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Complications after Breast Cancer Surgery and Oncological Outcomes

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Abstract

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Breast cancer is the most common cancer worldwide for females. A frequent complication following breast cancer surgery is surgical site infection (SSI). Complications can result in diminished quality of life, increased morbidity, elevated healthcare costs, delayed initiation of adjuvant therapy, loss of reconstruction, and potentially adverse oncological outcomes. In **Paper I**, the primary objective was to investigate the purported association between SSI and breast cancer recurrence. In addition, the study aimed to explore a potential link between any postoperative infection and breast cancer recurrence. This population-based, retrospective cohort study found that neither SSI nor other postoperative infections were associated with worse oncologic outcomes. **Paper II** investigated risk factors for SSI following breast cancer surgery, as well as risk factors for other wound complications. This research was conducted through a prospectively registered cohort study. Multivariable analysis identified BMI 25-30 and BMI >30 as the only significant risk factors for SSI. Additionally, significant risk factors for any wound complication included mastectomy with or without reconstruction, as well as BMI 25-30 and BMI >30. In **Paper III**, the primary aim was to evaluate whether SSI increases the risk of systemic breast cancer recurrence. Secondary objectives included assessing the impact of SSI on the risk of locoregional recurrence (LRR), breast cancer-specific survival (BCSS), and overall survival (OS). This analysis utilized high-quality data from national population-based registers, checking for confounding variables such as patient and tumour characteristics. In conclusion, SSI following breast cancer surgery does not significantly increase the risk of systemic recurrence, LRR, overall death, or breast cancer-specific death. **Paper IV** evaluated the risk of systemic breast cancer recurrence following major systemic postoperative infection or other major event. It also assessed the impact of these exposures on LRR, OS, and BCSS. Utilizing the same cohort as in **Paper III**, the findings indicated that postoperative major systemic infection was associated with an increased risk of systemic recurrence, overall death and breast cancer-specific death, but not with LRR.

In conclusion, this thesis does not support the hypothesis that SSI is associated with poorer oncological outcomes. However, it demonstrates an association between major systemic infections and worse oncological outcomes.

Keywords: Breast cancer surgery, postoperative complications, surgical site infection, systemic infection, postoperative major event, risk factors, recurrence, survival, population-based

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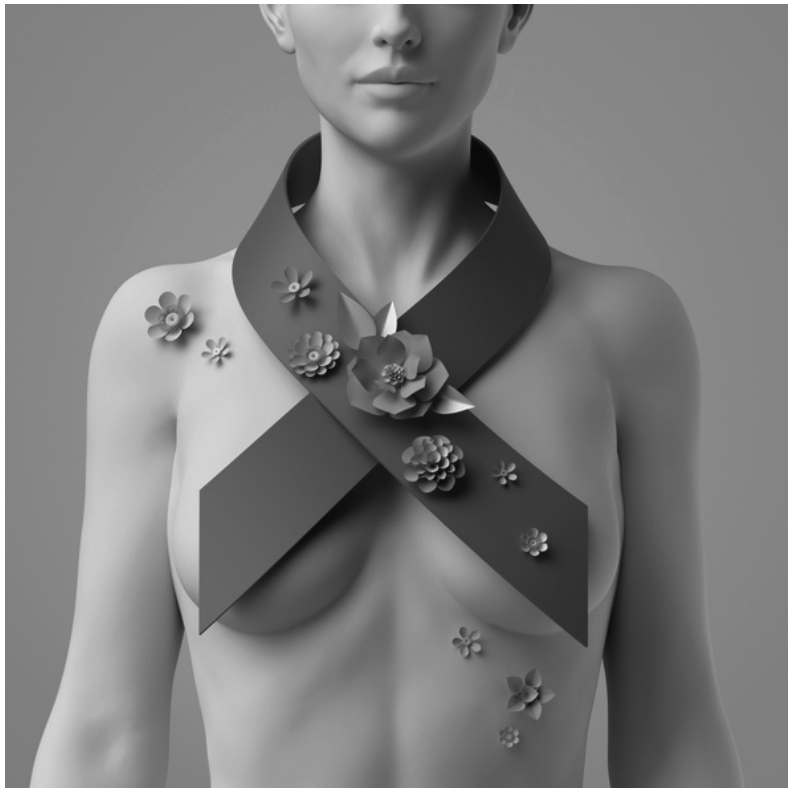


To women

List of Papers

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

I. Adwall L, Pantiora E, Hultin H, Norlén O. (2021) Association of postoperative infection and oncological outcome after breast cancer surgery. *BJS open*. 5(4).

II. Adwall L, Hultin H, Mani M, Norlén O. (2022) Prospective Evaluation of Complications and Associated Risk Factors in Breast Cancer Surgery. *Journal of Oncology*. p 6601066.

III. Adwall L, Fredriksson I, Hultin H, Mani M, Norlén O. (2024) Postoperative complications after breast cancer surgery and effect on recurrence and survival: population-based cohort study. Published *BJS Open 241214.*

IV. Adwall L, Fredriksson I, Hultin H, Stålberg P, Mani M, Norlén O, Sackey H. (2024) Postoperative major systemic infection following breast cancer surgery associated with worse oncological outcomes. *Manuscript*.

Contents

Abbreviations

AI	Aromatase inhibitor
AJCC	American Joint Committee on Cancer
ALND	Axillary lymph node dissection = axillary clearance
ASCO	American Society of Clinical Oncology
BCS	Breast-conserving surgery
BCSS	Breast cancer-specific survival
BMI	Body mass index
CAP	College of American Pathologists
CCI	Charlson Comorbidity Index
CDK4/6	Cycline-dependent kinases 4/6
CI	Confidence Intervals
CRP	C-reactive protein
DAG	Directed acyclic graph
DCIS	Ductal carcinoma in situ
DDFS	Distant disease-free survival
DFS	Disease-free survival
DRFS	Distant recurrence-free survival
EBCTCG	Early Breast Cancer Trialists´ Collaborative Group
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
ET	Endocrine therapy
FNR	False-negative rate
GDPR	General Data Protection Regulation
HAI	Healthcare-associated infections
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
IBR	Immediate breast reconstruction = immediate reconstruction
ICD	International Classification of Diseases
IDFS	Invasive disease-free survival
IHC	Immunohistochemistry
ITC	Isolated tumour cells
LCIS	Lobular carcinoma In Situ
Lpk	White blood cell count
LR	Local recurrence
LRR	Local regional recurrence

MGAs	Multigene assays
N	Nodal stage
NAT	Neoadjuvant therapy
NAC	Neoadjuvant chemotherapy
NHG	Nottingham Histological Grade
NST	No special type
OFS	Ovarian function suppression
OR	Odds ratio
OS	Overall survival
pCR	Pathologic complete response
PD-1	Programmed cell death-1 receptor
PD-L1	Programmed cell death-1 receptor, ligand 1
PR	Progesterone receptor
RCC	Regional Cancer Centre
RCT	Randomised controlled trial
RT	Radiotherapy
SSI	Surgical site infection
SLN	Sentinel lymph node
SLNB/SNB	Sentinel lymph node biopsy
T	Tumour stage
TAD	Targeted axillary dissection
TDLU	Terminal duct lobular unit
TILs	Tumour-infiltrating lymphocytes
TNBC	Triple-negative breast cancer
WBI	Whole-breast irradiation
yp	Pathological status of a tumour following NAT

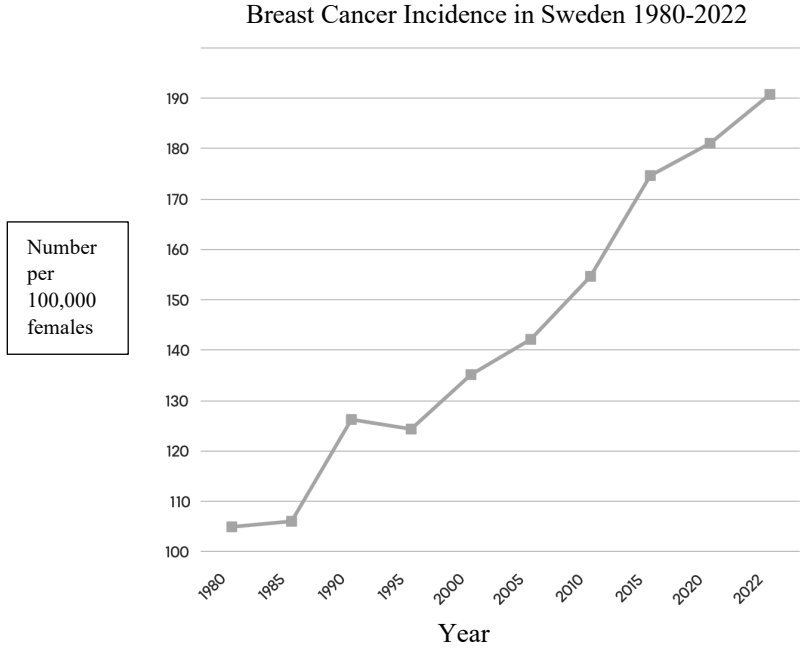
1 Introduction

Breast cancer is the most common cancer worldwide in females. Generally, breast cancer is a treatable disease and survival rates are increasing due to improvements in screening and treatment. W. S. Halsted performed the first clearly documented radical mastectomy in the United States in 1882 (1). The role of breast conserving surgery (BCS) was established during the 1980s, thanks to U. Veronesi in Italy and B. Fisher in the USA (2). Since then, de-escalating surgery has continued, especially where axillary surgery is concerned. Recent studies suggest that BCS + radiotherapy (RT) leads to even better survival than mastectomy regardless of RT (3). Aesthetic outcomes are also of great importance, and there has been a rapid expansion of oncoplastic techniques and advancements in different reconstruction methods. A diagnosis of breast cancer will have a huge impact on the patient's daily life with physical, social, economic, emotional and sexual concerns. Research is of paramount importance to understand and improve outcomes for patients with breast cancer. As someone who has worked as a breast cancer surgeon for over 10 years and witnessed the suffering that postoperative complications can cause, it is of utmost importance to study both the potential future impacts of these complications and to do our best to reduce them.

2 Breast cancer

2.1 Epidemiology

In 2020, there were 2.3 million women diagnosed with breast cancer, and 685,000 deaths occurred globally. At the end of 2020, there were 7.8 million women alive who had been diagnosed with breast cancer in the previous five years, making it the world´s most prevalent cancer (4). Since the late 1970s, breast cancer incidence rates in Europe increased by 50% between 1979-1981 and 1998-2000 and then by 10% between 1998-2000 and 2011-2013. In Sweden, 8,486 women and 57 men were diagnosed with breast cancer in 2022 (5). The increase in breast cancer incidence is likely due to several factors including improved breast cancer screening, an increased life expectancy, changes in lifestyle factors, and reproductive patterns (6). The median age at which breast cancer is diagnosed in Sweden is about 66 and one in ten women in Sweden will receive the diagnosis before the age of 75 (7).



https://www.cancerfonden.se/om-cancer/statistik/brostcancer
Reproduced with permission from the Swedish Cancer Society; source the National Board of Health and Welfare. 240923.

2.2 Aetiology

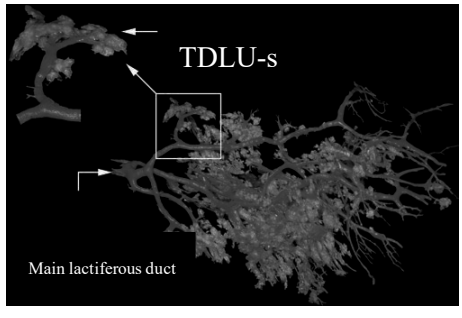
The aetiology of breast cancer is multifactorial and not completely understood. Oestrogens have proliferative effects on breast epithelial tissue and are involved in breast carcinogenesis. High levels of serum oestrogens have been linked with an increased breast cancer risk, especially among postmenopausal women (8). Several risk factors for breast cancer have been identified. Risk factors with a relative risk ≥ 4 are: female gender, increasing age, genetic mutations, a past history of breast cancer or other high-risk breast pathology and previous RT. Risk factors with a relative risk ≤ 4 are: positive family history of breast cancer without a known genetic mutation, personal history of benign breast disease, reproductive factors (younger age at menarche, older age at menopause, older age at first pregnancy), use of hormone replacement therapy, lack of physical activity, obesity in postmenopausal women and increased alcohol intake (6). According to the World Cancer Research Fund, 40% of postmenopausal breast cancer may be prevented by reducing alcohol consumption, physical inactivity and obesity (8).

2.3 Diagnosis

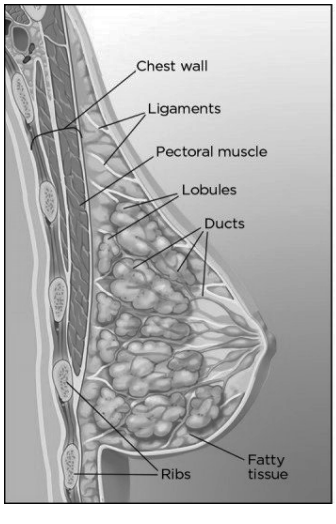
The diagnosis of breast cancer is based on triple diagnostics, including clinical examination of the breast and locoregional lymph nodes, mammography/ultrasound and histopathological examination of core biopsy, or cytological examination of fine-needle aspiration. Although Europe has led the world in implementing breast screening programmes, there are significant differences between countries. Sweden was one of the early adopters of breast screening in the mid-1980s (9). According to Swedish guidelines, women between the ages of 40 and 74 are offered regular mammograms. An updated overview of Swedish randomised trials reported a significant 21% reduction in breast cancer mortality. The reduction was greatest in the 60-69 age group (33%) (10). A recent systematic review across a range of study designs suggests that screening women aged 40-69 is associated with a reduction in breast cancer death. Their recommendation is that women with an average risk of breast cancer should undergo regular screening mammography starting at the age 45 and should continue as long as their overall health is good and the women have a life expectancy of 10 years or longer (11). Overdiagnosis is a potential disadvantage of breast cancer screening. The analysis of data by an independent panel of experts in the UK concluded that for every 10,000 UK women aged 50 invited for screening for the next 20 years, 43 deaths from breast cancer would be prevented and 129 cases of breast cancer, invasive or non-invasive, would be over-diagnosed. In other words, one breast cancer death can be prevented for about every three over-diagnosed cases identified and treated (12).

2.4 Histopathological subtype and grade

Breast glandular tissue in each breast consists of 15-20 lobes and as many main ducts. The main ducts branch and finally terminate in the terminal duct lobular unit (TDLU) which secretes milk during lactation. Epithelial breast malignancies arise from the TDLU (13).



Blue: ductal structure. White: TDLUs. Image from Breast Cancer Management for Surgeons, Gross Anatomy of the Breast and Axilla, Palhazi, P. Reproduced with permission from Springer Nature.



https://www.mskcc.org/cancer-care/types/breast/anatomy-breast

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Ductal carcinoma in situ (DCIS) represents an intraductal lesion without invasion of the surrounding tissue through the basal membrane and, hence, it does not metastasize. The widespread adoption of screening mammography has contributed to an increase of new cases being diagnosed with DCIS, and DCIS now represents some 25% of all breast cancer diagnoses. If not treated, it is estimated that 20% - 30% of DCIS will progress to invasive cancer (14).

The most common (70% - 80%) histological tumour type is invasive carcinoma of no special type (NST), formerly termed invasive ductal carcinoma. The second most frequent (10% - 12%) histological subtype is invasive lobular breast cancer, which is characterized by epithelial cadherin mutations and a dissociated growth pattern. Other more uncommon invasive types are tubular, mucinous, medullary, metaplastic, inflammatory and papillary carcinomas. Together, these account for the remaining 10% of all cases (15).

The most common and widely accepted grading system is the Nottingham Histological Grade (NHG) (the Scarff-Bloom-Richardson grade modified by Elston and Ellis). To establish the grade, three parameters are taken into account: differentiation, anisokaryosis (cellular variability) and mitoses. Each variable is scored from minimum 1 to maximum 3, total score 3-5 corresponding to grade 1; 6-7 to grade 2, and 8-9 to grade 3 (15).

2.5 Immunohistochemistry

2.5.1 Oestrogen Receptor (ER) and Progesterone Receptor (PR)

The majority of invasive breast cancers (up to 80% - 85%) express ER receptors. ER and PR expression is an independent prognostic factor in breast cancer. Patients with ER and/or PR positive tumours have a better survival rate than those with hormone receptor negative tumours. Hormone receptor status of invasive breast cancer cells is also predictive, since high expression predicts a benefit from endocrine therapy (ET) in the adjuvant and metastatic setting. The cut-off for positive status is 1% (recommended by the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP)) (15). According to German guidelines, ER levels should not only be categorised as positive or negative. Low ER levels ≤ 10% need to be handled differently since they are more similar to triple-negative breast cancer (TNBC) than to luminal (hormone-positive) tumours. Thus, omitting endocrine therapy may be an option in these cases (16). In Sweden, ER positivity is defined as ER ≥ 10 % (17).

2.5.2 HER2 (ERBB2)

Human epidermal growth factor receptor 2, known as HER2, is a tyrosine kinase receptor. It is coded by the ERBB2 gene and is overexpressed in approximately 15% - 20% of all breast cancer. HER2 is both prognostic and predictive. Overexpression of HER2 is an adverse prognostic factor that is associated with poorly differentiated, high-grade tumours, high rates of cell proliferation and lymph node involvement. About half of HER2-positive breast cancer also expresses ER and/or PR. However, the levels are typically lower

than in HER2-negative, hormone receptor positive breast cancer. All these factors contribute to a greater risk of recurrence. HER2 gene amplification is rare in cancers other than breast cancer. Eligible HER2-targeted therapy dramatically improves outcomes among patients with HER2-positive breast cancer (18).

2.5.3 Ki67

Breast cancer proliferation is a very important factor in the evaluation of disease aggressiveness and predicts prognosis and chemotherapy benefit. The nuclear protein Ki67 is expressed on proliferating tumour cells, reflecting the portion of dividing cancer cells. There is no international consensus about the scoring and cut-off values to discriminate between low, intermediate and high proliferating tumours (15). In accordance with new guidelines from the International KI67 Working Group, since 2022, Swedish pathologists have used these cut-offs: < 6% low, 6% - 29% intermediate and > 29% high (19).

2.6 Immunomarkers

2.6.1 Tumour-infiltrating lymphocytes (TILs)

Host microenvironment is an important factor in predicting response to immune checkpoint inhibition. TILs are a mixture of pro-inflammatory immune cells that are found in both the tumour and the surrounding stroma and are a marker of immunogenicity. Clinical trials have confirmed TILs as a prognostic biomarker, particularly in TNBC- and HER2-positive subtypes, where a relationship between increased TILs and improved recurrence-free survival has been shown. TILs also have a predictive value since high TILs have been associated with higher rates of pathological complete response (pCR) to neoadjuvant treatment across all breast cancer subtypes (20).

2.6.2 Programmed cell death-1 receptor, ligand 1 (PD-L1)

PD-1 is an immune checkpoint inhibitor which is expressed on immune cells. It is especially activated by PD-L1. Concerning cancer, the expression of PD-L1 seems to be an immune escape mechanism. Studies have reported efficacy of blocking PD-1/PD-L1 with immune checkpoint inhibitors (21).

2.7 Molecular subtypes

Thanks to advancements in histopathological diagnostics and gene expression made during the past 20 years, breast cancer today is viewed as a heterogenous disease. The intrinsic classification of Perou and Sorlie divides breast cancer into at least four distinct groups of molecular patterns which are based on a 50-gene expression signature (PAM50) (15, 22). The four original groups can be directly determined with a multigene assay or can be reconstructed with immunohistochemistry (IHC) determined hormone receptors, HER2 status and Ki67 into five surrogate intrinsic subtypes (22, 23):

- *Luminal A-like:* ER and/or PR strongly positive, HER2 negative, low proliferation and typically low grade. This is the most common subtype (60% - 70%) and the one with the best prognosis.
- *Luminal B-like, HER2 negative:* ER and/or PR weak positive, HER2 negative, higher grade and high proliferation. Approximately 10% - 20% of all breast cancer.
- *Luminal B-like, HER2 positive:* As above, but HER2 positive.
- *HER2 positive, non-luminal:* HER2 positive, ER and PR negative, high proliferation and grade. HER2 positive breast cancer accounts for 13% - 15% of all breast cancers.
- *Triple-negative:* HER2, ER and PR negative, high proliferation and grade. Ten to fifteen percent of breast cancers and the one with the worst outcomes.

These molecular subtypes are now used in clinical routine and could, in accordance with the St. Gallen consensus, guide systemic therapy decision-making for breast cancer.

2.8 Multigene assay (MGAs)

Although surrogate intrinsic subtypes guide clinicians in decision-making regarding systemic treatment, there are often cases where it is challenging to determine whether the subtype is Luminal A-like or Luminal B-like. Various MGAs have become available to clinicians treating early-stage breast cancer since the beginning of the 2000s. The most common ones are: Oncotype DX, MammaPrint, Prosigna (PAM 50), EndoPredict and the Breast Cancer Index. The benefit of using MGAs is to offer chemotherapy only to patients who are likely to profit from it, while sparing other patients an unnecessary treatment. Oncotype DX is the first MGA validated to predict the benefit of adjuvant chemotherapy in hormone-positive early stage breast cancer (24). The RxPonder study showed that postmenopausal women with ER-positive, HER2-negative breast cancer and 1-3 lymph node metastases who have a 21-

gene recurrence score of 25 or lower can safely exclude chemotherapy and only be prescribed adjuvant ET (no difference in 5-year invasive disease-free survival (IDFS) or death) (25). According to the Swedish national guidelines (26), the routine in Sweden is to use MGA (Prosigna) in postmenopausal women with lymph node-negative (should be considered even if 1-3 lymph node metastases), ER-positive, HER2-negative breast cancer if there is any uncertainty of the tumour subtype. Gene expression analysis with Oncotype Dx can be considered for premenopausal women with lymph node-negative, ER-positive, HER2-negative breast cancer where there is uncertainty regarding the tumour's risk categorization before choosing chemotherapy treatment.

2.9 Staging

The TNM staging system for cancer was developed in France by Pierre Denoiw in the mid-1900s (27). This system is used to stage patients by T (tumour size and invasiveness), N (number of lymph node metastases) and M (distant metastases). Patients are further grouped into Stage 0 (in situ) to Stage IV (distant metastases) (28). The American Joint Committee on Cancer (AJCC) has standardised the TNM system for cancer staging. The most recent, eighth, edition was globally adopted in 2018. The major change is the incorporation of prognostic biomarkers such as tumour grade, hormone receptor and multigene panel recurrence scores to allow a prognostic stage which will better correspond with the patient prognosis (stage migration). For example, a patient with a T2N1M0 Grade 2-3 TNBC would be categorized as stage IIIB and not, as previously, Stage IIB (27).

2.10 Treatment – a brief overview

2.10.1 Surgical treatment of the breast

Surgery of the primary tumour remains an important part of curative breast cancer treatment. In the 1980s, two randomized trials were published, showing that OS after BCS followed by adequate RT was similar to that following mastectomy (29, 30). Over the past few decades, BCS has become the primary surgical goal and has replaced mastectomy as standard treatment (22). Absolute contraindications to BCS are the inability to obtain negative margins without causing breast deformity, inflammatory breast cancer, and contraindications to RT (2, 31). Nowadays, multicentric cancer can be safely managed with BCS if two or more lumpectomies can be done with satisfactory cosmetic outcome (31).

Previously, local recurrences (LRs) were higher after BCS than after mastectomy (29, 32). Nowadays, LRs after BCS are much lower than before, at approximately 0.5% per year (33). The reason for this decreased risk of LR is multifactorial. Improved patient selection, better quality surgery, better histopathological evaluation of resection margins, more extensive use of systemic adjuvant treatment and use of RT boost, have all contributed, especially in younger patients (2, 34). The most important independent risk factors for LR after BCS include positive margins and young age (32, 35) A meta-analysis showed that positive resection margins increase the risk of LR with an odds ratio (OR) of 2.44 in patients with invasive breast cancer (35). For breast surgery, "no tumour on ink" is now the accepted standard for clear margins (36). A recently published systematic review and meta-analysis shows that even tumours with closed margins (< 2 mm) are associated with increased distant recurrence compared with wider margins (37). The authors recommend a minimum tumour-free distance of 1 mm and a reappraisal of existing international guidelines. Concerning DCIS, the margins should be at least 2 mm, but wider margins do not decrease the risk of LR (38). If DCIS is associated with invasive breast cancer, it should be managed according to the invasive guidelines. In those cases, the primary determinant of outcome is the biology of the invasive cancer and the majority of patients will receive adjuvant systemic therapy (39).

