A comprehensive approach for quality assessment of breast cancer care

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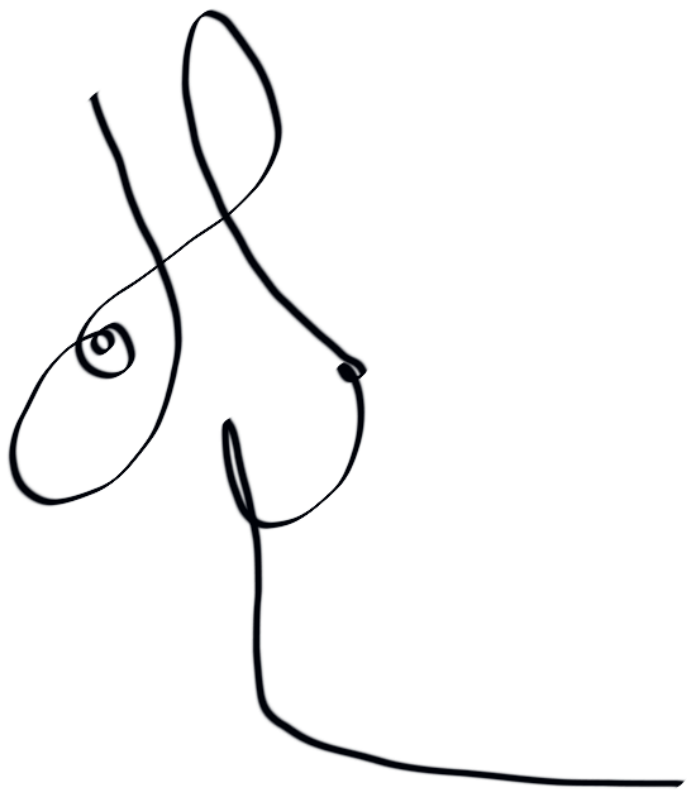
Chapter 1

General introduction and outline of this thesis



General introduction

In the last decades, there has been an increasing interest in the assessment and improvement of healthcare quality.[1-3] Advances in healthcare quality have been associated with positive effects on patient satisfaction, outcomes, productivity, and ultimately with lower healthcare costs.[4,5] However, defining healthcare quality is complicated due to subjective perspectives, multi-dimensional components, and changing cultural expectations. Defining quality of care might even be more challenging in breast cancer care due to the multidisciplinary setting, heterogeneity in tumor and patient populations, multitude of treatment pathways, and evolving diagnostic and treatment modalities.

Since defining healthcare quality depends on different perceptions of various stakeholders (e.g., physicians, patients, policymakers, taxpayers), several definitions and frameworks have been formulated to describe, monitor, and improve quality of care.[6] One of these frameworks was formulated by the Institute of Medicine (IOM) in the United States (US) in 2001.[7] Six dimensions of quality were described that could be used to assess and improve healthcare quality: *safety*, *effectiveness, patients-centeredness, timeliness, efficiency, and equity*.[7]

Although these six dimensions can be interpreted and used in various ways, in the current thesis they are used to assess the quality of breast cancer care in the following manner. The dimension of *safety* refers to not harming or limiting the harming of patients as a consequence of provided care. Safe care reduces or limits risks and hazards of adverse events for those involved. *Effectiveness* can be described as using care resources that have proven to result in the most superior clinical and non-clinical outcomes, such as the patients' health and satisfaction. Moreover, effective healthcare aims to limit the overuse of care with undesired or less optimal outcomes. On the other hand, it aims to limit the underuse of care that would result in superior outcomes. The dimension *patient-centeredness* refers to patients being well-informed and involved in care decisions. Patient-centeredness will provide patients a certain degree of control over the provided healthcare. The dimension of *timeliness* refers to receiving care without unnecessary delays. Extensive diagnostics or procedure preparation can require additional time and has been associated with delayed primary treatment.[8-10] Although some delay due to diagnostics may seem inevitable, there are unintentional delaying factors that could be dealt with when identified. The dimension of *efficiency* refers to limiting waste of care and resources (e.g. diagnostics, consultations, medicines, medical procedures, multidisciplinary reviews), thus the most optimal resource utilization. Efficient healthcare uses resources in the best order that

contribute to better outcomes while limiting the use of time, costs, and resources. The last dimension when assessing quality is *equity*. Equity refers to limiting unintentional disparities in quality of care among patients with differences in, for instance, gender, age, race, level of intelligence, social-economic status, sexual orientation, insurance, or location of residency.

