancer Cooperative Group protocols for 2004, were included. According to these treatment protocols, the patients could be divided into 12 distinct treatment groups. The prevalence of persistent pain, sensory disturbances, lymphedema and functional impairment was recorded for each group, and odds ratio estimates were calculated for the factors associated with these problems. Depending on their treatment group, 25-60% of the patients reported pain, 40-85% reported sensory disturbances, 13-65% lymphedema and 11-44% functional impairment.

Research into the recovery of patients after treatment for breast cancer has become increasingly complicated, as the process of tailoring the treatment to the individual breast cancer status has increased the number of treatment modalities affecting the course of recovery and long-term physical problems. The pace at which the treatment of breast cancer is changing highlights the importance of adjusting the postoperative care continuously, as well as monitoring the long term consequences in order to identify patients at high risk of developing physical problems and find ways to reduce this risk and improve the treatment of the treatment related problems.

Danish summary

Brystkræft er den hyppigste kræftform blandt kvinder i den vestlige verden. I Danmark lever over 45.000 kvinder i dag efter behandling for brystkræft og mere end 4.000 nye tilfælde diagnosticeres hvert år.

I følge litteraturen er smerter, kvalme og opkastning betydelige problemer i den tidlige postoperative fase og medvirker til at forsinke mobilisering og udskrivning.

Antallet af kvinder behandlet for brystkræft er stigende dels på grund af et øget antal tilfælde dels på grund af forbedret overlevelse. Fysiske gener som kroniske smerter, føleforstyrrelser, lymfødem og funktionsindskrænkning har således betydning for et stigende antal kvinder, der desuden har udsigt til at leve stadigt længere.

Studierne i denne afhandling havde 1) til formål at optimere det tidlige postoperative forløb efter kirurgi for brystkræft 2) at afdække prævalens af og faktorer forbundet med fysiske gener i senforløbet.

1. Det tidlige postoperative forløb efter brystkræftkirurgi.

Med henblik på at reducere de postoperative gener blev et multimodalt opioidbesparende regime til forebyggelse af smerter, kvalme og opkastning indført. Smerter, kvalme og opkastning såvel som bivirkninger blev løbende registreret de første 36 timer efter operationen. Endvidere blev patienternes ophold på opvågningsafsnittet undersøgt med henblik på at afklare, hvorfor patienterne lå på afsnittet og hvilke faktorer der forlængede deres ophold.

Det postoperative forløb blev ændret i overensstemmelse med resultaterne af undersøgelserne og resulterede i at 70% af patienterne nu køres direkte på afdelingen (uden om opvågningsafsnittet) og den samlede gennemsnitlige indlæggelsestid er blevet reduceret fra 3,6 til 1,2 dage.

2. Kroniske følger efter kirurgi for brystkræft og adjuverende behandling

Med henblik på at afdække prævalens af og faktorer forbundet med fysiske gener i senforløbet blev en landsdækkende spørgeskemaundersøgelse gennemført. Patienter der fulgte Danish Breast Cancer Cooperative Group's 2004-behandlingsprotokoller blev inkluderet. Patienterne kan jævnfør protokollerne inddeles i 12 forskellige behandlingsgrupper. Prævalensen af kroniske smerter, føleforstyrrelser, lymfødem og funktionsindskrænkning, blev afrapporteret for hver af disse grupper og odds ratioer beregnet for faktorer relaterede til generne.

Afhængigt af behandlingsgruppe rapporterede 25-60% af patienterne smerter, 40-85% føleforstyrrelser, 13-65% lymfødem og 11-44% funktionsindskrænkning.

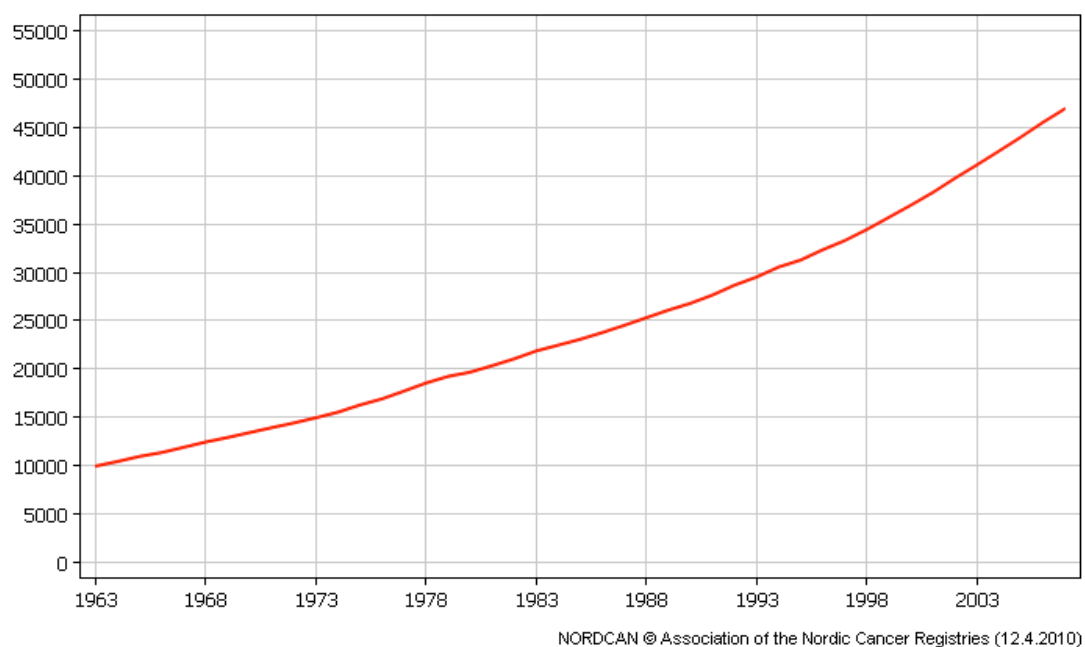
Forskning i gener efter behandling for brystkræft er blevet tiltagende kompliceret i takt med at behandlingen er blevet skræddersyet til den enkeltes sygdom, og antallet af behandlingsmodaliteter, der kan påvirke rehabilitering og fysiske langtidsgener, dermed er blevet øget. Tempoet hvormed behandlingen af brystkræft til stadighed ændres understreger vigtigheden af løbende at justere de postoperative forløb samt monitorere senfølger, for herved at kunne identificere patienter med øget risiko for at udvikle kroniske gener, finde nye veje til at reducere risikoen samt forbedre behandlingen af disse gener.

Background

Development in prevalence, incidence and survival of breast cancer

Today more than 45,000 women treated for breast cancer are living in Denmark and over 4,000 new breast cancer cases are diagnosed every year [1]. The incidence of breast cancer in Denmark has increased over the years and the overall 5-year survival rate for Danish women with breast cancer has improved and is today over 85% [2]. Thus the population of women treated for breast cancer is growing (Fig.1).

Figure 1. Prevalence of women with breast cancer in Denmark 1963-2007.



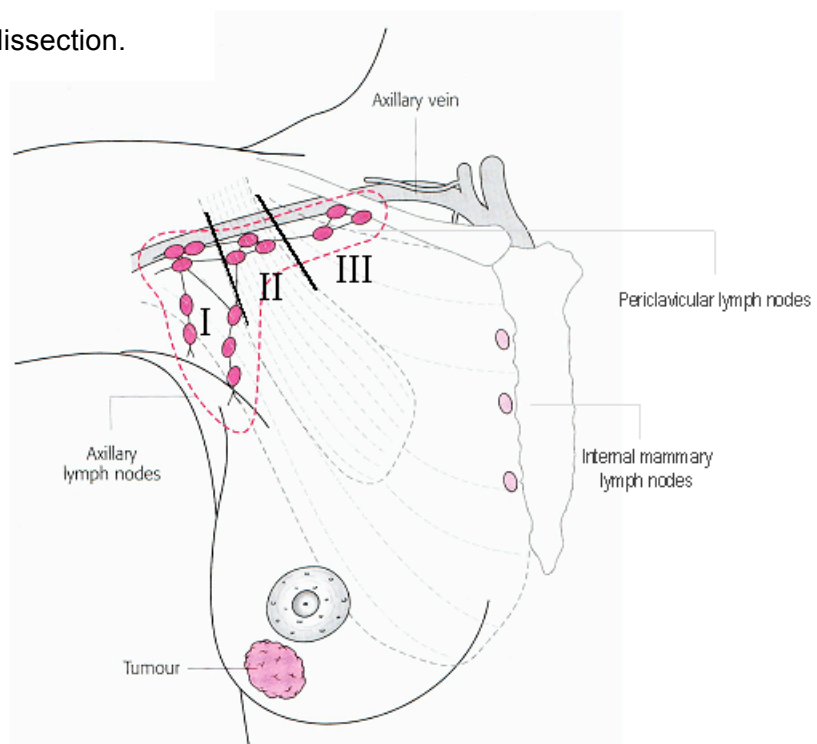
Development in treatment of breast cancer

Guidelines for the treatment of breast cancer in Denmark have been set up by The Danish Breast Cancer Cooperative Group (DBCG) since 1977, where the group established a database prospectively collecting detailed clinical data, histopathological status of the tumors, as well as data on treatment, recurrence and mortality in breast cancer patients [3].

The treatment of breast cancer has increasingly been tailored to the individual case over the last 15 years [3]. The dramatic changes in surgical procedures have aimed at reducing postoperative morbidity, while the intensified use of adjuvant therapy has secured improved survival rates [2,4].

At the end of the 20th century, the standard operation for breast cancer was modified radical mastectomy (including removal of the breast tissue and the fascia over the pectoralis muscle) combined with axillary lymph node dissection (ALND, Levels I and II, Fig. 2). In 1989 breast conserving surgery (BCS, also termed lumpectomy or tumorectomy) was introduced in Denmark [5], and in 1997 sentinel lymph node dissection (SLND, involving identification and biopsy of the first-line lymphnode(s) draining the breast) was introduced at four centres, spreading to all Danish breast cancer centres in 2001 [6].

Figure 2. Axillary lymph node dissection.



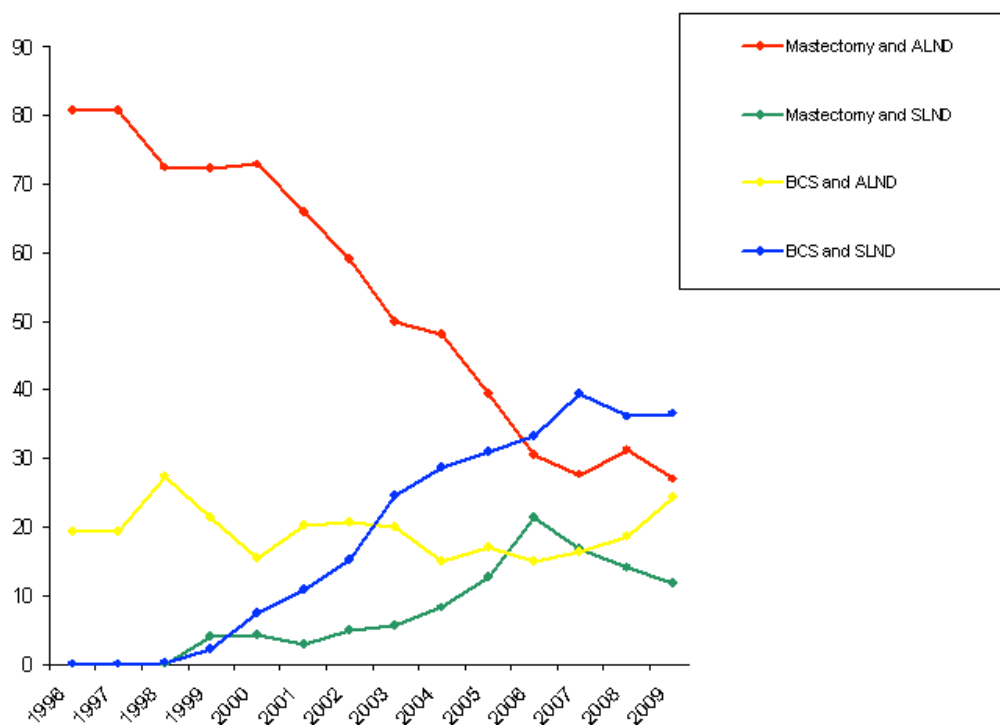
In 1996, 81% of women treated for breast cancer at the Department of Breast Surgery, Rigshospitalet, underwent mastectomy and ALND. In 2009 this figure was 27% and BCS and SLND had become the most frequent surgical procedures (Fig. 3).

With BCS, loco-regional breast radiotherapy (BRT) to the residual breast tissue was introduced as a mandatory part of the treatment in order to reduce the risk of recurrence. Thus modern treatment of breast cancer implies that more than 75% of patients undergo radiotherapy. In the case of macro-

metastasis, the radiation field is expanded to the axillary and periclavicular lymph nodes

corresponding to Level III and internal mammary lymph nodes for right-sided breast cancer [7] (Fig. 2). The regimen of adjuvant chemotherapy has changed several times over the years and has been increasingly adjusted to histopathological status, resulting in growing numbers of patients receiving adjuvant chemotherapy [3].

Figure 3. Development in the surgical breast cancer procedures in % performed at the university hospital, Rigshospitalet, Denmark 1996 to 2009.



1. Early recovery after breast cancer surgery

Introduction:

With the development in surgery, more patients undergo minor surgical procedures and the need for hospitalisation is consequently reduced [3,8]. Hospitalisation today is mainly due to postoperative problems such as pain and postoperative nausea and vomiting (PONV). However, having sufficient time to offer psycho-social support, giving general information and ensuring good coherence in the pathway of treatment are important concerns in the introduction of fast-track cancer surgery. Thus prevention of pain and PONV and structuring psycho-social support, giving general information and ensuring the patients' feeling of coherence in the course of treatment are important to secure fast rehabilitation and good "quality of life".

The aim of the first part of the thesis: Optimising the early recovery after surgery for breast cancer, focused on prevention of pain and PONV. The best existing evidence was searched, with the aim of constructing a simple oral multi modal opioid-sparing regimen for prevention of pain and PONV.

Subsequently two quality control studies were set up to evaluate the consequences at PACU and in the ward after the introduction of the regimen. Simultaneously with this work another part of the research group focused on structuring the psychosocial support and initiated a prospective study on psychological distress in order to evaluate tools for identification of patients at risk of developing depression.

Thus the outcome measures of the two studies presented in the first part of the thesis focused on the acute undesirable consequences of surgery and anaesthesia and the flow of the patient through PACU and were structured around the clinical setting at the department of anaesthesiology and breast cancer Clinic at Rigshospitalet.

The PACU, which served the department of Breast Surgery, can observe 18 patients and has very different groups of patients and no day-surgery functions. Additionally the resources at the unit are stretched to their limits. Thus, the premises for setting up a day-surgery unit for breast cancer surgery at the time of the studies was not present in the PACU. The purpose of the two studies was therefore,

through quality control of the implementation of a best evidence based multi model regimen for prevention of pain and PONV, to confirm the experience from other clinics [9-12] that day surgery could also be implemented at our institution.

Hence the purpose of Study I was to evaluate persisting problems at PACU after implementation of the regimen and pinpoint the problems of a non-specific PACU discharge-score at a non-breast-cancer-specialised PACU department questioning the need for PACU stay after treatment for breast cancer. The primary outcome measures were the number of patients fulfilling the discharge criteria at arrival at PACU, length of stay at PACU and factors preventing discharge from PACU. The secondary outcomes were the reasons for patients staying at PACU after fulfilment of the discharge criteria reflecting the clinical reality at PACU at the time.

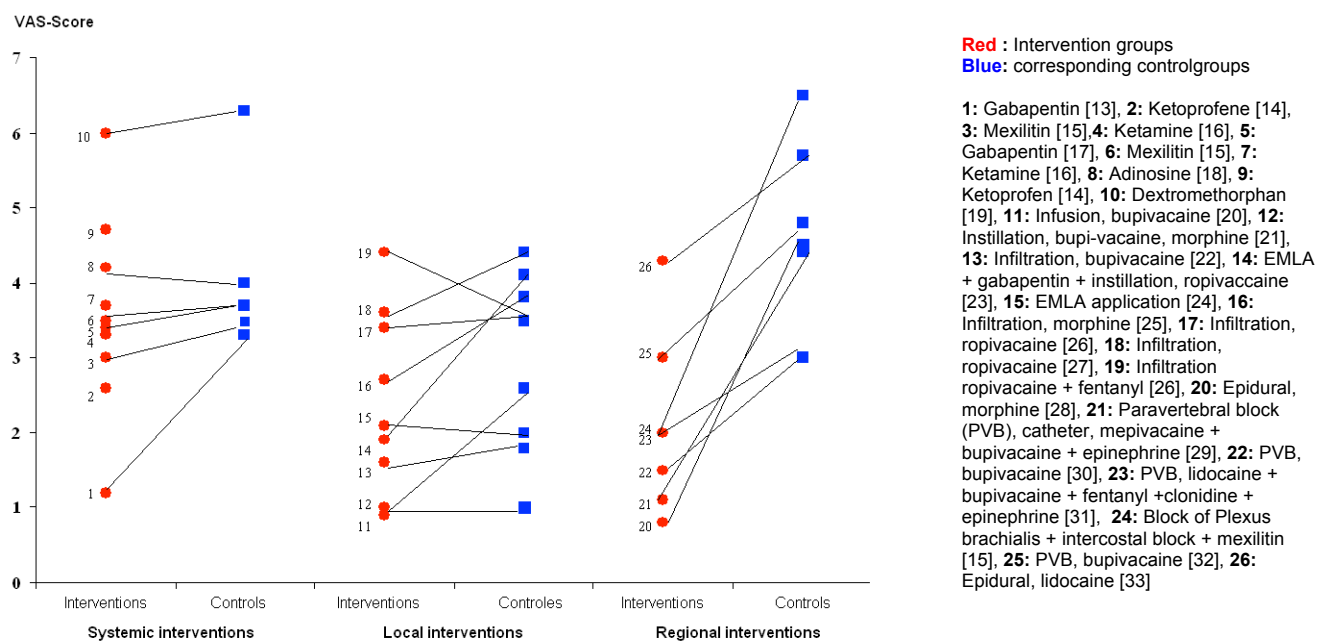
The aim of Study II was plain quality control of the regimen. Primary outcome measures were PONV and pain during rest and mobilisation as well as incidence of the major side effects: Dizziness, headache, diplopia, confusion and memory disorders for 36 hours after surgery. Secondary outcome measures were time from end of anaesthetic infusion to spontaneous breathing, and postoperative requirement of morphine at the post anaesthetic care unit (PACU) and in the ward.

Background:

Post-operative pain and prevention

According to the literature, patients undergoing surgery for breast cancer suffer moderate pain, Figure 4. However, the variation in surgical procedures, outcome measures for pain, populations studied and methods of measurements make studies of prevention of early postoperative pain difficult to compare.

Figure 4. 24-hours mean or median visual analogue scores (VAS) for different kinds of interventions and controls for preventing pain after breast cancer surgery.



Gartner R, Kroman N, Callesen T, Kehlet H. Ugeskr Laeger 2008 Jun 2;170(23):2035-8.

The most important pathogenic mechanisms behind early postoperative pain are nerve damage and inflammatory response [34].

Interventions aiming at preventing postoperative pain can in general be divided into 3 groups, following the same topographical system as in breast cancer treatment: **Local** interventions based on application, infiltration, instillation or infusion of local analgesics; **regional** analgesic techniques such as intercostal nerve blockade, paravertebral blockade and thoracic epidural; and **systemic** pharmacological interventions. More detailed descriptions and brief evaluation of the different kinds of interventions are presented in Fact box 1.

Fact box 1. Description of interventions aiming at preventing postoperative pain after surgery for breast cancer.

LOCAL analgesic interventions	
Local application of EMLA	Has shown to have an effect on early postoperative pain, but the size of the studies is small [24,35].
Local analgesic catheter	Continuous infusion in the wound(s) by catheter(s) has proven effective in many kinds of surgery [36], but limited procedure-specific studies are available.
Intraoperative infiltration of local analgesics	Has proven effective in procedure-specific studies [35] as well as in studies of other kinds of surgery [37].
REGIONAL analgesic techniques	
Intercostobrachial blockade	Has shown to be effective in a few procedure-specific studies [15,38]. Implies a risk of pneumothorax.
Paravertebral block	Effective in a large number of procedure-specific studies [29-32,39-43]. Implies special anaesthesiological expertise and risk of pneumothorax.
Thoracic epidural	Effective in a number of procedure-specific studies [28,33,44,45]. Implies special anaesthesiological expertise and a risk of severe complications e.g. intraspinal haematoma.
SYSTEMIC pharmaceutical interventions	
Gabapentin	An anticonvulsive drug used in the treatment of chronic neuropathic pain [46]. As nerve damage plays an important role in the mechanisms involved in early postoperative pain, it has proven effective in the reduction of postoperative pain after breast cancer surgery [13,46,47]. Single prophylactic dose: oral 600-1200 mg
Dextromethorphan	An n-methyl-d-aspartate (NMDA) receptor antagonist and originally an antitussive medicament [48,49]. It has a weak analgesic effect and a very strong safety profile [50]. Dextromethorphan lacks the psycho-mimetic side-effect of Ketamine (another NMDA receptor antagonist used in anaesthesia). Single prophylactic dose: oral 30-90 mg
Selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors)	Have selective effect on the COX-2 receptors involved in inflammatory pain response in contrast to the nonsteroidal anti-inflammatory drugs (NSAID) also inhibiting the COX-1 receptors known to compromise thrombocyte aggregation and thus increase the risk of haemorrhage [51-53]. Increased risk of thromboembolic cardiovascular events have been reported in long term users of COX-2 inhibitors [54] and in patients undergoing coronary-artery bypass grafting [55]. However, there is no evidence that increased risk of thromboembolic cardiovascular events is associated with single dose or short term perioperative use of COX-2 inhibitors in noncardiac surgery [56]. Single prophylactic dose: oral 200-400 mg
Paracetamol	Has a well-documented analgesic effect, a strong safety profile and, in combination with NSAID, a supra-additive analgesic effect [57,58]. Single prophylactic dose: 1000 mg

Breast cancer surgery is surface surgery and in general does not cause severe pain (Fig. 4.). The procedure-specific evidence, in favour of regional analgesic techniques (Fig. 4), is in concordance with the evidence from other types of surgery, but the analgesic advantages are limited compared to the risk of complications linked to such invasive procedures.

With the exception of intraoperative infiltration of local analgesics, proven safe as well as effective in a wide range of other surgical procedures [37], the local approach with "pain catheters" or topical application of local anaesthetics is impractical in a fast track setting and compromises mobilisation. In contrast, systemic prophylactic medication is easy to implement and agents like gabapentin [46,47], paracetamol [57,58], dextromethorphan [48,50] and cox-2 inhibitors [53] have proven effective in procedure-specific studies of postoperative pain prevention and in studies of equivalent surgery [59,60].

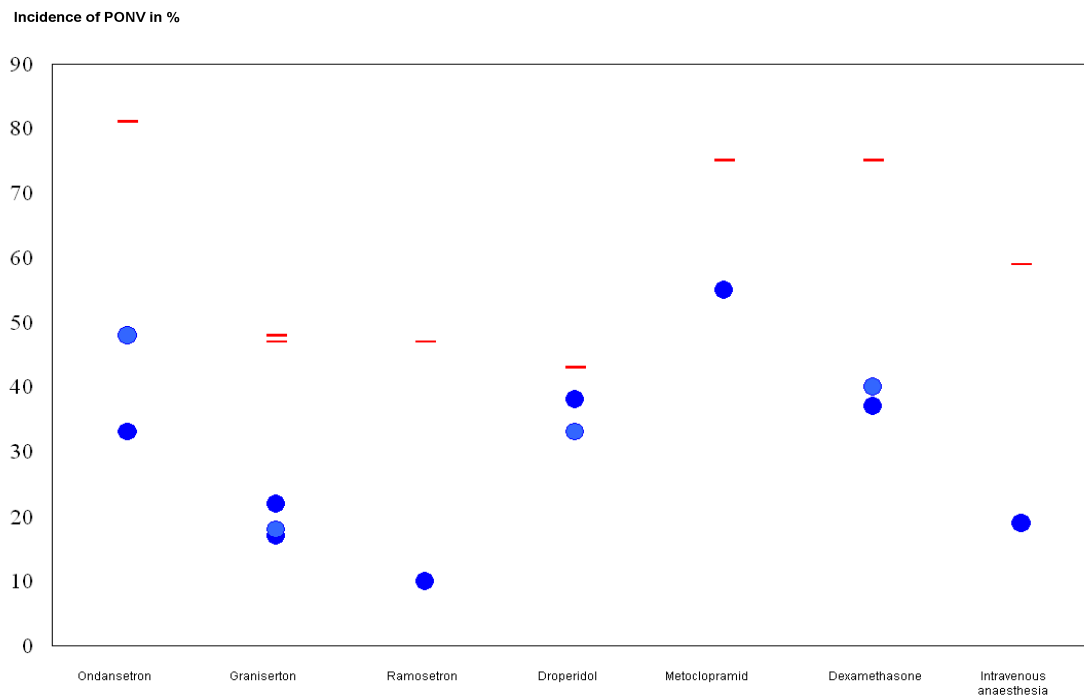
Since receptors and chemical substances involved in acute postoperative pain are multiple, a combination of non-opioid analgesic drugs with different mechanisms of action and synergistic effects may be feasible for prevention of acute postoperative pain after surgery for breast cancer [61,62] and potentially reduce the need for postoperative opioids and their side effects. This is the concept of multimodal opioid-sparing regimens for prevention of pain and PONV.

Post-operative nausea and vomiting (PONV) and prevention

In intervention-studies of prevention of PONV in women undergoing breast cancer surgery, the 24-hour incidence in the placebo groups was 50-80%, and 10-55% in the mono-pharmaceutical intervention-groups (Fig. 5). Most studies used volatile anaesthetic agents well known to cause PONV [63]. Use of intravenous anaesthesia reduces the risk considerably [64] (Fig. 5). More detailed descriptions of agents for preventing PONV are presented in Fact box 2.

The mechanisms causing PONV are multiple. Having a history of motion sickness, being non-smoker, being of a younger age, being female and undergoing general anaesthesia (as opposed to regional anaesthesia) all increase the risk of PONV [65]. Furthermore, the use of postoperative opioids increases risk of PONV as do a number of surgical procedures per se, breast cancer surgery being one of them [65]. Thus women undergoing surgery for breast cancer are at a high risk of developing PONV. Procedure-specific studies and evidence from equivalent surgical procedures suggest that a combination of intravenous anaesthesia, a 5-hydroxytryptamine-3 receptor antagonist (5HT₃-antagonist), dexamethasone and opioid-sparing pain prevention may be feasible for prevention of PONV [66].

Figure 5. 24-hour incidence of PONV in women undergoing breast cancer surgery.



Blue: Intervention groups. **Red:** control groups

Interventions: Ondansetron [64,67,68], granisetron [69,70], ramosetron [69], droperidol [70,71], metoclopramide [72], dexamethasone [68,72], intravenous anaesthesia [64].

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Fact box 2. Description of pharmaceutical agents for preventing PONV.

5-hydroxytryptamine-3 receptor antagonist (5HT₃-antagonists)

Ondansetron, granisetron or ramosetron are serotonin antagonists preventing nausea and vomiting by blocking peripheral as well as central 5-HT₃-receptors. 5HT₃-antagonists have proven to be the most efficient drugs in prevention of PONV [66] (fig.5).
Single PONV prophylactic dose of ondansetron: 4 mg 20 min. before end of surgery.

Dehydrobenzperidol (droperidol)

An antidopaminergic drug previously also used in psychotic patients. It has proven effective in the treatment and prevention of PONV [70,71], but can not be recommended as a first line preventive drug due to its potential side effects: dysphoria, sedation and hypotension caused by peripheral alpha adrenoceptor blockade.

Metoclopramide

A dopamin-2-antagonist with gastroprokinetic and antiemetic drug having limited effect on gastro kinetics, but shown to be inefficient in preventing PONV after treatment for breast cancer [72].

Dexamethasone

A potent synthetic member of the glucocorticoid class of steroid hormones has as single dose proven to be equally as effective as 5HT₃-antagonists and has in higher dose additionally a postoperative analgesic effect [66,73].
Single PONV prophylactic dose: 4-8 mg

Intravenous anaesthesia

Consisting of propofol and short or long lasting opioids is today standard in breast cancer surgery in Denmark and has proven to reduce PONV considerably compared to anaesthesia with volatile agents [64].

Fast-track surgery

Early discharge of women undergoing surgery for breast cancer has been an important topic for almost two decades [74]; so has the discussion of how far to go in order to reduce healthcare costs, as reflected by President Bill Clinton's remark in his State of the Union speech in 1997: "we must now stop the dangerous and demeaning practice of forcing women home from hospital only hours after a mastectomy" [75].

The priority in fast-track surgery must be to care for the needs of the patients. Most patients dislike hospitals: "It's awful being in hospital. All those noises and smells. I can't sleep in strange places" [76]. Telling the patients that there are no medical reasons for staying at the hospital after the surgery, and that most patients can go home the same night, is a relief to most patients, as it indicates that the surgery is just a minor procedure after which they will soon be back in their own safe environment [76]. This sort of expectation management is crucial in fast-track surgery, but also increases the demands for preventing PONV and pain to optimise the pathway of the patient at the hospital. Even though mild PONV and moderate pain are not life threatening, patients still feel sick and do not want to go home the same night.

The evidence in favour of fast-track surgery regarding safety [9-11,77], patients' satisfaction [9-12,77], quality of life [12,77], recovery and rehabilitation [12,77,78] is today well-established.

However, implementing fast-track surgery requires a consistent schedule of patient information and empowerment, which especially at many hospitals in the early nineties in the US, due to economic reasons, was neglected and the concept was thus discredited [79].

The main goal for fast-track surgery should be to reduce postoperative problems in order to ensure that the patients' energy is not wasted on recovering from surgery, but can be used to process the far more important psychosocial distress generated by the breast cancer diagnosis, the uncertainty of the future including the risk of death and the worries about adjuvant treatment.

The post-anaesthetic care unit (PACU) and transfer to the postoperative care at the ward.

In order to optimise the pathway of the patient in a fast-track setting, early recovery and evaluation of vital parameters postoperatively play a crucial role. Unnecessary observation time at the post-anaesthetic care unit can be a logistic problem, preventing patients operated on in the afternoon from going home the same night. On the other hand, transferral of patients scoring low in vital parameters could compromise patient safety.

In order to secure patient safety and quality in the service, The Danish Society of Anaesthesiology and Intensive Care Medicine (DASAIM) introduced a new set of recommendations in 2004, including a discharge-criteria scoring system for discharging patients from PACU to the surgical ward (www.dasaim.dk/menu-03/index.html).

The discharge system was based on the idea of a score introduced by Aldrete and Kroulik in 1970 including motor function, respiration, circulation, consciousness and skin colour [80]. The Aldrete score did not include heart rate and pulse oxymetry, which today are regarded as mandatory by a number of societies of anaesthesiology. However, the use of these parameters in PACU is based on the lowest grade of scientific evidence (www.dasaim.dk/menu-03/index.html), and a correlation between postoperative hypoxemia and the occurrence of morbidity has not been shown [81]. The DASAIM score additionally included PONV and pain as these were thought to be central in the field of anaesthesia and of great importance to the patients. Finally, hourly urinary output and temperature were included in the DASAIM score (Appendix I). The score recommended by DASAIM was designed to be applicable to all surgical patients who are to be transferred to the surgical ward and discharged from there. However, the duration of breast cancer surgery in Denmark is normally between 1 and 2 hours, the heat loss from the surgical field is limited, and anaesthesia is hardly ever carried out using muscle relaxants. Thus motor function; temperature and hourly urinary output must be considered irrelevant for routine breast cancer surgery. Consequently, a modified score for breast cancer patients, excluding these parameters, was introduced together with the implementation of the discharge-criteria scoring system during Autumn 2006 at Rigshospitalet.