Quality of life, patient satisfaction of aesthetic outcome and psychosocial aspects (anxiety, depression, body image, sexuality and self-esteem) are greater after BCS than after mastectomy with or without reconstruction. Greatest morbidity is seen after mastectomy alone (40-43). Mastectomy patients, with or without immediate breast reconstruction (IBR), are more likely to have unplanned reoperations for a complication compared to patients having BCS (44). Additionally, data from multiple observational studies suggest that BCS followed by RT is associated with better survival than after mastectomy with or without RT (3, 45-49). Possible explanations for this could be RT, selection bias, confounding by severity, unmeasured confounders or higher complication rates after mastectomy, which could have a negative impact on oncological outcome (3, 47, 50). A causal relationship explaining the superior outcome for BCS cannot be based on observational studies only, but the results show that BCS is at least equivalent to mastectomy. For these reasons BCS should always be performed in the absence of contraindications and if the patient does not have other preferences.

2.10.1.1 Oncoplastic surgery

Oncoplastic surgery was introduced in the early 1990s. The aim was to improve long-term cosmetic outcomes after BCS and RT. There are now many techniques available, which are frequently used when more than 20% of the breast needs to be excised or if the location of the tumour is adverse (medial/inferior). The techniques are divided into two groups: volume

displacement and volume replacement. Many studies (no randomized trials) have reported very good outcomes, similar to standard oncology outcomes, after oncoplastic surgery (51).

2.10.1.2 Reconstruction

Breast reconstruction has become widely available and should be offered to the majority of women undergoing mastectomy. Reconstruction can be immediate, simultaneously performed at the time of mastectomy (for breast cancer or as a risk reducing procedure), or delayed, at a later stage. Implant-based reconstruction is less invasive as it does not include donor sites. It is usually a shorter procedure, has a shorter hospital stay and a faster recovery, but the patient may often need repeat surgeries (52). In cases of adjuvant RT, there is a high risk of capsular contracture, worse aesthetic outcome and higher reconstruction failure. Therefore, when RT is planned or even more importantly if the patient had previous RT, then an autologous (patient's own tissue) flap-based reconstruction is often the preferred option (53). Autologous reconstruction provides natural and long-lasting results but involves more extensive surgery, needs enough donor tissue and may result in additional donor site scars. In a newly published study, which examined the long-term results of different breast reconstruction methods in Sweden, women with autologous reconstructions were more satisfied with the results and breast appearance compared to those with implants (54). Breast reconstruction is oncologically safe, improves cosmesis and quality of life, and has few absolute contraindications (for example, inflammatory breast cancer and severe comorbidities where prolonged surgical time would increase risks) (53).

2.10.2 Surgical treatment of the axilla

Lymph node status is one of the most important prognostic factors for patients with breast cancer and is important in decision-making about adjuvant and neoadjuvant treatment (NAT). Traditionally, the method of choice was axillary lymph node dissection (ALND), which has a high frequency of arm morbidity with shoulder pain, impaired movements, numbness and lymphoedema (20% - 40%) (55). Early in the 2000s, sentinel lymph node biopsy (SLNB) became established as the gold standard for axillar staging in breast cancer patients with a clinically and radiologically negative axilla (56). Arm morbidity and lymphoedema are significantly lower after SLNB than after ALND (55). However, several studies have shown that in patients with low-risk cT1N0 breast cancer, even SLNB can be avoided without harming patients (57-60). For example, the randomized controlled trial (RCT) SOUND showed an isolated 5-year axillary recurrence rate of 0.4% and no detrimental effect of distant disease-free survival (DDFS) in the group without any surgery in the axilla. Additionally, adjuvant treatment did not differ between patients who had an SLNB and patients who did not. Axillary surgery is just a staging

procedure and it is likely that fewer and fewer will be performed in the future, since guiding of adjuvant treatment will primarily rely on the use of biological parameters such as subtype rather than clinicopathological variables such as T- and N-stage.

The standard care for patients with metastases has been ALND, but this is no longer the initial approach for most patients with limited axillary disease. Four prospective randomised trials have reported no significant differences in locoregional recurrence (LRR) or survival in patients who are clinically node-negative with metastases in one or two sentinel lymph nodes and treated with SLNB alone (61, 62) or with SLNB plus RT (63, 64).

These days, SLNB is performed after NAT. In patients with clinically node-negative axilla before NAT, SLN identification rates (94% - 96%), false-negative rates (FNR, 6% - 7%) and nodal recurrence rates (<1.5%) are equal to those for patients who undergo primary surgery. High rates (>40%) of nodal pCR in patients with axillary metastases receiving NAT have questioned whether these patients need ALND after NAT (31). Four prospective multicentre trials and a metanalysis have shown that it is accurate to perform SLNB in patients with 1-3 axillary lymph node metastases before NAT who become clinically node negative, if at least three SLN are excised and the method includes dual mapping (FNR <10%) (65-69). Targeted axillary dissection (TAD = SLNB + removal of the marked lymph node metastasis) is an approach to further decrease FNR (70). Metastases in the SLN after NAT and an initial locally advanced tumour (T4) or ≥ 4 lymph node metastases (N2/3) are still often considered to be indications for ALND after NAT (31). Regarding isolated tumour cells (ITC) in the axilla after NAT, the risk of residual metastasis is significantly lower. In a retrospective multicentre study with a median follow-up of 3.2 years, presented in San Antonio, USA, in 2023, and recently published, the risk of axillary recurrence was not significantly higher, regardless of whether additional ALND was performed (71, 72). Regarding micro metastasis in SNB after NAT, the Swedish national treatment guidelines still recommend ALND. However, several studies (73-75) support the hypothesis that the prognosis is similar between patients with pathologically node-negative (ypN0) status after NAT and those with ypNitc/micro after NAT, leading many to consider regional RT instead of ALND as an adequate treatment for ypN1micro. The MARI study (76) indicates that ALND or regional RT may be overtreatment for patients with clinically node-positive (cN1) breast cancer who achieve ypN0 status after NAT. The study reports a 5-year axillary recurrence rate of 0.7% and an OS rate of 98% in patients who received no further axillary treatment after achieving a pCR. Moreover, as presented at the 14th European Breast Cancer Conference in Milan in March 2024, data from the MARI study show (77) that patients with more than three clinical lymph node metastases who become ypN0 and do not undergo ALND but receive regional

RT have a 5-year axillary recurrence rate of 2.9% and an OS rate of 95%, compared to 3.5% and 90%, respectively, for patients without pCR who underwent both ALND and regional RT. Consequently, even these patients might avoid ALND in the future. However, more evidence is needed.

2.10.3 Chemotherapy

Chemotherapy reduces the risk of recurrence by about 30%. The absolute benefit from neoadjuvant or adjuvant chemotherapy depends on the risk of recurrence. The optimal regimen for breast cancer patients consists of a taxane-based regimen, often with anthracyclines in sequence, at least in high-risk patients. Standard CMF (Cyclophosphamide, Methotrexate and Fluorouracil) reduces breast cancer mortality by 20% - 25%. A further proportional reduction of 15% - 20% could be achieved by the taxane-plus-anthracycline-based regimen (78, 79). Simply put, chemotherapy is the standard of care for women with TNBC and HER2+ breast cancer >5 mm, luminal B breast cancer >5-10 mm and for the majority of patients with lymph node metastases (usually not if postmenopausal luminal A or luminal with low/intermediate genomic risk) (31).

Neoadjuvant chemotherapy (NAC) refers to systemic treatment before surgery. In the past, NAC was reserved for patients with inoperable, locally advanced breast cancer. NAC is now used to allow BCS (downstaging) and possibly omit ALND and, in that way, reduce the extent and morbidity of curative surgery (80). Thus, NAC allows improved cosmetic outcomes and reduces postoperative complications such as lymphoedema. The first trial to compare adjuvant chemotherapy and NAC was NSABP B-18 in 1997. Tumour size was reduced in 80% of the patients and there was also a decrease in positive nodes, but there was no significant difference in DFS or OS. However, outcome was better in patients who achieved pCR than in those who did not (81). The observation that patients achieving pCR have a better prognosis has led to studies investigating the use of additional adjuvant therapy in patients without pCR. We now know that capecitabine adjuvant improves DFS and OS in patients with TNBC who do not achieve pCR (82). In the same way, trastuzumab emtansine reduces the risk of invasive breast cancer recurrence or death by 50% in patients with HER2-positive breast cancer (83). These studies show that appropriate candidates for NAC are -- in addition to the above mentioned -- those in whom residual disease may prompt a change in therapy. NAC has been accepted as a standard of care in patients with TNBC and HER2-positive breast cancer >1-2 cm and/or clinically node-positive. In patients with luminal B-like tumours, NAC can be used when a treatment decision can be made without surgical information. Another advantage with NAC is that it allows time for the genetic testing required for surgical treatment decision-making (80).

2.10.4 Endocrine therapy (ET)

Adjuvant ET for 5-10 years is the standard treatment for women with ER-positive breast cancer (84).

2.10.4.1 Tamoxifen

The selective oestrogen receptor modulator tamoxifen is used in premenopausal women to reduce the effect of oestrogen on hormone-sensitive breast cancer cells. Five years of adjuvant tamoxifen reduces the 15-year risk of breast cancer recurrence by 50% and death by 30% (85). Prolonged administration of tamoxifen over 10 years was investigated in the ATLAS and aTTom trials and resulted in a further survival benefit (absolute difference 2.8% (ATLAS)), independent of menopausal status (86, 87).

2.10.4.2 Aromatase inhibitor (AI)

AI decreases the amount of oestrogen circulating by inhibiting the conversion of androgen to oestrogen. In postmenopausal women, this aromatization is the primary source of oestrogen and therefore AI is used for treatment of postmenopausal women (84). Trials indicate that AI is more effective than tamoxifen. A meta-analysis (almost 32,000 postmenopausal women) shows that 5 years of AI reduces relative recurrence rates by about 30% and mortality rates by about 15% compared with tamoxifen (88). The BIG 1-98 and ATAC studies compare tamoxifen versus AI versus a combination for 5 years. In addition, to show that AI is better than tamoxifen, they indicate that sequential therapy is better than tamoxifen alone and AI seems to be better than sequential therapy (at least in ATAC) (89, 90).

2.10.4.3 Ovarian function suppression (OFS)

In premenopausal women, the production of oestrogen occurs mainly in the ovaries. Therefore, the first adjuvant treatment used was bilateral oophorectomy. Since the 1980s, luteinizing hormone-releasing hormone analogues have been used as OFS. This is a reversible therapeutic option with results similar to bilateral surgical oophorectomy (84). The SOFT and TEXT trials studied the role of AIs and tamoxifen in combination with OFS, versus tamoxifen alone. Women who remain premenopausal after adjuvant chemotherapy and receive tamoxifen/AI plus OFS have an absolute increase in 5-year breast cancer-free survival of 4.5%/7.7% versus tamoxifen alone (91). OS between the groups showed no significant difference (92). An EBCTCG (Early Breast Cancer Trialists´ Collaborative Group) meta-analysis shows a reduction in recurrence rates favouring AI over tamoxifen (absolute reduction of about 3% in 5- and 10-year recurrence risk) in premenopausal women receiving OFS. There was no difference in breast cancer or all-cause mortality, but this might be explained by the limited duration of follow-up (median 8.0 years) (93). The

St. Gallen consensus conference of 2015 recommends that higher-risk patients should receive OFS in addition to adjuvant endocrine therapy (84).

2.10.5 CDK4/6 inhibitors

The cell cycle is driven by cycline-dependent kinases (CDKs), such as CDK4 and CDK6, and is associated with tumour initiation and progression. CDK4/6 is considered to play a major role in tumour cell proliferation driven by oestrogen in breast cancer. In recent years, it has been established that targeting the cell cycle is a rational option that could be combined with endocrine therapy for breast cancer (94). Abemaciclib combined with ET is the first CDK4/6 inhibitor to demonstrate a significant improvement in IDFS in patients with ER-positive, HER2-negative, node-positive, high-risk breast cancer (95).

2.10.6 Anti-HER2 therapy

Trastuzumab is an antibody and was developed as a means of blocking the tyrosine kinase-linked HER2 receptor. Different randomised trials have investigated the benefit of at least 1 year of trastuzumab combined with standard adjuvant chemotherapy. This combination is associated with a statistically significant improvement in both OS (37%) and DFS (40%), but has a risk of severe cardiac toxicity. The improvements were observed in all subgroups, suggesting a benefit irrespective of tumour size, hormone receptor status, nodal status or patient age (96, 97). Two years of adjuvant trastuzumab has no additional benefit (98). Two studies analysed 6 versus 12 months' treatment with trastuzumab. The PHARE study concluded that the standard duration should remain 12 months (99), while the PERSEPHONE trial showed non-inferiority for 6-month adjuvant trastuzumab (100). This result signals the potential of reducing treatment duration and thereby toxicity and cost. Standard treatment is nevertheless one year. The APT trial shows that de-escalating treatment with just taxane (chemotherapy) and trastuzumab is possible for patients with small node-negative, HER2-positive breast cancer. The 7-year BCSS was 98.6% and indicates a risk for overtreatment if more aggressive treatment such as NAT is given to these patients (101).

Dual HER2 inhibition with trastuzumab and pertuzumab in the adjuvant setting improves IDFS for patients with node-positive, HER2-positive breast cancer (102). In the neoadjuvant setting, targeting HER2 with dual blockade improves the pCR rate, which translates into long-term survival benefits. Today, this is the gold standard (103, 104).

2.10.7 Immune checkpoint inhibitor

Pembrolizumab, an anti-programmed death 1 (PD-1) monoclonal antibody has been used in patients with metastatic TNBC and has shown anti-tumour activity and a range of mainly low-grade toxic effects. High-risk TNBC is frequently associated with early recurrence and high mortality, and NAC is the standard treatment. KEYNOTE-522 shows that, among patients with TNBC, the addition of pembrolizumab to NAC leads to a significantly higher percentage with pCR (105). A recently published follow-up shows that pembrolizumab neoadjuvant, followed by pembrolizumab adjuvant, results in significantly longer event-free survival (37%) than NAC alone (106). The 2024 European Society for Medical Oncology (ESMO) congress reported that even OS is significantly prolonged (107).

2.10.8 Radiation therapy (RT)

Whole-breast irradiation (WBI) of the breast after BCS halves the rate of LR and reduces the breast cancer death rate by about a sixth (108). The tumour bed is the area at highest risk for tumour cell contamination and a radiation boost (additional dose of radiation to the tumour bed after WBI) improves local control, with the largest absolute benefit in young patients. This boost has no effect on long-term OS and increases the risk for moderate to severe fibrosis (34). A shorter course of irradiation (3 weeks instead of 5-6) with higher dose per fraction (hypofraction) has advantages as it reduces treatment time, increases patient compliance, reduces waiting lists and costs. Hypofraction has rates of LRR and late adverse effects at least as favourable as standard treatment (109, 110). Based on these data and convenience, hypofraction is now considered the gold standard for adjuvant breast cancer radiotherapy. The FAST-Forward study even showed that hypofraction (26 Gy in five fractions over 1 week) is not inferior to the standard (40Gy over 3 weeks) for local tumour control (111). The 10-year follow-up of the IMPORT LOW trial demonstrates that it is safe to administer partial breast RT after BCS to patients ≥ 50 years old with NST tumours ≤ 3 cm who have undergone radical surgery (112).

Radiation therapy to the chest wall after mastectomy is recommended when there are tumours > 5 cm, positive surgical margins when further surgery is not possible or in case of pectoral muscle invasion. In cases of node-positive breast cancer (at least ≥ four), inflammatory breast cancer or chest wall/skin infiltration, RT includes the chest wall and regional lymph nodes (113). RT after mastectomy in high-risk patients who are node-negative significantly reduces the risk of LRR (114, 115). After mastectomy and ALND in node-positive breast cancer patients, locoregional RT reduces both LRR and breast cancer mortality (equal reduction in patients with ≤3 positive nodes as in patients

with ≥4 positive nodes) (116). The results of the randomised SUPERMO (Selective Use of Postoperative Radiotherapy After Mastectomy) is currently assessing the role of irradiation in women with intermediate-risk breast cancer following mastectomy (117). Locoregional RT in addition to WBI after BCS in node-positive patients reduces the rate of breast cancer recurrence but does not improve OS (118, 119).

Two ongoing studies are examining the extent of radiation based on the response to NAC. In NSABP B51/RTOG, biopsy-proven, node-positive patients who convert to node negativity after NAC are randomised to regional nodal irradiation (in addition to WBI) or postmastectomy radiotherapy including lymph nodes or no regional RT (120). The trial was presented at the 2023 San Antonio Breast Cancer Symposium: the rates of invasive breast cancer-free recurrence and OS were comparable between the 1,556 patients who received regional nodal RT and those who did not (121). The Alliance 011202 trial is examining the optimal approach to patients who remain node positive after NAC. Patients with a positive SLN are randomised to completion ALND plus nodal RT or nodal RT only. Patients in both arms receive WBI/chest wall RT and RT to all undissected lymph nodes in the axilla, supraclavicular fossa and internal mammary spaces (122). TAXIS is a similar study investigating the possibility of avoiding ALND if ypN+ status remains after NAT (123).

2.11 Breast cancer recurrence

Breast cancer recurrence may occur in the ipsilateral breast, chest wall, regional lymph nodes (ipsilateral axillary, internal mammary or infra/supraclavicular nodes), as well as distant sites and organs. Treatment options for LRR include surgical resection, RT and systemic treatment based on histological examination and staging. Distant metastases are usually treated with palliative intent with systemic treatment, RT, resection of metastases and sometimes even palliative surgery to the breast. In a population-based German study with patients diagnosed between 1999 and 2009, the 10-year cumulative incidence of recurrence was 16%, ranging from 9% in patients with tumour <2cm without positive nodes to 34% in patients with tumours >5 cm with positive nodes. For LLR and distant metastases alone, the results were 8% and 11% respectively (124).

2.11.1 Loco-regional recurrence (LRR)

About 75% of LRR occurs during the first 5 years (115). LR after BCS or mastectomy are diverse oncological events, differing in terms of clinical presentation, surgical treatment and prognosis. LR after BCS often represents growth of undetectable microscopic multifocal or multicentric tumour foci,

and is not often associated with distant disease. It may or may not be associated with a poor prognosis. In contrast, LR following mastectomy (subcutaneous nodules on the chest wall and dermal lymphatic) is usually a local manifestation of disseminated disease. Risk factors for LRR include young age at diagnosis, advanced tumour size, positive nodes, high grade, vascular invasion, ER negativity, HER2 positivity, TNBC, extensive intraductal component, positive resection margin and omitting an indicated adjuvant RT. Recurrence in ER-negative patients decreases over time, while among patients with ER-positive tumours the risk is lower, but persists at about the same annual rate for up to 20 years after diagnosis (124-126). LRR rates following BCS are currently much lower than in the past, at approximately 0.5% per year (33). The risk for LRR after BCS for DCIS is somewhat higher: the 10-year rate has been reported as between 6% and 13% when RT is given as adjuvant treatment (2).

All patients with LRR must undergo staging to diagnose possible metastatic disease before surgery. Mastectomy is the gold standard after BCS plus RT. A surgical approach is probably the best choice for local control even for LRR after mastectomy, but cannot always be performed. The excision must be as wide as possible, ideally at least two or three cm from the nodule. Sometimes the use of a flap-based technique or skin grafting to close the defect will be required (127). Axillary staging in LRR breast cancer is important for locoregional control and to predict prognosis (5-year DFS after ipsilateral breast recurrence varies from 67% if node-negative and 51% if node-positive) (127). Sentinel node identification is higher in patients who have undergone previous SLNB (81%) compared to previous ALND (52%). Lymphatic mapping is important since aberrant lymphatic drainage pathways are common after previous surgery (17% following SLNB and 69% following ALND). Predominant locations are in the contralateral axilla and internal mammary chain. More than a quarter of positive nodes can be found in aberrant pathways (128).

Systemic treatment is used to decrease the risk of relapse and death in patients with completely excised LRR. The CALOR trial is the first randomised trial to confirm that chemotherapy prolongs DFS in patients with ER-negative LRR. But adding chemotherapy to ET in patients with ER-positive LRR did not provide any benefit (129). Tamoxifen significantly improves DFS in breast cancer patients after local treatment for LRR (130).

Patients who develop LLR have worse DDFS and OS regardless of lymph node status (131, 132). Approximately one in four patients who experience a recurrence will eventually die from breast cancer (108).

2.11.2 Systemic recurrence

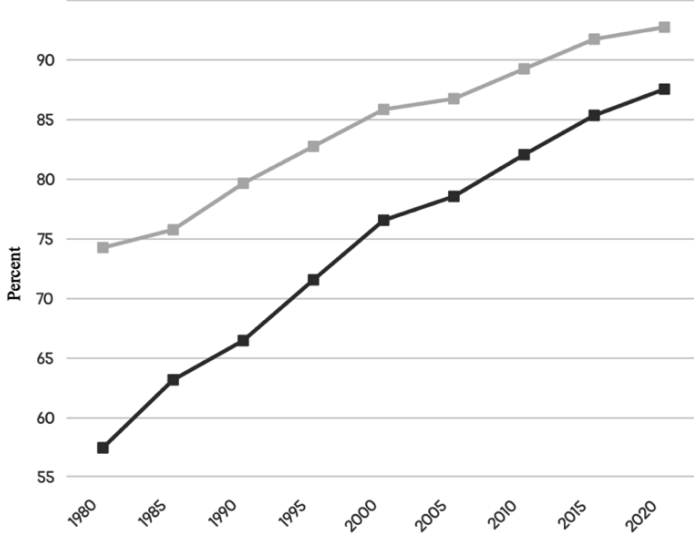
Metastatic breast cancer affects between 19% (in the USA) and 50% (in parts of Africa) of breast cancer patients, depending on the cure rate in their country. Lungs, bones, liver, brain and distant lymph nodes are the most common metastatic locations. Lobular breast cancer has different patterns of dissemination with frequent spread to the peritoneum, viscera, internal genital organs and leptomeninges (133). Tumour size, nodal status, high histological grade and vascular invasion are risk factors for distant metastases following BCS or mastectomy. Additional risk factors after BCS are age < 35 years and microscopic involvement of the excision margin (125).

Breast cancer with distant metastases is incurable. Enhanced treatment over the past few decades has improved survival duration, with median survival rates of between 2 (TNBC) and more than 5 years (luminal HER2 positive). Metastatic breast cancer patients should be treated by a multidisciplinary team of appropriate specialists (oncology, surgery, pathology, radiation, palliative care, psychosocial and physiotherapy). The aim of treatment is palliation, including prolongation of life and improvement or preservation of its quality, and therefore the least aggressive treatment should be used (133). In a randomised trial, there was no survival gain with breast surgery of the primary tumour, although there appears to be a benefit in terms of local control (134). Guidelines from the European Society for Medical Oncology (ESMO) state that "surgery of the primary should not be offered as a routine practice but can be discussed on a case-by-case basis and offered to selected patients" (135).

Less than 2% of breast cancer patients with Stages I and II have asymptomatic metastatic disease, and therefore routine-intensive laboratory and imaging staging is not indicated. Staging with computed tomography (CT) should be considered in cases of an abnormal routine laboratory test, tumours > 5 cm, clinically palpable regional lymph nodes, clinical signs of metastatic disease and all Stages III and IV. PDG-PET/CT detects about 25% more metastases compared to conventional imaging and can be considered in unconfirmed cases (28). However, imaging is often inconclusive, and a biopsy confirming the metastasis is obligatory before establishing the final diagnosis. A biopsy is also paramount in order to confirm the biomarker status of the metastatic tumour, as tumour phenotype can change relatively often (133). A substantial proportion of patients with LRR will be diagnosed with distant metastases, and, because of that, LRR is an indication for staging (28). Pooled data from two randomised clinical trials for Stages I and II breast cancer show that 24% of patients with LRR after BCS, and 33% of patients after mastectomy, were diagnosed with concomitantly distant disease (28, 125).