The different stakeholders previous described of healthcare may each encounter different challenges when assessing and improving quality of care. One of these challenges in assessing healthcare quality may be the difference in priority of the previously described six dimensions among the stakeholders. While patients may give priority to *timeliness*, *patient-centeredness*, and *safety*, physicians may well focus on *safety* and *effectiveness*, and policymakers may prioritize *effectiveness*, *efficiency*, and *equity*. Nonetheless, for improving the quality of breast cancer care, all six dimensions of quality should be assessed in a sensible and evidence-based manner.

In light of the increasing attention for assessing quality of healthcare, physicians increasingly receive questions that go beyond the focus of most conventional medical research such as “Do we have optimal resource utilization?”, “What factors endanger *effectiveness* and *timeliness*?”, “Can we give patients sufficient counseling regarding *safety*?” and “Can we identify *inefficiencies*?”. Hereby, physicians and healthcare policymakers are facing pressure to improve knowledge regarding all different dimensions of quality of healthcare. As a consequence, physicians, but also healthcare policymakers, seek for tools and structure on how to assess and compare the quality of healthcare that helps us to improve and learn from each other on both a national level, as on an international level.

The studies in the current thesis aim to improve the quality of breast cancer care by addressing one or more of the previously mentioned dimensions of quality of healthcare in each of the following chapters. The chapters in this thesis evaluate breast cancer care quality considering three different parts of care. In **Part I**, the extent of patients changing hospital after breast cancer diagnosis and its impact on the quality of care in the Netherlands is described. In **Part II**, the timing of adjuvant chemotherapy in relation to immediate breast reconstruction and patient survival is shown. In **Part III**, the variation in use and outcomes of different breast reconstructive strategies on a national and international level is presented.

Figure 1.1 visualizes the six dimensions of quality of healthcare, addressed in the chapters in this thesis. While the dimensions widely overlap and cannot be assessed separately, they influence one another and are dependent on several levels.

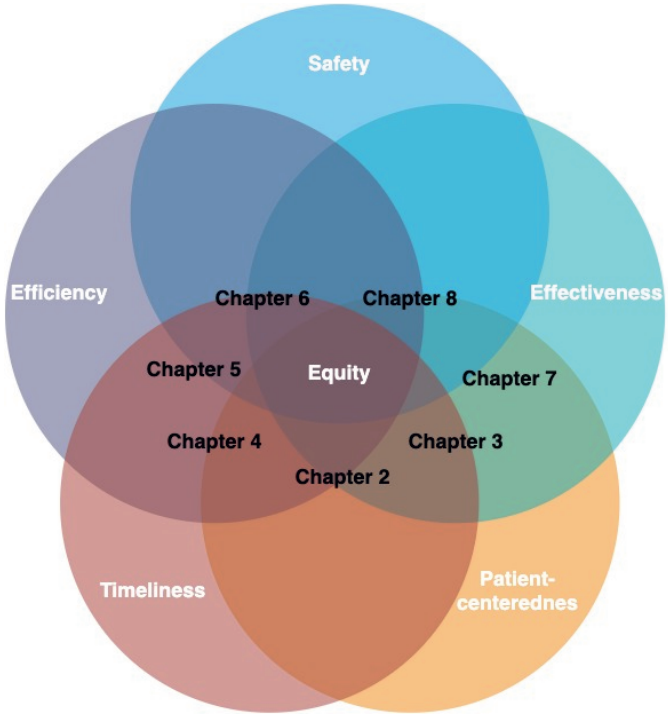


Figure 1.1. A robust illustration of the content of the seven chapters of this thesis, each chapter captures multiple dimensions of quality of healthcare.

