Department of Molecular Medicine and Surgery, Division of Surgery
Karolinska Institutet, Stockholm

Long-term follow-up after treatment of invasive and *in situ* breast cancer

- aspects on second breast cancers, HRQOL and lymphoedema

Helena Sackey

Karolinska Institutet

Stockholm 2014

Published by Karolinska Institutet. Printed by åtta.45 Tryckeri AB

Layout Soraya Abdi

ISBN 978-91-7549-504-0

To women

ABSTRACT

Breast cancer is the most frequent cancer among Swedish women and in 2012, 8490 new invasive breast cancers were diagnosed. The incidence of *in situ* breast cancer has markedly increased since nationwide mammography screening was introduced in the late 1980s. The increasing figures of *in situ* breast cancer are predominantly attributable to an increased frequency of ductal carcinoma *in situ* (DCIS). In 2012, 1443 *in situ* breast cancers were diagnosed in Sweden, which is approximately 15% of all diagnosed breast cancers.

The main aims of the first two papers were to study the long-term HRQOL after different types of surgical treatment in women with DCIS (paper I) and to study the risk of developing a new *in situ* or invasive breast cancer after a first *in situ* cancer in women with and without a family history for breast cancer (paper II). Since the 1980s, breast-conserving surgery for DCIS has been recommended whenever feasible. Several randomised trials have shown a decreased rate of ipsilateral DCIS or invasive breast cancer recurrence through the addition of adjuvant radiotherapy. Mastectomy is still recommended for women with either multifocal DCIS, and/or unfavourable proportion between tumour size and breast volume. For these women an immediate breast reconstruction (IBR) is an alternative to maintain a breast contour. As surgery is the primary treatment for this disease, it is essential to increase current understanding of its long-term consequences. In paper I, 162 women treated for DCIS with breast-conserving surgery with or without postoperative radiotherapy, or with mastectomy and IBR, had a satisfactory long-term HRQOL. However, body image appeared to be affected in women after mastectomy and IBR.

Using the population-based Swedish Multi-Generation and Cancer Registers we identified 8,111 women (paper II) diagnosed with *in situ* breast cancer between 1980 and 2004. The risk of a subsequent invasive breast cancer was increased more than fourfold [SIR 4.55 (95% CI 4.23- 4.88)] among women with *in situ* breast cancer as compared to women in the general population and the risk for a contralateral *in situ* breast cancer was almost sixteenfold increased [SIR 15.98(95% CI, 13.23-19.14)]. Having a family history for breast cancer increased the risk for contralateral invasive breast cancer by almost 50 % [incidence rate ratio 1.47 (95% CI 1.05-2.05)]. The risk for a subsequent invasive breast cancer, as well as mortality was substantially higher in younger women, which should be taken into account when planning their treatment and follow-up.

The main aims of paper III and IV were to evaluate the impact of axillary surgery on arm lymphoedema and long-term HRQOL. Axillary lymph node dissection (ALND) was the standard surgical procedure for staging well into the 1990s, when it was replaced by the sentinel lymph node biopsy (SLNB), in patients with preoperatively no signs of axillary metastases. In a multicentre study, including 557 women, we showed that SLNB alone is associated with a minimal risk of increased arm volume and few self-perceived symptoms of arm lymphoedema, significantly less than after ALND, regardless of lymph node status. Yet, 20% of the women who underwent SLNB, reported symptoms of arm lymphoedema, which emphasizes the importance of performing SLNB strictly on patients who can benefit from the staging results. Three years after surgery women in all three study groups appeared to have a satisfactory HRQOL. Women reporting self-perceived arm lymphoedema, regardless of objective lymphoedema or not, reported poorer HRQOL than those women who did not, indicating that more attention should be given to the subjective reports of symptoms, in order to better help these women.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I. **Ductal carcinoma *in situ* of the breast. Long-term follow-up of health-related qulity of life, emotional reactions and body image**

H. Sackey, K. Sandelin, J. Frisell, M. Wickman, Y. Brandberg. *EJSO 36 (2010) 756-762.*

II. **The impact of *in situ* breast cancer and family history on risk of subsequent breast cancer events and mortality – a population based study from Sweden**

H. Sackey, M. Hui, K. Czene, H.Verkooijen, G. Edgren, J. Frisell, M. Hartman. *Submitted for publication.*

III. **Arm lymphoedema after axillary surgery in women with invasive breast cancer. Objective and subjective assessment in a prospective multicenter study**

H. Sackey, A. Magnusson, K. Sandelin, G. Liljegren, L. Bergkvist, Z. Fülep, F. Celebioglu, J. Frisell. *Br J Surg. 2014 Mar;101(4):390-7*

IV. **Impact of arm-lymphoedema and different types of axillary surgery on long-term health-related quality of life in breast cancer patients**

H. Sackey, H Johansson, K. Sandelin, G. Liljegren, G. MacLean, J. Frisell, Y. Brandberg. *Submitted for publication.*

CONTENTS

LIST OF ABBREVIATIONS

ALND	Axillary lymph node dissections
AVD	Arm volume difference
BIS	Body Image Scale
BMI	Body mass index
BP	Bodily pain
DCIS	Ductal carcinoma *in situ*
EAR	Excess additive risk
EORTC	European Organisation for Research and Treatment of Cancer
ER	Oestrogen receptor
GEE	Generalised estimating equations
GH	General health
HADS	Hospital Anxiety and Depression Scale
HER2	Human epidermal growth factor receptor 2
HRQOL	Health-related quality of life
IBR	Immediate breast reconstruction
ICD	International Classification of Disease
LCIS	Lobular carcinoma *in situ*
MGR	Multi-Generation Register
MH	Mental health
MRI	Magnetic Resonance Imaging
PF	Physical functioning
RE	Role limitation due to emotional problems
RP	Physical problems
RT	Postoperative radiotherapy
SF	Social functioning
SIR	Standardised incidence ratios
SLNB	Sentinel lymph node biopsy
SMR	Standardised mortality ratio
SOC	Sense of coherence
SPS	Self-perceived symptoms
TNM	Tumor-Node-Metastasis
VT	Vitality

THESIS AT A GLANCE

	Aim	**Subjects and Methods**	**Results and Conclusion**
I	To investigate and compare long-term HRQOL, body image, and emotional reactions in women with *in situ* breast cancer treated with different surgical methods.	Women in Stockholm County with DCIS *N=162* HRQOL assessed with Questionnaires: SF-36, Hospital and Anxiety Scale and Body Image Scale	Women treated for DCIS have a satisfactory long-term HRQOL. Body image appears to be affected in women treated with mastectomy and immediate breast reconstruction.
II	To evaluate long-term risk of subsequent breast cancer and mortality in women diagnosed with *in situ* breast cancer. To evaluate the impact of family history on long-term risk of subsequent breast cancer and mortality in women diagnosed with *in situ* breast cancer.	All women in the Multi-Generation Register with first *in situ* breast cancer diagnosed 1980-2004 *N=8111* Relative risk for second breast cancer and relative mortality risk in women with *in situ* breast cancer.	The risk for a subsequent invasive breast cancer, as well as mortality is substantially higher in younger women, which should be taken into account when planning their treatment and follow-up. For women with *in situ* breast cancer a positive family history increases the risk only for a contralateral invasive breast cancer.
III	To compare arm lymphoedema after SLNB alone vs. ALND, both in node-negative and node-positive breast cancer patients. To examine the potential association between subjectively and objectively measured arm lymphoedema.	Women operated for invasive breast cancer in four hospitals in Sweden. *N=557* Arm lymphoedema measured with water displacement technique. Questionnaire regarding self-perceived symptoms of arm lymphoedema.	SLNB is associated with a minimal risk of increased arm volume and few self-perceived symptoms of arm lymphoedema. Yet, 20% of women report symptoms of arm lymphoedema after sentinel lymph node biopsy, which emphasizes the importance of performing axillary surgery strictly on patients who can benefit from the staging results. Three years after surgery there is a weak correlation between objectively measured arm lymphoedema and self-perceived symptoms of arm lymphoedema.
IV	To compare long-term HRQOL in patients undergoing SLNB alone vs. ALND with or without axillary metastases. To assess the impact of objective arm lymphoedema and subjective ratings on health-related quality of life	Women operated for invasive breast cancer in four hospitals in Sweden. *N=557* HRQOL assessed with SF-36 questionnaire. Questionnaire regarding self-perceived symptoms of arm lymphoedema.	Women treated for invasive breast cancer have a satisfactory long-term HRQOL. Women reporting self-perceived arm lymphoedema, regardless of objective lymphoedema or not, reported poorer HRQOL than those who did not, indicating that more attention should be given to the subjective reports of symptoms in order to better help these women.

"Where there is love for mankind, there is the love for the art of healing".

Hippocrates

BACKGROUND

Epidemiology and risk factors

In Sweden, breast cancer is the most frequent cancer among women, accounting for almost 30% of all female malignancies[1]. Breast cancer incidence and mortality demonstrate a distinct geographic variability, with high rates in Northern Europe and North America, intermediate rates in Southern Europe and Latin America and low rates in Asia and Africa[2]. In high incidence countries like Sweden, approximately every tenth to eight woman will be afflicted by breast cancer[1, 2]. In 2012, 8490 new invasive breast cancers were diagnosed in Sweden[1]. The incidence of breast cancer has increased markedly over time, and in the last two decades this increase has been observed in almost all countries[3, 4]. In Sweden, the incidence more than doubled between 1980 and 2013[5]. The introduction of population-based mammography screening have had a major influence on the increased incidence, but cannot fully explain it[3, 4]. Other factors that may have contributed are changes in risk factors, e.g. lower parity, increased use of hormone replacement therapy, higher age at first childbirth and higher mean weight[6].

The incidence of *in situ* breast cancer has markedly increased since nationwide mammography screening was introduced in Sweden in the late 1980s[1]. The increasing figures of *in situ* breast cancer are predominantly attributable to an increased frequency of ductal carcinoma in situ (DCIS). Today, the majority of all DCIS are screening detected[7, 8]. In 2012, 1443 *in situ* breast cancers were diagnosed in Sweden, which is approximately 15% of all diagnosed breast cancers. This compares with 30-50 cases of *in situ* breast cancer per year in the 1960s[9].

Age and sex are the most important determinants of breast cancer incidence[6]. Breast cancer incidence is low in women before 40 years of age, but then increases steeply. The mean age of developing breast cancer in Sweden is 63 years and approximately 10% of the breast cancer cases are diagnosed among women younger than 45 years of age[5]. Only 0.5% of all breast cancer cases are male[5] .

The aetiology of breast cancer is multifactorial and not fully known. Several risk factors have been identified in the development of the disease, although it is not clear why a breast cell mutates and becomes malignant. The association between hormonal activity and the risk of developing breast cancer has been studied extensively. Early menarche, late menopause, low parity and late childbirth, as well as hormone replacement therapy with combined oestrogen and gestagen increase the risk[6, 10, 11]. This is also true of oral contraceptives, but to a more moderate degree[6]. Obesity and high intake of alcohol are lifestyle factors that increase the risk of breast cancer in post-menopausal women[6, 12, 13], while physical activity decreases the risk[14]. A breast with a dense mammography pattern, i.e. a breast rich in connective and epithelial tissue, increases the risk for breast cancer[15], as does exposure to radiation at a young age[6].

The risk factors for developing an *in situ* breast cancer are largely the same as for invasive breast cancer[16, 17]. Population-based studies that use family history data predict that 5% of women with DCIS carry a mutation in the BRCA 1 or BRCA 2 genes[18]. The mean age of developing *in situ* breast cancer in Sweden is 59 years[19]. Women with *in situ* breast cancer have an increased risk of developing *in situ* or invasive breast cancer in the ipsi- or contralateral breast[20-30]. Moreover women with *in situ* breast cancer, even after treatment, are at increased risk of subsequent invasive breast cancer compared to women in the general population[20, 22-28, 31-33]. Several

factors have been associated with invasive recurrences after *in situ* diagnosis, including patient characteristics [23, 24, 27], tumor characteristics[23, 24, 34] and treatment[23, 35, 36].

Familial aggregation of breast cancer has been observed all over the world. In general, early onset and bilateral disease are two important features in these families [37]. A Scandinavian twin study has revealed that hereditary factors are important in 27% of all breast cancers[38] and 5-10 % of the cases appear to be the results of autosomal dominant genes[39]. In 1994 and 1995, respectively, the two tumour-suppressor genes BRCA 1 on chromosome 17 and BRCA 2 on chromosome 13 were cloned. Carrying a mutation in either of these suppressor genes entails a 50-80% lifetime risk of developing breast cancer [40], however, these mutations only account for 2-3% of all breast cancer cases[41, 42]. In the clinical setting, hereditary breast cancer is defined as ≥ three cases of breast cancer in the same branch of the family, of which at least one occurs prior to age 50[42]. An aggregation that does not fulfill these criteria is called familial breast cancer[42]. In population-based studies, a family history is defined as having one first degree family member with breast cancer. Two meta-analyses of familial risks for breast cancer presented the relative risks associated with having a first degree relative of breast cancer of 2.1 and 1.8, respectively[43, 44]. There are statistical models for estimating the risk for individual patients and these are used in oncogenetic counselling[45]. Genetic testing, risk prediction and counselling are offered to women with an accumulation of breast and ovarian cancer in their families[9, 42].

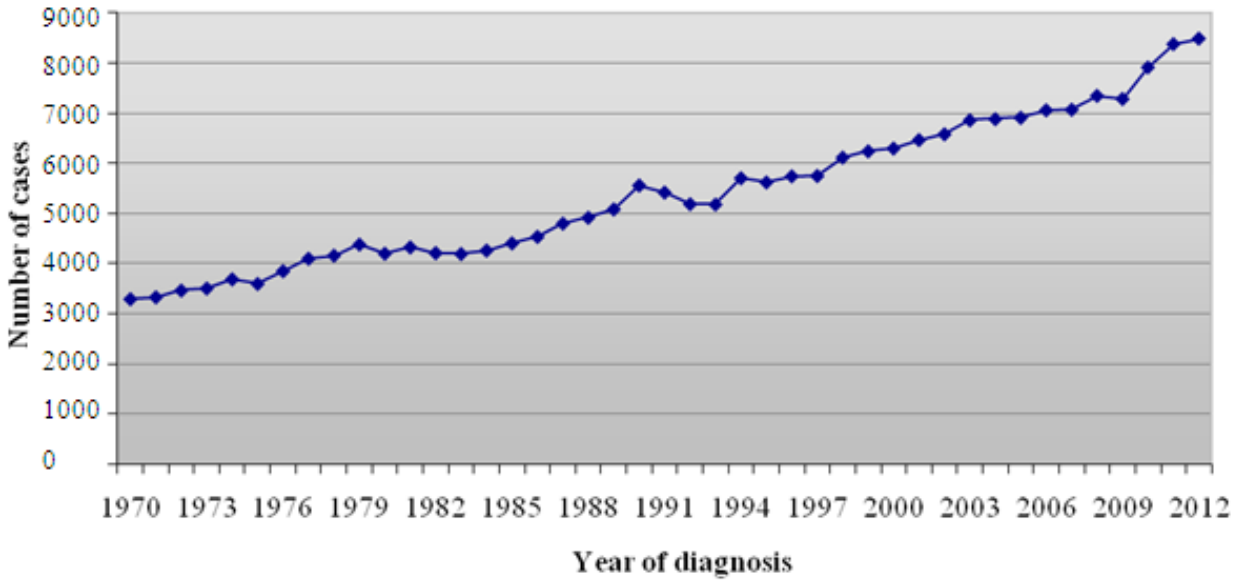


Figure 1. Number of new invasive breast cancers in Sweden by year of diagnosis.
Cancer i siffror 2012. The National Board of Health and Welfare.

Prognostic and treatment predictive factors

Despite the increasing incidence during the last 30-40 years, there has been a slight decrease in mortality rates since the 1980s and today, approximately 87% survive five years after diagnosis[5]. This is partly due to earlier diagnosis through mammography screening programmes, multidisciplinary team conferences, well established national guidelines, and high awareness among women together with more effective adjuvant treatment. Despite this, one in four women diagnosed with breast cancer dies of the disease[5]. In Sweden, breast cancer accounts for approximately 3% of the total mortality among women, and around 1500 women a year die from the disease[5].
The mortality for women diagnosed with *in situ* breast cancer is considered to be at most only marginally increased, but remains less well characterized and with few exceptions, studies are often limited by short follow-up and non-population based designs[32, 46] .

The factors that traditionally have been associated with breast cancer recurrence and death are patient´s age, tumor stage according to the Tumor-Node-Metastasis (TNM) classification and histological grade. Today, breast cancer characterisation has expanded and is also classified according to the expression of different receptors and biomarkers, which provide prognostic and/or predictive information regarding therapy response.

Age

The mean age for being diagnosed with breast cancer in Sweden is 63 years and only 5% of the breast cancers are diagnosed in women younger than 40 years of age[1]. Very young[47] and very old[48] women seem to have worse prognoses. Breast cancers in young women are more often oestrogen receptor (ER)-negative, of a higher histological grade and have a higher proliferation, which is associated with poor prognosis[49]. In older women, poor survival may be related to comorbidity or receiving adjuvant therapy less often than would be appropriate, given their tumour characteristics[48].

TNM classification

The TNM classification system is based on tumour size and invasiveness (T), number of lymph node metastases (N) and the presence of distant metastases (M). The prognostic information obtained from the size of the tumour is well established, only 10-20% of women with a tumour < 1 cm will have lymph node metastases compared with 50% of women with a tumour size > 2 cm[42].

This TNM classification is divided into four stages. Stage I means no nodal involvement (no tumour growth outside the breast) and the tumour is < 2cm. Stage II is a breast cancer > 2-5 cm with no metastases or that the tumor is <5 cm with movable lymph node metastases**.** Stage III includes cases with tumor spread to the skin of the breast or chest wall or fixed lymph node metastasis. In stage IV, there are distant metastases. In stage I, the 10-year survival is 80-100%, and with a limited spread to the lymph nodes, stage II, the prognosis is still good, at around 60-70%[42].

After the introduction of mammography screening the frequency of early breast cancer without lymph node metastases has increased and today about two thirds of all patients have no axillary metastases at diagnosis[42]. In addition to the traditionally used prognostic markers, biomarkers expressed by tumor cells are today more clinically relevant. In case of some biomarkers, like ER and human epidermal growth factor receptor 2 (HER2), they provide both prognostic and treatment predictive information.

Histopathological classification and the Nottingham Histological Grade

Breast cancer is not an entity but a collective name for malignancies in the breast tissue with different genetic background and prognosis. Roughly, there is invasive and *in situ* breast cancer and the classification according to the World Health Organisation (WHO) is based on the histological appearance of the cancer.

Invasive breast cancer

Invasive breast cancer is divided into six histological groups and ductal and lobular invasive breast cancer account for approxi-mately 50-80% and 5-15%, respectively. Other types of rare invasive breast cancers are tubular carcinoma, medullary carcinoma, mucinous carcinoma, invasive cribriform, invasive papillary carcinoma and metaplastic breast cancer. Inflammatory breast cancer has symptoms including all the signs of inflammation, and the symptoms are caused by obstruction of the lymphatics[42].

Invasive breast cancer is further graded according to the Nottingham Histological Grade, a three-grade scoring system for tumour aggressiveness based on mitotic count, tubular formation and degree of nuclear atypia. The score is a measure of how similar the tumour cell is to normal breast cell, i.e. the degree of differentiation. This grade is an independent prognostic factor with almost 100% 5-year survival among grade 1 patients and 60% in grade 3 patients[42].

In situ breast cancer

In situ breast cancer is by definition a cancer that respects the natural barrier, i.e. the basal membranes, and does not invade or infiltrate their surroundings. *In situ* breast cancer can be divided into ductal carcinoma in situ (DCIS) and lobular carcinoma *in situ* (LCIS)[42].

DCIS is a precursor lesion that has the potential to transform into an invasive cancer over a timespan that may be a few years or decades long. DCIS was rarely diagnosed before the introduction of national mammography screening programmes in the late 1990s and today, the majority of DCIS cases are screening detected, thus asymptomatic[19]. DCIS that presents with clinical signs is more likely to be extensive or to have an invasive component[42].

The traditional system for classifying DCIS was based primarily on the architectural pattern of the lesion and recognised five major subtypes: comedo, cribriform, micropapillary, papillary, and solid[50]. The hallmark of the comedo pattern is the presence of prominent necrosis in the involved spaces, which can be appreciated on macroscopic examination as cords of pasty material exuding from the cut surface of the specimen or readily expressed from involved ducts by palpation. Many of the involved spaces contain necrotic cellular debris within their centres. This necrotic material frequently becomes calcified, and these calcifications may be detected mammographically[51].

