# Exploring opportunities to de-escalate treatment of ductal carcinoma in situ and early-stage breast cancer

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Sena Alaeikhanehshir

The art of knowing,
is knowing what to ignore

*Rumi, Iranian Poet*

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# Exploring opportunities to de-escalate treatment of ductal carcinoma in situ and early-stage breast cancer

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# CHAPTER 1

## General introduction and outline thesis

# EXPLORING OPPORTUNITIES TO DE-ESCALATE TREATMENT OF DUCTAL CARCINOMA IN SITU AND EARLY-STAGE BREAST CANCER

## Breast cancer screening, overdiagnosis and overtreatment

Worldwide, breast cancer is the most common diagnosed cancer and primary cause of cancer related death in women[1]. Annually, in the US approximately 260,000 women receive the diagnosis breast cancer; in the Netherlands about 15,000 women are diagnosed with breast cancer each year[1,2]. The majority of breast tumors are Invasive Breast Cancer (IBC) constituting approximately 80% of all newly diagnosed breast tumors, while approximately 20% are Ductal Carcinoma In Situ (DCIS) lesions[1–3]. DCIS is an intraductal proliferation of neoplastic epithelial cells still confined to the basal membrane and the myoepithelial layer of the ducto-lobular system of the breast. In DCIS, the neoplastic cells have not invaded the surrounding stromal breast tissue[4,5]. In the event of IBC the neoplastic cells do not adhere to the natural boundary of the basal membrane and invasion into the surrounding tissue occurs. Moreover, IBC has the capacity to metastasize. Both DCIS and IBC represent a heterogeneous spectrum of breast tumors which vary in biological behavior and histological appearance on microscopy[6–12].

Three decades ago, several western countries including the US, UK and the Netherlands started screening their female population for breast cancer. For a screening program to be successful, two conditions should be met. First, timely detection of tumors that are bound to cause death. Secondly, clinical outcome of treatment of early detected tumors should be superior compared to treatment at clinical presentation[13,14]. Since the introduction of breast cancer screening, diagnostics, and treatment of patients with breast cancer have evolved. Survival has increased considerably due to the improved systemic therapies and optimized loco-regional treatment[15–22]. Synchronously with the evolution of systemic and loco-regional treatment, imaging has also improved over time. In addition to classical detection of breast abnormalities by mammography and ultrasound, imaging modalities such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Computed Tomography (CT)-scans have been integrated over the years in standard breast cancer care. These imaging modalities have demonstrated their value in diagnosis, (re)staging and follow-up of breast cancer patients[23–27]. Furthermore, gradual replacement of analogous mammography by digital mammography enabled radiologists to detect smaller lesions in the screening setting[28–30].

The combination of screening and advances in systematic treatment has resulted in increased survival of breast cancer patients over the last three decades[31,32]. However, the extent of the contribution of screening to this increased breast cancer survival is still debated[22,33,34].

In terms of survival, patients with DCIS alone have an excellent outcome. A Dutch study showed a 5-years survival probability of 98%[35] and a large US SEER-based study involving patients diagnosed with primary DCIS demonstrated a breast cancer-specific mortality of 3% at 20 years[36]. With the current management strategies, patients with IBC also demonstrate

very good survival rates, with 90% of patients being alive at 5 years[2]. In spite of the increased detection of early-stage breast cancer (including DCIS) and the treatment of the vast majority of these tumors, a substantial decline in the incidence of advanced stage breast cancer has not occurred since the introduction of breast cancer screening programs. This suggests overdiagnosis and concomitant overtreatment of these tumors[22,34]. Overdiagnosis is the detection of tumors in the screening setting that would not present clinically during a patient's lifetime. Detection of these tumors results in treatment, and consequently there is a risk for of overtreatment[34,37–39]. Overdiagnosis and overtreatment are major obstacles to overcome for physicians and researchers involved in breast cancer care. Fortunately, overtreatment in breast cancer is increasingly acknowledged worldwide and several clinical trials address overtreatment in different areas of breast cancer diagnostics and therapeutics, and explore opportunities to de-escalate treatment[40–47].



## De-escalation of treatment for low-risk DCIS

A likely candidate for de-escalation of local therapy is DCIS. DCIS is assumed to be a non-obligate pre-cursor of invasive breast cancer[48]. DCIS was a rare condition before the introduction of breast cancer screening. It currently accounts for around 20% of the newly diagnosed breast tumors[1–3], with an annual incidence of 60.000, 7,000 and 2,500 patients in the US, UK and the Netherlands, respectively[1–3]. The observed increase of DCIS incidence follows the introduction and implementation of the breast cancer screening programs[34,49] as the majority of the DCIS lesions are found during breast cancer screening, due to easily detected DCIS associated calcifications. More importantly, most DCIS patients do not experience any symptoms (i.e. palpable mass, bloody nipple discharge) which could lead to the clinical detection of DCIS lesion[50].

The recommended treatment for DCIS is breast conserving surgery followed by radiotherapy. Sometimes breast conservation is not possible, in which case a mastectomy with or without direct reconstruction will be performed[51]. Despite the increased incidence of DCIS and the fact that DCIS is always treated with surgery, a substantial decline of the incidence of advanced stage breast cancer is not observed[34,52], indicating that DCIS lesions do not necessarily progress to breast cancer[34,53–55]. Additional evidence supporting the hypothesis that not all patients with DCIS will develop IBC is demonstrated in a report from Erbas *et al.*[56] reporting on studies of DCIS patients who were initially misdiagnosed as having a benign breast lesion which was 'treated' by biopsy alone. Between 14-53% of these biopsy-only 'treated' DCIS patients developed IBC over a time period of 10-15 years[56]. Erbas concludes that not all DCIS lesions will progress to invasive cancer, but the limited data does not allow a precise estimate. Other evidence illustrating that DCIS will not always progress to invasive disease during a women's lifetime is provided in a study by Welch *et al.*, using autopsy series to estimate the 'disease' reservoir for DCIS[57]. This study demonstrated a prevalence of up to 39% of DCIS in women who did not die from breast cancer[57]. Although we know from these studies that a considerable part of DCIS lesions will never progress to invasive disease during a patient's lifetime, we must acknowledge that these studies are retrospective, and usually concern small biased series. A more precise estimate of overdiagnosis and overtreatment can therefore not be calculated.

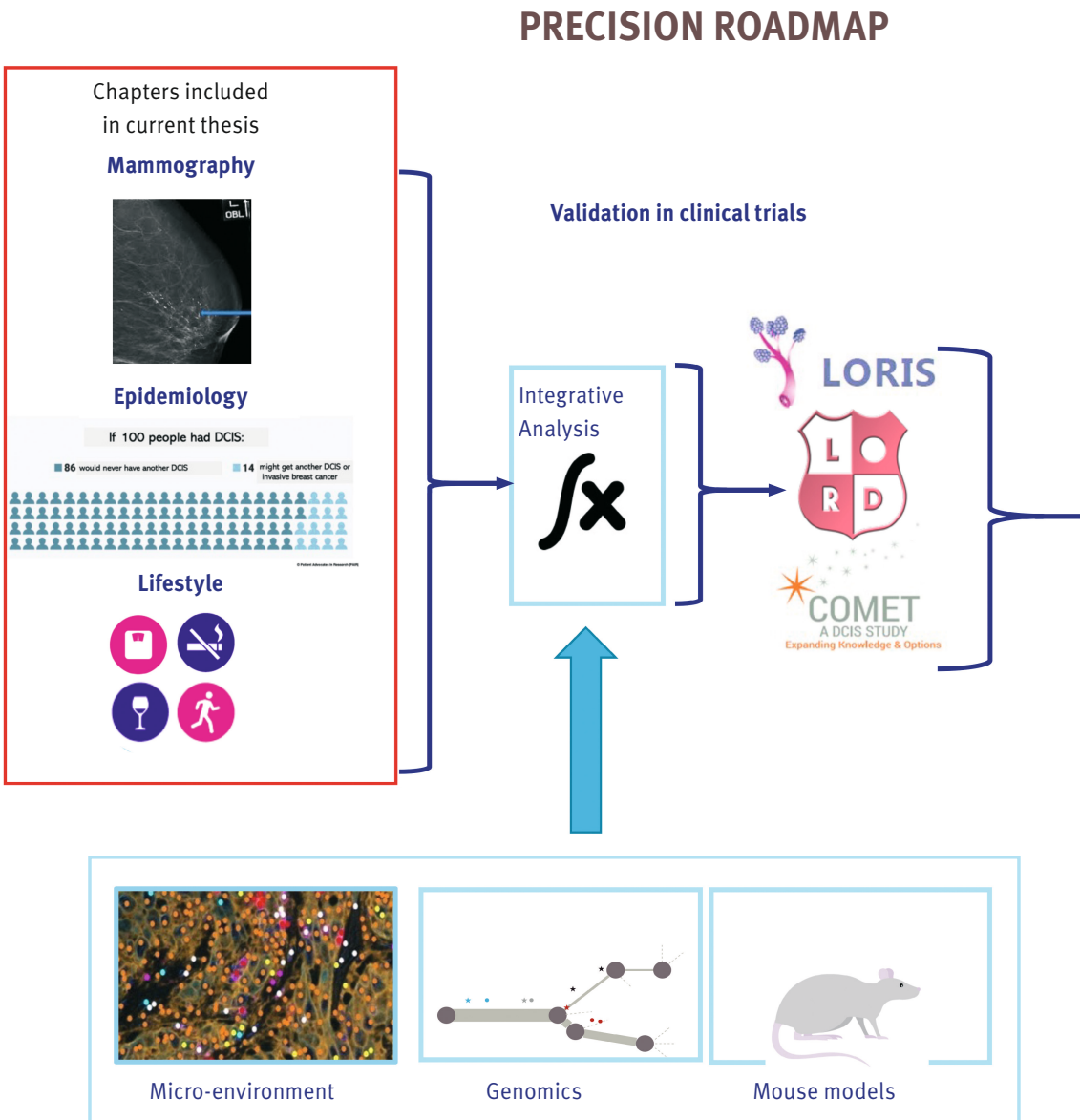
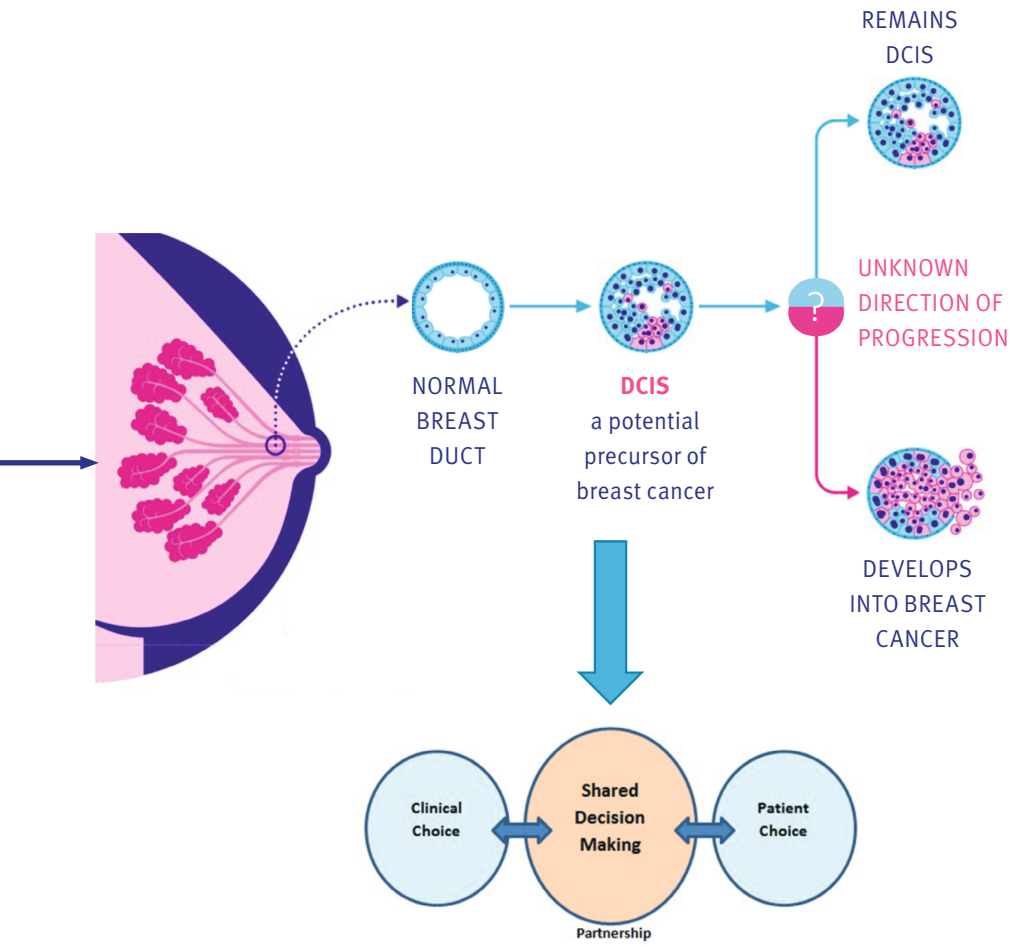