This thesis does not address all aspects and components that may contribute to improved quality of care nor does it claim to provide a blueprint for the most optimal care pathway for all stakeholders. However, the scientific questions raised and answered in the following chapters may contribute to a better understanding of how to improve breast cancer care.

In general

After lung cancer, breast cancer is the second most commonly diagnosed cancer in the world, with nearly 2.1 million newly diagnosed patients in 2018.[11] The incidence rate is highest in western countries and surpassed 15,000 patients in the Netherlands in 2018.[11-13] These high incidence rates in western countries are most likely related to a combination of an increase in risk factors such as aging of the population, obesity,[14] higher age at pregnancy, and lower number of gravidities[15,16] compared to other

countries and to improved breast cancer screening.[17,18] Although the prognosis of breast cancer patients has improved during the last decades, still more than 3,000 patients die from breast cancer in the Netherlands each year.[13] Due to the high incidence of breast cancer and the active role of patient advocacy groups and physicians in breast cancer organizations, improvement of the prognosis and quality of breast cancer care has been recognized as a major global challenge.

Progress in quality assurance

Before addressing different aspects or components of breast cancer care that may attribute to improving the dimensions, one should be aware of previous and current quality programs. Several (inter)national initiatives have contributed to the current quality of breast cancer care. During the last decades, a growing number of healthcare providers across the world have advocated for more transparency in the quality of breast cancer care.[19] The earliest initiatives were nationwide cancer registries that started in Northern Europe in the fifties and sixties of the last century.[20] These registries provided data concerning demographic characteristics, incidence, prevalence, and mortality of breast cancer patients.[20] However, data of these registries was limited for meaningful comparison between hospitals or relatively short-term improvement projects, because outcomes needed to be assessed during a prolonged period, making the feedback loop for improvements inadequate.

The interest in comparing healthcare outcomes has come on a fast track in Europe during the last decades, as the first studies showed improved outcomes and decreased variation between hospitals as a result of nationwide assessment of colorectal cancer care.[21-23] Subsequently, in the search for breast cancer quality assurance, the first hospital performer indicators were formulated, which focused not only on outcomes but also on the process and structure of the care pathway.[19,24] Many quality improvement projects hypothesized that by improving the process and structure of care, outcomes would consequently improve.[25]

In the Netherlands, the Dutch National Breast Cancer Organization (NABON), Dutch Institute for Clinical Auditing (DICA) and the Netherlands Cancer Registry (IKNL) founded the NABON Breast Cancer Audit (NBCA) in 2011.[26] Since then, data regarding clinicopathological characteristics, diagnostics and treatment modalities of all patients diagnosed with invasive or ductal carcinoma *in situ* (DCIS) in the Netherlands has been registered in the NBCA-database.[26] The NBCA aims to monitor the nationwide quality of breast cancer care by using a set of quality indicators (QIs) measured for all Dutch hospitals providing breast cancer care.

The quality of breast implant surgery is monitored by the Dutch Breast Implant Registry (DBIR) in the Netherlands since 2015.[27] Mandatory registration of every breast implant and explant resulted in more than 7,500 patients (aesthetic and reconstructive) being registered in the Netherlands in 2017.[28]

With both nationwide registries, benchmarking and inter-hospital comparison of healthcare quality is encouraged. In addition, the general public, such as policymakers, patients and media, receive insight into the quality of care in Dutch hospitals through an annual publication of a set of transparent QIs for external transparancy.[29] Physicians and hospital policymakers can also see their own outcomes in comparison to anonymized other hospitals regarding 'internal' Qis. QI that are considered 'internal' are still under development. The population-based databases are also used to address scientific questions. Some scientific questions are difficult to answer in conventional research settings due to ethical complexity and the need for a high number of patients. Moreover, the registries use a real-world patient population instead of a selection of patients used in most conventional research, such as randomized controlled trials or retrospective single-center studies.[30]