At present, there is no universally accepted histopathological classification of DCIS. In Sweden, DCIS is graded according to Holland's classification system[52]. This is based on cytonuclear differentiation and architectural differentiation (cellular polarisation). The presence of nuclear necrosis is also included in this system and, all together, DCIS is divided into three subgroups[52].

LCIS is considered to be a marker of increased risk of an invasive cancer rather than a precursor [42]. An incident finding of LCIS does not require treatment but warrants follow-up[9].

Bio- and proliferation markers

Breast cancer is further classified according to the expression of different receptors. In 1896, Beatson showed remarkable regression in some breast cancer patients with metastatic disease after oophorectomy.

In 1970, the ER was identified and the positive response to endocrine ablation could be explained[53]. ER activates transcription and is often up-regulated in tumour cells. ER is expressed in over three quarters of breast cancer patients and is associated with a better prognosis[42, 54].

The progesterone receptor is also often up-regulated in tumor cells and is simultaneously expressed in >50% of the Erpositive tumours[42]. The PR appears not to have any ER-independent mechanism of action. In a meta-analysis, no benefits of endocrine therapy in ER-negative, PR-positive tumours were found[54].

HER2 is a tyrosine kinase receptor located on the cell membrane and was identified and reported to be amplified in women with breast cancer in the late 1980s[55]. Approximately 20% of all breast cancers express HER2[56, 57] and it is strongly associated with increased disease recurrence and a poorer prognosis[58].

Ki67 is a proliferation marker expressed in the cell nucleus in all phases of the cell cycle except G0, with a maximal expression at mitosis[42]. The exact function of Ki67 is not known, out high expression is associated with poor prognosis and blocking Ki67 prevents cell proliferation[59]. All three receptors (ER, PR and HER2) and Ki67 can be assessed by immunohistochemistry[42].

Molecular subtypes

Global gene expression profiling describes the activity or level of expression of a particular gene by counting the mRNA instead of the protein for which the gene encodes. At the beginning of the 21st century, malignant breast tumours were analysed by hierarchical clustering and were shown to subdivide into five subgroups[60, 61]. These subgroups of tumours have revealed critical differences in response to treatment[62, 63] and survival[60, 61].

The technique of gene expression profiling has been developed and commercial multi-gene assays are available. These genetic techniques have, due to their high costs, led to surrogate molecular subtypes based on immunohistochemical analyses of the bio-markers used in the clinical setting, i.e. ER, PR, HER2 and Ki67. The surrogate molecular subtypes recommended by the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013[64] are:

- **luminal A:** ER+ and/or PR+, HER2- and Ki67low
- **luminal B:** ER+ and/or PR-, HER2- and Ki67 high or low ER+ and/or PR+, HER2- and Ki67 high
- **luminal HER2+:** ER+ and/or PR+, HER2+ and any Ki67
- **HER2 type:** ER-, PR- and HER2+
- **triple negative:** ER-, PR- and HER2-

Diagnostics

The diagnosis of breast cancer diagnosis is based on a triple diagnostic procedure with clinical examination of the breast and loco-regional lymph nodes, mammography and/or ultrasound of the breast and cytological examination of cell sample obtained by fine-needle aspiration or histopathological examination of core biopsy. Using this triple procedure the sensitivity is very high, with less than 1% missed cases[65, 66]. Mammography screening in Sweden started in 1986 and reached complete national coverage by 1997[67]. According to Swedish guidelines all women between the ages 40 and 74 are offered mammographic examination at regular intervals[68]. In Sweden, approximately 50% of all breast cancers are diagnosed by mammography screening[19]. In comparison to clinically detected breast cancer, screening-detected breast cancers are smaller, more often node-negative and in general have a lower histological grade and a better prognosis than clinically-detected tumours[69, 70]. The benefits of mammography screening have been debated and opponents claim that the benefits are cancelled out by the risks of over- diagnosis and over- treatment[71]. Data from a Cochrane review suggested that screening reduces breast cancer mortality by 15% and that over diagnosis and over treatment runs at 30%[72]. An overview of the Swedish randomised trials, show that the relative risk reduction in breast cancer mortality is approximately 21%[73].

Ultrasound is a routinely used complement to mammography and has a higher sensitivity, especially in women with high density breasts [74]. Magnetic resonance imaging (MRI) is recommended when screening women who are BRCA 1 and/or 2 carriers, as MRI is reported to have a higher sensitivity than other imaging modalities[75].

Treatment

Sweden has national and regional guidelines for the treatment of breast cancer and the primary treatment for the majority of patients is surgery[68, 76]. According to these guidelines, all breast cancer patients are to be discussed at pre- and postoperative multidisciplinary conferences. Surgery of the breast is currently performed either as a mastectomy or breast-conserving surgery, where the tumour-bearing part of the breast is removed. Since the 1990s, breast-conserving surgery has become more common than mastectomy and today approximately 55% of all patients in Sweden receive breast-conserving surgery[19]. The decision regarding the surgery is based on tumour size in relation to the size of the breast, whether there are multiple cancer regions in the breast and the patient's own wishes. Prospective randomised trials, with long follow-up times, have not shown any differences in survival between breast-conserving surgery, followed by radiotherapy of the breast and mastectomy[77-79].

History of breast cancer treatment

The contemporary history of breast cancer surgery is strongly associated with the American surgeon William Halsted (1852-1922). In 1882 he performed the first radical mastectomy at the John Hopkins Hospital[80]. The radical mastectomy comprised en-bloc extirpation of the breast gland, the pectoral major and minor muscles and extensive removal of axillary and adjacently located lymph nodes (exposing the subclavian vein and the brachial plexus). This extensive procedure resulted in comparatively superior locoregional control and became the gold standard for breast cancer surgery for the next hundred years. However, the severe disfigurement created by the radical mastectomy also raised doubts as to whether such extensive surgery was necessary. In 1948, Patey and Dyson described a

modification of the Halstedian operation and named it the "modified radical mastectomy". Here, the pectoralis major muscle was spared, which significantly decreased postoperative morbidity[81]. In the 1960s, Bernard Fisher revolutionised cancer treatment with the theory that breast cancer may be a systemic disease, the outcome of which would not merely depend upon the extent of locoregional treatment[82]. With the advent of radiotherapy in the1930s and 1940s, and the knowledge of the side effects of extensive surgery, alternative surgical procedures such as breast-conserving surgery and mastectomy, with or without radiotherapy, and more limited axillary dissection were introduced in clinical studies[77, 81, 83].

The application of oncoplastic surgery techniques further allows complete removal of the tumour with adequate surgical margins, and preserves the natural appearance of the breast[84]. In case of mastectomy, the loss of a breast might constitute a psychological trauma for some women and a breast reconstruction can help to restore body image and improve health-related quality of life (HRQOL) after mastectomy[85, 86].

Historically, DCIS was treated with mastectomy, but since the 1980s, breast-conserving surgery for DCIS has been recommended whenever feasible. Mastectomy and breast-conserving surgery for DCIS have not been compared in randomized trials. However data from observational studies suggest that the rates of local or regional recurrence are significantly lower after mastectomy than after breast-conserving surgery, but no significant differences in survival has been shown [87-89] . Mastectomy is still recommended for women with multifocal DCIS and/or an unfavourable proportion between tumor size and breast volume. For these women immediatebreast reconstruction (IBR) may be an alternative in order to maintain a breast contour.

Breast reconstruction

Reconstruction of the breast can be performed using an implant or autologous tissue, or a combination of both. In 1961, the first silicone implant was launched by Cronin and Gerow and, in 1963, the first implant was placed into a patient[90]. Becker further developed the tissue expander which came into frequent use in the 1990s. Since then, five generations of implants have been developed. The advances primarily include improvement of materials, design and contour.

The choice of a reconstructive method is a multifactorial issue with many aspects to take into consideration, e.g. oncological safety, primary or delayed reconstruction, autologous tissue or implant, and the patient's condition and preferences. The local expertise and competence in reconstructive surgery influences the choice of method. Breast reconstructions were initially made mainly by plastic surgeons as a delayed procedure. However, the number of IBRs has increased in recent years, and so has the number of breast surgeons performing the procedure.

Any woman planned for mastectomy may be a candidate for IBR. Absolute contraindications are inflammatory cancer, growth in skin or thoracic wall, and relative contraindications are distant metastases, patients who are active smokers and/or obese, and those with co-morbidities and unrealistic expectations. Although the number of performed IBRs has increased in recent years, the proportion of breast cancer patients undergoing the procedure in Sweden is only 6%[19].

Axillary surgery

Axillary surgery is indicated in all patients with invasive breast cancer, and axillary lymph node status is an important prognostic factor for breast cancer recurrence and death[91, 92]. Axillary surgery is primarily a staging procedure to determine prognosis and decide upon the appropriate adjuvant thera-

py[9]. However, it also protects against axillary recurrence and for some patients, it has a survival benefit[93-95]. The fewer the nodes that are removed the greater the likelihood of leaving involved nodes in the axillae, followed by a higher risk of axillary recurrence[95]. However, the more axillary lymph nodes removed, the greater risk of arm morbidity[96]. The removal of ten lymph nodes has been suggested as reasonable compromise[42]. Earlier detection of breast cancer by the introduction of mammography screening has resulted in an increasing number of patients with smaller tumors and node negative disease[69, 70]. For patients without axillary metastases, axillary lymph node dissection (ALND) is of no value. ALND was the standard surgical procedure well into the 1990s, when it was replaced by the sentinel lymph node biopsy (SLNB), for those patients being clinically node-negative[97].

Sentinel lymph node biopsy

The sentinel node is the first lymph node or group of lymph nodes draining a cancer. The term "sentinel node" was first used in 1951 by Gould *et al*, who, during a parotidectomy for a parotid cancer, noticed a normal looking lymph node at the junction of the anterior and posterior facial vein. The node was excised and sent for frozen section pathology and, surprisingly, was found to be a metastatic lymph node[98]. In 1977, Cabanas used the term sentinel node to describe a group of lymph nodes most likely to be the primary site for metastases in penile carcinoma. He suggested that these lymph nodes could be removed by limited surgery and examined to determine whether further lymph node dissection should be performed[99]. The injection of blue dye into the breast tissue was performed by Turner-Warwick to demonstrate the lymphatic drainage of the breast in the late 1950s[100]. In 1993, the SLNB technique was described in breast cancer patients using Tc99m-sulphur colloid and gamma detector[101]. The following year, the first study in breast cancer patients using the blue dye method was published[102]. Shortly thereafter a study using a combination of blue dye and isotope was published, which demonstrated improved detection rate[103]. In Sweden, the SLNB was introduced through nationwide studies before it become a clinical routine[97, 104].

The sentinel node is identified by injecting a radioactive isotope intradermally, close to the tumour prior to the operation. Blue dye is injected in the same area when the patient is on the operating table. The blue dye and the isotope follow the lymphatic drainage of the area in the same way metastatic tumor cells are drained. A gamma probe is used to locate the sentinel node in the axillae and the dissection can start 5-10 minutes after the injection of the dye. The isotope and the blue dye help the surgeon to identify the affected lymph node or nodes by following a blue lymphatic tract and listening to the gamma-probe. The resected lymph node or nodes can be sent for immediate histopathological analysis. If metastases are found, complementary ALND is performed.

The major advantage of SLNB is that in the case of absence of sentinel node metastases, the rest of the axillae is left intact; which decreases the risk of postoperative arm morbidity. In a meta-analysis, the incidence of arm lymphoedema was about four times higher in women after ALND than it was in those who had SLNB[96]. Despite the less invasive nature of SLNB, studies have indicated that there is still a risk of arm morbidity such as limitation in movement of the shoulder, arm lymphoedema and paraesthesia[105-108]. Another possible advantage is a more accurate staging, as the dye and isotope identifies the lymph node or nodes most likely to contain metastases, a lymph node that might have been left out during ALND. The SLNB has been validated in several studies and has a high sensitivity[97, 104, 109]. Furthermore, overall survival, disease-free survival, and regional control appear to be equivalent between groups[110, 111].

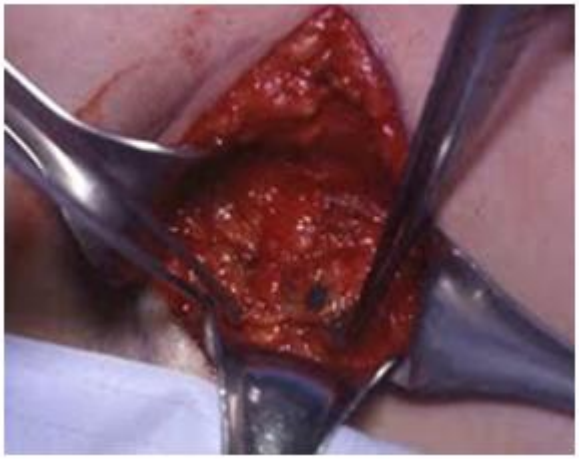


Figure 2. Sentinel lymph node biopsy.
With the kind permission of Jana de Boniface.

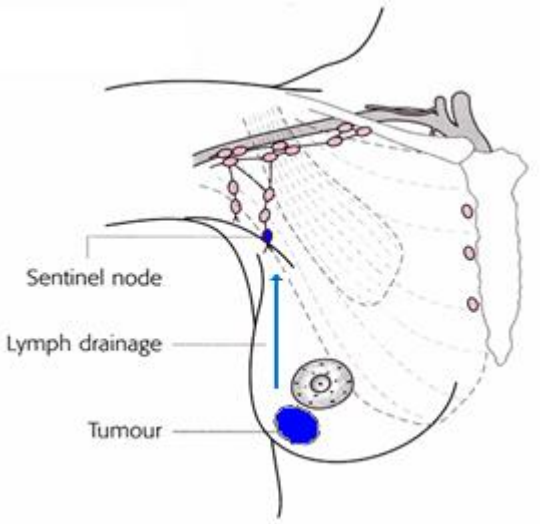


Figure 3. The sentinel lymph node.

The need for SLNB in patients with a preoperative diagnosis of DCIS is debated. There have been reports that question the need for SLNB in patients with pure DCIS due to the very low rate of axillary metastases[112-114]. However, in a meta-analysis, the overall estimate for the incidence of sentinel lymph node SLN metastases in patients with a preoperative diagnosis of DCIS was 7.4% [115]. In clinical practice, SLNB is considered in patients with high risk DCIS (grade III, with palpable mass or large size on imaging), as well as in patients undergoing mastectomy after a prior breast-conserving surgery for DCIS.

Radiotherapy

Already in the latter part of the 19th century, radiotherapy was given to breast cancer patients. Initially it was given mainly as palliation for advanced breast cancer cases, but from 1930 onwards radiotherapy was given as a complement after radical surgery[42]. Postoperative radiotherapy is given in order to eradicate microscopic residual tumours and, to reduce loco-regional recurrence and, potentially, improve overall survival. According to Swedish and International guidelines, radiotherapy to the breast or chest wall is recommended for those patients treated with breast-conserving surgery or after mastectomy for tumours >5cm, i.e. when the risk of local recurrence is >20% within the next 10 years[9]. A meta-analysis reported that after breast-conserving surgery, radiotherapy to the breast reduces the risk of recurrence by 50% and reduces breast cancer mortality by about a sixth [116].

There is no world-wide consensus on the radiation dose and fractions that are used after breast cancer surgery, and in Sweden there have been different regimes in different regions. Today, after breast-conserving surgery, the national guidelines recommend radiotherapy delivered as two opposed tangential fields in 25 fractions of 2 gray (Gy) up to a total dose of 50 Gy. An additional booster dose of 16 Gy is given to patients ≤ 40 years of age at diagnosis [9]. Women with ≥4 axillary lymph node metastases receive radiotherapy both to loco-regional lymph nodes and to the chest wall after mastectomy. For breast tumours < 5cm, in patients with 1-3 lymph node metastases, the benefits of loco-regional therapy of the axillae and supraclavicular area is uncertain[9]. According to present national guidelines radiotherapy should be considered in patients with 1-3 lymph node metastases,

in presence of lymphovascular invasion, age ≤ 40 and histological grade III. Radiotherapy should also be considered if >20% of the examined lymph nodes have metastases.

Four randomised clinical trials have shown that postoperative radiotherapy after breast-conserving surgery for DCIS significantly reduces the risk of a ipsilateral DCIS or invasive recurrence by almost 50%[36, 117-119]. An overview from 2010 reported that radiotherapy reduced the absolute 10-year risk of any ipsilateral breast event by 15%[120]. Older (>50 years) patients received greater benefit from radiotherapy than younger ones.

Early side effects from radiotherapy includes erythema, fatigue, nausea and pneumonitis[42, 121]. Years after radiotherapy, side effects such as arm lymphoedema, skin atrophy, pain, fibrosis of the lung, and ischemic heart disease can occur[42, 79, 122, 123]. Brachial plexus neuropathy with paralysis is a severe but uncommon side effect with the radiation dose and fractions that are used today[124].

Systemic therapy

Adjuvant systemic therapy is given to eliminate micro metastases remaining in any part of the body and includes endocrine therapy, chemotherapy and anti-HER2 therapy.

Endocrine therapy

The main source of oestrogen are the ovaries in premenopausal women, while in postmenopausal women most of the body's oestrogen is synthesised from adrenal and ovarian androgens in the muscles, adipose tissue and liver. Approximately 70-80% of all breast cancer tumours are ER-positive[42]. The effects of oestrogen on the tumour can be inhibited either by blocking the ER with tamoxifen, by binding, blocking and increasing the degradation of the ER by fulvestran, or by preventing the synthesis of oestrogen by aromatase inhibitors. Tamoxifen can be used for all ER- and/or PR-positive breast cancer regardless of menopausal status. In a meta-analysis, ER- positive breast cancer patients treated with tamoxifen for about five years, experienced a reduction in breast cancer mortality of about a third throughout the first 15 years[54]. Prolonged treatment with tamoxifen for total of 10 years has been reported to further reduce breast cancer death [125]. The most common side effects caused by tamoxifen are hot flushes, vaginal dryness, discharge, or irritation and decreased interest in sex[126, 127]. Other side effects that are rare but more severe include endometrial cancer and thromboembolic events[42, 127].

The effect of aromatase inhibitors is restricted to postmenopausal women as they work by inhibiting the action of the enzyme aromatase, which converts androgens into oestrogens in peripheral tissue and have no effect on the ovarian oestrogen production. Studies have shown a significantly reduced recurrence rate and mortality when comparing aromatase inhibitors with tamoxifen in postmenopausal women with hormone-sensitive breast cancer[128-130]. A recent meta-analysis, however, revealed no significant decrease in mortality, yet an absolute reduced recurrence rate of 2.9% when comparing five years of treatment with tamoxifen *versus* aromatase inhibitors[131]. Side effects for aromatase inhibitors include osteoporosis, fractures, arthralgia and hypercholesterolemia[127, 132].

In a randomised study, women treated with breast-conserving surgery and radiotherapy, tamoxifen reduced the likelihood of an ipsilateral breast cancer recurrence five years after surgery from 9 to 6%[133]. Today, tamoxifen is not routinely given to patients with DCIS.

Chemotherapy

Adjuvant chemotherapy was introduced in clinical trials in the 1950s and the first study reporting a significantly improved survival was published in 1968[82]. Bonadonna initiated the first randomised clinical trial comparing polychemotherapy versus no chemotherapy

in node-positive breast cancer patients and reported a decrease in recurrence rate[134]. Overall survival was also increased at 20-year follow-up[135]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was established in the early 1980s and the aim was to coordinate meta-analyses of all randomised trials of adjuvant breast cancer treatment. The first meta-analysis was presented in 1988 and the latest in 2012, which reported that the 10-year risk of death from breast cancer can be reduced by a third for women treated with modern regimes with the addition of taxanes to athracyclines compared with women treated with no chemotherapy[136]. These results were independent of age, nodal status, tumour size, histological grade, ER status and Tamoxifen use. These meta-analyses have provided the basis for modern chemotherapy and current guidelines recommend chemotherapy to patients with axillary lymph node metastases. Node-negative patients with unfavourable tumour characteristics such as large tumour size >1cm, high proliferation rate, ER-negative tumours, HER2 positivity and young age may also be recommended chemotherapy[9]. Chemotherapy for breast cancer has – like most chemotherapy regimens – a number of side effects. It is important to even further tailor the adjuvant chemotherapy so only women who benefit from the therapy receive it, as it has been shown to have several side-effects and symptoms that negatively affect quality of life[137, 138]. There is no role for che*m*otherapy in DCIS treatment [51].

