Ductal carcinoma in situ of the breast : cancer precursor or not?

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CHAPTER 7

Summarizing discussion

The general aims of this thesis were to identify prognostic markers predictive of the development of subsequent ipsilateral invasive breast cancer (iIBC) after DCIS and to explore the clonal relatedness of patient-matched DCIS and subsequent iIBC. In this concluding chapter we will discuss the main findings and interpret them in a broader context. The methodological challenges of performing observational research and the strengths and limitations of our studies are discussed. Finally, recommendations for future research and clinical implications are given.

Main findings in context of other literature

Risk factors for an invasive breast cancer after DCIS

These is a high need for robust prognostic markers that can reliably predict the disease course of DCIS. Numerous prognostic factors have been reported by previous studies, but none of them have shown to be of sufficient value for implementation into the clinic. So, what do we really know? To answer this question, we performed a systematic review and meta-analyses (**chapter 2**). Previously, three meta-analyses have been published on prognostic factors for recurrence after DCIS, although only one specifically focused on ipsilateral *invasive* recurrence after DCIS.[1–3] Yet, we are the first to perform bias assessment on prognostic factors studies for DCIS and incorporate the results into meta-analyses. We concluded that the following six factors had the strongest predictive value for subsequent IBC after DCIS: African-American race, premenopausal status, detection by palpation, involved margins, high histologic grade, and high p16 protein expression. Common biases were insufficient measurement and handling of confounders and poorly described study groups.

In **chapter 3** the results of our own prognostic factor study for DCIS are described. The large size of our series, the case-control design, the comprehensive data, and the long-term follow-up were essential to overcome biases, as often seen in previous studies. Our results showed a prognostic role for COX-2, HER2, and periductal fibrosis. Previous studies support these findings.[4–6] In addition, we found a 4-fold higher prevalence of subsequent iIBC for women diagnosed with $HER2^{+}/COX\text{-}2^{high}$ DCIS as compared to women with $HER2^{-}/COX\text{-}2^{low}$ DCIS lesions. Furthermore, patients with $COX\text{-}2^{low}$ DCIS were at lower risk of iIBC as their risk was comparable to the general population.

More information on the future disease course of DCIS may be found in the genomic and epigenomic profile present at diagnosis. This hypothesis is supported by the fact that DCIS and IBC are highly similar at the molecular level.[7,8] Previous molecular profiling studies on DCIS mainly focused on synchronous DCIS and IBC or pure DCIS and unmatched IBC lesions (from different individuals), whereby the two components were compared to find differences that may be related to invasion.[8–13] To date, only two studies evaluated the association of molecular alterations and recurrence (both *in situ* and invasive).[7,14] Furthermore, the

Oncotype DX DCIS score is the first and only commercially available multigene expression panel. This score enables risk prediction of local recurrence (in situ and invasive) after BCS for DCIS and estimates the benefit from RT.[15] Yet, prospective validation of the score is still lacking.

Despite the large patient numbers, our gene expression analysis comparing DCIS associated with and without subsequent IBC did not result in the identification of markers statistically significantly associated with subsequent IBC (**chapter 4**). This is in line with a previous study, showing that expression analysis is compromised when unmatched for intrinsic subtype as profiles are strongly driven by the PAM50 intrinsic subtypes.[16] Gene expression analysis, stratified by PAM50 subtype, showed that immune-related pathways play a role in the progression of DCIS. With this, we showed that although the subtypes have limited prognostic value for DCIS, it is still of value to stratify lesions based on intrinsic subtype because of distinct evolutionary disease paths. Additionally, we found that DCIS associated with subsequent IBC harbored more CNAs as compared to DCIS without invasive recurrence, which is in line with literature.[14] Alternatively, we might have to focus on the tumor microenvironment, epigenetics, genetic predispositions, and lifestyle factors in combination with integrative analysis to distinguish DCIS that will potentially progress to IBC from the ones that will not.

IBC and corresponding synchronous and preceding DCIS

As described above, studies aiming to find markers related to DCIS progression and invasion generally have compared characteristics of IBC lesions with those of adjacent synchronous DCIS. The question remains whether synchronous DCIS and IBC comparison are a good surrogate of primary DCIS and subsequent IBC. In **chapter 5**, we demonstrated that marker expression between primary DCIS and subsequent IBC is less concordant than synchronous DCIS and IBC. HER2 marker expression showed the largest discrepancy: 36% of HER2-positive primary DCIS lesions were followed by HER2-negative IBC. In previous studies, numbers of matched DCIS and IBC pairs were too small to notice the major finding presented here.[17,18] Intra-lesional heterogeneity was identified as a possible cause of the observed discordant marker expression.