2.12 Prognosis and survival

The earlier breast cancer is recognised, the better the prognosis. Due to improvements in early detection and treatment, the prognosis for breast cancer is generally good. For women with breast cancer in England, 85% will survive their cancer for 5 years or more and 75% for 10 years or more. The 5-year relative survival by stage for women in England diagnosed between 2013 and 2017 are: Stage I (tumour ≤ 2 cm, node negative or micrometastasis) 98%, Stage II (tumour ≤ 5 cm with 0-3 positive nodes or > 5 cm and node negative) 90%, Stage III (≥ 4 positive nodes and/or tumour with direct extension to the chest wall and/or to the skin or inflammatory breast cancer) 70% and Stage IV (distant metastasis) 25% (28, 136). In 2021, the relative 5- and 10-year survival in Sweden was 92.8% and 87.8% respectively. Men have a slightly worse prognosis, probably due to diagnosis at a later stage (91.1% and 78.3% respectively) (137).



Light Blue: Relative 5-year survival. Dark Blue: Relative 10-year survival.
https://www.cancerfonden.se/om-cancer/statistik/brostcancer
Reproduced with permission from the Swedish Cancer Society; source the National Board of Health and Welfare. 240923.

Relative 5- and 10-year survival in Sweden, 1980-2020 (women)

3 Infections

3.1 General

Infections are ubiquitous, impacting individuals globally to varying degrees. Lower respiratory infections represent the deadliest contagious disease worldwide, ranking as the 4th leading cause of death according to the World Health Organization (WHO) (138). In 2015, two conditions, upper respiratory infections and diarrheal diseases, each affected over a billion people, with a staggering 17.2 billion and 2.4 billion cases respectively (139). Healthcare-associated infections (HAI) constitute a substantial proportion of healthcare-related harm and are linked to significant expenses (140). In developing nations, SSIs are the most prevalent HAI in hospitals, with a pooled cumulative incidence of 5.6 per 100 surgical procedures (141).

3.2 SSI

SSI is one of the most commonly reported types of HAI, about 20% of all HAIs in Europe in 2011-2012 (142). The incidence of postoperative SSI following breast cancer surgery ranges from 0% - 26% (143, 144). A comprehensive review by O´Conner et al. (145) based on 99 studies and nearly 500,000 patients, reported a mean SSI incidence of 13.1%. The predominant causative bacteria identified were *S. aureus, E. coli and P. aeruginosa*. Factors known to elevate SSI risk are high age, obesity, diabetes, smoking (current or recent) and recent chemotherapy. Additional risk factors include hypertension, an ASA score of 3 or 4, a history of previous breast surgery or chest irradiation, insertion of a breast implant or tissue expander, inadequate prophylactic antibiotic dosing, increased intraoperative bleeding, haematoma, seroma, postoperative drain, the placement of a second drainage tube, and prolonged or bilateral procedures (146-151). Mitigating the risk for SSI after breast cancer surgery is crucial for several reasons. An SSI can delay the initiation of adjuvant treatment, cause morbidity, increase health care costs and result in reconstruction failure. A study from the USA estimated an additional cost over $4,000 per patient with an SSI (152). In 2012, the total annual cost for the five major healthcare-associated infections in the USA was $9.8 billion, with SSIs accounting for the most with 33.7% of the total cost (140). Prolonged hospitalization and increased morbidity due to an SSI also

adversely affect the patient's health-related quality of life (142). Moreover, some evidence suggests that an SSI may elevate the risk for breast cancer recurrence (145, 153-156), although these data are not yet conclusive. For instance, Murphy et al. have identified an increased risk for systemic recurrence in patients with wound complications compared to those without (155) and Beecher et al. have demonstrated a six-fold higher risk for breast cancer recurrence in patients with an SSI following immediate breast reconstruction (154). De Boniface et al. showed an association between major postoperative complications and worse OS and BCSS (157), and there are other studies showing worse outcomes after postoperative complications (145, 153, 156). Conversely, other studies indicate a lack of conclusive evidence on this topic (158-162). A systematic review and meta-analysis reveals that postoperative complications are associated with recurrence and survival outcomes in approximately half of the included studies, concluding that the relationship between postoperative complications and prognosis is complex (50).

One RCT showed that patients without risk factors undergoing standard breast cancer surgery do not require routine antibiotic prophylaxis (163). Patients suffering from an SSI have a risk of prolonged time to adjuvant oncological treatment. Evidence indicates that delays in cancer treatment can negatively impact oncological outcomes, with longer delays further exacerbating these adverse effects (164-166) It is important to understand risk factors for SSI after breast cancer surgery in order to develop infection-prevention strategies and improve surgical and maybe even oncological outcomes.

4 Theoretical link between SSI and recurrence

There is a theoretical link between SSI and breast cancer recurrence. In 1863, Rudolf Virchow identified the presence of white blood cells in malignant tissue, leading him to propose a connection between inflammation and cancer. Since the 1990s, an increased understanding of the inflammatory microenvironment and cancer tissue has enhanced this hypothesis (167). Experimental studies suggest that many factors involved in wound healing can stimulate tumour growths. TNFα, VEGF, and pro-inflammatory cytokines such as interleukin 1 and 6 are examples of factors that have been studied (167-171). One theory is that the release of local and systemic inflammatory mediators (cytokines, chemokines and growth factors) interacts with remaining tumour cells. This could stimulate tumour growth and increase the recurrence risk (154, 171). Growth factors released into the blood stream can stimulate the proliferation of distant metastases (171, 172). Infection results in a greater inflammatory response, and animal studies have shown that an SSI increases angiogenesis and the incidence of recurrence after cancer surgery (173).

Trauma caused by surgery and other stress factors may activate dormant micro metastases and cause local or distant recurrence (170). Cell-mediated immunity is important in controlling circulating tumour cells (174). However, surgery can cause immunosuppression. There are several theories about what causes this, such as the anaesthesia itself, anaesthesia drugs, hypothermia, tissue damage, blood loss, transfusion, pain, perioperative anxiety and stress. The mechanism behind this probably involves local factors and pro-inflammatory cytokines such as IL 6 and 8 and CNS-mediated neuroendocrine feedback. The suppression of cell-mediated immunity postoperatively may increase the recurrence risk. It is suggested that this, in combination with angiogenesis, tissue damage and the release of growth factors, increases the risk of distant metastases. The extent and duration of immunosuppression is correlated with the degree of tissue damage (171). Laparoscopic surgery reduces cell-mediated immunity to a lesser degree than open surgery. Animal studies have shown that minimally invasive surgery reduces the development of metastases, probably due to decreased immunosuppression (less tissue damage, bleeding, a lower neuroendocrine response and less pain) (175).

Breast cancer recurrence can manifest after extended latency periods, ranging from years to decades (108). One hypothesis to explain this phenomenon is cancer dormancy, a stage in cancer progression where residual disease remains asymptomatic (176-178). The perioperative period is crucial in determining oncological outcomes (179). Adjuvant therapy, aimed at eradicating residual microscopic disease, is typically initiated no earlier than one month post-surgery due to concerns regarding wound healing. Studies have suggested that perioperative administration of cyclooxygenase-2 (COX-2) and β-adrenergic blockade may benefit breast cancer patients by reducing systemic inflammation and inhibiting multiple pathways related to metastasis (171, 180, 181). Additionally, some researchers propose that immunomodulatory interventions during the perioperative period could potentially improve survival (171, 182).

Thus, a postoperative SSI with its inflammatory response could theoretically stimulate subclinical micro metastases and promote recurrence. This hypothesis is supported by evidence from other malignancies, such as the increased risk of recurrence following infection after colon cancer surgery (183). Likewise, infectious complications after surgeries for head/neck and gastric cancers, are correlated with poorer outcomes (184, 185).

5 Aims

The overall aim of this thesis was to evaluate whether there is an association between postoperative complications and oncologic outcomes in breast cancer patients.

More specifically, the aims were:

I. To investigate whether the risk of systemic recurrence, LRR, overall death and breast cancer-specific death was increased after SSI (**Papers I and III**).

II. To investigate whether the risk of systemic recurrence, LRR, overall death and breast cancer-specific death was increased after other local surgical or major local surgical complications (**Paper III**).

III. To investigate whether the risk of systemic recurrence, LRR, overall death and breast cancer-specific death was increased after major systemic infections or other major event (mainly **Paper IV** and partly **Paper I)**

IV. To assess risk factors for SSI and to examine whether there are other risk factors for other postoperative complications, such as wound dehiscence, skin necrosis, haematoma and flap failure (**Papers II and III**).

6 Materials and Methods

6.1 Data source and patients

6.1.1 Paper I

In connection with a project during my specialization in surgery, it was decided to conduct a medical record review of all patients within the Uppsala region who underwent breast surgery between 2009 and 2010, with the intention of investigating the frequency of SSI. Since we had data on which patients had suffered an SSI, the idea arose of investigating whether they had worse oncological outcomes, since some studies had shown such an association. All patients who underwent BCS or mastectomy to treat breast cancer between January 2009 and December 2010 were included. Patients with distant metastasis at surgery or within three months after surgery, and those who had other cancer at pathological anatomical diagnosis, were excluded

6.1.2 Paper II

To investigate risk factors for SSI and other postoperative complications in order to try to reduce them, forms with specified pre-chosen variables for breast cancer patients undergoing surgery at the Uppsala University Hospital between May 2017 and May 2019 were created. Thus, wound complications were prospectively registered. The surgeon filled out the first form on the day of surgery. The second form was filled out approximately three weeks later at the postoperative clinical appointment, by the breast nurse or the surgeon. The third form was filled out after approximately four weeks by the oncologist at the patient's first postoperative visit to the oncology department. If there were missing data, the patient's electronic records were scrutinized for completeness. Recordings of seromas were not noted in patients charts or records on a regular basis, so this information was deemed unreliable. The follow-up for postoperative complications was at least 30 days or until reoperation, whichever came first. The reason for selecting a 30-day follow-up period after surgery, rather than 90 days, was due to the clinical routine of postoperative follow-up visits with the surgeon approximately three weeks after surgery and new consultations with the oncologist approximately four weeks after surgery. Choosing a 90-day follow-up would have necessitated an additional visit

solely for the study, which was not feasible. Patients who underwent BCS or mastectomy for breast cancer were included.

6.1.3 Papers III and IV

Most of the studies showing an association between SSI and worse oncological outcomes are small (from a few hundred to just over one thousand patients), which should not allow for adjustments of a sufficient number of variables in the multivariate analysis, increasing the risk for uncontrolled confounding. Because of this, despite the results from Study I, we wanted to conduct a large study and decided to use BCBaSe 3.0. This is a population-based, nation-wide database including individuals diagnosed with breast cancer in Sweden between 2007 and 2019, created for the purpose of facilitating population-based epidemiological breast cancer research. BCBaSe 3.0 integrates individual-level records from the National Quality Register for Breast Cancer (NKBC) with national demographic and health care registers maintained by the National Board of Health and Welfare, Statistics Sweden, and the Swedish Social Insurance Agency.

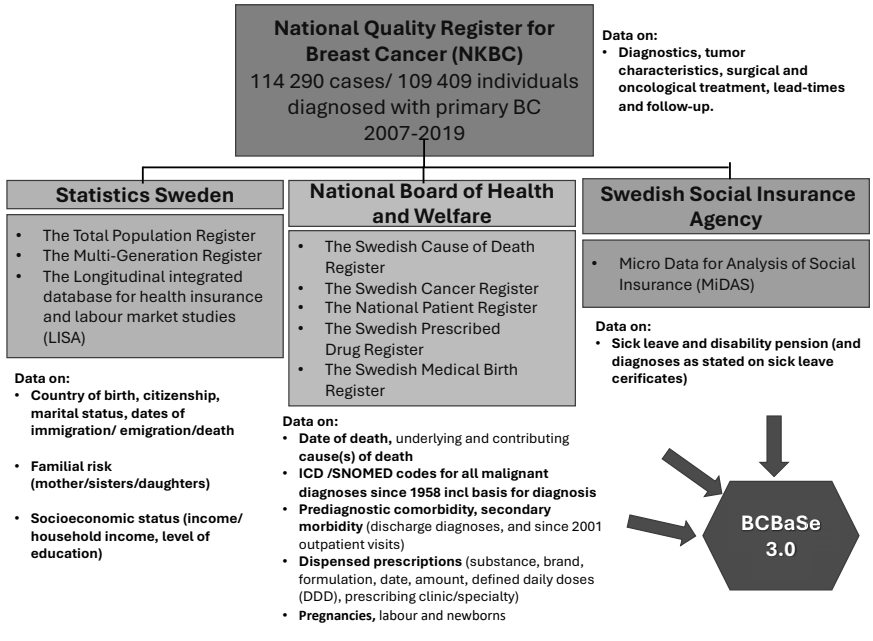


Image from Irma Fredriksson, printed with permission

The NKBC contains detailed clinical data on patient and tumour characteristics, treatment, and follow-up. Its completeness is high, exceeding 99%, as verified through cross-linkage with the National Cancer Register, which mandates reporting by law. The proportion of missing values is less than 5% for

most variables, and the reported information generally exhibits high exact concordance (186). The National Cancer Registry records data on all cancer diagnoses, including site and date, ICD code, morphological SNOMED code, and basis for diagnosis. It is estimated to cover more than 96% – 98% of all incident malignant tumours in Sweden, with 98% of diagnoses being morphologically verified (187, 188). The National Cause of Death Register records information on the date of death, underlying and contributing causes of death according to ICD (189). Overall, 96% of individuals in the Cause of Death Register have a specific cause of death recorded, with the accuracy of death certificates for breast cancer estimated at 93.1% (190). The National Patient Register encompasses comprehensive data on hospital inpatient and outpatient care, detailing up to eight diagnostic codes per patient encounter as per the International Classification of Diseases (ICD), alongside information on surgical interventions, and admission and discharge dates. This register is reputed to encompass approximately 99% of hospital admissions (191). The National Prescribed Drug Register catalogues all medications dispensed by Swedish pharmacies, categorised by the Anatomic Therapeutic Chemical (ATC) classification system, and includes dispensation dates as well as the quantity of defined daily doses (DDD) (192, 193). The Total Population Register maintains records on individuals' life status (alive or deceased), residential address, birth country, and migration details (194). In addition, LISA provides granular data on socioeconomic factors including marital status, highest educational attainment, disposable income, occupation, type of housing, country of birth and that of one's parents (195, 196). However, data from the Multi-Generation Register, the Swedish Medical Birth Register and the MIDAS database were not utilized in this particular study.

The studies included all patients who underwent surgery for primary invasive breast cancer or DCIS between January 1st, 2008, and September 30th, 2019. The reason for inclusion from 2008 and not from 2007, was because the NKBC was established in 2008. Patients with a history of invasive breast carcinoma or DCIS prior to January 2008, those presenting with distant metastasis at the time of or within three months of the primary surgery, and those with distant metastases originating from other malignancies were excluded. Additionally, a sensitivity analysis was conducted, excluding all patients with any prior malignancy before the diagnosis of breast cancer. Monitoring for systemic recurrence and survival analysis commenced 90 days after surgery, and one year after surgery for LRR, and continued until the patient's death or the conclusion of the study on December 31st, 2019.

6.2 Study design

6.2.1 Paper I

Retrospective cohort study. Conducted within the Uppsala region from 2009 to 2010.

6.2.2 Paper II

Prospectively registered cohort study. Conducted at the Uppsala University Hospital from May 2017 to May 2019.

6.2.3 Papers III and IV

Population-based cohort studies using the BCBaSe 3.0 database. Nationwide study with breast cancer patients from January 2008 to September 2019.

6.3 Methods and further considerations

6.3.1 Paper I

All patients underwent breast surgery, with exposure categorized as SSI, other postoperative infections, or no infection within 90 days of surgery. SSI was defined as treatment with antibiotics and/or drainage due to erythema or purulent discharge, with or without fever. Consequently, only SSIs categorized as Grade II or higher according to the Clavien-Dindo classification were included. Other infections were documented when patients received antibiotic treatment without erythema or purulent discharge from the breast. The definition of SSI varies significantly in the literature. Despite having a clear definition, it was still challenging to determine which patients should be classified as having an SSI during the review of medical records. Since white blood cell count (Lpk) and C-reactive protein (CRP) were not routinely measured and cultures were rarely available, it was difficult to ascertain whether the patients had an infection. To accurately identify patients with an SSI, a prospective registration where Lpk, CRP and wound cultures (when possible) are mandatory, would be necessary. However, the method used to identify SSIs was considerably better than relying solely on diagnostic International Classification of Diseases (ICD) codes, as SSIs were rarely coded, at least from 2009 to 2010.

The predictors included age at surgery, body mass index (BMI), smoking status, diabetes, NAT, the number of surgeries in the breast/axilla during 2009 and 2010, type of breast and axillary surgery, seroma aspiration, adjuvant chemotherapy, RT, ET, tumour size on pathology, tumour type, tumour grade,

histologic subtype, and lymph node status. Routine antibiotic prophylaxis was not administered.

6.3.2 Paper II

In an effort to make the SSI definition even more distinct, SSI was defined as at least one of the following: 1) purulent discharge, 2) positive wound culture or 3) treatment with antibiotics, drainage or an incision in conjunction with at least one of the following: A) increasing erythema, B) local heat and swelling, or C) increasing pain. Unfortunately, Lpk and CRP were not routinely measured to diagnose SSI, but a wound culture was routinely taken if an SSI was suspected. The possible risk factors analysed were: age at the time of surgery, BMI, smoking status, diabetes, baseline surgery (primary surgery or reoperation), type of breast and/or axillary surgery, antibiotic prophylaxis, the main surgeon, the assisting surgeon, reoperation within 24 hours, operation time and breast specimen weight. According to clinical routines, all patients who underwent a mastectomy received drainage until the following day, whereas patients who underwent BCS did not. Consequently, drainage was not considered a separate risk factor, as it was inherently part of the surgical procedure. Similarly, NAT was not included as a risk factor for SSI, based on findings from a quality follow-up of breast cancer surgeries conducted in Uppsala from 2014 to 2015 (where NAT was not a risk factor for SSI (OR 0.83 (95% CI 0.186, 3.672)). All breast cancer surgeries performed on each individual patient were included. This led to the data file becoming cumbersome to manage and even difficult to describe in the text. Another, more pragmatic way to record these data, and a learning point, is to register each patient once and use the final surgical procedure in the breast/axilla as the exposure.

6.3.3 Papers III and IV

In Study III, the primary exposure was SSI within 90 days of surgery. An SSI was identified based on the presence of specific diagnostic or intervention ICD-10 codes (T857, T814, HWB00, HWC00) or the dispensation of antibiotics (flucloxacillin J01CF05 or clindamycin J01FF01) within 4 to 90 days following surgery. Since surgeons sometimes prescribe patients prophylactic antibiotics, especially patients undergoing reconstructive procedures, we did not include patients receiving antibiotics immediately in connection with surgery in the SSI definition. For the sake of completeness, we also investigated bleeding or wound complications (defined by at least one of the following diagnostic or interventional codes (ICD; T810, T811, T817, HWD00, HWE00, HWA00, T813, HWF00)) and unspecified local complications (T854, T856, T858, T859, T812, T815, T818, T818W, T819, T889, HWW99) registered within 90 days of surgery. Any local complication was defined as SSI and/or bleeding or wound complication and/or unspecified local complication. Complications were further classified into early (within 30 days of

surgery) and late (31-90 days after surgery) occurrence. The reason for doing so was that, although the traditional definition of postoperative complications often refers to 30 days after surgery, a clinical quality-control study (non-published) performed at the Uppsala breast unit in 2014 and 2015, showed that the mean time to an SSI was 47 days.

Since the hypothesis was that a major complication causes a significantly more extensive inflammatory response than a minor complication, the decision was to sub-group complications. A major complication was defined as one necessitating readmission or an additional surgical intervention, whereas a minor complication did not require such measures. To further investigate risk factors for SSI in a large cohort, a separate analysis with primary surgery as exposure and SSI as the outcome was performed. However, those data were only presented in the supplementary files because it was merely a secondary analysis, to avoid making the article too lengthy.

Despite not showing an association between SSI and worse oncological outcome in Study III, the hypothesis was that a major systemic infection, for example pneumonia, would result in a significantly more extensive systemic inflammatory response compared with SSI. That hypothesis was examined in the same cohort, which includes 167 times more patients than the cohort in Study I, where infections other than SSI did not show a statistically significant connection to the oncological outcome. The primary exposure in Study IV was defined as the occurrence of a major systemic infection within 90 days of surgery. Secondary exposures included any systemic infection or other major event within 90 days of surgery. A systemic infection was identified using the following ICD-10 codes: N39.0, N30.9 (urinary tract infection), J09-J18 (pneumonia), R50.8, R50.9 (fever of unknown origin), J03 (tonsillitis), K57 (diverticulitis), L08, L03, L01, A46 (skin infection), A40, A41 (sepsis), J01 (sinusitis), H66 (otitis), I33, I38, I39 (endocarditis), I40, I41 (myocarditis), G04, G05 (encephalitis), G00, G01, G02, G03 (meningitis), M86 (osteomyelitis), N10 (acute pyelonephritis), J00-J06 (upper respiratory infection), J20-J22 (lower respiratory infection), B02 (herpes zoster), A00-A09 (gastroenteritis), B15, B16, B17 (acute hepatitis), L04 (acute lymphadenitis), A15-A19 (tuberculosis), A48, A49 (other bacterial infections), A80-A89 (virus infection of the central nervous system), B33, B34, B99 (unspecified virus infection), and A69.2 (Lyme disease). Alternatively, a systemic infection was defined as the dispensation of antibiotics within 90 days of surgery, classified under J01, excluding flucloxacillin (J01CF05) or clindamycin (J01FF01) (defined as SSI) or ciprofloxacin (J01MA02) when administered during adjuvant chemotherapy from 2008 to 2011 (during which time ciprofloxacin was used as antibiotic prophylaxis in the Panther study). A major systemic infection was defined as readmission because of that infection. Systemic infections were categorized as early (within 30 days of surgery) or any (0-90 days after

surgery). Other major events were defined using the following ICD-10 codes: I61, I63, I64 (stroke), I26 (pulmonary embolism), and/or I21, I22 (myocardial infarction).

Predictors in both studies were: age at surgery, country of birth, the highest level of education (9 years or less (primary), 10-13 years (secondary), or >13 years (tertiary)), family income (low (Q1: 0% - 25%), middle (Q2-Q3: >25% - 75%), or high (Q4: >75%)), menstrual status, hypertension, obesity, diabetes, autoimmune disease, immunodeficiency, the Charlson Comorbidity Index (CCI), breast cancer detection mode, breast cancer laterality, the year of breast cancer surgery, the region of residence at surgery, type of primary treatment (surgery or NAT), type of final breast/axillary surgery, the number of surgeries, RT, time to RT, chemotherapy, ET, anti-HER2 therapy, invasivity (invasive/in situ), tumour (T) stage, histological tumour type, NHG, ER, PR, HER2, Ki67, subtype and nodal (N) stage. Detailed information and definitions of the predictors are described in Study III. Unfortunately, the registers lack information about smoking habits, alcohol consumption, BMI and usage of prophylactic antibiotics, which of course is a limitation when studying postoperative complications. Furthermore, the variable "time to adjuvant chemotherapy" in the NKBC was inadvertently erased by The National Board of Health and Welfare during the process of linking the registers.

6.4 Outcomes and statistical methods

All analyses in Studies I and II were performed using SPSS (IBM, Armonk, New York, USA). In Study I, the analyses were done together with my main supervisor and in Study II, by myself with a re-count by my supervisor. In Studies III and IV, all analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), through specific files available by "remote server access" on the research Q-portal administered by the North Regional Cancer Centre (RCC). All processing of the original data and all statistical analyses in these studies were conducted by or in collaboration with statisticians. All tests in all studies were two-sided and $p < 0.05$ was considered statistically significant.

6.4.1 Paper I

The primary outcome was systemic recurrence of breast cancer, including recurrence in the supraclavicular fossa. For this analysis, patients who underwent surgery for in situ tumours were excluded. The secondary outcomes encompassed LRR, defined as recurrence in the ipsilateral breast or axilla, as well as BCSS and OS. Kaplan-Meier curves and unadjusted/adjusted Cox regressions were used to assess the relationship between SSI/other postoperative

infection and breast cancer recurrence. OS, BCSS and distant recurrence-free survival (DRFS) were calculated with the Kaplan-Meier method.