Monoclonal antibodies

Trastuzumab is a monoclonal antibody directed against the tyrosine kinase receptor HER2. Over-expression of HER2 occurs in approximately 15% of breast cancers patients[57] and is strongly associated with an increased risk of recurrence and a poorer prognosis[56, 58]. Adjuvant treatment with trastazumab reduces mortality by 30% and recurrences by 50%[139-141]. The most clinically significant side effect of trastuzumab is the risk of cardiac myocyte injury, leading to the development of congestive heart failure[56].

The lymphatic system and lymphoedema

The lymphatic system

Olof Rudbeck, a Swedish scientist published his theses *De Cirkulatione Sanguinis* in 1652 and became the first to describe the function of the lymphatic system[142]. The initial lymph vessels start blindly, are valveless, branch abundantly and are anastomose free. They consist of a single endothelial layer and communicate with larger vessels, the precollectors, which in addition also contain an accessory membrane, a few smooth muscle cells and valves. Next, the lymph collectors consist of three layers (intimae, media and adventitia) corresponding with the layers in veins and arteries. They also contain valves. The smooth muscle cells in the collectors, together with valves, direct the lymph towards the heart[143]. There are superficial, deep and visceral collectors. The later supply the inner organs, the superficial collectors merely follow the superficial veins and the deep lymphatic vessels are located beneath the muscle fascia and follow the main blood vessels. The superficial and deep lymphatic systems are considered to be anatomically separated from one another. Connections between them have, however, been demonstrated especially under pathological conditions[144]. There are also lymphovenous communications, some of which function constantly whereas others do so only under pathological conditions[145]. These connections could enable the transit of circulating tumor cells from one system to another[146].

On the way from the periphery to the central veins, the lymph passes at least one lymph node. The presence of lymph nodes is the major difference between the blood and the lymphatic vessel[143]. The most frequent metastatic location for breast cancer is in the axillary lymph nodes. There are three levels

of axillary lymph nodes in the axillae. Level I is the bottom level, below the lower edge of the pectoralis minor muscle. Level II lies underneath the pectoralis minor muscle and Level III is between the pectoralis minor muscle and the lower border of the clavicle. The sentinel lymph node is usually found in level I[42]. The ipsilateral axillary lymph nodes receive more than 75% of the lymphatic drainage from the breast with the lymph nodes below the pectoralis minor muscle receiving it first. The internal mammary chain represents another important pathway for the lymph drainage from the breast. There are reports that the incidence of a positive sentinel lymph node in the internal mammary chain in up to 32% of cases, although solitary metastases here are very rare[109, 147].

Arm lymphoedema

Lymphoedema is divided into primary and secondary lymphoedema. Primary lymphoedema is caused by a disease or malformation in the lymphatic vessels, whereas a secondary lymphoedema is a result of disease or trauma in another organ[143]. Unlike oedema caused by heart failure, lymphoedema is rich in proteins, which in the long-term has a negative effect on the tissue by stimulating the growth of fibrocytes[143]. Arm lymphoedema is defined as a chronic swelling of the upper limb caused by an impairment of lymph drainage. It is a well-recognised long-term complication related to breast and axillary surgery, radiotherapy and nodal status. Other factors such as recurrent infections may increase the incidence. It can also cause recurrent erysipelas, which increases the swelling even more[148, 149].

Arm lymphoedema in breast cancer patients was first described as a side effect of radical mastectomy by Halsted in 1921[150]. The destruction of lymphatic vessels, removal of lymph nodes and tissue scarring results in an incapacity for the remaining lymph vessels to remove the lymph. The vessels become dilated, overloaded and their valves incompetent. This spreads distally until the most peripheral lymph vessels become dilated, resulting in the accumulation of interstitial fluid, usually in the subcutaneous tissue[151]. At this stage the lymphoedema is soft and pitting oedema can be seen. In a parallel process, the mononuclear phagocyte system begins to lose its capacity to remove the proteins that accumulate. These proteins are osmotically active and attract even more fluid to the area. In time, there will be an increase in the adipose tissue, due to an effect of the decrease in lymph circulation[152-154]. The mechanism for this is not yet fully understood. It is the increase in adipose tissue that subsequently causes subcutaneous lymphoedema to become firm and denser[155]. Later, the activation of fibrocytes increases the component of connective tissue in chronic lymph oedema[143].
Due to increased breast cancer incidence and reduced mortality, more women will face the risk of developing lymphoedema. Arm lymphoedema can be severe and causes considerable psychological morbidity, pain, disability and impairs the activities of daily living[137, 156-159].

The reported incidence of arm lymphoedema after breast cancer surgery varies widely, from 6 to 49%, and can occur weeks to years after surgery [107, 159-164]. The true incidence is difficult to assess because of the varying criteria used to define lymphoedema, differences in measuring the oedema and different follow-up times across studies. ALND has previously been standard for staging the axillae in women with invasive breast cancer. However, it is associated with a number of side effects including lymphoedema, pain, numbness and limited shoulder movements[156, 157, 161, 165]. Despite the less invasive nature of SLNB, studies have indicated that there is still a risk for arm morbidity such as limitation in movement of the shoulder, arm lymphoedema and paraesthesia[105-108, 166].

Measurements

Mainly for therapeutic reasons there have been attempts to classify arm lymphoedema. Several techniques, classified as internal and external, have been used to measure the difference in the involved arm compared with the non-operated side after breast cancer surgery.

The internal techniques are expensive, highly technology-based and include computed tomography, magnetic resonance imaging, ultrasound with and without Doppler flow, bioimpedance spectroscopy and lymphoscintigraphic investigations[167, 168].

The external techniques involve clinical signs, measuring arm circumference or arm-volume by using water displacement volumetry, or they can be based on functional disabilities or self-perceived symptoms[169, 170]. Water displacement volumetry offers a reliable and objective method and is considered the gold standard for measuring arm lymphoedema[167, 169, 170]. The definition used by Stillwell is based on the volume of the oedema in relation to the contralateral limb expressed as a percentage: insignificant (<10% difference), slight (10-20%), moderate (20-40%), marked (40-80%) and severe (>80%)[171]. The lymphoedema can also be classified into clinical signs as proposed by the International Society of Lymphology; grade I is characterised by pits left after pressure and is largely reduced or completely restored after arm elevation. Grade II is characterised by fibrosis and does not respond to either pressure or arm elevation[172].

Treatment

In the initial phase of the lymphoedema there is only lymph in the oedema and it is reversible and more easily treated. The International Society of Lymphology and the Swedish guidelines recommend non-surgical treatment to prevent worsening of the lymphoedema and prevent increase in adipose tissue[172, 173]. Ideally, patients should be evaluated by a multidisciplinary rehabilitation team and be offered conservative treatment including information, skin treatment, standard elastic comprehension garments, exercise and a specific form of massage known as manual lymphatic drainage. This massage is thought to mobilise oedema fluid from the distal to proximal areas and from areas of stasis to healthy lymphatics. For patients with large lymphoedema, an intense period of treatment for 2-3 weeks is needed. Compression therapy may also be provided with the use of compression pumps. For patients who are not sufficiently responsive to nonsurgical treatment reconstructive microsurgery with lymphaticovenous anastomosis may be a therapy to consider[174-176]. However, it is only performed in some centres and the evidence is low.

The above therapies work when the excess swelling consists of accumulated lymph but do not work when the excess volume is dominated by adipose tissue [177]. Chronic non-pitting oedema can be removed by the use of liposuction. There are results that this can be done without further reduction in lymph transportation and that it has good long-term results[177-179]. However, the use of a compression garment after liposuction is necessary to maintain the normalised arm volume[179].

Patient-reported outcome measures

HRQOL, the term for quality of life used in research and clinical practice, is limited to the quality of life related to a disease, and its symptoms and treatment[180]. Half a century ago, the WHO introduced this multidimensional health concept by defining health as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity"[181]. Although there is no generally accepted definition of HRQOL, most definitions agree that HRQOL is a multidimensional concept including at least four dimensions: physical function, emotional function, cognitive and social function, as well as symptoms and problems related to the disease. It should preferably be estimated by the individual himself and is variable over time[180]. Several models of HRQOL have been presented, of which the model presented by Wilson and Cleary in 1995 is the most frequently used in published HRQOL studies[182, 183]. This model integrates biological and psychosocial aspects of health outcomes by linking measures of HRQOL to traditional clinical variables. Five core domains are depicted in the scheme, including biological and physiological factors, symptom status, functional status, general health, perceptions, and overall quality of life[182]. As stated above, HRQOL is a subjective experience and should preferably be reported by the patient. Studies have shown that there is poor correlation between patients' and health professionals' evaluation of patients' problems [184], as well as the experts versus the patients opinion on for example the outcome of a reconstructive breast reconstruction[185, 186]. The U.S. Food and Drug Administration recently coined the umbrella term patient-reported outcome (PRO),which further emphasises the subjective nature of HRQOL[187]. A PRO is any report coming directly from patients, without interpretation by physicians or others about how they function or feel in relation to their health condition, disease or its therapy. Thus, PRO is a broader term than HRQOL, encompassing the effects of treatment, symptoms, side effects, perception of treatment and satisfaction with care[187].

There is a wide variety of different HRQOL questionnaires available. These can schematically be categorised into generic, disease-specific, and aspects or domain-specific. Generic HRQOL questionnaires are intended for use across a wide range of populations, allowing for the comparison of data across studies and against the general population. The most widely used is the Medical Outcomes Study-36 item short form (SF-36). Disease-specific HRQOL-questionnaires cover issues that are relevant to certain groups of diseases, *e.g.* the Functional Assessment of Cancer Therapy-General (FACT-G) and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), which is intended for cancer patients. These questionnaires can be complemented with modules for a specific cancer site and treatment aspects *e.g.* the EORTC-BR23, intended to assess breast cancer specific topics.

Aspect- or domain-specific questionnaires address one specific domain of HRQOL in greater detail and include the Hospital Anxiety and Depression Scale (HADS), the Body Image Scale (BIS), and the McGill Pain Questionnaire.

Breast cancer and HRQOL

Among the HRQOL studies in cancer patients, breast cancer has received most attention for several reasons. Firstly, the number of women with breast cancer is increasing. Secondly, the early detection and treatment of breast cancer has improved and survivors now live longer; thus studying HRQOL in this context is important. Thirdly, breast cancer affects women's identities and therefore studying the HRQOL is vital.

There is a significant body of literature regarding HRQOL in breast cancer patients.

In summary, these studies report that the diagnosis and treatment, in particular chemotherapy and endocrine treatment, have a negative effect on patients' HRQOL[188-191]. The psychosocial impact of the type of primary surgery for breast cancer occurs largely in areas of body image and feelings of attractiveness, with women receiving breast conserving surgery experiencing the most positive outcome [85, 192, 193]. Beyond the first years after diagnosis, a woman's quality of life is more likely influenced by her age or exposure to adjuvant therapy than by her breast cancer surgery.

With this stated, the majority of "long-term survivors" after breast cancer report a good overall HRQOL, despite the fact that many patients have some specific problems such as arm morbidity and sexual problems[138, 194-198]. Comorbidity, lack of social support, financial problems, and previously having had adjuvant chemotherapy all appears to have negative impact on HRQOL[138, 198, 199].

AIMS OF THE THESIS

The main aim of this thesis was to extend the knowledge on health-related quality of life and lymphoedema after breast cancer surgery and to evaluate the risk of future invasive disease following an *in situ* breast cancer diagnosis.

The specific aims were:

1. To investigate and compare long-term health-related quality of life, body image, and emotional reactions in women with ductal carcinoma *in situ* breast cancer treated with different surgical methods.

2. To evaluate long-term risk of subsequent breast cancer and mortality in women diagnosed with *in situ* breast cancer.

3. To evaluate the impact of family history on long-term risk of subsequent breast cancer and mortality among women diagnosed with *in situ* breast cancer.

4. To compare arm lymphoedema after sentinel lymph node biopsy alone versus axillary lymph node dissection, both in node-negative and node-positive breast cancer patients.

5. To examine the potential association between self-perceived symptoms of arm lymphoedema and objectively measured arm lymphoedema.

6. To compare long-term health-related quality of life in patients undergoing sentinel lymph node biopsy alone versus axillary lymph node dissection, with or without axillary metastases.

7. To assess the impact of objective arm lymphoedema and self-perceived symptoms of arm lymphoedema on health-related quality of life in patients with invasive breast cancer.

"Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve".

Karl Popper

SUBJECTS AND METHODS

Data Sources

The Regional Breast Cancer Register Stockholm- Gotland (Paper I)

Since 1976, all new primary breast cancers in the Stockholm-Gotland Health Care Region have been reported to a central regional breast cancer registry[200]. The register holds information on the individually unique national registration number, International Classification of Disease (ICD)-code, date of diagnosis, receptor status, surgery, adjuvant treatment as well as data on locoregional and distant recurrences.

The Plastic Surgery Register (Paper I)

The register was initiated in 1990 to report on all immediate breast reconstructions performed at the Department of Reconstructive and Plastic Surgery at Karolinska University Hospital. The register holds information on the individually unique national registration number, diagnosis, date of surgery and surgery performed.

The Swedish National DCIS study (Paper I)

The Swedish National DCIS study was a multicentre study that assessed the effect of postoperative radiotherapy after breast conserving surgery[36]. A total of 1046 women with screening-detected DCIS were randomised to postoperative radiotherapy or not between 1987 and 1999. The primary endpoint was ipsilateral local recurrence.

Multi-Generation Register (Paper II)

The Multi-Generation Register (MGR) includes all Swedish residents born after 1931, who were alive in 1960, and all those born thereafter[201]. The Register was initiated in 1961 from written records in church parishes and country registration offices. It contains links between children and parents through their individually unique national registration numbers. From 1961 to 2001 the completeness of the MGR improved substantially and since 1991 it has been considered to be almost complete.

Swedish Cancer Register (Paper II)

The Swedish Cancer Register was established in 1958. It is a nationwide, population-based register that contains information on virtually all diagnosed cancers in Sweden since 1958[202]. Reporting new cancer diagnoses is mandatory for all clinicians and pathologists. The register is considered complete for invasive cancer[203-205] and almost complete with regard to *in situ* breast cancer from 1980 onwards[204]. All cancer diagnoses are registered according to ICD-code.

The Swedish Causes of Death Register (Paper II)

The nation-wide Swedish Causes of Death Register was established in 1952. It provides information on date and cause of death, as well as the underlying and contributory causes of death of all deceased Swedish residents. The completeness of the register is estimated to exceed 99%[206].

The Total Population Register (Paper II)

The Total Population Register records the vital life events of the inhabitants of Sweden[207]. The data is administered by the Swedish Tax Agency. The register spans several centuries of data and provides information on each citizen's personal identity number, sex, births, marital status, address, country of birth, immigration, emigration, and date of death.

Study Population

Paper I

All women who took part in the Swedish National DCIS study[36] between 1991 and 1999 in the County of Stockholm were eligible. Furthermore, all women with DCIS who underwent mastectomy and immediate breast reconstruction at Karolinska University Hospital, Stockholm, during the same period, were asked to participate in the present study. Only women with DCIS proven by final histopathology, a total of 162 women, were included in the study. Exclusion criteria were: Paget's disease of the nipple, invasive breast cancer, lobular carcinoma *in situ*, ongoing tamoxifen treatment, and a history of present or previous malignancy (except basalioma and cervical cancer). Furthermore, women with dementia, severe brain damage, and without sufficient knowledge of the Swedish language were excluded, as were those with an invasive recurrence after primary DCIS surgery. Prior to inclusion, all data were controlled against the Regional Breast Cancer Register to validate the DCIS diagnosis.

Paper II

Data from the Multi-Generation Register (including more than 11 million individuals, from around three million families) were combined with the Swedish Cancer Register, the Cause of Death Register, and the Total Population Register. Family history of breast cancer was defined as having at least one first-degree relative diagnosed with invasive breast cancer at any point in time. Our final study population consisted of 8111 women in the Swedish Multi-Generation Register diagnosed with primary diagnosis of *in situ* breast cancer between January 1st 1980 and January 1st 2005.

Papers III and IV

The study cohort consisted of 557 women with invasive breast cancer undergoing breast cancer surgery in four centres in Sweden between 1999 and 2004. Difficulty in understanding the Swedish language, bilateral breast cancer, clinically fixed axillary metastases, neoadjuvant treatment and previous surgery or radiation therapy to either axillae were exclusion criteria.

Methods

Treatment (Studies I, III and IV)

Patients were treated according to the prevailing national and regional guidelines; breast-conserving surgery was performed as a sector resection as previously defined[208]. For women who had mastectomy and immediate breast reconstruction, the reconstructive method was implant based with an expander prostheses (Paper I). All axillary lymph node dissections (ALND) included level I and II. The sentinel nodes were identified by the combined dye and isotope mapping-technique[102]. Experienced breast surgeons or trainees under supervision performed the operations.

Radiotherapy was administered with tangential fields with 2 Gy daily 25 times up to 50 Gy to the breast after breast-conserving surgery and to the chest wall after mastectomy for tumours over 5 cm. Postoperative adjuvant chemotherapy and/or endocrine treat-

ment was recommended according to the Swedish guidelines depending on the patient's age, hormone receptor status, lymph node status, Elston grade, HER2 status and comorbidity[9].

Arm volume (Papers III and IV)

Arm volume was measured using the water displacement technique[170, 209], which is considered a reliable and valid tool for estimating arm volume after breast cancer surgery[210]. A nurse, trained in the procedure, measured both arms repeatedly and the difference in ml between the arms was recorded. This difference defined the increase in arm volume and was followed over time and compared between study groups.

Figure 4. Arm volume measurement.
With the kind permission of Håkan Brorson and the patient.

Questionnaires

The Hospital Anxiety and Depression (HAD) scale (Paper I)

The HAD scale consists of 14 items, seven assessing anxiety and seven depression[211]. The possible sum score of each scale ranges from 0 to 21, with each item scored from 0 to 3 points. High summated scores represent high levels of problems. Cut-off points for each of the scales are: < 8 (within normal range), 8-10 (possible clinical case), and ≥11 (clinical case). The HAD scale is considered a reliable and valid instrument for the assessment of anxiety and depression in somatic, psychiatric, and primary care patients, as well as in the general population[212]. The Swedish version has been validated in breast cancer patients against diary recordings[213].

The Body Image Scale (BIS) (Paper I)

The BIS was designed for the assessment of body image in cancer patients[214]. It consists of 10 items concerning the impact of surgery on self-consciousness, physical and sexual attractiveness, femininity, satisfaction with body and scars, body integrity, and avoidance behaviour. The BIS items are scored from 0 (not at all) to 3 (very much). A high score represents problems with body image. The BIS scale has a high reliability and good clinical validity[214]. No formal validation or reliability testing of the Swedish version has been performed. The translation into Swedish was performed by a group of five professionals (three nurses, one sociologist, and one psychologist) at the Department of Oncology, Karolinska University Hospital.

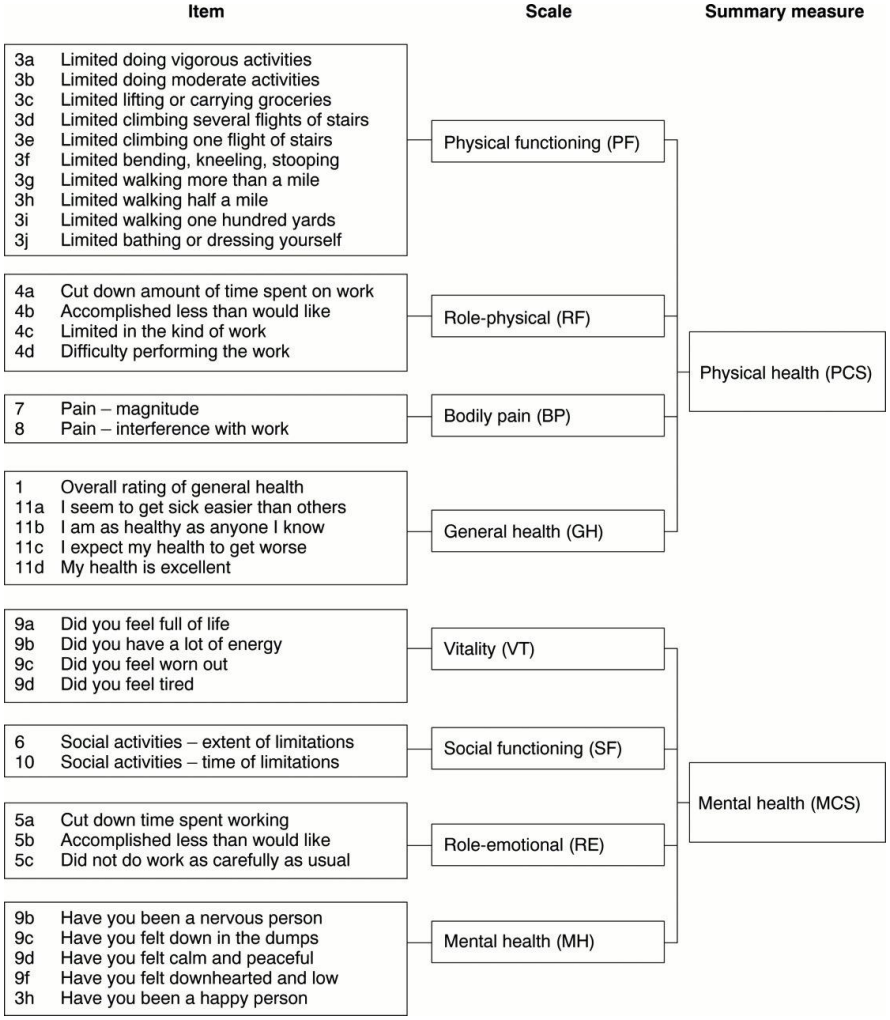


Figure 5. The measurement model of SF-36 questionnaire. ***Adapted from Ware et al. 1992.***

The Swedish SF-36 Health Survey (Papers I and IV)

The Swedish SF-36 Health Survey (SF-36) is used to asses health-related quality of life (HRQOL). It is a standardised questionnaire that has been widely used in international studies. The Swedish version has been validated, and normative data for Swedish women are available[215, 216]. The SF-36 consists of 36 items constituting eight domains: physical functioning (PF), role limitations as a result of physical problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitation due to emotional problems (RE), and mental health (MH). The first three domains (PF, RF, and BP) measure physical well-being and the last three (SF, RE, and MH) relate to emotional well-being. A high score on the subscales signifies a higher level of function and HRQOL.