Clonal relatedness of patient-matched DCIS and subsequent IBC

DCIS is regarded as a precursor of invasive breast cancer. Yet, not all DCIS progresses into IBC and proof of direct progression is lacking. To provide evidence of the direct progression of DCIS to IBC, we assessed the clonal-relatedness of patient-matched DCIS and subsequent IBC. Traditionally, whether a subsequent cancer is related to the preceding one, is primarily based on comparison of clinical and histopathologic information.[19–23] More recently, genetic markers have started to play an increasingly important role in assessing the clonal relatedness of two lesions.[24–28]

Strikingly, we found that approximately 30% of the subsequent IBC after DCIS treated with breast conserving surgery alone may be independent new primary cancers (**chapter 6**). This high rate of new primary tumors indicates that: 1) true recurrence rates after DCIS are likely to be overestimated; and, if true, 2) DCIS might not just be a precursor, but could also be risk lesion of IBC.

Strengths, limitations and methodological challenges

Access to large, well-annotated patient cohort

A strength of the studies presented in this thesis is that we made use of a case-case control study nested in a nation-wide population-based cohort of all women diagnosed with and treated for DCIS between 1989-2005 within the Netherlands.[29] Women with subsequent iIBC (cases) were matched to women without subsequent iIBC (controls) by age and follow-up time (**chapter 3 and 4**). The women in this cohort have been considered to represent the Dutch population of women with DCIS.[29] We were fortunate to have access to date of the Netherlands Cancer Registry (NCR), collected by the Netherlands Comprehensive Cancer Organization, and pathology data from PALGA, the nationwide histopathology and cytopathology data network and archive. Data provided by the NCR included information on age at and data of DCIS diagnosis, histology and treatment for DCIS, and any subsequent IBCs as well as any other history of cancer. The well-annotated nature of our patient series enabled us to prevent a great amount of bias often seen in previous studies. Yet, our cohort did have missing data on margin status and DCIS lesions size (15% and 65%) and information on and family history of breast cancer was unavailable. Still, the work described in **chapter 3, 4, 5, and 6** account for the high need of well-designed studies with large patient numbers.

Use of registry-based data

A challenge of the studies described in **chapter, 3, 4, 5, and 6** is that they are retrospective studies. A general concern when working with retrospective data is that you are dependent on the size, quality, and completeness of relevant variables of the registry on which the study is based.[30] Data quality related to end-point measures in registries often is incomplete, as end-point information such as migration abroad or death from other causes is not always included.[31,32] This challenge can only be solved by improving source data.

Availability of tumor tissue and high quality data due to central pathology review

With the help of PALGA, we succeeded in retrieving 85% of the requested material from 58 participating hospitals within the Netherlands. Next to the DCIS specimens, we also collected the invasive recurrences of women that experience subsequent IBC. This enables

us to compare both DCIS associated with and without a subsequent invasive breast cancer event, but also to study the clonal relatedness of patient-matched DCIS and subsequent IBC. New whole slides were developed for reassessment by specialized breast pathologists, yielding in high quality pathology data. In addition, all IHC stainings within our studies were performed in one center and scored by a panel of observers with good inter-observer agreement. With this, inter-laboratory an inter-observer variability was prevented.[33,34]

Use of a patient group that was treated for DCIS

Our study group comprised of women diagnosed with DCIS between 1989 and 2005 and treated by BCS alone. We refrained from including women who also received adjuvant radiotherapy to avoid confounding by radiation effects. Nonetheless, we have to keep in mind that treatment strategies, and also screening techniques, for DCIS have evolved over the years, which may have impacted treatment or other care for these patients. Between 1989 and 1998, mastectomy or BCS alone were standard of care, according to Dutch treatment guidelines. From 1999 onwards, the addition of radiotherapy after BCS was included, which significantly reduces ipsilateral breast recurrences (both *in situ* and invasive).[35,36] Also, our group has shown that women diagnosed with DCIS between 1999 and 2004 were less likely to develop iIBC that women diagnosed between 1989 and 1998, regardless of treatment and age.[29] In addition, the introduction of digital mammography significantly improved the coverage and sensitivity of screening and led to an increase in the percentage of screening-detected DCIS.[37]

The fact that all patients included in our study group were treated by BCS alone, also brings a limitation of the studies presented in **chapter 3 and 4**. As analysis for clonal-relatedness of patient-matched DCIS and IBC (**chapter 6**) was not yet performed at the time of selecting patients for our case-control study, we did not take into account whether subsequent IBCs were indeed all clonally related to the primary DCIS lesion. As they might be second primary tumors, the prognostic factors identified could have attenuated prognostic significance or could be risk factors for any second invasive breast event after DCIS. The most ideal patient group for these studies would have been a group of women with untreated DCIS that subsequently developed ipsilateral IBC. However, such study groups are not yet available. Therefore, using a group of women treated for DCIS with BCS alone was the best possible alternative.