6.4.2 Paper II

The primary outcome assessed was the identification of risk factors for SSI, while the secondary outcome focused on risk factors for other wound complications (wound dehiscence, skin necrosis, haematoma requiring surgical intervention, and flap failure). The outcomes were dichotomized into two categories: the presence of SSI or other wound complications and the absence of SSI or wound complications within 30 days of surgery. The association between predictors and outcome was analysed using simple logistic regression. Multiple logistic regression was performed to adjust for confounding predictors.

6.4.3 Papers III and IV

The primary outcome was the incidence of systemic breast cancer recurrence. This was characterized by the detection of ICD-10 codes C780-C788, C790-C791, C793-C799, C771, C772, C778 or a recorded death attributed to breast cancer occurring more than three months after surgery. The cohort for this analysis was restricted to those diagnosed with invasive breast cancer. The secondary endpoints were LRR, OS, and BCSS. Since the registration of LRR is not reliable in Sweden except in the Stockholm/Gotland region, the following definition was created: LRR encompassed instances of relapse within the same breast or regional lymph nodes as identified by ICD codes C50, D05 (with the exception of D05.0 indicating lobular carcinoma in situ (LCIS)), or codes C792, C770, C773, C778, and C779 when paired with Z853 and/or instances where RT was targeted at the breast and was administered more than one year following primary surgery. Additionally considered were ICD intervention codes signifying surgeries for ipsilateral breast cancer in either the breast or axillary regions (HAB00, HAB40, HAB99, HAC10, HAC15, HAC20, HAC22, HAC99, PJA10, VXA20, PJA42, VXK21, HAF00, HAF99) conducted more than one year after the initial surgery. In order not to include secondary plastic surgery interventions in the LRR definition, such intervention codes, not associated with diagnosis codes for either invasive carcinoma or DCIS, were excluded.

DRFS, and the cumulative risk of LRR, OS and BCSS were estimated utilizing the Kaplan-Meier method. The effect of exposure was subjected to univariable analyses using the log-rank test. The relationship between exposure, various predictors, and outcomes was examined through multivariable Cox regression analysis. A stepwise adjustment procedure was done in Study IV in order to easily see how the different variables affected the outcome. First, we adjusted for patient characteristics (age, year of surgery, region of

residence). Second, for the same variables as Model 1 plus disease characteristics (T-stage, subtype, N-stage, histological tumour type). Third, for the same variables as Model 2 plus comorbidity (CCI). Fourth, for the same variables as Model 3 plus socioeconomic factors (country of birth, highest level of education, family income). Fifth, for the same variables as Model 4 plus surgical treatment (type of primary treatment, final breast/axillary surgery, number of surgeries). Sixth, for the same variables as in Model 5 plus oncological treatment (RT, chemotherapy, ET, anti-HER2 therapy). To determine which predictors should be included in the multivariable analysis, a Directed Acyclic Graph (DAG) was employed for each study. The results are articulated as Hazard Ratios (HR) accompanied by 95% Confidence Intervals (CI).

In Study III, a supplementary analysis was conducted aimed at identifying risk factors for SSI, where both univariable and multiple logistic regression analyses were conducted to control for confounders that are clinically significant. These results are expressed as OR with 95% CI.

For Study III, a power analysis was conducted utilizing data from prior studies (124, 145, 197, 198). The parameters included a 10% incidence of SSI following breast cancer surgery and a 20% rate of systemic recurrence. The margin (δ) for systemic recurrence was established at 1.08. Consequently, a sample size of 57,920 patients was determined to achieve a power of 0.80 with a type I error rate of 0.05. The margin (δ) was based on the following reasoning: if a total of 20% of all patients experience a systemic recurrence, and 19.8% suffer from a systemic recurrence in the no-SSI group, that would be 21.4% in the SSI group. This could be viewed as a HR of 1.08 over the defined study period and is thus considerably less than HR 2.52 (155) and HR 6.15 (154). Reasonably, a relative difference of less than 1.08 ought not to have a clinically relevant difference. When choosing a 20% rate of systemic recurrence, the aim was a 10-year follow-up. Given that the median follow-up period was shorter than anticipated, at approximately five years, only 9.6% of cases experienced systemic recurrence which would increase the risk of a type 2 error. However, a higher SSI rate of 15.7%, compared with the 10% anticipated in the power calculation would theoretically have the reverse effect on the risk of a type 2 error.

6.5 Ethical considerations

The Ethical Review Act (Act 2003:460) (199) governs the ethical review of research involving human subjects and biological material from humans. The purpose of this legislation is to protect individual human beings and uphold respect for human dignity in research. Research that entails physical interventions or affects the research participants requires their consent, with the fundamental principle being that consent is always necessary. The General Data

Protection Regulation (GDPR) governs consent in research by requiring that it be voluntary, specific, informed, and unambiguous. Regarding consent for retrospective cohort studies, there are several important aspects to consider, and there may be certain exceptions to the requirement for consent, especially if it is difficult or impossible to obtain consent from all individuals whose data are used. Although retrospective cohort studies may have exceptions from the consent requirement, they must still undergo ethical review and adhere to strict ethical guidelines to protect participants' privacy and rights in accordance with GDPR. Research on previously collected personal data that involves a negligible privacy intrusion can normally be approved without the requirement for informed consent. The same applies to research on extensive amounts of pseudonymized data where the code key remains with the registry holder and where the possibility of identifying any person in the material is virtually non-existent. Reviewing medical records could be perceived by some individuals as an invasion of privacy. Another potential risk is that sensitive data might fall into the wrong hands. However, these risks are considered unlikely regarding this thesis, because the possibility of identifying any individual in the material is negligible. Furthermore, the knowledge gains are assessed to be significantly greater than the risks to the research participants in the articles of the thesis.

Studies I and II were approved by the Regional Ethical Committee at Uppsala University (DNR 2018/312). Concerning Studies III and IV, the construction of BCBaSe 3.0 was approved by the Ethical Committee (DNR 2019-02610, 2020-00886, 2020-06302) with an amendment for the present studies (DNR 2022-01020-02).

7 Results

7.I Paper I

A total of 492 patients were included in the study, with a mean age of 62 ± 13 years, ranging from 29 to 94 years. The mean BMI was 25.8 ± 4.8, ranging from 15.4 to 48.8. Among the study cohort, 439 patients had invasive breast cancer, while 53 had in situ tumours. The median follow-up period was 8.4 years, ranging from 0.2 to 10.1 years.

Seventy patients (14.2%) of all patients and 62 (14.1%) of those with invasive breast cancer had an SSI. Additionally, 49 patients (10.0%) of all patients and 43 (9.8%) of those with invasive cancer had an infection other than SSI.

LRR was observed in 26 patients, and systemic recurrence in 55 patients. The median time to LRR was 3.0 years (0.7-10.1), and to systemic recurrence, it was 2.6 years (0.4-10.1). The 5-year OS rate was 86.5 ± 2.9%, BCSS was 94.6 ± 2.0%, and DRFS was 90.6 ± 2.9%.

Unadjusted analysis revealed a significant increase in the risk of systemic recurrence following an SSI (Log-rank test, p = 0.035, *Fig. 1: Kaplan-Meier analysis*), whereas no significant association was found between SSI and LRR rates (p = 0.31).

In the univariate analysis, several factors were associated significantly with systemic recurrence, including age at surgery, receiving NAT, type of breast and axillary surgery, seroma aspiration, tumour size, tumour grade, histologic subtype, and lymph node status (*Table 1*).

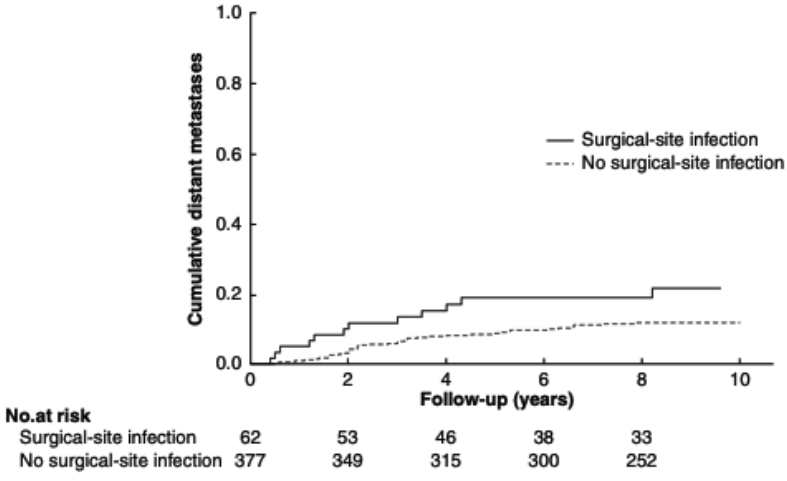


Fig 1 Kaplan-Meier analysis of distant recurrence in patients with and without surgical site infection. p = 0.035 (Log-rank test)

The occurrence of SSI did not predict systemic recurrence rates in the multivariate Cox regression analysis (*Table 1*). However, tumour size and lymph node status remained significant predictors in the multivariate analysis (*Table 1*).

Infections other than SSI were not associated with systemic recurrence (HR 1.57, p = 0.249) (*Table 1)* or LRR (HR 2.49, p = 0.068) in the univariate analysis, and thus, further multivariate testing was not pursued.

Table 1 Unadjusted and adjusted Cox regression analysis of factors associated with systemic recurrence with a median of 8.4 years' follow-up, based on patients with invasive breast cancer (n=439)

Factors	No of patients	Unadjusted results		Adjusted results	
		Hazard ratio (CI)	P	Hazard ratio (CI)	P
Age at surgery	439	1.02 (1.001, 1.046)	**0.038**	1.02 (0.992, 1.038)	0.201
BMI (kg/m²)					
18.5-24.9	189	1.00 (reference)			
<18.5	12	0.00 (0.000, 0.000)	0.974		
25-29.9	143	1.09 (0.596, 2.009)	0.772		
>30	80	1.15 (0.562, 2.364)	0.699		
Smoker					
No	228	1.00 (reference)			
Yes	74	0.45 (0.158, 1.279)	0.134		
Previous	111	1.43 (0.804, 2.557)	0.222		
Diabetic					
No	420	1.00 (reference)			
Yes	19	1.00 (0.243, 4.101)	0.998		
Neoadjuvant chemotherapy					
No	430	1.00 (reference)		1.00 (reference)	
Yes	9	3.25 (1.014, 10.420)	**0.047**	1.53 (0.429, 5.471)	0.512
No. of surgeries (breast/axilla)#					
1	381	1.00 (reference)			
>1	58	0.82 (0.350, 1.913)	0.643		
Breast surgery					
Breast-conserving surgery	264	1.00 (reference)		1.00 (reference)	
Mastectomy	175	3.70 (2.094, 6.542)	**0.000**	1.42 (0.676, 2.978)	0.355
Axillary surgery					
Sentinel node biopsy	247	1.00 (reference)			
Axillary clearance	150	2.90 (1.631, 5.149)	**0.000**		
No surgery	42	1.71 (0.580, 5.029)	0.331		
Seroma aspiration					
No	381	1.00 (reference)		1.00 (reference)	
Yes	58	2.18 (1.146, 4.150)	**0.018**	0.84 (0.350, 2.026)	0.702
Adjuvant chemotherapy					
No	269	1.00 (reference)			
Yes	170	1.68 (0.977, 2.873)	0.061		
Adjuvant radiotherapy					
No	132	1.00 (reference)			
Yes	294	0.89 (0.478, 1.654)	0.710		
Previous radiotherapy	13	2.61 (0.858, 7.922)	0.091		
Adjuvant hormone therapy					
No	103	1.00 (reference)			
Yes	336	0.61 (0.344, 1.089)	0.095		
Tumour size					
T1	230	1.00 (reference)		1.00 (reference)	
T2	177	5.58 (2.670, 11,672)	**0.000**	2.78 (1.234, 6.242)	**0.014**
T3	30	13.00 (5.272, 32.064)	**0.000**	5.36 (1.889, 15.210)	**0.002**
Tumour type					
Ductal	360	1.00 (reference)			
Lobular	54	1.26 (0.593, 2.678)	0.547		
Other invasive types	25	0.32 (00.44, 2.342)	0.263		
Tumour grade					
1	77	1.00 (reference)		1.00 (reference)	
2	231	10.02 (1.363, 73.637)	**0.024**	4.10 (0.540, 31.171)	0.172
3	125	15.73 (2.124, 116.462)	**0.007**	3.90 (0.464, 32.796)	0.210
Histological subtype					
Luminal A	220	1.00 (reference)		1.00 (reference)	
Luminal B	116	2.01 (1.027, 3.943)	**0.041**	1.42 (0.682, 2.962)	0.348
HER 2+ ER+	26	2.06 (0.692, 6.110)	0.195	1.02 (0.270, 3.870)	0.974
HER 2+ ER-	21	3.38 (1.248, 9.172)	**0.017**	1.85 (0.500, 6.811)	0.358
Triple negative	56	2.54 (1.165, 5.556)	**0.019**	2.68 (0.984, 7.311)	0.054
Lymph node status					
N0	271	1.00 (reference)		1.00 (reference)	
N1	92	2.87 (1.465, 5.637)	**0.002**	2.21 (1.075, 4.528)	**0.031**
N2	45	8.04 (4.179, 15.470)	**0.000**	3.89 (1.770, 8.552)	**0.001**
SSI					
No	377	1.00 (reference)		1.00 (reference)	
Yes	62	1.97 (1.037, 3.756)	**0.038**	0.99 (0.414, 2.340)	0.972
Other infection					
No	390	1.00(reference)			
Yes	49	1.57 (0.734, 3.302)	0.249		
SSI and/or other infection					
No	334	1.00(reference)			
Yes	105	1.79 (1.016, 3.168)	**0.044**		

SSI; Surgical Site Infection, #During years 2009-2010

7.2 Paper II

The study cohort comprised 592 patients who underwent a total of 707 procedures. The mean age was 62 ± 13 years, with a range of 24 to 96 years. The mean BMI was 26.2 ± 4.7, ranging from 16.0 to 47.0.

As detailed in *Table 2*, there were 66 instances (9.3%) of SSI and 95 cases (13.4%) of wound complications among the 707 surgeries. The mean time to the onset of SSI was 17.4 days, with a range from 2 to 36 days.

Table 2 Complication rates

Complication	Total cohort n=707
SSI	66 (9.3)
Wound dehiscence	25 (3.5)
Skin necrosis	16 (2.3)
Haematoma (requiring surgery)	15 (2.1)
Flap failure	1 (0.1)
Wound complication#	95 (13.4)

Values are number (per cent). SSI; Surgical Site Infection #SSI, wound dehiscence, skin necrosis, haematoma requiring surgery, flap failure

Table 3 presents the infection and wound complication rates based on the type of breast and axillary surgery performed. SSI occurred in 9.2% of patients following BCS, 19% after oncoplastic BCS, and 2.3% after doughnut mastopexy with SLNB. Among patients who underwent ALND, 9.9% experienced SSI. Wound complications were observed in 19.5% of patients after mastectomy without IBR and in 32.4% of those with IBR.

Table 3 Infection and Wound complication rates

Type of breast/axillary surgery	SSI	Wound complication#
BCS (n=292)	23 (7.9)	28 (9.6)
No axillary surgery (n=65)	3 (4.6)	3 (4.6)
SNB (n=196)	18 (9.2)	23 (11.7)
Axillary clearance (n=28)	2 (7.1)	2 (7.1)
Axillary sampling (n=3)	0 (0.0)	0 (0.0)
Oncoplastic BCS (n=99)	15 (15.2)	16 (16.2)
No axillary surgery (n=25)	2 (8.0)	3 (12.0)
SNB (n=58)	11 (19.0)	11 (19.0)
Axillary clearance (n=15)	2 (13.3)	2 (13.3)
Axillary sampling (n=1)	0 (0.0)	0 (0.0)
Doughnut mastopexy (n=66)	1 (1.5)	6 (9.1)
No axillary surgery (n=14)	0 (0.0)	2 (14.3)
SNB (n=43)	1 (2.3)	4 (9.3)
Axillary clearance (n=8)	0 (0.0)	0 (0.0)
Axillary sampling (n=1)	0 (0.0)	0 (0.0)
Mastectomy (no reconstr) (n=154)	20 (13.0)	30 (19.5)
No axillary surgery (n=36)	9 (25.0)	9 (25.0)
SNB (n=64)	5 (7.8)	12(18.8)
Axillary clearance (n=42)	5 (11.9)	8 (19.0)
Axillary sampling (n=12)	1 (8.3)	1 (8.3)
Immediate reconstruction (n=37)	4 (10.8)	12 (32.4)
SNB (n=414) (regardless of breast surgery)	39 (9.4)	56 (13.5)
Axillary clearance (n=111) (regardless of breast surgery)	11 (9.9)	14 (12.6)
Reoperation (within 24 hours) (n=16)	4 (25)	

Values are number (per cent). SSI; Surgical Site Infection BCS; Breast Conserving Surgery SNB; Sentinel Node Biopsy
SSI, wound dehiscence, skin necrosis, haematoma requiring surgery, flap failure

In the unadjusted analysis, BMI > 25, oncoplastic BCS, reoperation within 24 hours, and prolonged surgery duration (90-120 minutes) were identified as significant risk factors for SSI. However, in the multiple regression analysis, a BMI of 25-30 (OR 1.98, p = 0.036) and a BMI > 30 (OR 2.85, p = 0.003) remained the sole significant predictors for SSI *(Table 4)*.

Table 4 Unadjusted and adjusted logistic regression analysis of factors associated with SSI

Factors	No of patients	Unadjusted results		Adjusted results (n=705)	
		Odds ratio (CI)	P	Odds ratio (CI)	P
Age at surgery (years) (n=707)					
<46	79	1.00 (reference)			
46-60	228	1.91 (0.71, 5.14)	0.204		
61-74	299	1.41 (0.52, 3.80)	0.497		
>74	101	1.45 (0.47, 4.51)	0.523		
BMI (kg/m²) (n=705)					
18.5-24.9	309	1.00 (reference)		1.00 (reference)	
<18.5	11	0.00 (0.00, 0.00)	0.999	0.00 (0.00, 0.00)	0.999
25-30	247	1.90 (1.02, 3.56)	**0.044**	1.98 (1.05, 3.75)	**0.036**
>30	138	2.90 (1.49, 5.64)	**0.002**	2.85 (1.43, 5.67)	**0.003**
Tobacco user (n=700)					
No	627	1.00 (reference)			
Yes	73	1.04 (0.46, 2.37)	0.925		
Diabetic (n=707)					
No	668	1.00 (reference)			
Yes	39	2.26 (0.96, 5.34)	0.064		
Baseline surgery prime surg (n=707)					
Yes	609	1.00 (reference)			
No	98	0.85 (0.57, 0.26)	0.415		
Breast surgery (n=707)					
BCS	292	1.00 (reference)		1.00 (reference)	
Oncoplastic BCS	99	2.09 (1.04, 4.19)	**0.038**	2.02 (0.91, 4.51)	0.084
Doughnut mastopexy	66	0.18 (0.02, 1.36)	0.096	0.18 (0.02, 1.36)	0.095
Mastectomy no reconstruction	154	1.75 (0.93, 3.29)	0.085	1.59 (0.81, 3.12)	0.178
Immediate reconstruction	37	1.42 (0.46, 4.35)	0.542	1.62 (0.37, 7.01)	0.521
Only axillary surgery	59	0.63 (0.18, 2.16)	0.459	0.79 (0.22, 2.85)	0.720
Axillary surgery (n=707)					
Sentinel node biopsy	414	1.00 (reference)			
Axillary clearance	111	1.06 (0.52, 2.14)	0.876		
Axillary sampling	18	0.57 (0.07, 4.37)	0.585		
Only breast surgery	164	0.97 (0.52, 1.81)	0.919		
Antibiotic prophylaxis (n=662)					
No	335	1.00 (reference)			
Yes	327	1.31 (0.78, 2.22)	0.305		
Main operator (n=707)					
Breast Surgeon	604	1.00 (reference)			
Resid/Surg (other subspec) + BS ass	83	1.07 (0.49, 2.32)	0.875		
Surgeon (other subspec)	20	1.76 (0.50, 6.20)	0.378		
Assistant (n=707)					
Only scrub nurse	266	1.00 (reference)			
One assistant	404	1.15 (0.67, 2.00)	0.615		
Two assistants	37	2.15 (0.87, 5.70)	0.125		
Reoperation (within 24 hours) (n=707)					
No	691	1.00 (reference)		1.00 (reference)	
Yes	16	3.38 (1.06, 10.80)	**0.040**	2.67 (0.79, 9.10)	0.115
Surgery time (minutes) (n=707)					
<60	242	1.00 (reference)		1.00 (reference)	
60-89	229	1.73 (0.86, 3.47)	0.122	1.45 (0.69, 3.03)	0.322
90-120	153	2.59 (1.28, 5.27)	**0.009**	1.71 (0.75, 3.88)	0.202
>120	83	1.98 (0.82, 4.76)	0.127	1.18 (0.37, 3.74)	0.782
Breast specimen weight (g) (n=299)					
<16	34	1.00 (reference)			
16-50	108	2.64 (0.32, 21.90)	0.368		
51-100	55	6.46 (0.78, 53.46)	0.084		
>100	102	3.99 (0.50, 32.11)	0.194		

SSI; Surgical Site Infection, BCS; Breast-Conserving Surgery, prime surg; primary surgery, Resid/Surg; Resident/Surgeon, BS; Breast surgeon; subspec; subspeciality, Ass; Assistant, g;gram

The risk factors for wound complications were similar to those for SSI, with the exception of the type of breast surgery. In the adjusted analysis, mastectomy without IBR (OR 2.27, p = 0.006) and mastectomy with IBR (OR 4.42, p = 0.008) were identified as significant risk factors. BMI of 25-30 (OR 1.75, p = 0.036) and a BMI > 30 (OR 1.93, p = 0.032) were also significant predictors.

7.3 Paper III

The inclusion criteria were met by 87,558 patients. Patients with a history of breast cancer or DCIS, distant metastasis from other cancers, or distant metastasis within three months of breast cancer surgery were excluded (*Fig. 2*), resulting in a cohort of 82,102 patients, of whom 513 (0.6%) were men.

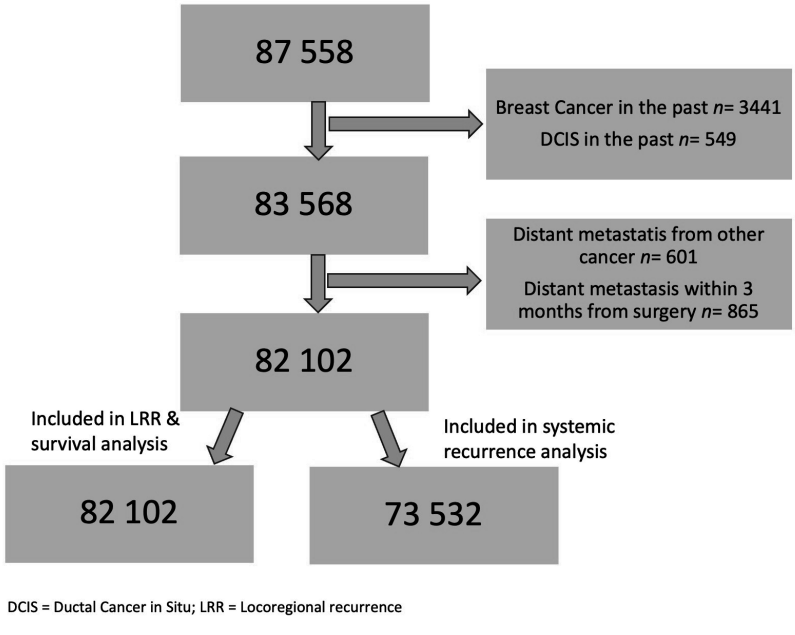


Fig 2 Flow chart

The mean (s.d.) age was 63 years (13), ranging from 19 to 104 years. Among the patients included in the study, 73,313 certainly had invasive breast cancer (219 cases with missing data) and 8,570 had in situ breast cancer. Among patients not treated with adjuvant chemotherapy who experienced an SSI, 21.3% initiated RT within 60 days, compared to 28.2% (P < 0.001) of patients without an SSI. The median (range) follow-up period was 4.8 years (0-11.8) for systemic recurrence, 5.0 years (0-11.8) for OS/BCSS, and 4.5 years (0-11.0) for LRR.