Self-perceived symptoms of lymphoedema (Paper III and IV)

At the time of the start of the study there was no existing validated instrument for assessment of symptoms after axillary surgery. Therefore, a questionnaire was designed by a group of breast surgeons, a physiotherapist specialized in arm lymphoedema treatment, a psychologist, and an anaesthetist specialising in pain management. The final questionnaire format was determined after using a pilot questionnaire in consultation with breast cancer patients. The questionnaire consists of eight questions: four regarding early signs of

lymphatic insufficiency (does your operated arm feel heavy, tired, sore or tense ?) and four regarding arm lymphoedema (are your fingers, hand, arm or axillae/breast/chest wall swollen?). The items scores were, 0 (never), 1 (sometimes) and 2 (always).

Statistical Analysis

Paper I

The scores derived from the SF-36 questionnaire were linearly transformed into a 0-100 scale according to the SF-36 manual[216]. The results were compared with normative data from an age-matched reference group consisting of 920 women from the general Swedish population. The mean HAD subscale values were compared between groups, as well as proportions of patients in each clinical stage, as suggested by the original authors[211]. Student's t-test was used to evaluate differences between the study sample and normative data (SF-36). ANOVA repeated measurement was used to evaluate differences between the three study groups on HAD subscales and SF-36 subscales. Chi-2 test was used for categorical data (HAD and BIS). Differences between groups were considered statistically significant when $p < 0.01$. Statistical analyses were done using StatView version 4.5 (SAS Institute, Cary, NC, USA).

Paper II

The standardised incidence ratios (SIRs), i.e., the ratio of the observed to the expected number of breast cancers (ipsi-or contralateral invasive or contralateral *in situ* breast cancer), standardised by age and calendar period, were used as a measure of relative risk, and were stratified by family history of breast cancer. All women were followed from the date of their first *in situ* breast cancer diagnosis until a subsequent breast cancer event, emigration, death, or end of follow-up, whichever came first. The expected number of subsequent breast cancer events was calculated as the product of the person-years accumulated by women with *in situ* breast cancer by the age and calendar period-specific incidence of unilateral *in situ*/invasive breast cancer of the general population in the Swedish Multi-Generation Register.

Excess additive risks (EARs), i.e. the difference between the observed number of subsequent invasive breast cancers and the expected number in the general population in the Swedish Multi-Generation register, were used as a measure of absolute risk for subsequent invasive cancer.

The standardised mortality ratio (SMR), i.e. the ratio of the observed to the expected number of deaths, standardised by age and calendar period, was used as a measure of relative mortality. The expected number of deaths was calculated from the general population in the Swedish Multi-Generation register. For overall SMRs, subjects were followed from the date of the first *in situ* breast cancer diagnosis until date of emigration, death, or end of follow-up, whichever came first. All data preparation and analysis were done using the SAS statistical package, version 8.2 or higher (SAS Institute Inc., Cary, NC, USA).

Paper III

A mixed model with first order autoregressive correlation structure was used to compare the mean arm-volume difference between the three study groups over time. In the unadjusted model, the study group, years after surgery and their interaction term were included. In the adjusted model, body mass index (BMI) at surgery, age at surgery, preoperative difference in arm volume, surgery on the dominant side, body mass index change from the preoperative value, and radiotherapy to breast and lymph nodes were included. A mixed model was also used to evaluate arm-volume differences with self-perceived symptoms of lymphoedema.

Logistic regression for repeated measurements by generalized estimating equations (GEE), with an exchangeable correlation structure was used to analyze differences in self-perceived symptoms of lymphoedema between groups, years after surgery and their interaction. In the adjusted model, age at surgery, BMI at surgery, and BMI change from the pre-operative value were also included. The same type of GEE model and analysis strategy was applied for self-perceived early signs of lymphatic insufficiency.

The unpaired t-test was used to compare continuous patient characteristics or, when appropriate, the Mann-Whitney U-test. A chi-2 test, or when appropriate, the Fisher's exact test, was used for categorical variables. A p-value less than 0.05 was regarded as statistically significant. All analyses were done using SPSS version 17 (SPSS Inc., Chicago, IL, USA) except GEE models where STATA release 11 (StataCorp. College Station, TX, USA) was used.

Paper IV

The scores derived from the SF-36 questionnaire were linearly transformed into a 0-100 scale according to the SF-36 manual[216]. Expected mean scale scores were calculated by using age-specific normative data from the Swedish population and the indirect standardisation technique[215]. Linear regression models were used to estimate the effect of surgery on the SF-36 scales at the three-year assessment. In the unadjusted models, surgery was the only variable included, whereas in the adjusted models, age, radiotherapy, chemotherapy, hormonal treatment and baseline (preoperative) SF-36 were included as well as surgery. Reported p-values refer to F-tests.

Lymphoedema was considered evident if the arm-volume difference (AVD) was >10%. Agreement between AVD and self-perceived symptoms of lymphoedema (SPS) was estimated using the kappa statistic. Bootstrap was used to obtain the 99% confidence interval.

The risk of SPS at three-years was modelled by generalised linear models with log link and binomial distribution. Both unadjusted and adjusted (age, BMI, operation on dominant side, radiotherapy to the axillae and preoperative difference in arm volume) effects of surgery (with sentinel lymph node biopsy (SLNB) as the reference category) were estimated, and were presented as risk ratios together with 99% confidence intervals and p-values from Wald tests.

A chi-2 test or, when appropriate Fisher's exact test was used to compare differences between the three study groups in categorical variables. The Kruskal-Wallis test was used to compare differences in continuous variables. A p-value less than 0.05 was regarded as statistically significant. All analyses were done with STATA release 11 (StataCorpCollege Station, TX, USA)

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Study Design	Cohort study	Population-based cohort study	Cohort study	
Data Sources	1.The Plastic Surgery Register ,Karolinska University Hospital 2.The Swedish National DCIS study 3. Stockholm Regional Oncological Cancer Centre Register	1.The Multi-Generation Register 2.The Swedish Cancer Register3.The Swedish Causes of Death Register 4.The Total Population Register		
Study Population	Women in Stockholm County in the Swedish National DCIS study and all women with DCIS who underwent mastectomy and IBR at Karolinska University Hospital *N=162*	All women in the Multi-Generation Register with first *in situ* breast cancer diagnosed *N=8111*	Women operated for invasive breast cancer in four hospitals in Sweden *N=557*	
Inclusion period	1991-1999	1980-2004	1999-2004	
Follow-up	1991 -2007	1980-2004	1999-2007	
Exposure/ Intervention	Breast conserving surgery with or without radiotherapy, or mastectomy and immediate breast reconstruction	*In situ* breast cancer Family history for breast cancer	Axillary surgery with/ without axillary metastases	
Outcome	HRQOL assessed with SF-36, HAD BIS	Second breast cancer (invasive/*in situ*) Mortality	Arm lymphoedema Self-perceived symptoms	HRQOL assessed with SF-36
Main statistical methods	Student's t-test ANOVA, Chi-2 test	SIR, SMR, EAR, life-table method	Linear mixed model Logistic regression by generalised estimating equations (GEE)	Kappa statistics Generalised linear models, Linear regression models

Table 1. Overview of Subjects and Methods.

"Just living is not enough," said the butterfly, "one must have sunshine, freedom and a little flower."

Hans Christian Andersen

RESULTS AND DISCUSSION

Paper I

In total, 162 women were included in the study and 131 (81%) responded to the questionnaires. The number of patients and reasons for attrition are presented in Figure 6. The median age was 58.5 years (range 40-77) for women treated with mastectomy and immediate breast reconstruction (IBR), 65.0 years (range 55-83) for those treated with sector resection alone, and 64.0 years (range 48-89) for women treated with sector resection and postoperative radiotherapy (RT). The mean time from surgery to completion of questionnaires was 7.0 years (SD 2.4) in the mastectomy and IBR group, 9.8 years (SD 2.8) in the sector resection and postoperative RT group and 9.9 years (SD 2.7) in the sector resection alone group.

Health-related quality of life (HRQOL)

Overall, women in all three study groups appeared to have a satisfactory HRQOL in the long term, similar to women in the general population. These findings are consistent with three other studies of long-term HRQOL among women with DCIS[217-219]. Women who underwent mastectomy and IBR scored higher on physical functioning and bodily pain than the other two study groups and also when compared with their age-adjusted norm groups (Table2). These findings, that women who underwent mastectomy and IBR reported better physical functioning and less bodily pain than the other two study groups, and their age-adjusted norm groups, was not expected. It might be explained by a response shift, which is an adaptation process that patients with a disease undergo to accommodate their illness[220]. It is therefore possible that the more extensive surgical procedures and, probably, the more prolonged rehabilitation period that these women experienced resulted in a response shift with respect to bodily pain and physical functioning.

The addition of postoperative radiotherapy to breast-conserving therapy did not appear to have negative impact on HRQOL in the long term.

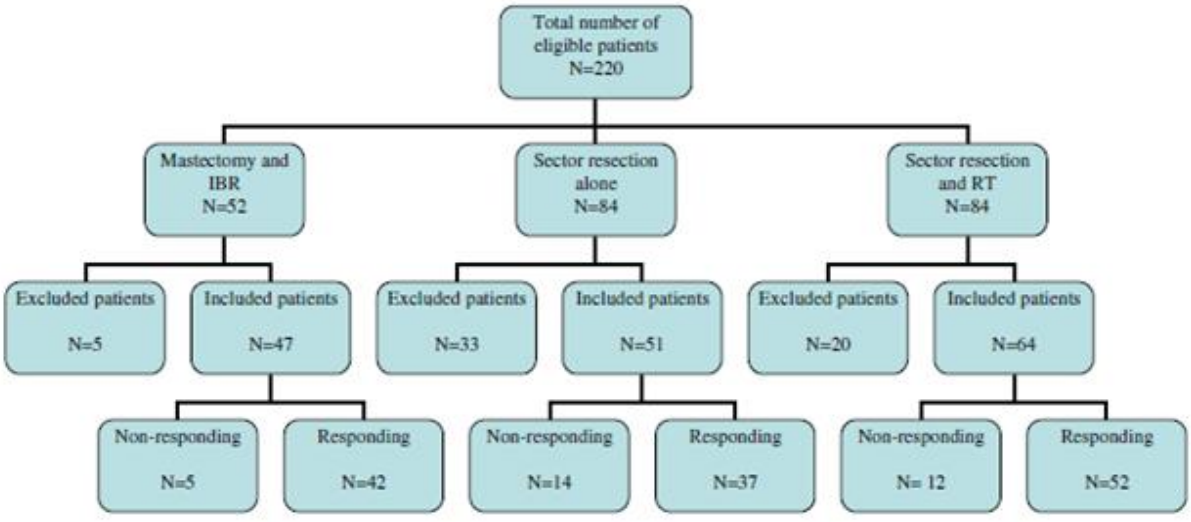


Figure 6. Number of patients and reasons for attrition.

Mean values and standard deviations for the SF-36 subscales for the three study groups and their respective age-adjusted norm values.

Variables	Mastectomy and IBR Mean[a] (SD) Sweden $N = 40–42$		Sector resection alone Mean[a] (SD) $N = 32–36$		Sector resection and radiotherapy Mean[a] (SD) $N = 45–52$		*P*-values for differences between the study samples	*P*-values for differences between mastectomy and IBR and the norm[b]
	Study sample	Norm	Study sample	Norm	Study sample	Norm		
Physical functioning PF	92.4 (10.4)	80.8 (20.8)	73.4 (26.6)	72.1 (24.3)	74.1 (25.5)	72.1 (24.2)	0.002	0.002
Role physical RP	90.2 (23.0)	77.8 (35.0)	75.0 (38.4)	67.2 (40.1)	79.5 (36.0)	65.5 (39.6)	NS	NS
Bodily pain BP	86.5 (19.7)	68.3 (27.4)	70.2 (28.0)	65.9 (28.4)	70.7 (28.1)	65.3 (28.5)	0.006	<0.001
General health GH	72.7 (20.5)	70.6 (23.1)	70.6 (22.4)	65.4 (23.8)	66.0 (22.4)	65.2 (23.6)	NS	NS
Vitality VT	56.4 (16.0)	67.0 (24.0)	63.6 (12.0)	65.6 (25.0)	57.8 (16.0)	63.6 (25.2)	NS	NS
Social functioning SF	86.6 (20.4)	87.0 (21.1)	93.2 (13.0)	85.3 (22.4)	85.2 (21.3)	84.4 (22.4)	NS	NS
Role emotional RE	78.9 (36.3)	83.3 (31.2)	82.9 (32.7)	77.6 (35.9)	83.7 (34.8)	76.9 (35.6)	NS	NS
Mental health MH	73.0 (20.0)	79.5 (20.3)	84.9 (13.3)	78.5 (21.3)	76.0 (18.7)	77.6 (21.3)	0.012	NS

[a] Range 0–100 (high values represent high functioning).
[b] No statistically significant differences were found between the other two study groups and their norm values.

Table 2. Mean values for the SF-36 subscales for the three study groups and their age-adjusted norm values

Anxiety and depression

No statistically significant differences between the study groups were found for the mean scores on the HAD anxiety or depression subscales, nor for the proportions of patients scoring in the clinical category on the subscale. Our results show however, a trend towards increased levels of anxiety in the mastectomy and IBR group compared with the two other study groups. The mean anxiety score was 6.24 (SD 5.00) in the mastectomy and IBR group, and 3.76 (SD 3.25) and 4.41 (4.22) in the sector resection alone group and sector resection and RT group, respectively (p-value=0.02). In addition, women in the mastectomy and IBR group also scored statistically significantly lower than the other two study groups on the mental health subscales of the SF-36, although there were no statistically significant differences with their age-adjusted norm group. It was expected that mastectomy and IBR, a treatment implying a lower risk of recurrence, would result in less anxiety than the two other treatment options. This hypothesis was not supported in this study, nor in an American study showing that the perception of risk of recurrence did not diminish in women with DCIS who underwent mastectomy[221].

A Dutch study found that women with DCIS had comparable perceptions of the risk of recurrence and breast cancer death to women with invasive breast cancer, despite their better prognosis[217]. We speculate that these trends, with increased anxiety and lower mental health, might reflect the more extensive and longer treatment that mastectomy and IBR implies when compared with sector resection alone or followed by RT, and that these women may have become more aware of and affected by their disease.

Body image

Overall, statistically significant differences between the three study groups were found for six of the items (self-consciousness, feeling less physically attractive, feeling less feminine, feeling less sexually attractive, being dissatisfied with body, being dissatisfied with scars) with larger proportions of women in the mastectomy and IBR group reporting problems. To our knowledge, this is the first study comparing different surgical treatments with respect to long-term body image among women with DCIS. Three previous studies on long-term postoperative body image among women with invasive breast cancer reported a

more favourable body image among women treated with breast-conserving surgery than those treated with mastectomy alone[85, 192, 193]. Contradictory results have been found in studies that address whether mastectomy with reconstruction results in a better long-term body image than mastectomy alone[85, 196, 222]. In addition, one long-term follow-up study showed no differences in body image between women treated with sector resection and mastectomy with reconstruction[223]. It is important to consider that sector resection was not an option for most women in the mastectomy and IBR group and that the alternative, mastectomy alone, is not represented in this study. Given that mastectomy and IBR is the surgical option that provides a superior esthetical result, emphasis on preoperative information about expected postoperative changes in body image may have improved these results.

Methodological considerations, strengths and limitations

This study has a number of limitations. No preoperative data on our study variables were collected and, therefore, it was not possible to ascertain differences in the studied variables before surgery. No women treated with mastectomy alone were included and better body image might have been expected with IBR than without. Potential confounders in this study are age, tamoxifen treatment, invasive breast cancer or other malignancies and comorbidity. All patients with tamoxifen treatment or an invasive cancer were excluded, but no adjustment for age was performed in the analysis, which is a limitation. The results on the SF-36 subscales are, however, compared with age-adjusted norm data, which minimises the influence of age on these results.

To our knowledge, there is no previous study evaluating long-term HRQOL and body image in women with DCIS treated with different surgical methods, including mastectomy with IBR and sector resection with or without radiotherapy. The assessments of the exposures were thoroughly reviewed through medical records and the patients filled in the questionnaires in present time, which minimises the risk for information and recall bias. The response rate to the questionnaires was 81%, which is high considering the long period between surgery and follow-up. Standardised questionnaires employed in many previous studies were used. A threat to all studies that include multiple testing is the occurrence of a false positive finding reaching the level of statistical significance, i.e. a type I error. To reduce this risk, differences between groups were considered statistically significant when $p < 0.01$.

Paper II

Over a follow-up period of 71 458 person-years, 825 (10.2%) women developed 886 subsequent breast events (118 contralateral *in situ* and 768 ipsi- or contralateral invasive breast cancers). The average time from first *in situ* breast cancer diagnosis to a second breast event was overall 5.6 years +/- 4.6 years.

Second breast cancers in women diagnosed with *in situ* breast cancer

Among women diagnosed with in situ breast cancer, the cumulative 10- and 20-year risk for a subsequent contra- or ipsilateral invasive cancer was approximately 10 and 18% respectively, while the cumulative 10- and 20-year risk for a subsequent contralateral in situ breast cancer was 1 and 2% respectively (Figure 7).

The risk of a subsequent ipsi- or contralateral invasive breast cancer was increased more than fourfold [SIR 4.55 (95% CI 4.23- 4.88)] among women with *in situ* breast cancer compared with women in the general population. The risk for a contralateral *in situ* breast cancer was increased almost sixteenfold [SIR 15.98 (95% CI, 13.23-19.14)]

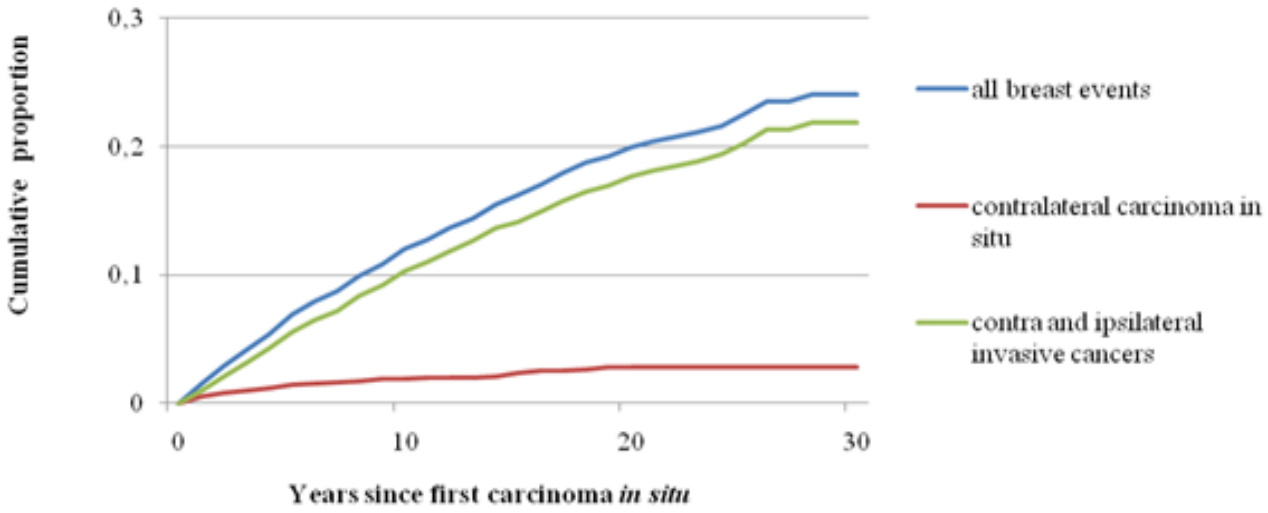


Figure 7. Cumulative incidence of second breast event among women diagnosed with *in situ* breast cancer, stratified by types of subsequent breast events.