PART I: Hospital transfer in breast cancer care

In the last two decades, breast cancer care has evolved somewhat into tailored-made care due to the increasing number of diagnostic and treatment modalities. Although most of previously mentioned developments have improved the quality of breast cancer care, unintentionally, the complexity of breast cancer care has simultaneously increased due to the expanding number of involved supporting (e.g., pathology, radiology), surgical (e.g., surgical oncology, plastic surgery) and nonsurgical (e.g., medical oncology, radiotherapy) disciplines. The constant evolving diagnostic and treatment modalities made it challenging to comprehend all information for patients.[31-33] This uncertainty might specifically be present among breast cancer patients compared to other patients as breast cancer patients are increasingly aware of different treatment modalities informed by strong organized patient advocacy groups.[34,35]

Since patients are free to choose their physicians and hospital in most Western countries, patients can change from one hospital to another during their care process. As a consequence of the increasing patient autonomy and complexity of care, it could well be possible that an increasing number of patients change from one hospital to another along the breast cancer care pathway. The contrary has also been hypothesized.[36] Since most Western countries have up-to-date guidelines, variation in

care between hospitals could decrease as physicians use evidence-based guidelines with similar diagnostic and treatment algorithms. These guidelines and algorithms aim, among other things, to increase evidence-based medicine and reduce unwanted variation in care between healthcare providers. As a result of this, the clinical necessity for a change of hospital could decrease as breast cancer care would be more or less similar in all hospitals. Literature focusing on patients changing hospital, however, is sparse. Moreover, the evidence whether a hospital change influences breast cancer care is limited. Therefore, the current knowledge regarding the impact of patients changing hospital on *effectiveness, timeliness, efficiency, and equity* of breast cancer care is limited.

Are breast cancer patients changing hospital after diagnosis and who are they?

The overall percentage of patients changing hospital after diagnosis can be defined as the hospital transfer rate. In **chapter 2**, a hospital transfer is defined as patients receiving treatment in another hospital compared to the hospital of diagnosis. For individual physicians and patients, overseeing the impact of a hospital transfer is challenging since it requires large quantities of data to assess its impact on quality of care. It has been suggested that hospital transfers negatively affect the quality of breast cancer care since hospital transfers have been associated with decreased quality of care among patients with diabetes, ischemic stroke, and different types of cancer.[37-43]

High-quality breast cancer care requires identification of delaying factors and components. Evaluating the extent of hospital transfers, predictive characteristics of hospitals transfers and whether it has an impact on the *timeliness* of care has the potential to improve breast cancer care. With this information, physicians and healthcare policymakers could alter the care process and structure to minimize a potential negative impact of hospital transfers on the quality of breast cancer care. Hypothesizing that hospital transfers delay care, *equity* of care could also be improved when those at risk are identified.

Therefore, **Chapter 2** focuses on patients who transferred hospital after their breast cancer diagnosis.[44] In this chapter, we describe the extent and trend over time of hospital transfers of breast cancer patients on a national level in the Netherlands. Secondly, we analyzed which factors are of predictive value for a hospital transfer. To gain insight into the independent impact of hospital transfers on *timeliness*, time from diagnosis to primary treatment is compared between patients with and without a hospital transfer.

Second opinions in breast cancer care

Part of the extent of patients changing hospitals could be patients who seek an second opinion (SO). An SO is defined as an assessment of a diagnosis or treatment proposal by an independent second physician of the same medical discipline. Second opinion (SO) programs have officially been introduced in surgery in the 70ties and 80ties of the last century, as the first reports not only showed a major impact of SOs on treatment recommendations, but also demonstrated that SOs were cost effective by preventing unnecessary procedures.[45-48] Among patients with cancer seeking for an SO, the majority is breast cancer-related.[49,50] Previous studies reported SO rates among breast cancer patients between 1% and 31%,[50-55] although an exact nationwide percentage is unknown.