**Figure 1.** Precision roadmap, current thesis investigates mammography features, epidemiological data and lifestyle factor for DCIS.


REMAINS
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a potential
precursor of
breast cancer
DEVELOPS
INTO BREAST
CANCER
Clinical
Choice
Shared
Decision
Making
Patient
Choice
Partnership

Current evidence about prognostic factors for progression of DCIS to IBC is lacking and requires independent validation[58]. The poor understanding about relevant prognostics factors for DCIS prevents clinicians to adequately discriminate which DCIS patients might or might not benefit from locally invasive treatment. The incapability to distinguish between hazardous and harmless DCIS has led to the initiation of the CRUK/KWF Grand Challenge PRECISION initiative[59]. The main goal of PRECISION is to differentiate harmless DCIS, for which no surgical treatment is necessary, from hazardous DCIS, requiring surgical treatment to prevent progression to IBC. In the PRECISION initiative researchers and physicians with different backgrounds from the US, UK, and the Netherlands collaborate to tackle the 'DCIS dilemma' from different angles. Patients' advocates are involved in the design and execution of studies thus constituting the important connection between professionals and patients. The PRECISION initiative consists of different work-packages in which potential risk factors and biological mechanisms of progression of DCIS to invasive disease are studied. For example, mouse PDX models have been developed where DCIS cells are intraductally injected to generate DCIS lesions, enabling in vivo studies of DCIS progression. Molecular and genomic markers from human tissue can unravel pathways involved in DCIS progression. A Dutch study performed in the PRECISION initiative showed that the combination of COX2/HER2 overexpression was significantly associated with the risk of subsequent IBC after DCIS diagnosis[60]. Ultimately, all factors associated with the progression of DCIS to IBC will be incorporated in a risk prediction model, which then needs to be validated (Figure 1). This will be done in the patient cohorts of three ongoing active surveillance trials (COMET, LORIS, LORD) which are also being performed under the umbrella of PRECISION[40,41,61]. Participants in COMET and the LORIS-trial are randomized to conventional treatment or to active surveillance. Conventional treatment consists of surgery +/- adjuvant therapies (radiotherapy, endocrine therapy). In the active surveillance group, patients will not undergo surgery and will be monitored with mammography. In the LORD trial, patients are not randomized but allowed to choose the study arm of their preference.

## De-escalation of treatment for Early-Stage Breast cancer

Invasive breast cancer is a heterogeneous disease in appearance and biological behavior[6,7] and can be divided in subtypes, based on histology (i.e. ductal and lobular), or receptor expression, such as estrogen, progesterone and HER2 or based on gene expression patterns[7]. The treatment of IBC depends on the stage of disease and subtype. In some cases only loco-regional treatment is sufficient but in patients with more extensive disease systemic therapies are administered[62]. Due to the improvement of systemic and local therapies, a considerable decrease in the rate of both distant metastases and loco-regional recurrences (LRR) in breast cancer has been observed. However, not every breast cancer requires intensive treatment to prevent recurrences and would also have excellent survival without adjuvant therapies. Consequently, de-escalation strategies are currently considered, especially for early-stage breast cancer. Treatment of early-stage breast cancer often includes adjuvant therapy such as endocrine treatment, chemotherapy, and immunotherapy to reduce the risk of recurrence, distant metastases and increase survival[15,16,63,64]. Clinicopathological factors such as tumor size, grade, number of involved lymph nodes, hormone- and HER2 receptor status, and patient

characteristics (e.g. age, menopausal status) are assessed to estimate the risk of recurrence and distant disease[64,65]. Online tools such as Adjuvant Online! (now discontinued)[46,66] and PREDICT PLUS[67] estimate the benefit of adjuvant therapies by incorporating these clinicopathological factors for risk assessment. Several clinical trials address overtreatment in different areas of breast cancer diagnostics and therapeutics and explore opportunities to de-escalate treatment. Prognostic gene assays including a 21-gene signature (OncotypeDX), and a 70-gene signature (MammaPrint) were developed to determine in which early-stage breast cancer patients adjuvant chemotherapy may be omitted without compromising survival[46,47]. The 70-gene signature predicts the risk of 5 and 10 year distant breast cancer recurrence[46,68]. The MINDACT trial has demonstrated the ability of this signature to identify patients with adverse clinicopathological risk factors and a genomic low-risk profile in whom chemotherapy could be safely omitted, as these patients had a 8.7-year distant disease free survival of 95.1% (95%CI: 93.1-96.6) without chemotherapy[46,68]. The 70-gene signature thus enables de-escalation of systemic therapy in appropriately selected early-stage breast cancer patients.



Previous studies have reported an association between the occurrence of local recurrences and distant metastases[69–71]. This led to the idea to apply gene expression assays like OncotypeDX® and Mammaprint® to assess local recurrence risk as well. Several retrospective studies have demonstrated an independent association between gene-assays results and the risk for Loco-Regional Recurrence (LRR)[72,73]. In a study by Drukker *et al.* a low-risk MammaPrint® was independently associated with a lower risk of LRR compared to patients with a high MammaPrint risk score[74]. The potential role for gene-assays such as MammaPrint® and OncotypeDX® as a prognostic factor for LRR as first loco-regional relapse creates a new field to further explore local de-escalation approaches in patients treated with breast conserving surgery. Several ongoing trials are currently investigating de-escalation of treatment by omitting radiotherapy in patients with a low-risk of in-breast relapse based on clinicopathological factors and multigene arrays[43–45].

## Outline Thesis

In this thesis several stepping stones for the de-escalation of treatment of DCIS and Early-stage breast cancer are explored. In **Chapter 2** the influence of modifiable and non-modifiable risk factors on progression of DCIS to invasive disease were studied. This chapter aims to identify gaps in knowledge and potential targets for risk reduction (i.e. lifestyle factors). As a significant number of future patients will likely left untreated for their DCIS lesions, risk reducing strategies will become increasingly important.

In **Chapter 3** the results of a Dutch population-based cohort, based on data from the Netherlands Cancer registry (NCR) and Dutch nationwide network and registry of histology (PALGA) are presented. In this chapter we determine cumulative incidences for ipsilateral invasive breast cancer after DCIS. Additionally, we aim to identify clinicopathological factors possibly associated with the risk for a subsequent ipsilateral invasive breast cancer.

**Chapter 4** describes the application of artificial intelligence (AI) in DCIS and assesses its potential to differentiate between DCIS grades I/II and III, as well as identify the presence of IBC based on pre-surgery mammograms. As the suspicion of concomitant invasive disease and grade of DCIS are essential eligibility criteria for the ongoing active surveillance trials, we aim at improving the accuracy of DCIS grade assessment and final diagnosis by introducing AI methods.

In **Chapter 5** we discuss the possibility to omit radiotherapy in appropriately selected patients with early-stage breast cancer and explore whether there is a role for MammaPrint® to de-escalate the treatment of early-stage breast cancer. **Chapter 6** elaborates on the results from chapter 2, 3, 4, 5 and aims to draw conclusions and give future perspectives, mainly translating our results into feasible short and long-term practice changing evidence.

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# CHAPTER 2

## The impact of patient characteristics and lifestyle factors on the risk of an ipsilateral event after a primary DCIS: A systematic review

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# ABSTRACT

**Objective**

The majority of 'low-risk' (grade I/II) Ductal Carcinoma In Situ (DCIS) may not progress to invasive breast cancer during a women's lifetime. Therefore, the safety of active surveillance versus standard surgical treatment for DCIS is prospectively being evaluated in clinical trials. If proven safe and selectively implemented in clinical practice, a significant group of women with low-risk DCIS may forego surgery and radiotherapy in the future. Identification of modifiable and non-modifiable risk factors associated with prognosis after a primary DCIS would also enhance our care of women with low-risk DCIS.

**Methods**

To identify modifiable and non-modifiable risk factors for subsequent breast events after DCIS, we performed a systematic literature search in PUBMED, EMBASE and Scopus.

**Results**

Six out of the 3,870 articles retrieved were included for final data extraction. These six studies included a total of 4,950 patients with primary DCIS and 640 recorded subsequent breast events. There was moderate evidence for an association of a family history of breast cancer, premenopausal status, high BMI, and high breast density with a subsequent breast cancer or further DCIS.

**Conclusion**

There is a limited number of recent studies published on the impact of modifiable and non-modifiable risk factors on subsequent events after DCIS. The available evidence is insufficient to identify potential targets for risk reduction strategies, reflecting the relatively small numbers and the lack of long-term follow-up in DCIS, a low-event condition.

**Key words**

Lifestyle factors; DCIS; invasive breast cancer; in situ recurrences; recurrence; active surveillance; surgery; radiotherapy

# INTRODUCTION

Knowledge about the natural course of disease of women with Ductal Carcinoma In Situ (DCIS) is scarce, but available evidence suggests that if left untreated, not all DCIS will progress to invasive breast cancer (IBC)[1,2]. Treated women diagnosed with primary DCIS have a 5 year risk of developing a subsequent invasive ipsilateral breast cancer of approximately 6% [3]. A Dutch study showed, if treated with surgery (and radiotherapy if indicated) that women with DCIS have a 5-year overall survival probability of about 98% [4], and a US study showed a breast cancer-specific mortality probability of approximately 3% [5]. The modest risks of experiencing an invasive breast event and breast cancer death also mean that many women with DCIS may safely forego immediate treatment, and many are potentially at risk for overtreatment. These women are at risk for therapy-induced side effects, and negative treatment dependent psychological effects without deriving any clear treatment benefit in terms of progression-free, recurrence-free, or overall survival[6–10].