Material and methods:

The two studies on which the first part of this thesis is based were prospective, consecutive, observational, quality control studies after implementation of a multi modal opioid-sparing regimen for prevention of pain and PONV. The regimen consisted of oral paracetamol 1 g, dexamethasone 8 mg, dextromethorphan 30 mg, celecoxib 400 mg and gabapentin 1200 mg (600 mg in patients >70 years) given 1-2 hours preoperatively, and 4 mg ondansetron given intravenously 20 minutes before the end of surgery.

In the first study all patients were to be referred from the operating theatre to the PACU before going to the ward in order to evaluate dischargeability. To evaluate the reasons why patients stayed at the PACU, we used a modified version of the DASAIM discharge criteria scoring system for discharge of patients from the PACU to the surgical ward.

In the second study the overall worst scores regarding pain and PONV at PACU as well as data on the anesthesia and major side effects, were noted on a separate sheet following the patient the first 36 postoperative hours.

Population

The patients included in the two studies presented in Articles I and II were included consecutively over two distinct time periods. The patients included were all admitted for primary surgical treatment of unilateral breast cancer at our department at Rigshospitalet (University of Copenhagen).

The 116 patients in Article I were included consecutively from **27-11-2006 to 26-2-2007**.

The 200 patients in Article II were included consecutively from **11-04-2007 to 30-08-2007**.

Nine of the 200 patients (4,5%) did not receive, or only partially received, the PONV and pain prevention package and were thus excluded from analyses.

The patients in the two studies had either mastectomy or breast conserving surgery (BCS) combined with sentinel lymph node dissection (SLND), or axillary lymph node dissection (ALND) in the case

of lymph node metastasis. Accordingly, four major surgical groups, which accounts for 85% of all breast cancer operations.

As part of the SLND procedure, patients had 0.5-1.0ml of 2.5% Patent Blue solution injected intradermally into the breast, potentially affecting pulse oxymetry measurements.

Analgesic drugs

The analgesic drugs (paracetamol, celecoxib, dextromethorphan and gabapentin) were chosen in order to cover the main pain mechanisms in postoperative pain combining clinical evidence and safety considerations. Paracetamol has a well-documented analgesic effect, a strong safety profile and in combination with NSAID a supra-additive analgesic effect [57,58]. Paracetamol has in combination with Cox-2 inhibitors been used successfully in other breast surgical clinics [9]. Celecoxib was chosen partly due to its supra-additive effect with paracetamol and its well-documented effect on pain under mobilisation, and partly due to its selective effect on the COX-2 receptors involved in inflammatory pain response and thus not compromising thrombocyte aggregation in contrast to ordinary non-steroidal anti-inflammatory drugs (NSAID), which also inhibit the COX-1 receptors known to compromise thrombocyte aggregation and increase the risk of haemorrhage [51-53]. Questions have been raised regarding the risk of thromboembolic cardiovascular events reported after long term use of COX-2 inhibitors [54] and in patients undergoing coronary-artery bypass grafting [55]. However, there is no evidence to suggest that increased risk of thromboembolic cardiovascular events is associated with single dose or short term perioperative use of COX-2 inhibitors in healthy women [56]. Dextromethorphan, having a weak analgesic effect, was chosen in order to cover the n-methyl-d-aspartate receptor (NMDA) [48,49], a receptor which could also have been covered by ketamine. However, ketamine is known to have some undesirable psycho-mimetic side-effects in contrast to dextromethorphan, which additionally is a much used antitussive medicament with a very strong safety profile [50]. The choice of dextromethorphan was a bit controversial as some uncertainty remains concerning the optimal dosage and route of administration, thus we decided for a relatively low oral dose of 30 mg, corresponding to the dose and route of administration used for alleviating coughing. The risk of developing drug addiction with a single in-hospital administered dose was

regarded as negligible. Finally, gabapentin, an anticonvulsive drug used in the treatment of chronic neuropathic pain, was chosen for its central pain modelling effect on the gamma-aminobutyric acid (GABA) neurotransmitter system [46]. GABA is the chief inhibitory neurotransmitter in the mammalian central nervous system and plays a role in regulating neuronal excitability throughout the nervous system. As nerve damage seems to play an important role in the mechanisms involved in early postoperative pain, gabapentin has proven effective in the reduction of postoperative pain after breast cancer surgery [13,46,47]. Additionally, gabapentin may be the ideal drug where tissue injury or inflammation have induced sensitisation in the central nervous system acting selectively on pathophysiological neurotransmitter systems [82].

Anti-emetic drugs

The choice of anti-emetic drugs was based on procedure-specific studies and evidence from equivalent surgical procedures suggesting the use of a combination of intravenous anaesthesia, a 5HT₃-antagonist (ondansetron), dexamethasone and opioid-sparing pain prevention [66].

Dehydrobenzperidol (droperidol) proved equally effective in preventing PONV [70,71], and was chosen as the rescue medicament in PACU as it is not recommended as a first line preventive drug, due to its potential side effects: dysphoria, sedation and hypotension caused by peripheral alpha adrenoceptor blockade [66].

Anesthesia

As volatile agents are known to cause PONV [63,65], total intravenous anaesthesia (TIVA) was chosen. Propofol was chosen, being the standard sedative drug of modern anaesthesia. For economical reasons fentanyl was chosen as the analgesic component instead of remifentanyl, even though the most recent systematic review states that “remifentanyl might be quite useful in patients where early ambulation is desirable” [83]. TIVA was induced with 0.15 mg fentanyl and 2 mg/kg body weight propofol. Five minutes before incision, another 0.15 mg fentanyl was added, and anaesthesia was maintained with 0.15-0.20 mg/kg body weight/minute propofol. If the heart rate increased above 20 % compared to base line, fentanyl 0.05 mg was added.

Recording of data

In Study I sedation, RR, SpO₂, SBP, HR, pain at rest and PONV were recorded from arrival at the PACU and every 15 minutes thereafter until discharge. Each parameter was scored 0, 1, 2 or 3 respectively, corresponding to the following degrees of severity: none, light, moderate or severe (Appendix I). Patients were considered dischargeable by the PACU nurses, when the score sum was four or less, with no single score exceeding one. Patients who did not fulfill these two criteria but were otherwise dischargeable had to be discharged by the anaesthesiologist on duty. Additionally, the nurses were asked to explain why discharge was delayed if patients were not discharged at the time the criteria were met.

In Study II the duration of general anaesthesia and time from end of the infusion of propofol to recovery of spontaneous breathing, as well as cumulative fentanyl and propofol dosages were recorded. Dizziness, headache, diplopia, confusion, memory disorders, PONV, and pain at rest and on mobilization were evaluated every 15 minutes in the PACU. To distinguish between side effects and habitual troubles, the patients were asked preoperatively whether their everyday life was troubled by these symptoms. PONV and pain were scored zero, one, two or three, e.g. no complaint = 0, mild = 1, moderate = 2 and severe complaint = 3. Mobilisation was defined as active arm abduction to an angle of 90 degrees out from the body. At discharge to the ward, worst scores during the stay in the PACU were recorded. Dizziness, headache, diplopia, confusion and memory troubles were recorded as “yes” or “no”. On the day of the operation, the same parameters were recorded in the ward at 8 pm, the next day at 8 am and 8 pm; and on the second day after the operation at 8 am. Additionally, the patients were asked whether they had experienced any of the above-mentioned symptoms between these measurements. Nurses recorded all information during hospitalisation. Patients discharged less than 36 hours postoperatively completed the registration form at home and data were retrieved by telephone contact. Patients scoring moderate or severe pain in the PACU at rest and/or severe pain with mobilisation received morphine 0.1 mg/kg intravenously (0.05mg/kg>70 yrs). In the ward, patients had oral paracetamol 1g 6-hourly and oral celecoxib 200 mg the evening of operation and the morning and evening next day.

Patients who needed analgesics after the first postoperative day continued with oral ibuprofen 600 mg 8-hourly and paracetamol 1g 6-hourly. Rescue analgesic in the ward was oral morphine 15 mg as required.

Statistics:

In Studies I and II the results were presented as mean and standard deviations (SD), or as amounts and percentages, as appropriate.

Confidence intervals for frequencies were required by the reviewers of Article II and estimated by:

$p \pm 2 \sqrt{p(1-p)/n}$, where p is the frequency/likelihood and n is the total number.

The significance level for the p-value was set to 0.05% (Kruskal-Wallis one-way analysis of variance (asymmetric p-value) and Fisher's exact test for 2×2 contingency tables (2-tailed p-value)).

Results

In Study I regarding stay at PACU, 116 consecutive patients aged 33 to 86 years were included.

A total of 95 patients were administered Patent Blue.

Upon arrival at the PACU, 36 patients (31%) fulfilled the criteria for discharge. The mean time from the patients regaining spontaneous respiration to the first scoring at the PACU was 16 min (SD = 14 min). The mean time until the discharge criteria were met was 40 min (SD = 46 min). A total of 94 patients fulfilled the discharge criteria upon arrival or while staying at the PACU. In 22 patients (19%), discharge had to be approved by the anaesthesiologist on duty, mainly due to low SpO₂. The overall mean time spent at the PACU was 110 min (SD = 75min).

Figure 6 displays the number of patients scoring higher than one on any of the discharge criteria for the first 105 min after arrival at the PACU.

Low SpO₂ scores (two and three, corresponding to SpO₂ < 90% without supplementary oxygen) remained the most frequent cause for not fulfilling discharge criteria upon arrival to the PACU (36 patients; 31%) and until 75 min after arrival (14 patients; 12%). In the same period, scores two and three for RR fell from 18 to nine patients (16% to 8%).

Seven out of 16 patients belonging to the American Society of Anesthesiologists (ASA) group 3-4 scored more than one on SpO₂ upon arrival to the PACU, which was not significantly different from patients belonging to ASA group 1-2, which was 28 patients of 100 ($p = 0.24$). Nor did we find any significant differences in SpO₂ between the patients who received Patent Blue and those who did not ($p = 0.61$).

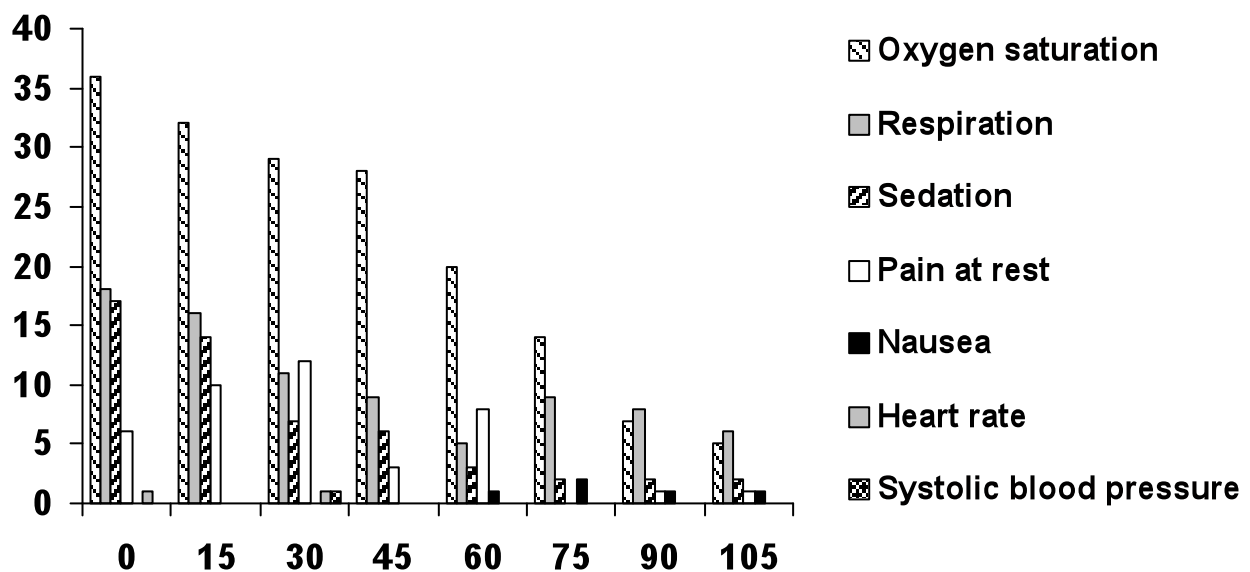
Pain peaked after 30 minutes, with 12 patients (10%) scoring > 1 , decreasing to only one patient after 90 minutes.

Upon arrival at the PACU, 17 patients (15%) scored > 1 on sedation. One hour later this number was reduced to three patients.

One patient scored > 1 on heart rate upon arrival at the PACU. No patients scored > 1 on PONV or systolic blood pressure upon arrival. At the PACU, only very few patients developed scores > 1 (see Figure 6). Thus, PONV, systolic blood pressure and heart rate had no overall influence on delay of discharge from the PACU.

In 36 cases (31%), the nurses at the PACU stated that discharge was delayed by logistic factors such as, the workload at the PACU and/or waiting for patient transport to the ward.

Figure 6. Recovery profile of the 116 consecutive patients operated on for breast cancer



The numbers of patients scoring higher than 1 at any of the DASAIM discharge criteria in the first 105 minutes after arrival at the PACU

In Study II regarding postoperative pain and PONV 200 consecutive patients aged 30 to 92 years were included in the study. Nine patients were excluded from the study analysis due to inadequate preoperative medication.

Mean duration of anaesthesia was 150 min (SD = 38 min) including time from end of infusion of propofol until spontaneous breathing, which was 22 min (SD = 13 min). The cumulative mean dosage (including the induction dosage) of propofol was 1417 mg (SD = 567 mg). The cumulative mean dosage of fentanyl was 0.401 mg (SD = 0,094 mg).

Throughout the 36-hour study period (including PACU) 151 patients (79%, CI=73;85) had no PONV following surgery. At some point of time during the first 36 hours 25 patients (13.0 %, CI=0.08;0.18) experienced mild PONV, 8 patients (4.1%, CI=1;7) experienced moderate PONV, and 7 patients (3.7%, CI=1;6) experienced severe PONV.

Throughout the 36-hour study period (including PACU) 43 patients (22.5%, CI=16;29) had no pain at all, 90 patients (47.1%, CI=40;54) experienced light pain, 52 (27.2%, CI=21;34) moderate pain, and six patients (3.1%, CI=1;6) severe pain as worst pain at rest. Thus 133 patients (69.6%, CI=63;76) experienced no or light pain at rest as worst pain during the entire 36-hours period.

Throughout the 36-hour study period 34 patients (17.8%, CI=12;23) experienced no pain at all during arm mobilization, 80 patients (41.9%, CI=35;49) experienced light pain during arm mobilization, 60 patients (31.4%, CI=25;38) experienced moderate pain, and 17 (8.9%, CI=5;13) experienced severe pain during arm mobilization (Fig. 3). Thus 114 patients (60,2%, CI=53;67) experienced no or light pain at arm mobilisation during the entire 36-hour study period.

Fifty-five patients had i.v. morphine in the PACU (mean 7.5 mg; SD=5.0 mg) and none requested opioids in the ward.

The distribution of morphine consumption in relation to different surgical groups is shown in Table 3. Side effects were recorded in 116 patients. In 71 patients (61 %, CI=52;70) the side effects were similar to preoperative complaints: dizziness (n = 25), headache (n = 21), diplopia (n = 5), confusion (n = 6), and memory disorders (n = 9). Throughout the 36-hour study duration 96 patients (50.3%,

CI=43;57) experienced some degree of dizziness, 44 (23.0 %, CI=17;29) headache, 17 (8.9%, CI=5;13) diplopia, 28 (14.6 %, CI=10;20) confusion and 20 (10.5 %, CI=6;15) memory disorders.

Discussion

In order to facilitate faster recovery after surgery for breast cancer we implemented a multimodal regimen consisting of paracetamol, dexamethasone, dextromethorphan, celecoxib, gabapentin, ondansetron and intravenous anaesthesia to prevent postoperative pain and PONV (Studies I and II). The goal was firstly to spare the patients the unnecessary inconvenience of PONV and pain and secondly to facilitate the discharge of patients who wanted to go home the same evening or the next morning. Crucial to the latter was the flow of the patients from the ward to the operation theatre and back again. At our department almost all patients were postoperatively brought to PACU, and due to the stay at PACU patients operated on in the afternoon came back to the ward too late to be discharged the same evening. In the literature 50-80% of women operated on for breast cancer are reported to have PONV (Fig. 5) and up to 50% moderate to severe pain (Fig. 4). In a recent overview, more than half of patients undergoing all kinds of surgical procedures have opioids administered postoperatively, and in breast surgery this was the case in two thirds of the patients [84]. After the introduction of the new regimen at our department, more than two thirds of the patients experienced no PONV and no, or only light, pain during their stay at PACU and the first 36 hours postoperatively. Less than one third of the patients had a need for postoperative rescue medication in the form of morphine at PACU and no patients required morphine at the ward. Introducing the multimodal regimen and evaluating reasons why patients stayed at PACU, using the modified DASAIM discharge scoring system, it was revealed that PONV and pain was of no significant importance for the discharge from PACU. The main reason for staying at PACU turned out to be oxygen saturation < 90%. Evaluating this result in the light of the type of surgery (surface surgery, with no involvement of vital organs), the potential bias of Patent Blue and the grade of evidence of pulse oximetry in DASAIMS' scoring system (background), we decided to discharge patients presenting with only a modest decrease in SpO₂ (measured by pulse oximetry) with binasal oxygen supply. After implementation of this procedure, 70% of the patients undergoing breast cancer surgery could go

directly from the operating theatre to the ward, gaining time to secure proper information before discharging patients who wished to go home the same night or the next morning.

Since no safety issues were apparent, these observations call for a more detailed assessment of the DSAIM discharge criteria on a procedure specific basis. Also, more detailed studies on the relative role of multimodal “package” for pain and PONV prevention are required.

After the introduction of the multimodal “package”, the organisation of the work at the department of breast cancer surgery was changed, as a consequence of the improved conditions of the patients regarding pain and PONV, towards a fast-track regimen. In the process of reorganizing the procedures at the ward, the criteria regarding drain removal were brought up, as drains cause patient discomfort [85], carry a risk of surgical site infection [86], and delay discharge [87]. The discussion resulted in new guidelines implying removal of drains on the first postoperative day. The implementation of early drain removal was supported by the creation of a nurse-led outpatient consultation. The consultation was primarily created to take care of patient information and psychosocial support, but would also take care of puncture and evacuation of postoperatively-developed seroma.

The conduction of randomised studies regarding postoperative pain after breast cancer surgery is difficult as severe pain is rare and the pain reduction benefits are therefore relatively small.

Consequently secondary outcome measures such as morphine induced PONV, time to mobilisation, patients satisfaction and risk- and benefit-evaluations of different techniques becomes increasingly important.

The treatment of breast cancer in Denmark follows national guidelines set by DBCG, but there is no standard regarding prophylaxis and treatment of pain and PONV, which predominantly has been based on paracetamol and morphine. In order to implement a fast-track concept a multimodal regimen for preventing pain and PONV was implemented. This regimen was based on experiences from other surgical procedures [59,60] and was implemented without conducting randomised studies of the different components and dose response effect in the population of breast cancer women. Thus, the studies in this part of the thesis were not designed to conclude that the regimen provided is the optimal regimen for prevention of pain and PONV after surgery for breast cancer, but rather to

provide clinical-relevant data for future studies and for the development of the fast-track concept. The implementation of the concept reduced hospitalisation from 3.6 days to 1.2 days (Table 1, [8]).

Table 1. Admission time for breast cancer patients classified after type of operation.

MASTECTOMY	Average length of stay before intervention	Average length of stay January-February 2009	Average length of stay March-May 2009
Mastectomy and axillary lymph node dissection	5 days (n=126)	2,2 days (n=24)	1,4 days (n=37)
Mastectomy and sentinel lymph node dissection	4,5 days (n=95)	1,7 days (n=36)	1,4 days (n=53)
BREAST CONSERVING SURGERY	Average length of stay before intervention	Average length of stay January-February 2009	Average length of stay March-May 2009
Breast conserving surgery and axillary lymph node dissection	4,1 days (n=50)	1,0 day (n=12)	1,2 day (n=12)
Breast conserving surgery and sentinel lymph node dissection	1,4 days (n=122)	1,0 day (n=25)	0,9 day (n=48)

Mertz BG, Williams HB. Eur J Oncol Nurs 2010 Jan 15 [8]

2. Chronic sequelae after breast cancer surgery and adjuvant treatment

Introduction:

Chronic sequelae after treatment for breast cancer covers a wide range of psychological problems such as cognitive dysfunction, lack of sexual drive, changed body image, post traumatic distress, depression and fatigue, as well as a number of physical problems such as chronic pain, sensory disturbances, lymphedema, functional impairment, dried-up mucous membranes in the mouth and vagina, osteoporosis and dental degeneration. All potentially have an impact on quality of life, socio-economic status of the individual and health care costs. A large number of factors potentially affect chronic sequelae (Fact box 3).

Quality of life and impact of socio-economic characteristics have been explored in large well-conducted studies of long-term breast cancer survivors by Peuckmann et al. [88,89]. Depression is currently being examined in a large nationwide cohort study of 4917 women operated on for breast cancer [90]. Cognitive dysfunction and fatigue are new and interesting areas of research and are most probably connected to posttraumatic distress and depression. A part of our research group is currently conducting a prospective study with enrolment of 357 patients focusing on the prediction of patients

at risk of developing depression, using the distress thermometer [91] and the Hospital anxiety and depression scale (HADS) [92].

In order to narrow the topic we decided to focus only on four major physical sequelae: pain, sensory disturbances, lymphedema and functional impairment, and to examine the impact of breast cancer treatment in a nationwide questionnaire study addressing these problems.

Thus, the aim of the study was to explore the impact of modern breast cancer treatment on these four main parameters enrolling patients following the DBCG 2004 treatment protocol.

As the treatment of breast cancer has changed dramatically over the last 15 years (Fig. 3) studies of long-term survivors have limited value in predicting the risk of physical sequelae for the breast cancer patients of tomorrow. Furthermore, changes in chemotherapy and anti-hormonal therapy (DBCG protocol 2004 and 2007), underlines the need for on-going surveillance of treatment related sequelae.

The primary outcomes of our study were the self-reported prevalence and severity of: pain, sensory disturbances, lymphedema and functional impairment, and associated treatment-related riskfactors.

The secondary outcomes were: detailed self-reported information on where (location) and with what frequency pain, sensory disturbances and lymphedema occurred. Furthermore, limitations caused by functional impairment and the medical consequences of reporting pain were examined.

In order to ensure a high response rate and not overwhelm vulnerable patients with too many questions we decided not to include questions on socio-economic status, weight, height and current physical activities or employ standardised questionnaires on self-perceived health, depression or quality of life, recognising that these topics are already addressed in other projects. Furthermore, women over 70 years of age were excluded. This was partly in order to secure a high response rate and partly due to a higher frequency of protocol violations in this group.

Background:

Estimates for treatment-related risk factors in the development of chronic sequelae have been reported in a number of studies, showing that axillary lymph node dissection and radiotherapy play important roles [93,94]. However, the consequences of late recovery regarding mastectomy, breast-conserving

surgery, sentinel lymph node dissection, chemotherapy and individual factors like age are more diverse [93,94].

Research on chronic sequelae after treatment for breast cancer is complicated as the number of factors potentially affecting the outcome is considerable, Fact box 3.

Fact box 3. Factors potentially affecting chronic sequelae after treatment for breast cancer.

Treatment-related factors	Individual factors
Surgery Mastectomy BCS SLND ALND (primary or secondary) High/low volume centres Radiation therapy BRT ATRT LRRT Chemotherapy CEF Taxotere Anti hormonal treatment Aromatase inhibitors Estrogen receptor antagonists	Constitutional Age BMI Ethnicity Genetics Cancer related Tumour size Tumour location Recurrence of cancer Socioeconomic Social status Educational level Cultural background Treatment related Complications Psychological distress

BCS: Breast conserving surgery. **SLND:** Sentinel lymph node dissection. **ALND:** Axillary lymph node dissection. **BRT:** Breast radiotherapy corresponding to residual breast tissue. **ATRT:** Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. **LRRT:** Loco-regional radiotherapy corresponding to periclavicular, axillary level III, and for right side breast cancers, the internal mammary nodes. **CEF:** cyclophosphamide, epirubicin, and fluorouracil. **BMI:** Body mass index

Pain and sensory disturbances

Persistent pain after treatment for breast cancer has been reported in 25-60 % of patients [34,89,95-105] and sensory disturbances in 20-80% [34,95-98,102,103]. The definition of chronic pain is well established [106], but the time of follow-up differs between studies, as do the methods of measurement [34].

Acute pain after breast cancer surgery can be divided into nociceptive pain due to the postoperative inflammatory response, and neuropathic pain due to nerve damage mainly caused by traction, laceration or transection of medial cutaneous nerve of the arm and the intercostobrachial nerves and their branches [34]. Usually the nociceptive pain resolves as damaged tissues heal, while the neuropathic pain persists.

Persistent pain after breast cancer surgery was first described as a specific syndrome in the eighties by Foley and colleagues, and termed post-mastectomy pain syndrome (PMPS)[107,108]. However, as the most common cause of the syndrome is thought to be damage to the intercostobrachial nerves due to ALND, and BCS is the most prevalent surgical procedures in breast cancer today, the term must be

regarded as obsolete. Instead, Jung et al. have proposed the more descriptive term: “Intercostobrachial Neuralgia” (ICN) in their proposed classification of neuropathic pain after breast cancer surgery [34]. Furthermore, Foyle et al. proposed to divide neuropathic pain into “phantom breast pain”, “Neuroma pain” and “other nerve injury pain”[34]. Phantom breast pain was defined as: “sensory experience of a removed breast that is still present and is painful”. Neuroma pain is pain from neuromas formed in scar tissue when peripheral nerves are severed or injured. Neuromas can be macroscopic and palpable or microscopic and identifiable by histological methods [109]. Other nerve injury pain was defined as “neuropathic pain, which cannot be related to the intercostobrachial nerves”, e.g. other intercostals nerves. This classification gives more detailed information of the different phenomena causing persistent pain after treatment for breast cancer, but has not yet been applied to clinical studies and thus the clinical and therapeutic consequences remain to be seen.

Even though most persistent pain in breast cancer may originate from intra-operative nerve damage, secondary nerve compression by scar tissue, radiation induced fibrosis or tumour invasion as well as chemotherapy associated neuropathy, radiation plexitis and plexopathy can be contributory factors [34,96]. Furthermore, the development of lymphedema probably contributes considerably to chronic pain as treatment of lymphedema has been shown to reduce pain in these patients dramatically [110]. However, the character and mechanisms for lymphedema-induced pain is not described in the literature.

Arm lymphedema

Lymphedema, according to the literature, affects 2-86 % of patients treated for breast cancer [94,111-127], reflecting differences in treatment regarding surgical procedures, radiotherapy and multiple methods of measurement, and accordingly definitions [94], Fact box 4.

Fact box 4. Methods of measurements of lymphedema in women operated on for breast cancer.

Methods of measurements:	
Circumference	[94,128]
Water displacement	[94,128]
Self reported symptoms	[94]
Clinical assessment	[94]
Single-frequency bioelectrical impedance analysis	[129]
Multi-frequency bioelectrical impedance analysis	[130]
Computed tomography (CT)	[128]
Magnetic resonance imaging (MRI)	[128]
Infrared scanning	[131]

Lymphedema can be divided into inherited primary lymphedema and secondary lymphedema.

Secondary lymphedema is initiated by damage to the lymphatic system due to e.g. surgery, infections or parasites (in some cases causing lymphedema directly after the damage) and continues with a slow decrease in transport capacity, maybe due to overload of the remaining system [132], with an onset of symptoms at the time when the capacity of the lymph drainage is exceeded. This results in a feeling of swelling and/or heaviness of arm/hand, accompanied by a palpable increasing thickness, particularly in sub cutis and progressing to swellings with eventual pitting [133]. If untreated, the lymphedema causes irreversible fibrotisation of the subcutis and sclerosation of the dermis. The progression can be accelerated by further direct or indirect damage to the lymph vessels due to radiotherapy [115-118,124,134] and infections [135,136], but not by physical activity [137-140].

The treatment of manifest lymphedema has proven effective, and includes daily sessions with lymph drainage massage, compression bandaging and intensive skin care lasting for several weeks [110,141]. If lymphedema is identified early, the treatment is less complicated and self care treatment consisting of upper-extremity exercises, good skin care and compressing garments can probably prevent progression [141]. Thus early identification and treatment of lymphedema is crucial.

Many of the objective definitions for lymphedema are problematic, as they do not take into account that the swelling can be confined to a specific part of the arm or to the hand and does not always include the whole arm [132]. Hence, localised lymphedema will most probably turn out to be insignificant when using general arm-volume definitions. Furthermore, the absence of measurable swelling (swelling greater than 5 or 10 % volume increase) does not rule out the presence of lymphedema, but such discrete lymphedema is very difficult to measure objectively without having preoperative data, and even with these data it is further complicated by the potential postoperative loss of muscle mass due to patients' tendency to use the arm of the operated side less than the "healthy" arm.

More advanced methods of measurements such as computed tomography imaging, well correlated to water displacement measurements [128], and bioelectrical impedance measurements for early diagnosis of lymphedema in breast cancer patients [129,140,142] have been suggested, but in the end

the patients are probably the best experts on their own bodies. Accordingly, some studies of self-reported swelling and heaviness and objectively measured lymphedema have found greater numbers of patients reporting symptoms of lymphedema than the number of patients fulfilling the objective definitions of lymphedema, indicating self-reported symptoms of lymphedema to be a more sensitive method [127,143,144].

Impairment of function

Functional impairment after treatment for breast cancer is generally ascribed to the development of chronic sequelae such as pain, lymphedema, restriction of shoulder motion, loss of physical strength and psychological well-being [145]. Pain and lymphedema, as described above are well-established factors. Detailed clinical studies concerning restriction of shoulder motion and loss of strength have shown relatively fast recovery rates after treatment for breast cancer and quite limited long-term impact on objective measures [146-153]. Nevertheless, this does not necessarily reflect the patients' subjective experience of their limitations in daily life.

Furthermore, a well-conducted Danish population-based quality of life study of long-term survivors has shown that breast cancer survivors in general do not differ in quality of life from the normal population [88]. However, this cannot be taken as an expression of this group of women not being bothered by chronic sequelae after their treatment for breast cancer, but merely that the majority of these women are coping very well with their limitations compared to the normal population, maybe covering up for smaller specific subgroups, which might be far more distressed than average.

Some studies have described the consequences of functional impairment regarding economy [154], productivity [155] and changes in working life [156], all concluding a significant negative influence of functional impairment, indicating that the subject is very complex.

Most studies examining functional impairment are based on relatively small samples, due to the longitudinal design and the time consuming measurements of a broad variety of influencing factors, and thus either describe the problem in selected groups or fail to adjust for the many treatment modalities involved in modern treatment for breast cancer. Thus, searching the literature it proved quite difficult to find population based answers stratified according to modern treatment to simple

questions like: “How many women have had to give up activities after their treatment for breast cancer?” or “How many women have experienced problems regarding their occupational or sports activities after their treatment for breast cancer?”