Risk stratified by family history

The proportion of subsequent breast events was similar in women with and without a family history (11.3%, n=97 versus 10.0%, n=728). In women with a positive family history, the risk for a contralateral invasive breast cancer was more than four times higher compared with women in the general population, and almost 50% higher compared with women with no family history of breast cancer (Table. 3). This observed increased risk is approximately twice as high as the risk of breast cancer that women with a positive family history without a previous breast cancer face. Two meta-analyses of familiar risks for breast cancer presented the relative risk associated with having a first degree relative of breast cancer to 2.1 and 1.8, respectively[44, 224]. The observed diluted additional risk in women with a family history, i.e. only a 50 % increased risk for a contralateral invasive cancer, was lower than expected. We speculate that women with a positive family history were likely more prone to choose mastectomy, which would reduce the risk for an ipsilateral cancer in these women. Additional stratification into one, two or even three affected first-degree members to better quantify the hereditary component may have allowed a deeper understanding of these results.

The reduced risk may also be a reflection of heterogeneity of the *in situ* breast cancer phenotype. Several studies have shown that the molecular profile of the primary invasive breast cancer can predict the risk of recurrence, metastatic behaviour and survival[225-227]. Much less attention has focused on the subtypes of *in situ* breast cancer. A population-based study from Sweden failed to demonstrate a prognostic value for the surrogate molecular subtyping of DCIS using the St. Gallen criteria[228]. Theoretically, it should be possible to identify an *in situ* expression profile that predicts a high probability of progression to the invasive form of the disease. We do not know however, if any of these subtypes occur to a greater degree in women with familial breast cancer.

	All		No family history		Family history		
	No. of cases	SIR (95 % CI)	No. of cases	SIR (95 % CI)	No. of cases	SIR (95 % CI)	**Incidence Rate Ratio*** (95% CI)
2nd breast cancer[1]	886	5.08 (4.75,5.43)	781	4.95 (4.61,5.31)	105	6.27 (5.13,7.60)	1.17 (0.95,1.44)
2nd contralat[4] *in situ*	118	15.98 (13.23,19.14)	104	15.80 (12.91,19.15)	14	17.44 (9.54,29.26)	1.09 (0.62,1.92)
2nd invasive[2]	768	4.55 (4.23,4.88)	677	4.40 (4.07,4.74)	91	5.62 (4.53,6.91)	1.19 (0.95,1.49)
2nd ipsilat invasive[3]	376	4.26 (3.84,4.72)	334	4.19 (3.75,4.66)	42	4.97 (3.58,6.72)	1.00 (0.72,1.38)
2nd contralat invasive[3]	303	3.42 (3.05, 3.83)	262	3.28 (2.89,3.70)	41	4.82 (3.46,6.54)	1.47 (1.05, 2.05)

[1]background rate of *in situ* breast cancer was divided by 2.[2]includes ipsilateral, contralateral and missing side.
[3]background rate of invasive breast cancer was divided by 2. *Reference group is No Family History. IRR has been adjusted for age and year of first diagnosis of *in situ* and time since first diagnosis.

Table 3. SIR of second breast event after diagnosis of first *in situ* breast cancer and its 95% CI, by type of second breast event and family history.

Risk stratified by age

Regardless of family history, women under forty years of age at diagnosis had a significantly higher risk of subsequent invasive breast cancer compared with women above forty years, SIR 8.54 (95% CI 6.07-11.67) and 4.44 (95% CI 4.12-4.77) respectively (p-value <0.001). These young women would experience an excess absolute risk (EAR) ranging from about eight events per 1000 person-years to as high as 15 events per 1000 person-years depending on family history. This absolute excess risk decreased with older age only for women with a positive family history. In contrast, women with a family history of breast cancer had the highest EAR, with women under 40 years of age carrying the greatest EAR (154.10 per 10000 person-years; 95% CI 77.14-266.30), compared with women older than 40 years at diagnosis (105.72 per 10000 person-years; 95% CI 78.88-136.82). This suggests that both relative and absolute risks are higher with younger age of onset of *in situ* disease in women with a positive family history. Given that a younger woman with both a high risk of a subsequent event as well as a longer life expectancy, which translates to a higher cumulative risk, mastectomy may be considered for this patient population.

Risk stratified by calendar year

Women with *in situ* breast cancer with no family history experienced an increasing risk of subsequent invasive cancer during the study period, SIR 3.09 (95% CI 2.42-3.89) in 1980-1984, versus SIR 5.05 (95% CI 3.88-6.46) in 2000-2004 (p-trend <0.001). In contrast, women with a family history experienced no such increased risk for a subsequent invasive breast cancer over the study period.

The increased relative risk of subsequent invasive breast cancer by almost 60% from 1980-84 to 2000-04, exclusively in women with no family history, may be related to a combination of screening and treatment patterns. During the study period, nationwide mammography screening was introduced, and had achieved complete national coverage by 1997[67]. With increasing mammography screening, and subsequently, a larger number of detected smaller lesions–the majority of which are non-palpable–the use of breast-conserving surgery has become the norm since 1990 onwards[68]. In comparison with mastectomy, breast-conserving surgery poses an increased risk of both local recurrence and new ipsilateral primary cancers[42]. In contrast, women with a positive family history had no increased risk during the study period and we speculate that these women, who had relatives with breast cancer, were more prone to choose mastectomy.

Risk stratified by time since diagnosis

Regardless of family history, the risk of subsequent invasive cancer during the first five years after the first *in situ* breast cancer was increased more than fivefold compared with the general population (SIR 5.20; 95% CI 4.71-5.74). In women with no family history there was a significant decline in both the relative and absolute risk over time, but this was not observed in women with a family history. However, it remains that 15 years after the first *in situ* breast cancer diagnosis, the overall risk of an invasive breast cancer was almost three times higher than for women in the general population. This indicates that women diagnosed with *in situ* breast cancer have a lifelong increased risk, which needs to be taken into account when planning their follow-up.

	All		No family history		Family history		<50		>50	
	No. of deaths	SMR (95 % CI)	No. of deaths	SMR (95 % CI)	No. of deaths	SMR (95 % CI)	No. of deaths	SMR (95 % CI)	No. of deaths	SMR (95 % CI)
Overall	1343	1.28 (1.22,1.36)	1258	1.28 (1.21,1.35)	85	1.44 (1.15,1.78)	122	2.19 (1.82,2.61)	1221	1.24 (1.17,1.31)
No event + 2nd contralat in situ	927	1.01 (0.95,1.08)	875	1.01 (0.94,1.08)	52	1.02 (0.76,1.34)	58	1.17 (0.89,1.52)	869	1.00 (0.93,1.07)
2nd invasive[1]	132	2.06 (1.72,2.44)	122	2.03 (1.68,2.42)	10	2.54 (1.22,4.67)	29	8.03 (5.38,11.54)	103	1.70 (1.39,2.06)
2nd ipsilateral invasive	63	2.16 (1.66,2.77)	58	2.12 (1.61,2.74)	5*	2.75 (0.89,6.43)	17	12.89 (7.51,20.64)	46	1.65 (1.21,2.21)
2nd contralat invasive	55	1.99 (1.50,2.59)	49	1.92 (1.42,2.54)	6*	2.82 (1.04,6.15)	10	7.85 (3.77,14.44)	45	1.71 (1.24,2.28)

*one subject has both ipsilateral and contralateral invasive breast cancer, that is why total is 6+5=11> 10. [1] includes ipsilateral, contralateral and missing side

Table 4. SMR of second breast event after diagnosis of first *in situ* breast cancer, by type of second breast event and family history.

Mortality after *in situ* breast cancer

The overall risk of death in women with *in situ* breast cancer was significantly increased, by 30% compared to the general population, but highly dependent on the occurrence of a second invasive breast cancer event. Women, who did not develop a second invasive event following *in situ* breast cancer, had a similar mortality to the background population [SMR 1.01(95% CI 0.95-1.08)]. In contrast, women who were diagnosed with a second invasive event had a twice as high mortality rate compared with women in the general population [SMR 2.06 (95% CI 1.72-2.44)], with no significant differences between women with and without a family history of breast cancer (Table 4).

Given that deaths were rare at younger ages we compared mortality among women above and below 50 years of age. Women below the age of 50 at the first *in situ* breast cancer diagnosis and who were diagnosed with a second invasive cancer had significantly higher mortality compared with women over 50 years at diagnosis, (SMR 8.03; 95% CI 5.38-11.54 versus SMR 1.70; 95% CI 1.39-2.06).

Young age at onset was an important predictor of death for women with *in situ* disease due to an increased risk of second invasive cancers and thus a substantially higher mortality. This should be taken into account when planning their treatment and follow-up.

Methodological considerations, strengths and limitations

This study has some limitations. We have no treatment data nor have we distinguished between ductal carcinoma *in situ* breast cancer and lobular carcinoma *in situ* breast cancer. With this stated, a previous Swedish case-control study has shown that the risk of a subsequent invasive breast cancer was equal after lobular and ductal carcinoma *in situ* breast cancer[34]. Due to regional differences in how to report second ipsilateral *in situ* breast cancer, such events were not included in the study.

Strengths of the current study include the population-based design, its large sample size and complete follow-up. The information regarding family history is unlikely to be subjected to any bias since it is not dependent on personal reporting but is collected by the tax authorities. In addition, the reporting of cancers to the Cancer Register is mandatory and the register is considered almost complete for invasive breast cancer[203-205]. Since 1980 it has also been of a very high reliability with regards to *in situ* breast cancer[204], which makes the risk of information bias unlikely. To the best of our knowledge, this is the largest study yet carried out to assess the impact of a positive family history of breast cancer on risk and mortality after *in situ* breast cancer.

Papers III and IV

Of the original 516 women who were operated in the axillae, 420 (81.4%) had a preoperative and at least one postoperative measurement of the difference in arm-volume; 96 were non-attenders. The study groups were defined by the axillary procedure performed and the presence of axillary metastases: 1) sentinel lymph node biopsy (SLNB) alone (N=140), 2) axillary lymph node dissection (ALND) in patients without axillary metastases (N=125) and 3) ALND in patients with axillary metastases (N=155). In the third study group we included patients with ALND performed due to preoperatively known axillary metastases, as well as those with ALND performed after a positive SLNB. Clinical characteristics according to study group are shown in Table 5. No differences were seen between attenders and non-attenders in the three groups, except in the node-positive ALND group, where chemotherapy was given less frequently and more mastectomies were performed among non-attenders (data not shown).

	SLNB (n=140)	Node-negative ALND (n=125)	p-value [1]	Node-positive ALND (n=155)	p-value [2]
Operated on right side if right handed or left side if left handed, %	48.1 (n=133)	50.9 (n=108)	0.665	52.5 (n=141)	0.470
Age at operation, mean (SD)	60.0 (9.4)	58.8 (11.1)	0.349	57.2 (11.2)	0.020
Body mass index					
Normal (<25 kg/m^2), %	52.9	52.8	0.468	51.0	0.723
Overweight (25-29 kg/m^2), %	31.4	26.4		35.5	
Obesity (=30 kg/m^2), %	15.7	20.8		13.5	
Type of operation					
Breast conserving surgery, %	91.4	67.2	<0.001	59.4	<0.001
Mastectomy, %	8.6	32.8		40.6	
Adjuvant chemotherapy, %	14.3	20.0	0.216	77.4	<0.001
Adjuvant anti-hormonal treatment, %	74.3	70.4	0.480	80.6	0.191
Radiotherapy to the breast, %	81.4	69.6	0.025	87.7	0.132
Radiotherapy to the axillae, %	7.1	8.0	0.792	70.3	<0.001
Infections, %	2.9	4.9		2.6	
	(n=138)	(n=123)		(n=151)	
Lymph nodes, median (min-max)	2.0 (0-14)	10.0 (2-25)		12.0 (4-42)	
Metastasis lymph nodes, median (min-max)	0 (0-1)	0 (0-0)		2.0 (1-31)	
Tumour diameter (cm), median (min-max)	1.6 (0.5 – 7.0)	1.9 (0.4 – 17)		2.0 (0.7-10)	

[1] Comparison between SLNB vs node negative ALND. Unpaired t-test for test of age at operation and chi-2 test for all other tests.[2] Comparison between SLNB vs node positive ALND. Unpaired t-test for test of age at operation and chi-2 test for all other tests.

Table 5. Description of patient characteristics and treatment. All patients have at least one postoperative measurement of arm-volume.

Lymphoedema after axillary surgery

In paper III, the adjusted mean arm-volume difference, three years after surgery, was 61 ml (95% CI 10 to 113) in the node-negative ALND group and 61 ml (95 % CI 6 to 116) in the node-positive ALND group, both significantly higher than the SLNB group (Table 6). Among women operated with SLNB alone there was no increase in postoperative mean arm-volume difference over time, while both ALND groups showed a statistically significant increase (Figure 8**).**

In paper IV, a dichotomous definition of arm lymphoedema was used, commonly used in the literature, i.e. the proportion of women having ≥10 % increase in arm volume difference. By this definition, we found that 5% in the SLNB group, compared with 13% and 24% in the node-negative and node- positive ALNB groups, respectively, had an arm lymphoedema ($p<0.001$). There are two possible reasons for the lack of an increase in mean arm-volume difference over time even though 5% in the SLNB group had a ≥10% increase

in arm- volume difference. There was a great variance in measured arm-volume and a wide range of harvested lymph nodes even in the SLNB group. Thus, some patients in this group had more than just the sentinel lymph nodes harvested.

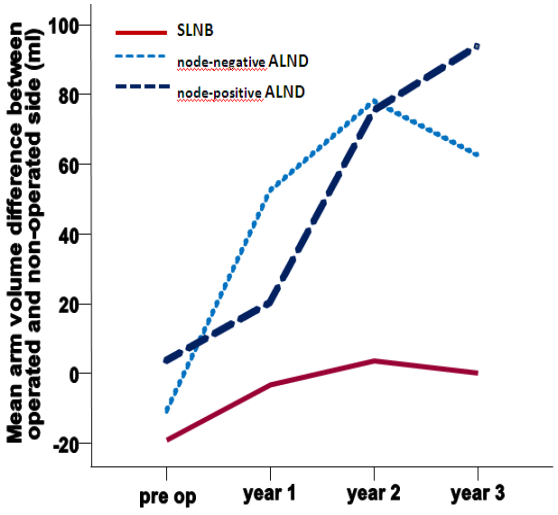


Figure 8. Mean arm-volume difference between operated and non-operated side over time

In a recent meta-analysis the overall incidence for lymphoedema, when restricted to data from prospective studies, was 21.4% (14.9-29.8)[96]. The incidence was around four times higher in women who had ALND than it was among those having SLNB, 19.9% and 5.6%, respectively. Although this pooled estimate was from studies with many different definitions of arm lymphoedema, our results are in line with previous studies and today around one fifth of all women diagnosed with breast cancer are expected to develop arm lymphoedema[96].

Previous studies have shown that the majority of patients will develop arm-lymphoedema within the first two to three years after diagnosis[96, 163]. Our follow-up time in Papers III and IV was three years and the adjusted mean arm-volume difference three years after surgery was 61 ml in both the node-negative and the node-positive group. However, the unadjusted mean-arm volume difference was 67 ml (95% CI 15,120) in the node-negative ALND group and 96ml (95%CI 45, 147) in the node positive group, which probably reflects the late effects of radiotherapy.

	SLNB		Node-negative ALND		Node-positive ALND	
	Unadjusted (n=140) β (95 % CI) p-value	Adjusted[1] (n=133) β (95 % CI) p-value	Unadjusted (n=125) β (95 % CI) p-value	Adjusted[1] (n=108) β (95 % CI) p-value	Unadjusted (n=155) β (95 % CI) p-value	Adjusted[1] (n=140) β (95 % CI) p-value
Preop	ref	ref	ref	ref	ref	Ref
1 year postop	9 (-26 to 45) p=0.626	12 (-26 to 49) p=0.546	49 (10 to 88) p=0.014	36 (-6 to 78) p=0.089	16 (-19 to 52) p=0.367	8 (-30 to 46) p=0.673
2 years postop	26 (-18 to 70) p=0.242	15 (-29 to 59) p=0.498	73 (25 to 122) p=0.003	58 (6 to 110) p=0.029	70 (25 to 115) p=0.002	53 (6 to 101) p=0.028
3 years postop	12 (-34 to 59) p=0.610	8 (-38 to 54) p=0.737	61 (12 to 111) p=0.015	50 (-2 to 101) p=0.059	89 (44 to 135) p<0.001	62 (15 to 109) p=0.009

[1]Adjusted for operation on dominant side, age at operation, BMI at operation and BMI change from preop, radiotherapy to the breast and radiotherapy to the axillae.

Table 6. Mixed model with arm-volume difference between operated and non-operated side as outcome variable, comparison between time periods, n=420.

Self-perceived symptoms of arm lymphoedema

It may take up to several years, before a lymphoedema develops; the water displacement technique therefore has little sensitivity in the preclinical setting. Bioimpedance spectroscopy has been shown to be sensitive to detect early extracellular fluid changes and can thereby be used in early diagnosis of lymphoedema[229]. Self-report methods are an alternative way of capturing early signs of lymphoedema which were also used in Papers III and IV in addition to the water displacement technique. The proportion of women reporting early signs of lymphoedema (does your operated arm feel heavy, tired, sore or tense?), one year after surgery, was 36% in the SLNB group, and 56% and 74% in the node-negative and node-positive ALND groups, respectively. Both ALND groups had a significantly higher risk compared with women in the SLNB group, adjusted odds ratio 2.2(95% CI 1.3-3.9) and 4.7(95% CI 2.7-8.3), respectively. The differences remained statistically significant two and three years after surgery.

Two years after surgery there was a positive correlation between greater mean arm-volume difference and self-perceived arm lymphoedema which remained after three years. As shown in previous studies, using self-reported symptoms as a diagnostic indicator of lymphoedema has its limitations, because many symptoms that are associated with lymphoedema are also common after breast cancer surgery in women without lymphoedema[230, 231].

In study IV, we defined arm lymphoedema as ≥10% increase in arm volume difference and there was no statistically significant agreement between self-perceived and objectively measured arm lymphoedema one and three years after surgery; kappa 0.05(95% CI -0.01-0.12) and 0.10 (95% CI 0.02-0.18). These results indicate that it might not be those women with the most severe lymphoedema who report self-perceived symptoms of lymphoedema.