The clinical value of breast cancer second opinions is still under debate, despite a vast number of previous studies focusing on this subject. Evaluating the clinical impact of SOs is warranted as SOs can have unintentional effects on quality of care. Previous studies have shown that repeating diagnostics, additional consultation and other discontinuities of care were associated with an increased workload for physicians, healthcare costs and delayed primary treatment.[9,10,38-40,43,49,56] Moreover, SOs might even increase uncertainty in case of a contradicting diagnosis or treatment proposal.[57] When aiming for *efficient* and *effective* breast cancer care, high-quality research regarding its medical value is warranted to limit potential overuse or undesired or less optimal outcomes, hereby, optimizing resource utilization. To do so, one could analyze the absolute 'medical' difference between the first and SOs. The evidence regarding the impact of SOs may also improve patient-counseling and the shared-decision process, which fosters *patient-centeredness*. In **Chapter 3** of this thesis, we report on SOs in a comprehensive manner of breast cancer patients who visit the Netherlands Cancer Institute and investigate the impact of SOs on diagnostics and treatment proposals.[58] In this chapter, discrepancies between first and SOs are quantified using a newly defined categorization of discrepancy specific for SOs among breast cancer patients.

PART II: Continuity of the adjuvant chemotherapy pathway

A discontinuity of the care process, defined as a delay of treatment, has been a universal concern of patients and physicians since the beginning of breast cancer treatment. In 1907, the pioneer of the radical mastectomy William Halsted stated "*we no longer need the proof which our figures so unmistakably give that the slightest delay is dangerous…"*.[59] This fear may still be present among many patients, as most breast

cancer lawsuits claim unnecessary delay up to diagnosis or treatment, rather than medical misconducts.[60]

Current evidence-based breast cancer guidelines[61-63] are less rigorous regarding the slightest delay compared to these statements of William Halsted. The current general opinion is that time to treatment should not be needlessly delayed for two reasons: 1) to limit psychological distress for the patient,[64] and 2) to minimize the negative impact on breast cancer outcomes, such as disease-free and overall survival.[65]

Regarding time from surgery to adjuvant chemotherapy (TTC), literature shows decreased disease-specific and overall survival in patients with delayed TTC, though using heterogeneous time limits ranging between 6 to 12 weeks.[66-68] Despite the contradicting evidence and lack of consensus of the optimal time intervals, the European Society of Medical Oncologists (ESMO) stated that adjuvant chemotherapy should preferably be started within 6 weeks after surgery and that chemotherapy has a decreased efficiency when initiated after more than 12 weeks.[61,69]

Due to the lack of high-quality evidence, physicians and healthcare policymakers receive questions such as 'Should I start treatment as soon as possible?' and 'What procedures or factors endanger timely care?'. As a consequence, optimizing the *timeliness* of breast cancer care has been the subject of many studies. When aiming for a minimal number of discontinuities of care, all different factors that can result in a delay of treatment should be evaluated. **Part II** of this thesis focuses on the *timeliness* of postoperative care, explicitly concerning the timely initiation of adjuvant chemotherapy.

Impact of postmastectomy immediate breast reconstruction

Post mastectomy immediate breast reconstruction (IBR) has often been mentioned as a potential delaying factor for initiating adjuvant chemotherapy. As a result of this discussion, physicians may be cautious to use post mastectomy IBR in patients who have an indication for adjuvant chemotherapy.[70] It has been suggested that IBR after mastectomy increases TTC due to a longer time to recover and a higher risk of postoperative complications. However, reports regarding both associations have shown contradicting findings.[71-76] High-quality evidence is warranted regarding the impact of IBR on TTC since there has been an increasing interest of IBR in most industrialized countries in the last decade.[77] IBR is associated with good esthetic results and better psychosocial well-being compared to mastectomy only or delayed reconstruction.[78-81]

Therefore, we investigated in **Chapter 4** whether IBR after mastectomy reduces the likelihood of timely initiation of adjuvant chemotherapy compared to mastectomy alone.[82] The association was evaluated in a population-based setting while limiting

confounding by indication since patients do not have the same likelihood of receiving IBR based on baseline characteristics that also affect the timely initiation of adjuvant chemotherapy. Hereby, we aim to improve the *timeliness* of the postoperative treatment pathway of breast cancer patients.