To reduce overtreatment, it is crucial to be able to accurately differentiate between indolent and aggressive DCIS. Evidence on which factors are predictors of progression in DCIS is still limited. Some characteristics of DCIS lesions, such as nuclear grade, tumour size, and detection by palpation have been shown to be associated with a subsequent breast event specifically, ipsilateral Invasive Breast Cancer ($IBC_{ipsilateral}$), or ipsilateral DCIS recurrence (iDCISr)[11]. Further, known risk factors for the development of primary IBC, such as body weight, breast density, and a family history of breast cancer (see for example[12–38]), may or may not be predictors of DCIS progression, but have not been validated. The association between characteristics of women with DCIS and clinical outcomes was studied by Shamliyan *et al.*, synthesizing data from five randomized controlled clinical trials, and 64 observational studies published up to 2009[39]. They reported statistically significant associations between ipsilateral breast tumour recurrence and a younger age, premenopausal status at diagnosis, obesity, and a high breast density[39]. However, the strength of the evidence they retrieved was modest to weak; it is not yet clear to what degree these factors are associated with DCIS progression.

At present, three international randomized controlled trials (i.e., COMET, LORIS, LORD-trial)[40–42] and one single arm trial (JCORG, LORETTA)[43] are studying whether, and in which patients it is safe to omit surgical treatment (and radiotherapy) for 'low-risk' DCIS (i.e., DCIS grade I and II). These ongoing active surveillance trials have the potential to change the current clinical approach towards the management of DCIS, resulting in an increasing number of women with DCIS remaining in the breast at risk of experiencing a subsequent breast event. With this future scenario in mind, it becomes increasingly important to identify predictors of DCIS progression to IBC. Insight into predictors of progression can be used to estimate the risk of experiencing a subsequent breast event for an individual patient and can aid tailoring DCIS management strategies. Lifestyle factors (e.g. smoking, alcohol consumption, weight/BMI) possibly associated with an increased risk to develop IBC are potential targets for risk reduction interventions (e.g., smoking cessation or weight loss). Knowledge of the effect of

non-modifiable and modifiable factors on the risk of progression to IBC could help women together with their clinician make an informed decision about active surveillance and screening for early detection and lifestyle changes.

In the wake of the ongoing active surveillance trials, we anticipate a shift in thinking towards less invasive management strategies for low-risk DCIS in the coming decades. Therefore, a systematic literature review was performed to evaluate the impact of established breast cancer risk factors on the risk of developing in situ or invasive disease after treatment of primary DCIS.

# MATERIALS & METHODS

## Systematic literature search and inclusion/exclusion criteria

Relevant articles were identified by performing a systematic literature search in consultation with an experienced information specialist (P.A.B.). The bibliographic databases PUBMED, EMBASE (Ovid), and Scopus were searched for articles from 1970 till September 19, 2018. During primary review, the study by Shamliyan *et al.* 2010 was encountered[39], which identified five randomized controlled clinical trials and 64 observational studies published from January 1970 to January 2009 by searching trial registries and American cancer registries. Ten publications reporting results from the Surveillance Epidemiology and End Results (SEER) database were also included[39]. Considering the extent of overlap in the research questions, the current review was amended to focus on articles published after January 2009, and only before January 2009 if not already included by Shamliyan *et al.* Eligible studies were full-text English language involving women diagnosed with primary DCIS (all grades). Observational studies, case-control studies, and randomized controlled trials were included. Animal studies, case reports/case series, conference abstracts, commentaries and letters to the editor were excluded. See Figure 1 for the PRISMA flow diagram and Appendix A for the detailed search strategy.

All the articles from the initial search were independently reviewed by E.G.E and S.A. based on title and abstract. Any discrepancies were resolved by consensus, and if consensus could not be reached, the full-text was reviewed. Full-text assessment was reviewed by E.G.E. and S.A., and any disagreement during this phase was settled by a third reviewer (M.v.S.).

## Data extraction

Data extracted from the articles by one of the reviewers included: patient cohort used; population source; the period of recruitment; number of patients included; the number of patients with the studied outcomes: ipsilateral invasive breast cancer recurrence; in situ recurrence in the ipsilateral breast; development of a regional and/or distant metastasis ≥ 6 months after DCIS diagnosis; median follow-up time (years); type of treatment; patient age; Hazard Ratios (HR), Odds Ratios (OR), and Relative Risks (RR) with their concomitant 95% confidence intervals (CI). A complete overview of the risk factors of interest for this review are listed in Table 1.

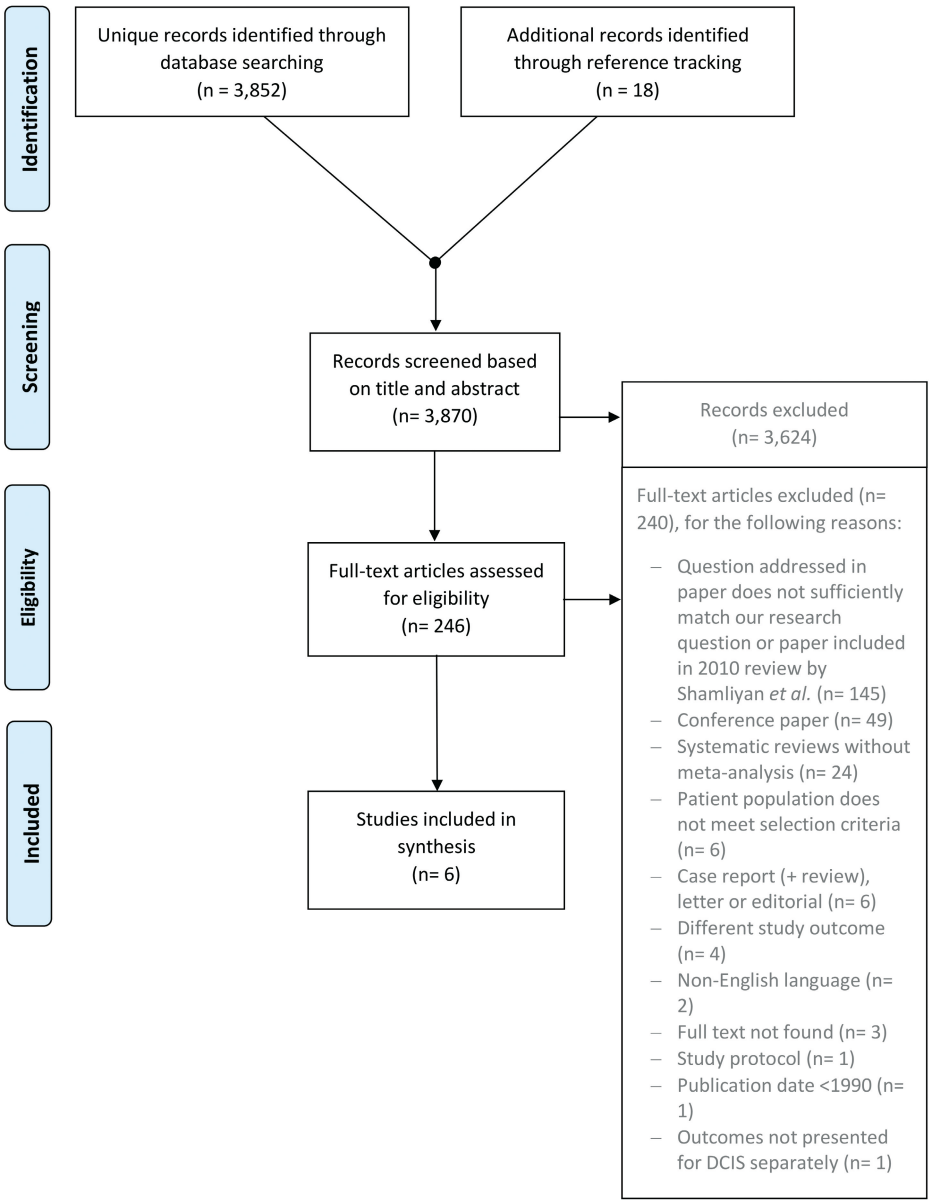


**Figure 1.** PRISMA flow diagram.

## Methodological quality assessment

An adjusted Newcastle-Ottawa scale was used to assess methodological quality and potential bias in the included articles[44]. The Newcastle-Ottawa scale assessment is based on study population selection, assessment of confounders, and quality of outcome measurement (see Appendix B for the adapted version used in this study).

# RESULTS

## Study & patients characteristics

Six articles were included (Figure 1). These studies reported data from 4,950 women of European descent (sample sizes ranging between 50 and 1,533 patients per study) with primary DCIS. A total of 640 (range: 13-239) breast events ($IBC_{ipsilateral}$, iDCISr, locoregional, and/or distant metastasis) were observed and the median follow-up varied between 4.4 and 9.0 years. Most patients underwent breast conserving surgery often followed by radiotherapy and sometimes by endocrine therapy or mastectomy (see Table 2 for the characteristics of included studies).

The studies included in this review lacked data on smoking, alcohol consumption, physical activity, diet/fat intake, use of hormonal contraception, breast feeding, hormone replacement therapy, gravidity/parity/age at birth of first child, ethnicity, length, and age at menarche. For four factors significant associations were reported (Table 1).

**Table 1.** Factors of interest for a breast event after primary DCIS*

| ***Modifiable factors*** | ***Non-modifiable factors*** |
|---|---|
| Smoking<br>Alcohol consumption<br>Physical activity<br>**Weight / BMI*** | **Family history of breast cancer***<br>Ethnicity<br>Height |
| | Age at menarche |
| Diet / fat intake | **Menopausal status*** |
| Use of hormonal contraception | **Breast density*** |
| Breast feeding | |
| Hormone Replacement Therapy (HRT)<br>Gravidity and parity<br>Age at birth of first child | |

***Statistically significant associations found in this systematic review are in bold

### Family history

Of the three studies[45–47] reporting on family history, one reported a statistically significant association[47]. Baglia *et al.* found that women with more than two first degree relatives with breast cancer gives a two-fold risk increase for a subsequent breast event after a primary DCIS ($OR_{(multivariate)}$ 1.78 (95%-CI: 1.02–3.10)) compared to women with no first degree family members with breast cancer. Also, having an affected first degree relative younger than 50 years, increased the risk for a subsequent breast event, ($OR_{(multivariate)}$ 1.56 (95%-CI: 1.05–2.33)) compared to having an affected first degree family member aged 50 years or older.