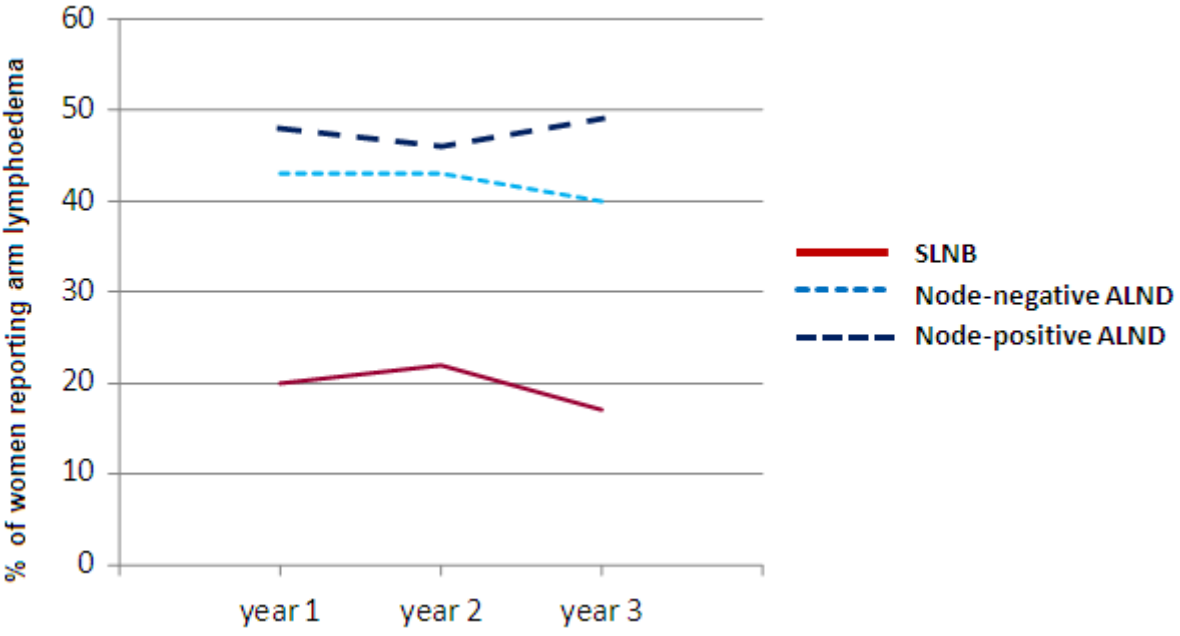
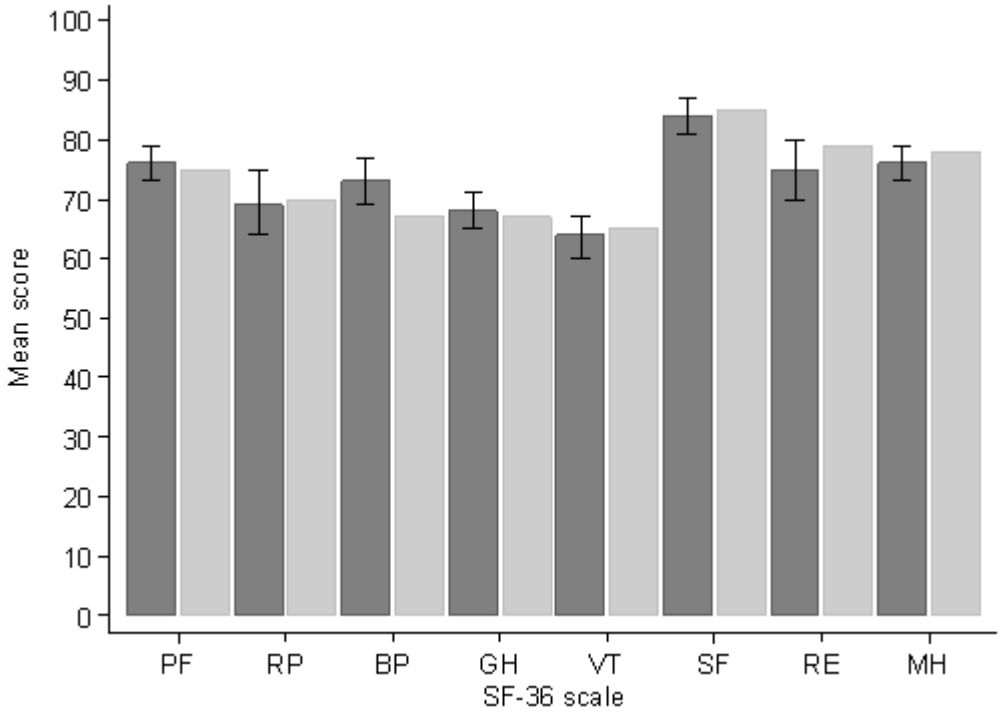


Figure 9. Proportion of women in the three study groups reporting self-perceived symptoms of arm lymphoedema

The poor agreement between patient perceptions and objective measures has also been reported in two other studies[231, 232]. One of these studies suggested that factors other than limb enlargement, such as sensory nerve injury, may play a significant role as patients with numbness were more likely to report self-perceived arm lymphoedema[231].

Even if women treated with SLNB have a limited increase in mean arm-volume difference and fewer self-perceived symptoms of lymphoedema, as many as 20% report self perceived symptoms of arm lymphoedema and 5% experience ≥10% increase in arm-volume difference. This emphasizes the importance of performing SLNB strictly on patients who can benefit from the staging results.

Today, there is an ongoing discussion whether ALND in sentinel node positive breast cancer is necessary. Further studies are needed to answer the question if ALND in sentinel node positive cases could be omitted, without effect on survival or local control[233, 234]. However, if only considering the risk for arm lymphoedema, our study supports the trend to omit ALND in patients with positive sentinel node.



Based on342 patients with HRQoL data. Observed scores in dark gray and expected in light gray. In black 99% CI for the observed scores

Figure 10. SF-36 assessment at 3 years.

HRQOL after axillary surgery

Three years after surgery, the overall mean-score for all study groups was statistically significantly higher for the bodily pain domain when compared with their age-specific norm-group (Figure 10). No other statistically significant differences were found between the study groups and their respective age-specific norm groups.

In the unadjusted model, one year after surgery, the score for physical role functioning was statistically significantly lower in the node positive ALND group compared with the two other study groups; mean score 51 compared with 69 and 64, respectively (p=0.001). Patients in this group more often received chemotherapy, a well-known risk factor for poorer HRQOL[137, 190, 191, 235]. No other statistically significant differences were seen between the three study groups.

In a recent published study from France, with a follow-up time of six years no statistically significant differences appeared in the HRQOL scores for global health between patients treated for ALND and SLNB[236]. However, on the scores for arm symptoms women treated with SLNB reported fewer symptoms than women treated with ALND. In addition, patients reporting arm lymphoedema had affected arm dimension subscores on HRQOL[236]. The SF-36 questionnaire used in our study is generic and it is possible that if we had used a disease- or aspect specific questionnaire we would have found an impact on surgery on certain domains on HRQOL. Our study indicates that after a few years treatment has less impact on the overall HRQOL, as women with breast cancer have the same HRQOL as the background population. Figure 11 shows the SF-36 profiles grouped by correlation between objective and subjective arm lymphoedema three years after surgery. Women with an objective lymphoedema but reporting no self-perceived symptoms of lymphoedema, reported the highest levels of HRQOL. On the other hand, women with no objective lymphoedema, but reporting self-perceived symptoms of lymphoedema scored the lowest HRQOL.

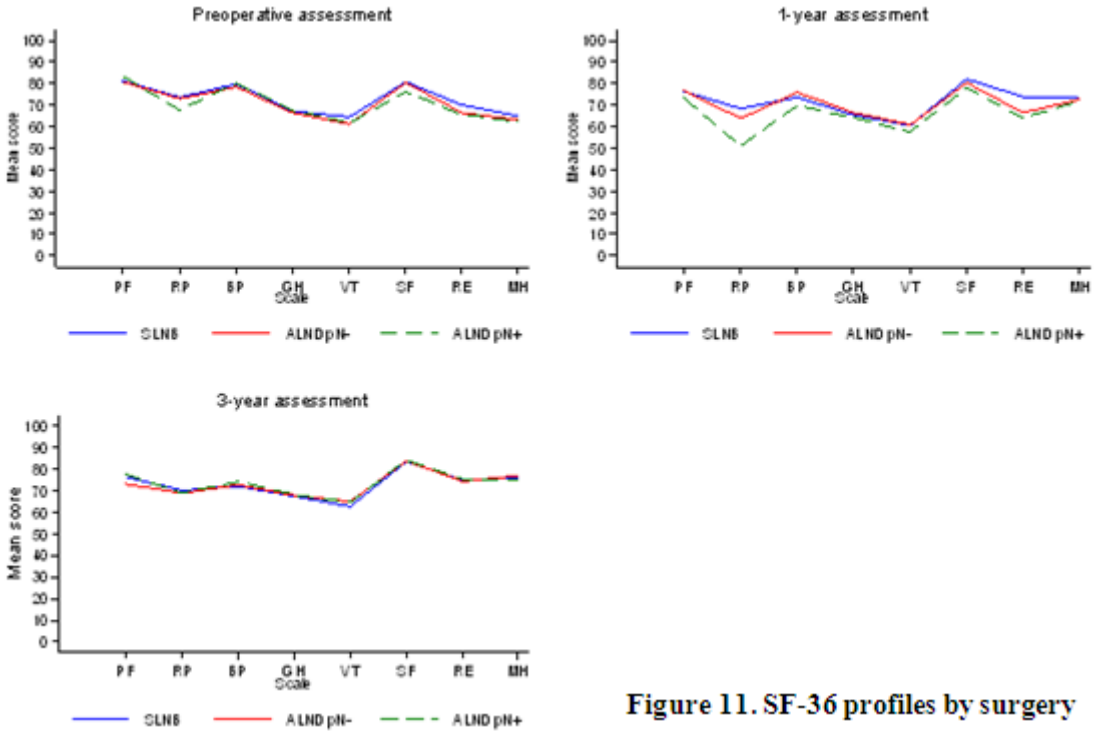


Figure 11. SF-36 profiles by surgery

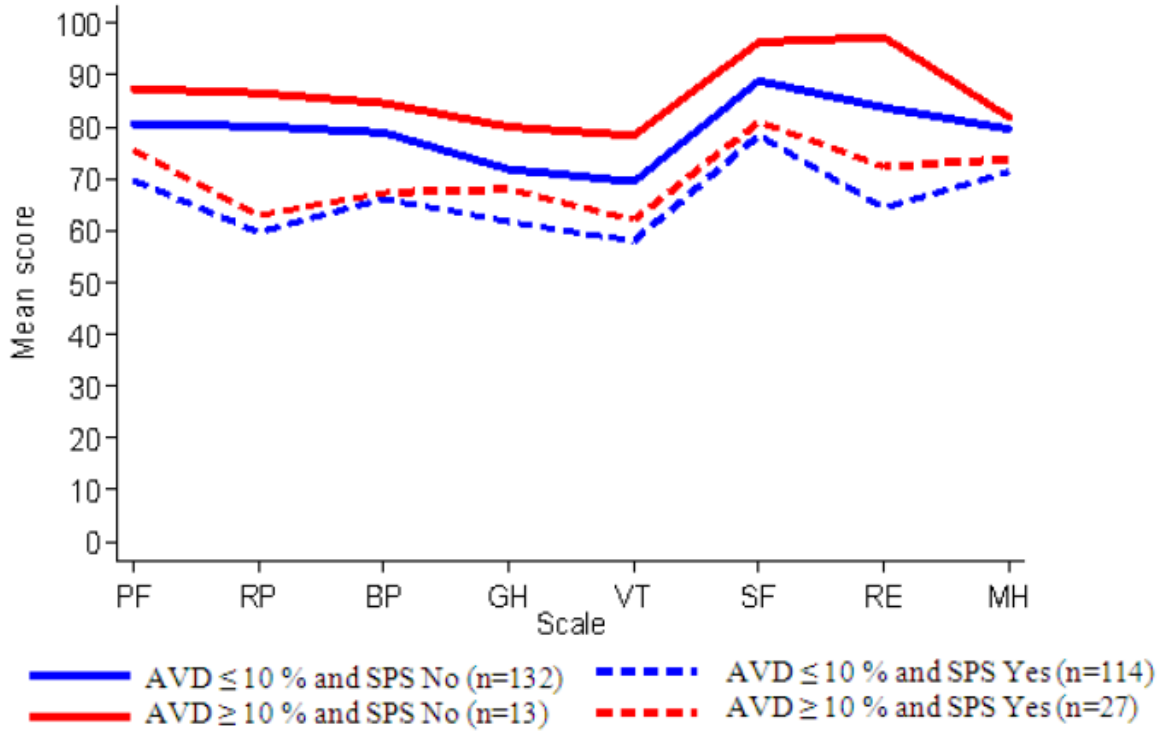


Figure 12. The SF-36 profiles grouped by correlation between objective and subjective arm lymphoedema three years after surgery

It has been shown in a few studies that specific arm symptoms, such as reduced shoulder abduction and pain – related or unrelated to arm lymphoedema – are more associated with poor HRQOL outcomes than the arm swelling per se[237-239]. We speculate that women reporting symptoms of arm lymphoedema might associate other diffuse symptoms after surgery such as numbness, paraesthesia and wound pain as a sign of lymphoedema, and, in line with previous studies[237-239], report lower levels of HRQOL. For the clinician, this is an important finding, as it indicates that it is as important to focus on arm symptoms and pain, as it is to treat arm lymphoedema in order to help these patients. Another explanation might be that, three years after surgery, other factors such as personality and ability to cope with problems, have a greater impact on the HRQOL than the symptoms and disease itself.

Methodological considerations, strengths and limitations

Papers III and IV are based on the same prospectively follow cohort. Regarding self-perceived arm lymphoedema, one limitation is that baseline data were not available for these items and that the arm symptoms questionnaire was not validated. The questionnaire was, however, constructed by a group of breast care professionals and piloted in a group of breast cancer patients before use in the present study.

Another limitation is that no power analysis was carried out. There is therefore a potential risk for type II error, i.e. that the study is too small to reveal potential between group differences.

The strengths of this study are that it is prospective, with assessments of both objective and subjective lymphoedema at multiple time points, and was performed at four large-volume university-affiliated hospitals and

with a long follow up time. The HRQOL questionnaire is validated. In addition, we were able to include node-negative patients, treated with ALND in the study in order to evaluate the impact of surgery per se on arm lymphoedema.

.

CONCLUSIONS

1. Women treated for DCIS have a satisfactory long-term health-related quality of life. The addition of radiotherapy to breast-conserving surgery does not seem to have any negative impact on health-related quality of life in the long-term. However, body image appears to be affected in women treated with mastectomy and immediate breast reconstruction.

2. Young women diagnosed with their first *in situ* breast cancer have both a higher risk for a future invasive breast cancer and higher mortality than their older counterparts, which should be taken into account when planning their treatment and follow-up

3. Among women with *in situ* breast cancer, a positive family history increases the risk only for a contralateral invasive breast cancer.

4. Sentinel lymph node biopsy is associated with a minimal risk of increased arm volume and few self-perceived symptoms of arm lymphoedema, significantly less than after axillary lymph node dissection, regardless of lymph node status. Yet, 20% percent of women report symptoms of arm lymphoedema after sentinel lymph node biopsy, which emphasizes the importance of performing axillary surgery strictly on patients who can benefit from the staging results.

5. Three years after surgery there is a weak correlation between mean arm volume difference and self-perceived symptoms of arm lymphoedema.

6. Women treated for invasive breast cancer have a satisfactory long-term health-related quality of life.

7. Women reporting self-perceived arm lymphoedema, regardless of objective lymphoedema or not, scored lower on all eight SF-36 domains than those who did not, indicating that more attention should be given to the subjective reports of symptoms in order to better help these women.

FUTURE PERSPECTIVES

In situ breast cancer

Young women diagnosed with their first *in situ* breast cancer have both a higher risk for a future invasive breast cancer and a higher mortality than their older counterparts. In addition, they have less effect of post-operative radiotherapy[240, 241]Paper II in this thesis, further indicates that the risk of a second invasive event after previous *in situ* diagnosis increased when breast-conserving surgery became more common in Sweden than mastectomies. Taken together, these facts indicate that mastectomy, with or without primary reconstruction, might be considered for young patients with *in situ* breast cancer, in order to prevent an invasive breast recurrence. To answer the question – whether the type of surgery, i.e. breast conserving surgery *versus* mastectomy affects survival – we plan to study the incidence of second invasive and *in situ* and mortality in regard to surgical treatment in women diagnosed with *in situ* in the Stockholm-Gotland Region from 1980-2012.

A subgroup of women with *in situ* breast cancer is most likely over-treated, and thus neither benefits from extensive surgery nor adjuvant treatment. Theoretically, it should be possible to identify an *in situ* expression profile predicting a low probability of an invasive cancer recurrence. A population-based study from Sweden, however, failed to demonstrate a prognostic value for the surrogate molecular subtyping of DCIS using the St. Gallen criteria [228]. It would also be of interest to analyse whether any of such hypothetical subtypes are more common in women with familial breast cancer.

Arm lymphoedema

Women treated with SLNB develop significantly less arm lymphoedema and report fewer self-perceived symptoms of lymphoedema than women treated with ALND, regardless of nodal status. In Paper II we observed a trend towards a continued increase in arm lymphoedema in the node-positive ALND group when compared with the node-negative group. It would be of interest to conduct a long-term follow-up 10 years after surgery in order to study whether this trend continues; this would indicate that the side effects of radiotherapy occur later and continue to increase for a longer period than the side effects of surgery.

Patient-reported outcome

Women treated for *in situ* and invasive breast cancer overall appeared to have a satisfactory long-term HRQOL, similar to women in the general population. Women with self-perceived symptoms of lymphoedema, regardless of its objective measurable confirmation, scored lower on all HRQOL domains than women without symptoms. Thus, there might be other arm symptoms not analysed in this study that have an impact on HRQOL. It would therefore be of interest to study the impact of pain, numbness and reduced shoulder mobility on HRQOL.

The concept of sense of coherence (SOC) was put forward by Aaron Antonovsky in 1979 to explain why some people become ill under stress and while others stay healthy[242]. A high SOC was suggested to mirror successful coping with stressors, thereby increasing

resilience. In our arm-lymphoedema study, the SOC-scale was used preoperatively and one year postoperatively. We aim to study correlations between preoperatively SOC scores, and HRQOL three years after surgery in order to investigate if the SOC-scale can be used as a predictive tool to identify women with risk for decreased long-term HRQOL.

ACKNOWLEDGEMENTS

I would like to express my profound gratitude to all of you who have contributed in many different, but all necessary, ways so I have been able to complete this journey. I would especially like to give my thanks to:

My main supervisor, **Jan Frisell**, for your never-ending positive attitude towards me and my work. You have helped me build a scientific self-esteem and I have always felt that you trust my ability. You are a brilliant, clinically-oriented, down-to-earth researcher and I am thankful for your excellent navigation through this journey.

Kerstin Sandelin, co-supervisor, always on the run, enthusiastic and full of new ideas. Thank you for inviting me to the world of research and for sharing your solid knowledge of breast cancer. Hope we can share many more "lyxkaffes" in the future.

Yvonne Brandberg co-supervisor, for invaluable, clear-sighted and constructive input into my work. Always with a positive attitude, laughing at my jokes and making me feel smart. I am always in a better mood after our very time-efficient meetings!

All the breast cancer patients participating in the studies. Thank you!

Irma Fredriksson, for being my living encyclopedia when it comes to breast cancer research. Your fascination and joy for research is contagious and you have always had time for a chat and for giving good advice.

Kamila Czene, co-author, your knowledge is as impressive as your willingness to share it. Thanks for excellent input into my research, for teaching me a lot (although I didn't get everything…), but also for many laughs and for sharing my view of the importance of a good "fika".

Marie Wickman Chanterau, co-author paper I, for help with planning the study and for valuable input regarding the manuscript. Co-authors paper IV, **Hemming Johansson** for excellent statistical help and **Gael MacLean** for a short but fruitful collaboration.

Co-authors paper II, **Gustaf Edgren, Mikael Hartman, Miao Hui, Helena Verkooijen** for your vast knowledge in epidemiology and invaluable input regarding the manuscript. A special thanks to Miao, for lots of statistical work and for always answering my questions on very short notice.

Co-authors paper III, **Leif Bergkvist, Fuat Celebioglu, Zoltan Fulep**, **Göran Liljegren** and **Anders Magnuson**. I will remember all the trips to Örebro and the fruitful discussions we had, as the best part of my doctoral education. It was a joy working with all of you! A special thanks to Anders for you calm, clinically-oriented statistical input – you thought me a lot.

The Research school in epidemiology for clinicians at Karolinska Institutet for an excellent, well-organised and fun education. Special thanks to my class-mates **Marcus Aly, Eva Olsson,**

David Petterson, Josefin Segelman and **Magdalena Plecka Östlund** for many laughs and interesting discussions during the coffee- breaks.

My mentor **Inga-Lena Nilsson**, for being such a warm and wise woman, encouraging me in difficult times and following my research with great interest.

Ing-Liss Bryngelsson and Viveca Åberg for generous help with the data-collection and the data files of the lymphoedema study.

Lennart Helleday, former it-supporter, for help with all kinds of computer-trouble and for managing to resuscitate my drowned computer twice!

Håkan Brorson, for good advice and for providing me with literature regarding lymphoedema. Thanks also for the picture of arm volume measurement.

Former heads of the Surgical Clinic and Gastrocentrum Kirurgi, **Harald Blegen, Martin Bäckdahl, Claes Jönsson**, **Anna Martling, Magnus Nilsson, Johan Permert,** and present head of Gastrocentrum **Annika Bergquist** for contributing to an open, lively and generous clinical and academic atmosphere at our Department.