Clinical implications of postoperative treatment delay in high-risk breast cancer

When reviewing literature, delay of adjuvant treatment is associated with worse breast cancer outcomes regarding recurrence and survival.[65-67,83] In the last five years, there is increasing evidence suggesting that the association between decreased outcomes and time from surgery to chemotherapy might be subtype dependent.[66,84-87] The subtype dependent relationship between TTC and survival is not contra-intuitive as consensus exists on the more aggressive biology and proliferation rate of high-risk tumors, such as triple-negative breast cancer (TNBC).[88,89] A recent report demonstrated decreased outcomes in TNBC patients receiving adjuvant chemotherapy beyond 30 days after surgery.[86] However, the suggested association of the subtype dependent relationship justify further investigation, since most previous studies had a single-center character and used a small number of patients without stratifying for type of surgery.[66,84-87] Although TNBC represents only 15% of breast cancer subtypes, patients with TNBC have a worse prognosis compared to other subtypes.[88,90,91] Moreover, optimizing the effect of adjuvant chemotherapy is especially warranted in patients with TNBC as chemotherapy is the only current established therapeutic option in most of the patients with TNBC.[92] Furthermore, despite the fact that previous studies have demonstrated that patients with TNBC are less likely to have delayed time from surgery to chemotherapy,[67,93] between 35% to 74% of patients with TNBC receive chemotherapy beyond 30 days after surgery.[67,84,87,93,94]

When high-quality evidence would support the suggested relationship between decreased survival and TTC beyond 30 days in patients with TNBC, it could be argued that timely adjuvant treatment is warranted and guidelines should be adjusted accordingly. A randomized study regarding survival data of patients with TNBC receiving adjuvant chemotherapy within and beyond 30 days is not likely to be conducted, because of the complex ethical considerations.

While patients who undergo BCS compared to mastectomy have better survival outcomes most likely partly based on underlying baseline characteristics, patients undergoing mastectomy are more likely to have a delayed time from surgery to chemotherapy. Therefore, survival analyses should be stratified by type of primary surgery. In **Chapter 5,** we describe whether time from surgery to chemotherapy beyond

30 days is related to a decreased overall survival in high-risk patients diagnosed with TNBC using a prospectively registered population-based cohort. The findings of this chapter aim to improve the *safety* and *timeliness* of high-risk breast cancer care.

PART III: Quality assessment of breast reconstruction strategies

During the last decade, there has been an increasing interest in reconstructive surgery with more acceptable cosmetic results. Loss of the breast mound due to mastectomy negatively affects different aspects of the quality of life of patients such as decreased body image and self-estreem.[78,81,95-97]
Following the increasing interest in reconstructive surgery, a growing number of patients have undergone a breast reconstruction after mastectomy in most western countries.[77,98] More than 90% of breast reconstructions was implant-based.[77,99,100] Breast reconstructions can be performed during the mastectomy (immediate) or in a second operation at a later time (delayed reconstruction). IBR following mastectomy has shown to result in similar postoperative patient satisfaction compared to BCS.[81] Since there is no current golden strategy for the most optimal breast reconstruction, high-quality evidence regarding *safety*, *effectiveness* and *efficiency* is warranted. **Part III** of this thesis aims this provide crucial evidence for physicians regarding the different breast reconstruction strategies on a national and international level.

