A comprehensive approach for quality assessment of breast cancer care

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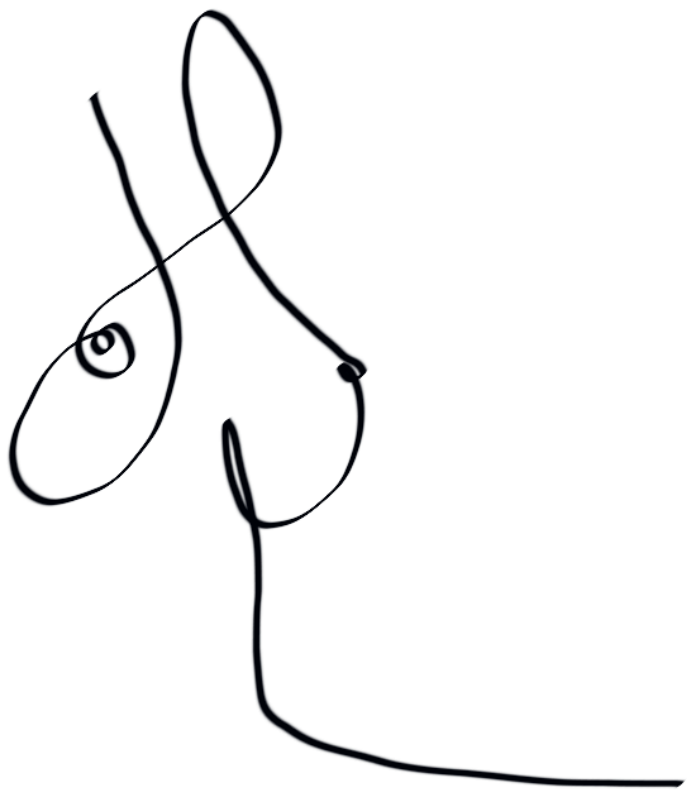
Chapter 9

General discussion and future perspectives



General discussion and future perspectives

Assessing and improving quality of breast cancer care has received an increasing attention in the last decades due to several reasons. Among these reasons are the increase in different treatment options and efficacy, but also the increased patients' autonomy and own responsibility due to the rising popularity of the concept of 'shared decision making'.[1,2] In this thesis, the six dimensions of healthcare quality (Table 9.1) according to the definition of the Institute of Medicine (IOM) were used to assess and improve the quality of breast cancer care.[3] For this purpose, data from different nationwide clinical breast cancer registries were compared and analyzed. In summary, quality aspects of hospital transfers, the continuity of the adjuvant chemotherapy pathway and several breast reconstruction strategies were assessed by addressing one or more of the six quality dimensions.

Table 9.1. Six dimensions of quality of healthcare defined by the Institute of Medicine

Dimension	Definition
Safety	Not harming or limiting the harm and risks for patients as a consequence of provided care
Effectiveness	Using care resources that have proven to result in the most superior clinical and non-clinical outcomes
Patient-centeredness	Providing care that considers patients' preferences after assuring patients are well-informed
Timeliness	Providing care that is timely without unnecessary delays considering time consuming factors
Efficiency	Maximizing resource use and limiting waste of care and resources
Equity	Limiting unintentional disparities in quality of care among patients with differences such as gender, race, intelligence, social-economic status, sexual orientation, insurance or location of residence

PART I: Hospital transfer in breast cancer care

The extent and impact of hospital transfers in breast cancer care

Delay of treatment is a frequent expressed concern of breast cancer patients. Analyzing potential delaying factors and components is emphasized for sufficient patient-counselling and improvement of the quality dimension *timeliness*. Various treatment delaying factors have been identified by previous studies,[4-7] but literature focusing on patients changing hospital after a breast cancer diagnosis (defined as a hospital transfer) and its impact on the continuity of breast cancer care is sparse. In **Chapter 2** we demonstrate that hospital transfers after diagnosis occurred in 24% of breast cancer

patients in the Netherlands, most commonly when patients were treated with neoadjuvant chemotherapy (NAC).[8] Primary treatment was significantly delayed for patients who transferred hospital,[8] especially in those who underwent primary surgery. Optimizing hospital transfers seems most warranted for patients who undergo mastectomy followed by immediate breast reconstruction (IBR) as the longest delay in primary treatment was observed in these patients. While the extent of hospital transfers is smaller compared to findings in the US, the treatment delaying impact is comparable.[5,6]