Material and methods:

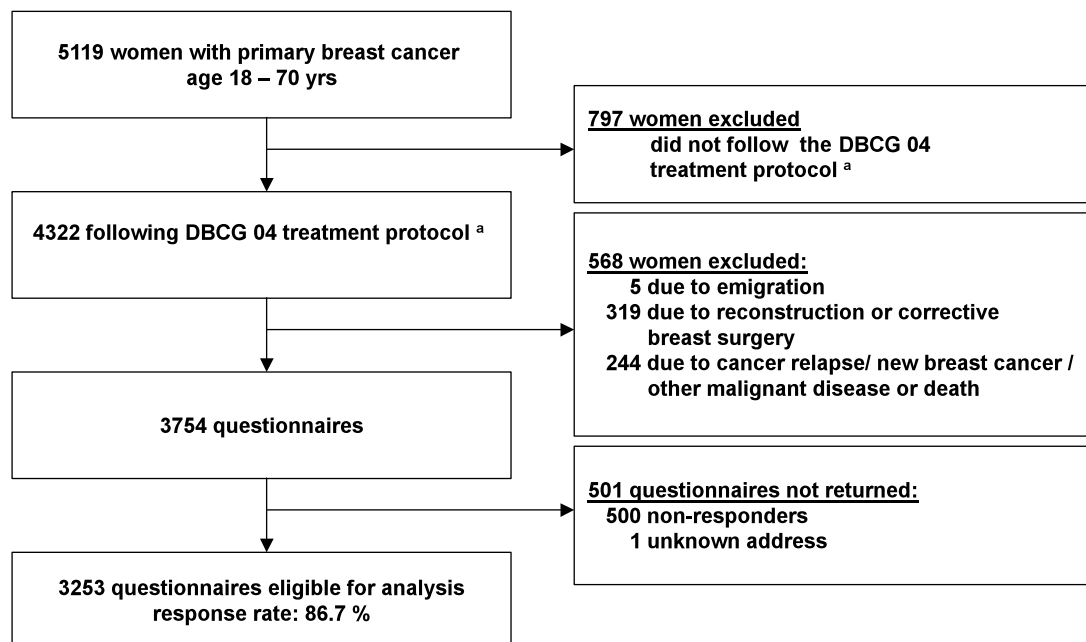
The study presented in Articles III and IV on which the second part of the thesis is based was a cross sectional nationwide questionnaire study with prospectively collected data on treatment.

Population

The patients included in the study were operated on for unilateral primary breast cancer in Denmark between 1-1-2005 and 31-12-2006. In all, 5119 women between 18 and 70 years of age underwent surgery for breast cancer in the period. Exclusion criteria were: non-standardized treatment, reconstruction or corrective breast surgery, cancer relapse, contra-lateral breast cancer, other malignant disease, and emigration or death (n=1365). There were 3754 women who matched the inclusion criteria (Fig. 7).

A study questionnaire (Appendix II) was sent to the 3754 eligible women between January and April 2008. Reminders were sent three weeks later. In June 2008 a total of 3253 questionnaires had been returned (response rate 87%) and were eligible for analysis.

Figure 7. Inclusion procedure and response among 5119 Danish women treated for primary breast cancer 2005–2006.



^a The DBCG (Danish Breast Cancer Cooperative group) 04 treatment protocol prescribes standardized surgery based on the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003.

Registries

Patients identity, demographics and treatment data were retrieved from DBCG's database which covers > 95 % of patients operated on for breast cancer in Denmark [3,157]. DBCG prospectively collects detailed clinical data, histopathological status, data on treatment as well as data on recurrence and mortality [3].

Addresses and mortality were retrieved from the Danish Civil Registration System (CRS).

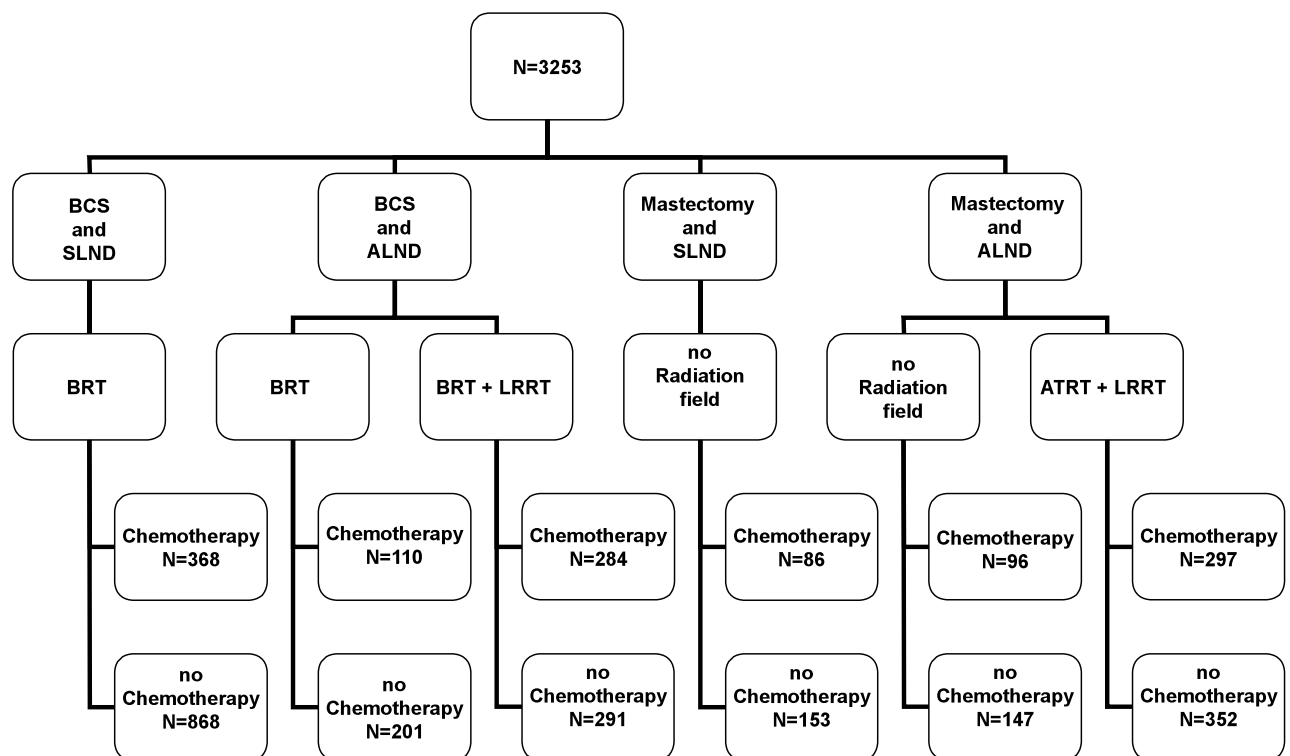
Information regarding reconstruction or corrective breast surgery was retrieved from The Danish National Patient Registry [158].

Treatment

Breast cancer treatment in Denmark is standardized in national protocols designed by DBCG [3] in accordance with European guidelines.

All women in the study received treatment according to the DBCG 2004 treatment protocol [3,159], which is based on the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003 [160]. The patients were split into 12 major treatment groups according to the type of surgery and adjuvant radiation and chemotherapy (Fig. 8). Surgery included mastectomy or breast conserving surgery (BCS) with either sentinel lymph node dissection (SLND) or axillary lymph node dissection levels I and II (ALND) [160]. Women with biopsy confirmed involvement of the axillary lymph nodes were selected for ALND and women without suspicion of nodal involvement at clinical examination and ultra sonography were offered axillary staging by SLND [161]. All BCS patients received radiotherapy to the residual breast tissue (BRT). Women with axillary lymph node macro-metastasis (node-positive) also received radiation to loco-regional lymph nodes (periclavicular, axillary level 3 (Fig. 2), and for right side breast cancers also the internal mammary nodes (Fig.2)) termed loco-regional radiation therapy (LRRT). Node-positive patients who had undergone a mastectomy also received radiotherapy to the anterior thoracic wall (anterior thoracic radiation therapy (ATRT)) [7]. Allocations to anti-estrogen treatment and standard chemotherapy (cyclofosphamide, epirubicin, and fluorouracil, CEF) followed estrogen receptor status and histopathological criteria according to the DBCG 2004 protocols [3].

Figure 8. Treatment groups according to type of surgery, adjuvant chemo- and radiotherapy among 3253 Danish women operated on for primary breast cancer 2005-2006.



BCS: Breast conserving surgery. **SLND:** Sentinel lymph node dissection. **ALND:** Axillary lymph node dissection. **BRT:** Breast radiotherapy corresponding to residual breast tissue. **ATRT:** Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. **LRRT:** Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes.

Questionnaire

We reviewed the literature for existing relevant questionnaires in order to determine prevalence, location, intensity and frequency of pain, sensory disturbances, lymphedema, and functional impairment and their associations with different treatment modalities. The most commonly used and well-validated questionnaires in breast cancer research were the quality of life questionnaires EORTC QLQ-C30/BR23 and FACIT-B [162]. However, we decided not to employ these, as they did not provide detailed information on our four main parameters: pain, sensory disturbances, lymphedema and functional impairment regarding severity, localization, how often symptoms were present and the consequences. We found no other single standardized questionnaire with documented validity and reliability in comparable populations to match these demands. Thus, a detailed questionnaire had to be designed. Content validation of the questionnaire was based upon questions/topics identified in the literature and open interviews with 20 women operated on for breast cancer. Before the study began,

the reliability of the questionnaire was tested qualitatively by asking 11 women to answer the questionnaire while “thinking out loud”, sharing their reflections question by question with the breast care nurse involved in the study. The questionnaire was then revised in accordance with the comments and retested on another 17 patients in the same manner.

To determine the prevalence of symptoms for each major topic dichotomous “yes“ or “no” questions were used. To estimate severity we used a numeric rating scale from 0–10 [163,164] where 0 was “no symptom“ and 10 “worst imaginable symptom”. For the reporting of results regarding severity of symptoms 1–3 was categorized as light, 4–7 moderate and 8–10 severe. Regarding pain and sensory disturbances and lymphedema the women were asked to specific regions of symptoms pre-defined in the questionnaire.

“Worst pain” and “Worst self reported lymphedema” were defined as the highest score of the respective regional scores.

The frequency of symptoms was assessed by a 3-point verbal categorical scale: 1) every day or almost every day, 2) 1–3 days a week, 3) more rarely.

To elucidate consequences of pain questions were asked on physician visits due to pain in the operated region, use of analgesics and/or other treatment for pain in the operated region, and pain in other locations (e.g. low back pain, headache).

Estimation of associated factors was based on associations with the four main dichotomous “yes“ or “no” questions:

1. “Do you have pain in the area of the breast, armpit, side of the body, or arm on the side where you were operated?”
2. “Do you have sensory disturbances or discomfort in the area of the breast, armpit, side of the body, or arm on the side where you were operated?”
3. “Does the armpit, the arm or the back of the hand, on the side where you were operated, sometimes or always feel swollen or heavy?” (lymphedema)
4. “Are there activities you have had to renounce on after your treatment of breast cancer?”

Statistics:

The primary outcomes of our study were: self-reported prevalence and severity of pain, sensory disturbances, lymphedema, and functional impairment, along with factors associated with these four main outcome parameters (Table 2). The secondary outcomes were: detailed self-reported information on where (location) and with what frequency pain, sensory disturbances and lymphedema occurred. Furthermore, limitations caused by functional impairment and medical consequences of reporting pain were examined.

Prevalence, severity, frequency, location and consequences were reported as numbers and in term of percentages.

For analysing associated factors the statistical method of multiple logistic regression was taken into account. This was partly due to the character of data being categorical, e.g. describing the presence or absence of conditions such as BCS or mastectomy, and partly in order to be able to give an estimate of the strength of the association between the outcome (the variable) and depending factors in term of odds ratios (ORs) and to adjust for the eventual concomitant influence of the different factors on each other by constructing multivariate models including the factors shown to be significant in univariate models.

Firstly univariate logistic regression models were applied to examine the influence of treatment related factors and individual factors (Table 2) on the four main outcome parameters: pain, sensory disturbances, lymphedema and functional impairment. Multivariate logistic regression models were then applied to the significant factors in the univariate models in order to examine the concomitant influence of treatment-related and individual factors on the four main outcome parameters.

Factors included and thus adjusted for in the multivariate models were type of surgery (mastectomy vs. BCS), lymph node dissection (ALND vs. SLND), radiotherapy (LRRT + BRT/ATRT, BRT vs. none), chemotherapy (cyclophosphamide, epirubicin, and fluorouracil vs none), and age.

Additionally, pain and swelling/heaviness, year of surgery and surgery on the dominant side were considered in the analyses of functional impairment. Year of surgery as well as tumour location in the

breast had no statistically significant effect on pain, sensory disturbances and lymphedema, and were thus excluded from these multivariate models.

Table 2 shows factors included in the multivariate models analysing the four main outcome parameters.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and the Wald chi-square test was used to test the overall significance of each factor.

In order to control for the potentially different influence of one factor on the subcategories of another factor, e.g. age influencing differently on the two subcategories of surgery to the breast (BCS and mastectomy) regarding pain, testing for the interaction between covariates on pain, sensory disturbances, lymphedema and functional impairment were performed pair-wise in separate models applying the Wald chi-square test.

Associations between pairs of variables were analysed by chi-square tests. Two-tailed p-values were calculated and the level of significance was set to 5%.

The analyses were performed by the DBCG Data Center.

Table 2. Factors included in the uni- and multivariate models analysing the 4 main outcome parameters.

Treatment-related factors	Individual factors
Surgery	Constitutional
Mastectomy ^{a,b,c,d}	Age ^{a,b,c,d}
BCS (reference)	Surgery on the dominant side ^d
ALND ^{a,b,c,d}	Surgery on the non dominant side (reference)
SLND (reference)	
Radiation therapy	Year of surgery (time elapsed since surgery)
BRT ^{a,b,c,d}	2005 ^d
LRRT + BRT/ATRT ^{a,b,c,d}	2006 (reference)
None (reference)	
Chemotherapy	Pain
CEF ^{a,b,c,d}	Yes ^d
None (reference)	No (reference)
	Self-reported lymphedema
	Yes ^d
	No (reference)
	Cancer related
	Tumour location in upper lateral quadrant
	Other tumour locations (reference)

BCS: Breast conserving surgery. SLND: Sentinel lymph node dissection. ALND: Axillary lymph node dissection. BRT: Breast radiotherapy corresponding to residual breast tissue. ATRT: Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. LRRT: Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes

Factors included in the multivariate models analysis regarding pain^a

Factors included in the multivariate models analysis regarding sensory disturbances^b

Factors included in the multivariate models analysis regarding self-reported lymphedema^c

Factors included in the multivariate models analysis regarding functional impairment^d

Results

The overall response rate was 86.7% (n=3253) varying from 79% to 93% between the 12 treatment groups (Table 3 and 4). Mean time from surgery to questionnaire response was 26 months (range 13–41 months). There was no significant difference in pain prevalence between patients operated on in 2005 vs. 2006 (Tables 2 and 3)(p=0.75).

Pain

In all 1543 patients (47%) reported pain, but with a considerable variation between treatment groups varying from 25% in women undergoing mastectomy and SLND but no adjuvant treatment to 60% among women undergoing BCS, ALND, BRT+LRRT and Chemotherapy (Table 3). 201 patients (13%) reported severe pain, 595 (39%) moderate pain and 733 (48%) light pain. Among those reporting pain the mean pain score in the 4 different areas varied between 3.5 and 4.0 on the numeric rating scale from ranging from 0 to 10. Among women reporting severe pain 77% were troubled every day, whereas only 36% of women experiencing light pain had pain every day. 278 patients (18%) reported pain in only one area, 435 (28%) in two areas, 429 (28%) in three areas and 400 (26%) in all four areas. The most frequently reported area of pain was the breast area (n=1331; 86%) followed by the axilla (n=975; 63%), the arm (n=872; 57%) and on the side of the body (n=857; 56%).

Of the patients reporting pain 306 (20%) had contacted a physician within the prior 3-months due to pain, 439 (28%) had taken analgesics due to pain in the surgical area, and 397 (26%) had received other treatment(s) for pain, (physiotherapy, massage, etc.). 1265 women (40%) reported pain in other parts of the body/non-surgical areas (e.g. low back pain, headache). Pain complaints in non-surgical areas were associated with a higher incidence of chronic postoperative pain since 810 (65%) of these women had pain in the surgical regions whereas 674 (37%) of women without pain in the non-surgical area had pain in the surgical area (p<.0001)).

There was a significant impact of age on reporting pain, where young age was associated with higher risk, especially for patients receiving BCS, the risk being highest for those aged 18-39 years receiving BCS compared with women aged 60-69 years (OR=3.62; CI: 2.25–5.82, p<.0001). Although young

age was associated with reporting pain young age was not associated with a higher risk of reporting moderate to severe pain compared to light pain (OR (18-39 years)=0.81; CI: 0.50–1.31, $p<.28$). Among women undergoing mastectomy the highest risk of pain was in the age group 40–49 years. A statistically significant interaction ($p=0.03$) was observed between age and type of surgery. Mastectomy had no significant impact on odds ratio for reporting pain compared to BCS, but those reporting pain after mastectomy had a higher risk of moderate to severe pain compared to light pain (OR=1.37; CI: 1.00–1.87; $p=0.048$). ALND was associated with an increased risk of pain (OR=1.77; CI: 1.43–2.19, $p<.0001$) with SLND as reference, and also a risk factor for moderate to severe pain (OR=1.39; CI 1.03–1.88; $p=0.03$).

Adjuvant radiotherapy increased the risk of reporting pain (OR (BRT)=1.50; CI:1.08;2.07, OR (LRRT+BRT/ATRT)=1.35; CI:1.04;1.76, $p=0.03$), but without relation to the extension of the radiation field or pain severity (OR (BRT)=1.26; CI:0.79;2.01, OR (LRRT+BRT/ATRT)=1.15; CI:0.78;1.68, $p=0.63$). Use of adjuvant chemotherapy had no independent impact on adjusted odds ratio for pain despite consistent differences between the 12 different treatment groups.

Sensory disturbances

Sensory disturbances or discomfort was reported by 1882 women (58%), ranging from 31% among women who had BCS with SLND and BRT to 85% of women who had BCS, ALND, and chemotherapy with BRT or BRT+LRRT (Table 3). The most frequently reported areas were the axilla ($n=1239$, 66%) followed by the arm ($n=986$, 52%), the breast area ($n=816$, 43%), and the side of the body ($n=573$, 30%).

After mastectomy and BCS there was a higher incidence of sensory disturbances with decreasing age. Thus, women aged 18–39 years had the highest risk compared with women aged 60-69 years (BCS: OR=5.00;CI:2.87–8.69, $p<.0001$; mastectomy: OR=6.06;CI:2.07–17.7, $p<.0001$). ALND was associated with increased incidence of sensory disturbances (OR=4.97;CI: 3.92–6.30, $p<.0001$) compared with SLND.

1204 (65%) women reporting sensory disturbances reported pain as well compared to 292 (23%) reporting pain but not sensory disturbances ($p<.0001$).

Adjuvant chemo- and radiotherapy did not increase the risk of reporting sensory disturbances in the multivariate model.

Table 3. Pain and sensory disturbances among 3253 Danish women operated on for primary breast cancer 2005-2006 according to the 12 different treatment groups (Figure 1).

Type of surgery	Treatment modalities												No. total (%)
	BCS SLND	ALND				Mastectomy SLND				ALND			
Breast													
Axilla													
Adjuvant treatment													
Radiation therapy	BRT	BRT	BRT	BRT	BRT + LRRT	BRT + LRRT	-	-	-	-	ATRT + LRRT	ATRT + LRRT	
Chemo therapy	-	+	-	+	-	+	-	+	-	+	-	+	
Non-respond., No. (%)	118(12)	56(13)	22(10)	14(11)	39(12)	35(11)	40(21)	15(15)	36(20)	7(7)	62(15)	56(16)	500(13)
Median age, years	59.0	47.0	59.0	42.5	61.0	47.0	62.0	54.0	59.5	48.0	62	48.0	
(IQR)	(54-64)	(39-53)	(55-63)	(41-45)	(57-67)	(40-51)	(58-66)	(41-62)	(55-64)	(46-51)	(59-66)	(41-52)	
Responders, No.(%)	868(88)	368(87)	201(90)	110(89)	291(88)	284(89)	153(79)	86(85)	147(80)	96(93)	352(85)	297(84)	3253(87)
Median age, years	60.0	49.5	61.0	49.0	60.0	48.0	62.0	53.0	60.0	48.5	61.0	48.0	
(IQR)	(55-65)	(44-56)	(56-64)	(44-54)	(57-64)	(44-53)	(58-66)	(48-61)	(56-65)	(43-56)	(57-65)	(44-55)	
Report. pain, No. (%)	345(40)	183(50)	105(52)	64(58)	146(50)	171(60)	39(25)	31(36)	63(43)	51(53)	181(51)	164(55)	1543(47)
Worst pain ^a													
Light	186(54)	96(53)	44(42)	34(53)	75(52)	76(45)	24(62)	13(42)	30(48)	18(36)	69(39)	68(42)	733(48)
Moderate	123(36)	61(34)	44(42)	22(34)	58(40)	65(38)	14(36)	14(45)	22(35)	26(52)	73(41)	73(45)	595(39)
Severe	34(10)	23 (13)	17(16)	8(13)	12 (8)	29(17)	1 (3)	4(13)	10(16)	6(12)	35(20)	22(14)	201(13)
Sensory dist., No.(%)	273(31)	153(42)	142(71)	94(85)	216(74)	240(85)	61(40)	48(56)	94(64)	78(81)	245(70)	238(80)	1882(58)

BCS: Breast conserving surgery. SLND: Sentinel lymph node dissection. ALND: Axillary lymph node dissection. BRT: Breast radiotherapy corresponding to residual breast tissue. ATRT: Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. LRRT: Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes. IQR: Interquartile range.

^a"Worst pain" was defined as the highest pain score of the 4 regional pain scores. 1–3 was regarded light pain, 4–7 moderate pain and 8–10 severe pain.

Swelling and sensation of heaviness of the arm (lymphedema)

1249 (38%) reported swelling or sensations of heaviness of the arm, hand or axilla ranging from 13% in the group of women undergoing BCS, SLND, BRT to 65% in the group of women undergoing either BCS or mastectomy and having ALND, BRT/ATRT, LRRT and chemotherapy (Table 4). 148 (12%) reported severe swelling/heaviness, 468 (38%) moderate and 609 (50%). Among those reporting swelling/heaviness the mean score for the upper arm and axilla was 3.9 and for the forearm and back of the hand 4.0 on the numeric rating scale from ranging from 0 to 10. 619 women (50%) reporting swelling/heaviness had these symptoms every day or almost everyday, 309 (25%) 1–3 days a week and 298 (24%) reported having these symptoms more rarely.

Among women reporting severe swelling/heaviness, 128 women (86%) were troubled every day, whereas only 204 (33%) of women experiencing light swelling/heaviness had these symptoms every day, $p < 0.0001$. 354 patients (28%) reported swelling/heaviness in only one region, 483 (39%) in two regions, 278 (22%) in three regions and 103 (8%) in all four regions and 31 (2%) did not report on region of swelling/heaviness. The most frequently reported region was the upper arm ($n=818$; 65%)

followed by the axilla (n=761; 61%), the forearm (n=601; 48%) and the back of the hand (n=386; 31%).

In univariate models, younger age, mastectomy, ALND, radiotherapy and chemotherapy were significantly associated with swelling/heaviness, whereas time elapsed since surgery, and being operated on the dominant side were nonsignificant. In multivariate models, the most important association was between swelling/heaviness and axillary procedure (OR=5.57; CI: 4.40–7.05, $p<0.0001$). Additionally, young age was associated with a higher risk ($p<0.0001$) – especially for those aged 18–39 years compared with women aged 60–69 (OR=2.60; 1.72–3.94). Furthermore, loco-regional radiotherapy (LRRT + BRT/ATRT) was significantly associated with swelling/heaviness (OR=1.72; CI: 1.30–2.27, $p=0.0005$). Type of surgery to the breast and use of chemotherapy were not associated with swelling/heaviness in multivariate models.

There was a significant interaction between age and type of surgery to the breast: in the BCS group younger women had a significantly higher risk of reporting swelling/heaviness compared to women aged 60–69 years whereas no such association was found in women undergoing mastectomy.

Furthermore, a significant interaction was found between type of surgery and radiotherapy. Adding ALND to BCS,BRT gives an OR of 6.75 (with BCS,BRT and SLND as reference=1) whereas adding ALND to mastectomy without radiotherapy raises the OR from 1.48 to 5.55, i.e. only a 3.75-fold compared to the OR of 6,75.

Finally, swelling/heaviness was strongly associated with reporting pain ($p<0.0001$) as well as reporting of sensory disturbances ($p<0.0001$).

Impairment of function

787 patients (24%) reported that they had to give up activities after treatment for breast cancer ranging from 11% in the group of women undergoing BCS, SLND and BRT to 44% in the group of women undergoing mastectomy, ALND and chemotherapy (Table 4). Of women who reported themselves as working 716 (36%) indicated that it had affected their work. 726 (36%) women engaged in sports reported that it affected their activity. 1519 (47%) reported light work above

shoulder level as problematic. 849 (27%) reported daily activity with involvement of shoulder rotation as troublesome. Heavy work was associated with difficulties for 1884 women (59%).

In the multivariate models the most important associations for reporting functional impairment was pain (OR=2.65; CI: 2.18–3.21, $p<0.0001$) and swelling of the arm (OR=2.39; CI: 1.96–2.92, $p=0.002$), but younger age, ALND, chemotherapy, time elapsed since surgery, and surgery on the dominant side were also associated with an increased risk of reporting impairment of function.

Radiotherapy and type of breast surgery were not associated with functional impairment in multivariate models.

Table 4. Functional impairment and perceived sensation of swelling/heaviness among 3253 Danish women operated on for primary breast cancer 2005-2006 according to the 12 different treatment groups (Figure 8).

BCS: Breast conserving surgery. SLND: Sentinel lymph node dissection. ALND: Axillary lymph node dissection. BRT: Breast radiotherapy corresponding to

Treatment modalities													
Type of surgery													No. total (%)
Breast	BCS						Mastectomy						
Axilla	SLND			ALND			SLND			ALND			
Adjuvant treatment													
Radiation therapy	BRT	BRT	BRT	BRT	BRT + LRRT	BRT + LRRT	-	-	-	-	ATRT + LRRT	ATRT + LRRT	
Chemo therapy	-	+	-	+	-	+	-	+	-	+	-	+	
Non-responders, No. (%)	118(12)	56(13)	22(10)	14(11)	39(12)	35(11)	40(21)	15(15)	36(20)	7(7)	62(15)	56(16)	500(13)
Median age, years (IQR)	59.0 (54-64)	47.0 (39-53)	59.0 (55-63)	42.5 (41-45)	61.0 (57-67)	47.0 (40-51)	62.0 (58-66)	54.0 (41-62)	59.5 (55-64)	48.0 (46-51)	62 (59-66)	48.0 (41-52)	
Responders, No.(%)	868(88)	368(87)	201(90)	110(89)	291(88)	284(89)	153(79)	86(85)	147(80)	96(93)	352(85)	297(84)	3253(87)
Median age, years (IQR)	60.0 (55-65)	49.5 (44-56)	61.0 (56-64)	49.0 (44-54)	60.0 (57-64)	48.0 (44-53)	62.0 (58-66)	53.0 (48-61)	60.0 (56-65)	48.5 (43-56)	61.0 (57-65)	48.0 (44-55)	
Report. swelling, No. (%)	113 (13)	86 (23)	102 (51)	67 (61)	153 (53)	185 (65)	20 (13)	20 (23)	62 (42)	45 (47)	204 (58)	192 (65)	1249(38)
Worst swelling ^a													
Light	63 (56)	51 (61)	51 (50)	32 (49)	80 (53)	92 (50)	13 (65)	10 (50)	25 (42)	20 (45)	73 (37)	99 (52)	609 (50)
Moderate	38 (34)	26 (31)	40 (39)	27 (42)	54 (36)	67 (36)	7 (35)	8 (40)	26 (44)	20 (45)	82 (42)	73 (38)	468 (38)
Severe	11 (10)	7 (8)	11 (11)	6 (9)	16 (11)	25 (14)	0 (0)	2 (10)	8 (14)	4 (9)	40 (21)	18 (9)	148 (12)
Func. impair., No. (%)	95 (11)	74 (20)	56 (28)	31 (28)	78 (27)	117 (41)	26 (17)	22 (26)	30 (20)	42 (44)	97 (28)	119 (40)	787(24)

residual breast tissue. ATRT: Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. LRRT: Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes. IQR: Interquartile range.

^aWorst swelling" was defined as the highest pain score of the armpit and/or upper arm and forearm and/or back of your hand. 1–3 was regarded light swelling, 4–7 moderate swelling and 8–10 severe swelling.

Discussion of results

After treatment for breast cancer, 47 % of the women reported pain and 58 % reported sensory disturbances in the surgical region. Of 3253 women, 292 (9 %) reported pain but no sensory disturbances, whereas 1204 (37 %) reported pain as well as sensory disturbances, indicating neuropathic pain as being the most important element in chronic pain after breast cancer surgery.

ALND and radiotherapy were confirmed as treatment related risk factors of chronic pain and as most

chronic pain in breast cancer seems related to sensory disturbances the induced pain is likely due to nerve damage. Some preliminary observations suggest that preservation of the intercostal brachial nerve could decrease chronic pain, however the results are ambiguous [95,103,165-167].

Surgery to the breast (mastectomy vs. BCS) had no influence on reporting pain, indicating that radiotherapy to residual breast tissue in the case of BCS might be an important risk factor for reporting pain, reducing the benefit of the reduced surgical trauma. Thus intraoperative radiation of the tumour-bed in women after BCS might have the potential to reduce nerve damage due to radiotherapy and thereby reduce pain. However, extending the radiation field with LRRT did not increase the risk of reporting pain, contradicting the theoretical benefit of reducing the radiated area. Another approach in trying to reduce chronic pain after breast cancer surgery is the use of agents with the potential of preventing central neuroplasticity/sensitisation of the nociceptive pathway, a pathophysiological mechanism believed to play an important role in the development of chronic pain [95]. This approach is promising, but unexplored in breast cancer.

Reporting on pain and the interpretation of reported pain is difficult as pain itself and the word “pain” are perceived differently by different individuals. In the process of testing the reliability of the questionnaire it appeared that the word “pain” (in Danish = “smerte”) by many patients was perceived as something for which you would need medication. Whereas “something that is hurting” (in Danish = “noget gør ondt”), was perceived as unpleasant but not something which would require medication. Furthermore, most patients did not perceive soreness (in Danish = “ømhed”) as pain at all. Therefore using the wording “no pain” and “worst imaginable pain” in a numeric 10-points rating scale might not reflect the same level of pain in different individuals and may tend to under-estimate mild, unpleasant, “painful” sensations. In an attempt to encounter this problem, “pain” was defined in the preface of the questionnaire as “just something which is hurting”, and it was made explicitly clear that we did not wish the patients to discriminate between “pain” and “something hurting” while answering the questionnaire (Appendix II). By asking the patients to specify the regions of pain and sensory disturbances, we aimed at targeting pain triggered by the treatment for breast cancer without directly asking the patients whether they themselves thought that the treatment was the reason for their pain. The most common sites of pain were the area of the breast and the axilla probably corresponding to

scar pain as well as ICN. Less frequently, pain was reported in the areas of the arm and the side of body, most likely to be explained by ICN. As we did not ask for specific pain syndromes, nor tried to qualify them with detailed questions regarding pain quality, we did not ask about shoulder pain. Pain in the shoulder may be related to restriction of motion and does play a role in sequelae after treatment for breast cancer, but as restriction of motion is reduced over time [146,147], shoulder pain might decrease as well. Moreover, pain in the shoulder and neck are very common in the normal population [168], and thus difficult to discriminate from pain caused by the treatment of breast cancer in questionnaire studies.