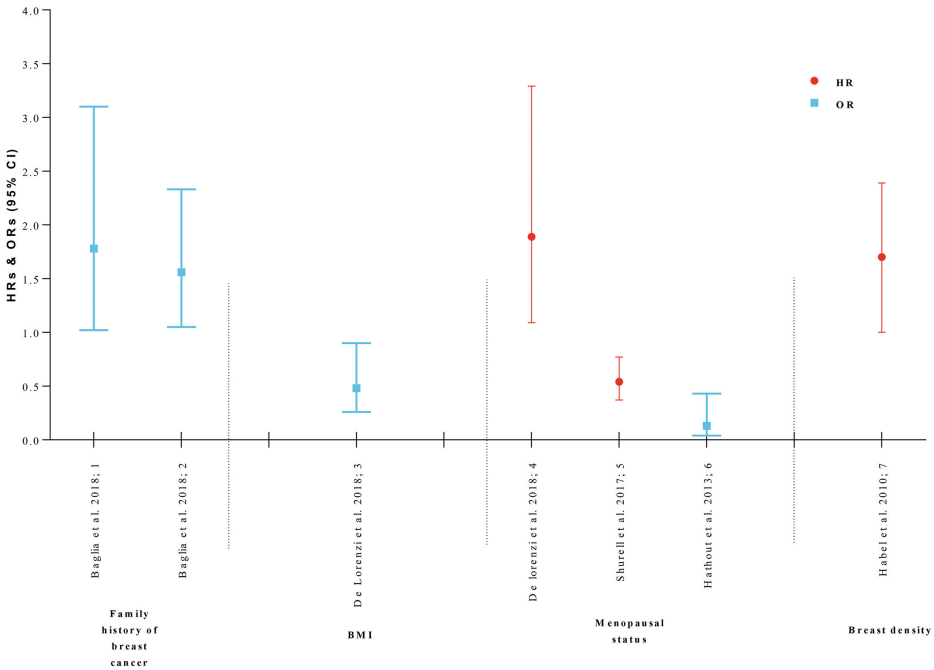


**Figure 2.** Overview of significant multivariable Hazard Ratios (HR) and Oddd Ratios (OR) for the risk of a subsequent breast even after primary DCIS.
**Please note these are not pooled estimates but point estimates from individual included studies**
1: No. of first-degree relatives with breast cancer (two or more affected family members)
2: Age at diagnosis of first-degree family member (affected family member younger than 50 years)
3: Body Mass Index greater than 25 Kg/m$^2$
4: Premenopausal vs postmenopausal
5: Postmenopausal vs premenopausal
6: Highest quintile of area of breast density
HR: hazard ratio; OR: odds ratio; bars represent the 95% confidence intervals (CI)

### BMI

One study reported on BMI[46] documenting a 52% risk reduction for a subsequent breast event in women with a BMI lower than 25 compared to women with a BMI of 25 or higher ($HR_{(multivariate)}$ 0.48 (95%-CI: 0.26-0.90)).

### Menopausal status

Three studies[45,46,48] described statistically significant associations between menopausal status and the risk of developing a subsequent breast event. De Lorenzi *et al.*[46] stated that the risk for a subsequent breast event was higher in women who were pre- or peri-menopausal ($HR_{(multivariate)}$ 1.89 (95%-CI: 1.09-3.29)) compared to post-menopausal women. Shurell *et al.*[45] reported a lower risk of experiencing a subsequent breast event in post-menopausal compared to pre-menopausal women ($HR_{(multivariate)}$ 0.54 (95%-CI: 0.37-0.77)). Similarly, Hathout *et al.*[48], reported that post-menopausal women have a decreased risk of developing a subsequent breast event compared to pre-menopausal women ($OR_{(multivariate)}$ 0.13 (95%-CI: 0.04-0.43)).

**Table 2.** Description of included studies and populations.

| Articles | $N_{population}$ | $N_{events}$ | Cohort Source Country | Recruitment period | Median follow-up (years) | Age at diagnosis | Treatment received for primary DCIS | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Surgery | Adjuvant treatment |
| De Lorenzi *et al.* 2018 | 419 | 34 iDCISr<br>37 $IBC_{ipsilateral}$<br>1 Distant metastasis<br>3 Regional metastasis | **Cohort:** Women with primary DCIS<br>**Source:** Single hospital-based<br>**Country:** Italy | 2000-2008 | 7.7 | <50 years: n=152<br>50-69 years: n=130<br>≥60 years: n=137 | Oncoplastic surgery n= 44<br>BCS n= 375 | RT n= 419<br>ET n= 189 |
| Baglia *et al.* 2018 | 1,533<br>Cases: 539<br>Controls: 994 | 239 $IBC_{ipsilateral}$<br>296 contralateral breast cancers<br>4 bilateral breast cancers | **Cohort:** Women with primary DCIS<br>**Source:** Population-based<br>**Country:** United States | 1995-2013 | NR | <50 years: n=531<br>50-69 years: n=530<br>60-69 years: n=317<br>70-79 years: n=155 | BCS n= 1,239<br>MST n= 294 | RT n= 721 |
| Shurell *et al.* 2018 | 1,323 | 71 iDCISr<br>55 $IBC_{ipsilateral}$ | **Cohort:** Women with primary DCIS<br>**Source:** Single hospital-based<br>**Country:** United States | 1980-2010 | 6.6 | Median: 56 (range 27-86) | BCS n= 1,323 | RT n= 1,323 |
| Hathout *et al.* 2013 | 440 | 8 iDCISr<br>5 $IBC_{ipsilateral}$ | **Cohort:** Women with primary DCIS<br>**Source:** Multi-Centre<br>**Country:** Canada | 2003-2010 | 4.4 | Median: 58 (range NR) | BCS n= 440 | RT n= 440 |
| Shah *et al.* 2013 | 300 | 13 Unspecified recurrences<br>1 Distant metastases | **cohort:** Women with primary DCIS<br>**Source:** Multi-Centre<br>**Country:** United States | 1993-2010 | 4.7 | Median: 66 (range 41-88) | BCS n= 300 | RT n= 300 |
| Habel *et al.* 2010 | 935 | 164 Unspecified recurrences<br>5 regional/distant metastasis** | **Cohort:** Women with primary DCIS<br>**Source:** Multi-Centre<br>**Country:** United States | 1990-1997 | 8.6 | Median: NA (range NR) | BCS n= 935 | RT: n= 446<br>ET: n= 44 |

*WBRT: Whole Breast Radiation Therapy, BCS: Breast Conserving Surgery, MST: Mastectomy, RT: Radiotherapy, ET: Endocrine Treatment, IBC: Invasive Breast Cancer, NR: Not Reported ** Regional or distant metastases (without ipsilateral breast involvement)

**Breast density**

Breast density assessment was variously considered: assessment of parenchymal patterns, area of density (quintiles), percentage of density, and BI-RADS (Breast Imaging Reporting and Data System) classification. Habel *et al.* reported the strongest association between a subsequent breast event after DCIS and parenchymal patterns ($HR_{(univariate)}$ 2.0 (1.0–3.7)). For area of density in quintiles, the second ($HR_{(univariate)}$ 1.6 (1.0–2.8)) and fifth ($HR_{(univariate)}$ 1.9 (1.2–3.20)) quintile were associated with a statistically significant increase in the risk of developing a subsequent breast event after DCIS compared to the first quintile[49].

In Figure 2 the multivariable adjusted estimates of all statistically significant associations reported by the included studies are shown. A complete overview of all estimates reported by the included studies is provided in Appendix C.

## Study quality assessment

Out of a maximum of nine points that could be achieved on the adjusted Newcastle-Ottawa scale, quality scores ranged from four to eight points. Only one study[50] reported adequately about the loss to follow-up, and in three of the six studies[47,48,50] the length of follow-up was less than five years or the length of follow-up was not reported. Table 3 provides more details regarding the findings of the quality assessment.



# DISCUSSION

This systematic review was performed to evaluate the impact of established modifiable and non-modifiable breast cancer risk factors on the risk of developing further in situ or invasive disease after treatment of primary DCIS. We concluded that the available studies and evidence on the association between established modifiable and non-modifiable breast cancer risk factors and progression to invasive disease after a primary DCIS remains limited, particularly regarding modifiable factors. Also, all of the studies we identified used cohorts of women of European-descent. Thus, it is unclear whether the associations reported apply to women of non-European descent, for example in the United States or Asia. DCIS is a low-event rate disease, which requires large cohorts with long-term follow-up to identify potential risk factors for subsequent invasive breast cancer. Most studies we identified were retrospective in nature and data on particularly lifestyle and reproductive factors are not routinely collected (e.g., in cancer registries or trials that do not focus on lifestyle). Based on this and a prior review[39], there is moderate evidence for an increased risk of developing a subsequent breast event after a primary DCIS in women with a family history of breast cancer, those being premenopausal at diagnosis, or in women with high breast density. The results for BMI were conflicting. We did not perform a meta-analysis because the level of the studies included in the article by Shamliyan *et al.* and our own review are of insufficient quality to yield meaningful pooled estimates.

**Table 3.** Assessment of the methodological quality of included studies.

| **COHORT STUDIES** | | | | |
|---|---|---|---|---|
| | **Selection** | | | |
| Study | *Representa-tiveness of exposed cohort* | *Selection of non-exposed cohort* | *Ascertainment of exposure* | *Demonstration outcome not present at start study* |
| De Lorenzi *et al.* 2018 | ★ | ★ | ★ | ★ |
| Shurell *et al.* 2018 | ★ | ★ | ★ | ★ |
| Hathout *et al.* 2013 | ★ | ★ | ★ | Unclear |
| Shah *et al.* 2013 | ★ | ★ | ★ | ★ |
| Habel *et al.* 2010 | ★ | ★ | ★ | ★ |
| **CASE CONTROL STUDY** | | | | |
| | **Selection** | | | |
| Study | *Adequate case definition* | *Representati-veness of cases* | *Selection of controls* | *Definition of controls* |
| Baglia *et al.* 2018 | Record linkage | ★ | ★ | ★ |

*** Thresholds for converting the Newcastle-Ottawa scales to the United States Agency for Healthcare Research and Quality (AHRQ; https://www.ahrq.gov/) standards (good, fair, or poor quality): Good quality:** 3 or 4 stars in selection 0domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; **Fair quality:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; **Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

A family history of breast cancer is associated with the development of primary breast cancer and DCIS[23,51,52]. Compared to women with no history of breast cancer in their family, women with one first degree family member have an approximately two-fold risk to develop invasive disease, and women with more than one affected first-degree family member have a three to four-fold increased risk[5,52–54]. Few studies have investigated whether the risk for subsequent breast events in women with primary DCIS is associated with having a positive family history. In this systematic review, one study addressed family history and the risk for subsequent breast event[47] confirming the previous review[39]. Shamliyan *et al.* identified four studies that considered family history and the risk for a subsequent breast event, with one showing a three-fold statistically significant increased risk for a subsequent breast event[55]. Notably, the study included in this systematic review did not report on breast cancer specific mutations in their included population[47].

In contrast to the published literature[56–58], de Lorenzi *et al.*[46] found that a high BMI was associated with a risk reduction of 52%[46], whereas the literature consistently shows high BMI to be a risk factor for invasive disease in post-menopausal women[55–58]. The majority of patients included by de Lorenzi *et al.* were post-menopausal at diagnosis (62%), indicating that their findings

| | Outcome | | | |
|---|---|---|---|---|
| **Comparability** | *Assessment of outcome* | *Adequate length follow-up* | *Adequacy of follow-up of cohorts* | **Overall quality assessment*** |
| Unclear | ★ | ★ | No statement | **Poor** |
| ★ | ★ | ★ | No statement | **Good** |
| ★ | ★ | Not sufficient | Unclear | **Poor** |
| Unclear | ★ | ★ | High drop-out rate (49.7%) | **Poor** |
| ★ | ★ | Unclear | ★ | **Good** |

| | Exposure | | | |
|---|---|---|---|---|
| **Comparability** | *Ascertain-ment of exposure* | *Ascertain-ment cases and controls the same* | *Non-response rate* | **Overall quality assessment** |
| ★ | ★ | ★ | High non-response rate | **Good** |



are in contrast to published literature. Two of the studies included by Shamliyan *et al.* showed that women in the highest decile of BMI had approximately twice the risk for developing a recurrence after DCIS compared to women in the four lowest deciles, with the associations remaining the same when analyses were stratified for menopausal status[56,57]. Considering that the increase in risk for breast cancer attributable to BMI differs by menopausal status[58–60]. More studies are needed to clarify whether BMI is associated with the development of a subsequent breast event after DCIS, the direction of the association and potential underlying mechanisms.