Use of FFPE tissue for molecular studies

Another challenge was the use of archival FFPE tissue for our molecular studies. Tissue blocks were collected from several pathology laboratories within the Netherlands, and as a result the embedding and storage of the tissue blocks may have been different between laboratories. This could have affected the results presented in this thesis. However, this would only have confounded the analyses if case-control status would have been differently

distributed between laboratories and this was not the case.

Use of archival FFPE tissue also has a limitation, since formalin-fixation induces cross-links between the nucleic acids that cause fragmentation of DNA and RNA with prolonged storage and sequence artefacts after amplification by PCR.[38,39] However, the use of FFPE tissue for molecular studies has been proven to be successful by others.[40–45] On top of this, we were challenged by the fact that DCIS lesions are often small and thus yield small amounts of DNA and RNA. Thus, we selected methods and kits that were compatible with low inputs of low-quality FFPE-derived DNA and RNA extracted.

A strength of the molecular studies described in **chapter 4 and 6** is the use of laser-microdissection. Morphologically, breast tumors are generally highly heterogeneous. Hence, to reassure a more cellular-based rather than a tissue-based resolution for our molecular studies, laser-microdissection is essential.[46,47] In addition, we succeeded in collecting both gene expression, copy number, and mutation data for a large number of DCIS samples included in our molecular studies. Mutation analysis was restricted to a 53-gene panel and thus represents a part of the full picture. Whole exome sequencing would have given us more information, although with the cost of lower sequencing depth, but is not feasible for this cohort of old-FFPE derived DNA.

Clinical implications and suggestions for further research

With the work described in this thesis, we have identified several prognostic markers for subsequent IBC after DCIS (e.g. HER2 and COX-2), but before implementation into the clinic validation in independent cohorts is needed. We encourage researchers to set up new unbiased patient cohorts for validation purposes and to remain searching for new prognostic markers. Furthermore, the type of recurrence should be specified, *in situ* or invasive, as it are the invasive recurrences that increase a woman's risk of dying from breast cancer and are the most clinically relevant end-point in prognostic factor studies for DCIS. Currently, there are multiple initiatives that are setting up study cohorts including primary DCIS and subsequent IBC (PRECISION, https://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/grand-challenge-award/funded-teams-wesseling).[48–51] In addition, non-inferiority trials, such as LORD, LORIS and COMET, will be important in prospective validation of prognostic factors.[49–51]

The results from our clonality analysis may substantially impact personalized risk stratification for women with DCIS, as two different risk issues have to be addressed. First, the risk of the DCIS lesion progressing to IBC. Second, the risk to develop a non-clonally related, most likely independent new IBC. Future risk stratification for women with DCIS, therefor should include the risk of the DCIS lesion progressing to IBC as well as the risk to develop a new independent breast cancer.

Lastly, we advise future researchers to take an integrated, comprehensive approach that involves new technologies and areas of research (e.g., detailed genomics and epigenomics analysis, the role of the microenvironment, and creation of a risk stratification tool) to assess the likelihood of DCIS progression.

Conclusions

Based on the results presented in this thesis, we can conclude that we have identified excellent candidate prognostic markers for use in personalized risk stratification. From previous high quality prognostic factor studies we identified six factors that predict invasive breast cancer risk after DCIS and are highly recommended for validation. The results of our case-control study underline the importance of assessment of DCIS stromal compartment and protein expression of HER2 and COX-2 to estimate the risk of subsequent invasive disease after a diagnosis of DCIS and are excellent candidate prognostic markers for use in personalized patient risk stratification. Lastly, although our molecular study is one of the largest in its sort, we only identified subtle differences between DCIS with and without a subsequent IBC.

Furthermore, we have provided evidence of the direct progression of DCIS into IBC. The results from our clonality analysis have changed our view on DCIS as *true* recurrence rates after DCIS may be overestimated and it seems that DCIS might not just be a precursor, but could also be risk lesion of IBC, as has been estimated for LCIS.

We hope our efforts will ultimately contribute to the identification of reliable and clinically relevant prognostic factors for DCIS in the near future. This will subsequently help to distinguish indolent from potential hazardous DCIS, and thereby putting an end to the current overtreatment of an often indolent disease.

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