It was a deliberate choice to keep the questionnaire as simple as possible, as a more detailed description of the pain syndromes in women treated for breast cancer ought to involve careful clinical examination including quantitative sensory testing [169,170]. However, the questionnaire included more detailed questions regarding pain and the consequences of the pain than any other population-based study, and demonstrated the pain to be clinically relevant.

Even though most chronic pain in women treated for breast cancer is light or moderate, it reminds the patients of the cancer and may provoke anxiety [98]. Frequently being reminded of the cancer probably increases the distress in long-term survivors and might be one of the reasons why long-term survivors, scoring better in all other areas of quality of life, score significantly worse in mental health compared to the normal population [88]. Thus, reducing the number of women experiencing even light to moderate chronic pain might have the potential of improving mental health.

Self-reported symptoms of arm-lymphedema were overall indicated by 38 % of the patients. The overall prevalence of lymphedema is, however, of little clinical interest, more important is the large variation between treatment groups (13-65 %). Dividing the patients into well-defined treatment groups allows more detailed information about the patients regarding their risk for developing symptoms of lymphedema and helps in identifying high-risk groups in general. Informing patients about the symptoms and risk of developing lymphedema is crucial in early identification and treatment, but also carries a risk of unnecessary worry, over-treatment with compressing garments and self-inflicted restrictions of daily living. It is thus important to stress that the need for compressing garments should be evaluated by specialists and that physical work does not provoke lymphedema.

Furthermore, it should be stressed that the transient increased pain caused by early mobilisation of the arm most probably is due to the primary inflammatory response after surgery, and does not increase the risk of lymphedema or chronic pain [137].

Functional impairment was evident in women treated for breast cancer. In long-term breast cancer survivors, however, the level of physical function is reported to be better than in the general population [88]. This contradiction might be explained by the possibility of breast cancer survivors valuing life more and therefore under-reporting functional impairment compared to the general population. In our questionnaire two factors might have played an important role in disclosing functional impairment. Firstly the options of 1) doing something in another way than before, 2) having pain afterwards or 3) doing it slower or with difficulties, were all defined as functional impairments. Secondly, the women were directly asked if there were activities which they had to renounce after their treatment for breast cancer.

Describing chronic sequelae after treatment for breast cancer and giving estimates of associated factors is complicated. Pain and sensory disturbances, lymphedema and functional impairment are not isolated phenomena, but closely related and the large number of potential associated factors are influencing the different phenomena in different ways and to different extents. The model used to describe chronic sequelae in this thesis has focused on treatment related factors. However, many other important factors such as social status, anxiety and depression play important roles and offer another approach to identification of vulnerable patients, and should not be forgotten in the process of preventing and treating chronic sequelae after breast cancer.

Conclusion

Showing in Study I that the main problem at the PACU was moderate decreased saturation and confirming in Study II that PONV and pain were of no real significance after introduction of a multi-modal opioid-sparing regimen for the prevention of pain and PONV, the pathway of the patients was optimised by transferring the majority of the patients directly from the operating theatre to the ward providing patients with a moderate saturation deficit with binasal oxygen supply. Accordingly, both

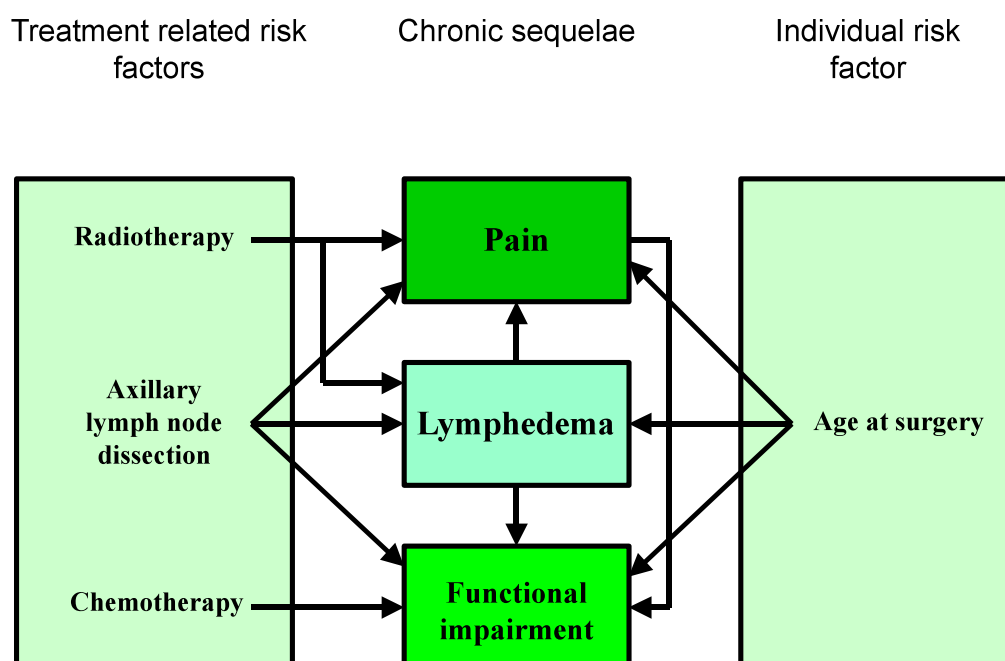
studies played an important role in the process of developing a short stay practice at the department for breast cancer surgery at Rigshospitalet.

As pain and PONV are common in the early postoperative phase, chronic sequelae in the form of pain, lymphedema and functional impairment are common 1-3 years after treatment for breast cancer. However, the variation in chronic sequelae between treatment groups is considerable, underlining that the population treated for breast cancer must be split into subgroups according to treatment when dealing with late sequela.

Throughout all subgroups younger age showed to be the most important predictor of reporting chronic sequelae. ALND showed to be the strongest treatment related associated factor, whereas mastectomy vs. BCS was not associated with pain, sensory disturbances, lymphedema or functional impairment which definitively makes the term “postmastectomy pain syndrome” obsolete. Adjuvant radiation therapy played a minor role whereas chemotherapy (CEF) was of no importance (except for functional impairment, probably due to loss of muscle mass).

Overall, the relation between chronic sequelae and associated factors in women treated for breast cancer is complex, as pain, lymphedema and functional impairment are closely related and associated with different treatment factors in different ways. Proposed relations supported by this thesis are depicted in Fig. 8.

Figure 8. Proposed relations, supported by the thesis, between chronic sequelae, treatment related and individual risk factors in women treated for breast.



Perspectives

The results presented in the first part of the thesis facilitated the introduction of a patient-centred, nurse-driven, fast-track concept with the potential of not only controlling physical discomfort associated with anaesthesia and surgery, but also reducing the psychological trauma. These early results call for larger multi-centre studies, and in time the development of standards for the perioperative treatment, as has been the case for many years regarding the surgical treatment. Main questions which ought to be in focus are: dosage of gabapentin and sedation especially in elderly people; dosage, effect and route of administration regarding dextromorphan and exploration of the benefit of replacing fentanyl with alfentanil for intraoperative analgesics in terms of reducing time from end of surgery to extubation, controlling for the effect on postoperative pain and morphine consumption. Additionally, the potential for reducing chronic pain by reducing acute postoperative pain [98,171], should be explored [172].

The results presented in the second part of the thesis enable clinicians to give far more detailed information regarding late sequelae to women undergoing treatment for breast cancer. However, addressing problems after treatment for breast cancer is delicate. Increased information on late sequelae might induce unnecessary worries in women who might just want to get on with their lives. On the other hand, recognising that late sequela after treatment for breast cancer is common, mostly of mild character and not signs of reoccurrence of cancer, might enable the women to cope with these symptoms and reduce anxiety.

With the increasing number of women living after breast cancer treatment, the interest for long-term sequelae is growing. However, studies of sequelae are always looking at the treatment of yesterday. With the pace at which the treatment for breast cancer develops today it might be time to start monitoring sequelae/morbidity, just as recurrence and death today is monitored in the database of DBCG. Monitoring acute, as well as chronic, pain and lymphedema will not only provide us with knowledge about treatment consequences, but will also offer the opportunity for early identification of these problems. This could be done by screening patients systematically for self-reported symptoms

early postoperatively and at their ambulatory control visits by, for example, electronic questionnaires developed to address specific actual problems of a physical as well as psychological nature. This would provide us with useful clinical information, enabling us to allocate resources to the patients needing a clinical examination, start up early treatment and potentially prevent manifest lymphedema and chronic pain as well as anxiety and depression. Additionally, data could contribute to the development of treatment guidelines and act as a monitoring tool of the consequences related to the ongoing changes in the treatment of breast cancer.

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Articles

Article I:

Recovery at the post-anaesthetic care unit after breast cancer surgery

Recovery at the post anaesthetic care unit after breast cancer surgery

Rune Gärtner, Torben Callesen, Niels Kroman & Henrik Kehlet

ABSTRACT

INTRODUCTION: Extant literature shows that women having undergone breast cancer surgery have substantial problems at the post-anaesthesia care unit (PACU). Based on nursing reports and elements of the discharge scoring system recommended by The Danish Society of Anaesthesiology and Intensive Care Medicine, the present prospective, observational study aims to determine why these patients stayed at PACU.

METHODS: The study included 116 consecutive patients having undergone surgery for breast cancer. Postoperative nausea and vomiting (PONV), pain, sedation, respiration, oxygen saturation (SpO_2), blood pressure and heart rate were scored at the PACU, and nurses were asked why discharge was delayed in case patients were not discharged at the time the discharge criteria were met. The outcome measures were the proportion of patients ready for discharge upon arrival at the PACU, patient time spent until discharge criteria were met, time to actual discharge, and the contribution of each discharge criterion in postponing discharge from the unit, as well as nurse-reported factors for the delay.

RESULTS: 31% of the patients were ready for discharge upon arrival at the PACU. The mean time until the discharge criteria were met was 40 min (standard deviation (SD) = 46 min). The actual time spent at the PACU was 110 min (SD = 75 min). A total of 36 patients had low SpO_2 (< 90%) upon arrival to the PACU. In 36 cases, discharge was delayed by the workload at the PACU and/or waiting for patient transport to the ward.

CONCLUSION: Low SpO_2 (< 90%), the workload at the PACU and time spent waiting for transport to the ward were the primary reasons why patients stayed at the PACU after breast cancer surgery.

In Denmark, 4,000 women undergo breast cancer surgery annually. Extant literature shows that women are facing severe early recovery problems at the post-anaesthesia care unit (PACU). Thus, surgery for breast cancer is associated with postoperative nausea and vomiting (PONV) in up to 80% of patients, and moderate pain occurs in about 50% of patients receiving uni- or bi-modal analgesic intervention during the first 24 postoperative hours [1]. Other studies have identified problems with evaluation of oxygen saturation [2].

A retrospective study exploring why patients stay at recovery units after elective colonic surgery concluded that PACU practices varied considerably, and the study called for prospective studies applying modern surgical techniques and specific scoring systems for observations and discharge from PACUs [3].

In 2004, The Danish Society of Anaesthesiology and Intensive Care Medicine (DASAIM) introduced a new set of recommendations including a criteria-based scoring system for the discharge of patients from PACUs to surgical wards. The system was fully implemented at our department during the autumn of 2006.

The present study explores potential problems at the PACU using the DASAIM scoring system. This involved an evaluation of PONV and pain at rest, as well as sedation, respiratory rate (RR), oxygen saturation (SpO_2), systolic blood pressure (SBP) and heart rate (HR).

We have previously reported data on pain, PONV and sedation at the PACU and the ward [4]. Based on the various elements of the DASAIM discharge scoring system and nursing reports, the present article aims to evaluate why patients who had undergone breast cancer surgery stayed at the PACU.

MATERIAL AND METHODS

The present prospective, consecutive, observational study includes all patients admitted for primary surgical treatment of unilateral breast cancer at our department during a 3-month period from 27 November 2006 to 26 February 2007. The patients had either mastectomy or breast conserving surgery (BCS) combined with sentinel lymph node dissection (SLND), or axillary lymph node dissection (ALND) in case of lymph node metastasis. As part of the SLND procedure, patients had 0.5-1.0 ml 2.5% Patent Blue solution injected intradermally into the breast.

The prophylactic treatment of PONV, pain and the method of anaesthesia have been described previously [4]. All patients were to be referred from the operating theatre to the PACU before going to the ward in order to evaluate dischargeability.

To evaluate the reasons why patients stayed at the PACU, we used a modified version of the DASAIM discharge criteria scoring system for discharge of patients

ORIGINAL ARTICLE

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 TABLE 1

Modified version of the discharge criteria scoring system recommended by the Danish Society of Anaesthesiology and Intensive Care Intensive Medicine. Patients were considered dischargeable from the post-anaesthesia care unit when the score sum of all criteria was four or less and the patients had no single score above one.

Modality	Score	Criteria
<i>Sedation</i> (Nurse evaluation)	0	The patient is fully awake
	1	The patient is asleep, aroused by verbal stimulation
	2	The patient is asleep, aroused by physical stimulation
	3	The patient asleep, can not be aroused
<i>RR</i> (nurse count)	0	Regular rate > 10
	1	Snoring, 10 > RR > 30
	2	RR < 10 or RR > 30/min.
	3	Periods of apnoea or obstructive pattern
Oxygen saturation, no supplementary oxygen for 10 min	0	SpO ₂ ≥ 94%
	1	90% ≤ SpO ₂ < 94%
	2	85% ≤ SpO ₂ < 90%
	3	SpO ₂ < 85%
<i>Systolic blood pressure</i> (automatic NIBP)	0	SBP ≥ 100 mmHg
	1	90 ≤ SBP < 100 mmHg
	2	80 mmHg ≤ SBP < 90 mmHg or SBP > 220 mmHg
	3	SBP < 80 mmHg
<i>Heart rate</i> (automatically derived from ECG)	0	50 < HR ≤ 100
	1	100 < HR ≤ 120
	2	40 < HR ≤ 50 or 120 < HR ≤ 130
	3	HR < 40 or HR > 130
<i>Pain at rest</i> (patient evaluation)	0	No pain
	1	Light pain
	2	Moderate pain
	3	Severe pain
<i>Nausea</i> (patient evaluation and nurse observation)	0	No nausea and not vomiting
	1	Light nausea or vomiting without previous nausea
	2	Moderate nausea and/or vomiting
	3	Severe nausea and/or reoccurring vomiting

RR = respiratory rate; SpO₂ = oxygen saturation; SBP = systolic blood pressure; HR = heart rate; NIBP = non invasive blood pressure; ECG = electrocardiography.

from the PACU to the surgical ward, **Table 1**. As from arrival at the PACU, sedation, RR, SpO₂, SBP, HR, pain at rest and PONV were recorded every 15 minutes. Each parameter was scored 0, 1, 2 or 3, respectively, corresponding to the following degrees of severity: none, light, moderate or severe, see Table 1.

Patients were considered dischargeable by the PACU nurses when the score sum was four or less, with no single score exceeding one. Patients who did not fulfil these two criteria but were otherwise dischargeable had to be discharged by the anaesthesiologist on duty. Additionally, the nurses were asked to explain why discharge was delayed if patients were not discharged at the time the criteria were met.

The work was performed in accordance with the Helsinki Declaration and with the acceptance of the local Ethics Committee as a quality assurance study. The collection and handling of data was approved by the Danish Data Protection Agency.

Results are presented as mean and standard deviations (SD) or as amounts and percentages, as ap-

propriate. The significance level for the p-value was set to 0.05% (Kruskal-Wallis one-way analysis of variance (asymmetric p-value) and Fisher's exact test for 2 × 2 contingency tables (2-tailed p-value)).

RESULTS

A total of 116 consecutive patients aged 33 to 86 years were included in the study (**Table 2**).

In all, 29 women underwent mastectomy with the SLND procedure, 19 underwent mastectomy with ALND. 55 women had BCS with the SLND procedure and 13 had BCS with ALND. A total of 95 patients were administered Patent Blue.

All patients were transferred from the operation theatre to the PACU as prescribed by the protocol, except one who by mistake was transferred directly to the ward. Upon arrival at the PACU, 36 patients (31%) fulfilled the criteria for discharge. The mean time from the patients regained spontaneous respiration to the first scoring at the PACU was 16 min (SD = 14 min). The mean time until the discharge criteria were met was 40



TABLE 2

Demographic data describing the 116 consecutive patients who underwent breast cancer surgery.

	Number (percentage)	Mean (standard deviation)
Age, years		62.0 (11.7)
Weight, kg		68.2 (12.0)
Height, cm		165.5 (6.29)
Body mass index, kg/m ²		24.9 (4.2)
Opioid users	6 (5.1)	
Smokers	25 (21.6)	
Motion sickness/previous PONV	40 (34.5)	
Preoperative pain in ipsilateral arm	13 (11.2)	
Preoperative pain in the breast	26 (22.4)	
ASA-score 1-2	100 (84.2)	
ASA-score 3-4	16 (13.8)	
<i>Surgical procedures</i>		
Mastectomy with axillary dissection	19 (16.4)	
Mastectomy with sentinel node	13 (11.2)	
Breast conserving surgery with axillary dissection	29 (25.0)	
Breast conserving surgery with sentinel node	55 (47.4)	

PONV = Postoperative nausea and vomiting; ASA = Classification from the American Society of Anesthesiologists.

min (SD = 46 min). A total of 94 patients fulfilled the discharge criteria upon arrival or while staying at the PACU. In 22 patients (19%), discharge had to be approved by the anaesthesiologist on duty, mainly due to low SpO₂. The overall mean time spent at the PACU was 110 min (SD = 75 min).

Figure 1 displays the number of patients scoring higher than one on any of the discharge criteria for the first 105 min after arrival at the PACU.

Low SpO₂ (scores two and three, corresponding to SpO₂ < 90% without supplementary oxygen) remained the most frequent cause for not fulfilling discharge criteria upon arrival to the PACU (36 patients; 31%) and until 75 min after arrival (14 patients; 12%). In the same period, scores two and three for RR fell from 18 to nine patients (16% to 8%).

Seven out of 16 patients belonging to the American Society of Anesthesiologists (ASA) group 3-4 scored more than one on SpO₂ upon arrival to the PACU, which was not significantly different from patients belonging to ASA group 1-2, 28 patients of 100 ($p = 0.24$). Nor did we find any significant differences in SpO₂ between the patients who received Patent Blue and those who did not ($p = 0.61$). Pain peaked after 30 min, with 12 patients (10%) scoring > 1, decreasing to only one patient after 90 min.

Upon arrival to the PACU, 17 patients (15%) scored > 1 on sedation. One hour later this number was reduced to three patients.

One patient scored > 1 on heart rate upon arrival to the PACU. No patients scored > 1 on PONV or systolic blood pressure upon arrival. At the PACU, only very few patients developed scores > 1 (see Figure 1). Thus, PONV, systolic blood pressure and heart rate had no overall influence on delay of discharge from the PACU.

In 36 cases (31%), the nurses at the PACU stated that discharge was delayed by logistic factors like the workload at the PACU and/or waiting for patient transport to the ward.

DISCUSSION

Our results show that with a multimodal regimen, described elsewhere [1], low oxygenation and logistic problems were the two major causes for staying at the PACU.

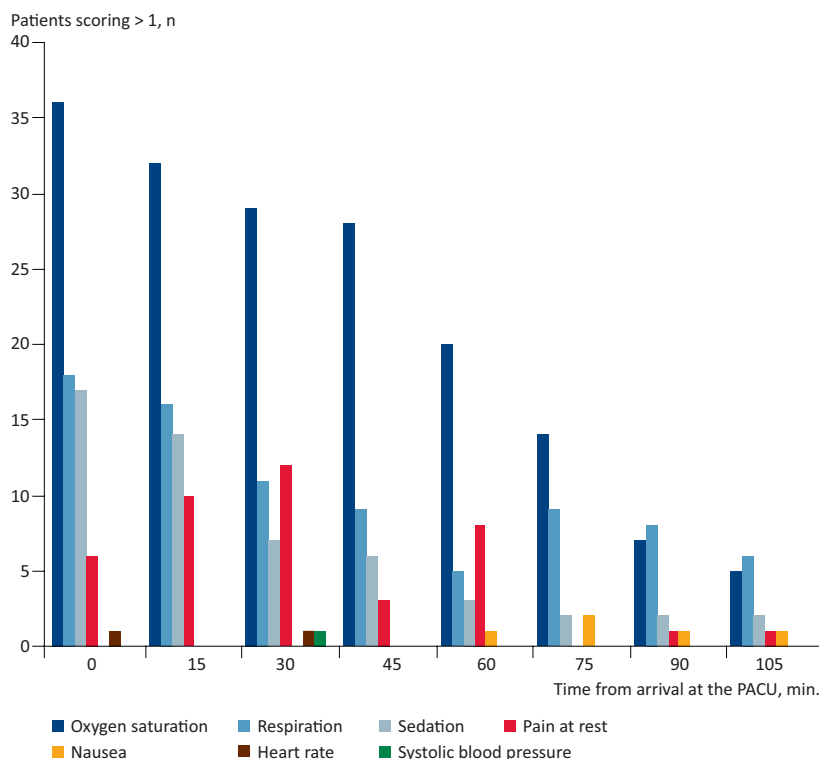
Due to the sentinel node procedure, 95 patients (82%) had Patent Blue injected. Patent Blue is known to cause falsely low peripheral SpO₂ values [2]. However, there were no significant differences regarding SpO₂ at the PACU between the patients who received Patent Blue and those who did not. Nor could the observed low SpO₂ levels be explained by the relatively high proportion of ASA group 3-4 patients (13%). Yet the number of ASA group 3-4 patients and the number of patients who did not receive Patent Blue were too small to rule out possible effects on SpO₂ measurement. Finally, the intraoperative use of long-acting opioids, well known to suppress respiratory drive, may pose a third explanation for the fact that SpO₂ was the most common reason for keeping the patients at the PACU. However, only half of the patients with low SpO₂ levels had a low respiratory rate (< 10) upon arrival to the PACU. As fentanyl is the standard analgesic for breast cancer surgery at our department, we did not use remifentanyl in this study. The



Scoring situation at the post-anaesthesia care unit.

FIGURE 1

Recovery profile of the 116 consecutive patients operated on for breast cancer. The numbers of patients scoring higher than 1 on any of the DASAIM discharge criteria during the first 105 minutes after arrival at the post-anaesthesia care unit (PACU).

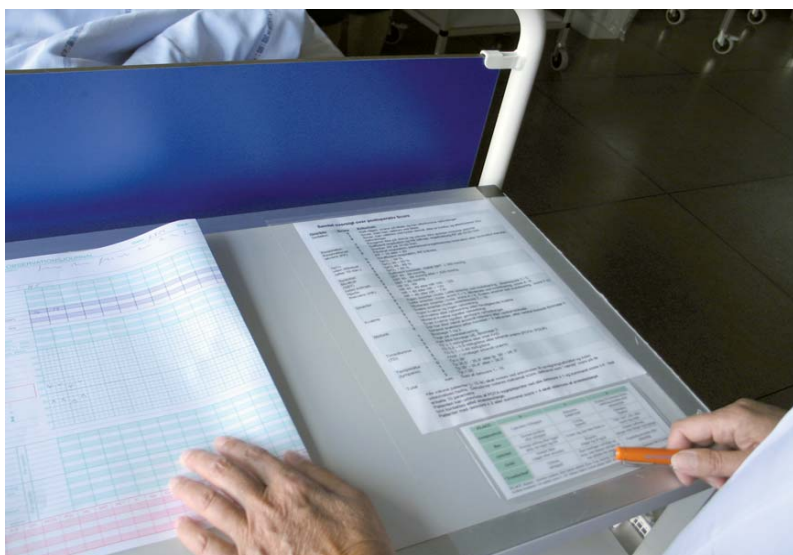


use of the short acting opioid remifentanyl might have resolved this question, but there is no available evidence that remifentanyl should improve the outcome at the PACU for PONV, pain control or speeding up discharge in general after breast cancer surgery [5].

The procedures used in this study may all be con-

sidered surface surgery, and they have hardly interfered as such with post-operative respiratory function. In combination with other surgical interventions such as laparoscopic cholecystectomy, positive pressure ventilation is, however, known to cause microatelectases and reduced respiratory function [6-8]. Correspondingly, a study of recovery after laparoscopic cholecystectomy showed that one third of the patients had a supplemental oxygen demand for one hour or more, but it questioned whether oxygen saturation was a relevant discharge criterion [9]. In a similar study of abdominal hysterectomy, the same authors found that half of the patients required supplemental oxygen for one hour or more to sustain an $SpO_2 > 92\%$ [10]. In our study, 20% of the patients needed supplementary oxygen for one hour or more. However, the consequence of modest desaturation in patients operated for breast cancer is questionable. A pragmatic solution could be to discharge patients from the PACU regardless of such mild pulmonary dysfunction, provided that the patients have binasal oxygen supply on the ward for a few hours.

Though 31% of the patients were dischargeable already upon the arrival to the PACU, the actual time to discharge was two and a half fold longer than the average time to fulfilment of the discharge criteria. This was mostly due to hospital logistics. At our PACU, the pa-



Scoring at the post-anaesthesia care unit with use of the discharge scoring system recommended by The Danish Society of Anaesthesiology and Intensive Care Medicine.

tients having had surgery for breast cancer is the group needing the least amount of care at the PACU, and thus the group that waits when PACU nurses are busy. Additionally, patients brought to the PACU are to be monitored for a minimum of 30 min before discharge. Hence, the postoperative course of these patients would be much helped by critically reviewing procedures at the PACU and by discharging patients meeting these discharge criteria already at the operating theatre directly to the ward.

In conclusion, a modest decrease in SpO₂ (<90%), the workload at the PACU and time spent waiting for transport to the ward were the primary reasons why patients stayed at the PACU after breast cancer surgery.

Discharging patients fulfilling the DASAIM discharge criteria at the operating theatre directly to the ward, reviewing logistics at the PACU, and discharging patients presenting with only a modest decrease in SpO₂ with binasal oxygen supply to the ward have the potential of reducing the time spent at the PACU and the number of women operated for breast cancer who needs care at the PACU. This would, in turn, facilitate the development of breast cancer surgery towards an outpatient clinic practice enhancing fast recovery and rehabilitation.

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Article II:

Multimodal prevention of pain, nausea and vomiting
after breast cancer surgery

Erratum: The patients in the study were included consecutively from 11-4-2007 to 30-08.2007 and not as stated in the article from 04-11-2006 to 30-08-2007.

Multimodal prevention of pain, nausea and vomiting after breast cancer surgery

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ABSTRACT

Background. Despite many one- or two-modal attempts to relieve postoperative nausea and vomiting (PONV) and pain, postoperative issues following breast cancer surgery remain a substantial problem. Therefore, the aim of this explorative, hypothesis-generating study was to evaluate the effect of a multimodal, opiate-sparing, evidence-based regimen for prevention of PONV and pain.

Methods. Two hundred consecutive patients scheduled for breast cancer surgery were included. The prevention regimen included a package consisting of preoperative paracetamol, dextromethorphan, celecoxib, gabapentin, dexamethasone, total intravenous anaesthesia and intraoperative ondansetron. The patients were prospectively scored according to PONV, pain during rest and mobilization and major side effects.

Results. Of 200 consecutive breast cancer patients, 191 received the full package. During the first 36 postoperative hours, 79.1% reported no PONV at all and only 3.7% reported severe PONV. At rest, 69.6% reported no or light pain and 3.1% reported severe pain, with corresponding values of 59.7% and 8.9% during arm mobilization. Mean postoperative morphine consumption was 2.2 mg. The only significant side effect was transient dizziness.

Conclusion. A multimodal, opiate-sparing regimen to prevent pain and PONV seems to be more effective than one- or two-component regimens on PONV and pain after breast cancer surgery, a result which calls for large-scale multicenter or randomized studies. (*Minerva Anestesiologica* 2010;76:805-13)

Key words: Pain - Postoperative nausea and vomiting - Anaesthesia recovery period.

Postoperative discomfort is a major problem in patients undergoing breast cancer surgery; postoperative nausea and vomiting (PONV) occurs in 50-80% of patients undergoing general anaesthesia without antiemetics^{1,2} and in about 10-50% who receive one- or two-component PONV prophylaxis.^{3,4} In most studies of one- or two-component analgesic interventions, moderate pain is found in the intervention groups along with a postoperative morphine consumption of about 10-15 mg/24 h.⁵⁻¹¹ Further improvements have been achieved by invasive techniques such as par-

avertebral blockade and epidural anaesthesia,¹² but these methods require expertise and impose the risk of rare but severe side effects.

Since transmitter substances involved in acute postoperative pain sensation are diverse, analgesic therapy can be composed of two or more drugs with different mechanisms of action and synergistic effects.¹³ Thus, the aim of the study was to evaluate a simple, oral preoperative, multimodal pain and PONV prevention package, based upon evidence from one- and two- component studies and reviews and upon safety considerations. Parts

of the package are recommended by PROSPECT (*i.e.*, "the PROSPECT website", www.postoppain.org) for non-cosmetic breast surgery. The package consisted of paracetamol,^{14, 15} dextromethorphan,^{16, 17} celecoxib,¹⁸ gabapentin,^{11, 19} dexamethasone and ondansetron.²⁰ Since the objective of the study was to cover the variety of mechanisms involved in pain, dextromethorphan was chosen to cover the n-methyl-d-aspartate (NMDA) receptor due to its lack of psychomimetic side effects and safety profile compared to ketamin.^{13, 16, 17} Dexamethasone was chosen due to its antiemetic and potential pain modulating effects.^{20, 21}

We have previously reported on PONV and pain in a smaller study of a related but not identical population.²² This study was primarily designed to deal with the reasons for patients' staying at the post-anesthetic care unit after breast cancer surgery. The study had some methodological problems regarding the time of follow-up, and additionally, it did not report side effects.

Therefore, the primary outcome measures of the present study were PONV and pain during rest and mobilization, as well as the incidence of dizziness, headache, diplopia, confusion and memory disorders for 36 hours after surgery. Secondary outcome measures were time from end of anesthetic infusion to spontaneous breathing, and the postoperative requirement for morphine at the post-anesthetic care unit (PACU) and in the ward.

Materials and methods

Ethics

The Local Research Ethic Committee considered the study to be a pure quality assessment study and deemed that written informed consent was not necessary; hence, it was not obtained. The collection and handling of data was approved by the Danish Data Protection Agency.

Patients

Two hundred consecutive patients admitted for primary surgical treatment of unilateral breast cancer at Rigshospitalet (University of Copenhagen) were included from 04-11-2006 to 30-08-2007. Nine patients did not receive or only partially received the PONV and pain prevention package and were thus excluded from analyses.

Surgery

Mastectomy or breast conserving surgery (BCS) was performed in combination with either sentinel lymph node dissection (SLND) or axillary lymph node dissection (ALND).