Overall, 12,875 patients (15.7%) experienced an SSI within 90 days of surgery, with 1.3% having a major SSI. Additionally, 9.5% had an SSI within 30 days of surgery *(Table 5).*

Table 5 Complication rates (within 90 days) in a population-based cohort of 82,102 individuals diagnosed with breast cancer in Sweden 2008-2019

Complication	Total cohort n=82,102
SSI	12,875 (15.7)
early	7,830 (9.5)
late	6,900 (8.4)
Major SSI	1,072 (1.3)
Bleeding or wound complication	5,710 (7.0)
early	4,843 (5.9)
late	1,332 (1.6)
Major bleeding or wound complication	1,751 (2.1)
Unspecified local complication	1,663 (2.0)
early	991 (1.2)
late	773 (0.9)
Major unspecified local complication	590 (0.7)
Any local complication#	17,294 (21.1)
early	11,920 (14.5)
late	8,149 (9.9)
Major local complication#	3,214 (3.9)

Values are number (per cent). # SSI, bleeding/wound/unspecified local complication; SSI; Surgical Site Infection

A total of 2,770 patients (3.7%) experienced LRR, while 7,033 patients (9.6%) had a systemic recurrence. The 5- and 10-year DRFS rates were 91.2% (95% CI 90.9-91.4) and 84.6% (84.1-85.0) for patients without an SSI, compared to 87.6% (86.9-88.2) and 80.7% (79.5-81.7) for patients with an SSI.

In the unadjusted analysis, the risk of systemic recurrence (HR 1.36, $p < 0.001$), overall death (HR 1.26, $p < 0.001$), and breast cancer-specific death (HR 1.49, $p < 0.001$) were all significantly increased after an SSI *(Fig. 3b-d),* but not the risk of LRR (HR 0.92, $p = 0.132$) *(Fig. 3a).*

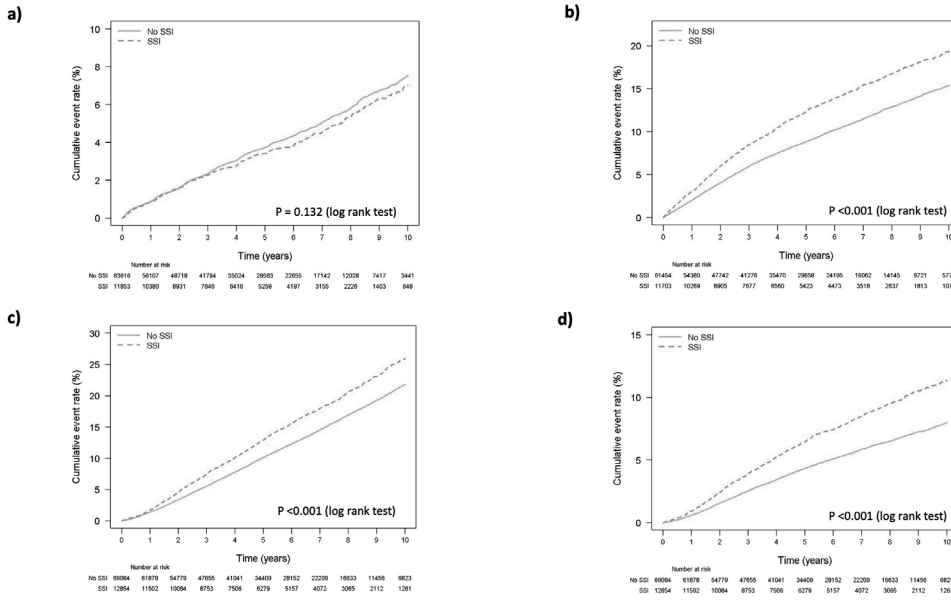


Fig 3 Kaplan-Meier analysis in patients with and without SSI: a) LRR, b) systemic recurrence, c) overall death, d) breast cancer-specific death

After adjusting for age, country of birth, highest level of education, family income, CCI, region of residence, primary treatment, final breast and axillary surgery, number of surgeries, T-stage, subtype, and N-stage, the occurrence of an SSI was still significantly associated with higher overall death (HR 1.06, p = 0.030), but not with systemic recurrence (HR 1.05, p = 0.089) or breast cancer-specific death (HR 1.07, p = 0.102) *(Table 6)*. In the sensitivity analysis excluding all patients with any malignancy before the breast cancer diagnosis (n = 7,418), the risk of systemic recurrence was not significant (HR 1.04, p = 0.171), nor was the association with all-cause death (HR 1.05, p = 0.098).

Table 6. Adjusted Cox regression analysis of risk of SSI on time to Iocoregional recurrence, systemic recurrence, overall death and breast cancer death

Endpoint	No of patients	HR (95% CI)	P
Locoregional recurrence	75,469	0.98 (0.88-1.09)	0.657
Systemic recurrence	73,157	1.05 (0.99-1.12)	0.089
Overall death	81,938	1.06 (1.01-1.11)	0.030
Breast cancer death	81,938	1.07 (0.99-1.15)	0.102

Adjusted for age, country of birth, highest level of education, family income, CCI, region of residence, primary treatment, final breast and axillary surgery, number of surgeries, tumour stage, subtype and nodal stage; SSI Surgical Site Infection

Other complications

A total of 5,710 patients (7.0%) experienced bleeding or wound complications, and 1,663 patients (2.0%) encountered unspecified complications *(Table 5).* After adjusting for age, country of birth, highest level of education, family income, CCI, region of residence, primary treatment, type of final breast and axillary surgery, number of surgeries, T-stage, subtype, and N-stage, the occurrence of unspecified complications was significantly associated with systemic recurrence (HR 1.22, p = 0.005). However, it was not significantly associated with all-cause death (HR 1.07, p = 0.298), breast cancer-specific death (HR 1.14, p = 0.183), or LRR (HR 1.19, p = 0.171) *(Table 7).* This significant association persisted in the sensitivity analysis (HR 1.22, p = 0.006).

Table 7. Adjusted Cox regression analysis of risk of unspecified complication on time to Iocoregional recurrence, systemic recurrence, overall death and breast cancer death

Endpoint	No of patients	HR (95% CI)	P
Locoregional recurrence	75,469	1.19 (0.93-1.53)	0.171
Systemic recurrence	73,157	1.22 (1.06-1.40)	0.005
Overall death	81,938	1.07 (0.94-1.22)	0.298
Breast cancer death	81,938	1.14 (0.94-1.37)	0.183

Adjusted for age, country of birth, highest level of education, family income, CCI, region of residence, primary treatment, final breast and axillary surgery, number of surgeries, tumour stage, subtype and nodal stage; SSI Surgical Site Infection

Bleeding or wound complications were not significantly associated with any of the outcomes. Within 90 days of surgery, 17,294 patients (21.1%) experienced local complications, with 3.9% classified as major (2.8% major within 30 days). After adjusting for the same predictors, the occurrence of any major local complication was significantly associated with all-cause death (HR 1.11, $p = 0.027$), but not with systemic recurrence (HR 1.08, $p = 0.184$), LRR (HR 0.95, $p = 0.628$), or breast cancer-specific death (HR 1.05, $p = 0.526$). The significant relationship with all-cause death did not persist in the sensitivity analysis (HR 1.09, $p = 0.106$).

An analysis conducted exclusively on patients from the Stockholm/Gotland region also did not reveal any association between SSI and any of the outcomes. Among these patients, 546 (3.3%) experienced LRR, and 1,573 (9.8%) developed systemic recurrence.

Secondary analysis concerning risk factors for developing SSI

In the adjusted analysis, patients aged 40-49 years ($p = 0.041$) and 50-64 years ($p < 0.001$) were more likely to experience an SSI, as were patients with obesity ($p < 0.001$) and higher CCI scores ($p < 0.001$). Conversely, patients with middle ($p = 0.003$) and high ($p < 0.001$) family income had a lower risk of SSI. Patients with an SSI had large tumours more frequently (T2, $p < 0.001$; T4, $p = 0.016$), were node-positive ($p < 0.001$), and had non-luminal A subtypes ($p < 0.001$). The SSI rate was linked significantly to mastectomy +IBR, ALND, and sampling ($p < 0.001$), while NAT was not a risk factor. The risk

of SSI increased with the number of surgeries a patient underwent ($p < 0.001$). Furthermore, the region of residence was significantly associated with the risk of SSI ($p < 0.001$). Due to multicollinearity, age was included in the multivariable analysis instead of menstrual status, and family income was included instead of the highest level of education. Similarly, CCI was included, but not hypertension, diabetes, autoimmune disease, or immunodeficiency, while T/N stage and subtype were included instead of the mode of detection.

7.4 Paper IV

The patients included here are the same as those in Study III, resulting in the same cohort of 82,102 patients (*Fig. 2*).

Overall, 1,461 patients (1.8%) experienced a major systemic infection within 90 days of surgery, with 348 patients (0.4%) affected within the first 30 days. In total, 11,870 patients (14.5%) suffered from a systemic infection within 90 days, of whom 3,559 patients (4.3%) had an early systemic infection. In addition, 516 patients (0.6%) experienced other major event within 90 days, including 178 patients (0.2%) with a stroke, 262 patients (0.3%) with a pulmonary embolism, and 81 patients (0.1%) with a myocardial infarction.

Among patients not treated with adjuvant chemotherapy who experienced a major systemic infection within 90 days of surgery, the mean (s.d.) time to RT was 79.7 days (42.4), compared to 71.9 days (31.0) for those without a major systemic infection ($p <0.001$).

A total of 2,770 patients (3.7%) had an LRR, and 7,033 (9.6%) had a systemic recurrence. The 5- and 10-year DRFS rates were 90.7% (95% CI 90.5-90.9) and 84.1% (83.7-84.5), respectively, for patients who did not experience a major systemic infection within 90 days of surgery. In contrast, these rates were 84.4% (82.1-86.4) and 76.3% (72.6-79.6) for patients who did experience a major systemic infection.

In the unadjusted analysis, all risks, except for LRR, were significantly elevated following a major systemic infection within 90 days of surgery. Specifically, the HR was 1.78 for systemic recurrence ($p <0.001$), 0.89 for LRR ($p= 0.483$), 2.20 for overall death ($p <0.001$), and 2.17 for breast cancer-specific death ($p <0.001$). (*Fig 4a-d*).

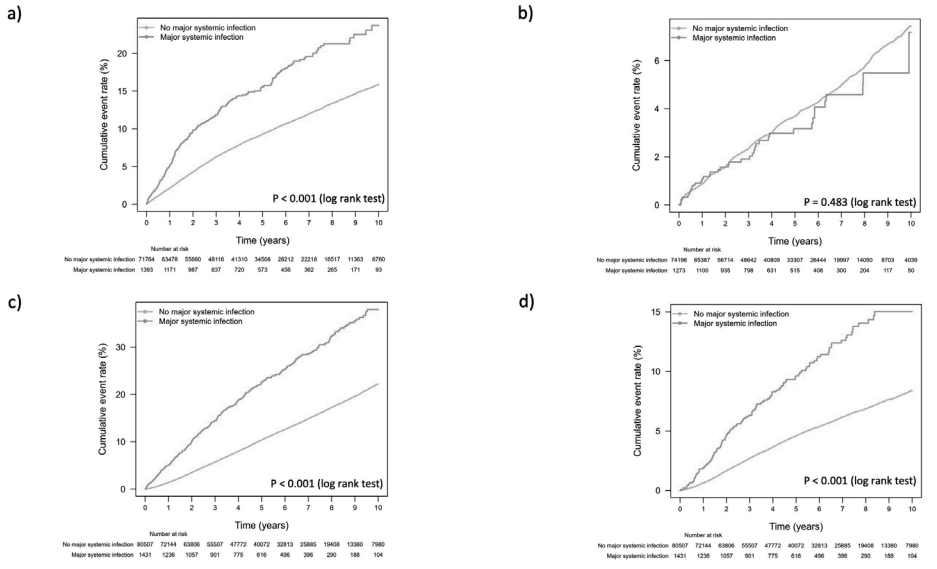


Fig 4 Kaplan-Meier analysis in patients with and without major systemic infection within 90 days a) systemic recurrence, b) LRR, c) overall death, d) breast cancer-specific death

After adjusting for patient characteristics, disease characteristics, comorbidities, socioeconomic factors, surgical and oncological treatments, major systemic infection within 90 days remained significantly associated with higher rates of systemic recurrence (HR 1.23, p = 0.003), overall death (HR 1.47, p <0.001), and breast cancer-specific death (HR 1.27, p = 0.008), but not with LRR *(Table 8).* The sensitivity analysis, which excluded all patients with any prior malignancy before the breast cancer diagnosis (n=7,415), did not alter these results (systemic recurrence: HR 1.21, p = 0.012; overall death: HR 1.45, p <0.001; breast cancer-specific death: HR 1.28, p = 0.008).

The adjusted outcomes for patients who experienced an early major systemic infection were even more pronounced, with significantly higher rates of systemic recurrence (HR 1.66, p < 0.001), overall death (HR 1.79, p < 0.001), and breast cancer-specific death (HR 1.86, p < 0.001). There was also a significantly increased risk of LRR (HR 1.84, P = 0.015) *(Table 8).* These results were consistent in the sensitivity analysis.

Any systemic infection within 90 days was significantly associated with higher rates of overall death (HR 1.10, p < 0.001) in the adjusted analysis, but not with systemic recurrence (HR 1.02, p = 0.557), LRR (HR 1.06, p = 0.302), or breast cancer-specific death (HR 1.04, p = 0.371). In addition to overall death, early systemic infection (HR 1.18 (CI 1.10-1.28) was associated with increased risk of LRR (HR 1.37 (CI 1.16-1.61).

Table 8. Stepwise adjusted Cox regression analysis of risk of major systemic infection and/or major event on time to systemic recurrence, locoregional recurrence (LRR), overall death and breast cancer-specific death

	Hazard ratio (95%CI)						
Endpoint	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**
Systemic recurrence (n = 73 157)							
Systemic infection							
early	2.37 (1.83-3.05)	1.96 (1.52-2.53)	1.72 (1.34-2.22)	1.68 (1.30-2.17)	1.67 (1.29-2.15)	1.69 (1.31-2.18)	1.66 (1.29-2.14)
within 90 days	1.78 (1.55-2.04)	1.70 (1.48-1.95)	1.23 (1.07-1.41)	1.21 (1.06-1.39)	1.21 (1.05-1.38)	1.20 (1.05-1.38)	1.23 (1.07-1.41)
Major event	1.86 (1.47-2.35)	1.64 (1.30-2.08)	1.27 (1.00-1.60)	1.24 (0.98-1.58)	1.23 (0.97-1.56)	1.25 (0.98-1.58)	1.24 (0.98-1.57)
LRR (n = 75 469)							
Systemic infection							
early	1.76 (1.08-2.88)	1.83 (1.12-2.99)	1.90 (1.16-3.11)	1.88 (1.15-3.08)	1.85 (1.13-3.03)	1.92 (1.17-3.14)	1.84 (1.12-3.02)
within 90 days	0.89 (0.65-1.22)	0.91 (0.66-1.24)	0.96 (0.70-1.33)	0.96 (0.70-1.31)	0.95 (0.69-1.31)	0.97 (0.71-1.33)	0.99 (0.72-1.36)
Major event	0.74 (0.40-1.38)	0.78 (0.42-1.46)	0.82 (0.44-1.52)	0.81 (0.44-1.51)	0.82 (0.44-1.52)	0.82 (0.44-1.53)	0.87 (0.46-1.61)
Overall death (n = 81 938)							
Systemic infection							
early	3.47 (2.88-4.16)	2.05 (1.71-2.47)	1.93 (1.61-2.33)	1.82 (1.52-2.19)	1.80 (1.50-2.17)	1.83 (1.52-2.21)	1.79 (1.49-2.15)
within 90 days	2.20 (1.97-2.45)	1.87 (1.68-2.08)	1.55 (1.39-1.72)	1.48 (1.33-1.65)	1.47 (1.32-1.64)	1.45 (1.30-1.62)	1.47 (1.32-1.64)
Major event	2.97 (2.52-3.51)	1.95 (1.65-2.30)	1.64 (1.39-1.94)	1.61 (1.37-1.91)	1.58 (1.34-1.86)	1.62 (1.37-1.91)	1.62 (1.37-1.91)
Breast cancer-specific death (n = 81 938)							
Systemic infection							
early	2.99 (2.18-4.10)	2.22 (1.62-3.05)	1.87 (1.36-2.57)	1.84 (1.34-2.52)	1.82 (1.32-2.49)	1.88 (1.37-2.59)	1.86 (1.35-2.55)
within 90 days	2.17 (1.82-2.58)	1.98 (1.67-2.36)	1.25 (1.05-1.49)	1.25 (1.05-1.49)	1.24 (1.04-1.48)	1.25 (1.05-1.48)	1.27 (1.06-1.51)
Major event	2.10 (1.54-2.86)	1.73 (1.27-2.36)	1.20 (0.88-1.64)	1.19 (0.87-1.62)	1.16 (0.85-1.58)	1.20 (0.87-1.64)	1.19 (0.87-1.62)

M1: Unadjusted; M2: Adjusted for patient characteristics (age, year of surgery and region of residence); **M3: + disease characteristics** (T stage, subtype, N stage and histological tumor type); **M4: + comorbidity** (CCI); **M5: + socioeconomy** (country of birth, highest level of education and family income); **M6: + surgical treatment** (type of primary treatment, final breast/axillary surgery and number of surgeries); **M7: + oncological treatment** (RT, chemotherapy, endocrine therapy and anti-HER2 therapy). CCI Charlson comorbidity index; RT Radiotherapy

After adjustment, patients who experienced another major event did not exhibit a significantly higher risk of systemic recurrence (HR 1.24, $p = 0.074$), LRR (HR 0.87, $p = 0.650$), or breast cancer-specific death (HR 1.19, $p = 0.286$). However, they did demonstrate a significantly increased risk of overall death (HR 1.62, $p < 0.001$) (*Table 8)*. This significant association persisted in the sensitivity analysis (HR 1.62, $p < 0.001$).

8 Discussion

8.1 Breast cancer and SSI

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among females globally, with an estimated 2.3 million new cases and 685,000 deaths in 2020 (200). In most cases, breast cancer is a treatable condition, with survival rates continuing to improve due to advancements in screening and treatment (201). The majority of breast cancer patients undergo surgery at some stage of their treatment. Complications specific to breast surgery can negatively impact quality of life, lead to reconstruction failure, delay the administration of adjuvant therapies and increase healthcare costs. One study suggests an incremental cost of over $4,000 US per patient in the event of an SSI (152) The most common postoperative complication is seroma, followed by SSI, and chronic neuropathic postoperative pain (146, 149, 150). Many of these wound complications are relatively minor and typically managed on an outpatient basis, making it challenging to determine precise incidence rates. Consequently, the reported postoperative SSI rates after breast cancer surgery vary widely, often ranging from 0% to 26% (143-145, 149). The reason for this variation is likely due to differing definitions of SSI and varying lengths of follow-up periods. In Study I, 14.2% of patients suffered an SSI within 90 days of surgery and in Study III, the rate was 15.7%. Within 30 days, 9.3% had an SSI in Study II, and 9.5% in Study III. These findings are thus, in accordance with the existing literature (143, 145, 149). Major SSI, requiring readmission or additional surgical intervention is reassuringly low at 1.3% within 90 days of surgery in Study III. Despite a clear definition in Study I, it was challenging to determine retrospectively from medical records whether an SSI had occurred. The more precise definition of SSI and the prospective data collection in Study II increased the reliability of the SSI data. The definition in Study III is broad, and although antibiotic prescriptions were defined as starting from day 3 after surgery, some patients will be classified as having had an SSI even though they received antibiotics prophylactically. Additionally, some patients may have been prescribed flucloxacillin or clindamycin for infections other than SSI. However, our definition must be considered adequate based on the proportion of patients classified as having had an SSI.

8.2 Risk factors for SSI

In the unadjusted analysis of Study II, risk factors for SSI included a BMI > 25, oncoplastic BCS, reoperation within 24 hours, and surgery duration of 90-120 minutes. However, in the adjusted analysis, only a BMI > 25 remained a significant risk factor, although there was a trend towards increased SSI following oncoplastic BCS (HR 2.02, p = 0.084). While obesity (BMI > 30) is a well-known risk factor for SSI (146, 148-150, 158), Study II indicates that even being overweight (BMI 25-30) is associated with a doubled risk of SSI.

Several previously identified risk factors for SSI were not significant in Study II. Although age, diabetes, and smoking are known to influence SSI rates (146, 149-151), the current study found that age and smoking were not significant risk factors. However, there was a trend towards a higher risk of SSI in patients with diabetes. A meta-analysis revealed that smoking was not a significant risk factor for SSI, whereas diabetes was (148). Despite numerous studies suggesting that smoking is a risk factor for SSI (146, 147, 149-151), evidence remains conflicting. In Study II, only 73 patients were current smokers, which may have influenced the lack of correlation between smoking and SSI.

Previous studies have demonstrated an association between ALND and SSI (155, 198). However, this correlation was not observed in the Study II cohort. In our earlier study involving a cohort from 2009 and 2010, the incidence of SSI was three times higher for breast surgeries that included ALND compared to those without (198). This discrepancy may be attributed to changes in clinical protocols for antibiotic prophylaxis, which were administered to all patients undergoing ALND in the later period, whereas only a few selected cases received such prophylaxis in the 2009-2010 period. The absolute percentage of patients with SSI following ALND was 22.2% (39/176) in the 2009-2010 cohort compared to 9.9% (11/111) in the Study II cohort.

The frequency of SSI was low (<10%) for BCS, particularly for doughnut mastopexy, despite the absence of antibiotic prophylaxis. In contrast, the SSI frequency was significantly higher for oncoplastic BCS, with mastectomy alone exhibiting the highest SSI rate. The elevated SSI rate in the mastectomy-only group was likely influenced by confounding factors, as the most fragile patients, unsuitable for reconstruction and/or axillary surgery, were selected for mastectomy alone according to clinical routine. Additionally, patients undergoing reconstruction and/or ALND received antibiotic prophylaxis, which was not administered to those undergoing mastectomy alone.

In Study III, obesity was identified as a risk factor for SSI, consistent with the findings of Study II. The study also found that more extensive surgeries, such as mastectomy +/-IBR and ALND, increased the risk of SSI. Furthermore, the

age group of 40-65 years was a risk factor, possibly due to the higher prevalence of oncoplastic surgery and reconstructions in this demographic. Unfortunately, smoking data were not available in the NKBC during the period studied. However, we found that patients with lower family income had an increased risk of SSI, and smoking rates are higher among individuals with poorer socioeconomic conditions (202). Thus, smoking is likely a contributing factor to the higher SSI risk observed in patients with lower family income. We did not examine diabetes separately but used the CCI, which includes diabetes. Not surprisingly, a higher CCI index was a risk factor for SSI. Furthermore, there were regional differences in SSI rates, which could be partially explained by the varying frequencies of different surgical procedures across regions. Other risk factors for SSI identified in Study III were reoperations, higher T- and N-stage and breast cancer subtypes other than luminal A. Many of these are known risk factors for SSI (146, 148, 149, 151, 203). The reason we were able to identify multiple risk factors for SSI in Study III compared to Study II is probably partly due to the lager number of variables examined and partly because the larger cohort size allowed for the testing of additional variables.

8.3 Wound complications and risk factors

In Study II, the wound complication (SSI, wound dehiscence, skin necrosis, haematoma requiring surgery, flap failure) frequency was 13.4% within 30 days of surgery, with the highest rates among patients undergoing mastectomy (19.5%) and mastectomy +IBR (32.4%). Despite the difference in the definition between the two studies, 14.5% suffered any local complication (SSI, bleeding/wound/unspecified local complication) within 30 days of surgery and 21.1% within 90 days in Study III. Since Study II was a prospectively registered study, the definition of any local complication in Study III seems adequate.