Three studies[45,46,48] assessed whether menopausal status was associated with the risk for experiencing a subsequent breast event after DCIS. All three studies concluded that pre- or peri-menopausal status is correlated with a higher risk of subsequent breast event compared to post-menopausal status[45,46,48], concordant with the findings in Shamliyan *et al*. The association between menopausal status and breast cancer incidence has been extensively described in the literature and cannot be disconnected from BMI[45,46,48,58,60]. The results regarding BMI and menopausal status suggest that the risk for experiencing a breast event after DCIS has a potential underlying mechanism involving body weight, menopausal status, and age. Such mechanisms could be driven by hormonal pathways, fat compositions, micro-environmental

reactions, however, these underlying mechanisms are yet poorly understood. The correlation between pre-menopausal status and increased risk of developing subsequent breast events is also in line with the evidence showing that younger age is a prognostic factor for invasive disease in patients with DCIS[4,5,39,48,50,61–63].

Though, given the mandatory reporting of breast density at least in some US states conducting breast screening, this review retrieved only one study[49] assessing the relationship between breast density and the risk of developing a subsequent breast event in women with DCIS. High breast density has been reported to be an independent risk factor for breast cancer due to two reasons[64–66]. First a potentially cancerous lesion can be more difficult to detect in dense breasts, thereby negatively impacting the sensitivity of mammography[67–69]. Second, characteristics involving biological processes associated with dense breast tissue and breast density may increase the likelihood of the transformation of normal epithelium to malignant cells[70]. This potential biological mechanism could also play a role in malignant transformation of DCIS. Indeed the literature suggests that breast density might also play a role in the progression of DCIS to IBC[39,49,71.]

Our study has strengths and limitations. A strength of this review was the comprehensive search strategy, rigorously developed in collaboration with an experienced information specialist. Furthermore, we adhered to the PRISMA method to ensure a complete and transparent reporting of studies. A limitation of this systematic review is that the inconsistent terminology used in the literature to define DCIS between studies (e.g. Breast Carcinoma In Situ, Non infiltrating Breast Cancer, Intraductal Carcinoma) made it difficult to identify relevant papers. However, with reference tracking we expect to have limited the impact of this potential bias. This challenge to recover relevant studies highlights the need for more consistent use of terminology. Another limitation is the different types of subsequent breast events were not always considered separately in the analyses. For example, we had to exclude one relevant publication since the analyses did not discriminate between ipsilateral and contralateral events[72]. In addition, most of the included studies in this systematic review did not discriminate between ipsilateral invasive disease and re-occurrence of DCIS in their analyses.

This work was carried out in the broader context of the current randomized controlled active surveillance trials (The COMET, LORIS and LORD-trial)[40–42] evaluating the safety of active surveillance for the management of low-risk DCIS. If these trials are positive, half of all women diagnosed with low-risk DCIS may be eligible for active surveillance[40–42]. Therefore, there is an urgent need for insight into factors involved in progression from DCIS to invasive disease in these women as well as about potential targets for interventions (e.g., weight loss) to further reduce these risks[4,73] In conclusion, our findings highlight the knowledge gap about the association between known risk factors for developing IBC and subsequent breast events after a primary DCIS.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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## Conflict of interest statement

None declared.

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# APPENDIX

**The impact of patient characteristics and lifestyle factors on the risk of an ipsilateral event after a primary DCIS: A systematic review**

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## Appendix A: Search strategy per database

| Source | Search terms |
|---|---|
| Pubmed | "Life Style"[Mesh] OR life style* [tiab] OR "Smoking"[Mesh] OR smoke* [tiab] OR smoking [tiab] OR "Alcohol Drinking"[Mesh] OR alcohol drink* [tiab] OR alcohol consum* [tiab] OR alcohol abus* [tiab] OR "Exercise"[Mesh] OR exercis* [tiab] OR physical activ* [tiab] OR sport [tiab] OR sports [tiab] OR work out* [tiab] OR working out [tiab] OR physical fitness [tiab] OR "Body Weight"[Mesh] OR body weight* [tiab] OR weight* [tiab] OR "Body Height"[Mesh] OR body height* [tiab] OR height [tiab] OR "Body Mass Index"[Mesh] OR body mass index* [tiab] OR BMI* [tiab] OR quetelet index* [tiab] OR quetelets index* [tiab] OR quetelet's index* [tiab] OR "Diet"[Mesh] OR diet [tiab] OR diets [tiab] OR dieting [tiab] OR food intake* [tiab] OR eating habit* [tiab] OR fat intake* [tiab] OR "Contraceptive Agents"[Mesh] OR contraceptiv* [tiab] OR the pill [tiab] OR ((Menstruation-Inducing [tiab] OR Sperm Immobilizing [tiab] OR Spermatocidal [tiab] OR Antispermatogenic [tiab]) AND (agent [tiab] OR agents [tiab])) OR "Menarche"[Mesh] OR menarch* [tiab] OR menstrual cycl* [tiab] OR menstruat* [tiab] OR "Pregnancy"[Mesh] OR "Parturition"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Gravidity"[Mesh] OR Gravidit* [tiab] OR Nulligravidit* [tiab] OR Primigravidit* [tiab] OR Multigravidit* [tiab] OR pregnan* [tiab] OR parturit* [tiab] OR birth* [tiab] OR childbirth* [tiab] OR labour* [tiab] OR delivery [tiab] OR deliveries [tiab] OR partus [tiab] OR "Breast Feeding"[Mesh] OR breast feed* [tiab] OR breast fed [tiab] OR breastfeed* [tiab] OR breastfed [tiab] OR "Menopause"[Mesh] OR menopaus* [tiab] OR "Estrogen Replacement Therapy"[Mesh] OR Estrogen Replacement Therap* [tiab] OR Estrogen Replacement Therap* [tiab] OR menopausal hormone therap* [tiab] OR Estrogen Replace* [tiab] OR ("Hormone Replacement Therapy"[Mesh] AND ("Menopause"[Mesh] OR menopaus* [tiab])) OR "Breast Density"[Mesh] OR breast densit* [tiab] OR Mammographic Densit* [tiab] OR "Hereditary Breast and Ovarian Cancer Syndrome"[Mesh] OR ((hereditary [tiab] OR family histor* [tiab] OR first degree* [tiab]) AND breast cancer* [tiab]) OR (("Neoplasm Metastasis"[Mesh] OR metastatic [tiab] OR metastas* [tiab] OR secondary tumor*[tiab] OR secondary tumour* [tiab] OR secondary cancer* [tiab]) AND ipsilat* [tiab]) "Neoplasm Recurrence, Local"[Mesh] OR ((recurren* [tiab] OR residual [tiab] OR relaps* [tiab] OR return* [tiab] OR recrudescence* [tiab]) AND (cancer* [tiab] OR neoplas* [tiab] OR tumor* [tiab] OR tumour* [tiab] OR carcinom* [tiab] OR malignan* [tiab] OR DCIS [tiab] OR in situ* [tiab])) "Breast Neoplasms"[Mesh] OR breast neoplasm* [tiab] OR breast tumor* [tiab] OR breast tumour* [tiab] OR breast cancer* [tiab] OR breast malign* [tiab] OR breast oncolog* [tiab] OR breast carcinom* [tiab] "Carcinoma, Intraductal, Noninfiltrating"[Mesh] OR DCIS [tiab] OR Ductal Carcinoma In Situ* [tiab] OR Intraductal Carcinoma* [tiab] OR Atypical Ductal Hyperplasia* [tiab] |

*[continued on next page]*

**Appendix A.** *[continued]*

| Source | Search terms |
|---|---|
| EMBASE | exp intraductal carcinoma/ or (DCIS or Ductal Carcinoma In Situ* or Intraductal Carcinoma* or Atypical Ductal Hyperplasia*).ti,ab. exp breast tumor/ or (Breast* adj3 (neoplasm* or tumor* or tumour* or cancer* or malign* or oncolog* or carcinom*)).ti,ab. exp lifestyle/ or exp smoking/ or exp drinking behavior/ or exp exercise/ or exp body weight/ or exp body height/ or exp body mass/ or exp diet/ or exp contraceptive agent/ or exp menarche/ or exp pregnancy/ or exp birth/ or exp pregnancy rate/ or exp pregnancy/ or exp breast feeding/ or exp estrogen therapy/ or exp menopause/ or exp breast density/ exp menopause/ or menopaus*.ti,ab. exp hormone substitution/ and ((hereditary or family histor* or first degree*) adj breast cancer*).ti,ab. (life style* or smoke* or smoking or alcohol drink* or alcohol consum* or alcohol abus* or exercis* or physical activ* or sport or sports or work out* or working out or physical fitness or body weight* or weight* or body height* or height or body mass index* or BMI* or quetelet index* or quetelets index* or quetelet's index* or diet or diets or dieting or food intake* or eating habit* or fat intake* or contraceptiv* or the pill or menarch* or menstrual cycl* or menstruat* or Gravidit* or Nulligravidit* or Primigravidit* or Multigravidit* or pregnan* or parturit* or birth* or childbirth* or labour* or delivery or deliveries or partus or breast feed* or breast fed or breastfeed* or breastfed or menopaus* or Estrogen Replacement Therap* or Estrogen Replacement Therap* or menopausal hormone therap* or Estrogen Replace* or breast densit* or Mammographic Densit*).ti,ab. ((Menstruation-Inducing or Sperm Immobilizing or Spermatocidal or Antispermatogenic) adj2 (agent or agents)).ti,ab. ((recurren* or residual or relaps* or return* or recrudescence*) adj3 (cancer* or neoplas* or tumor* or tumour* or carcinom* or malignan* or DCIS or in situ*)).ti,ab. exp tumor recurrence/ or (exp metastasis/ or (metastatic or metastas* or secondary tumor* or secondary tumour* or secondary cancer*).ti,ab.) and ipsilat*.ti,ab. 1 and 11 |
| Scopus | ( ( TITLE-ABS-KEY ( "Life style*" OR smoke* OR smoking OR "alcohol drink*" OR "alcohol consum*" OR "alcohol abus*" OR exercis* OR "physical activ*" OR sport OR sports OR "work out*" OR "working out" OR "physical fitness" OR "body weight*" OR weight* OR "body height*" OR height OR "body mass index*" OR bmi* OR "quetelet index*" OR "quetelets index*" OR "quetelet's index*" OR diet OR diets OR dieting OR "food intake*" OR "eating habit*" OR "fat intake*" OR contraceptiv* OR "the pill" OR menarch* OR "menstrual cycl*" OR menstruat* OR gravidit* OR nulligravidit* OR primigravidit* OR multigravidit* OR pregnan* OR parturit* OR birth* OR childbirth* OR labour* OR delivery OR deliveries OR partus OR "breast feed*" OR "breast fed" OR breastfeed* OR breastfed OR menopaus* OR "Estrogen Replacement Therap*" OR "Estrogen Replacement Therap*" OR "menopausal hormone therap*" OR "Estrogen Replace*" OR "breast densit*" OR "Mammographic Densit*" ) ) OR ( TITLE-ABS-KEY ( menopaus* ) AND KEY ( "Hormone Replacement Therapy" ) ) OR ( TITLE-ABS ( hereditary OR "family histor*" OR "first degree*" ) AND TITLE-ABS ( "breast cancer*" ) ) OR ( TITLE-ABS ( "Menstruation-Inducing" OR "Sperm Immobilizing" OR spermatocidal OR antispermatogenic ) AND TITLE-ABS ( agent OR agents ) ) OR (TITLE-ABS-KEY(metastatic OR metastas* OR secondary tumor* OR secondary tumour* OR secondary cancer*) AND TITLE-ABS-KEY(ipsilat*))) AND ( ( TITLE-ABS-KEY ( ( ( recurren* OR residual OR relaps* OR return* OR recrudescence* ) W/2 ( cancer* OR neoplas* OR tumor* OR tumour* OR carcinom* OR malignan* OR dcis OR "in situ*" ) ) ) ) OR ( TITLE-ABS-KEY ( ( breast* W/2 ( neoplasm* OR tumor* OR tumour* OR cancer* OR malign* OR oncolog* OR carcinom* ) ) ) ) ) ) AND ( TITLE-ABS-KEY ( "Noninfiltrating Intraductal Carcinoma*" OR dcis OR "Ductal Carcinoma In Situ*" OR "Intraductal Carcinoma*" OR "Atypical Ductal Hyperplasia*" ) ) |

## Appendix B: Newcastle-Ottawa quality assessment scale (adapted)

Case control and cohort studies are scored separately. Studies are scored for the Selection, Comparability, and Exposure or Outcome categories. A study can be awarded a maximum of one star for each item in the categories (number of items varies among categories). Per category the total number of stars are summed up.