Premedication

One to two hours preoperatively, the patients received the PONV and pain prevention package consisting of 1 g oral paracetamol, 8 mg dexamethasone, 30 mg dextromethorphan, 400 mg celecoxib and 1200 mg gabapentin (600 mg in patients >70 years). Oral triazolam 0.125 mg was only given on specific patient request to alleviate preoperative anxiety.

Anesthesia

Intravenous anaesthesia was induced with 0.15 mg fentanyl and 2 mg/kg body weight propofol. Five minutes before incision, another 0.15 mg fentanyl was added, and anesthesia was maintained with 0.15-0.20 mg/kg body weight/minute propofol. If the heart rate increased above 20% of base line, fentanyl 0.05 mg was added. Approximately 20 min before end of surgery, 4 mg ondansetron was given.

Airway

A laryngeal mask airway was used for oxygen/air ventilation at an aimed FiO₂ of 0.7. If, for medical reasons, tracheal intubation was necessary, we used suxamethonium 1-1.5 mg/kg or cisatracurium 0.15 mg/kg for muscle relaxation. Depth of anesthesia was clinically monitored by heart rate, blood pressure and pupil reaction to light and was recorded every 5 min.

Recording of data

Duration of general anesthesia and time from the end of propofol infusion to the recovery of spontaneous breathing, as well as cumulative fentanyl and propofol dosages, were recorded.

Dizziness, headache, diplopia, confusion, memory disorders, PONV, and pain at rest and on mobilization were evaluated every 15 min in the PACU. To distinguish between side effects and

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TABLE I.—Demographic data on 200 consecutive patients undergoing surgery for breast cancer.

	Full prevention package (N.=191)		No prevention package or only parts of the prevention package (N.=9)	
	Mean	(SD)	Mean	(SD)
Age; years	62.7	(12.5)	65.4	(8.2)
Weight; kg	70.1	(14.8)	67.7	(17.1)
Height; cm	165.4	(6.3)	163.0	(6.0)
BMI; kg/m ²	25.6	(5.3)	25.7	(7.6)
	Number	Percentage	Number	Percentage
Opioid users	15	(8)	1	(11)
ASA Grade				
I	60	(31)	6	(66)
II	97	(51)	2	(22)
III	34	(18)	1	(11)
Surgical procedures				
Mastectomy + ALND	43	(23)	4	(44)
Mastectomy + SLND	36	(19)	1	(11)
BCS + ALND	18	(9)	1	(11)
BCS + SLND	94	(49)	3	(33)

BMI: body mass index; ASA: American Society of Anesthesiologists; SD: standard deviation; BCS: breast conserving surgery; ALND, axillary lymph node dissection, SLND, sentinel lymph node dissection.

habitual troubles, the patients were asked preoperatively whether their everyday life was troubled by these symptoms. PONV and pain were scored zero, one, two or three (*i.e.*, no complaint=0, mild=1, moderate=2 and severe complaint=3). Mobilization was defined as active arm abduction to an angle of 90 degrees out from the body. At discharge to the ward, the worst scores during the stay in the PACU were recorded. Dizziness, headache, diplopia, confusion and memory troubles were recorded as “yes” or “no”. On the day of the operation, the same parameters were recorded in the ward at 8 pm, on the next day at 8 am and 8 pm and on the second day after the operation at 8 am. In addition, the patients were asked whether they had experienced any of the above-mentioned symptoms between these measurements. Nurses recorded all information during hospitalization. Patients discharged less than 36 hours postoperatively completed the registration form at home and the data were retrieved by telephone contact. Patients scoring moderate or severe pain in the PACU at rest and/or severe pain with mobilization received morphine 0.1 mg/kg intravenously (0.05 mg/kg if older than 70 yrs). In the ward,

patients had oral paracetamol 1g q6 hours and oral celecoxib 200 mg the evening of operation and the morning and the evening of the next day.

Patients who needed analgesics after the first postoperative day continued with oral ibuprofen 600 mg q8 hours and paracetamol 1g q6 hours. Rescue analgesic in the ward was oral morphine 15 mg as required.

Statistical analysis

Results are presented as mean and standard deviations (SD) or as number and percentages, as appropriate. Confidence intervals for frequencies were estimated by: $p \pm 2\sqrt{p(1-p)/n}$ where p is the frequency/likelihood, and n the total number. The P-value limit was set to 5% (Kruskal-Wallis one-way analysis of variance, asymmetric P-value or Fisher's exact test for 2×2 contingency tables, 2-tail P-value).

Results

A total of 200 consecutive patients aged 30 to 92 years were included in the study (Table I). Nine patients were excluded from the study analysis due

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TABLE II.—*Pain within the first 36 postoperative hours in relation to type of surgery in 191 women undergoing surgery for breast cancer.*

	Mastectomy + ALND	Mastectomy + SLNDd	BCS+ ALNDc	BCS+ SLND	P-value	Total
<i>Number (%)</i>	43 (23)	36 (19)	18 (9)	94 (49)		191 (100)
<i>Pain at rest</i>					P=0.18	
No pain, number (%; CI)	6 (14, 3;24)	6 (17, 4;29)	5 (28, 7;49)	26 (27,18;36)		43 (22.5, 16;29)
Light pain, number (%; CI)	20 (47, 31;62)	19 (53, 36;69)	6 (33, 11;55)	45 (48, 38;58)		90 (47.1, 40;54)
Moderate pain, number (%; CI)	16 (37, 22;52)	9 (25, 11;39)	6 (33, 11;55)	21 (22, 14;31)		52 (27.2, 21;34)
Severe pain, number (%; CI)	1 (2, 0;7)	2 (5, 0;13)	1 (5, 0;16)	2 (2, 0;5)		6 (3.1, 1;6)
<i>Pain during mobilisation</i>					P=0.01	
No pain, number (%; CI)	4 (9, 0;18)	2 (6, 0;13)	5 (28, 7;49)	23 (24, 16;23)		34 (17.8, 12;23)
Light pain, number (%; CI)	17 (40, 25;54)	17 (47, 31;64)	4 (22,3;41)	42 (45, 34;55)		80 (41.9, 35;49)
Moderate pain, number (%; CI)	14 (33, 18;47)	14 (39, 23;55)	8 (44, 21;68)	24 (26, 17;35)		60 (31.4, 25;38)
Severe pain, number (%; CI)	8 (19, 7;30)	3 (8, 0;18)	1 (6, 5;16)	5 (5, 1;10)		17 (8.9, 5;13)
CI: confidence interval; BCS: breast conserving surgery; ALND:axillary lymph node dissection; SLND: sentinel lymph node dissection						

TABLE III.—*Morphine consumption, in relation to type of surgery in 191 women undergoing surgery for breast cancer.*

	Mastectomy +ALND	Mastectomy + SLND	BCS+ ALNDc	BCS+ SLND	Total	P value
<i>Number, N.</i>	43	36	18	94	191	
<i>Morphine consumption</i>						
Number requiring morphine, N.	18	14	7	16	55	
% (CI)	42 (27; 57)	39 (23; 55)	39 (16; 62)	17 (9; 25)	29 (22; 35)	
Mean morphine consumption mg N= 55 (SD)	7.6 (6.7)	8.6 (5.6)	7.3 (3.0)	6.4 (3.0)	7.5 (5.0)	P=0.82
Mean morphine consumption N=191 (SD)	3.6 (5.6)	3.0 (5.5)	2.8 (4.1)	1.1 (2.7)	2.2 (4.3)	P<0.05
CI: confidence interval, SD: standard deviation; BCS: breast conserving surgery; ALND:axillary lymph node dissection; SLND: sentinel lymph node dissection.						

to inadequate preoperative medication.

Complications

Four patients underwent additional surgery due to postoperative wound hemorrhage. These patients were not excluded from the study, as the re-operations were performed the same day. The data retrieved in the PACU from the first operation and the data retrieved in the ward were included in the analysis.

Anesthesia

Mean duration of anaesthesia was 150 min

(SD=38 min), including the time from the end of the propofol infusion until the resumption of spontaneous breathing, which was 22 min (SD=13 min). The mean cumulative dose (including the induction dose) of propofol was 1,417 mg (SD=567 mg). The mean cumulative dose of fentanyl was 0.401 mg (SD=0.094 mg).

Airway

Due to medical reasons, 18 patients were tracheally intubated; 9 patients had suxamethonium, and 9 had cisatracurium.

Postoperative period

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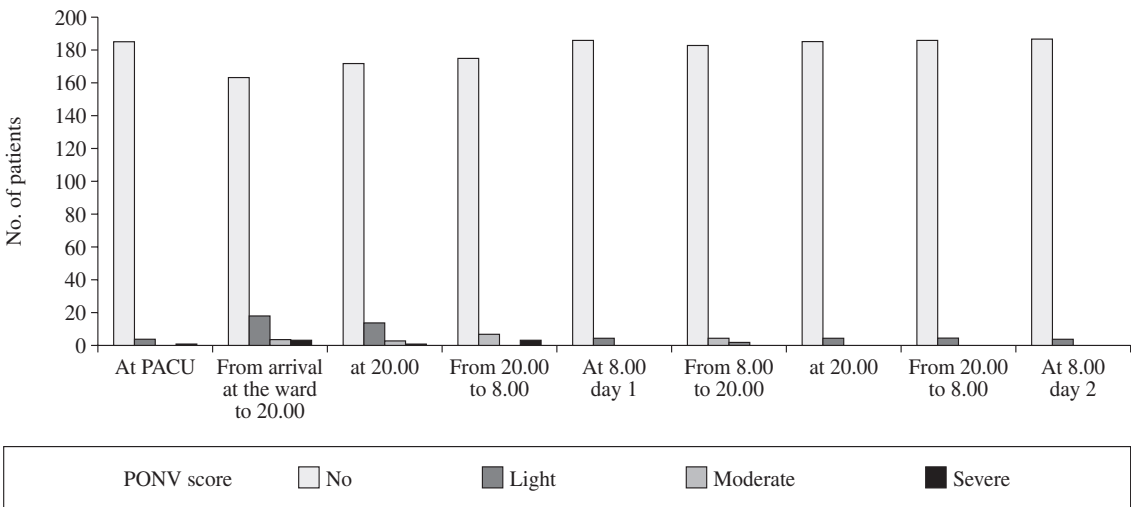


Figure 1.—Postoperative nausea and vomiting (PONV).

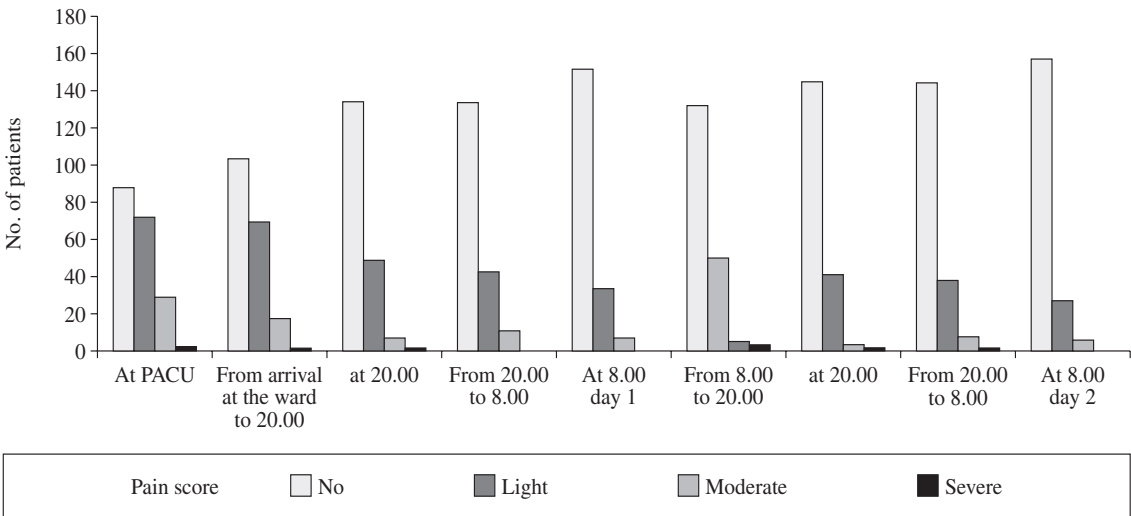


Figure 2.—Pain at rest.

The time course of PONV and pain during rest and mobilization is shown in Figures 1-3.

PONV

Throughout the 36-hour study period (including the PACU) 151 patients (79%, 73-85% CI) had no PONV following surgery. At some point of time during the first 36 hours, 25 patients (13.0%, 0.08-0.18% CI) experienced mild PONV, 8 patients (4.1%, 1-7% CI) experienced moderate PONV, and 7 patients (3.7%, 1-6% CI) experienced severe PONV.

Pain at rest

Throughout the 36-hour study period (including the PACU), 43 patients (22.5%, 16-29% CI) had no pain at all, 90 patients (47.1%, 40-54% CI) experienced light pain, 52 (27.2%, 21-34% CI) experienced moderate pain, and six patients (3.1%, 1-6% CI) experienced severe pain as their worst pain at rest. Thus, 133 patients (69.6%, 63-76% CI) experienced no or light pain at rest as their worst pain during the entire 36-hour period.

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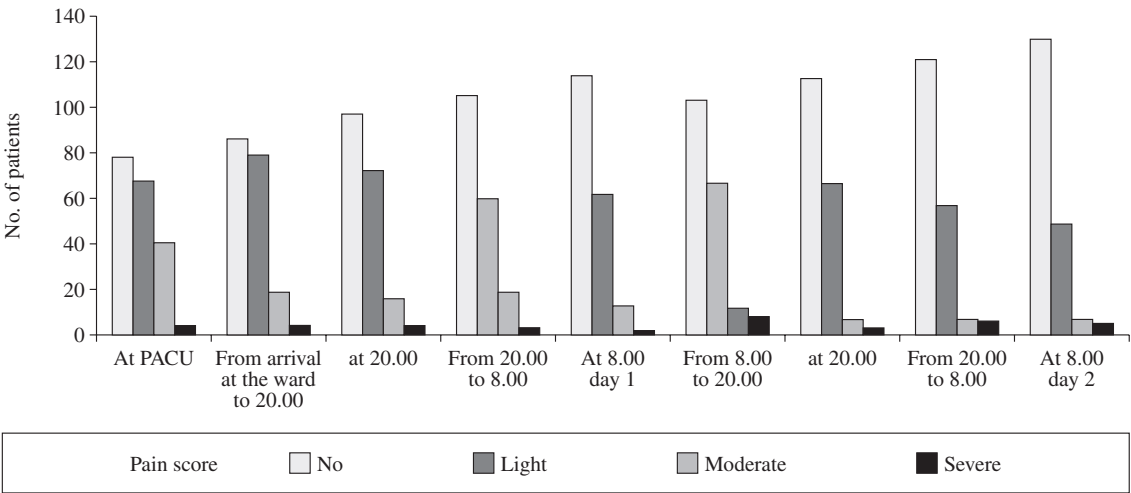


Figure 3.—Pain under mobilization.

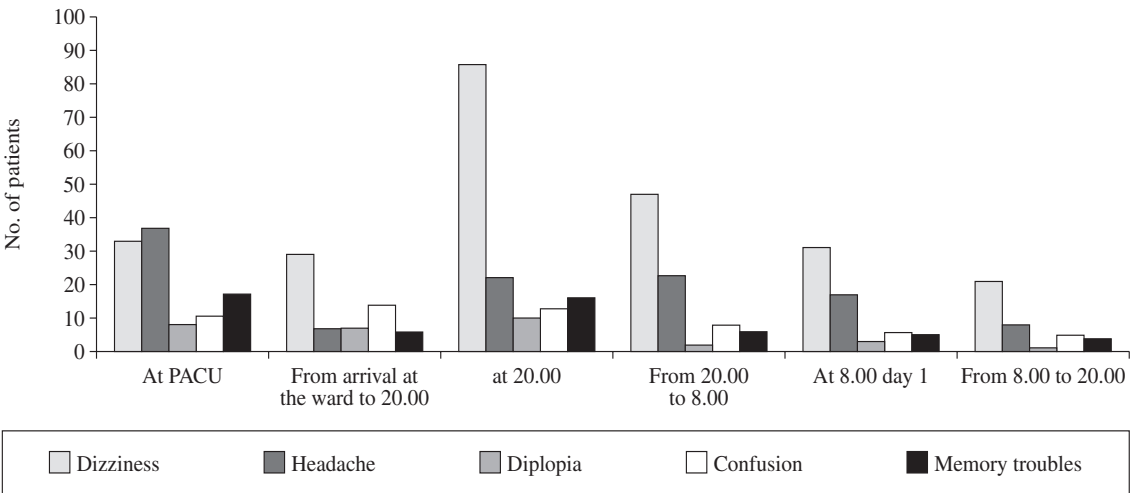


Figure 4.—Side effects.

Pain during mobilization

Throughout the 36-hour study period, 34 patients (17.8%, 12-23% CI) experienced no pain at all during arm mobilization, 80 patients (41.9%, 35-49% CI) experienced light pain during arm mobilization, 60 patients (31.4%, 25-38% CI) experienced moderate pain during arm mobilization, and 17 (8.9%, 5-13% CI) experienced severe pain during arm mobilization (Figure 3). Thus 114 patients (60.2%, 53-67% CI) experienced no or light pain at arm mobilization during the entire 36-hour study period.

Morphine consumption

Fifty-five patients had i.v. morphine in the PACU (mean 7.5 mg; SD=5 mg), and none requested opiates in the ward.

The distribution of morphine consumption in relation to different surgical groups is shown in Table III.

Side effects

Were recorded in 116 patients. Preoperative values and the development of side effects over time are shown in Figure 4.

In 71 patients (61%, 52-70% CI) the side-effects were similar to preoperative complaints: dizziness (N=25), headache (N=21), diplopia (N=5), confusion (N=6) and memory disorders (N=9). Throughout the 36-hour study duration, 96 patients (50.3%, 43-57% CI) experienced some degree of dizziness: 44 (23.0%, 17-29% CI) headache, 17 (8.9%, 5-13% CI) diplopia, 28 (14.6%, 10-20% CI) confusion and 20 (10.5%, 6-15% CI) memory disorders.

Discussion

Postoperative discomfort after surgery for breast cancer represents a substantial problem, in clinical practice.^{1-10, 12}

Antiemetic drugs, as single compound intervention^{1, 4, 23} or in combination,^{2, 24} have been well-established to reduce PONV from 50-80% to 10-50% in breast cancer surgery. In all studies except for one that was reported by Gan *et al.*,²⁴ however, anesthesia was performed with only volatile anesthetics, which are well-known to increase PONV.²⁵ Since the cumulative incidence of severe PONV in our study was only 0.5% while in the PACU and 3.7% throughout the 36 hour registration period, our regimen supports the proposition that total intravenous anaesthesia, in combination with antiemetics and non-opiate analgesics, further reduces the incidence of PONV.

The interventions for preventing pain after breast cancer surgery vary considerably, ranging from pharmacological single-compound interventions (e.g. morphine) and infusion/instillation or infiltration with local anesthetics (e.g. bupivacaine) to invasive techniques like paravertebral block, thoracic epidural anaesthesia and intercostal block.^{5-10, 12, 26} In most studies of pharmacological interventions, the average patient experienced moderate pain at rest within the first 24 h after the operation.^{5-7, 9-11} Throughout the 36-hour registration period, 22.5% of our patients never experienced any pain, 47.6% experienced only light pain, 26.7% experienced moderate pain and only 3.1% experienced severe pain.

The treatment of moderate to severe pain, which is common after breast cancer surgery in other studies, is mostly by opiates.^{5, 9, 26} In our study, the patients only required a mean dose of 2.2 mg morphine, which is in contrast to other regimens

that have a median or mean morphine consumption of 10-15 mg.^{5, 8-10} Although we found a significant difference between surgical subgroups in morphine consumption, the mean morphine consumption did not exceed 4 mg in any of the groups.

Apart from achieving apparently better results than single- or two-component studies,⁵⁻¹⁰ our results were comparable to those achieved by regional block, paravertebral block or epidural anesthesia.²⁶

Our approach employed 6 different agents with a potential for several different side effects. Apart from pain and PONV, postoperative symptoms/side effects have been only sparsely reported in the literature. A review of the efficacy and safety of perioperative gabapentin found that the numbers needed to produce excessive sedation and dizziness were 35 and 12, respectively.²⁷ In a prospective study of 1,017 patients undergoing different kinds of ambulatory surgery, Chung *et al.*²⁸ found that the overall 24 hour incidence of headache was 11.6% and of dizziness was 9.7%, although the incidence after laparoscopy was higher: 22.9% and 24.1%, respectively. In our study, the cumulative 36 hour incidences of headache and dizziness were 23.5% and 51.0%, respectively, which should also be compared to an overall 36% incidence of balance problems in elderly women.²⁹ We also asked the patients preoperatively whether they, in their everyday lives, were bothered by headache, dizziness, diplopia, confusion and memory disorders. Overall, about half of the patients experiencing these troubles postoperatively were also bothered preoperatively. Thus, the high incidence of headache and dizziness in our study might be due to the elderly population, as well as to the prior presence of these complaints before surgery.

Whether the benefits of acceptable control of PONV and pain, as well as the minimal morphine consumption achieved in the present study, are counterbalanced by the relatively high but short lasting (about 16 hours) incidence of dizziness is an open question. However, the dizziness reported in the present study did not seem to bother the patients much.

Furthermore, to our knowledge, no other regimens investigating the prevention of PONV and postoperative pain after surgery for breast cancer

have controlled for dizziness as side effect using pre- and postoperative assessments.

Comparisons between different studies of PONV and pain after breast cancer surgery are complicated, not only due to different interventions, designs and anesthetic regimens, but also due to different types of surgery. One could argue that the favorable results obtained in our study were due to the fact that half of our patients had BCS+SLND and thus had a less mutilating surgery (and consequently less pain) than those who had mastectomy+ALND. In a subgroup analysis, we found a significant difference in morphine consumption between the 4 surgical groups and a significant difference in pain during mobilization, but not at rest. Only 2% of the women undergoing mastectomy+ALND reported severe pain at rest, however.

The choice of a multimodal regimen was based on efficacy and safety considerations, but was also economically beneficial compared to more invasive procedures. The price of our prevention package was 4.20 EUR, whereas the cost of a paravertebral blockade is 9.40 EUR and the cost of a thoracic epidural anaesthesia 17.65 EUR at our hospital, not including the time spent by the anesthesiologist.

Conclusions

A simple preoperative, multimodal, opiate-sparing oral regimen for the prevention of PONV and pain proved effective and substantially lowered morphine consumption, compared to reports in the literature. The regimen may therefore have the potential to facilitate implementation of fast-track surgery for breast cancer,³⁰ and should be evaluated in large multi-center cohort or randomized studies.

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Article III:

Prevalence of and Factors Associated With Persistent Pain
Following Breast Cancer Surgery

Prevalence of and Factors Associated With Persistent Pain Following Breast Cancer Surgery

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PERSISTENT POSTSURGICAL PAIN has been demonstrated to be clinically relevant in 10% to 50% of patients undergoing various common operations, including breast cancer surgery.¹ With breast cancer, the pathogenic mechanisms are multiple, including nerve damage related to surgical technique resulting in risk of intercostobrachial neuralgia, neuroma pain, or phantom breast pain.² Different types of sensory disturbances (eg, allodynia, hyperpathia, aftersensations, burning, or sensory loss) are sequelae to other surgical procedures and may be an important part of the pain characteristics in breast cancer.¹

Pain has also been reported to be associated with adjuvant therapy, such as chemotherapy and radiotherapy.³ Other risk factors may include age (<40 years), psychosocial status, preoperative breast pain,⁴ and acute postoperative pain intensity.⁵ However, almost all information is retrospective based on questionnaires, often from single centers or small cohorts, not allowing sufficient analyses of the many risk factors. In addition, surgical principles of treatment have changed in recent years, including more breast-conserving surgery (BCS) and use of the sentinel node

Context Persistent pain and sensory disturbances following surgical treatment for breast cancer is a significant clinical problem. The pathogenic mechanisms are complex and may be related to patient characteristics, surgical technique, and adjuvant therapy.

Objective To examine prevalence of and factors associated with persistent pain after surgical treatment for breast cancer.

Design, Setting, and Patients A nationwide cross-sectional questionnaire study of 3754 women aged 18 to 70 years who received surgery and adjuvant therapy (if indicated) for primary breast cancer in Denmark between January 1, 2005, and December 31, 2006. A study questionnaire was sent to the women between January and April 2008.

Main Outcome Measures Prevalence, location, and severity of persistent pain and sensory disturbances in 12 well-defined treatment groups assessed an average of 26 months after surgery, and adjusted odds ratio (OR) of reported pain and sensory disturbances with respect to age, surgical technique, chemotherapy, and radiotherapy.

Results By June 2008, 3253 of 3754 eligible women (87%) returned the questionnaire. A total of 1543 patients (47%) reported pain, of whom 201 (13%) had severe pain, 595 (39%) had moderate pain, and 733 (48%) had light pain. Factors associated with chronic pain included young age (18-39 years: OR, 3.62; 95% confidence interval [CI], 2.25-5.82; $P < .001$) and adjuvant radiotherapy (OR, 1.50; 95% CI, 1.08-2.07; $P = .03$), but not chemotherapy (OR, 1.01; 95% CI, 0.85-1.21; $P = .91$). Axillary lymph node dissection (ALND) was associated with increased likelihood of pain (OR, 1.77; 95% CI, 1.43-2.19; $P < .001$) compared with sentinel lymph node dissection. Risk of sensory disturbances was associated with young age (18-39 years: OR, 5.00; 95% CI, 2.87-8.69; $P < .001$) and ALND (OR, 4.97; 95% CI, 3.92-6.30; $P < .001$). Pain complaints from other parts of the body were associated with increased risk of pain in the surgical area ($P < .001$). A total of 306 patients (20%) with pain had contacted a physician within the prior 3 months for pain complaints in the surgical area.

Conclusion Two to 3 years after breast cancer treatment, persistent pain and sensory disturbances remain clinically significant problems among Danish women who received surgery in 2005 and 2006.

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technique, and principles for radiotherapy and chemotherapy have been adjusted to more recent scientific data, thereby limiting interpretation of previous studies except for an agreement on persistent pain being a significant clinical problem.

The goal of our study was to examine the prevalence, associated factors, and severity of chronic pain and sensory disturbances after surgery for breast cancer in a nationwide study, taking advantage of the unique possibi-

ties in Denmark with a national database managed by Danish Breast Cancer Cooperative Group (DBCG),⁶ which

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For editorial comment see p 2034.

prospectively collects detailed clinical data, histopathological status, treatment, and data on recurrence and mortality.^{1,4,7} Furthermore, treatment principles are standardized at all Danish breast cancer departments according to European guidelines⁸ and national protocols designed by the DBCG.⁷

METHOD

Population

Between January 1, 2005, and December 31, 2006, 5119 women aged 18 to 70 years received surgery for unilateral primary breast cancer in Denmark. Exclusion criteria were non-standardized treatment (n = 797); reconstruction or corrective breast surgery (n = 319); emigration (n = 5); and cancer relapse, new breast cancer, other malignant disease, or death (n = 244). A total of 3754 women matched the inclusion criteria.

A study questionnaire (eAppendix; available at <http://www.jama.com>) was sent to 3754 eligible women between January and April 2008. Reminders were sent 3 weeks later. In June 2008, 3253 questionnaires (87%) had been returned and were eligible for analysis.

Distribution between surgical procedures for responders and nonresponders and median age are shown in TABLE 1.

Treatment

All women in the study received treatment according to the DBCG 2004 treatment protocol,^{6,7} which was based on the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003.⁸ The patients were divided according to type of surgery and adjuvant radiotherapy and chemotherapy into 12 major treatment groups (Table 1). Surgery included mastectomy or BCS with either sentinel lymph node dissection (SLND) or axillary lymph node dissection (ALND) levels I and II.⁸

All patients having BCS received radiotherapy corresponding to a total dose of 48 Gy in 24 fractions to the residual breast tissue (BRT). Those women with at least 1 axillary lymph node macrometastasis (node positive) also received radiation to locoregional lymph nodes (periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes)

with 48 Gy over 24 fractions (locoregional radiotherapy [LRRT]). Node-positive patients who had a mastectomy also received radiotherapy to the anterior thoracic wall with 48 Gy in 24 fractions (anterior thoracic radiotherapy [ATRT]).⁹ Allocation to anti-estrogen treatment and standard chemotherapy (cyclophosphamide, epirubicin, and fluorouracil) followed estrogen receptor status and histopathological criteria according to the DBCG 2004 protocol.⁷

Registries

With approval from all Danish breast cancer departments, demographic and treatment data were retrieved from DBCG's database, which includes more than 95% of patients who underwent surgery for breast cancer in Denmark.^{7,10} The database includes primary clinical and histopathological data, data on surgical procedure, post-operative adjuvant therapy, and status at follow-up, including information on site of recurrence, all based on specific case report forms submitted by the departments of surgery, pathology, and oncology in Denmark.

Table 1. Pain and Sensory Disturbances Among 3253 Danish Women Who Had Surgery for Primary Breast Cancer According to 12 Different Treatment Groups

	Treatment Modalities, No. (%)												Total
	Breast-Conserving Surgery						Mastectomy						
	SLND			ALND			SLND			ALND			
	BRT Without Chemo-therapy	BRT With Chemo-therapy	BRT Without Chemo-therapy	BRT With Chemo-therapy	BRT + LRRT Without Chemo-therapy	BRT + LRRT With Chemo-therapy	None	With Chemo-therapy	None	With Chemo-therapy	ATRT + LRRT Without Chemo-therapy	ATRT + LRRT With Chemo-therapy	
Nonresponders	118 (12)	56 (13)	22 (10)	14 (11)	39 (12)	35 (11)	40 (21)	15 (15)	36 (20)	7 (7)	62 (15)	56 (16)	500 (13)
Age, median (IQR), y	59 (54-64)	47 (39-53)	59 (55-63)	42.5 (41-45)	61 (57-67)	47 (40-51)	62 (58-66)	54 (41-62)	59.5 (55-64)	48 (46-51)	62 (59-66)	48 (41-52)	
Responders	868 (88)	368 (87)	201 (90)	110 (89)	291 (88)	284 (89)	153 (79)	86 (85)	147 (80)	96 (93)	352 (85)	297 (84)	3253 (87)
Age, median (IQR), y	60 (55-65)	49.5 (44-56)	61 (56-64)	49 (44-54)	60 (57-64)	48 (44-53)	62 (58-66)	53 (48-61)	60 (56-65)	48.5 (43-56)	61 (57-65)	48 (44-55)	
Reporting pain	345 (40)	183 (50)	105 (52)	64 (58)	146 (50)	171 (60)	39 (25)	31 (36)	63 (43)	51 (53)	181 (51)	164 (55)	1543 (47)
Worst pain ^a													
Light	186 (54)	96 (53)	44 (42)	34 (53)	75 (52)	76 (45)	24 (62)	13 (42)	30 (48)	18 (36)	69 (39)	68 (42)	733 (48)
Moderate	123 (36)	61 (34)	44 (42)	22 (34)	58 (40)	65 (38)	14 (36)	14 (45)	22 (35)	26 (52)	73 (41)	73 (45)	595 (39)
Severe	34 (10)	23 (13)	17 (16)	8 (13)	12 (8)	29 (17)	1 (3)	4 (13)	10 (16)	6 (12)	35 (20)	22 (14)	201 (13)
Sensory disturbances	273 (31)	153 (42)	142 (71)	94 (85)	216 (74)	240 (85)	61 (40)	48 (56)	94 (64)	78 (81)	245 (70)	238 (80)	1882 (58)

Abbreviations: ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to the anterior thoracic wall; BRT, breast radiotherapy corresponding to residual breast tissue; IQR, interquartile range; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes; SLND, sentinel lymph node dissection.