Risk factors for wound complications in Study II include BMI > 25 and mastectomy, particularly when combined with IBR (which carried a risk more than 4 times higher than that for BCS). In reconstructive and oncoplastic surgery, extensive tissue manipulation is common, which can compromise the blood supply to the flaps, leading to necrosis and flap dehiscence (146). Proper surgical technique, grounded in adequate training and knowledge of flap blood supply, is essential to prevent these complications. Reoperation for surgical bleeding is more frequent after mastectomy than after BCS (160). Seroma is also more common after mastectomy than BCS (204). Haematoma and seroma are known risk factors for SSI (148) and likely contribute to other wound complications, increasing the risk of such complications after mastectomy.

Therefore, achieving adequate haemostasis, handling tissue gently, and closing the incision without tension are crucial to avoid complications.

Given that excess weight is the sole modifiable significant predictor for the onset of SSI or wound complications following breast cancer surgery, it becomes imperative to incorporate this factor into preoperative discussions with affected women. It is crucial for patients to understand that a BMI exceeding 25 may elevate their susceptibility to postoperative complications, potentially delay the initiation of adjuvant treatment (158) and possibly even increase the risk for breast cancer recurrence (145, 153-156). The probability of encountering such complications escalates in tandem with increasing obesity levels. For individuals grappling with overweight or obesity issues, delayed reconstructive surgery after targeted weight reduction presents a viable strategy worth considering. In cases where BCS is feasible, opting for mastectomy may not be advisable due to a higher incidence of postoperative complications, and moreover, some studies even suggest that the oncological outcome is worse (3, 45-49).

8.4 Antibiotic prophylaxis

Administering antibiotic prophylaxis for breast cancer surgery was recommended in the 2010 report by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) regarding antibiotic prophylaxis in surgical procedures (205). The conclusions drawn in the report are based on studies from various parts of the world, where infection issues and patterns often differ from those in Sweden (144). The SBU project group called for data from Swedish studies. At that time, antibiotic prophylaxis was only administered to patients at increased risk for SSI (after NAC, before reoperation, during reconstruction, and in the presence of other specific patient risk factors). Following the review of medical records, which formed the basis for Study I, antibiotic prophylaxis was started at Uppsala University Hospital, for patients undergoing ALND due to the high infection risk (13% for BCS + ALND and 22.8% for mastectomy + ALND). Following a quality review of breast cancer surgeries conducted in Uppsala in 2014 and 2015, antibiotic prophylaxis was also started for surgeries expected to last more than 90 minutes, as longer operation times were observed to increase the risk of SSI. Because of the short half-life of cloxacillin, an additional dose was recommended if surgery was still ongoing after 90 minutes. After Study II, antibiotic prophylaxis was also recommended for patients with BMI > 25.

One plausible explanation for the higher risk of SSI in patients with BMI > 25 is that being overweight or obesity may result in reduced effectiveness of prophylactic antibiotics due to the increased body mass, as antibiotic

penetration into adipose tissue is relatively poor (206). For instance, Olsen et al. have demonstrated that receiving a suboptimal dose of prophylactic antibiotics is associated with a 5.1-fold increase in the likelihood of developing SSI in breast surgeries (147).

In Sweden, there is no standardised protocol for antibiotic prophylaxis in breast cancer surgery. Different regimens are used, from antibiotic prophylaxis administered to all patients undergoing breast operations, including those for benign lesions, to antibiotic prophylaxis only to selected patients. Some hospitals administer per oral prophylaxis, whereas other hospitals administer intravenous prophylaxis.

A study by Xue et al. found that the efficacy of antibiotic prophylaxis in preventing SSIs was not statistically significant (148). Furthermore, in the PAUS study (RCT), there was no significant reduction in SSI at 30 days post-breast cancer surgery in patients who received a single dose of antibiotic prophylaxis preoperatively (163). Conversely, a cohort study indicated a substantial reduction in SSIs when antibiotic prophylaxis was administered exclusively to patients at high risk (207). When controlling for confounding variables, it was observed that antibiotic prophylaxis led to an 81% decrease in the risk of SSIs among high-risk breast cancer surgery patients. Penel et al. recommend reserving antibiotic prophylaxis for cases where patient-specific risk factors are present rather than employing it as a standard practice. Study II suggests that patients with a BMI > 25 and those undergoing oncoplastic breast surgery may derive the most benefit from antibiotic prophylaxis. This is in addition to previously recognized risk factors such as obesity, NAC, reoperation, reconstruction, ALND, surgeries exceeding 90 minutes in duration, and other specific patient risk factors.

8.5 Association between complications and oncological outcomes

In Studies I and III, SSI was not significantly associated with systemic recurrence or LRR. In Study III, SSI was associated with worse OS, but not with BCSS.

Study III does not conclusively rule out an elevated relative risk of systemic recurrence below 8%, which corresponds to an absolute risk difference of 0.8% - 1.6% when the estimated risk of recurrence is between 10% and 20%. However, this potential risk difference is considered small from a clinical perspective. Conversely, other research has indicated a significantly greater relative risk for systemic recurrence in patients who have suffered an SSI after breast cancer surgery. Notably, Murphy et al. (155) identified a more than

twofold increase in the risk for systemic recurrence in patients with wound complications compared to those without, with a HR of 2.52 (1.69-3.77). Similarly, Beecher et al. (154) reported a sixfold increased risk for breast cancer recurrence (HR 6.15 (3.33-11.33) in patients with SSI following IBR. Nevertheless, given the findings at hand, it is improbable that such an elevated risk for systemic recurrence after SSI following breast cancer surgery would apply to the general population of breast cancer patients.

Although the adjusted analysis was non-significant, the unadjusted analysis indicated a higher risk of systemic recurrence in patients with SSI, suggesting that confounding factors may influence the risk of recurrence. ALND is a well-known risk factor for SSI (198, 203), and axillary lymph node metastasis also increases the risk of systemic recurrence (124). Therefore, this is likely an important confounding factor. In the study by Murthy et al., all patients underwent ALND, whereas in the current studies, most patients underwent SNLB only, which may influence the results. Murthy et al. and Beecher et al. also used the Nottingham Prognostic Index (good, intermediate, and poor), calculated from NHG (1, 2, or 3), N-status (no positive nodes = 1, 1–3 nodes = 2, and >3 nodes positive = 3), and tumour size (0.2 x size in cm), while the current studies calculated these predictors individually. Interestingly more advanced breast cancer subtypes increased the risk of SSI in Study III, which may be another confounding factor influencing the risk of systemic recurrence since more advanced subtypes are associated with worse prognosis. It is crucial to adjust for potential confounders affecting both the risk of SSI and oncological outcomes to reduce the risk of overestimating the influence of complications. Many of the published studies are relatively small and limited by missing data when performing multivariable adjustments, increasing the risk of uncontrolled confounding (153-156). The definition of complications and the length of follow-up also vary between studies, leading to diverse results. Moreover, several published studies have shown no relationship between complications and oncological outcomes (158-161, 198).

In Study III, SSI exhibited an increased unadjusted absolute 5-year risk for all-cause death of 2.8% (2.3 – 3.2). This finding aligns with another large Swedish population-based registry study, which reported a 5-year all-cause death rate that was 6.2% (4.6 - 7.8) higher in patients experiencing major local complications (bleeding, wound complication, SSI and/or unspecified local complications in connection with the initial surgery or requiring readmission) within 30 days of breast cancer surgery (157). In that study, 3.2% suffered a major local complication within 30 days after surgery, compared to 3.9% within 90 days and 2.8 % within 30 days after surgery in Study III. Both studies demonstrated that more extensive surgery was significantly associated with a higher rate of local complications. Moreover, patients with postoperative complications had a higher comorbidity burden, likely impacting OS.

Local major complications were associated with all-cause death in both studies. In Study III, the association between SSI/major local complications and OS did not remain significant in the sensitivity analysis, possibly due to deaths from other cancers (competing causes of death). It is plausible to speculate that postoperative complications after breast cancer surgery could activate dormant micro metastases from other cancers, leading to poorer oncological outcomes. The HR for all-cause death was nearly identical in the sensitivity analysis (SSI: 1.05/major local complications: 1.09) compared to the entire cohort (SSI: 1.06/major local complications: 1.11), indicating a potential power issue. Nonetheless, there is no substantial difference in OS between patients with and without SSI/major local complications.

Patients who experienced an SSI had a significantly longer time to the initiation of adjuvant RT, regardless of whether they received adjuvant chemotherapy. This is important, as evidence suggests that delays in cancer treatment can negatively impact oncological outcomes, with longer delays further exacerbating the prognosis (164-166).

Bleeding or wound complication was not significantly connected with any of the outcomes in Study III. This is in line with another large Danish registry study, which also showed no correlation between reoperation for bleeding after breast cancer surgery and breast cancer recurrence (160).

In Study III, 1,663 patients (2.0 %) suffered an unspecified local complication within 90 days of surgery. The definition includes patients who have experienced complications from implants, accidental punctures or injuries during surgical procedures, foreign bodies inadvertently left in the surgical wound after surgery, other specific complications related to surgery not classified elsewhere, nonspecific procedural complications, and additional reoperations on the mammary gland. Interestingly, patients who experienced an unspecified local complication within 90 days of surgery had an increased risk of systemic recurrence (HR 1.22 (1.06-1.40)). This may be because these complications more frequently lead to delayed initiation of oncological treatment. Unfortunately, since we do not have data on time to chemotherapy, this cannot be confirmed in the current study. Another theory is that many of these complications were classified as major (35% (590/1,663)) compared to SSI, where only 8.3% (1,072/12,875) of infections were classified as major. It is reasonable to assume that a major complication induces a significantly greater inflammatory response.

There are data that support a link between cancer and inflammation. It is estimated that 20% of all cancer-related deaths are associated with infection and inflammation (167, 208). The relationship between inflammation and cancer is now widely accepted (167, 168, 208). Inflammatory cells contribute to

tumour progression through various mechanisms, including the secretion of growth factors, the enhancement of angiogenesis and lymph angiogenesis, the induction of DNA damage, and remodelling of the extracellular matrix to aid in invasion. These cells also facilitate the dissemination of tumour cells by coating them with receptors that allow for their transport through lymphatic channels and capillaries, while helping them to evade host defence mechanisms (168). Therefore, a postoperative complication, with its associated inflammatory response, could theoretically activate subclinical micro metastases and promote cancer recurrence. This hypothesis is corroborated by evidence from other malignancies, which have shown that postoperative infectious complications are associated with worse survival outcomes (183-185).

8.6 Systemic infection/other major event and association with oncological outcomes

In Study I, 10% of the patients suffered an infection other than SSI within 90 days of surgery. In Study IV, 14.5% suffered a systemic infection within 90 days of surgery and 4.3% within 30 days of surgery. The likely reason for this discrepancy is that in Study IV, the search was conducted using diagnostic codes and/or records of antibiotic prescriptions, whereas Study I involved a review of medical records carried out locally in the province of Uppland. This means that patients who sought care for a systemic infection in other provinces were not identified. In Study IV, 1.8% had a major systemic infection within 90 days of surgery, whereof 0.4% were within the first 30 days.

In Study I, infection other than SSI was not associated with the rate of systemic recurrence or LRR on unadjusted analysis and further multiple testing was not performed.

In the nationwide Study IV, experiencing a major systemic infection within 90 days was associated with higher rates of systemic recurrence (HR 1.23, $p = 0.003$), overall death (HR 1.47, $p < 0.001$), and breast cancer-specific death (HR 1.27, $p = 0.008$). Early systemic infection was even more clearly associated with the aforementioned outcomes (systemic recurrence (HR 1.66, $p < 0.001$), overall death (HR 1.79, $p < 0.001$), and breast cancer-specific death (HR 1.86, $p < 0.001$)) and was also linked to LRR (HR 1.84, $p = 0.015$). However, any systemic infection within 90 days was only significantly associated with higher rates of overall death (HR 1.10, $p < 0.001$). It appears that only major infections are linked to worse oncological outcomes, whereas simpler infections with a lesser inflammatory response do not affect prognosis. This observation aligns with a previously published Swedish study by De Boniface et al. (157), who found that patients with major postoperative local

complications within 30 days of surgery had poorer overall and BCS survival. Moreover, in Study III, SSI did not increase the risk of recurrence or death. However, we observed that patients with unspecified local complications had a higher risk of systemic recurrence (HR 1.22, CI 1.06 - 1.40). And as described above, unspecified complications were classified as major considerably more frequently than SSI (35% versus 8%). It is reasonable to assume that major complications lead to a significantly greater inflammatory response, contributing to poorer outcomes.

Another factor could be that major complications more frequently delay adjuvant oncological treatment. In Study IV, patients with major systemic infections had a significantly longer time to RT compared to those without major systemic infections. Unfortunately, data on the time to chemotherapy were lacking, but it is reasonable to assume that chemotherapy may also need to be postponed due to major systemic infections. Furthermore, it is unfeasible to control for all variables (residual confounding). These patients may have an inherent susceptibility to postoperative infections, which could also affect their diminished effectiveness or suboptimal response to adjuvant therapy, ultimately resulting in poorer oncological outcomes.

It has been suggested that the perioperative period is critical in determining oncological outcomes (179-182). During this short period, factors such as heightened stress, inflammatory responses, and pro-angiogenic or growth factors may contribute to the advancement of pre-existing micro metastasis (171, 182). Adjuvant oncological treatment, aimed at eradicating residual microscopic disease and reducing the risk of recurrence and death (79), is typically initiated no earlier than one month after surgery due to concerns about wound healing. Data support the fact that delays in adjuvant treatment increase the risk of recurrence and death (164, 166, 209), and postoperative complications may result in delayed adjuvant treatment (158), as seen in Studies III and IV. Conversely, major systemic infections predominantly affect the elderly and patients with comorbidities, who often do not receive the most effective adjuvant treatment, which could potentially contribute to a higher risk of recurrence and death. Furthermore, one can speculate whether the systemic inflammatory response to a major systemic infection may affect residual microscopic disease, and potentially facilitate recurrence.

Surprisingly, in Study IV, patients with any early systemic infections not only had an increased risk of overall death (HR 1.18 (1.10-1.28), but also a higher risk of LRR (HR 1.37 (1.16-1.61). Patients who experienced a systemic infection within 30 days of surgery had an increased unadjusted absolute 5-year risk for LRR of 1.4% (0.7-2.2) and a 10-year risk of 1.7% (0.5-3.2). This corresponds to a relative risk increase of 38% for a 5-year LRR. The likely reason for the discrepancy between the results in Studies I and IV is the difference in

cohort size, which resulted in far fewer LRR events in Study I (26 patients compared to 2,770 in Study IV). Additionally, the ability of a registry study to identify the majority of patients affected by infections other than SSI may also have contributed. It can be speculated that the systemic inflammatory response to a systemic infection may influence residual microscopic disease, potentially promoting LRR. Moreover, the observed association in this study between any early systemic infection and LRR, unlike the relationship between SSI and LRR noted in Studies I and III, could be due to the significantly more extensive systemic inflammatory response following conditions such as pneumonia, compared to SSI. Additionally, defining SSI is challenging, and it is likely that some patients classified as having SSI may not actually have the condition, whereas diagnoses of systemic infections like pneumonia are generally more reliable. The finding that only early systemic infection is associated with LRR reinforces the theory that the perioperative period is crucial for prognosis.

In Study IV, 0.6% suffered other major events within 90 days of surgery, confirming that serious complications and major events following breast surgery are uncommon. According to previous data, both the mortality rate and the risk of thromboembolism are less than 1% (210, 211). In Study IV, other major events were not associated with systemic recurrence, LRR or breast cancer-specific death, but were associated with overall death (HR 1.62 (1.37-1.91)). The observation that patients experiencing a systemic infection or other major event exhibit reduced OS, even after adjustments, may appear self-evident. This is because the likelihood of such events increases with advancing age (212-215), and these events can be life-threatening.

To more clearly understand how different variables influenced the outcomes, a stepwise adjustment was conducted in Study IV, similar to the approach used in de Boniface's study (157). In addition to the variables adjusted for in Study III, we included the year of surgery and histological tumour type. Furthermore, we added oncological treatments (RT, chemotherapy, ET and anti-HER2 therapy) at the final stage of the adjustment model. In Study III, we chose not to include oncological treatments because they are determined by disease and surgical factors. As shown in the *Table 8*, there is essentially no difference between Model 6 and Model 7, which supports the concept that treatment factors do not add additional explanatory power.

To the best of our knowledge, no studies prior to those in this thesis, have investigated whether systemic infection or other major event, (stroke, pulmonary embolism and/or myocardial infarction) affects oncological outcome after breast cancer surgery. Breast cancer recurrence can manifest after latency periods that span from years to decades. One hypothesis explaining these latency periods is *cancer dormancy*, a phase in cancer progression during which

residual disease exists but remains asymptomatic (176-178). It has been suggested that the perioperative period is a critical window influencing the risk of recurrence (179). Surgical procedures suppress cell-mediated immunity through both local and systemic physiological responses. This immunosuppression, often referred to as 'surgical stress', along with tissue damage, triggers the activation of the sympathetic nervous system and the endocrine stress response. Additionally, tissue damage induces the local release of prostaglandins and catecholamines as part of the inflammatory response (171, 174, 175, 179). The severity and duration of immunosuppression are directly proportional to the extent of the surgery, i.e. the degree of tissue damage (175) and it may take weeks to months for the immune system to fully recover. During this period, patients are more susceptible to potentially life-threatening infections such as pneumonia and sepsis (175). Given these considerations, it is theoretically possible that postoperative complications, such as systemic infections, pulmonary embolism, stroke, or myocardial infarction, could stimulate subclinical micro metastases and promote recurrence due to their secondary inflammatory response (168, 216). These considerations and this hypothesis prompted the investigation in Study IV.

8.7 Strengths and limitations

Currently, there is no universally accepted gold standard for diagnosing SSI. A review by O'Conner et al. highlighted significant variation in the criteria used to define SSI, with 45% of the studies not defining it at all (145). The main strength of Study II is that it is prospective and the SSI definition is clear, as was also the case in Study I. Another strength of Study I is its relatively long follow-up period for all cases, which is longer compared to other studies on this topic (154, 155, 159). One limitation of Studies I, II and III is the potential underestimation or overestimation of the true incidence of SSI due to the absence of wound cultures in many cases. Although Study II recommended obtaining wound cultures, it was sometimes challenging to establish a clear SSI diagnosis. For instance, in cases of fever and erythema of the breast without discharge or seroma, a wound culture was not possible. Consequently, not all patients underwent a wound culture. In Study II, wound cultures were taken in 59.1% (n=39) of patients with a clinical SSI diagnosis, and 64.1% (n=25) of these had a positive culture. This rate is higher compared to the review by O'Conner et al., where only 10% of the studies used a culture-positive result to establish an SSI (145). Another limitation is that tests for Lpk or CRP were not routinely conducted. These tests could potentially aid in the diagnosis of SSI. However, due to logistical constraints in the outpatient clinic, they were rarely performed. Despite these limitations, the frequency of SSI in Study II is likely more reliable due to its prospective design.

Furthermore, the relatively consistent frequency of SSI across the studies supports the validity of our SSI definitions. Regarding Study II, seroma was unfortunately not assessed using any validated or quantitative methods, such as ultrasound, during the study period. The patient charts/forms contained an unreasonably low number of seroma diagnoses, rendering this data unreliable. Consequently, it was not feasible to analyse seroma formation, which represents an additional limitation of the study.

The primary strengths of Studies III and IV include the large cohort size and the national, population-based setting with high-validity registries, which provide nearly complete coverage and follow-up. Additionally, the availability of comprehensive data on numerous potential confounders allowed for thorough adjustments in the multivariate analysis. However, these studies also have limitations, such as the lack of information on smoking habits, alcohol consumption, BMI, time to adjuvant chemotherapy, and the use of prophylactic antibiotics. Another potential limitation is the under-reporting of systemic and LRR in the registers, which could lead to an underestimation of the true recurrence rate. Nevertheless, in Studies III and IV, with a median follow-up of 4.8 years, 9.6% of patients developed a systemic recurrence. This aligns with a previous Swedish study where 7.5% of breast cancer patients diagnosed between 2009 and 2016 experienced a systemic recurrence (217). This supports the adequacy of recurrence reporting in the current study. With regard to LRR, breast cancer patients undergoing BCS in the MINDACT trial had an 8-year cumulative LRR incidence of 3.2% (range 2.7-3.7%) (218), compared to 3.7% in Studies III and IV with a median follow-up of 4.5 years. These findings, along with the observation that the proportion of systemic and locoregional recurrences was approximately the same across the entire cohort as in the Stockholm/Gotland region, further validate the adequacy of recurrence reporting in the current studies. However, it should be noted that the median follow-up period is relatively short, given the ongoing risk of late recurrences in oestrogen receptor-positive breast cancer (108, 197).

Furthermore, since the incidence of SSI noted in the current studies is in line with previously published studies (143, 145), the present SSI definition is considered adequate. However, for patients undergoing reconstruction, the SSI definition in Study III may be less reliable, as those with primary implant-based reconstruction are likely to receive prolonged antibiotic prophylaxis or treatment even with ambiguous SSI symptoms.

The shorter-than-expected median follow-up period and the lower recurrence rates than anticipated in the power calculation (Study III) should be taken into account. However, a post-hoc analysis of the sample size revealed a higher SSI rate (15.7%) than initially expected (10%).

Finally, a limitation of registry studies is the inability to definitively establish causal relationships. However, not all research questions can be adequately addressed through RCTs (219). We believe that a large registry study, such as Studies III and IV, which allows for the adjustment of important confounders, provides the best possible evidence for our research question.

9 Conclusions

In conclusion, this thesis shows no association between SSI following breast cancer surgery and systemic recurrence or death. However, it suggests that major postoperative systemic infections are associated with a higher risk of recurrence and death in breast cancer.

Study-specific conclusions:

I) Neither SSI nor other infections following breast cancer surgery are associated with increased risk of LRR or systemic breast cancer recurrence. Instead, factors associated with both SSI and recurrence may account for the correlation observed in previous studies.

II) BMI > 30 is a significant risk factor for SSI and other wound complications. However, even a BMI between 25 and 30 is linked to a doubled risk of SSI and wound complications. Both mastectomies +/-IBR, are risk factors for wound complications.

III) SSI following breast cancer surgery does not significantly impact the risk of systemic recurrence, LRR, overall death or breast cancer-specific death. However, unspecified local complications are associated with a higher risk of systemic recurrence. Risk factors for SSI include age 40-64 years, obesity, higher CCI scores, low family income, larger tumours, lymph node metastases, non-luminal A subtypes, extensive surgeries, and region of residence.

IV) Major systemic infection within 90 days of surgery is associated with increased risk of systemic recurrence, overall death, and breast cancer-specific death, but not with LRR. Other major events are only associated with overall death.

10 Future perspectives

Understanding the risk factors for SSI and other wound complications following breast cancer surgery is crucial for developing prevention strategies, improving outcomes, and reducing morbidity and costs in breast cancer patients. Antibiotic prophylaxis should be administered on an individual basis and tailored to the needs of overweight or obese patients to ensure adequate tissue levels. The data from this dissertation form the basis for the guidelines on antibiotic prophylaxis in breast surgery currently being developed at Stockholm South General Hospital. These guidelines will subsequently be discussed further in the Stockholm region.

Prioritizing the principle of surgical de-escalation is essential: opting for BCS over mastectomy when both options are viable, utilizing NAT to facilitate BCS, and choosing TAD instead of ALND. Additionally, careful patient selection for IBR and oncoplastic BCS is of utmost importance.

The finding that SSI, one of the most common complications after breast cancer surgery, does not seem to be associated with worse oncological outcomes has important clinical implications. It reassures both patients and physicians that the risk of systemic recurrence after SSI is not increased to clinically relevant levels and does not necessitate more aggressive adjuvant treatment or follow-up. However, it remains essential to continue efforts to minimize local complication rates to alleviate patient suffering. However, emphasis should also be placed on minimizing systemic infections, and in case of an infection, administering timely and appropriate treatment, which may potentially improve outcomes. Future studies should investigate interventions to reduce the risk of postoperative complications.