The well-organised administrative personnel at the 3rd floor at the Helicopter house, **Tina Ahlbäck, Kicki Edberg, Madeleine Lehander, Chatrin Lindahl, Liselotte Stenmalm** and research-nurse **Madelene Ahlberg** for friendly smiles, always providing a helping hand when needed, and for all the nice buns at our weekly "onsdagsfika".

My colleagues at Norrtälje hospital, **Lars Eriksson, Ashok Gadré, Christoffer Grimås, Bo Hellström, Richard Ideström, Nils Lundqvist, David Stillström, Urs Wenger**, for providing a good base for a young surgeon and for making me feel like one.

Former and present heads of the Division of Coloproctology, **Torbjörn Holm**, **Annika Sjövall** and **Pelle Nilsson** for being such excellent role-models as doctors and surgeons and for welcoming me to your team! You will see more of me now…

My hardworking colleagues at the colorectal- and trauma-team, **Naseer Baloch, Olle Bernell, Richard Bernhoff, Johannes Blom, Björn Bolmstrand, Chistian Buchli, Leonard Clay, Anders Hansson Elliott, Magnus Falkén, Henrik Iversen, Gabriella Jansson Palmer, Frida Ledel, Patrik Lundström, Mirna Abraham Nordling, Anna Martling, Petri Rantanen, Louis Riddez, Deborah Saraste, Kristina Stenstedt, Lisa Strömmer, Martin Sundelöf** for friendship and joyful work! My research has been possible since someone else was working clinically – thank you!

Soraya Abdi, thank you for your invaluable help during the absolute final hours before I completed this thesis and for making this book look good☺. I owe you!

My dear room-mates, **Jana de Boniface, Amelia Chiorescu, Hanna Fredholm** and **Cia Ihre-Lundgren**. You have surrounded me with joy, care, coffee-breaks, wisdom and many shoulders to lean on the past years. I am so grateful to have you in my everyday-life; you have become my extended family. Special thanks to Hanna, for being there – always – and for solving all my data issues. Without you my computers (and I) would not have survived this journey!

My dear friends, **Caroline Elmér, Christin Edmark, Eva Enocsson, Pia Fogelberg, Anna-Carin Horne, Ulrika Palmer Kazen, Helena Kopp Kallner, Ann-Sophie Jansson Rehnberg, Beatrice Skiöld, Maria Sjöstrand** and their families for adventures, parties and fun but most of all for just being my friends. You all enrich my life!

Dear **Karin** and late **Johan Pollack**, for giving me a different perspective to many things in life. Together we have enjoyed many good times, but also been through some really bad times. Karin – thank you for caring so much for me and my family and for you interest in this thesis. Johan – miss you.

Evangelos Chandanos, for keeping in touch and for reminding me of my father-tongue.

Clara, Erik, Helen, Ingrid, Peter and **Ulrika Radell**. Your home has always been open to our family and you have helped out in so many ways. Looking forward to springtime, drinking beer together in the sun and polish our sailboat Esther.

Our neighbor **Anisa Husain**, for being such a sweet and wise girl, helping us look after our boys.

My family-in law, **Victor** and **Edja Sackey**, and, **Anna** and **Adrain Drake** for caring so much for me and for being a wonderful family to be part of.

My dear brothers **Thomas** and **Peter Ikonomidis**, and my sister-in law **Zina** and nephew **Dennis**. Thank you for sharing so many memories, for fun family-gatherings, but most of all for being there for each other, when needed.

My late father **Dimitris Ikonomidis,** I wish you were here now… and I think you would have been a great παππούς.

My dear mother **Eva Ikonomidis**, for being so generous with your love and support. Thank you for being the best γιαγιά ever!

In the end, the most important people in the world, the men in my life; my beloved husband **Peter** in whose nearness I grow, laugh and long for. Thank you so much for all your support, in innumerous ways, during the final stage of this thesis, but also for giving me perspective and QoL. And our dearest treasures: **William, Daniel** and **Leo**, for just being who you are; the greatest gift in my life. I love you so much! ♥♥♥♥

This thesis was supported by grants from Johan and Jakob Söderbergs Foundation, The Swedish Breast Cancer Association (BRO), Karolinska Institutes Doctoral foundation, Olle Engkvist Byggmästare Foundation, Swedish Cancer Foundation and Cancer Society of Stockholm, Paola Brunetti Foundation.

REFERENCES

1. National Board of Health and Welfare. Cancer i siffror. 2013 http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19108/2013-6-5.pdf
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA: a cancer journal for clinicians 2005 Mar-Apr;55(2):74-108.
3. Hortobagyi GN, de la Garza Salazar J, Pritchard K, et al. The global breast cancer burden: variations in epidemiology and survival. Clinical breast cancer 2005 Dec;6(5):391-401.
4. Hery C, Ferlay J, Boniol M, Autier P. Changes in breast cancer incidence and mortality in middle-aged and elderly women in 28 countries with Caucasian majority populations. Ann Oncol 2008 May;19(5):1009-1018.
5. National Board of Health and Welfare . Cancerincidens i Sverige 2012. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19291/2013-12-17.pdf
6. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. Bmj 2000 Sep 9;321(7261):624-628.
7. Holland R, Hendriks JH. Microcalcifications associated with ductal carcinoma in situ: mammographic-pathologic correlation. Semin Diagn Pathol 1994 Aug;11(3):181-192.
8. Stomper PC, Connolly JL, Meyer JE, Harris JR. Clinically occult ductal carcinoma in situ detected with mammography: analysis of 100 cases with radiologic-pathologic correlation. Radiology 1989 Jul;172(1):235-241.
9. Group SBC. Nationella riktlinjer för behandling av bröstcancer/ National Guidelines for Treatment of Breast Cancer. 2012 http://www.swebcg.se
10. Ewertz M, Duffy SW, Adami HO, et al. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. Int J Cancer 1990 Oct 15;46(4):597-603.
11. Magnusson C, Holmberg L, Norden T, Lindgren A, Persson I. Prognostic characteristics in breast cancers after hormone replacement therapy. Breast Cancer Res Treat 1996;38(3):325-334.
12. Carmichael AR, Bates T. Obesity and breast cancer: a review of the literature. Breast 2004 Apr;13(2):85-92.
13. Mattisson I, Wirfalt E, Wallstrom P, Gullberg B, Olsson H, Berglund G. High fat and alcohol intakes are risk factors of postmenopausal breast cancer: a prospective study from the Malmo diet and cancer cohort. Int J Cancer 2004 Jul 1;110(4):589-597.
14. Monninkhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. Epidemiology 2007 Jan;18(1):137-157.
15. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006 Jun;15(6):1159-1169.
16. Kerlikowske K, Barclay J, Grady D, Sickles EA, Ernster V. Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. J Natl Cancer Inst 1997 Jan 1;89(1):76-82.
17. Claus EB, Stowe M, Carter D. Breast carcinoma in situ: risk factors and screening patterns. J Natl Cancer Inst 2001 Dec 5;93(23):1811-1817.
18. Claus EB, Stowe M, Carter D. Family history of breast and ovarian cancer and the risk of breast carcinoma in situ. Breast Cancer Res Treat 2003 Mar;78(1):7-15.

19. Stockholm-Gotland RCC. Bröstcancer. Nationell årsrapport 2011. http://www.cancercentrum.se/Global/Diagnoser/br%c3%b6stcancer/rapporter/%c3%85rsrapport_br%c3%b6st_2011.pdf
20. Chuba PJ, Hamre MR, Yap J, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005 Aug 20;23(24):5534-5541.
21. Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: a review. Breast Cancer Res Treat 2006 May;97(2):135-144.
22. Franceschi S, Levi F, La Vecchia C, Randimbison L, Te VC. Second cancers following in situ carcinoma of the breast. Int J Cancer 1998 Jul 29;77(3):392-395.
23. Innos K, Horn-Ross PL. Risk of second primary breast cancers among women with ductal carcinoma in situ of the breast. Breast Cancer Res Treat 2008 Oct;111(3):531-540.
24. Li CI, Malone KE, Saltzman BS, Daling JR. Risk of invasive breast carcinoma among women diagnosed with ductal carcinoma in situ and lobular carcinoma in situ, 1988-2001. Cancer 2006 May 15;106(10):2104-2112.
25. Robinson D, Holmberg L, Moller H. The occurrence of invasive cancers following a diagnosis of breast carcinoma in situ. British journal of cancer 2008 Aug 19;99(4):611-615.
26. Habel LA, Moe RE, Daling JR, Holte S, Rossing MA, Weiss NS. Risk of contralateral breast cancer among women with carcinoma in situ of the breast. Ann Surg 1997 Jan;225(1):69-75.
27. Rawal R, Lorenzo Bermejo J, Hemminki K. Risk of subsequent invasive breast carcinoma after in situ breast carcinoma in a population covered by national mammographic screening. Br J Cancer 2005 Jan 17;92(1):162-166.
28. Levi F, Randimbison L, Te VC, La Vecchia C. Invasive breast cancer following ductal and lobular carcinoma in situ of the breast. Int J Cancer 2005 Sep 20;116(5):820-823.
29. Warnberg F, Yuen J, Holmberg L. Risk of subsequent invasive breast cancer after breast carcinoma in situ. Lancet 2000 Feb 26;355(9205):724-725.
30. Soerjomataram I, Louwman WJ, van der Sangen MJ, Roumen RM, Coebergh JW. Increased risk of second malignancies after in situ breast carcinoma in a population-based registry. Br J Cancer 2006 Aug 7;95(3):393-397.
31. Eusebi V, Feudale E, Foschini MP, et al. Long-term follow-up of in situ carcinoma of the breast. Semin Diagn Pathol 1994 Aug;11(3):223-235.
32. Warnberg F, Bergh J, Holmberg L. Prognosis in women with a carcinoma in situ of the breast: a population-based study in Sweden. Cancer Epidemiol Biomarkers Prev 1999 Sep;8(9):769-774.
33. Hemminki K, Granstrom C. Familial breast carcinoma risks by morphology: a nationwide epidemiologic study from Sweden. Cancer 2002 Jun 1;94(11):3063-3070.
34. Warnberg F, Bergh J, Zack M, Holmberg L. Risk factors for subsequent invasive breast cancer and breast cancer death after ductal carcinoma in situ: a population-based case-control study in Sweden. Cancer Epidemiol Biomarkers Prev 2001 May;10(5):495-499.
35. Falk RS, Hofvind S, Skaane P, Haldorsen T. Second events following ductal carcinoma in situ of the breast: a register-based cohort study. Breast Cancer Res Treat 2011 Oct;129(3):929-938.
36. Emdin SO, Granstrand B, Ringberg A, et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol 2006;45(5):536-543.

37. Claus EB, Risch NJ, Thompson WD. Age at onset as an indicator of familial risk of breast cancer. American journal of epidemiology 1990 Jun;131(6):961-972.
38. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000 Jul 13;343(2):78-85.
39. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. American journal of human genetics 1991 Feb;48(2):232-242.
40. Bougie O, Weberpals JI. Clinical Considerations of BRCA1- and BRCA2-Mutation Carriers: A Review. International journal of surgical oncology 2011;2011:374012.
41. Loman N, Johannsson O, Kristoffersson U, Olsson H, Borg A. Family history of breast and ovarian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. J Natl Cancer Inst 2001 Aug 15;93(16):1215-1223.
42. Jönsson P-E. Bröstcancer; 2009.
43. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet 2001 Oct 27;358(9291):1389-1399.
44. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 1997 May 29;71(5):800-809.
45. Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. British journal of cancer 2004 Oct 18;91(8):1580-1590.
46. Bradley SJ, Weaver DW, Bouwman DL. Alternatives in the surgical management of in situ breast cancer. A meta-analysis of outcome. Am Surg 1990 Jul;56(7):428-432.
47. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. PloS one 2009;4(11):e7695.
48. Louwman WJ, Vulto JC, Verhoeven RH, Nieuwenhuijzen GA, Coebergh JW, Voogd AC. Clinical epidemiology of breast cancer in the elderly. Eur J Cancer 2007 Oct;43(15):2242-2252.
49. Kollias J, Elston CW, Ellis IO, Robertson JF, Blamey RW. Early-onset breast cancer--histopathological and prognostic considerations. British journal of cancer 1997;75(9):1318-1323.
50. Douglas-Jones AG, Morgan JM, Appleton MA, et al. Consistency in the observation of features used to classify duct carcinoma in situ (DCIS) of the breast. Journal of clinical pathology 2000 Aug;53(8):596-602.
51. Burstein HJ, Polyak K, Wong JS, Lester SC, Kaelin CM. Ductal carcinoma in situ of the breast. N Engl J Med 2004 Apr 1;350(14):1430-1441.
52. Holland R, Peterse JL, Millis RR, et al. Ductal carcinoma in situ: a proposal for a new classification. Semin Diagn Pathol 1994 Aug;11(3):167-180.
53. Jensen EV, Block GE, Smith S, Kyser K, DeSombre ER. Estrogen receptors and breast cancer response to adrenalectomy. National Cancer Institute monograph 1971 Dec;34:55-70.
54. Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011 Aug 27;378(9793):771-784.
55. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000 Jan 7;100(1):57-70.
56. Mitri Z, Constantine T, O'Regan R. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. Chemotherapy research and practice 2012;2012:743193.

57. Ryden L, Haglund M, Bendahl PO, et al. Reproducibility of human epidermal growth factor receptor 2 analysis in primary breast cancer: a national survey performed at pathology departments in Sweden. Acta Oncol 2009;48(6):860-866.
58. Press MF, Bernstein L, Thomas PA, et al. HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1997 Aug;15(8):2894-2904.
59. Colozza M, Azambuja E, Cardoso F, Sotiriou C, Larsimont D, Piccart MJ. Proliferative markers as prognostic and predictive tools in early breast cancer: where are we now? Ann Oncol 2005 Nov;16(11):1723-1739.
60. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000 Aug 17;406(6797):747-752.
61. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proceedings of the National Academy of Sciences of the United States of America 2001 Sep 11;98(19):10869-10874.
62. Prat A, Parker JS, Karginova O, et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. Breast cancer research : BCR 2010;12(5):R68.
63. Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clinical cancer research : an official journal of the American Association for Cancer Research 2005 Aug 15;11(16):5678-5685.
64. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013 Sep;24(9):2206-2223.
65. Hermansen C, Skovgaard Poulsen H, Jensen J, et al. Diagnostic reliability of combined physical examination, mammography, and fine-needle puncture ("triple-test") in breast tumors. A prospective study. Cancer 1987 Oct 15;60(8):1866-1871.
66. Vetto J, Pommier R, Schmidt W, et al. Use of the "triple test" for palpable breast lesions yields high diagnostic accuracy and cost savings. Am J Surg 1995 May;169(5):519-522.
67. Olsson S, Andersson I, Karlberg I, Bjurstam N, Frodis E, Hakansson S. Implementation of service screening with mammography in Sweden: from pilot study to nationwide programme. J Med Screen 2000;7(1):14-18.
68. National Guidelines for Breastcancer Healthcare. Medical and Healtheconomic document. 2013 [cited; Available from:
69. Palka I, Kelemen G, Ormandi K, et al. Tumor characteristics in screen-detected and symptomatic breast cancers. Pathology oncology research : POR 2008 Jun;14(2):161-167.
70. Dawson SJ, Duffy SW, Blows FM, et al. Molecular characteristics of screen-detected vs symptomatic breast cancers and their impact on survival. British journal of cancer 2009 Oct 20;101(8):1338-1344.
71. Jorgensen KJ, Keen JD, Gotzsche PC. Is mammographic screening justifiable considering its substantial overdiagnosis rate and minor effect on mortality? Radiology 2011 Sep;260(3):621-627.
72. Gøtzsche PC JK. Screening for breast cancer with mammography.
. Cochrane Database Syst Rev 2013 Jun 4;6:CD001877 2013.
73. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002 Mar 16;359(9310):909-919.

74. Crystal P, Strano SD, Shcharynski S, Koretz MJ. Using sonography to screen women with mammographically dense breasts. AJR American journal of roentgenology 2003 Jul;181(1):177-182.
75. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005 May 21-27;365(9473):1769-1778.
76. Stockholm-Gotland. RCC. Vårdprogram för Bröstcancer 2009. http://www.cancercentrum.se/Global/RCCSthlmGotland/Regionla%20v%C3%A5rdprogram/Br%C3%B6stcancerUppdat2011%5b1%5d.pdf
77. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002 Oct 17;347(16):1233-1241.
78. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002 Oct 17;347(16):1227-1232.
79. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005 Dec 17;366(9503):2087-2106.
80. Halsted WS. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. Ann Surg 1894 Nov;20(5):497-555.
81. Patey DH, Dyson WH. The prognosis of carcinoma of the breast in relation to the type of operation performed. British journal of cancer 1948 Mar;2(1):7-13.
82. Fisher B, Ravdin RG, Ausman RK, Slack NH, Moore GE, Noer RJ. Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. Ann Surg 1968 Sep;168(3):337-356.
83. Fisher B, Costantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 1993 Jun 3;328(22):1581-1586.
84. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. Ann Surg Oncol 2010 May;17(5):1375-1391.
85. Rowland JH, Desmond KA, Meyerowitz BE, Belin TR, Wyatt GE, Ganz PA. Role of breast reconstructive surgery in physical and emotional outcomes among breast cancer survivors. J Natl Cancer Inst 2000 Sep 6;92(17):1422-1429.
86. Brandberg Y, Malm M, Blomqvist L. A prospective and randomized study, "SVEA," comparing effects of three methods for delayed breast reconstruction on quality of life, patient-defined problem areas of life, and cosmetic result. Plastic and reconstructive surgery 2000 Jan;105(1):66-74; discussion 75-66.
87. Cutuli B, Cohen-Solal-Le Nir C, De Lafontan B, et al. Ductal carcinoma in situ of the breast results of conservative and radical treatments in 716 patients. Eur J Cancer 2001 Dec;37(18):2365-2372.
88. Silverstein MJ, Barth A, Poller DN, et al. Ten-year results comparing mastectomy to excision and radiation therapy for ductal carcinoma in situ of the breast. Eur J Cancer 1995;31A(9):1425-1427.
89. Ernster VL, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R. Mortality among women with ductal carcinoma in situ of the breast in the population-based surveillance, epidemiology and end results program. Archives of internal medicine 2000 Apr 10;160(7):953-958.

90. Braley SA. The use of silicones in plastic surgery. A retrospective view. Plastic and reconstructive surgery 1973 Mar;51(3):280-288.
91. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989 Jan 1;63(1):181-187.
92. Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2002 Sep 1;20(17):3628-3636.
93. Polednak AP. Survival of lymph node-negative breast cancer patients in relation to number of lymph nodes examined. Ann Surg 2003 Feb;237(2):163-167.
94. Bland KI, Scott-Conner CE, Menck H, Winchester DP. Axillary dissection in breast-conserving surgery for stage I and II breast cancer: a National Cancer Data Base study of patterns of omission and implications for survival. Journal of the American College of Surgeons 1999 Jun;188(6):586-595; discussion 595-586.
95. Weir L, Speers C, D'Yachkova Y, Olivotto IA. Prognostic significance of the number of axillary lymph nodes removed in patients with node-negative breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2002 Apr 1;20(7):1793-1799.
96. Disipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. The lancet oncology 2013 Mar 26.
97. Bergkvist L, Frisell J, Liljegren G, Celebioglu F, Damm S, Thorn M. Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer. The British journal of surgery 2001 Dec;88(12):1644-1648.
98. Gould EA, Winship T, Philbin PH, Kerr HH. Observations on a "sentinel node" in cancer of the parotid. Cancer 1960 Jan-Feb;13:77-78.
99. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977 Feb;39(2):456-466.
100. Turner-Warwick RT. The lymphatics of the breast. The British journal of surgery 1959 May;46:574-582.
101. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surgical oncology 1993 Dec;2(6):335-339; discussion 340.
102. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994 Sep;220(3):391-398; discussion 398-401.
103. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 1996 Dec 11;276(22):1818-1822.
104. Bergkvist L, Frisell J. Multicentre validation study of sentinel node biopsy for staging in breast cancer. The British journal of surgery 2005 Oct;92(10):1221-1224.
105. Wilke LG, McCall LM, Posther KE, et al. Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. Ann Surg Oncol 2006 Apr;13(4):491-500.
106. Rietman JS, Dijkstra PU, Geertzen JH, et al. Treatment-related upper limb morbidity 1 year after sentinel lymph node biopsy or axillary lymph node dissection for stage I or II breast cancer. Ann Surg Oncol 2004 Nov;11(11):1018-1024.
107. McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008 Nov 10;26(32):5213-5219.