Comparing revision rates of implant-based breast reconstructions

An implant-based breast reconstructions (IBBR) can be achieved in a one-stage (direct-to-implant) or a two-stage reconstruction. During a two-stage reconstruction, a temporary tissue expander (TE) is inserted followed by definitive implant during a second operation. Use of direct-to-implant IBBR has increased due to advancements in oncological surgery (e.g. skin-sparing mastectomy) and plastic surgery (e.g., acellular dermal matrices (ADM), meshes). Two-stage IBBRs are commonly used for patients in whom significant skin loss is expected or for those who have a wish for an increase in breast size.[101]
Currently, no consensus exists regarding the risk for a revision after direct-to-implant compared to two-stage IBBRs, as previous meta-analyses report a low level of evidence regarding this topic.[102,103] The lack of consensus regarding the risk for revisions may increase variation among hospital protocols in using direct-to-implant and two-stage

IBBR as current practice might be more a reflection of personal experience or local policy.

Outcomes regarding the *safety* of both direct-to-implant and two-stage IBBR using data from a population-based nationwide database could improve treatment-counseling by increasing the knowledge regarding revision indications and risk factors. Moreover, it could reduce potential unwanted variation between physicians. **Chapter 6** compares the revision incidence, revision indications, and the additional number of operations between direct-to- implant and two-stage IBBR.

Cross country evaluation of breast cancer care

In 2018, almost one-third of the breast cancer patients underwent mastectomy as final surgical treatment for local control of the disease In the Netherlands.[104] Immediate breast reconstruction, as being described in chapter 6, is performed in one-fourth of patients with invasive breast cancer and almost half of those with ductal carcinoma in situ (DCIS) undergoing a mastectomy in the Netherlands.[104]

Previous studies demonstrated equal survival outcomes when comparing BCS followed by radiation therapy and mastectomy.[105,106] Recent reports even suggested better outcomes in those who underwent BCS and radiation therapy compared to mastectomy in early-stage breast cancer, although residual confounding might be present.[107-109] However, since not all patients are eligible for BCS, increasing the number of patients who undergo breast contour preservation (BCP) using other methods is warranted.

There are various factors determining whether patients are eligible for NAC, primary BCS or IBR. While the introduction of neoadjuvant chemotherapy (NAC) as a down staging procedure made more patients eligible for BCS,[110,111] BCP has also been achieved by increasing the number of patients undergoing IBR postmastectomy.[100,112,113]

In 2015, the NBCA formulated a comprehensive parameter aiming for better reflection of the multidisciplinary effort to preserve the breast mound, defined as BCP.[114] BCP is thought to be achievable for most breast cancer patients, specifically those who are diagnosed with early-stage breast cancer.

Chapter 7 describes the prevalence of BCP among women with early-stage breast cancer in Denmark and the Netherlands using nationwide databases from both countries. Hereby, this chapter aims to identify opportunities for improvement within both countries. This information is warranted for increasing the use of BCP and reduce potential unwanted variation between hospitals. Moreover, potential room for

improvement in the breast cancer care organization may be identified and clues for future research might be highlighted.

Quality assessment of oncoplastic surgery

Alongside post mastectomy reconstruction techniques, reconstructive techniques during BCS have evolved in the last decades.[77] The combination of oncological and plastic surgery during BCS is commonly defined as oncoplastic breast surgery.[115] Applying oncoplastic breast surgery enables physicians to *safely* perform breast conservation even in patients with large and multifocal tumors, who otherwise had to undergo mastectomy due to the indication for an large excision.[115,116]

In reviewing literature, oncoplastic breast surgery shows promising long term outcomes regarding survival, local recurrence, and quality of life compared to patients who underwent BCS or mastectomy.[117-120] Moreover, it has been hypothesized that it results in fewer re-excisions due to insufficient tumor margins as oncoplastic breast surgery has been associated with wider excisions compared to BCS alone.[121-123]

However, the level of evidence regarding the impact of oncoplastic breast surgery on the number of re-excisions is limited due to weak methodology, single-center settings, and a small number of patients.[118,121-125] **Chapter 8** focuses on the re-excision rate after oncoplastic breast surgery compared to BCS using a real-world Danish population-based database. Secondary, we evaluate the impact of oncoplastic breast surgery on the risk for conversion to mastectomy compared to BCS. Hereby, this chapter aims to foster the knowledge regarding the *safety* and e*ffectiveness* of this breast reconstructive strategy.

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