Several studies indicate that prophylactic wound treatment with negative pressure wound therapy can reduce the risk of wound complications, particularly for high-risk patients undergoing reconstruction or reduction mammoplasty (220-227). While the positive effects of negative pressure wound therapy are well-documented, there are no RCTs on high-risk patients undergoing complex oncologic plastic breast surgery. To the best of our knowledge, negative pressure wound therapy is not routinely used prophylactically for breast patients in Sweden. Therefore, we propose to investigate whether prophylactic negative pressure wound therapy reduces wound complications for high-risk

Swedish patients undergoing breast surgery. If proven effective, this method should be used more frequently to reduce wound complications and alleviate the suffering these complications cause our patients. Additionally, this would lead to reduced healthcare costs and decrease the risk of delaying important adjuvant treatments.

11 Svensk sammanfattning (Summary in Swedish)

Bröstcancer är den vanligaste cancersjukdomen hos kvinnor i Sverige och 2022 diagnostiserades 8,486 kvinnor med bröstcancer och 1,374 kvinnor dog av bröstcancer (5). Globalt insjuknade ca 2,3 miljoner kvinnor i bröstcancer 2022 och 685,000 dog av bröstcancer (200). Bröstcancer hos män är ovanligt, 2022 insjuknade 57 (0,7 %) män i Sverige (5).

Kirurgi är oftast förstahandsbehandling vid bröstcancer och majoriteten opereras med bröstbevarande kirurgi, men fortfarande opereras cirka en fjärdedel med mastektomi (borttagande av hela bröstet), med eller utan direktrekonstruktion. Strålbehandling, cytostatika, endokrin terapi, monoklonala antikroppar och immunterapi används som tilläggsbehandlingar (228).

Den relativa dödligheten i bröstcancer har minskat avsevärt under de senaste decennierna, främst på grund av införandet av generell mammografiscreening och förbättrade kompletterande onkologiska behandlingar (229). Lokala återfall i bröstet eller lymfkörtlarna har också minskat och ligger nu på cirka 0,5% per år. (33) En del patienter som upplever lokala återfall kommer även att drabbas av fjärrspridning (metastaser), vanligast till lungor, lever, skelett och hjärna (28, 133). Fjärrspridning av bröstcancer drabbar från cirka 20 % av patienterna i västvärlden till cirka 50% i vissa delar av Afrika (133). Ungefär var fjärde patient som får återfall beräknas dö till följd av sin bröstcancer (108). Den relativa fem- och tioårsöverlevnaden för kvinnor i Sverige var år 2021 92,8% respektive 87,8 % (137).

I Sverige genomgår ungefär 92 % av de som drabbas av bröstcancer kirurgisk behandling (230). Senaste årtiondet har allt fler operationstekniker utvecklats, bland annat för att minska antalet patienter som behöver ta bort hela bröstet. Onkoplastik kirurgi förenar tumörkirurgi med plastikkirurgiska tekniker, för att möjliggöra borttagandet av större tumörer och ändå kunna bevara bröstets form och symmetri och har blivit allt mer vanligt förekommande. Termen onkoplastik myntades på 1980-talet när cytostatika och strålbehandling bidrog till att mer konservativ kirurgi var möjlig vid avancerad bröstcancer. Målet var att öka livskvalitet och minska morbiditet (231).

Komplikationer efter bröstkirurgi kan leda till sämre livskvalitet, ökad morbiditet, ökade sjukvårdskostnader, fördröjd start av adjuvant behandling (onkologisk efterbehandling) och att en rekonstruktion går förlorad. Den vanligaste komplikationen efter bröstkirurgi är serom. Blödning, postoperativ sårinfektion och kronisk neuropatisk smärta är andra frekvent förekommande komplikationer (146). Den postoperativa sårinfektionsfrekvensen efter bröstcancerkirurgi varierar stort i litteraturen (0–26 %) (144, 145). Efter bröstcancerkirurgi kan en sårkomplikation medföra förlängd tid till adjuvant behandling. Denna fördröjning till onkologisk behandling kan påverka det onkologiska utfallet negativt (164-166). Sårkomplikationer är även kostsamma och en studie från USA uppskattar kostnaden för en patient som drabbas av en postoperativ sårinfektion till ca 4,000 dollar (152). Vidare finns det data som indikerar att sårkomplikationer efter bröstcancerkirurgi kan försämra det onkologiska utfallet (145, 153-157). Det finns således många skäl till att eftersträva att minska sårkomplikationer efter bröstkirurgi.

Redan 1863, upptäckte Rudolf Virchow vita blodkroppar i malign vävnad och drog slutsatsen att det finns ett samband mellan cancer och inflammation (167). Denna teori har sedan dess fått ökat stöd, och det uppskattas att cirka 20% av alla cancerrelaterade dödsfall är associerade med infektion och inflammation (208). Sambandet mellan inflammation och cancer är numera allmänt accepterat (167, 168, 208).

Perioden runtomkring operationen har föreslagits vara kritisk för att bestämma det onkologiska utfallet (179-182). Under denna korta tidsperiod kan flera faktorer, såsom ökad stress, inflammatoriska reaktioner och pro-angiogena och/eller tillväxtfaktorer, bidra till utvecklingen av befintliga mikrometastaser (171, 182). En postoperativ komplikation med dess inflammatoriska respons kan teoretiskt stimulera subkliniska mikrometastaser och främja återfall. Denna teori stöds av andra maligniteter där till exempel infektion efter koloncanceroperation ökar risken för återfall (183). Infektiösa komplikationer efter operation för hals- och magcancer korrelerar också med sämre utfall (184, 185). Återfall av bröstcancer kan utvecklas med latensperioder som sträcker sig från år till årtionden. En teori om dessa latensperioder är *cancer dormancy*, ett stadium i cancerprogressionen där kvarvarande sjukdom är närvarande men förblir asymtomatisk (176-178). Adjuvant behandling som syftar till att utrota kvarvarande mikroinvasiv sjukdom initieras vanligtvis tidigast en månad efter operationen och kan därför ha begränsad effekt på de potentiellt stimulerade mikrometastaserna orsakade av den inflammatoriska responsen på grund av komplikationer inom den första månaden. Patienter som drabbas av postoperativa komplikationer har en risk för förlängd tid till adjuvant onkologisk behandling. Data indikerar att förseningar i cancerbehandling kan påverka onkologiska utfall negativt, med längre förseningar som ytterligare förvärrar dessa negativa effekter (164-166) Att förstå riskfaktorer till

komplikationer efter bröstcanceroperation är avgörande för att utveckla infektionsförebyggande strategier och förbättra det kirurgiska och kanske även onkologiska utfallet (145, 153-157). Avhandlingen avser att undersöka om det finns en association mellan komplikationer efter bröstcancerkirurgi och onkologiskt utfall samt att undersöka riskfaktorer till komplikationer.

I **Studie I** var syftet att undersöka den föreslagna associationen mellan postoperativ sårinfektion efter bröstcancerkirurgi och återfall av bröstcancer. Som ett sekundärt mål studerades även en möjlig koppling mellan någon postoperativ infektion (såsom urinvägsinfektion eller lunginflammation) och återfall av bröstcancer. Den första studien är en populationsbaserad, retrospektiv kohortstudie som inkluderade alla patienter som genomgick bröstcancerkirurgi från januari 2009 till december 2010 i Uppland. Data inkluderade patient-, behandlings- och tumöregenskaper, infektionsfrekvenser och utfall. Totalt inkluderades 492 patienter, med en medianuppföljning på 8,4 år. Medelåldern var 62 ± 13 år. Sjuttio (14,2 %) av patienterna drabbades av en postoperativ sårinfektion och 49 (10,0 %) fick en annan infektion inom 90 dagar från operationen Totalt fick 26 patienter lokalt återfall och 55 fjärrspridning av sin bröstcancer. Patienter som drabbats av postoperativ sårinfektion hade signifikant ökad risk för fjärrspridning i ojusterad analys, men detta observerades inte i den justerade analysen. Däremot förblev större tumörstorlek och lymfkörtelmetastas signifikanta riskfaktorer för återfall av bröstcancer. Andra postoperativa infektioner var inte associerade med återfall. Sammanfattningsvis var varken postoperativ sårinfektion eller annan postoperativ infektion associerade med sämre onkologiskt utfall.

Studie II är en prospektivt registrerad kohortstudie, med syftet att undersöka riskfaktorer för sårinfektioner och andra postoperativa sårkomplikationer efter bröstcancerkirurgi. Patienter som genomgick bröstbevarande kirurgi eller mastektomi i Uppsala mellan maj 2017 och maj 2019 inkluderades. Data inkluderade patient- och behandlings karakteristika samt infektions- och andra sårkomplikationsfrekvenser. Studien omfattade 592 patienter som genomgick 707 ingrepp. Det förekom 66 (9,3%) sårinfektioner och 95 (13,4%) sårkomplikationer. Studien bekräftar att BMI > 30 är en riskfaktor för sårinfektioner och andra sårkomplikationer, men även att BMI 25-30 är associerat med en fördubblad risk för sårinfektioner. Mastektomi med eller utan omedelbar rekonstruktion var båda riskfaktorer för sårkomplikationer och det fanns en trend för att onkoplastisk bröstbevarande kirurgi var en riskfaktor för sårinfektioner.

Studie III och IV är registerstudier där vi använde oss av forskningsdatabasen BCBaSe 3.0 (Breast Cancer DataBase Sweden), där NKBC (Nationellt Kvalitetsregister för BröstCancer) är länkat till hälso- och sjukvårdsregister samt demografiska databaser via socialstyrelsen, statistiska centralbyrån och

försäkringskassan. Patienter som genomgick kirurgi för primär bröstcancer i Sverige från januari 2008 till september 2019 inkluderades.

Det primära syftet med **Studie III** var att undersöka om postoperativ sårinfektion efter bröstcancerkirurgi ökar risken för fjärrspridning av bröstcancer. Sekundära syften var att bedöma påverkan av sårinfektion på risken för lokoregionalt återfall (LRR), bröstcancer-specifik överlevnad (BCSS) och total överlevnad (OS). För fullständighetens skull registrerades även andra lokala kirurgiska komplikationer. Av de 82,102 patienter som inkluderades i studien, drabbades 15,7% en sårinfektion och 21,1% av någon form av sårkomplikation inom 90 dagar efter operation. Sårinfektion var inte signifikant associerad med fjärrspridning, LRR eller BCSS efter justering för andra patient/behandling/tumörfaktorer. Sårinfektion var däremot associerat med sämre OS, men den associationen försvann i en analys som exkluderade alla patienter med någon form av cancer före bröstcancerdiagnosen. Som bifynd såg vi att patienter som drabbats av ospecificerad sårkomplikation hade signifikant högre risk för fjärrspridning. Riskfaktorer för postoperativ sårinfektion inkluderade ålder 40–64 år, fetma, komorbiditet (högre CCI-index), låg familjeinkomst, större tumörer, lymfkörtelmetastaser, mer aggressiv tumör subtyp, omfattande operationer och bostadsregion.

I **Studie IV** var syftet att utvärdera risken för fjärrspridning av bröstcancer efter allvarliga (major) systemiska postoperativa infektioner som krävde sjukhusinläggning (t ex sepsis eller lunginflammation) eller annan större händelse (stroke, hjärtinfarkt eller lungemboli). Studien undersökte även dessa händelser inverkan på LRR, OS och BCSS. Av de studerade patienterna drabbades 1,8 % (1,461 patienter) av en allvarlig systemisk infektion inom 90 dagar efter operationen, där 0,4 % (348 patienter) drabbades inom 30 dagar. Dessutom upplevde 0,6 % (516 patienter) en annan större händelse inom 90 dagar. En allvarlig systemisk infektion inom 90 dagar efter operationen var signifikant associerad med en ökad risk för fjärrspridning samt total och bröstcancer-specifik dödlighet. Patienterna som drabbades av en sådan infektion inom 30 dagar efter operationen hade även en ökad risk för LRR. Andra större händelser visade sig endast vara signifikant associerade med ökad total dödlighet.

Sammanfattningsvis stödjer inte denna avhandling hypotesen att postoperativa sårinfektioner ökar risken för återfall eller död. Det är sannolikt att andra faktorer, som är kopplade till både postoperativa sårinfektioner och återfall, bidrar till den association som tidigare studier har observerat. Däremot identifierades en signifikant koppling mellan allvarliga systeminfektioner och både återfall samt total och bröstcancer-specifik dödlighet. Såvitt vi vet har effekterna av systeminfektioner eller andra större händelser efter bröstcancerkirurgi inte studerats tidigare. Det verkar som att mindre infektioner, som har en begränsad påverkan på det generella inflammationssvaret, inte påverkar

prognosen. Men att, allvarligare infektioner och komplikationer, som har ett större generellt inflammationssvar, är associerade med en högre risk för återfall och död i bröstcancer. Alla möjliga åtgärder bör vidtas för att minska frekvensen av komplikationer och systeminfektioner efter bröstcancerkirurgi, dels för att minska det lidande dessa händelser orsakar våra patienter. Dels för att detta leder till minskade sjukvårdskostnader, minskar risken för att viktig adjuvant behandling fördröjs, minskar förlusten av rekonstruktioner och möjligen även förbättrar det onkologiska utfallet.

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13 References

1. Charalampoudis P KT. Surgery to the Breast: Mastectomy, Breast Cancer Management for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: springer; 2018. 204 p.
2. Leidenius M. Surgery to the Breast: Breast Conservation Techniques, Breast Cancer management for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 215 p.
3. de Boniface J, Szulkin R, Johansson ALV. Survival After Breast Conservation vs Mastectomy Adjusted for Comorbidity and Socioeconomic Status: A Swedish National 6-Year Follow-up of 48 986 Women. JAMA Surg. 2021;156(7):628-37.
https://www.who.int/news-room/fact-sheets/detail/breast-cancer.
https://www.cancerfonden.se/om-cancer/statistik/brostcancer.
6. Parks RM. Breast Cancer Epidemiology, Breast Cancer Management for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 21-5 p.
https://static-files.cancerfonden.se/Cancer%20i%20siffror%202018_laddaner.pdf.
8. Petridou ET. Effect of Oestrogen Exposure, Obesity, Exercise and Diet on Breast Cancer risk, Breast Cancer Management for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 38-9 p.
9. J Methew MS. Breast Cancer Screening, Breast Cancer Management for Surgeons Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 152-5 p.
10. Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet. 2002;359(9310):909-19.
11. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al. Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. Jama. 2015;314(15):1599-614.
12. The benefits and harms of breast cancer screening: an independent review. Lancet. 2012;380(9855):1778-86.
13. Palhazi P. Gross Anatomy of the Breast and the Axilla, Breast Cancer Managegment for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 4 p.
14. Carter SA. Ductal Carcinoma in Situ, Breast Cancer Management for Breast Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 116 p.
15. F Penault-Llorca NR-R. Pathology of Breast Cancer, Breast Cancer Management for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 178-89 p.

16. Ditsch N, Kolberg-Liedtke C, Friedrich M, Jackisch C, Albert US, Banys-Paluchowski M, et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2021. Breast Care (Basel). 2021;16(3):214-27.
17. Kjällquist U, Acs B, Margolin S, Karlsson E, Kessler LE, Garcia Hernandez S, et al. Real World Evaluation of the Prosigna/PAM50 Test in a Node-Negative Postmenopausal Swedish Population: A Multicenter Study. Cancers (Basel). 2022;14(11).
18. Burstein HJ. The distinctive nature of HER2-positive breast cancers. N Engl J Med. 2005;353(16):1652-4.
https://kunskapsbanken.cancercentrum.se/diagnoser/brostcancer/vardprogram/kvalitetsdokument-for--patologi/#chapter--Proliferationsmarkor-Ki67--immunhistokemisk-metod.
20. Blackley EF, Loi S. Targeting immune pathways in breast cancer: review of the prognostic utility of TILs in early stage triple negative breast cancer (TNBC). Breast. 2019;48 Suppl 1:S44-s8.
21. Schütz F, Stefanovic S, Mayer L, von Au A, Domschke C, Sohn C. PD-1/PD-L1 Pathway in Breast Cancer. Oncol Res Treat. 2017;40(5):294-7.
22. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66.
23. Harbeck N, Gnant M. Breast cancer. Lancet. 2017;389(10074):1134-50.
24. Markopoulos C. Molecular Profiling of Breast Cancer and DCIS, Breast Cancer Management for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 90-7 p.
25. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021;385(25):2336-47.
https://kunskapsbanken.cancercentrum.se/diagnoser/brostcancer/vardprogram/Postoperativ-medicinsk-behandling/#chapter-15-2-3-Genexpressionsanalys-infor-beslut-om-adjuvant-cytostatika.
27. Kalli S, Semine A, Cohen S, Naber SP, Makim SS, Bahl M. American Joint Committee on Cancer's Staging System for Breast Cancer, Eighth Edition: What the Radiologist Needs to Know. Radiographics. 2018;38(7):1921-33.
28. Zgajnar J. Clinical Presentation, Diagnosis and Staging of Breast Cancer, Breast Cancer Management for Surgeons. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 160-74 p.
29. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985;312(11):665-73.
30. Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med. 1981;305(1):6-11.
31. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. The Lancet. 2021;397(10286):1750-69.
32. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer. 2006;42(3):351-6.

33. Bosma SC, van der Leij F, van Werkhoven E, Bartelink H, Wesseling J, Linn S, et al. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. Breast Cancer Res Treat. 2016;156(2):391-400.
34. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56.
35. Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat. 2017;165(2):273-83.
36. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Ann Surg Oncol. 2014;21(3):704-16.
37. Bundred JR, Michael S, Stuart B, Cutress RI, Beckmann K, Holleczek B, et al. Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. Bmj. 2022;378:e070346.
38. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ. Ann Surg Oncol. 2016;23(12):3801-10.
39. Pilewskie M, Morrow M. Margins in breast cancer: How much is enough? Cancer. 2018;124(7):1335-41.
40. Marinkovic M, Djordjevic N, Djordjevic L, Ignjatovic N, Djordjevic M, Karanikolic V. Assessment of the quality of life in breast cancer depending on the surgical treatment. Support Care Cancer. 2021;29(6):3257-66.
41. Davis LE, Fulton C, Bubis LD, Sussman J, Moody L, Barbera L, et al. Patient-reported symptoms following mastectomy alone or lumpectomy plus radiation for early stage breast cancer: a cohort study. Breast Cancer Res Treat. 2019;175(3):721-31.
42. 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;36(15):1938-43.
43. Kim M, Tadros AB, Boe LA, Vingan P, Allen RJ, Jr., Mehrara BJ, et al. Breast-Conserving Therapy Versus Postmastectomy Breast Reconstruction: Propensity Score-Matched Analysis. Ann Surg Oncol. 2024.
44. Al-Hilli Z, Thomsen KM, Habermann EB, Jakub JW, Boughey JC. Reoperation for Complications after Lumpectomy and Mastectomy for Breast Cancer from the 2012 National Surgical Quality Improvement Program (ACS-NSQIP). Ann Surg Oncol. 2015;22 Suppl 3:S459-69.
45. Hofvind S, Holen Å, Aas T, Roman M, Sebuødegård S, Akslen LA. Women treated with breast conserving surgery do better than those with mastectomy independent of detection mode, prognostic and predictive tumor characteristics. Eur J Surg Oncol. 2015;41(10):1417-22.
46. van Maaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol. 2016;17(8):1158-70.

47. Lagendijk M, van Maaren MC, Saadatmand S, Strobbe LJA, Poortmans PMP, Koppert LB, et al. Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. Int J Cancer. 2018;142(1):165-75.
48. Chu QD, Hsieh MC, Lyons JM, Wu XC. 10-Year Survival after Breast-Conserving Surgery Compared with Mastectomy in Louisiana Women with Early-Stage Breast Cancer: A Population-Based Study. J Am Coll Surg. 2021;232(4):607-21.
49. Kim H, Lee SB, Nam SJ, Lee ES, Park BW, Park HY, et al. Survival of Breast-Conserving Surgery Plus Radiotherapy versus Total Mastectomy in Early Breast Cancer. Ann Surg Oncol. 2021;28(9):5039-47.
50. Savioli F, Edwards J, McMillan D, Stallard S, Doughty J, Romics L. The effect of postoperative complications on survival and recurrence after surgery for breast cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2020;155:103075.
51. Sanidas E.E FF. Oncoplastic Breast-Conserving Therapy. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 230-1 p.
52. Cook LJ DM. Specific Implant-Based Techniques for Breast Reconstruction. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 366-77 p.
53. Cardoso M.J CG. Immediate reconstruction: General and oncological considerations. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 316-22 p.
54. Gümüscü R, Wärnberg F, de Boniface J, Sund M, Åhsberg K, Hansson E, et al. Timing and type of breast reconstruction in SweBRO 3: long-term outcomes. Br J Surg. 2024;111(9).
55. Bergkvist L FJ. Management of the axilla: Sentinel lymph node biopsy. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 276-82 p.
56. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003;349(6):546-53.
57. Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, et al. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial. JAMA Oncol. 2023;9(11):1557-64.
58. Ingvar C, Ahlgren J, Emdin S, Lofgren L, Nordander M, Niméus E, et al. Long-term outcome of pT1a-b, cN0 breast cancer without axillary dissection or staging: a prospective observational study of 1543 women. Br J Surg. 2020;107(10):1299-306.
59. Thompson J, Le J, Hop A, Melnik M, Paulson J, Wright GP. Impact of Choosing Wisely Recommendations on Sentinel Lymph Node Biopsy and Postoperative Radiation Rates in Women Over Age 70 Years with Hormone-Positive Breast Cancer. Ann Surg Oncol. 2021;28(10):5716-22.
60. Reimer T. Omission of axillary sentinel lymph node biopsy in early invasive breast cancer. Breast. 2023;67:124-8.
61. Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385-93.

62. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. Jama. 2017;318(10):918-26.
63. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303-10.
64. Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017;43(4):672-9.
65. Classe JM, Loaec C, Gimbergues P, Alran S, de Lara CT, Dupre PF, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2019;173(2):343-52.
66. Boileau JF, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol. 2015;33(3):258-64.
67. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. Jama. 2013;310(14):1455-61.
68. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609-18.
69. Tee SR, Devane LA, Evoy D, Rothwell J, Geraghty J, Prichard RS, et al. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. Br J Surg. 2018;105(12):1541-52.
70. Simons JM, van Nijnatten TJA, van der Pol CC, Luiten EJT, Koppert LB, Smidt ML. Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging After Neoadjuvant Systemic Therapy in Node-positive Breast Cancer: A Systematic Review and Meta-analysis. Ann Surg. 2019;269(3):432-42.
https://aacrjournals.org/cancerres/article/84/9_Supplement/GS02-02/743891/Abstract-GS02-02-Are-nodal-ITCs-after-neoadjuvant.
72. Montagna G, Laws A, Ferrucci M, Mrdutt MM, Sun SX, Bademler S, et al. Nodal Burden and Oncologic Outcomes in Patients With Residual Isolated Tumor Cells After Neoadjuvant Chemotherapy (ypN0i+): The OPBC-05/ICARO Study. J Clin Oncol. 2024:Jco2401052.
73. van Nijnatten TJA, Simons JM, Moossdorff M, de Munck L, Lobbes MBI, van der Pol CC, et al. Prognosis of residual axillary disease after neoadjuvant chemotherapy in clinically node-positive breast cancer patients: isolated tumor cells and micrometastases carry a better prognosis than macrometastases. Breast Cancer Research and Treatment. 2017;163(1):159-66.
74. Canavese G, Tinterri C, Carli F, Garrone E, Spinaci S, Della Valle A, et al. Correlation between outcome and extent of residual disease in the sentinel node after neoadjuvant chemotherapy in clinically fine-needle proven node-positive breast cancer patients. Eur J Surg Oncol. 2021;47(8):1920-7.