This thesis does not propagate that primary breast cancer treatment should be rushed as diagnostics, patient-counselling and commonly multidisciplinary treatment requires time. Moreover, modest treatment delay is not per se associated with decreased survival of breast cancer patients. However, a critical approach towards treatment delay seems defensible as several studies have shown an association between increased time from diagnosis to treatment and decreased outcomes.[9-11]

Hospital transfers seem inevitable in the Netherlands and several other European countries since healthcare systems and health insurances allow patient-initiated transfers and free choice of hospital. Furthermore, the call for centralization of high-expertise care will force certain patients to change hospital. The findings in this chapter may be useful for optimization the quality of care dimension *timeliness* as patients and physicians may not be aware of the delaying impact of breast cancer hospital transfers.

Current findings did not include whether treatment delay originated at the hospital of diagnosis or the treating hospital. Therefore, with the current level of evidence, both hospitals should analyze their care process aiming to minimize potential treatment delay due to a hospital transfer. Collaboration of breast cancer care between hospitals and formal referral agreements might allow optimization of the care pathway and thereby decreasing the delaying impact of a hospital transfer.

Second opinions in breast cancer care: waste of resources or added medical value?

Most of the hospital transfers in the Netherlands may have resulted from patients seeking a second opinion rather than a hospital transfer initiated by the medical specialist. Currently, there is a continuous discussion regarding the medical value with respect to the diagnosis and treatment of breast cancer second opinions. Evaluating breast cancer second opinions and the discrepancy of diagnosis and treatment between first and second opinions allows answering this question. Moreover, defining and categorizing discrepancy will allow quantification and comparison of the findings with future studies. Thereby *effectiveness* and *efficiency* of this part of breast cancer care

can be assessed. **Chapter 3** demonstrated a considerable discrepancy between first and second opinions, especially in primary treatment. Although part of these findings might be explained by the high-expertise character of the hospital of second opinion and consequently deviation from national guidelines, the findings in this chapter are in concordance with previous literature.[12-18] Moreover, we are first to describe breast cancer care discrepancy between first and second opinions in a multidisciplinary manner using a well-defined categorization as opposed to discrepancy within one medical discipline without clear definitions of discrepancy as seen in previous literature.[13,15,17-21]

The surprisingly high number of missing information in referral letters is in concordance with previous literature,[12-14] although part of the missing information might be explained by unfinished diagnostics at first opinion. The suggested lack of consensus regarding indications for certain primary breast cancer treatment modalities, such as use of NAC and IBR is in concordance with previous Dutch studies focusing on variation in the use of treatment modalities between hospitals.[22-25] Although national and international guidelines clearly state which patients are eligible for NAC,[26,27] the type of surgery after NAC is a challenging outcome of balancing tumor biology and size, tumor-to-breast ratio, patient characteristics[28] and preferences, the physicians' experience with for instance NAC or extensive reconstructive techniques, and to some degree organizational factors.[29] Although a certain degree of variation between physicians in weighing these factors might be inevitable, the high discrepancy found in this chapter, together with previous literature suggesting unwanted variation,[22,23,29,30] emphasizes the need for more consensus among physicians on indications of these breast cancer treatment modalities.

Altogether, the findings in this chapter demonstrate a considerable added value of second opinions after breast cancer diagnosis, and they highlight room for improvement in *effectiveness* (e.g. use of NAC or breast conservation) and *efficiency* of care (e.g. resource utilization such as repeated or additional imaging and biopsies).

PART II: Continuity of the adjuvant chemotherapy pathway

Is timely initiation of adjuvant chemotherapy compromised by immediate breast reconstruction after mastectomy?

Mastectomy followed by IBR has been associated with delayed adjuvant chemotherapy, although reviewing previous literature demonstrated various limitations and biases.[31] Therefore, high-quality evidence focusing on the *timeliness* of the postoperative breast

cancer care is warranted. **Chapter 4** demonstrated a modest delay in initiating adjuvant chemotherapy in patients that were treated with mastectomy plus IBR in the Netherlands, though most likely without clinical relevance in the majority of breast cancer patients.[32] Therefore, IBR after mastectomy should not be considered a contra-indication for the majority of patients with an indication for adjuvant chemotherapy. The findings in this chapter are in line with a recently published large multicenter study from the United Kingdom.[33] Interestingly, they furthermore demonstrated that major complications resulted in significant delay, irrespective of type of surgery that was performed. This latter conclusion supports our finding that axillary surgery is associated with delay in initiating adjuvant chemotherapy, as mastectomy plus IBR in combination with axillary surgery is a known risk factor for postoperative complications.[32]

In line with **chapter 3**, the study in **chapter 4** showed that hospital transfers were associated with delayed care as patients with hospital transfers between surgery and chemotherapy were less likely to receive chemotherapy within 6 weeks after surgery.