### CASE CONTROL STUDIES

**Selection**

1) Is the case definition adequate?
   a) Yes, with independent validation ★
   b) Yes, e.g., record linkage or based on self-reports
   c) No description

2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases ★
   b) Potential for selection biases or not stated

3) Selection of Controls
   a) Community controls ★
   b) Hospital controls
   c) No description

4) Definition of Controls
   a) No history of disease (endpoint) ★
   b) No description of source

**Comparability**

1) Comparability of cases and controls on the basis of the design or analysis
   a) Study controls for _____ ★ (Select the most important factor.)
   b) Study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

**Exposure**

1) Ascertainment of exposure
   a) Secure record (e.g., surgical records) ★
   b) Structured interview where blind to case/control status ★
   c) Interview not blinded to case/control status
   d) Written self-report or medical record only
   e) No description

2) Same method of ascertainment for cases and controls
   a) Yes ★
   b) No

3) Non-Response rate
   a) Same rate for both groups ★
   b) Non-respondents described
   c) Rate different and no designation
   d) Not reported

## COHORT STUDIES

### Selection

1) Representativeness of the exposed cohort
   a) Truly representative of the average _____ (describe) in the community ★
   b) Somewhat representative of the average _____ in the community ★
   c) Selected group of users e.g. nurses, volunteers
   d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort ★
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) Secure record (e.g. surgical records) ★
   b) Structured interview ★
   c) Written self-report
   d) No description

4) Demonstration that outcome of interest was not present at start of study
   a) Yes ★
   b) No

### Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for _____ ★ (select the most important factor)
   b) Study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

### Outcome

1) Assessment of outcome
   a) Independent blind assessment ★
   b) Record linkage ★
   c) Self-report
   d) No description

2) Was follow-up long enough for outcomes to occur
   a) Yes (At least five years follow-up for DCIS recurrence and ten years for survival) ★
   b) No

3) Adequacy of follow up of cohorts
   a) Complete follow up - all subjects accounted for ★
   b) Subjects lost to follow up unlikely to introduce bias - small number lost - › ____ %
      (select an adequate %) follow up, or description provided of those lost) ★
   c) Follow up rate ‹ ____% (select an adequate %) and no description of those lost
   d) No statement

## Appendix C: Overview of the effect of lifestyle factors on breast events* after primary diagnosis of primary pure DCIS

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | **Articles** | **HR (95%-CI)** | **OR (95%-CI)** | **HR (95%-CI)** | **OR (95%-CI)** |
| **Family history** | Shurell *et al.* 2018 | Family history Yes vs no:<br>1.13 (0.79-1.62) p=0.49 | | | |
| | De Lorenzi *et al.* 2018 | | | Family history yes vs no:<br>0.87 (0.50-1.50) | |
| | Baglia *et al.* 2018 | | | | First-degree family history of breast cancer yes vs no:<br>1.26 (0.97–1.63) |
| | Baglia *et al.* 2018 | | | | No. of first-degree relatives with breast cancer:<br><br>0:1 ref: 1<br>1: 1.18: (0.80–1.50)<br>**2: 1.78; (1.02–3.10)** |
| | Baglia *et al.* 2018 | | | | Age at diagnosis of first-degree family member:<br><br>no history: 1<br>≥50: 1.10: (0.80–1.50)<br>**‹50: 1.56: (1.05–2.33)** |
| | Baglia *et al.* 2018<br>**Subsequent invasive** | | | | First-degree family history of breast cancer yes vs no:<br>1.30 (0.94–1.79) |
| | Baglia *et al.* 2018<br>**Subsequent invasive** | | | | No. of first-degree relatives with breast cancer:<br>0:1 ref: 1<br>1: 1.,25: (0.88–1.77)<br>2+: 1.73: (0.87–3.43) |
| | Baglia *et al.* 2018<br>**Subsequent invasive** | | | | Age at diagnosis of first-degree family member:<br>no history: 1≥50: 1.23 (0.83–1.81)<br>‹50: 1.42 (0.89–2.28) |

*[continued on next page]*

**Appendix C:** *[continued]*

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | **Articles** | **HR (95%-CI)** | **OR (95%-CI)** | **HR (95%-CI)** | **OR (95%-CI)** |
| **Body Mass Index** | De Lorenzi *et al.* 2018 | | | **BMI high vs Low: 0.48 (0.26-0.90)** | |
| **Menopausal status** | De Lorenzi *et al.* 2018 | | | **pre-perio vs post-menopausal: 1.89 (1.09-3.29)** | |
| | Shurell *et al.* 2018 | **Post-menopausal: 0.50 (0.35-0.71) (p= < 0.0001)** | | **Post-menopausal: 0.54 (0.37-0.77)** | |
| | Hathout *et al.* 2013 | | **0.23 (p= 0.01)** | | Menopausal state (yes vs no): **0.13 (0.04-0.43) (p= 0.001)** |

*[continued on next page]*

**Appendix C:** *[continued]*

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | **Articles** | **HR (95%-CI)** | **OR (95%-CI)** | **HR (95%-CI)** | **OR (95%-CI)** |
| **Breast density** | Habel *et al.* 2010<br>*Parenchymal pattern* | N1= 1.0 N1=(1.0)<br>P1= 1,8 (0.93-3.7)<br>**P2=2.0 (1.0-3.7)**<br>**DY=3.3 (1.1-9.7)** | | N1= 1.0 (1.0)<br>P1= 1.8 (0.93-3.7)<br>P2=1.7 (0.8-3.3)<br>DY=2.7 (0.9-8.2) | |
| | Habel *et al.* 2010<br>*area of density* | Quintile 1= 1.0 (1.0)<br>**Quintile 2= 1.6 (1.0-2.8)**<br>Quintile 3= 1.6 (0.9-2.6)<br>Quintile 4= 1.5 (0.9-2.6)<br>**Quintile 5= 1.9 (1.2-3.2)** | | Quintile 1= 1.0 (1.0)<br>Quintile 2= 1.5 (0.9-2.7)<br>Quintile 3= 1.5 (0.8-2.6)<br>Quintile 4= 1.2 (0.7-2.2)<br>**Quintile 5= 1.7 (1.0-2.9)** | |
| | Habel *et al.* 2010<br>*Percent density* | 0=1 (1)<br>1-21=1.6 (0.8-3.6)<br>25-49=1.9 (0.9-4.1)<br>50-75=2.1 (0.9-4.6)<br>›75=1.8 (0.6-5.5) | | 0=1 (1)<br>1-21=1.6 (0.7-3.6)<br>25-49=1.7 (0.7-3.8)<br>50-75=1.6 (0.7-3.8)<br>›75=1.2 (0.4-4.1) | |
| | Habel *et al.* 2010<br>*B-RADS density* | Almost all fat=1 (1)<br>Scatterd fibroglandu-lar=1.3 (0.7-2.1)<br>Heterogeneously dense=1.6 (0.8-2.1)<br>Extremely dense=1.8 (0.7-2.6) | | Almost all fat=1 (1)<br>Scatterd fibroglandu-lar=1.2 (0.7-2.1)<br>Heterogeneously dense=1.4 (0.8-2.4)<br>Extremely dense=1.3 (0.7-2.6) | |

* subsequent breast event is defined as either an ipsilateral invasive breast cancer recurrence and/or ipsilateral DCIS recurrence, and/or regional/distant metastases. The hazard ratios and odds ratios are based on analyses in which the different types of subsequent breast events are not consistently addressed separately

# CHAPTER 3

# The effects of contemporary treatment of DCIS on the risk of developing an ipsilateral invasive breast cancer (iIBC) in the Dutch population

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# ABSTRACT

**Purpose**

To assess the effects of contemporary treatment of ductal carcinoma in situ (DCIS) on the risk of developing an ipsilateral invasive breast cancer (iIBC) in the Dutch female population.

**Methods**

Clinical data was obtained from the Netherlands Cancer Registry (NCR), a nationwide registry of all primary malignancies in the Netherlands integrated with the data from PALGA, the Dutch nationwide network and registry of histo- and cytopathology in the Netherlands, on all women in the Netherlands treated for primary DCIS from 2005 through 2015, resulting in a population-based cohort of 14,419 women. Cumulative iIBC incidence was assessed and associations of DCIS treatment type with subsequent iIBC risk were evaluated by multivariable Cox regression analyses.

**Results**

Ten years after DCIS diagnosis, the cumulative incidence of iIBC was 3.1% (95% CI: 2.6-3.5%) in patients treated by breast conserving surgery (BCS) plus radiotherapy (RT), 7.1% (95% CI: 5.5-9.1) in patients treated by BCS alone, and 1.6% (95% CI: 1.3-2.1) in patients treated by mastectomy. BCS was associated with a significantly higher risk for iIBC compared to BCS+RT during the first 5 years after treatment (HR 2.80, 95% CI: 1.91-4.10%). After 5 years of follow-up, the iIBC risk declined in the BCS alone group but remained higher than the iIBC risk in the BCS+RT group (HR 1.73, 95% CI: 1.15-2.61).

**Conclusions**

Although absolute risks of iIBC were low in patients treated for DCIS with either BCS or BCS+RT, risks remained higher in the BCS alone group compared to patients treated with BCS+RT for at least 10 years after DCIS diagnosis.

**Keywords**

Ductal carcinoma in situ, Invasive breast cancer, Surgery, Radiotherapy, Population-based cohort study, Breast cancer-screening

# INTRODUCTION

Ductal Carcinoma In Situ (DCIS) is considered a potentially pre-invasive lesion in the ductal-lobular system of the breast[1], which may progress into Invasive Breast Cancer (IBC) if left untreated. It remains uncertain in which patients DCIS remains indolent and in which DCIS will develop into invasive disease[2,3]. Before the introduction of population breast cancer screening, DCIS was rarely diagnosed. Nowadays, DCIS accounts for roughly 20% of all newly diagnosed breast tumors[4–6]. The standard management for DCIS includes breast conserving surgery (BCS) often followed by radiotherapy (RT) and in in some countries like the US endocrine treatment is also administered. If BCS is not achievable i.e. due to the ratio of the lesion size to breast size, a mastectomy (MST), with or without direct reconstruction, can be performed[7]. Nonetheless, the treatment of patients with DCIS is widely debated since not all DCIS patients will experience survival benefit from invasive treatment [8–12].