75. Cabıoğlu N, Karanlık H, Yıldırım N, Müslümanoğlu M, Çakmak Karadeniz G, Trabulus Can D, et al. Favorable outcome with sentinel lymph node biopsy alone after neoadjuvant chemotherapy in clinically node positive breast cancer at diagnosis: Turkish Multicentric NEOSENTI-TURK MF-18-02-study. Eur J Surg Oncol. 2021;47(10):2506-14.
76. van Hemert A, van Loevezijn A, Baas M-S, Stokkel M, Groen E, van der Noort V, et al. Oncologic outcome of response-guided axillary treatment in patients with cN1 breast cancer after primary systemic therapy. Journal of Clinical Oncology. 2024;42:514-.
77. https://event.eortc.org/ebcc14/2024/03/22/breast-cancer-patients-can-safely-avoid-extensive-removal-of-lymph-nodes-if-they-respond-well-to-primary-systemic-treatment/.
78. Peto R, Davies C, Godwin J, Gray R, Pan HC, Clarke M, 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;379(9814):432-44.
79. Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. Lancet. 2023;401(10384):1277-92.
80. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. J Clin Oncol. 2021;39(13):1485-505.
81. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997;15(7):2483-93.
82. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017;376(22):2147-59.
83. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-28.
84. Rabaglio M CM. Adjuvant Endocrine Therapy. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. pp 428-33 p.
85. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, 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;378(9793):771-84.
86. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. 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. Lancet. 2013;381(9869):805-16.
87. Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. Journal of Clinical Oncology. 2013;31(18_suppl):5-.
88. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341-52.
89. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11(12):1135-41.

90. Ruhstaller T, Giobbie-Hurder A, Colleoni M, Jensen MB, Ejlertsen B, de Azambuja E, et al. Adjuvant Letrozole and Tamoxifen Alone or Sequentially for Postmenopausal Women With Hormone Receptor-Positive Breast Cancer: Long-Term Follow-Up of the BIG 1-98 Trial. J Clin Oncol. 2019;37(2):105-14.
91. Francis PA, Regan MM, Fleming GF, Láng I, Ciruelos E, Bellet M, et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372(5):436-46.
92. Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Láng I, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014;371(2):107-18.
93. Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022;23(3):382-92.
94. Li Z, Zou W, Zhang J, Zhang Y, Xu Q, Li S, et al. Mechanisms of CDK4/6 Inhibitor Resistance in Luminal Breast Cancer. Front Pharmacol. 2020;11:580251.
95. Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol. 2020;38(34):3987-98.
96. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE, Jr., et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744-52.
97. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;2012(4):Cd006243.
98. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-205.
99. Pivot X, Romieu G, Debled M, Pierga JY, Kerbrat P, Bachelot T, et al. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial. Lancet. 2019;393(10191):2591-8.
100. Earl HM, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. Lancet. 2019;393(10191):2599-612.
101. Bellon JR, Guo H, Barry WT, Dang CT, Yardley DA, Moy B, et al. Local-regional recurrence in women with small node-negative, HER2-positive breast cancer: results from a prospective multi-institutional study (the APT trial). Breast Cancer Res Treat. 2019;176(2):303-10.
102. Piccart M, Procter M, Fumagalli D, de Azambuja E, Clark E, Ewer MS, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021;39(13):1448-57.
103. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32.

104. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Waldron-Lynch M, et al. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. Eur J Cancer. 2018;89:27-35.
105. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020;382(9):810-21.
106. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022;386(6):556-67.
https://cslide.ctimeetingtech.com/esmo2024/attendee/confcal/show/session/170.
108. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, 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;378(9804):1707-16.
109. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9(4):331-41.
110. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008;371(9618):1098-107.
111. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020;395(10237):1613-26.
112. Kirby A, Griffin C, Finneran L, Sydenham M, Alhasso A, Brunt AM, et al. Partial Breast Radiotherapy for Women with Early Breast Cancer: 10-Year Outcomes from IMPORT LOW (CRUK/06/003). International Journal of Radiation Oncology, Biology, Physics. 2023;117(4):e7.
113. Jereczek-Fossa B A LMC, Dicuonzo S. Radiotherapy for Breast Cancer. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. pp 464 p.
114. Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother Oncol. 2009;91(1):23-32.
115. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, 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;366(9503):2087-106.
116. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935):2127-35.
117. Kunkler IH, Canney P, van Tienhoven G, Russell NS. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. Clin Oncol (R Coll Radiol). 2008;20(1):31-4.

118. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015;373(4):307-16.
119. Poortmans PM, Weltens C, Fortpied C, Kirkove C, Peignaux-Casasnovas K, Budach V, et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol. 2020;21(12):1602-10.
120. Mamounas EP, Bandos H, White JR, Julian TB, Khan AJ, Shaitelman SF, et al. NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to whole breast RT post breast-conserving surgery (BCS) reduces invasive breast cancer recurrence-free interval (IBCR-FI) in patients (pts) with pathologically positive axillary (PPAx) nodes who are ypN0 after neoadjuvant chemotherapy (NC). Journal of Clinical Oncology. 2019;37(15_suppl):TPS600-TPS.
121. Mamounas E BH, White J, et al: Loco-regional irradiation in patients with biopsy-proven axillary node involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: Primary outcomes of NRG Oncology/NSABP B-51/RTOG 1304. 2023 San Antonio Breast Cancer Symposium. Abstract GS02-07. Presented December 7, 2023. https://clinicaltrials.gov/ct2/show/NCT01901094.
123. Henke G, Knauer M, Ribi K, Hayoz S, Gérard MA, Ruhstaller T, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. Trials. 2018;19(1):667.
124. Holleczek B, Stegmaier C, Radosa JC, Solomayer EF, Brenner H. Risk of loco-regional recurrence and distant metastases of patients with invasive breast cancer up to ten years after diagnosis - results from a registry-based study from Germany. BMC Cancer. 2019;19(1):520.
125. Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J Clin Oncol. 2001;19(6):1688-97.
126. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med. 2017;377(19):1836-46.
127. Agresti R SA, Bianchi G, Trecate G. Surgery for locally recurrent breast cancer. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. pp264-71 p.
128. Maaskant-Braat AJ, Voogd AC, Roumen RM, Nieuwenhuijzen GA. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat. 2013;138(1):13-20.
129. Wapnir IL, Price KN, Anderson SJ, Robidoux A, Martín M, Nortier JWR, et al. Efficacy of Chemotherapy for ER-Negative and ER-Positive Isolated Locoregional Recurrence of Breast Cancer: Final Analysis of the CALOR Trial. J Clin Oncol. 2018;36(11):1073-9.
130. Waeber M, Castiglione-Gertsch M, Dietrich D, Thürlimann B, Goldhirsch A, Brunner KW, et al. Adjuvant therapy after excision and radiation of isolated postmastectomy locoregional breast cancer recurrence: definitive results of a phase III randomized trial (SAKK 23/82) comparing tamoxifen with observation. Ann Oncol. 2003;14(8):1215-21.

131. Anderson SJ, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. J Clin Oncol. 2009;27(15):2466-73.
132. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE, Jr., Jeong JH, Tan-Chiu E, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol. 2006;24(13):2028-37.
133. Senkus E LA. Metastatic breast cancer: prognosis, diagnosis and oncological management. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. 580-90 p.
134. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol. 2015;16(13):1380-8.
135. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast. 2014;23(5):489-502.
https://www.cancerresearchuk.org/about-cancer/breast-cancer/survival.
https://static-files.cancerfonden.se/Cancer-i-siffror-2023.pdf?_gl=1*1im7rkc*_up*MQ..&gclid=Cj0KCQjwxsm3BhDrARIsAMtVz6MyBffRL97WZy3wH6bd3oua4_pnD7Cc9VcLl-mSOfjrEXwfzQXXGzcaApmjEALw_wcB&gbraid=0AAAAAD0_Xv8QkqbtKTQSFOmOuuI1dFB_W.
https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
139. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602.
140. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med. 2013;173(22):2039-46.
141. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011;377(9761):228-41.
142. Badia JM, Casey AL, Petrosillo N, Hudson PM, Mitchell SA, Crosby C. Impact of surgical site infection on healthcare costs and patient outcomes: a systematic review in six European countries. J Hosp Infect. 2017;96(1):1-15.
143. Jones DJ, Bunn F, Bell-Syer SV. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. Cochrane Database Syst Rev. 2014(3):Cd005360.
144. Cunningham M, Bunn F, Handscomb K. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. Cochrane Database Syst Rev. 2006(2):Cd005360.
145. O'Connor R, Kiely PA, Dunne CP. The relationship between post-surgery infection and breast cancer recurrence. J Hosp Infect. 2020;106(3):522-35.
146. Kontos M MC. Complications of Breast Surgery and Their Management. Wyld L MC, Leidenius M, Senkus-Konefka E, editor. Cham, Switzerland: Springer; 2018. pp 412-8 p.

147. Olsen MA, Lefta M, Dietz JR, Brandt KE, Aft R, Matthews R, et al. Risk factors for surgical site infection after major breast operation. J Am Coll Surg. 2008;207(3):326-35.
148. Xue DQ, Qian C, Yang L, Wang XF. Risk factors for surgical site infections after breast surgery: a systematic review and meta-analysis. Eur J Surg Oncol. 2012;38(5):375-81.
149. Vitug AF, Newman LA. Complications in breast surgery. Surg Clin North Am. 2007;87(2):431-51, x.
150. Al-Hilli Z, Wilkerson A. Breast Surgery: Management of Postoperative Complications Following Operations for Breast Cancer. Surg Clin North Am. 2021;101(5):845-63.
151. de Blacam C, Ogunleye AA, Momoh AO, Colakoglu S, Tobias AM, Sharma R, et al. High body mass index and smoking predict morbidity in breast cancer surgery: a multivariate analysis of 26,988 patients from the national surgical quality improvement program database. Ann Surg. 2012;255(3):551-5.
152. Olsen MA, Chu-Ongsakul S, Brandt KE, Dietz JR, Mayfield J, Fraser VJ. Hospital-associated costs due to surgical site infection after breast surgery. Arch Surg. 2008;143(1):53-60; discussion 1.
153. Lee KT, Jung JH, Mun GH, Pyon JK, Bang SI, Lee JE, et al. Influence of complications following total mastectomy and immediate reconstruction on breast cancer recurrence. Br J Surg. 2020.
154. Beecher SM, O'Leary DP, McLaughlin R, Sweeney KJ, Kerin MJ. Influence of complications following immediate breast reconstruction on breast cancer recurrence rates. Br J Surg. 2016;103(4):391-8.
155. Murthy BL, Thomson CS, Dodwell D, Shenoy H, Mikeljevic JS, Forman D, et al. Postoperative wound complications and systemic recurrence in breast cancer. British Journal of Cancer. 2007;97(9):1211-7.
156. Indelicato D, Grobmyer SR, Newlin H, Morris CG, Haigh LS, Copeland EM, 3rd, et al. Association between operative closure type and acute infection, local recurrence, and disease surveillance in patients undergoing breast conserving therapy for early-stage breast cancer. Surgery. 2007;141(5):645-53.
157. de Boniface J, Szulkin R, Johansson ALV. Major surgical postoperative complications and survival in breast cancer: Swedish population-based register study in 57 152 women. Br J Surg. 2022;109(10):977-83.
158. Valente SA, Liu Y, Upadhyaya S, Tu C, Pratt DA. The effect of wound complications following mastectomy with immediate reconstruction on breast cancer recurrence. Am J Surg. 2019;217(3):514-8.
159. Mousa M, Barnea Y, Arad U, Inbal A, Klausner J, Menes T. Association Between Postoperative Complications After Immediate Alloplastic Breast Reconstruction and Oncologic Outcome. Clin Breast Cancer. 2018;18(4):e699-e702.
160. Pedersen RN, Bhaskaran K, Heide-Jorgensen U, Norgaard M, Christiansen PM, Kroman N, et al. Breast cancer recurrence after reoperation for surgical bleeding. Br J Surg. 2017;104(12):1665-74.
161. Abdullah N, O'Leary DP, Hegarty A, Albathali M, Mushtaque M, Ajmal N, et al. The effect of surgical site infection in immediate breast reconstruction on breast cancer recurrence. Breast J. 2019;25(1):166-8.
162. Adwall L, Hultin H, Mani M, Norlén O. Prospective Evaluation of Complications and Associated Risk Factors in Breast Cancer Surgery. J Oncol. 2022;2022:6601066.

163. Stallard S, Savioli F, McConnachie A, Norrie J, Dudman K, Morrow ES, et al. Antibiotic prophylaxis in breast cancer surgery (PAUS trial): randomised clinical double-blind parallel-group multicentre superiority trial. Br J Surg. 2022;109(12):1224-31.
164. Gupta S, King WD, Korzeniowski M, Wallace DL, Mackillop WJ. The Effect of Waiting Times for Postoperative Radiotherapy on Outcomes for Women Receiving Partial Mastectomy for Breast Cancer: a Systematic Review and Meta-Analysis. Clin Oncol (R Coll Radiol). 2016;28(12):739-49.
165. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. Bmj. 2020;371:m4087.
166. Morante Z, Ruiz R, Araujo JM, Pinto JA, Cruz-Ku G, Urrunaga-Pastor D, et al. Impact of the Delayed Initiation of Adjuvant Chemotherapy in the Outcome of Triple Negative Breast Cancer. Clin Breast Cancer. 2021;21(3):239-46.e4.
167. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357(9255):539-45.
168. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7.
169. Dvorak HF. Tumors: wounds that do not heal-redux. Cancer Immunol Res. 2015;3(1):1-11.
170. Retsky MW, Demicheli R, Hrushesky WJ, Baum M, Gukas ID. Dormancy and surgery-driven escape from dormancy help explain some clinical features of breast cancer. Apmis. 2008;116(7-8):730-41.
171. Alieva M, van Rheenen J, Broekman MLD. Potential impact of invasive surgical procedures on primary tumor growth and metastasis. Clin Exp Metastasis. 2018;35(4):319-31.
172. Al-Sahaf O, Wang JH, Browne TJ, Cotter TG, Redmond HP. Surgical injury enhances the expression of genes that mediate breast cancer metastasis to the lung. Ann Surg. 2010;252(6):1037-43.
173. Bohle BMD, Pera MMD, Pascual MMD, Alonso SMD, Mayol XP, Salvado MMD, et al. Postoperative intra-abdominal infection increases angiogenesis and tumor recurrence after surgical excision of colon cancer in mice. Surgery: Official Journal of the Society of University Surgeons, Central Surgical Association, and the American Association of Endocrine Surgeons. 2010;147(1):120-6.
174. Neeman E, Ben-Eliyahu S. Surgery and stress promote cancer metastasis: new outlooks on perioperative mediating mechanisms and immune involvement. Brain Behav Immun. 2013;30 Suppl(Suppl):S32-40.
175. Ben-Eliyahu S. The promotion of tumor metastasis by surgery and stress: immunological basis and implications for psychoneuroimmunology. Brain Behav Immun. 2003;17 Suppl 1:S27-36.
176. Kim RS, Avivar-Valderas A, Estrada Y, Bragado P, Sosa MS, Aguirre-Ghiso JA, et al. Dormancy signatures and metastasis in estrogen receptor positive and negative breast cancer. PLoS One. 2012;7(4):e35569.
177. Wikman H, Vessella R, Pantel K. Cancer micrometastasis and tumour dormancy. Apmis. 2008;116(7-8):754-70.
178. Aguirre-Ghiso JA. Models, mechanisms and clinical evidence for cancer dormancy. Nat Rev Cancer. 2007;7(11):834-46.

179. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncol. 2015;12(4):213-26.
180. Haldar R, Shaashua L, Lavon H, Lyons YA, Zmora O, Sharon E, et al. Perioperative inhibition of β-adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor Ki-67 expression, serum cytokine levels, and PBMCs transcriptome. Brain Behav Immun. 2018;73:294-309.
181. Shaashua L, Shabat-Simon M, Haldar R, Matzner P, Zmora O, Shabtai M, et al. Perioperative COX-2 and β-Adrenergic Blockade Improves Metastatic Biomarkers in Breast Cancer Patients in a Phase-II Randomized Trial. Clin Cancer Res. 2017;23(16):4651-61.
182. Matzner P, Sandbank E, Neeman E, Zmora O, Gottumukkala V, Ben-Eliyahu S. Harnessing cancer immunotherapy during the unexploited immediate perioperative period. Nat Rev Clin Oncol. 2020;17(5):313-26.
183. Salvans S, Salvans S, Mayol X, Mayol X, Alonso S, Alonso S, et al. Postoperative peritoneal infection enhances migration and invasion capacities of tumor cells in vitro: An insight into the association between anastomotic leak and recurrence after surgery for colorectal cancer. Annals of Surgery. 2014;260(5):939-44;4;.
184. Jackson RM, Rice DH. Wound infections and recurrence in head and neck cancer. Otolaryngol Head Neck Surg. 1990;102(4):331-3.
185. Hayashi T, Yoshikawa T, Aoyama T, Hasegawa S, Yamada T, Tsuchida K, et al. Impact of infectious complications on gastric cancer recurrence. Gastric Cancer. 2015;18(2):368-74.
186. Löfgren L, Eloranta S, Krawiec K, Asterkvist A, Lönnqvist C, Sandelin K. Validation of data quality in the Swedish National Register for Breast Cancer. BMC Public Health. 2019;19(1):495.
187. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol. 1984;23(5):305-13.
188. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.
189. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765-73.
190. Nyström L, Larsson LG, Rutqvist LE, Lindgren A, Lindqvist M, Rydén S, et al. Determination of cause of death among breast cancer cases in the Swedish randomized mammography screening trials. A comparison between official statistics and validation by an endpoint committee. Acta Oncol. 1995;34(2):145-52.
191. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
192. Socialstyrelsen. The Swedish Prescribed Drug Register: Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-prescribed-drug-register/ 2020 [08 Jan 2021]. [
193. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-35.
https://www.scb.se/contentassets/8f66bcf5abc34d0b98afa4fcbfc0e060/rtb-bar-2016-eng.pdf.

195. Sweden. S. Longitudinal integrated database for health insurance and labour market studies: Available from: https://www.scb.se/en/services/ordering-data-and-statistics/register/longitudinal-integrated-database-for-health-insurance-and-labour-market-studies-lisa/ [08 Jan 2021]. [
196. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-37.
197. Colleoni M, Sun Z, Price KN, Karlsson P, Forbes JF, Thürlimann B, et al. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. J Clin Oncol. 2016;34(9):927-35.
198. Adwall L, Pantiora E, Hultin H, Norlén O. Association of postoperative infection and oncological outcome after breast cancer surgery. BJS Open. 2021;5(4).
https://etikprovningsmyndigheten.se/for-forskare/vad-sager-lagen/.
200. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
201. Maajani K, Jalali A, Alipour S, Khodadost M, Tohidinik HR, Yazdani K. The Global and Regional Survival Rate of Women With Breast Cancer: A Systematic Review and Meta-analysis. Clin Breast Cancer. 2019;19(3):165-77.
https://www.folkhalsorapportstockholm.se/rapporten2/levnadsvanor/rokning/.
203. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol. 2007;25(24):3657-63.
204. Hashemi E, Kaviani A, Najafi M, Ebrahimi M, Hooshmand H, Montazeri A. Seroma formation after surgery for breast cancer. World J Surg Oncol. 2004;2:44.
https://www.yumpu.com/sv/document/view/33049130/antibiotikaprofylax-vid-kirurgiska-ingrepp-sbu.
206. Forse RA, Karam B, MacLean LD, Christou NV. Antibiotic prophylaxis for surgery in morbidly obese patients. Surgery. 1989;106(4):750-6; discussion 6-7.
207. Penel N, Yazdanpanah Y, Chauvet MP, Clisant S, Giard S, Neu JC, et al. Prevention of surgical site infection after breast cancer surgery by targeted prophylaxis antibiotic in patients at high risk of surgical site infection. J Surg Oncol. 2007;96(2):124-9.
208. Basith S, Manavalan B, Yoo TH, Kim SG, Choi S. Roles of toll-like receptors in cancer: a double-edged sword for defense and offense. Arch Pharm Res. 2012;35(8):1297-316.
209. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. Radiother Oncol. 2008;87(1):3-16.
210. Andtbacka RH, Babiera G, Singletary SE, Hunt KK, Meric-Bernstam F, Feig BW, et al. Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. Ann Surg. 2006;243(1):96-101.
211. Maesaka JY, Reis YN, Elias LM, Akerman D, Baracat EC, Filassi JR. Venous thromboembolism incidence in postoperative breast cancer patients. Clinics (Sao Paulo). 2023;78:100229.

212. Yousufuddin M, Young N. Aging and ischemic stroke. Aging (Albany NY). 2019;11(9):2542-4.
213. Yoshikawa TT. Epidemiology and unique aspects of aging and infectious diseases. Clin Infect Dis. 2000;30(6):931-3.
214. Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular Risks Associated with Gender and Aging. J Cardiovasc Dev Dis. 2019;6(2).
215. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol. 2013;18(2):129-38.
216. Bohle B, Pera M, Pascual M, Alonso S, Mayol X, Salvado M, et al. Postoperative intra-abdominal infection increases angiogenesis and tumor recurrence after surgical excision of colon cancer in mice. Surgery. 2010;147(1):120-6.
217. Valachis A, Carlqvist P, Szilcz M, Freilich J, Vertuani S, Holm B, et al. Use of classifiers to optimise the identification and characterisation of metastatic breast cancer in a nationwide administrative registry. Acta Oncol. 2021;60(12):1604-10.
218. Alaeikhanehshir S, Ajayi T, Duijnhoven FH, Poncet C, Olaniran RO, Lips EH, et al. Locoregional Breast Cancer Recurrence in the European Organisation for Research and Treatment of Cancer 10041/BIG 03-04 MINDACT Trial: Analysis of Risk Factors Including the 70-Gene Signature. J Clin Oncol. 2024;42(10):1124-34.
219. Yeh RW, Valsdottir LR, Yeh MW, Shen C, Kramer DB, Strom JB, et al. Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial. Bmj. 2018;363:k5094.
220. Akhter HM, Macdonald C, McCarthy P, Huang Y, Meyer BR, Shostrum VK, et al. Outcomes of Negative Pressure Wound Therapy on Immediate Breast Reconstruction after Mastectomy. Plast Reconstr Surg Glob Open. 2023;11(8):e5130.
221. Vidya R, Khosla M, Baek K, Vinayagam R, Thekkinkattil D, Laws S, et al. Prophylactic Use of Negative Pressure Wound Therapy in High-risk Patients Undergoing Oncoplastic and Reconstructive Breast Surgery. Plast Reconstr Surg Glob Open. 2023;11(12):e5488.
222. Galiano RD, Hudson D, Shin J, van der Hulst R, Tanaydin V, Djohan R, et al. Incisional Negative Pressure Wound Therapy for Prevention of Wound Healing Complications Following Reduction Mammaplasty. Plast Reconstr Surg Glob Open. 2018;6(1):e1560.
223. Irwin GW, Boundouki G, Fakim B, Johnson R, Highton L, Myers D, et al. Negative Pressure Wound Therapy Reduces Wound Breakdown and Implant Loss in Prepectoral Breast Reconstruction. Plast Reconstr Surg Glob Open. 2020;8(2):e2667.
224. Ferrando PM, Ala A, Bussone R, Bergamasco L, Actis Perinetti F, Malan F. Closed Incision Negative Pressure Therapy in Oncological Breast Surgery: Comparison with Standard Care Dressings. Plast Reconstr Surg Glob Open. 2018;6(6):e1732.
225. Kim DY, Park SJ, Bang SI, Mun GH, Pyon JK. Does the Use of Incisional Negative-Pressure Wound Therapy Prevent Mastectomy Flap Necrosis in Immediate Expander-Based Breast Reconstruction? Plast Reconstr Surg. 2016;138(3):558-66.

226. Gabriel A, Sigalove S, Sigalove N, Storm-Dickerson T, Rice J, Maxwell P, et al. The Impact of Closed Incision Negative Pressure Therapy on Postoperative Breast Reconstruction Outcomes. Plast Reconstr Surg Glob Open. 2018;6(8):e1880.
227. Cagney D, Simmons L, O'Leary DP, Corrigan M, Kelly L, O'Sullivan MJ, et al. The Efficacy of Prophylactic Negative Pressure Wound Therapy for Closed Incisions in Breast Surgery: A Systematic Review and Meta-Analysis. World J Surg. 2020;44(5):1526-37.
https://www.internetmedicin.se/onkologi/brostcancer-primarbehandling.
https://kunskapsbanken.cancercentrum.se/diagnoser/brostcancer/vardprogram/bakgrund-och-orsaker/.
https://cancercentrum.se/globalassets/cancerdiagnoser/brost/kvalitetsregister/nationell_rapport_2013-web.pdf.
231. Macmillan RD, McCulley SJ. Oncoplastic Breast Surgery: What, When and for Whom? Curr Breast Cancer Rep. 2016;8:112-7.

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