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

Visser, L.L.

CHAPTER 1

Scope of the thesis

Introduction

Primum non nocere, "first do no harm", is one of the promises within the Hippocratic Oath, that medical students must take as an important step in becoming a doctor. In order to honor this promise, doctors must be able to reliably estimate the risks and benefits of treatment for a patient. However, in daily practice these estimates are often uncertain and prone to error. This is a reminder that we need high-quality research to help us make a more balanced treatment choice for every patient. One disease that is in high need of reliable risk estimation is ductal carcinoma in situ (DCIS).

Carcinoma in situ

DCIS belongs to the group of non-invasive breast lesions, called carcinoma in situ (CIS). It is known that CIS lesions have the potential to progress to invasive breast cancer within a time period varying from a few years to several decades.[1] Only a subset of CIS lesions will undergo the transition from in situ to invasive cancer, and not all invasive cancers arise from CIS lesions.[2,3] Most CIS lesions are asymptomatic. Before the introduction of population-based breast cancer screening in 1989, CIS was rarely diagnosed, but nowadays they represent about 20-25% of all newly diagnosed breast cancers.[4–6]

DCIS is the most common form of CIS. It is characterized by the neoplastic proliferation of epithelial cells inside the milk duct of the breast. DCIS is considered a different entity than lobular carcinoma in situ (LCIS), as the latter is characterized by the proliferation of epithelial cells in the lobules of the breast. Whereas DCIS is generally accepted to be a potential precursor of invasive breast cancer, LCIS is considered to be a risk factor of future development of invasive disease.

DCIS as breast cancer precursor

DCIS is considered a precursor of invasive breast cancer, because DCIS and IBC are frequently found next to each other sharing genetic alterations as well as risk factors (e.g. age, family history of breast cancer, etc).[2,7–10] However, other findings reject DCIS being a precursor. First, in contracts to other in situ carcinoma, it has never been demonstrated that surgical removal of DCIS reduces the incidence of subsequent invasive breast cancer. A possible explanation for this is that most DCIS is nowadays detected by mammography screening, which next to an increased detection of DCIS also results in overdiagnosis of breast cancer, thus masking a possible reduction in incidence caused by removal of DCIS.[2] Second, not all DCIS progresses to IBC and definite proof of DCIS progression to IBC is still lacking. The fact that most DCIS is treated, hinders studies on the natural course of DCIS.

Dilemma of overdiagnosis and overtreatment

Although some DCIS will develop into IBC, the majority of DCIS, if left untreated, is not destined to progress and thus will never become life-threatening.[11] This implies that many women are "overdiagnosed", as they are diagnosed with a disease that would not have caused any symptoms or death.[12,13] Nonetheless, we are lacking prognostic markers that can predict which DCIS patients will subsequently develop invasive disease. As a result, current treatment guidelines for DCIS dictate that all women diagnosed with DCIS should undergo treatment to prevent the development of invasive breast cancer. This treatment consists of breast conserving surgery (BCS), often followed by radiotherapy and/or endocrine therapy, or a mastectomy. This makes that many women, who have a low-risk to develop subsequent IBC, are being harmed by this intensive treatment without any benefit.[14] Prognostic markers are urgently needed to avoid such "overtreatment". A better risk prediction will safely spare many women intensive treatment and so preserve their quality of life.

The thesis

Objectives

The objectives of this thesis were to identify prognostic markers predictive of the development of subsequent ipsilateral IBC after DCIS and to explore the clonal relatedness of patient-matched DCIS and subsequent ipsilateral IBC. This will help to stratify a woman's individual risk of subsequent invasive breast cancer development and will help to avoid overtreatment.

Thesis outline

Numerous prognostic markers 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, in **chapter 2** we performed a systematic literature review to identify the factors with the strongest predictive value of subsequent IBC after DCIS that should be considered for validation. In addition, we provide insight into frequently introduced biases in prognostic factor studies for DCIS.

In **chapter 3**, we performed our own prognostic factors study for DCIS, by comparing clinicopathological characteristics of DCIS lesions associated with or without subsequent IBC. Next to this, information on the future disease course of DCIS might be encoded in the genomic and transcriptomic profile present at diagnosis. In **chapter 4**, we aimed to identify molecular alterations differentiating lesions that will remain indolent from those that will likely progress to IBC.

To shed light upon the mechanism of DCIS progression, most studies performed so far compared IBC with an adjacent DCIS component, referred to as synchronous DCIS. However, to our knowledge, it has never been investigated whether the synchronous DCIS

and IBC comparison is a good surrogate of primary DCIS and subsequent IBC. In **chapter 5**, we analyzed immunohistochemical marker expression between IBC and corresponding synchronous and preceding DCIS. Furthermore, in **chapter 6** we evaluated the clonal relatedness of 78 patient-matched DCIS and subsequent ipsilateral IBC, to provide evidence of direct progression from DCIS to IBC,.

Lastly, in **chapter 7** the main findings of this thesis are described and put in perspective. Furthermore, strengths, limitations, and methodological challenges are discussed, concluding with recommendations for future research and clinical implications.

References

1. Barnes NLP, Ooi JL, Yarnold JR, Bundred NJ. Ductal carcinoma in situ of the breast. *BMJ*. 2012;344:e797.
2. To T, Wall C, Baines CJ, Miller AB. Is Carcinoma in Situ a Precursor Lesion of Invasive Breast Cancer? *Int J Cancer*. March 2014:1-7.
3. Levi F, Randimbison L, Te V-C, La Vecchia C. Invasive breast cancer following ductal and lobular carcinoma in situ of the breast. *Int J cancer*. 2005;116(5):820-823.
4. Ernster VL, Ballard-Barbash R, Barlow WE, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. *J Natl Cancer Inst*. 2002;94(20):1546-1554.
5. Netherlands Comperhencive Cancer Organization (IKNL). DCIS incidence trends over time, the Netherlands.
6. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2014*. National Cancer Institute. Bethesda, MD
7. O'Connell P, Pekkel V, Fuqua SAW, Osborne CK, Clark GM, Allred DC. Analysis of loss of heterozygosity in 399 premalignant breast lesions at 15 genetic loci. *J Natl Cancer Inst*. 1998;90(9):697-703.
8. Burkhardt L, Grob TJ, Hermann I, et al. Gene amplification in ductal carcinoma in situ of the breast. *Breast Cancer Res Treat*. 2010;123(3):757-765.
9. Buerger H, Otterbach F, Simon R, et al. Comparative genomic hybridization of ductal carcinoma in situ of the breast-evidence of multiple genetic pathways. *J Pathol*. 1999;187(4):396-402.
10. Buerger H, Otterbach F, Simon R, et al. Different genetic pathways in the evolution of invasive breast cancer are associated with distinct morphological subtypes. *J Pathol*. 1999;189(4):521-526.
11. Lopez-Garcia MA, Geyer FC, Lacroix-Triki M, Marchió C, Reis-Filho JS. Breast cancer precursors revisited: molecular features and progression pathways. *Histopathology*. 2010;57(2):171-192.
12. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst*. 2010;102(9):605-613.
13. Løberg M, Lousdal ML, Bretthauer M, Kalager M. Benefits and harms of mammography screening. *Breast Cancer Res*. 2015;17(1):63.
14. Groen EJ, Elshof LE, Visser LL, et al. Finding the balance between over- and under-treatment of ductal carcinoma in situ (DCIS). *Breast*. September 2016:1-10.