108. Ashikaga T, Krag DN, Land SR, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol 2010 Aug 1;102(2):111-118.
109. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer--a multicenter validation study. N Engl J Med 1998 Oct 1;339(14):941-946.
110. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. The lancet oncology 2010 Oct;11(10):927-933.
111. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003 Aug 7;349(6):546-553.
112. Intra M, Rotmensz N, Veronesi P, et al. Sentinel node biopsy is not a standard procedure in ductal carcinoma in situ of the breast: the experience of the European institute of oncology on 854 patients in 10 years. Ann Surg 2008 Feb;247(2):315-319.
113. Zavagno G, Carcoforo P, Marconato R, et al. Role of axillary sentinel lymph node biopsy in patients with pure ductal carcinoma in situ of the breast. BMC cancer 2005 Mar 11;5:28.
114. Kelly TA, Kim JA, Patrick R, Grundfest S, Crowe JP. Axillary lymph node metastases in patients with a final diagnosis of ductal carcinoma in situ. Am J Surg 2003 Oct;186(4):368-370.
115. Ansari B, Ogston SA, Purdie CA, Adamson DJ, Brown DC, Thompson AM. Meta-analysis of sentinel node biopsy in ductal carcinoma in situ of the breast. The British journal of surgery 2008 May;95(5):547-554.
116. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011 Nov 12;378(9804):1707-1716.
117. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1998 Feb;16(2):441-452.
118. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000 Feb 12;355(9203):528-533.
119. Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 2003 Jul 12;362(9378):95-102.
120. Early Breast Cancer Trialists' Collaborative G, Correa C, McGale P, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. Journal of the National Cancer Institute Monographs 2010;2010(41):162-177.
121. Lind PA, Wennberg B, Gagliardi G, Fornander T. Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. Breast Cancer Res Treat 2001 Aug;68(3):199-210.
122. Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. N Engl J Med 2013 Jun 27;368(26):2527.

123. Swedborg I, Wallgren A. The effect of pre- and postmastectomy radiotherapy on the degree of edema, shoulder-joint mobility, and gripping force. Cancer 1981 Mar 1;47(5):877-881.
124. Johansson S, Svensson H, Denekamp J. Dose response and latency for radiation-induced fibrosis, edema, and neuropathy in breast cancer patients. International journal of radiation oncology, biology, physics 2002 Apr 1;52(5):1207-1219.
125. Davies C PH, Godwin J, Gray R, Arriagada R, Raina V, Abraham M, Medeiros Alencar VH, Badran A, Bonfill X, Bradbury J, Clarke M, Collins R, Davis SR, Delmestri A, Forbes JF, Haddad P, Hou MF, Inbar M, Khaled H, Kielanowska J, Kwan WH, Mathew BS, Mittra I, Müller B, Nicolucci A, Peralta O, Pernas F, Petruzelka L, Pienkowski T, Radhika R, Rajan B, Rubach MT, Tort S, Urrútia G, Valentini M, Wang Y, Peto R; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. The lancet oncology 2013;Mar 9;381(9869)::805-816.
126. Whelan TJ, Pritchard KI. Managing patients on endocrine therapy: focus on quality-of-life issues. Clinical cancer research : an official journal of the American Association for Cancer Research 2006 Feb 1;12(3 Pt 2):1056s-1060s.
127. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010 Aug 10;28(23):3784-3796.
128. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. The lancet oncology 2010 Dec;11(12):1135-1141.
129. Chirgwin J, Sun Z, Smith I, et al. The advantage of letrozole over tamoxifen in the BIG 1-98 trial is consistent in younger postmenopausal women and in those with chemotherapy-induced menopause. Breast Cancer Res Treat 2012 Jan;131(1):295-306.
130. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. The lancet oncology 2011 Nov;12(12):1101-1108.
131. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010 Jan 20;28(3):509-518.
132. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005 Jan 1-7;365(9453):60-62.
133. Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. Seminars in oncology 2001 Aug;28(4):400-418.
134. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976 Feb 19;294(8):405-410.
135. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med 1995 Apr 6;332(14):901-906.
136. Early Breast Cancer Trialists' Collaborative G, Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of

long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012 Feb 4;379(9814):432-444.
137. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. Journal of experimental & clinical cancer research : CR 2008;27:32.
138. Mols F, Vingerhoets AJ, Coebergh JW, van de Poll-Franse LV. Quality of life among long-term breast cancer survivors: a systematic review. Eur J Cancer 2005 Nov;41(17):2613-2619.
139. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005 Oct 20;353(16):1659-1672.
140. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007 Jan 6;369(9555):29-36.
141. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005 Oct 20;353(16):1673-1684.
142. Chikly B. Who discovered the lymphatic system. Lymphology 1997 Dec;30(4):186-193.
143. Tor-Göran Henriksson IW. Lymfödem; 1994.
144. Malek P, Belan A, Kocandrle V. The Superficial and Deep Lymphatic System of the Lower Extremities and Their Mutual Relationship under Physiological and Pathological Conditions. The Journal of cardiovascular surgery 1964 Nov-Dec;5:686-690.
145. Aboul-Enein A, Eshmawy I, Arafa S, Abboud A. The role of lymphovenous communication in the development of postmastectomy lymphedema. Surgery 1984 May;95(5):562-566.
146. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. Nature reviews Cancer 2002 Aug;2(8):563-572.
147. Lawson LL, Sandler M, Martin W, Beauchamp RD, Kelley MC. Preoperative lymphoscintigraphy and internal mammary sentinel lymph node biopsy do not enhance the accuracy of lymphatic mapping for breast cancer. The American surgeon 2004 Dec;70(12):1050-1055; discussion 1055-1056.
148. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. Ann Surg Oncol 2009 Jul;16(7):1959-1972.
149. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Thiadens SR, Taylor ME. The grading of lymphedema in oncology clinical trials. Seminars in radiation oncology 2003 Jul;13(3):214-225.
150. WS H. The swelling of the arm after operations for cancer of the breast—elephantiasis chirurgica—its cause and prevention. Bulletin of the Johns Hopkins Hospital 1921;32:309–313.
151. Olszewski WL. Episodic dermatolymphangioadenitis (DLA) in patients with lymphedema of the lower extremities before and after administration of benzathine penicillin: a preliminary study. Lymphology 1996 Sep;29(3):126-131.
152. Brorson H. Adipose tissue in lymphedema: the ignorance of adipose tissue in lymphedema. Lymphology 2004 Dec;37(4):175-177.
153. Brorson H, Ohlin K, Olsson G, Nilsson M. Adipose tissue dominates chronic arm lymphedema following breast cancer: an analysis using volume rendered CT images. Lymphatic research and biology 2006;4(4):199-210.
154. J S. Adipose tissue in plastic surgery. Ann Plast Surg 1986(16(5)):444-453.

155. Brorson H, Ohlin K, Olsson G, Karlsson MK. Breast cancer-related chronic arm lymphedema is associated with excess adipose and muscle tissue. Lymphatic research and biology 2009;7(1):3-10.
156. Kuehn T, Klauss W, Darsow M, et al. Long-term morbidity following axillary dissection in breast cancer patients--clinical assessment, significance for life quality and the impact of demographic, oncologic and therapeutic factors. Breast Cancer Res Treat 2000 Dec;64(3):275-286.
157. Hack TF, Cohen L, Katz J, Robson LS, Goss P. Physical and psychological morbidity after axillary lymph node dissection for breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1999 Jan;17(1):143-149.
158. Rief W, Bardwell WA, Dimsdale JE, Natarajan L, Flatt SW, Pierce JP. Long-term course of pain in breast cancer survivors: a 4-year longitudinal study. Breast Cancer Res Treat 2011 Nov;130(2):579-586.
159. Kwan W, Jackson J, Weir LM, Dingee C, McGregor G, Olivotto IA. Chronic arm morbidity after curative breast cancer treatment: prevalence and impact on quality of life. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2002 Oct 15;20(20):4242-4248.
160. Norman SA, Localio AR, Potashnik SL, et al. Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009 Jan 20;27(3):390-397.
161. Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat 2006 Feb;95(3):279-293.
162. Liljegren G, Holmberg L. Arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy in breast cancer stage I. Results from a randomised trial. Uppsala-Orebro Breast Cancer Study Group. Eur J Cancer 1997 Feb;33(2):193-199.
163. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 2001 Sep 15;92(6):1368-1377.
164. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. Cancer 1998 Dec 15;83(12 Suppl American):2776-2781.
165. Helms G, Kuhn T, Moser L, Remmel E, Kreienberg R. Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection--data from a prospective randomised trial. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2009 Jul;35(7):696-701.
166. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005 Oct 20;23(30):7703-7720.
167. Gerber LH. A review of measures of lymphedema. Cancer 1998 Dec 15;83(12 Suppl American):2803-2804.
168. Bourgeois P, Leduc O, Leduc A. Imaging techniques in the management and prevention of posttherapeutic upper limb edemas. Cancer 1998 Dec 15;83(12 Suppl American):2805-2813.
169. Megens AM, Harris SR, Kim-Sing C, McKenzie DC. Measurement of upper extremity volume in women after axillary dissection for breast cancer. Archives of physical medicine and rehabilitation 2001 Dec;82(12):1639-1644.

170. Swedborg I. Voluminometric estimation of the degree of lymphedema and its therapy by pneumatic compression. Scand J Rehabil Med 1977;9(3):131-135.
171. Stillwell GK. Treatment of postmastectomy lymphedema. Modern treatment 1969 Mar;6(2):396-412.
172. Lymphology. ISo. Summary of the 10th International Congress of Lymphology Working Group Discussions and Recommendations. Lymphology 1986;18:175-180.
173. Lymfödem. Nationellt vårdprogram. 2003 http://www.lymfologi.nu/userfiles/file/Vardprogram_lymfodem.pdf
174. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. Breast Cancer Res Treat 2009 Jan;113(2):199-206.
175. Chang DW SH, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. Plastic and reconstructive surgery 2013;Nov;132(5):1305-1314.
176. Campisi C, Boccardo F. Microsurgical techniques for lymphedema treatment: derivative lymphatic-venous microsurgery. World journal of surgery 2004 Jun;28(6):609-613.
177. Brorson H, Svensson H. Liposuction combined with controlled compression therapy reduces arm lymphedema more effectively than controlled compression therapy alone. Plastic and reconstructive surgery 1998 Sep;102(4):1058-1067; discussion 1068.
178. Brorson H, Svensson H, Norrgren K, Thorsson O. Liposuction reduces arm lymphedema without significantly altering the already impaired lymph transport. Lymphology 1998 Dec;31(4):156-172.
179. Brorson H. Liposuction gives complete reduction of chronic large arm lymphedema after breast cancer. Acta Oncol 2000;39(3):407-420.
180. Fayers P MD. Quality of life: The assessment, analysis and interpretation of patient-reported outcomes.: John Wiley & Sons Ltd 2007.
181. Organization. WH. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference.. 1948: 100.
182. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995 Jan 4;273(1):59-65.
183. Bakas T, McLennon SM, Carpenter JS, et al. Systematic review of health-related quality of life models. Health and quality of life outcomes 2012;10:134.
184. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. Journal of clinical epidemiology 2002 Nov;55(11):1130-1143.
185. Eriksen C, Lindgren EN, Frisell J, Stark B. A prospective randomized study comparing two different expander approaches in implant-based breast reconstruction: one stage versus two stages. Plastic and reconstructive surgery 2012 Aug;130(2):254e-264e.
186. Lindegren A HM, Docherty Skogh AC, Edsander-Nord A. Postmastectomy breast reconstruction in the irradiated breast: a comparative study of DIEP and latissimus dorsi flap outcome. Plast Reconstr Surg 2012;130(1)::10-18.
187. Administration. UDoHaHSFaD. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.
188. Grimison PS, Stockler MR. Quality of life and adjuvant systemic therapy for early-stage breast cancer. Expert review of anticancer therapy 2007 Aug;7(8):1123-1134.
189. Kayl AE, Meyers CA. Side-effects of chemotherapy and quality of life in ovarian and breast cancer patients. Current opinion in obstetrics & gynecology 2006 Feb;18(1):24-28.

190. DiSipio T, Hayes S, Newman B, Janda M. Health-related quality of life 18 months after breast cancer: comparison with the general population of Queensland, Australia. Support Care Cancer 2008 Oct;16(10):1141-1150.
191. Sagen A, Karesen R, Sandvik L, Risberg MA. Changes in arm morbidities and health-related quality of life after breast cancer surgery - a five-year follow-up study. Acta Oncol 2009;48(8):1111-1118.
192. Arndt V, Stegmaier C, Ziegler H, Brenner H. Quality of life over 5 years in women with breast cancer after breast-conserving therapy versus mastectomy: a population-based study. J Cancer Res Clin Oncol 2008 Dec;134(12):1311-1318.
193. Hartl K, Janni W, Kastner R, et al. Impact of medical and demographic factors on long-term quality of life and body image of breast cancer patients. Ann Oncol 2003 Jul;14(7):1064-1071.
194. Dorval M, Maunsell E, Deschenes L, Brisson J, Masse B. Long-term quality of life after breast cancer: comparison of 8-year survivors with population controls. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1998 Feb;16(2):487-494.
195. Tomich PL, Helgeson VS. Five years later: a cross-sectional comparison of breast cancer survivors with healthy women. Psycho-oncology 2002 Mar-Apr;11(2):154-169.
196. Parker PA, Youssef A, Walker S, et al. Short-term and long-term psychosocial adjustment and quality of life in women undergoing different surgical procedures for breast cancer. Ann Surg Oncol 2007 Nov;14(11):3078-3089.
197. Kornblith P, Wells A, Gabrin MJ, et al. In vitro responses of ovarian cancers to platinums and taxanes. Anticancer research 2003 Jan-Feb;23(1B):543-548.
198. Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: quality of life of young breast cancer survivors. Psycho-oncology 2004 Mar;13(3):147-160.
199. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. J Natl Cancer Inst 2002 Jan 2;94(1):39-49.
200. Stockholm Regional Oncological Cancer Center. Information regarding The Regional Breast Cancer Registry. http://www.cancercentrum.se/sv/stockholmgotland/VP_register/Brostcancer1/
201. Statistics Sweden. Multi-generation Register. A description of contents and quality. http://www.scb.se/sv_/Vara-tjanster/SCBs-data-for-forskning/SCBs-datalager/Flergenerationsregistret/
202. The National Board of Health and Welfare. Information regading The Swedish Cancer Register.
203. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta radiologica Oncology 1984;23(5):305-313.
204. Garne JP, Aspegren K, Moller T. Validity of breast cancer registration from one hospital into the Swedish National Cancer Registry 1971-1991. Acta Oncol 1995;34(2):153-156.
205. Rutqvist LE, Wallgren A. Inconsistencies in breast carcinoma registration. An investigation of 855 cases reported to the Swedish Cancer Registry. Acta radiologica Oncology 1983;22(2):109-112.
206. The National Board of Health and Welfare. Information regarding The Swedish Causes of Death Registry. .
207. Swedish Tax Agency/ Skatteverket. Information regarding The Total Population Registry. http://www.skatteverket.se/privat/folkbokforing/omfolkbokforing.4.76a43be412206334b89800022999.html

208. Aspegren K, Holmberg L, Adami HO. Standardization of the surgical technique in breast-conserving treatment of mammary cancer. The British journal of surgery 1988 Aug;75(8):807-810.
209. Witte MH, Witte CL, Bernas M. ISL Consensus Document revisited: suggested modifications (summarized from discussions at the 16th ICL, Madrid, Spain, September 1997 and the Interim ISL Executive Committee meeting). Lymphology 1998 Sep;31(3):138-140.
210. Sagen A, Karesen R, Skaane P, Risberg MA. Validity for the simplified water displacement instrument to measure arm lymphedema as a result of breast cancer surgery. Archives of physical medicine and rehabilitation 2009 May;90(5):803-809.
211. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67(6):361-370.
212. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 2002 Feb;52(2):69-77.
213. Arving C, Glimelius B, Brandberg Y. Four weeks of daily assessments of anxiety, depression and activity compared to a point assessment with the Hospital Anxiety and Depression Scale. Qual Life Res 2008 Feb;17(1):95-104.
214. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. Eur J Cancer 2001 Jan;37(2):189-197.
215. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med 1995 Nov;41(10):1349-1358.
216. Sullivan M KJ, Ware Jr J., ed. Swedish manual and interpretation guide. International Quality of Life Assessment (IQLA) Project. Heath care Research Unit. Medical faculty. Gothenburg University and Sahlgrenska Hospital. Gothenburg: Heath care Research Unit. Medical faculty. Gothenburg University and Sahlgrenska Hospital.; 1994.
217. van Gestel YR, Voogd AC, Vingerhoets AJ, et al. A comparison of quality of life, disease impact and risk perception in women with invasive breast cancer and ductal carcinoma in situ. Eur J Cancer 2007 Feb;43(3):549-556.
218. Nekhlyudov L, Kroenke CH, Jung I, Holmes MD, Colditz GA. Prospective changes in quality of life after ductal carcinoma-in-situ: results from the Nurses' Health Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006 Jun 20;24(18):2822-2827.
219. Amichetti M, Caffo O, Arcicasa M, et al. Quality of life in patients with ductal carcinoma in situ of the breast treated with conservative surgery and postoperative irradiation. Breast Cancer Res Treat 1999 Mar;54(2):109-115.
220. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999 Jun;48(11):1507-1515.
221. Partridge A, Adloff K, Blood E, et al. Risk perceptions and psychosocial outcomes of women with ductal carcinoma in situ: longitudinal results from a cohort study. J Natl Cancer Inst 2008 Feb 20;100(4):243-251.
222. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J Cancer 2000 Oct;36(15):1938-1943.
223. Schover LR, Yetman RJ, Tuason LJ, et al. Partial mastectomy and breast reconstruction. A comparison of their effects on psychosocial adjustment, body image, and sexuality. Cancer 1995 Jan 1;75(1):54-64.
224. Collaborative Group on Hormonal Factors in Breast C. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including

58,209 women with breast cancer and 101,986 women without the disease. Lancet 2001 Oct 27;358(9291):1389-1399.
225. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010 Jul 10;28(20):3271-3277.
226. Blows FM, Driver KE, Schmidt MK, et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS medicine 2010 May;7(5):e1000279.
227. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010 Apr 1;28(10):1684-1691.
228. Zhou W, Jirstrom K, Amini RM, et al. Molecular subtypes in ductal carcinoma in situ of the breast and their relation to prognosis: a population-based cohort study. BMC cancer 2013;13:512.
229. Cornish BH, Chapman M, Hirst C, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology 2001 Mar;34(1):2-11.
230. Hayes SC, Rye S, Battistutta D, Newman B. Prevalence of upper-body symptoms following breast cancer and its relationship with upper-body function and lymphedema. Lymphology 2010 Dec;43(4):178-187.
231. Goldberg JI, Riedel ER, Morrow M, Van Zee KJ. Morbidity of sentinel node biopsy: relationship between number of excised lymph nodes and patient perceptions of lymphedema. Ann Surg Oncol 2011 Oct;18(10):2866-2872.
232. Lopez Penha TR, Slangen JJ, Heuts EM, Voogd AC, Von Meyenfeldt MF. Prevalence of lymphoedema more than five years after breast cancer treatment. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2011 Dec;37(12):1059-1063.
233. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. The lancet oncology 2013 Apr;14(4):297-305.
234. Shah-Khan M, Boughey JC. Evolution of axillary nodal staging in breast cancer: clinical implications of the ACOSOG Z0011 trial. Cancer control : journal of the Moffitt Cancer Center 2012 Oct;19(4):267-276.
235. Hoyer M, Johansson B, Nordin K, et al. Health-related quality of life among women with breast cancer - a population-based study. Acta Oncol 2011 Oct;50(7):1015-1026.
236. De Gournay E, Guyomard A, Coutant C, et al. Impact of sentinel node biopsy on long-term quality of life in breast cancer patients. British journal of cancer 2013 Nov 26;109(11):2783-2791.
237. Hormes JM, Bryan C, Lytle LA, et al. Impact of lymphedema and arm symptoms on quality of life in breast cancer survivors. Lymphology 2010 Mar;43(1):1-13.
238. Nesvold IL, Reinertsen KV, Fossa SD, Dahl AA. The relation between arm/shoulder problems and quality of life in breast cancer survivors: a cross-sectional and longitudinal study. J Cancer Surviv 2011 Mar;5(1):62-72.
239. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life. Acta Oncol 2010 Apr;49(3):347-353.
240. Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in

situ of the breast. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008 Mar 10;26(8):1247-1252.

241. Solin LJ, Fourquet A, Vicini FA, et al. Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. Cancer 2005 Mar 15;103(6):1137-1146.

242. Antonovsky A. The structure and properties of the sense of coherence scale. Soc Sci Med 1993 Mar;36(6):725-733.