Several previous studies have assessed the risk of developing a subsequent iIBC following locoregional therapy of DCIS[13–15]. We have reported results from a population-based nationwide cohort study with a median follow-up of 15.7 years that included 10,045 patients diagnosed from 1989 through 2004. In this cohort, 13.9% of patients treated with BCS alone developed a subsequent iIBC compared to 5.2% of patients treated by BCS+RT, and 1.1% of patients treated by MST developed a subsequent iIBC[15]. However, the population included in this study consisted of patients diagnosed with DCIS during 1989-2004 when adjuvant RT was not yet standard of care and the Dutch nationwide breast cancer screening program was not yet fully implemented[14,15]. More recently, much lower rates of invasive recurrences have been reported in patients with DCIS treated with BCS[16,17]. Therefore, the current study investigates the effect of more contemporary treatment for DCIS on invasive recurrence rates in a Dutch population-based nationwide cohort comprising patients diagnosed with DCIS from 2005 through 2015.



# METHODS

## Patient selection

This study includes all women treated for primary DCIS in the Netherlands from 2005 through 2015. Clinical data have been obtained from the Netherlands Cancer Registry (NCR), a nationwide registry of all primary malignancies in the Netherlands[18]. Data were subsequently linked with data from the nationwide network and registry of histology and cytopathology in the Netherlands (PALGA)[19]. PALGA data was used to check the medical history of breast cancer (including DCIS) and the presence of pure DCIS. Eligibility criteria were a diagnosis of pure DCIS, and surgical treatment with or without RT. Patients were excluded if DCIS diagnosis was determined at autopsy, if diagnosis of a subsequent iIBC occurred within three months of initial DCIS diagnosis, or if systemic therapy for initial DCIS diagnosis was administered. Systemic treatment is not administered as part of DCIS treatment in the Netherlands. If NCR reported an oncological medical history other than non-melanoma skin cancer, patients were

also excluded. Ultimately the study cohort consisted of 14.419 patients with pure primary DCIS (see figure 1). The study was approved by the institutional review boards of NCR and PALGA.

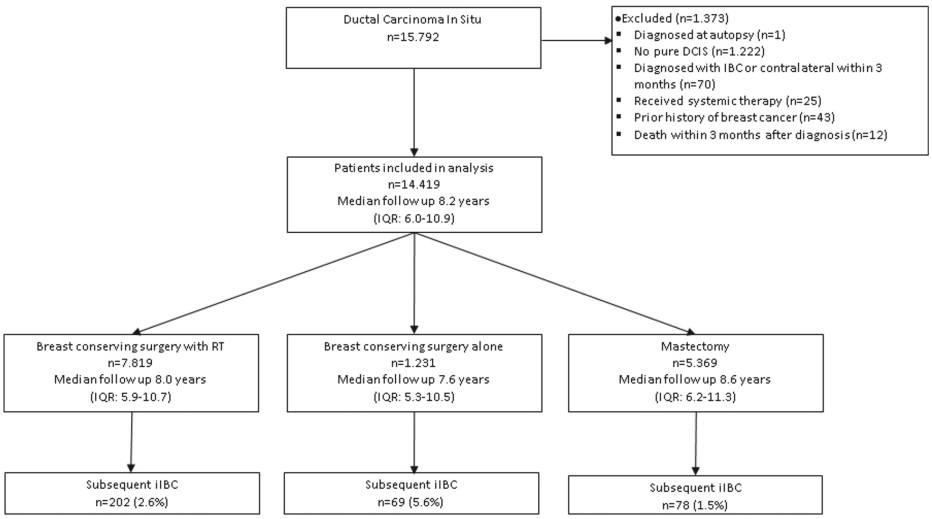


**Figure 1.** Flow diagram for patient selection and median follow-up by initial treatment type, RT, radiotherapy; IQR, interquartile range; iIBC, ipsilateral invasive breast cancer.

## DCIS treatment and other characteristics

Data on age, year, histological grade, and treatment at DCIS diagnosis were provided by the NCR. Treatment for the primary DCIS lesion was categorized as (1) BCS+RT; (2) BCS alone; and (3) MST. All treatments for the ipsilateral breast within 3 months after DCIS diagnosis were considered primary treatment. If type of treatment for primary DCIS (n=11) was unknown, treatment type information was extracted from pathology reports obtained from pathology laboratories through PALGA.

## Follow-up data

The occurrence of any iIBC at least 3 months after the primary DCIS diagnosis was ascertained based on NCR data. For patients initially treated with BCS, pathology data from PALGA were reviewed to identify ipsilateral MSTs (Interim MST) without a diagnosis of iIBC. Patients who underwent interim MST were classified as being initially treated by MST (n= 194). Data concerning subsequent iIBC and vital status was complete until February 1, 2020.

## Statistical analyses

Time at risk started 3 months after the diagnosis of primary DCIS and stopped at date of diagnosis of the event of interest (iIBC), date of death, or most last date of follow-up (February 1, 2020), whichever came first. Cumulative incidences were calculated for iIBC, with death considered as a competing risk. Contralateral IBCs and ipsilateral or contralateral DCIS recurrences were not considered events of interest and treatment for a contralateral event was not taken into

account. The cumulative risk of a subsequent iIBC in patients with low-grade (grade I/II) versus patients with high-grade (grade III) DCIS was also determined, and for patients younger than 50 versus 50 years and older, in order to compare our results to prior publications[14]. P-values were based on competing risk regression[20], with time since DCIS diagnosis as time-scale and adjusted for age (continuous). Cox proportional hazards analyses, using age as primary time-scale and time since DCIS diagnosis as secondary time-scale (0–5, 5–10, and ≥10 years), were used to quantify the effects of different treatments on iIBC risk. We assessed interaction of treatment with age and grade. Proportional hazard assumptions were verified using graphical and residual-based methods. Potential confounders were included as confounders if the hazard ratio for treatment was changed by 10% or more in a model including the potential confounder(s) and treatment compared with a model with treatment alone. All statistical analyses were performed using STATA/SE 13.1 (StataCorp LP, College Station, TX). A two-sided P value less than 0.05 was considered statistically significant.

# RESULTS

## Patient characteristics & treatment characteristics



The median age at DCIS diagnosis was 58 years (interquartile range (IQR) 51-66 years) and 83.8% was ≥50 years. Treatment consisted of BCS+RT in 54.2%, BCS alone in 8.5%, and of MST in 37.2%. Median follow-up was 8.2 years (IQR 6.0-10.9); 1.160 (8.0 %) patients died during follow-up. Table 1 shows patient characteristics, follow-up duration and number of iIBC cases by treatment type.

## Risk of Ipsilateral Invasive Breast Cancer

Overall, 349 (2.4%) patients developed an iIBC with a median time to iIBC of 4.8 years (interquartile range 2.8-7.0 years). The 10-year cumulative incidence was 3.1% (95% CI: 2.6-3.5) in patients treated with BCS+RT, 7.1% (95% CI: 5.5-9.1) in patients treated by BCS alone, and 1.6% (95% CI: 1.3-2.0) in patients treated with MST (figure 2). The cumulative incidence of a subsequent iIBC was 3.2% (95% CI: 2.5-3.8) at 10 years in patients with grade III DCIS treated with BCS+RT and 2.7% (95% CI: 2.1-3.4) in patients with grade I/II DCIS treated with BCS+RT. In grade III DCIS patients treated with BCS alone the cumulative incidence of iIBC was 6.1% (95% CI: 3.2-10.2), versus a cumulative incidence of 7.1% (95% CI: 5.2-9.7) in grade I/II DCIS patients (figure 3). At 5 years, the cumulative incidence of subsequent iIBC was 2.1% (95% CI: 1.6-2.6) for patients treated with BCS+RT and grade III DCIS versus 1.6% (95% CI: 0.94-1.7) patients with grade I/II DCIS treated with BCS+RT. For patients treated with BCS alone and grade III DCIS the cumulative incidence of iIBC was 5.3% (95% CI: 2.7-9.3), versus a cumulative incidence of 3.3% (95% CI: 2.2-4.7) in grade I/II DCIS patients at 5 years (figure 3).

**Table 1.** Characteristics of the study population by strategy.

| Initial DCIS treatment | BCS + RT | BCS alone | MST | Total |
|---|---|---|---|---|
| **Characteristics** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| **Age at DCIS diagnosis (years)** | | | | |
| ‹40 | 120 (1.6) | 30 (2.4) | 325 (6.0) | 475 (3.3) |
| 40–49 | 767 (9.8) | 169 (13.7) | 921 (17.2) | 1.857 (12.9) |
| 50–59 | 3.074 (39.3) | 487 (39.6) | 1.966 (36.6) | 5.527 (38.3) |
| 60–69 | 2.767 (35.4) | 308 (25.0) | 1.379 (25.7) | 4.554 (30.9) |
| 70–79 | 1.051 (13.4) | 167 (13.6) | 657 (12.2) | 1.875 (13.0) |
| ›80 | 40 (0.5) | 70 (5.7) | 121 (2.3) | 231 (1.6) |
| Median (interquartile range) | 59 (52-66) | 57 (51-67) | 56 (50-65) | 58 (51-66) |
| **Period of DCIS diagnosis** | | | | |
| 2005-2009 | 2.557 (32.7) | 427 (34.7) | 2.158 (40.2) | 5.124 (35.7) |
| 2010-2015 | 5.262 (67.3) | 804 (65.3) | 3.211 (59.8) | 9.277 (64.3) |
| **Screen-detected** | | | | |
| Yes | 3.699 (47.3) | 482 (39.1) | 1.693 (31.5) | 5.874 (40.7) |
| No | 941 (12.0) | 193 (15.7) | 1.132 (21.1) | 2.266 (15.7) |
| Missing | 3.179 (40.7) | 556 (39.1) | 2.544 (47.4) | 6.279 (43.6) |
| **DCIS grade** | | | | |
| I | 1.070 (13.7) | 626 (50.9) | 496 (8.8) | 2.165 (15.0) |
| II | 2.814 (36.0) | 274 (22.2) | 1.558 (29.0) | 4.646 (32.2) |
| III | 3.675 (47.0) | 190 (15.4) | 3.173 (59.1) | 7.038 (48.8) |
| Missing | 260 (3.3) | 141 (11.5) | 169 (3.1) | 570 (4.0) |
| **Follow-up interval (years)** | | | | |
| 0-5 | 1.098 (14.1) | 250 (20.3) | 698 (13.0) | 2.046 (14.2) |
| 5-10 | 4.366 (55.8) | 616 (50.0) | 2.717 (50.6) | 7.699 (53.4) |
| ›10 | 2.355 (30.1) | 365 (26.7) | 1.954 (36.4) | 4.674 (32.4) |
| Median (interquartile range) | 8.0 (5.9-10.7) | 7.6 (5.3-10.5) | 8.6 (6.2-11.3) | 8.2 (6.0-10.9) |
| **Subsequent iIBC** | | | | |
| No | 7.617 (97.4) | 1.162 (93.4) | 5.291 (98.5) | 14.070 (97.6) |
| yes | 202 (2.6) | 69 (6.6) | 78 (1.5) | 349 (2.4) |
| **Total** | 7.819 | 1.231 | 5.369 | 14.419 |

BCS, breast conserving surgery; RT, radiotherapy; MST, Mastectomy; n, number, iIBC ipsilateral invasive breast cancer.