^a Defined as the highest pain score of the 4 regional pain scores. Scores of 1 to 3 were regarded as light pain, scores of 4 to 7 as moderate pain, and scores of 8 to 10 as severe pain.

Mortality was retrieved from the Danish Civil Registration System, in which a unique personal identification number is assigned to all persons residing in Denmark. It is used in all national registries, allowing accurate linkage of information between registries. Information for reconstruction or corrective breast surgery was retrieved from the Danish National Patient Registry, which contains information on all patients admitted at clinical hospital departments in Denmark regarding diagnosis, surgical procedures, and date of admission.

The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee H-D-2007-0099, the Danish Data Protection Agency, and the Danish National Patient Registry under the Danish National Health Board.

Questionnaire

The literature for existing relevant questionnaires was reviewed to determine prevalence, location, intensity, and frequency of pain, sensory disturbances, and their associations with different treatment modalities. The most commonly used and well-validated questionnaires in breast cancer research were the quality of life questionnaires EORTC QLQ-C30/BR23 (European Organization for Research and Treatment of Cancer, the Core Cancer Quality of Life Questionnaire/Breast Cancer Specific Questionnaire) and FACIT-B (Functional Assessment Chronic Illness Therapy Questionnaire, the breast cancer module).¹¹ However, these questionnaires were not used because they did not provide detailed information on chronic pain localization or sensory disturbances. No other single standardized questionnaire with documented validity and reliability in comparable populations was found to match these demands.

A detailed questionnaire was designed (eAppendix; available at <http://www.jama.com>) based on questions or topics identified in the literature and open interviews with 20 women who received surgery for breast cancer. Before

the start of the study, the questionnaire was tested and revised twice in accordance with the comments from pilot testing in 11 and 17 patients, respectively. To determine the prevalence of symptoms for each major topic, dichotomous yes or no questions were used. Regarding pain and sensory disturbances, the women were asked systematically to address 4 specific regions of symptoms: (1) area of the breast (defined as either the affected breast or the area from which the breast was removed), (2) the axilla, (3) the arm, and (4) the side of the body, rating pain severity and frequency in each region. To estimate severity of pain, a numeric rating scale from 0 to 10 scores was used in which 0 indicated no pain and 10 indicated worst imaginable pain.^{12,13} For the reporting of results regarding severity of pain, scores of 1 to 3 were categorized as light pain, scores of 4 to 7 as moderate pain, and scores of 8 to 10 as severe pain. Worst pain was defined as the highest pain score of the 4 regional pain scores.

The frequency of symptoms was assessed by a 3-point verbal categorical scale: (1) every day or almost every day, (2) 1 to 3 days a week, or (3) more rarely. Questions were asked about physician visits due to pain in the operated region, use of analgesics, other treatment for pain in the affected region, or all 3, and pain in other locations (eg, low back pain, headache).

Statistics

Data analysis was performed by the DBCG data center. Multivariate logistic regression models were applied to examine the concomitant influence of treatment modalities and age on pain, localization, intensity, and sensory disturbances, using the PROC LOGISTIC in SAS version 9.1 (SAS Institute, Cary, North Carolina). Factors included in the models were type of surgery (mastectomy vs BCS), lymph node dissection (ALND vs SLND), radiotherapy (LRRT + BRT/ATRT, BRT vs none), chemotherapy (cyclophosphamide, epirubicin, and fluorouracil vs none), and age. Year of surgery as well as tu-

mor location in the breast had no statistically significant effect and were excluded from the multivariate models.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated (adjusted for age, mastectomy/BCS, ALND/SLND, radiotherapy, and chemotherapy), and the Wald χ^2 test was used to test the overall significance of each parameter. Tests for interaction between covariates on pain and sensory disturbances were performed pairwise in separate models applying the Wald test statistics.

Associations between pain in the surgical area and sensory disturbances, and pain in the surgical area and pain elsewhere were analyzed by χ^2 test. Two-tailed *P* values were calculated and the level of significance was set at 5%.

RESULTS

The overall response rate was 87% (*n*=3253), varying from 79% to 93% between the 12 treatment groups (Table 1). Mean time from surgery to questionnaire response was 26 months (range, 13-41 months). There was no significant difference (*P*=.75) in pain prevalence between patients operated in 2005 vs 2006 (TABLE 2 and TABLE 3).

Pain

A total of 1543 patients (47%) reported pain in 1 or more areas (Table 1), of which 201 (13%) reported severe pain (scores of 8-10 on the numeric rating scale of 0-10 scores), 595 (39%) reported moderate pain (scores of 4-7), and 733 (48%) reported light pain (scores of 1-3). Fourteen patients (1%) did not rate severity of pain. Among those patients reporting pain, the mean pain score in the 4 different areas varied between 3.5 and 4.0 (range, 0-10). Among women reporting severe pain, 77% experienced pain every day, whereas only 36% of women experiencing light pain had pain every day.

Severity and frequency of pain in the 4 regions are shown in (TABLE 4). A total of 278 patients (18%) reported pain in only 1 area, 435 (28%) in 2 areas, 429 (28%) in 3 areas, and 400

(26%) in all 4 areas. The most frequently reported area of pain was the breast area (n=1331; 86%), followed by axilla (n=975; 63%), arm (n=872; 57%), and side of the body (n=857; 56%).

Of patients reporting pain, 306 (20%) had contacted a physician within the prior 3 months due to pain, 439 (28%) had taken analgesics due to pain in the surgical area, and 397 (26%) had received other treatments for pain (ie, physiotherapy, massage). A total of

1265 women (40%) reported pain in other parts of the body/nonsurgical areas (eg, low back pain, headache). Pain complaints in nonsurgical areas were associated with a higher incidence of chronic postoperative pain because 810 women (65%) had pain in the surgical regions, whereas 674 women (37%) without pain in the nonsurgical area had pain in the surgical area ($P<.001$).

There was a significant association of age on reporting pain, where young

age was associated with higher risk, especially for patients receiving BCS, the risk being highest for those women aged 18 to 39 years receiving BCS compared with women aged 60 to 69 years (OR, 3.62; 95% CI, 2.25-5.82; $P<.001$) (Table 2). Although young age was associated with reporting pain, young age was not associated with higher risk of reporting moderate to severe pain compared with light pain (18-39 years: OR, 0.81; 95% CI, 0.50-1.31; $P=.28$).

Table 2. Pain Adjusted for Age, Type of Surgery, Radiotherapy, and Chemotherapy Among 3253 Danish Women Having Surgery for Primary Breast Cancer

	No. (%) of Women		Unadjusted		Adjusted ^a	
	With Pain	Without Pain	OR (95% CI)	P Value	OR (95% CI)	P Value
Age group, y						
18-39	96 (64)	53 (36)	2.62 (1.84-3.73)	<.001		
40-49	367 (59)	251 (41)	2.11 (1.74-2.57)			
50-59	554 (49)	580 (51)	1.38 (1.18-1.62)			
60-69	526 (41)	760 (59)	1 [Reference]			
Breast surgery by age group, y ^b						
Breast-conserving surgery						
18-39	72 (71)	29 (29)			3.62 (2.25-5.82)	<.001
40-49	240 (60)	160 (40)			2.20 (1.68-2.89)	
50-59	378 (49)	395 (51)			1.42 (1.16-1.74)	
60-69	324 (40)	489 (60)			1 [Reference]	
Mastectomy						
18-39	24 (50)	24 (50)			1.18 (0.64-2.19)	.03
40-49	127 (58)	91 (42)			1.72 (1.21-2.45)	
50-59	176 (49)	185 (51)			1.21 (0.91-1.60)	
60-69	202 (43)	271 (57)			1 [Reference]	
Breast procedure						
Mastectomy	529 (48)	571 (52)	0.98 (0.85-1.14)	.79	1.13 (0.84-1.53)	.41
Breast-conserving surgery	1014 (49)	1073 (51)	1 [Reference]		1 [Reference]	
Axillary procedure						
ALND	945 (54)	795 (46)	1.69 (1.47-1.94)	<.001	1.77 (1.43-2.19)	<.001
SLND	598 (41)	849 (59)	1 [Reference]		1 [Reference]	
Radiotherapy						
LRRT + BRT/ATRT	662 (55)	539 (45)	1.88 (1.51-2.33)	<.001	1.35 (1.04-1.76)	.03
BRT	697 (46)	824 (54)	1.29 (1.05-1.60)		1.50 (1.08-2.07)	
None	184 (40)	281 (60)	1 [Reference]		1 [Reference]	
Chemotherapy						
With	664 (54)	556 (46)	1.48 (1.28-1.71)	<.001	1.01 (0.85-1.21)	.91
Without	879 (45)	1088 (55)	1 [Reference]		1 [Reference]	
Year of surgery						
2005	716 (48)	772 (52)	0.98 (0.85-1.12)	.75		
2006	827 (49)	872 (51)	1 [Reference]			
Tumor location						
Upper lateral quadrant	608 (49)	639 (51)	1.02 (0.89-1.18)	.76		
Other parts of the breast	935 (48)	1005 (52)	1 [Reference]			

Abbreviations: ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to the anterior thoracic wall; BRT, breast radiotherapy corresponding to residual breast tissue; CI, confidence interval; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes; OR, odds ratio; SLND, sentinel lymph node dissection.

^aAdjusted for age, mastectomy/breast-conserving surgery, ALND/SLND, radiotherapy, and chemotherapy.

^bA statistically significant interaction was observed between age and type of surgery ($P=.03$).

Among women with mastectomies, the highest risk of pain was in the age group 40 to 49 years. A statistically significant interaction ($P=.03$) was observed between age and type of surgery.

Mastectomy had no significant association on OR for reporting pain compared with BCS (Table 2), but those women reporting pain after mastectomy had a higher risk of moderate to severe pain compared with light pain (OR, 1.37; 95% CI, 1.00-1.87; $P=.048$).

ALND was associated with an increased risk of pain (OR, 1.77; 95% CI, 1.43-2.19; $P<.001$) compared with SLND, and also a risk factor for moderate to severe pain (OR, 1.39; 95% CI, 1.03-1.88; $P=.03$).

Adjuvant radiotherapy increased the risk of reporting pain (BRT: OR, 1.50; 95% CI, 1.08-2.07; vs LRRT+BRT/ATRT: OR, 1.35; 95% CI, 1.04-1.76; $P=.03$), but without relation to the extension of the radiation field (Table 2) or pain severity (BRT: OR, 1.26; 95%

CI, 0.79-2.01; vs LRRT+BRT/ATRT: OR, 1.15; 95% CI, 0.78-1.68; $P=.63$). Use of adjuvant chemotherapy had no independent association on adjusted OR for pain (Table 2), despite consistent differences between subgroups (Table 1).

In the multivariate models, type of surgery of the breast was not significantly related to pain in the axilla (OR, 0.92; 95% CI, 0.66-1.28; $P=.61$), arm (OR, 1.10; 95% CI, 0.80-1.53; $P=.55$), or side of the body (OR, 1.37; 95% CI,

Table 3. Sensory Disturbances Adjusted for Age, Type of Surgery, Radiotherapy, and Chemotherapy Among 3253 Danish Women Having Surgery for Primary Breast Cancer

	No. (%) of Women		Unadjusted		Adjusted ^a	
	With Sensory Disturbances	Without Sensory Disturbances	OR (95% CI)	P Value	OR (95% CI)	P Value
Age group, y						
18-39	123 (83)	25 (17)	5.09 (3.27-7.94)	<.001		
40-49	443 (73)	167 (27)	2.75 (2.23-3.39)			
50-59	696 (62)	430 (38)	1.68 (1.42-1.97)			
60-69	620 (49)	642 (51)	1 [Reference]			
Breast surgery by age group, y ^b						
Breast-conserving surgery						
18-39	79 (79)	21 (21)			5.00 (2.87-8.69)	<.001
40-49	263 (67)	131 (33)			2.67 (1.97-3.61)	
50-59	437 (58)	321 (42)			1.83 (1.46-2.29)	
60-69	339 (43)	452 (57)			1 [Reference]	
Mastectomy						
18-39	44 (92)	4 (8)			6.06 (2.07-17.7)	<.001
40-49	180 (83)	36 (17)			2.95 (1.90-4.59)	
50-59	259 (70)	109 (30)			1.46 (1.07-1.98)	
60-69	281 (60)	190 (40)			1 [Reference]	
Breast procedure						
Mastectomy	764 (69)	339 (31)	1.86 (1.60-2.18)	<.001	0.84 (0.60-1.17)	.29
Breast-conserving surgery	1118 (55)	925 (45)	1 [Reference]		1 [Reference]	
Axillary procedure						
ALND	1347 (78)	387 (22)	5.71 (4.88-6.67)	<.001	4.97 (3.92-6.30)	<.001
SLND	535 (38)	877 (62)	1 [Reference]		1 [Reference]	
Radiotherapy						
LRRT + BRT/ATRT	939 (79)	256 (21)	2.47 (1.96-3.11)	<.001	0.88 (0.65-1.20)	.02
BRT	662 (45)	819 (55)	0.54 (0.44-0.67)		0.61 (0.42-0.89)	
None	281 (60)	189 (40)	1 [Reference]		1 [Reference]	
Chemotherapy						
With	851 (70)	367 (30)	2.02 (1.73-2.35)	<.001	1.08 (0.89-1.31)	.46
Without	1031 (53)	897 (47)	1 [Reference]		1 [Reference]	
Year of surgery						
2005	875 (60)	595 (40)	0.98 (0.85-1.13)	.75		
2006	1007 (60)	669 (40)	1 [Reference]			
Tumor location						
Upper lateral quadrant	735 (60)	483 (40)	1.04 (0.90-1.20)	.63		
Other parts of the breast	1147 (59)	781 (41)	1 [Reference]			

Abbreviations: ALND, axillary lymph node dissection; ATRT, anterior thoracic radiotherapy corresponding to the anterior thoracic wall; BRT, breast radiotherapy corresponding to residual breast tissue; CI, confidence interval; LRRT, locoregional radiotherapy corresponding to periclavicular, axillary level 3, and for right-side breast cancers, the internal mammary nodes; OR, odds ratio; SLND, sentinel lymph node dissection.

^aAdjusted for age, mastectomy/breast-conserving surgery, ALND/SLND, radiotherapy, and chemotherapy.

^bNo statistically significant interaction was observed between age and type of surgery ($P=.52$).

Table 4. Pain Among 1515 Danish Women Reporting Light, Moderate, or Severe Persistent Pain in 4 Regions for Primary Breast Cancer^a

Body Part	No. (%) of Women in Pain		
	Light	Moderate	Severe
Breast area			
Every day or almost every day	278 (47)	243 (41)	66 (11)
1-3 times a week	226 (60)	135 (36)	14 (4)
More rarely	255 (77)	69 (21)	6 (2)
Side of the body			
Every day or almost every day	165 (44)	160 (43)	46 (12)
1-3 times a week	138 (54)	105 (41)	13 (5)
More rarely	141 (75)	42 (22)	5 (3)
Axilla			
Every day or almost every day	183 (42)	190 (44)	60 (14)
1-3 times a week	168 (64)	80 (31)	14 (5)
More rarely	174 (75)	52 (22)	6 (3)
Arm			
Every day or almost every day	144 (33)	191 (44)	96 (22)
1-3 times a week	123 (52)	97 (41)	15 (6)
More rarely	136 (76)	38 (21)	5 (3)

^aTwenty-eight of 1543 patients (2%) reporting pain did not report severity and/or frequency of pain in any of the 4 locations. Patients scored their pain in 4 different areas on a numeric rating scale, in which 0 indicated no pain, 10 indicated worst imaginable pain; and scores of 1 to 3 were regarded as light pain, scores of 4 to 7 as moderate pain, and scores of 8 to 10 as severe pain.

1.00-1.87; $P = .053$); whereas ALND increased risk of pain in the axilla (OR, 2.17; 95% CI, 1.58-2.99; $P < .001$) and arm (OR, 3.77; 95% CI, 2.73-5.20; $P < .001$).

Sensory Disturbances

A total of 1882 women (58%) reported sensory disturbances or discomfort, ranging from 31% ($n = 273$) among women who had BCS with SLND and BRT to 85% of women who had BCS, ALND, and chemotherapy with BRT ($n = 94$) or BRT and LRRT ($n = 240$) (Table 1). The most frequently reported areas were the axilla ($n = 1239$, 66%), followed by arm ($n = 986$, 52%), breast area ($n = 816$, 43%), and side of the body ($n = 573$, 30%).

After mastectomy and BCS (Table 3), there was a higher incidence of sensory disturbances with decreasing age. Thus, women aged 18 to 39 years had the highest risk compared with women aged 60 to 69 years (BCS: OR, 5.00; 95% CI, 2.87-8.69; $P < .001$; and mastectomy: OR, 6.06; 95% CI, 2.07-17.7; $P < .001$). ALND was associated with increased incidence of sensory disturbances compared with SLND (OR, 4.97; 95% CI, 3.92-6.30; $P < .001$).

A total of 1204 women (65%) reporting sensory disturbances reported pain as well compared with 292 (23%) reporting pain but not sensory disturbances, indicating sensory disturbances and nerve injury were related to an increased risk of chronic pain ($P < .001$).

Adjuvant chemotherapy and radiotherapy did not increase the risk of reporting sensory disturbances in the multivariate model (Table 3).

COMMENT

This large nationwide study shows that 47% of women treated for breast cancer experience pain and 58% of women experience sensory disturbances in the surgical region 1 to 3 years after surgery. Half the women reporting pain reported moderate to severe pain. In general, the prevalence estimates are in agreement with those estimates of the literature varying for pain between 25% and 60%^{1-5,14-21} and for sensory disturbances between 20% and 80%.^{1-5,18,19}

The wide range of pain complaints in the literature is likely due to differing definitions of persistent pain, differing measurements of pain and its consequences, a varying mix of type of

surgery and adjuvant treatment, and variations in time since surgery. Although some studies have tried to differentiate the role and type of surgery and also regarding adjuvant therapy,³ the number of included patients compared with the many treatment modalities has been insufficient to draw valid conclusions for each treatment-related risk factor.

The goal of the questionnaire designed for our study was the greatest possible simplicity, asking in general whether patients had pain or sensory disturbances in relevant areas according to literature and open interviews. Asking patients how long the pain had been present or demanding the patient to consider whether pain and sensory disturbances were due to the treatment of breast cancer was deliberately avoided. Also avoided was the potential recall bias by retrospectively asking about the intensity of pain experienced in the early postoperative phase.

The most important determinant of persistent pain and sensory disturbances was young age (< 40 years), although age was not related to the severity of the pain reported. This association was more clear in our study than in other studies.^{5,14,22} Although our univariate analyses showed a strong association between chemotherapy and reporting of pain and sensory disturbances as reported in the literature,²⁻⁴ the effect disappeared in the multivariate analyses. Therefore, the observed association between chronic pain and chemotherapy could be due to age, because young women more often receive chemotherapy. Our results may be regarded as valid for chemotherapy with cyclophosphamide, epirubicin, and fluorouracil, but not for more recent regimens containing taxans with potential neurotoxicity.

In the DBCG 2004 protocol, the standard endocrine treatment was tamoxifen for 2.5 years followed by treatment with aromatase inhibitor for 2.5 years. Thus, very few women in our cohort were receiving aromatase inhibitor treatment, known to cause muscular and joint pain, at the time when the

questionnaire was returned. Hence, treatment with aromatase inhibitor was not included in the statistical models.

Having adjusted for other therapeutic modalities, radiotherapy was an independent and significant risk factor for reporting pain, but the extent of the radiation field did not influence the risk of reporting pain. Although other studies^{14,15} have found radiotherapy to be a risk factor for sensory disturbances, this was not confirmed in our study. Altogether, comparison of our results with the literature is difficult because no previous study has indicated exact information about the dose and location of radiotherapy. In the future, intraoperative, localized radiotherapy may be a way to reduce radiotherapy-related persistent pain due to more well-defined anatomical application.

Pain was reported most frequently in "the area of the breast," but similar to other studies,¹⁴ we found that the frequency appeared independent of type of breast surgery, although women who underwent mastectomy reported slightly but significantly more severe pain than women undergoing BCS. An association between location of tumor in the upper lateral quadrant and reporting of pain could not be confirmed in our study.¹⁵

The strengths of our study are that it is based on the entire population of Denmark with a high response rate and is sufficiently large to provide reasonably precise risk estimates of all treatment modalities, such as surgery, radiotherapy, and chemotherapy. In addition, patients were treated according to the same guidelines. Our results on the effects of age and chemotherapy demonstrate the importance of multivariate analysis to disentangle independent effect on risk factors for chronic pain. Many previous studies have been based on relatively small selected patient series from 1 or a few centers, often focusing on only 1 or 2 elements.^{4,5,15,17,22}

The main limitation of our study is that it is a cross-sectional study that provided only 1 estimate of pain prevalence, 1 to 3 years after the primary

treatment. It did not follow patients over time and thus does not provide information on if and how the reported pain and sensory disturbances will develop with time since breast cancer treatment. Also, the cross-sectional study design does not allow drawing conclusions regarding causality, but can merely describe factors associated with pain and sensory disturbances. Another limitation is in the 13% of patients who did not complete the questionnaire. If these patients experienced more pain than the responders, our estimates are too low. Additionally, the results might have been biased by the patients who were excluded due to death or cancer relapse who might have had different patterns of pain than survivors included in the study.

Our nationwide study reflects the Danish population, which is generally well-educated, ethnic homogeneous (white), and benefiting from a uniform public health care system covering all citizens, and thus limiting the generalizability to other populations with different health care systems, demographics, or treatment protocols. However, our study with its population-based nature, high response rate, lack of recall bias, and standardized treatment offers very precise estimates of prevalence regarding pain and sensory disturbances and associated factors following breast cancer surgery in Denmark.

Based on the results of our study together with previously reported findings,^{1-4,17} chronic pain after breast cancer surgery and adjuvant therapy may predominantly be characterized as a neuropathic pain state and probably related to intraoperative injury of the intercostal-brachial nerve. In accordance with these findings, preliminary observations with nerve-sparing techniques^{19-21,23-25} may suggest such approaches to reduce the risk of developing a chronic neuropathic pain state. However, such studies need to be larger and more detailed taking all the different subgroups as studied in our investigation into consideration. Also, there is a need for detailed psychophysical examina-

tion of patients with postmastectomy pain, because existing data were from very limited patient groups and included different treatment modalities.²⁶ Such extensive neurophysiological examinations may also provide a rational basis for mechanism-based pharmacological interventions in the future. Because psychosocial status, preoperative breast pain, and acute postoperative pain intensity are well-known risk factors related to a persistent postsurgical pain state,^{1,4,5,27,28} large-scale therapeutic interventions in relevant subpopulations are required to outline rational strategies for prevention and treatment. So far, analgesic and other interventions with paravertebral blocks,²⁹ topical capsaicin,³⁰ gabapentin and local anesthetics,³¹ N-methyl-D-aspartate-receptor antagonists,³² or glucocorticoids³³ may suggest certain benefits, but large-scale studies including well-characterized relevant subpopulations are required before general recommendations can be made. These results and those of other studies¹ clearly show that a persistent postsurgical pain state may be related to existence of other pain syndromes (headache, low back pain), which may suggest that a preoperative general pain hypersensitivity due to psychosocial or genetic factors may be important pathogenic mechanisms, and therefore to be included in future preventive and therapeutic trials.

In our study, sensory disturbances and specific pain complaints were studied, but other pain syndromes may occur after breast cancer treatment,⁴ including phantom breast sensations and pain,^{34,35} which were not included in our study.

CONCLUSION

Persistent pain in the surgical area after breast cancer surgical treatment is a clinically significant problem in approximately 25% to 50% of patients. Although BCS and sentinel node dissection have reduced complaints, future strategies for further improvement should include nerve-sparing axillary dissection and attention to patients with other chronic pain symptoms.

Author Contributions: Ms Jensen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gärtner, Nielsen, Kroman, Kehlet.

Acquisition of data: Gärtner, Jensen, Nielsen.

Analysis and interpretation of data: Gärtner, Jensen, Ewertz, Kroman, Kehlet.

Drafting of the manuscript: Gärtner, Jensen, Ewertz, Kehlet.

Critical revision of the manuscript for important intellectual content: Jensen, Nielsen, Ewertz, Kroman, Kehlet.

Statistical analysis: Jensen.

Obtained funding: Gärtner, Kroman, Kehlet.

Administrative, technical, or material support: Gärtner, Jensen, Nielsen, Kroman.

Study supervision: Ewertz, Kroman.

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Additional Information: An eAppendix is available at <http://www.jama.com>.

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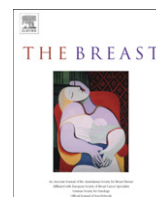
Article IV:

Self-reported arm-lymphedema and functional impairment after breast cancer treatment – A nationwide study of prevalence and associated factors



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Original article

Self-reported arm-lymphedema and functional impairment after breast cancer treatment – A nationwide study of prevalence and associated factors

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ABSTRACT

Lymphedema and impairment of function are well-established sequelae to breast cancer treatment and affect an increasing number of women due to continually improved survival. The aim of the present nationwide questionnaire study was to examine the impact of breast cancer treatment on perceived swelling/sensation of heaviness (lymphedema) and on function, reporting prevalence in 12 subgroups of modern treatment and offering estimates for treatment-related associated factors.

3253 Women (87%) returned the study questionnaire. Depending on treatment group prevalence of perceived swelling/heaviness varied from 13 to 65%. Associated factors were young age, axillary lymph node dissection (ALND) and radiotherapy but not type of breast surgery or use of chemotherapy. Depending on treatment group 11–44% had to give up activities. Giving up activities was associated with pain and swelling/heaviness, younger age, ALND, chemotherapy, time elapsed since surgery, and surgery on the dominant side. Radiotherapy and type of breast surgery were of no importance.

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Introduction

Lymphedema and functional impairment are well-established sequelae of breast cancer treatment which affect an increasing number of women due to continually improved survival.¹ The improvement of surgical techniques moving towards more breast conserving surgery (BCS) and sentinel lymph node dissection (SLND) has reduced the extent of the surgical treatment. However, an increasing number of patients receives adjuvant chemotherapy and patients treated with BCS also receive radiotherapy to reduce risk of recurrence.² The rapid change in breast cancer treatment over the last 20 years tailoring the treatment to the individual breast cancer status² has made the group of women treated for breast cancer very heterogeneous. Consequently, overall prevalences of lymphedema and functional impairment have lost their relevance and studies of associated factors become increasingly complicated.

A large number of studies with various designs have examined the impact of surgery and adjuvant therapy on lymphedema.³ However, most studies are single-center clinical studies with large variation in follow-up and measurement of outcome, either describing very

selected groups with respect to treatment or without sufficient power to evaluate the impact of each treatment modality.

Objective definitions based on volume differences, measured by e.g., water displacement or circumference measurements, may be rather insensitive of early lymphedema. Thus, self-reported symptoms of lymphedema such as swelling and sensation of heaviness could offer a sensitive alternative to objective definitions⁴ and might secure early detection as most cases of self-reported lymphedema occur within a year.⁵

Reports on impairment of function have primarily focused on restriction of shoulder motion^{6–8} and overall quality of life.^{9,10}

A broad spectrum of risk factors resulting in arm morbidity has been suggested: mastectomy, axillary lymph node dissection (ALND), radiotherapy, chemotherapy, age, body mass index, time elapsed since surgery, and tumor in upper lateral quadrant. Few population-based studies give estimates for the contribution of these risk factors,^{11–14} but these studies do not reflect modern treatment. Thus, no population-based studies have yet reported from all subgroups of modern standardized treatment.

The aim of the present study was to examine the impact of breast cancer treatment on self-reported lymphedema and functional impairment in a nationwide study – taking advantage of the unique possibilities in Denmark with uniform national guidelines for treatment,¹⁵ performed by highly specialized breast cancer

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departments and registered by a nearly complete national database managed by The Danish Breast Cancer Cooperative group, (DBCG).¹⁶

Material and method

The data in the present study were retrieved as a part of a nationwide questionnaire study dealing with chronic pain and sensory disturbances.¹⁷

Population

Between January 1, 2005 and December 31, 2006, 5119 women between 18 and 70 years of age were operated for unilateral primary breast cancer in Denmark. Exclusion criteria were: non-standardized treatment, reconstruction or corrective breast surgery, cancer relapse, contra-lateral breast cancer, other malignant disease, and emigration or death ($n = 1365$). 3754 women matched the inclusion criteria (Fig. 1).

A study questionnaire (Appendix) was sent to 3754 eligible women between January and April 2008. Reminders were sent 3 weeks later. In June 2008 a total of 3253 questionnaires had been returned (response rate 87%) and were eligible for analysis. Distribution between surgical procedures for responders and non-responders, as well as median age, is given in Table 1.

Registries

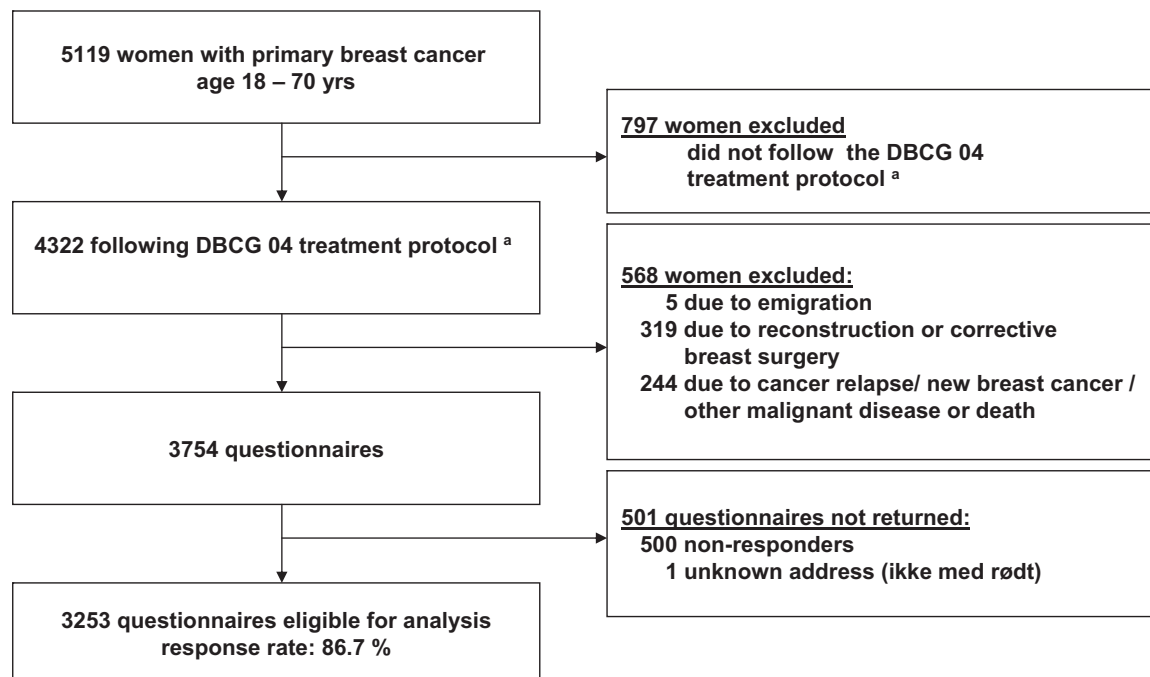
Patients identity, demographics and treatment data were retrieved from DBCG's database which covers >95% of patients operated for breast cancer in Denmark.^{2,18} DBCG prospectively collects detailed clinical data, histopathological status, data on treatment as well as data on recurrence and mortality.²

Addresses and mortality were retrieved from the Danish Civil Registration System (CRS), which assigns a unique personal identification number to all Danish residents and is used in all national registries, allowing accurate linkage of data between registries. Information regarding reconstruction or corrective breast surgery was retrieved from The Danish National Patient Registry.¹⁷

Treatment

Breast cancer treatment in Denmark is standardized in national protocols designed by DBCG² in accordance with European guidelines.