The findings in this chapter can be used to improve the quality of breast cancer care for patients who undergo mastectomy plus IBR by optimizing *timeliness* in the postoperative care setting. Patient counselling can be improved as physicians can use this information to inform their patients. Hereby, the dimension *patient-centeredness* can be enhanced.

What is the time-survival relationship when using adjuvant chemotherapy for patients with triple-negative breast cancer?

Despite that chemotherapy will most likely be initiated in the neoadjuvant setting for most TNBC patients in the future as this is recommend by national guidelines[34,35], currently use of chemotherapy is still in the adjuvant setting and of these patients up to 74% receive chemotherapy beyond 30 days after surgery.[36-40] Therefore, we will focus first on the time-survival relationship in the adjuvant setting of TNBC patients. Reliable conclusions regarding the time-survival relationship in the neoadjuvant setting are difficult to make, since NAC is only administered to a small number of TNBC patients and follow-up is short since introduction and nationwide use of NAC in the Netherlands.[41]

The increased risk of death due to initiation of adjuvant chemotherapy beyond 30 days after BCS in TNBC patients presented in **chapter 5** is within the range of previous literature.[36,38-40] It could be suggested that the more aggressive biology of TNBC requires earlier initiation of chemotherapy after BCS. Interestingly, a different time-survival relationship between BCS and mastectomy was observed. Unfortunately,

comparing this latter finding to previous literature is not possible as previous studies did not stratify analysis for type of surgery.

Residual confounding after propensity score matching may explain part of the association. However, previous studies reported that the toxicological effect of chemotherapy seems to be reduced in delayed time from surgery to chemotherapy as residual tumor and micrometastases have more time to grow.[42-44] It has been suggested that there even might be a decreased sensitivity of the tumor cells to chemotherapy due to delayed time from surgery to chemotherapy, although this was only shown in mouse models.[45] The different time-survival relationship between BCS and mastectomy may partly be explained by a reduced toxicologic effect of chemotherapy on potential remaining cancer cells which in theory are more at risk of being present in those undergoing BCS compared to mastectomy. This theory requires additional future high-quality evidence.

Interestingly, it has been hypothesized that the delay-survival relationship might even be different among TNBC patients,[38] as evidence is growing suggesting that TNBC is a heterogenous disease which in the future should be treated accordingly.[46] The current definition of TNBC is a diagnosis of exclusion and is characterized by lacking expression of molecular targets of hormone receptors and an absence of HER2 overexpression.[47] Subtypes of TNBC have been described using protein, gene and mRNA expression which may have different treatment sensitivity and a time-survival relationship.[46] Moreover, other promising prognostic factors of TNBC such tumor-stroma ratio might be imbalanced in current analyses.[48] Current findings were not adjusted for potential unbalanced distribution of previous mentioned potential subtypes within TNBC as these are still under debate and had not been routinely registered. However, as the heterogeneity of TNBC is currently poorly understood, equal distribution among the time intervals could be expected in the cohort of this chapter.

The findings in this chapter should raise awareness among physicians and patients regarding the importance of timely initiation of chemotherapy in TNBC patients. The findings in this chapter can be used to improve the quality dimension *safety*, *effectiveness* and *timeliness*. Guidelines should highlight timely initiation of chemotherapy for TNBC patients, specifically if physicians deviate from the guidelines by initiating chemotherapy in the adjuvant instead of the neo-adjuvant setting.

In **chapters 4** and **5**, the focus was on *safety*, *effectiveness* and *timeliness* of breast cancer care. Continuous evaluation of these dimensions of care is essential as organizational factors or systemic treatment protocols, and the understanding of disease heterogeneity may change over time.