All women in the study received treatment according to the DBCG 2004 treatment protocol,^{2,16} which is based on the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003.¹⁵ The patients were split into 12 major treatment groups according to the type of surgery and adjuvant radiation- and chemotherapy (Fig. 2). Surgery included mastectomy or breast conserving surgery (BCS) with either sentinel lymph node dissection (SLND) or axillary lymph node dissection levels I and II (ALND).¹⁵ Women with biopsy confirmed involvement of the axillary lymph nodes were selected for ALND and women without suspicion of nodal involvement at clinical examination and ultra sonography were offered axillary staging by SLND, as described elsewhere were.¹⁹ All BCS patients received radiotherapy with a total dose of 48 Gy in 24 fractions to the residual breast tissue (BRT). Women with axillary lymph node macro-metastasis (node-positive) also received radiation to loco-regional lymph nodes (periclavicular, axillary level 3, and for right side breast cancers also the internal mammary nodes) with 48 Gy over 24 fractions (loco-regional radiation therapy (LRRT)). Node-positive patients who had undergone a mastectomy also received radiotherapy to the anterior thoracic wall with 48 Gy in 24 fractions (anterior thoracic radiation



^a The DBCG (Danish Breast Cancer Cooperative group) 04 treatment protocol prescribes standardized surgery based on the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003.

Fig. 1. Inclusion procedure and response among 5119 Danish women treated for primary breast cancer 2005–2006.

Table 1
Functional impairment and perceived sensation of swelling/heaviness among 3253 Danish women operated for primary breast cancer 2005–2006 according to the 12 different treatment groups (Fig. 2).

Type of surgery	Treatment modalities										No. total (%)
	BCS	SLND	ALND	ALND	SLND	ALND	ALND	ALND	ALND	ALND	
Breast											
Axilla											
Adjuvant treatment											
Radiation therapy											
Chemo therapy											
Non-responders, No. (%)	118 (12)	56 (13)	22 (10)	14 (11)	39 (12)	35 (11)	40 (21)	15 (15)	36 (20)	7 (7)	500 (13)
Median age, years (IQR)	59.0 (54–64)	47.0 (39–53)	59.0 (55–63)	42.5 (41–45)	61.0 (57–67)	47.0 (40–51)	62.0 (58–66)	54.0 (41–62)	59.5 (55–64)	48.0 (46–51)	48.0 (41–52)
Responders, No. (%)	868 (88)	368 (87)	201 (90)	110 (89)	291 (88)	284 (89)	153 (79)	86 (85)	147 (80)	96 (93)	3253 (87)
Median age, years (IQR)	60.0 (55–65)	49.5 (44–56)	61.0 (56–64)	49.0 (44–54)	60.0 (57–64)	48.0 (44–53)	62.0 (58–66)	53.0 (48–61)	60.0 (56–65)	48.5 (43–56)	48.0 (44–55)
Reporting swelling, No. (%)	113 (13)	86 (23)	102 (51)	67 (61)	153 (53)	185 (65)	20 (13)	20 (23)	62 (42)	45 (47)	1249 (38)
Worst swelling ^a											
Light	63 (56)	51 (61)	51 (50)	32 (49)	80 (53)	92 (50)	13 (65)	10 (50)	25 (42)	20 (45)	609 (50)
Moderate	38 (34)	26 (31)	40 (39)	27 (42)	54 (36)	67 (36)	7 (35)	8 (40)	26 (44)	20 (45)	468 (38)
Severe	11 (10)	7 (8)	11 (11)	6 (9)	16 (11)	25 (14)	0 (0)	2 (10)	8 (14)	4 (9)	148 (12)
Functional impairment, No. (%)	95 (11)	74 (20)	56 (28)	31 (28)	78 (27)	117 (41)	26 (17)	22 (26)	30 (20)	42 (44)	787 (24)

BCS: Breast conserving surgery. SLND: Sentinel lymph node dissection. ALND: Axillary lymph node dissection. BRT: Breast radiotherapy corresponding to residual breast tissue. ATRT: Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. LRRT: Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes. IQR: Interquartile range.

^a “Worst swelling” was defined as the highest pain score of the armpit and/or upper arm and forearm and/or back of your hand. 1–3 was regarded light swelling, 4–7 moderate swelling and 8–10 severe swelling.

therapy (ATRT)).²⁰ Allocations to anti-estrogen treatment and standard chemotherapy (cyclophosphamide, epirubicin, and fluorouracil, CEF) followed estrogen receptor status and histopathological criteria according to the DBCG 2004 protocols.²

Questionnaire

A detailed questionnaire was designed (Appendix) based upon questions and topics identified in the literature and on open interviews with 20 women operated for breast cancer. Before study start, the questionnaire was tested and revised twice in accordance with the comments from the pilot tests in 11 and 17 patients.¹⁷

To determine whether the patients were operated on their dominant side, the patients were asked whether they were right-handed or left-handed (Appendix question 1 (q1)) and this information was combined with the treatment data retrieved from the DBCG database described above.

Lymphedema was defined by the sensation of swelling or heaviness. To determine the prevalence of perceived lymphedema following dichotomous “yes” or “no” question was used: “Does the armpit, the arm or the back of the hand, on the side where you were operated, sometimes or always feel swollen or heavy?” (Appendix q3). Women were asked to address swelling/heaviness of the axilla, upper arm, forearm and the back of the hand (q4). Severity was rated in two regions: clustering the axilla with the upper arm and the forearm with the back of the hand (q5–6). To estimate the severity, a numeric rating scale from 0 to 10 was used, where 0 was “no swelling/heaviness” and 10 “worst imaginable swelling/heaviness” (q5–6). 1–3 was categorized as light, 4–7 as moderate and 8–10 as severe swelling/heaviness. “Worst swelling/heaviness” was defined as the highest score of the 2 regional scores.

Frequency of symptoms was assessed by a 3-point verbal categorical scale: 1) every day or almost every day, 2) 1–3 days a week, 3) more rarely (q7).

To determine the prevalence of overall functional impairment, following dichotomous “yes” or “no” question was asked: “Are there activities you have had to renounce on after your treatment of breast cancer?” (Appendix q22). To assess functional impairment regarding the arm/shoulder of the operated side questions regarding work, sports activities, functional range of motion and level of difficulty were applied on four different statements regarding function (Appendix q8–21). Light physical work above shoulder level was reflected in q8–9, q11, q13 and q17–18. Daily activities with involvement of shoulder rotation were reflected in q10, q12, q14, and generally heavy work in q15–16 and q19. The patients had the opportunity to tick “not relevant” if they did not regard the respective task relevant to them (e.g., not working, not doing any sport or not cleaning floors).

Statistics

Analyses of data were performed by the DBCG Data Center.

Univariate and multivariate logistic regression models were applied to examine the influence of age at surgery, treatment modalities, year of surgery (time elapsed since surgery), and surgery on the dominant side on function and self-reported lymphedema, using the PROC LOGISTIC in SAS 9.1. Factors included in the models were: age at surgery (18–39, 40–49, 50–59, 60–69), type of surgery to the breast (mastectomy vs. BCS), lymph node dissection (ALND vs. SLND), radiotherapy (LRRT + BRT/ATRT, BRT, none) and chemotherapy (CEF vs. none), year of surgery (2005 vs. 2006), surgery on the dominant side (yes vs. no). Additionally, pain (yes vs. no) and swelling/heaviness (yes vs. no) were included in the analyses of functional impairment. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, and the Wald χ^2 -test was used to test the overall significance of each parameter. Tests for interaction between

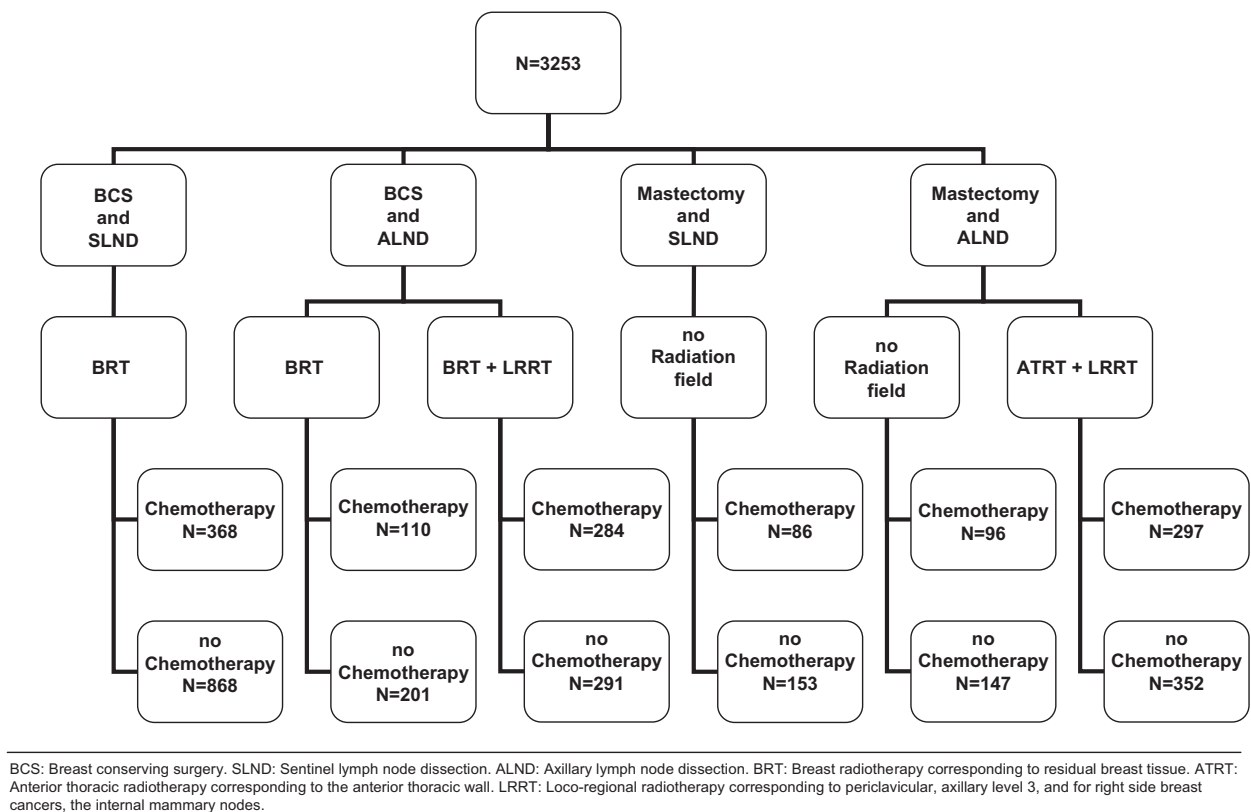


Fig. 2. Treatment groups according to type of surgery, adjuvant chemo- and radiotherapy among 3253 Danish women operated for primary breast cancer 2005–2006.

covariates on swelling and functional impairment were done pair-wise in separate models applying the Wald test statistics.

Associations between pairs of variables were analyzed by chi-square tests. Two-tailed *p*-values were calculated and the level of significance was set to 5%.

Results

The overall response rate was 86.7% ($n = 3253$) varying from 79% to 93% between the 12 treatment groups. Mean time from surgery to questionnaire response was 26 months (range 13–41 months).

Swelling and sensation of heaviness of the arm

1249 (38%) reported swelling or sensations of heaviness of the arm, hand or axilla ranging from 13% in the group of women undergoing BCS, SLND, BRT to 65% in the group of women undergoing either BCS or mastectomy and having ALND, BRT/ATRT, LRRT and chemotherapy (Table 1). 148 (12%) reported severe swelling/heaviness (score 8–10), 468 (38%) moderate (score 4–7) and 609 (50%) light (score 1–3) (Table 1). Three patients reported their swelling/heaviness as being of no importance (score 0), 21 patients did not grade the severity at all. Among those reporting swelling/heaviness the mean score for the upper arm and axilla was 3.9 and for the forearm and back of the hand 4.0. 619 women (50%) reporting swelling/heaviness had these symptoms every day or almost every day, 309 (25%) 1–3 days a week and 298 (24%) reported having these symptoms more rarely.

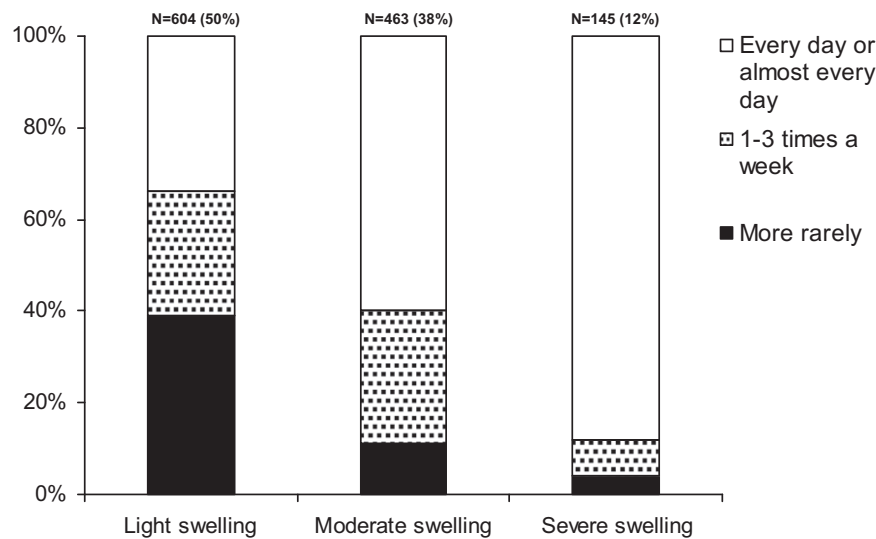
Among women reporting severe swelling/heaviness, 128 women (86%) were troubled every day, whereas only 204 (33%) of women experiencing light swelling/heaviness had these symptoms every day, $p < 0.0001$ (Fig. 3). 354 patients (28%) reported swelling/heaviness in only one region, 483 (39%) in two regions, 278 (22%) in

three areas and 103 (8%) in all four regions and 31 (2%) did not report on region of swelling/heaviness. The most frequently reported region was the upper arm ($n = 818$; 65%) followed by the axilla ($n = 761$; 61%), the forearm ($n = 601$; 48%) and the back of the hand ($n = 386$; 31%).

In univariate models, younger age, mastectomy, ALND, radiotherapy- and chemotherapy were significantly associated with swelling/heaviness, whereas time elapsed since surgery, and being operated on the dominant side were nonsignificant (Table 2). In multivariate models, the most important association was between swelling/heaviness and axillary procedure (OR = 5.57; CI: 4.40–7.05, $p < 0.0001$). Additionally, young age was associated with a higher risk ($p < 0.0001$) – especially for those aged 18–39 years compared with women aged 60–69 (OR = 2.60; 1.72–3.94). Furthermore, loco-regional radiotherapy (LRRT + BRT/ATRT) was significantly associated with swelling/heaviness (OR = 1.72; CI: 1.30–2.27, $p = 0.0005$). Type of surgery to the breast and use of chemotherapy were not associated with swelling/heaviness in multivariate models.

There was a significant interaction between age and type of surgery to the breast: In the BCS group younger women had significantly higher risk of reporting swelling/heaviness compared to women aged 60–69 years whereas no such association was found in women undergoing mastectomy (Table 3a). Furthermore, a significant interaction was found between type of surgery and radiotherapy. Table 3b shows the OR estimates of the combinations of surgery and radiotherapy (as these are closely related), with women undergoing BCS, SLND, BRT as the reference group. Adding ALND to BCS, BRT gives an OR of 6.75 whereas adding ALND to mastectomy without radiotherapy raises the OR from 1.48 to 5.55, i.e., only a 3.75-fold.

Finally, swelling/heaviness was strongly associated with reporting pain ($p < 0.0001$) as well as reporting of sensory disturbances ($p < 0.0001$).



Patients scored their swelling in two different regions: axilla/upper arm and forearm/back of the hand. Severity was reported on a numeric rating scale where zero was labeled "no swelling" and 10 was labeled "worst imaginable swelling". 1-3 was regarded light swelling, 4-7 moderate swelling and 8-10 severe swelling. The patients worst score of the swelling scores in the two different regions is depicted.

*37 patients of the 1249 patients reporting pain did not report severity and/or frequency of pain.

Fig. 3. Perceived swelling among 1212* Danish women treated for primary breast cancer 2005–2006 reporting light, moderate or severe swelling.

Impairment of function

787 Patients (24%) reported that they had to give up activities after treatment of breast cancer ranging from 11% in the group of women undergoing BCS, SLND, BRT to 44% in the group of women undergoing mastectomy, ALND and chemotherapy (Table 1). Of women who

reported themselves as working 716 (36%) indicated that it had affected their work. 726 (36%) women engaged in sports reported that it affected their activity. 1519 (47%) reported light work above shoulder level as problematic. 849 (27%) reported daily activity with involvement of shoulder rotation as troublesome. Heavy work was associated with difficulties for 1884 women (59%) (Fig. 4).

Table 2

Odds ratio for reporting swelling/heaviness adjusted for age, type of surgery, adjuvant radiation- and chemotherapy among 3176^a Danish women operated for primary breast cancer 2005–2006.

		Unadjusted			Adjusted			No. (%)	
		OR	95% CI	P-value	OR	95% CI	P-value	+ Swelling	– Swelling
Age				<0.0001			<0.0001		
	18–39 year	2.95	2.09–4.17		2.60	1.72–3.94		85 (57)	64 (43)
	40–49 year	2.19	1.80–2.67		1.95	1.50–2.53		307 (50)	311 (50)
	50–59 year	1.52	1.29–1.80		1.47	1.21–1.78		462 (41)	675 (59)
	60–69 year	1			1			395 (31)	877 (69)
Surgery				<0.0001			0.23		
	Breast procedure								
	Mastectomy	1.87	1.61–2.17		1.16	0.91–1.46		543 (49)	562 (51)
Axillary procedure				<0.0001			<0.0001		
	BCS	1			1			706 (34)	1365 (66)
	ALND	6.84	5.78–8.09		5.57	4.40–7.05		1010 (58)	736 (42)
Adjuvant treatment				<0.0001			0.0005		
	Radiotherapy								
	LRRT + BRT/ATRT	3.37	2.68–4.23		1.72	1.30–2.27		734 (61)	473 (39)
Chemotherapy				<0.0001			.14		
	BRT	0.70	0.56–0.88		1.41	0.99–2.01		368 (24)	1135 (76)
	None	1			1			147 (32)	319 (68)
Year of surgery				0.32					
	+	1.92	1.66–2.22		1.16	0.95–1.42		595 (49)	620 (51)
	–	1			1			654 (33)	1307 (67)
Surgery on dominant side				0.84					
	2005	1.08	0.93–1.24					596 (40)	885 (60)
	2006	1						653 (39)	1042 (61)
Surgery on dominant side									
	Yes	1.05	0.91–1.22					575 (40)	873 (60)
	No	1						568 (39)	906 (61)

BCS: Breast conserving surgery. SLND: Sentinel lymph node dissection. ALND: Axillary lymph node dissection. BRT: Breast radiotherapy corresponding to residual breast tissue. ATRT: Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. LRRT: Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes.

^a Of the 3253 women responding to the questionnaire 77 women did not report on swelling/heaviness.

Table 3a

Adjusted^a odds ratio for reporting swelling/heaviness according to age by type of surgery among 3176^b Danish women.

Type of surgery to the breast and age	OR	95% CI	P-value ^c
Mastectomy			0.19
–39	1.23	0.64–2.35	
40–49	1.51	1.03–2.19	
50–59	1.22	0.91–1.64	
60–69	1		
BCS			<0.0001
–39	4.10	2.48–6.77	
40–49	2.39	1.74–3.27	
50–59	1.70	1.33–2.18	
60–69	1		

BCS: Breast conserving surgery.

^a Adjusted for type of surgery, adjuvant radiation- and chemotherapy.

^b Of the 3253 women responding to the questionnaire 77 women did not report on swelling/heaviness.

^c Test of interaction between type of surgery and age; $p = 0.01$.

In the univariate models all variables in Table 4 were significant and therefore included in the multivariate analyses. In the multivariate models the most important associations for reporting functional impairment (Appendix q22) was pain (OR = 2.65; CI: 2.18–3.21, $p < 0.0001$) and swelling of the arm (OR = 2.39; CI: 1.96–2.92, $p = 0.002$), but younger age, ALND, chemotherapy, time elapsed since surgery, and surgery on the dominant side, were also associated with an increased risk of reporting impairment of function (Table 4). Radiotherapy and type of breast surgery were not associated with functional impairment in multivariate models.

Discussion

In the present study, we estimate the prevalence of self-reported lymphedema and functional impairment 1 to 3 years after treatment for breast cancer in 12 well-defined treatment groups, among Danish women operated in 2005 and 2006 and offer OR estimates for associated factors.

Table 3b

Adjusted^a odds ratio for reporting swelling/heaviness according to combinations of surgery and radiation therapy among 3176^b Danish women.

Type of surgery to the breast, Radiation therapy and axillary dissection	OR	95% CI	P-value ^c
Mastectomy			<0.0001
LRRT + ATRT	10.9	8.01–14.9	
ALND	5.55	3.82–8.04	
Mastectomy			
No radiation	1.48	0.96–2.27	
SLND	7.24	5.74–9.14	
BCS			
LRRT + BRT	6.75	5.10–8.94	
ALND	1		
BCS			
BRT			
SLND			

BCS: Breast conserving surgery. SLND: Sentinel lymph node dissection. ALND: Axillary lymph node dissection. BRT: Breast radiotherapy corresponding to residual breast tissue. ATRT: Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. LRRT: Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes.

^a Adjusted for age and adjuvant chemotherapy.

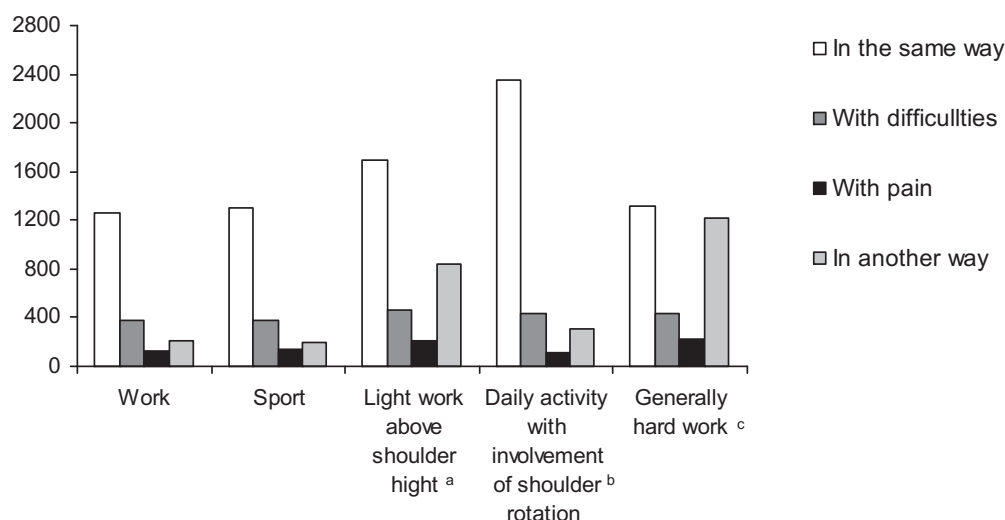
^b Of the 3253 women responding to the questionnaire 77 women did not report on swelling/heaviness.

^c Test of interaction between surgery and radiation therapy; $p = 0.02$.

The prevalence of self-reported lymphedema ranged from 13% to 65% in the different treatment groups, in accordance with the wide range of prevalences reported in literature, varying from 2% to 86%.^{13,21–37}

The most important risk factor for reporting lymphedema was ALND, confirming previous studies.³ Also, younger age and radiotherapy were associated with the reporting of lymphedema in accordance with previous findings on self-reported lymphedema.^{3,38} The impact of ALND varied between women undergoing BCS and mastectomy (Table 3b) possibly reflecting the fact that all women having BCS also received BRT. BCS combined with radiotherapy is generally considered as a more gentle treatment than mastectomy, but the present study indicates that this treatment is associated with more side effects than earlier presumed.

Our study showed that 11–44% of women, depending on treatment group, had to give up activities after treatment for breast cancer. More than one in three women in work reported that their work had been affected after the treatment for breast cancer. This



^a Washing/combing/fixing hair, washing neck, pulling sweater over the head, reaching for a shelf, lifting.

^b Brushing teeth, taking a bra or a coat on/off.

^c Opening a heavy door, carrying shopping bag, cleaning floor.

Fig. 4. Impairment of function among 3253 Danish women treated for primary breast cancer 2005–2006 reporting different degrees of activity related difficulties.

Table 4
Odds ratio for reporting impairment of function adjusted for age, type of surgery, adjuvant radiation- and chemotherapy, year of surgery, surgery on dominant side, pain and swelling among 3104^a Danish women operated for primary breast cancer 2005–2006.

		Unadjusted			Adjusted			No. (%)	
		OR	95% CI	P-value	OR	95% CI	P-value	+ Impairment of function	– Impairment of function
Age				<0.0001			0.02		
	18–39 year	2.75	1.91–3.94		1.42	0.92–2.17		56 (38)	92 (62)
	40–49 year	2.34	1.87–2.92		1.36	1.02–1.81		203 (34)	392 (66)
	50–59 year	1.68	1.38–2.04		1.39	1.12–1.73		301 (27)	809 (73)
	60–69 year	1			1			227 (18)	1024 (82)
Surgery									
Breast procedure				<0.0001			0.59		
	Mastectomy	1.65	1.40–1.95		1.07	0.83–1.39		336 (32)	720 (68)
	BCS	1			1			451 (22)	1597 (78)
Axillary procedure				<0.0001			0.005		
	ALND	2.89	2.42–3.45		1.47	1.12–1.93		570 (34)	1103 (66)
	SLND	1			1			217 (15)	1214 (85)
Adjuvant treatment									
Radiotherapy				<0.0001			0.05		
	LRRT + BRT/ATRT	1.54	1.21–1.96		0.87	0.64–1.19		411 (36)	742 (64)
	BRT	0.57	0.45–0.74		0.64	0.44–0.94		256 (17)	1241 (83)
	None	1			1			120 (26)	334 (74)
Chemotherapy				<0.0001			0.001		
	+	2.08	1.76–2.45		1.43	1.15–1.78		405 (34)	783 (66)
	–	1			1			382 (20)	1534 (80)
Year of surgery				0.005			0.02		
	2005	1.26	1.07–1.48		1.23	1.03–1.47		401 (28)	1047 (72)
	2006	1			1			386 (23)	1270 (77)
Surgery on dominant side				0.003			0.02		
	Yes	1.35	1.34–1.60		1.38	1.14–1.66		401 (28)	1020 (72)
	No	1			1			324 (23)	1110 (77)
Reporting pain				<0.0001			<0.0001		
	Yes	3.66	3.07–4.36		2.65	2.18–3.21		547 (38)	902 (62)
	No	1			1			226 (14)	1369 (86)
Reporting swelling/heaviness				<0.0001			0.002		
	Yes	4.32	3.64–5.13		2.39	1.96–2.92		498 (43)	669 (57)
	No	1			1			277 (15)	1608 (85)

BCS: Breast conserving surgery. SLND: Sentinel lymph node dissection. ALND: Axillary lymph node dissection. BRT: Breast radiotherapy corresponding to residual breast tissue. ATRT: Anterior thoracic radiotherapy corresponding to the anterior thoracic wall. LRRT: Loco-regional radiotherapy corresponding to periclavicular, axillary level 3, and for right side breast cancers, the internal mammary nodes.

^a Of the 3253 women responding to the questionnaire 149 women did not report on impairment of function.

was also the case regarding sports activities. In the literature, limitations of daily activities have been reported in 13–28% of women treated for breast cancer³⁹ but not in relation to modern treatment. Regarding functional impairment the most important associations were with the reporting of swelling and pain.

Patients operated in 2005 had an increased risk of reporting functional impairment compared to patients operated in 2006, which could partly be explained by normal aging and not exclusively the treatment for breast cancer. Treatment modalities associated with functional impairments were ALND and chemotherapy. Previously we have reported that chemotherapy was not an independent significant risk factor for pain, sensory disturbances¹⁷ nor self-reported lymphedema (Table 2) and the effect of chemotherapy on functional impairment is, thus, likely to be due to other mechanisms. In this context, fatigue, loss of muscle mass and psychological factors may play important roles calling for more detailed studies. Personal characteristics such as younger age and having surgery on the dominant side played a smaller, but significant role.

The questionnaire designed for the present study aimed at the greatest possible simplicity, asking dichotomous “yes” or “no” questions regarding symptoms of lymphedema and functional impairment. We deliberately avoided asking the patients when or for how long the sensation of swelling/heaviness or functional impairment had been present or asking the patient to consider whether or not it was due to treatment of breast cancer.

The strengths of this study are that it is based on the entire population of Denmark with a high response rate and that it is

sufficiently large to provide estimates of prevalences in all major treatment groups while additionally offering estimates for the major treatment-related associated factors such as type of surgery to the breast and the axilla as well as radiation- and chemotherapy. Furthermore, patients were treated according to the same up-to-date guidelines.

The main limitation of this study is that it is cross-sectional and only provides one estimate of prevalence: one to three years after the primary treatment. It does not follow the patients over time and therefore does not give information on the time course of self-reported lymphedema and functional impairment following breast cancer treatment. Previous studies with less well-defined treatment groups have suggested that functional impairment decreases in breast cancer survivors,¹⁰ whereas the prevalence of lymphedema increases.^{10,40} Moreover, the cross-sectional study design does not offer the possibility of drawing conclusions regarding causality, but can merely describe factors associated with symptoms of lymphedema and functional impairment. Another limitation lies in the 13% of patients who did not complete the questionnaire. If these patients suffered from more severe functional impairment and symptoms of lymphedema than the responders, our estimates are likely to be too low. Additionally, the results may have been biased by the patients who were excluded due to death or cancer relapse who might have had different problems than the surviving respondents included in the study. Furthermore, our definition of lymphedema, defined as the presence of swelling/sensation of heaviness, reflects the patients' subjective experience and may lead to an overestimation of

lymphedema compared to earlier reports based on clinically objective measurements.⁴

Finally the present nationwide study reflects the Danish population which is generally well-educated, ethnic homogenous (Caucasian), benefiting from a uniform public healthcare system covering all citizens, and thus limiting the generalizability to other populations with different healthcare systems, demographics or treatment protocols.

However, the present study with its population-based nature, high response rate, lack of recall bias and standardized treatment offers precise estimates of the prevalences of perceived lymphedema, functional impairment, and associated factors following breast cancer treatment in Denmark.