PART III: Quality assessment of breast reconstruction strategies

Direct-to-implant *versus* two-stage implant-based breast reconstruction

There is no golden standard for the optimal breast reconstruction strategy since it depends on various factors. While immediate reconstructions are increasingly popular in most countries, the vast majority of these reconstructions is an implant-based breast reconstruction (IBBR), either direct or in two-stages.[41,49-51] Current literature is contradictory regarding *safety* outcomes of direct-to-implant and two-stage IBBR.[52-54] **Chapter 6** demonstrated the revision incidence of both IBBR approaches in the Netherlands. Both short- and long-term revision rate was lower in patient with a direct-to-impact IBBR compared to patient that obtained two stage IBBR. Comparing these findings to previous literature is problematic due to heterogeneity in outcome definitions and duration of follow-up.[53-55] Furthermore, the majority of previous studies were conducted in a single-center setting while including only a small number of revisions.[53-55] The findings of this chapter do not support the direct-to-implant approach in all patients undergoing IBBR, but rather provide high-quality evidence regarding revision indications and rates of both approaches. Current findings may also reflect optimized patient selection for the two types of IBBR in the Netherlands.

The final choice of IBBR approach and additional techniques should be a shared-decision balancing all factors, risks and preferences. Therefore, the findings of our current study may be useful during patient-counselling concerning breast reconstruction strategies.

The observed revision indications in this chapter suggest that short-term revision rates of both approaches could be reduced by focusing on mastectomy skin flap quality and strategies preventing seroma and deep wound infection. The risk of seroma and potentially a deep wound infection may be reduced by minimizing the dead space using for instance quilting sutures or an axillary drain.[56] Long-term revision rates may be reduced by focusing on optimizing implant and patient selection, because the majority of these revisions after both approaches was due to complaints about asymmetry and pain in the reconstructed breast. Furthermore, optimizing both expectation management regarding the risk of asymmetry and volume, and the risk of postoperative pain and malposition may result in better clinical and patient-reported outcomes (PROs).

Improving breast-contour preserving strategies: why not look beyond our own borders?

There is a vast body of literature reporting on outcome of single breast cancer treatment modalities and recently one study in the Netherlands reported on comprehensive breast-contour preserving (BCP) strategies (Figure 9.1) using multiple treatment modalities [22-24,30,51,57,58] . Breast contour preservation is a quality aspect that gained an increase in popularity.

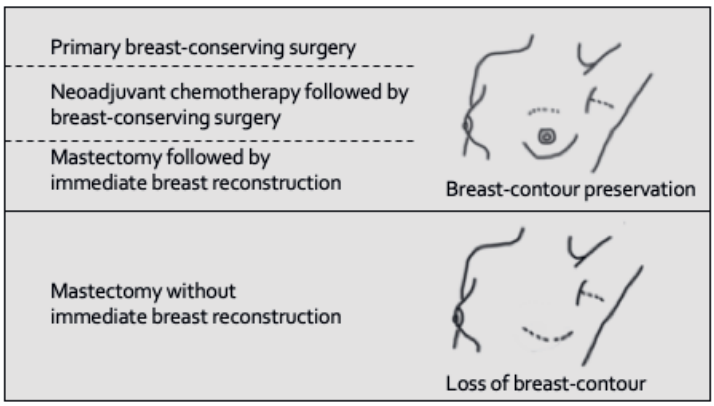


Figure 9.1. Breast-contour preserving procedures.

However, no literature exists comparing the different strategies enabling breast contour preservation on an international level. The findings in **chapter 7** provide insight into the comprehensive treatment of early-stage breast cancer patients in Denmark and the Netherlands with a focus on breast contour preservation.[59] An interesting finding was the difference in BCP strategies specifically in patients younger than 50 years. Although in both countries the proportion of BCP achieved with NAC followed by BCS and mastectomy followed by IBR was highest in patients younger than 50 years, the use of these two BCP modalities was considerable higher in the Netherlands. In addition, while in Denmark a stable high BCP rate over time was achieved predominantly by using primary BCS, a steady increase in BCP rate over time was observed in the Netherlands. The increase in BCP rate in the Netherlands was specifically achieved by an increasing use of NAC followed by BCS and IBR following mastectomy. Part of the increase in BCP rate in the Netherlands over time may reflect the incentive of hospitals to improve their BCP rate as the BCP rates of each Dutch hospitals is published annually.

These findings may be used by future studies focusing on modifiable factors to improve the percentage of patients that will receive a BCP strategy. In 2016, Tan *et al.* suggested several approaches for modification of factors that could be used to increase BCP.[60] He categorized factors into patient, disease, surgeon, and treatment units.[60] Modifiable patient factors could among other things be an unrealistic fear of recurrence,[61] lack of information regarding reconstructive options,[62] or having an unrealistic perception of survival benefit from mastectomy.[63,64] These factors may be improved by optimizing the accuracy of perceived information and information transmission.[65] Regarding surgeon and treatment unit factors, previous studies showed that factors such as study participation, type of hospital, plastic surgeon attendance in multidisciplinary meeting were associated with increased use of NAC and postmastectomy IBR in the Netherlands.[22,25,29]

Together with previous literature demonstrating substantial variation in the use of treatment modalities[22,30,57,58,66], this chapter highlights room for improvement in BCP strategies and raises the question what to do with (un)wanted variation between hospitals in achieving BCP. This may among other things be achieved by improving consensus on (contra)indications on the treatment modalities and breast reconstructive strategies, specifically for early-stage breast cancer. However, a certain degree of variation between physicians is justified allowing patient-tailored care considering personal wishes, preferences and circumstances.

What is the impact of oncoplastic surgery on re-excision rates and breast conservation?

In reviewing literature, the combination of oncological and reconstructive plastic surgery during BCS, defined as oncoplastic breast surgery (OPS), shows promising results compared to BCS or mastectomy.[67-70] The question remains whether OPS results in fewer re-excisions and conversions to mastectomy due to insufficient tumor margins after primary BCS. This is an interesting scientific question as OPS has been associated with wider excisions compared to BCS alone.[71-73] Not surprisingly, excision of a larger proportion of the breast without OPS is associated with poorer patient satisfaction.[74]

Chapter 8 demonstrated a modest decrease in re-excision rates and less frequent conversion to mastectomy after OPS compared to BCS while adjusting for a wide set of confounders using nationwide data,[75] opposed to most previous studies.[69,71,76-78] These findings, together with previous literature,[69,71,73,77] support the safe use of OPS. OPS may be considered more often in the future, especially for those women who otherwise would not be eligible for BCS. Increasing the use of OPS in those eligible may consequently increase the BCP rate as described in **chapter 7**. Interestingly, among

patients older than 50 years who underwent a secondary intervention (re-excision or boost) boost radiation was more frequently used in patients who underwent OPS compared to BCS. This finding may reflect the challenging patient-tailored care required in those with insufficient margins. Physicians have to balance potential morbidity of a re-excision and side effects of boost radiation,[79-81] challenges in identification of the tumor bed after primary surgery,[82] preservation of remaining breast volume, together with patients' preferences. By increasing the proportion of patients eligible for BCP using OPS, *safety* and *effectiveness* of breast cancer care may be improved. These findings may be useful for future studies focusing on how to improve BCP as described in **chapter 7**.

Methodological strengths and limitations

The prospectively registered data in nationwide population-based databases used in this thesis was essential in answering important clinical questions which would have been nearly impossible to answer with conventional research such as a retrospective analysis or in a randomized controlled trial (RCT). Nationwide population-based databases allow insight into treatment effects in a real-world breast cancer population on the condition that these findings are interpreted carefully. It is important to note that the results described in all chapters merely show associations and are not necessarily causal due to the observational setting. However, well-designed observational studies using strong methodology show comparable effect estimates compared to RCTs.[83,84] And, in the current era where shared decision making plays an important role in the tailored breast cancer treatment it is becoming more difficult to include patients in randomized trials. Quality of breast cancer care is most likely improved by using both the methodology from conventional research and nationwide observational studies.