Conclusion

One to three years after surgery for breast cancer 13–65% of patients report lymphedema (defined as swellings/heaviness of the arm), while 11–44% reports functional impairment (defined as having to give up activities). The large variation in prevalence is due to the modern tailoring of breast cancer treatment to the individual breast cancer status and differences in age between the treatment groups. Reporting lymphedema was associated with ALND, radiotherapy, and younger age. Reporting functional impairment was associated with perceived lymphedema and pain, as well as younger

age, ALND, chemotherapy, time elapsed since surgery, and surgery on the dominant side. By contrast, radiotherapy and type of surgery to the breast were not associated with functional impairment.

Ethics

The study was performed in accordance with the Helsinki Declaration and approved by the local ethics committee **H-D2007-0099**, the Danish Data-protection Agency and the Danish National Patient Registry under the Danish National Health Board.

Conflict of interest statement

The authors had no conflict of interest in relation to the present study.

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Appendix

QUESTIONNAIRE

General question

- 1 Are you right-handed or left-handed?

☐ Right-handed

☐ Left-handed

Question regarding pain

In this questionnaire we define "the area of the breast" as either the operated breast or the area from which the breast was removed.

- 2 Do you have pain in the area of the breast, armpit, side of the body or the arm on the side where you were operated?

☐ Yes

☐ No

Questions regarding swelling or heaviness (lymph edema)

- 3 Does the armpit, the arm or the back of the hand, on the side where you were operated, sometimes or always feel swollen or heavy?

☐ Yes

☐ No

If "No", please go on to question 8.

- 4 If "Yes", where do you then feel the armpit, arm or back of the hand is swollen or heavy? (please tick off more than one box if relevant)

☐ Back of the hand

☐ Forearm

☐ Upper arm

☐ Armpit

- 5 How severe are the swellings/sensations of heaviness of your armpit and/or upper arm? (0 is no swellings/sensations of heaviness and 10 is worst imaginable swellings/sensations of heaviness)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

- 6 How severe are the swellings/sensations of heaviness of your forearm and/or back of your hand (0 is no swellings/sensations of heaviness and 10 is worst imaginable swellings/sensations of heaviness)

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

- 7 How often do the swellings/sensations of heaviness occur?

☐Every day or almost every day ☐1-3 days a week ☐More rarely

Questions regarding restriction of function

How do you now manage the following activities compared with the time before your treatment for breast cancer? Please choose those statements, which fit you the best. (Please tick off more than one box if relevant, tick off the box “not relevant” by activities you do not do)

	The same way as before	The same way as before, but with difficulties/slower and/or more tiered afterwards	The same way as before, but I have more pain afterwards	In another way than before, for example I am using the other arm/both hands	Not relevant
8 Washing hair	☐	☐	☐	☐	☐
9 Combing/fixing my hair	☐	☐	☐	☐	☐
10 Brushing teeth	☐	☐	☐	☐	☐
11 Washing my neck	☐	☐	☐	☐	☐
12 Taking a bra off/on	☐	☐	☐	☐	☐
13 Pulling a sweater over the head	☐	☐	☐	☐	☐
14 Taking a coat off/on	☐	☐	☐	☐	☐
15 Opening a heavy door	☐	☐	☐	☐	☐
16 carrying shopping bag	☐	☐	☐	☐	☐
17 Reaching for a shelf above the height of my head	☐	☐	☐	☐	☐
18 Lifting above the height of my shoulders	☐	☐	☐	☐	☐
19 Cleaning floors	☐	☐	☐	☐	☐
20 Doing sportactivities	☐	☐	☐	☐	☐
21 Doing my job	☐	☐	☐	☐	☐
22 Are there activities you have had to renounce on after your treatment of breast cancer?					
	☐ Yes				
					☐ No

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Appendices

APPENDIX I

[DASAIMs discharge-criteria scoring system](#)

Forslag til scoringssystem

Område	Point	Kriterium	Ank.	10 min før udskr.	Udskr.
1. Sedation	3 2 1 0	Sover hele tiden, kan ikke vækkes Sover hele tiden vækkes ved fysiske stimuli Sover en del af tiden, vækkes verbalt Vågen og klar			
2. Respiration	3 2 1 0	Apnøperioder eller obstruktivt mønster RF < 10 eller RF > 30 Snorker 10 < RF < 30 Normal RF ≥ 10			
3. SpO₂ Uden Ilttilskud e. 10 min	3 2 1 0	< 85 85 ≤ SpO ₂ < 90 90 ≤ SpO ₂ < 94 ≥ 94			
4. Blodtryk (Systolisk) Uden Inotropika	3 2 1 0	< 80 80 ≤ BT < 90 eller BT > 220 90 ≤ BT < 100 ≥ 100			
5. Puls (HR)	3 2 1 0	< 40 eller > 130 < 50 eller > 120 50 ≤ HR ≤ 120 50 < HR ≤ 100			
6. Smerter I Hvile	3 2 1 0	Udtalte eller VAS ≥ 70 mm Moderate eller 30 mm ≤ VAS < 70 mm Lette eller VAS < 30 mm Ingen eller VAS = 0 mm			
7. Kvalme	3 2 1 0	Udtalt Moderat Let Ingen			
8. Motorik	3 2 1 0	Bevæger ikke UE Kan kun bevæge fødder Kan kun bevæge fødder og bøje knæ Bevæger bg. UE frit			
9. Time Diurese	3 2 1 0	Anuri 0 < TD < 0.5 ml/kg /time 0.5 ≤ TD < 1.0 ml/kg /time 1.0 ≤ TD eller uden KAD			
10. Tp	3 2 1 0	Tp < 35,0 35,0 ≤ Tp < 35,5 35,5 ≤ Tp < 36,0 Tp ≥ 36,0			
Total	Sum	Sum af delscores 1. – 10.			

Som omtalt under litteraturgennemgangen er der ikke evidensbaserede argumenter for den ene samlede scoringsmodel frem for den anden, men der er evidensbaserede argumenter for at

APPENDIX II

[Danish Questionnaire](#)

Spørgeskema

Id nr.

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Vejledning:

Vinter 2008

Sådan udfylder du spørgeskemaet:



- 1) Brug kun en sort eller blå kuglepen
- 2) Læs hvert spørgsmål og alle svarkategorierne til det enkelte spørgsmål igennem før du svarer. Vær opmærksom på om du må sætte mere end et kryds. Hvis du må sætte mere end et kryds vil det være angivet således: "(sæt gerne flere krydser)".
- 3) Markér det udsagn, der passer bedst på din mening således:

☐ Ja ☐ Nej ☐ Ikke relevant
- 4) Hvis du laver en fejl eller skifter mening, fylder du bare den forkerte kasses helt ud og markerer den nye kasse således:

☐ Ja ☐ Nej ☐ Ikke relevant
- 5) Nogle spørgsmål er lettere at besvare end andre. Hvis du er i tvivl, sætter du kryds i den kasse, der passer bedst på dig. Er der spørgsmål, du ikke kan eller ønsker at besvare går du videre til næste spørgsmål
- 6) Når du er færdig, er det vigtigt, at du returnerer hele spørgeskemaet i vedlagte frankerede svarkuvert, også selv om der eventuelt er spørgsmål du har sprunget over.

I dette spørgeskema forstår vi ved smerter blot at noget gør ondt, vi skelner således ikke mellem smerter eller at have ondt.

Spørgeskemaet er delt op i følgende spørgsmålsgrupper:

- Generelt
- Spørgsmål vedrørende smerter
- Spørgsmål vedrørende føleforstyrrelser eller ubehag
- Spørgsmål vedrørende andre smerter, føleforstyrrelser eller ubehag
- Spørgsmål vedrørende hævelser (lymfødem)
- Spørgsmål vedrørende funktionsindskrænkning
- Andet

Nederst på spørgeskemaet vil du desuden blive spurgt om vi må kontakte dig direkte på et senere tidspunkt med henblik på andre undersøgelser vedrørende følger efter behandling for brystkræft.

Vær opmærksom på, at der er spørgsmål på begge sider af papiret.

Generelt

1 Er du højrehåndet eller venstrehåndet?

☐ Højrehåndet

☐ Venstrehåndet

Spørgsmål vedrørende smerter

I dette spørgeskema forstår vi med ordet ”brystområde” enten det opererede bryst eller det område, hvorfra brystet er fjernet

2 Har du ondt i brystområdet, armhulen, på siden af brystkassen eller armen på den side, hvor du er blevet opereret?

☐ Ja

☐ Nej

Hvis ”Nej”, fortsæt da til spørgsmål 16.

3 Hvis ”Ja”, hvor har du da ondt? (sæt gerne flere krydser)

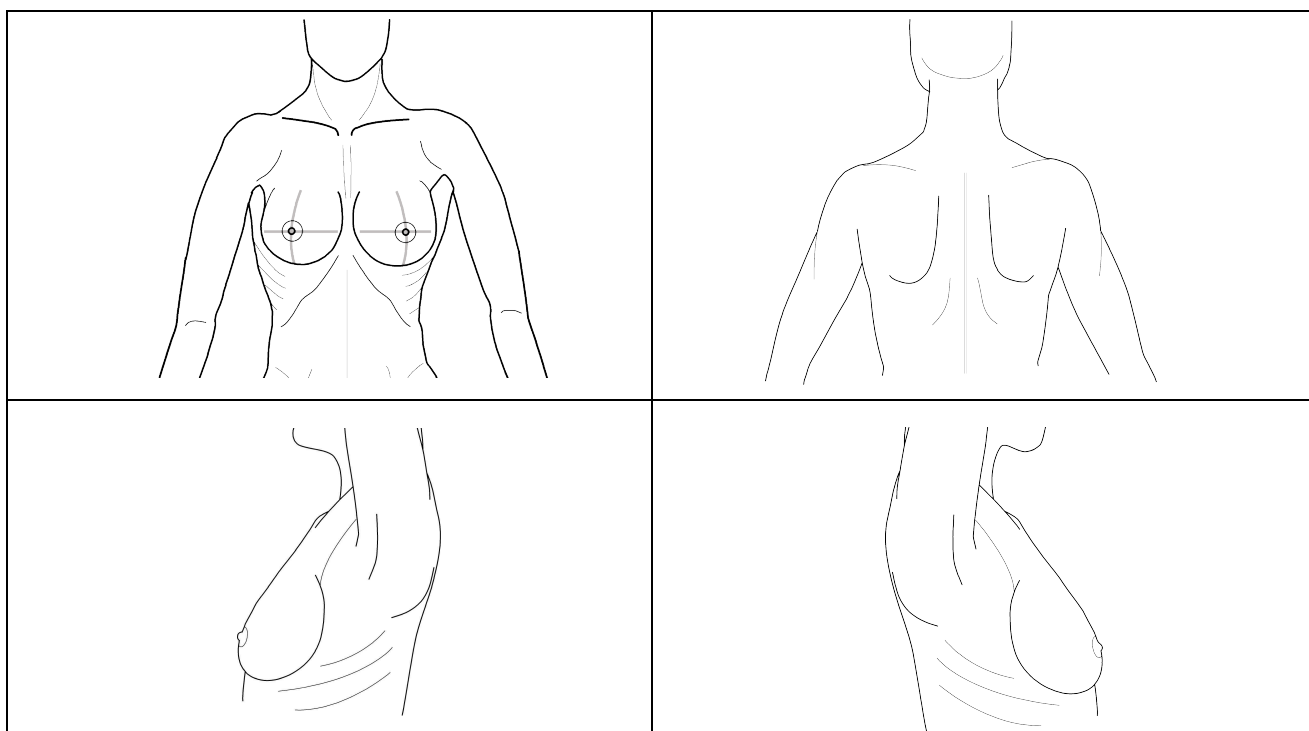
☐ Brystområdet

☐ På siden af brystkassen

☐ Armhulen

☐ Armen

Tegn også på figurene hvor du har ondt:



4 Hvis du har ondt i brystområdet, hvor stærke er smerterne så i gennemsnit? (0 er ingen smerter og 10 er værst tænkelige smerter)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

5 Hvis du har ondt i brystområdet, hvor ofte har du så ondt?

☐ Hver dag eller næsten hver dag

☐ 1-3 dage om ugen

☐ Sjældnere

- 6 Hvis du har ondt **på siden af brystkassen**, hvor stærke er smerterne så i gennemsnit? (0 er ingen smerter og 10 er værst tænkelige smerter)
- ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
- 7 Hvis du har ondt på siden af brystkassen, hvor ofte har du så ondt?
- ☐ Hver dag eller næsten hver dag ☐ 1-3 dage om ugen ☐ Sjældnere
- 8 Hvis du har ondt **i armhulen**, hvor stærke er smerterne så i gennemsnit? (0 er ingen smerter og 10 er værst tænkelige smerter)
- ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
- 9 Hvis du har ondt i armhulen, hvor ofte har du så ondt?
- ☐ Hver dag eller næsten hver dag ☐ 1-3 dage om ugen ☐ Sjældnere
- 10 Hvis du har ondt **i armen**, hvor stærke er smerterne så i gennemsnit? (0 er ingen smerter og 10 er værst tænkelige smerter)
- ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
- 11 Hvis du har ondt i armen, hvor ofte har du så ondt?
- ☐ Hver dag eller næsten hver dag ☐ 1-3 dage om ugen ☐ Sjældnere
- 12 **Har du søgt læge** inden for de sidste 3 måneder fordi du har haft ondt i brystområdet, armhulen, på siden af brystkassen eller armen på den side, hvor du er blevet opereret?
- ☐ Ja ☐ Nej
- 13 **Tager du smertestillende medicin** på grund af smerter i brystområdet, armhulen, på siden af brystkassen eller armen på den side, hvor du er blevet opereret?
- ☐ Ja ☐ Nej
- 14 Hvis ”Ja”, da hvilken smertestillende medicin? (sæt gerne flere krydser)
- ☐ Svag smertestillende medicin (eksempelvis: paracetamol, panodil, pamol, pinex, ibuprofen, ipren, ibumetin, brufen, magnyl, aspirin, treo, idotyl, kodimagnyl, kodipar, kodein)
- ☐ Morfinpræparater (eksempelvis: morfin, ketogan, contalgin, oxycontin, tramadol, tradolan)
- ☐ Andet Skriv hvilken anden smertestillende medicin: _____
- 15 **Får du anden behandling** (end medicin) fordi du har ondt i brystområdet, armhulen, på siden af brystkassen eller armen på den side, hvor du er blevet opereret (eksempelvis: fysioterapi, massage, kiropraktik)?
- ☐ Ja ☐ Nej

Spørgsmål vedrørende føleforstyrrelser eller ubehag

16 Har du føleforstyrrelser eller ubehag i brystområdet, armhulen, på siden af brystkassen eller armen på den side, hvor du er blevet opereret?

☐ Ja

☐ Nej

Hvis ”Nej”, fortsæt da til spørgsmål 19.

17 Hvis ”Ja”, hvor har du da føleforstyrrelser eller ubehag? (sæt gerne flere krydser)

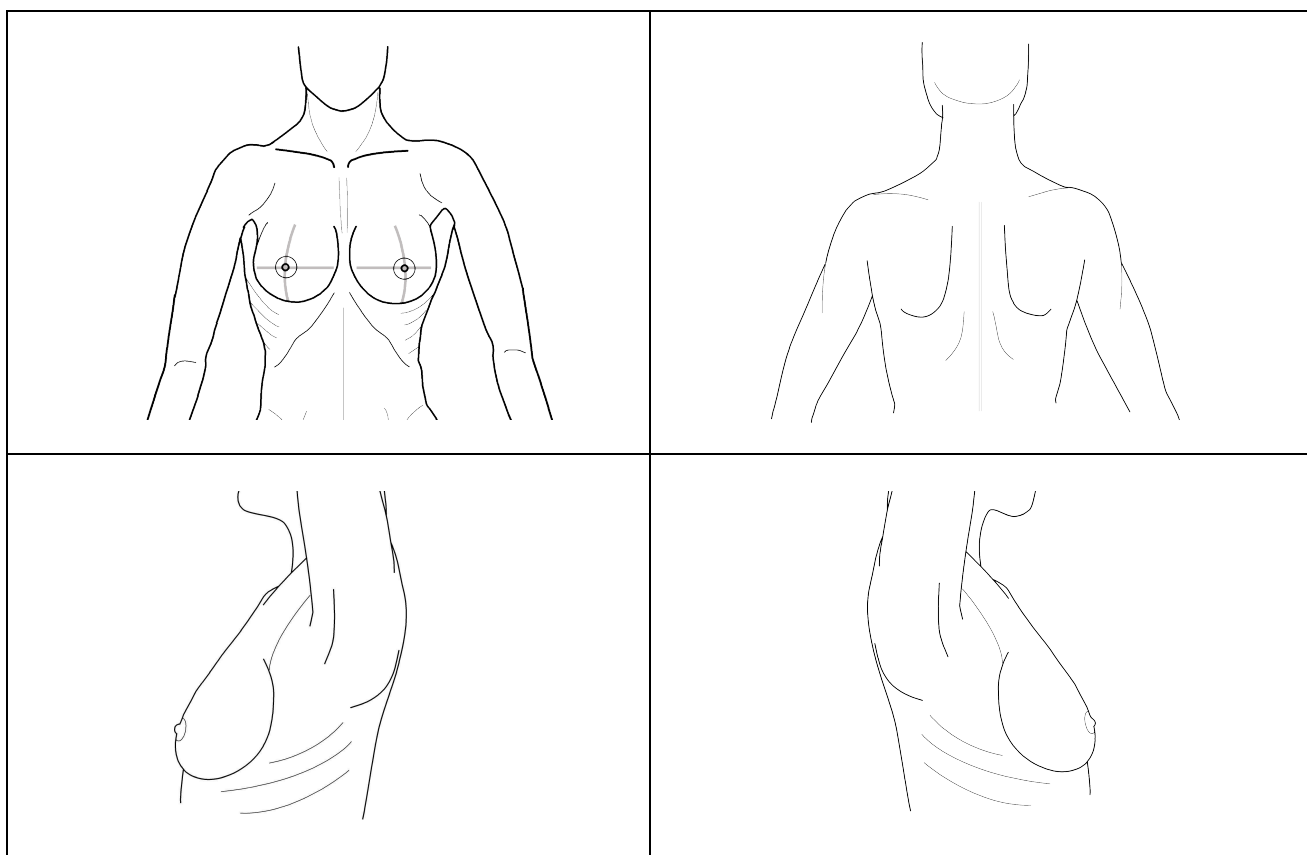
☐ Brystområdet

☐ Siden af brystkassen

☐ Armhulen

☐ Armen

Tegn også på figurene hvor dine føleforstyrrelser eller ubehag sidder:



18 Hvis du har både smerter og føleforstyrrelser/ubehag, hvad generer dig da mest?

☐ Smerterne

☐ Føleforstyrrelserne/ubehaget

☐ Både smerterne og føleforstyrrelserne

Spørgsmål vedrørende andre smerter, føleforstyrrelser eller ubehag

19 Har du ofte smerter andre steder i kroppen (eksempelvis rygsmerter, hovedpine eller lignende)?

☐ Ja ☐ Nej

Hvis ”Ja”, hvor har du da smerter: _____

20 Har du smerter, føleforstyrrelser eller ubehag i hænder eller fingre?

☐ Ja ☐ Nej

21 Hvis ”Ja”, er smerterne, føleforstyrrelserne eller ubehaget til stede på **både** højre og venstre side?

☐ Ja ☐ Nej

22 Har du smerter, føleforstyrrelser eller ubehag i fødder eller tæer?

☐ Ja ☐ Nej

23 Hvis ”Ja”, er smerterne, føleforstyrrelserne eller ubehaget da til stede på **både** højre og venstre side?

☐ Ja ☐ Nej

24 Kan du ligge/sove på den side du er opereret?

☐ Ja ☐ Nej

25 Har du gener om natten på grund af din skulder/arm på den side hvor du er opereret?

☐ Ja ☐ Nej

26 Hvis du har du gener om natten på grund af din skulder/arm på den side, hvor du er opereret, hvor udtalte er generne? (0 er ingen gener og 10 er værst tænkelige gener)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Du skal kun svare på nedenstående spørgsmål, hvis du har fået fjernet det ene bryst. Hvis du har fået lavet en brystbevarende operation, går du videre til spørgsmål 28.

27 Har du fantomfornemmelser efter din operation? (ved en fantomfornemmelse forstås her, at man stadigvæk har fornemmelse af det fjernede bryst)

☐ Ja ☐ Nej

Spørgsmål vedrørende hævelse eller tyngdefornemmelse (lymfødem)

- 28** Føles armhulen, armen eller håndryggen på den side, hvor du er blevet opereret, nogle gange eller altid hævet eller tung?

☐ Ja

☐ Nej

Hvis ”Nej”, fortsæt da til spørgsmål 33.

- 29** Hvis ”Ja”, hvor føles armhulen, armen eller håndryggen da hævet eller tung? (sæt gerne flere krydser)

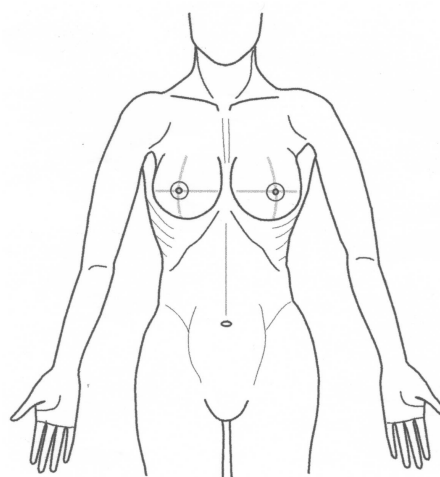
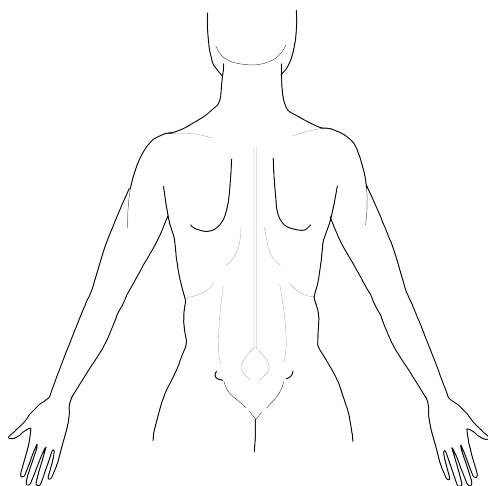
☐ Håndryg

☐ Underarm

☐ Overarm

☐ Armhule

Tegn også på figuren, hvilke del af hånden/armen/armhulen, der føles hævet eller tung:



- 30** Hvor udtalte er hævelserne/tyngdefølelsen af armhule og/eller overarm? (0 er ingen hævelser/tyngdefølelse og 10 er værst tænkelige hævelser/tyngdefølelse)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

- 31** Hvor udtalte er hævelserne/tyngdefølelsen af underarm og/eller håndryg? (0 er ingen hævelser/tyngdefølelse og 10 er værst tænkelige hævelser/tyngdefølelse)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

- 32** Hvor ofte forekommer hævelserne/tyngdefølelsen?

☐ Hver dag eller næsten hver dag

☐ 1-3 dage om ugen

☐ Sjældnere

Spørgsmål vedrørende funktionsindskrænkninger

Hvordan udfører du nu følgende aktiviteter i forhold til før din behandling for brystkræft? Vælg det eller de udsagn, der passer bedst på dig. (sæt gerne flere krydser, kryds af i feltet "Ikke relevant" ved aktiviteter du ikke udfører)

	På samme måde som før	På samme måde som før, men med besvær/langsommere og/eller er mere træt bagefter	På samme måde som før, men har ondt bagefter	På en anden måde end før, f.eks. bruger den anden arm/begge hænder	Ikke relevant
33 Vasker hår	☐	☐	☐	☐	☐
34 Reder/sætter hår	☐	☐	☐	☐	☐
35 Børster tænder	☐	☐	☐	☐	☐
36 Vasker dig i nakken	☐	☐	☐	☐	☐
37 Tager BH af/på	☐	☐	☐	☐	☐
38 Tager sweater over hovedet	☐	☐	☐	☐	☐
39 Tager frakke af/på	☐	☐	☐	☐	☐
40 Åbner tung dør	☐	☐	☐	☐	☐
41 Bærer indkøbsposer	☐	☐	☐	☐	☐
42 Rækker op til hylder over hovedhøjde	☐	☐	☐	☐	☐
43 Løfter over skulderhøjde	☐	☐	☐	☐	☐
44 Vasker gulv/støvsuger	☐	☐	☐	☐	☐
45 Udfører havearbejde	☐	☐	☐	☐	☐
Anfør hvilket:					
46 Dyrker sportsaktiviteter	☐	☐	☐	☐	☐
Anfør hvilke:					
47 Spiller på et instrument	☐	☐	☐	☐	☐
Anfør hvilket:					
48 Udfører dit arbejde	☐	☐	☐	☐	☐
Anfør hvilket:					

49 Er der aktiviteter du nu har måttet opgive efter din behandling for brystkræft?

☐ Ja

☐ Nej

Hvis ”Ja”, anfør da hvilke? (du må meget gerne beskrive problemet på linierne nedenfor)

Andet

50 Har du andre gener efter din behandling for brystkræft, som du ikke synes er dækket af ovenstående spørgsmål (eksempelvis ting i din hverdag eller, hvis du arbejder, på din arbejdsplads, som du i dag må gøre på en anden måde eller helt må lade være med at gøre)?

☐ Ja

☐ Nej

Hvis ”Ja”, skriv da meget gerne hvad og hvordan. Har du andre kommentarer, er du også meget velkommen til at skrive dem her:

Tilladelse til at kontakte dig på et senere tidspunkt

51 Må vi kontakte dig direkte på et senere tidspunkt med henblik på andre undersøgelser vedrørende følger efter behandling for brystkræft?

☐ Ja

☐ Nej

Hvis du i spørgsmål 51 har krydset af i feltet ”Ja” vil vi, hvis det bliver aktuelt, kontakte dig igen per brev. Selv om du har krydset af i feltet ”Ja”, er du på ingen måde forpligtet til at deltage i en eventuel efterfølgende undersøgelse.

Mange tak for hjælpen

Niels, Jens, Birgit, Lise, Jeanette og Rune

APPENDIX III

English Questionnaire (Translated from Danish)

Appendix

QUESTIONNAIRE

Questions regarding pain

In this questionnaire we define “the area of the breast” as either the operated breast or the area from which the breast was removed.

- 1 Do you have pain in the area of the breast, armpit, side of the body, or arm on the side where you were operated?

☐ Yes

☐ No

If “No”, please go on to question 14.

- 2 If “Yes”, where do you have pain? (Please tick off more than one box if relevant.)

☐ Area of the breast

☐ Side of the body

☐ Armpit

☐ Arm

- 3 If you have pain in the area of the breast, how strong on average is this pain? (0 is no pain and 10 is the worst pain imaginable)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

- 4 If you have pain in the area of the breast, how often do you have this pain?

☐ Every day or almost every day

☐ 1–3 days a week

☐ More rarely

- 5 If you have pain on the side of the body, how strong on average is this pain? (0 is no pain and 10 is the worst pain imaginable)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

- 6 If you have pain on the side of the body, how often do you have this pain?

☐ Every day or almost every day

☐ 1–3 days a week

☐ More rarely

- 7 If you have pain in the armpit, how strong on average is this pain? (0 is no pain and 10 is the worst pain imaginable)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

- 8 If you have pain in the armpit, how often do you have this pain?

☐ Every day or almost every day

☐ 1–3 days a week

☐ More rarely

- 9 If you have pain in the arm, how strong on average is this pain? (0 is no pain and 10 is the worst

pain imaginable)

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

10 If you have pain in the arm, how often do you have this pain?

☐Every day or almost every day ☐1–3 days a week ☐More rarely

11 **Have you contacted a doctor** within the last 3 months because of pain in the area of the breast, armpit, side of the body, or arm on the side where you were operated?

☐Yes ☐No

12 **Do you take painkiller(s)** because of pain in the area of the breast, armpit, side of the body, or arm on the side where you were operated?

☐Yes ☐No

13 Do you receive other treatment(s) (than medicine) because of pain in the area of the breast, armpit, side of the body, or arm on the side where you were operated (for example, physiotherapy, massage, chiropractic)?

☐Yes ☐No

Questions regarding sensory disturbances or discomfort

14 Do you have sensory disturbances or discomfort in the area of the breast, armpit, side of the body, or arm on the side where you were operated?

☐Yes ☐No

If “No”, please go on to question 16.

15 If “Yes”, where do you have sensory disturbances or discomfort? (Please tick off more than one box if relevant.)

☐Area of the breast ☐Side of the body ☐Armpit ☐Arm

Question regarding other pain

16 Do you frequently have pain in other parts of your body (e.g. back pain, headache or similar)?

☐Yes ☐No

Appendix

QUESTIONNAIRE

General question

1 Are you right-handed or left-handed?

☐ Right-handed

☐ Left-handed

Question regarding pain

In this questionnaire we define "the area of the breast" as either the operated breast or the area from which the breast was removed.

2 Do you have pain in the area of the breast, armpit, side of the body or the arm on the side where you were operated?

☐ Yes

☐ No

Questions regarding swelling or heaviness (lymph edema)

3 Does the armpit, the arm or the back of the hand, on the side where you were operated, sometimes or always feel swollen or heavy?

☐ Yes

☐ No

If "No", please go on to question 8.

4 If "Yes", where do you then feel the armpit, arm or back of the hand is swollen or heavy? (please tick off more than one box if relevant)

☐ Back of the hand

☐ Forearm

☐ Upper arm

☐ Armpit

5 How severe are the swellings/sensations of heaviness of your armpit and/or upper arm? (0 is no swellings/sensations of heaviness and 10 is worst imaginable swellings/sensations of heaviness)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

6 How severe are the swellings/sensations of heaviness of your forearm and/or back of your hand (0 is no swellings/sensations of heaviness and 10 is worst imaginable swellings/sensations of heaviness)

☐ 0

☐ 1

☐ 2

☐ 3

☐ 4

☐ 5

☐ 6

☐ 7

☐ 8

☐ 9

☐ 10

7 How often do the swellings/sensations of heaviness occur?

☐ Every day or almost every day

☐ 1-3 days a week

☐ More rarely

Questions regarding restriction of function

How do you now manage the following activities compared with the time before your treatment for breast cancer? Please choose those statements, which fit you the best. (please tick off more than one box if relevant, tick off the box "not relevant" by activities you do not do)

	The same way as before	The same way as before, but with difficulties/slower and/or more tiered afterwards	The same way as before, but I have more pain afterwards	In another way than before, for example I am using the other arm/both hands	Not relevant
8 Washing hair	☐	☐	☐	☐	☐
9 Combing/fixing my hair	☐	☐	☐	☐	☐
10 Brushing teeth	☐	☐	☐	☐	☐
11 Washing my neck	☐	☐	☐	☐	☐
12 Taking a bra off/on	☐	☐	☐	☐	☐
13 Pulling a sweater over the head	☐	☐	☐	☐	☐
14 Taking a coat off/on	☐	☐	☐	☐	☐
15 Opening a heavy door	☐	☐	☐	☐	☐
16 carrying shopping bag	☐	☐	☐	☐	☐
17 Reaching for a shelf above the hight of my head	☐	☐	☐	☐	☐
18 Lifting above the hight of my shoulders	☐	☐	☐	☐	☐
19 Cleaning floors	☐	☐	☐	☐	☐
20 Doing sportactivities	☐	☐	☐	☐	☐
21 Doing my job	☐	☐	☐	☐	☐

22 Are there activities you have had to renounce on after your treatment of breast cancer?

☐ Yes

☐ No