Besides the limitations that are already mentioned in the different chapters, some other shortcomings should be noted. Although we were able to adjust for an extensive set of confounders and limit confounding by indication, several unknown and not-registered confounders should ideally have been included, which may (partly) change our findings in each previous chapter. Furthermore, it remains unknown what part of hospital transfers in **chapter 2** was due to second opinions as these are not registered in the Dutch nationwide database. The second opinions in **chapter 3** may reflect discrepancy between secondary and tertiary care as discrepancy might be less substantial between hospitals with similar expertise. Also, the cause of delayed initiation of adjuvant chemotherapy was not registered in **chapter 4**, leaving a blind spot regarding the association with IBR. The current unknown completeness of revision

surgery registration limits the implications of **chapter 7**. Finally, the findings of **chapter 8** are limited as the rationale of using specific OPS techniques remains unknown, although it would be difficult to include this on a large scale.
Although the aspects and components identified in this thesis may contribute to optimizing different dimensions of quality of breast cancer care, they may only be useful when taking all dimensions into account as they are highly overlapping, linked to and dependent on each other. In addition, the priority of end-points used in this thesis may not reflect the most optimal care pathway for all stakeholders as the priority of the dimensions of quality of care differ as described in **chapter 1** of this thesis.

Future perspectives and suggestions for future research

Although it seems like the quality dimensions *safety, effectiveness*, *timeliness* and *efficiency* have the largest share in this thesis, *patient-centeredness* and *equity* are strongly connected and hinge on insight into the first four dimensions. These latter two are not less important and future studies should focus on the relationship between the six dimensions.
The quality and completeness of national clinical audit databases are essential for continuous improvement of breast cancer care. They may be improved by optimizing source data. Automatic digital data extraction with clear definitions of for instance radiological findings, surgery and systemic treatment regiments would allow insight into clinical practice and moreover significantly reduce the administrative burden. Standardized synoptic reports may facilitate this and improve data completeness as literature showed that synoptic reporting compared to narrative reporting improved completeness of pathology reports.[85] It could be expected that the success of standardized synoptic surgery reports depends on a well thought out implementation and the support of the national physician societies.
Increasing the attention for the continuity of breast cancer care, such as hospital transfers and SOs may result in less repeated diagnostics, biopsies and consultations, and treatment delay. Improved *timeliness* of the postoperative care process might be achieved by future studies focusing on the combination of IBR and axillary surgery such as sentinel node biopsy or ALND as this combination was specifically associated with treatment delay.[32] Future studies focusing on the time-survival relationship should also include characteristics surrogate for patient frailty to adjust for potential imbalances. Better understanding heterogeneity of TNBC might alter the time-survival relationship found in this thesis. Furthermore, breast cancer survival may be improved by awareness among physicians and patients of the clinical impact of the treatment

continuity in the future. Further optimization of modifiable factors may increase BCP rate and reduce unwanted variation between hospitals. Future studies focusing on the *safety* of OPS may include more detailed information regarding the type of OPS as the categorization used in this thesis was rather robust.

Current breast cancer registrations such as the NBCA and DBCG allow insight during introduction of new diagnostics and therapies on a nationwide level. Together with recently started registration of PROMs, these databases might be used during patient consultation in the future. This real-world data would allow patients together with their physician to select 'patients like me'. Selecting patients with for example the same tumor- and patient characteristics and treatment, but also preoperative PROs could provide insight into various expected symptoms such as pain, numbness, confidence, but also outcomes such as complications, recurrence and survival rate. This type of information has shown to be an attribute for patients with various diseases.[86,87] It might be useful during patient consultation regarding breast reconstructive strategies, but also in self-assessment of patients, 'am I recovering as to be expected?'. Moreover, physicians could hereby focus more on outliers as these patients could be detected automatically. However, the accuracy of information of 'patients like me' remains dependent of the number of 'patients like me' and should only be seen as an attribute to the current shared-decision making. Currently, evidence-based guidelines and the experience of physicians form the basis for patient-counselling since 'patients like me' has only been introduced recently in breast cancer care in the Netherlands. Altogether, combining PRO and clinical breast cancer registrations have the potential to substantially improve all dimensions of quality.

Achieving quality improvement of breast cancer care may require several changes. First, the findings in this thesis could be considered when formatting new guidelines. Second, the structure of current local care pathways should be re-evaluated when new insights into treatment delaying factors or their clinical impact are demonstrated. A clear breast cancer care pathway allows mapping of different factors and modification if necessary. Third, (inter)national governance and transparent publication of structure, process and outcome indicators allow benchmarking, comparison and identification of outliers which can be used to identify room for improvement.

Conclusions

Assessing and improving quality of breast cancer care relies on having high-quality evidence of all dimensions of quality of healthcare. Based on the findings presented in this thesis, together with previous literature, several associations and points of

improvements addressing these dimensions were identified, specifically regarding the dimension's *safety*, *effectiveness, timeliness and efficiency*.

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