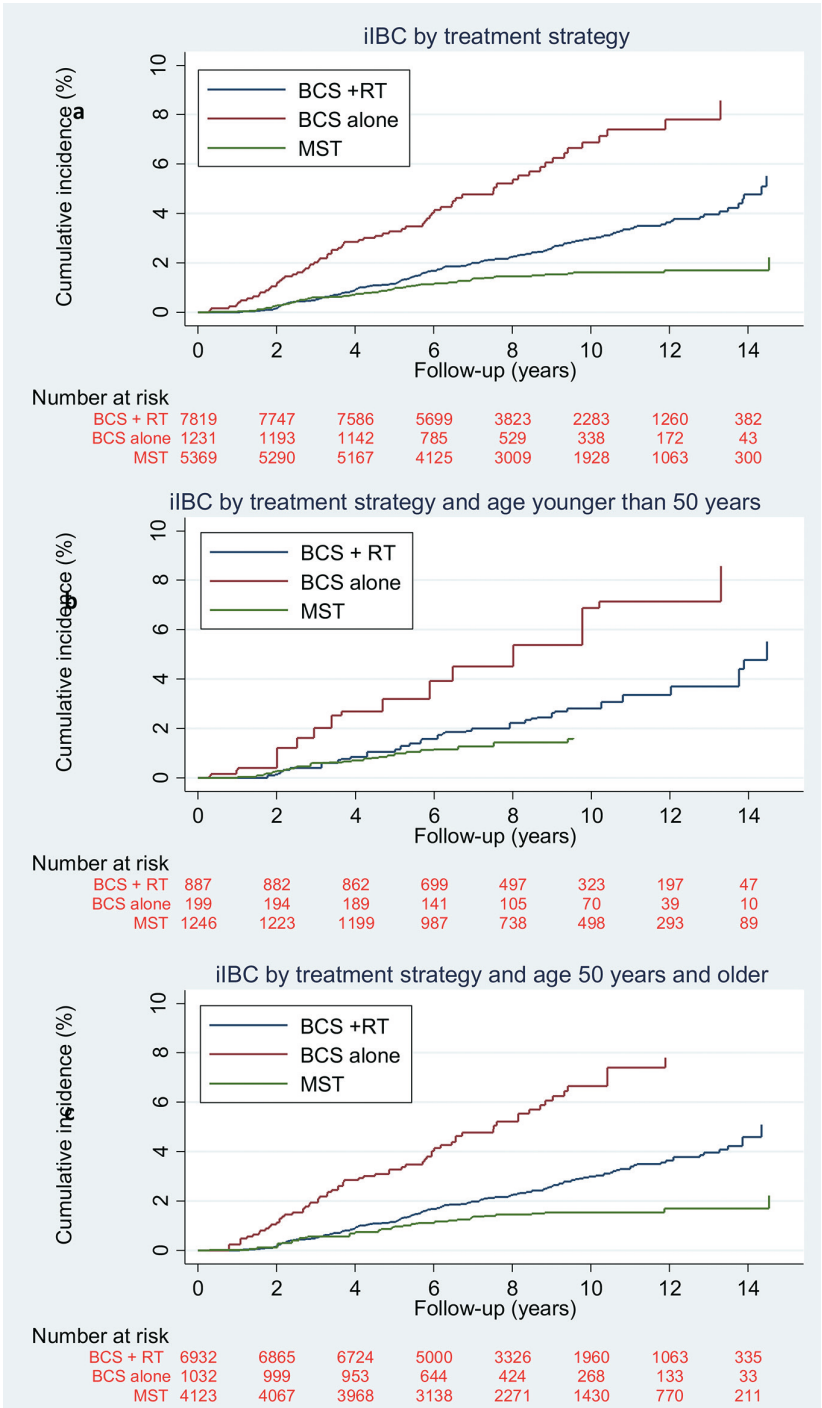


**Figure 2.** Cumulative incidence of iIBC by treatment strategy for:
a) all patients; b): patients <50 years; c) patients ≥ 50 years.

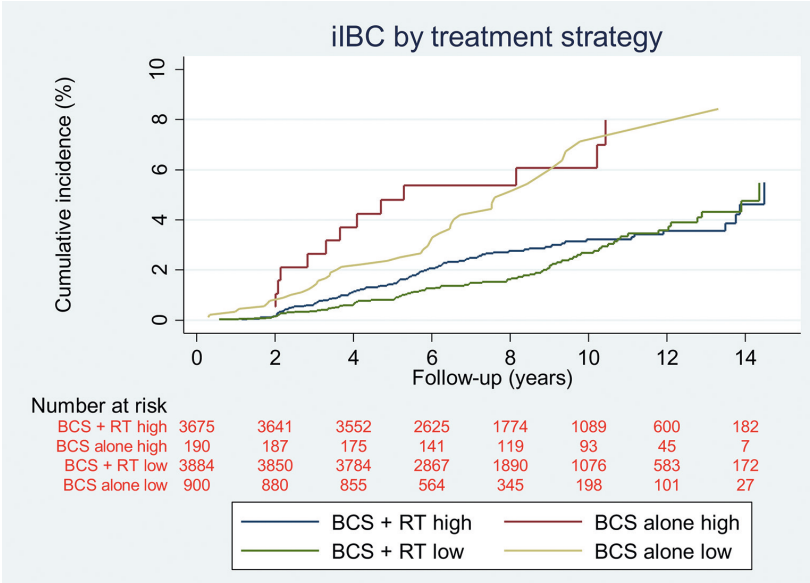


**Figure 3.** Cumulative incidences of iIBC in patients with high and low grade DCIS by treatment strategy.

Analysis showed that hazard rates for the association of treatment with iIBC risk was non proportional over time. Therefore, the final model included a cross product of treatment type and time. In the multivariable analysis, patients treated by BCS alone had a 2.80 (95% CI: 1.91-4.10) higher risk of developing iIBC compared to BCS+RT, whereas patients treated with MST had a HR of 0.70 (95% CI:0.50-0.99) for developing iIBC compared to BCS+RT within the first 5 years after primary treatment. After 5 years, the risk of iIBC remained 1.73 (95% CI: 1.15-2.61) times higher for BCS alone compared to BCS+RT whereas, for the MST treated patients, the hazard-ratio further decreased (HR 0.30; 95% CI: 0.20-0.40). There was no significant interaction of DCIS grade with treatment type and DCIS grade was no confounding factor in the association of treatment type with the risk of iIBC.

**Table 2.** Multivariable Cox regression analysis for iIBC in women treated for DCIS.

| Follow-up time (years) | Treatment | iIBCs number | HR (95% CI)* | p-value |
|---|---|---|---|---|
| 0-5 | BCS + RT | 89 | ref | |
| | BCS alone | 40 | 2.80 (1.91-4.10) | ‹0.001 |
| | MST | 52 | 0.70 (0.50-0.99) | 0.046 |
| ≥5 | BCS + RT | 113 | ref | |
| | BCS alone | 29 | 1.73 (1.15-2.61) | 0.008 |
| | MST | 26 | 0.30 (0.20-0.40) | ‹0.001 |

*[continued on next page]*

**Table 2.** *[continued]*

| Follow-up time (years) | Treatment | iIBCs number | HR (95% CI)* | p-value |
|---|---|---|---|---|
| **Per age group** | | | | |
| ‹50 years | | | | |
| 0-5 | BCS + RT | 14 | ref | |
| | BCS alone | 10 | 3.20 (1.41-7.18) | 0.005 |
| | MST | 32 | 1.40 (0.73-2.62) | 0.308 |
| ≥5 | BCS + RT | 24 | ref | |
| | BCS alone | 6 | 1.12 (0.50-2.80) | 0.799 |
| | MST | 8 | 0.20 (0.08-0.42) | ‹0.001 |
| ≥50 years | | | | |
| 0-5 | BCS + RT | 75 | ref | |
| | BCS alone | 30 | 2.80 (1.82-4.30) | ‹0.001 |
| | MST | 20 | 0.44 (0.30-0.73) | 0.002 |
| ≥5 | BCS + RT | 89 | ref | |
| | BCS alone | 23 | 1.94 (1.22-3.10) | 0.005 |
| | MST | 18 | 0.30 (0.20-0.50) | ‹0.001 |

*With age as primary time-scale, and treatment as time-varying variableiIBC, ipsilateral invasive breast cancer; HR, hazard ratio; CI, confidence interval; BCS, breast-conserving surgery; RT, radiotherapy; MST, mastectomy



# DISCUSSION

Here we show a low absolute risk for a subsequent iIBC at 10-year after a diagnosis and treatment of primary DCIS without invasive breast cancer. With a median time to iIBC of 4.8 years and median follow-up of 8.2 years from patients diagnosed with DCIS from 2005 through 2015, the cumulative incidences of subsequent iIBC are 3.1% after BCS+RT, 7.3% after BCS alone and 1.6% after MST. Although absolute risks of iIBC are low in patients treated for DCIS by either BCS and or BCS+RT, the risk remained higher for patients treated by BCS alone compared to patients treated with BCS+RT for at least 10 years after DCIS diagnosis. Compared to our previous study of van Seijen *et al.*[15], which included 10,045 primary DCIS patients diagnosed from 1989 through 2004 the current study reports lower absolute risks for iIBCs for the different treatment strategies for primary DCIS. Van Seijen *et al.* reported 10-year cumulative incidences of 5.2% after BCS+RT, 13.9% after BCS alone and 1.1% after MST with a median follow-up of 15.7 years after diagnosis. Comparing the 10 years cumulative incidences of our previous study to the current study, a reduced risk of approximately 50% for the different treatment strategies, with exception of the MST treated group, is demonstrated.

In addition, trends of decreasing hazard ratios over time in the current study were also seen, similar to those reported by van Seijen *et al.*[15]. The current study more accurately reflects the daily practice in managing DCIS nowadays, since patients included in this study were diagnosed from 2005 through 2015. Current practice comprises a fully implemented Dutch breast cancer screening program and the addition of RT in standard care for DCIS in case of BCS[21]. Luijten *et al*[22]*.,* demonstrated the patterns of treatment in DCIS patients over time since the introduction of breast cancer screening in the Dutch population. They showed that use of BCS increased from 47.7% in 1995–1996 to 72.7% in 2017–2018. Also, a sharp rise in the use of adjuvant radiotherapy in patients treated with BCS was observed, from 28.9% in 1995–1996 to almost 90% in 2011–2012, followed by a drop to 74.9% in 2017-2018. The addition of radiotherapy could be an explanation for the lower absolute risks for subsequent iIBC as 86.4% of the patients treated with BCS received adjuvant RT compared to just 49.6% of patients from our previous study[14]. The decline in risk of a subsequent breast event after a diagnosis of DCIS over time has been observed in two earlier studies as well[16,17]. Halasz *et al.* reported on 246 consecutive patients who underwent BCS and RT for DCIS from 2001 to 2007 and attributed the risk decline to improved resection margins and better detection in modern era mammography[17]. Subhedar *et al.* retrospectively reviewed a prospectively collected cohort of 2,996 DCIS patients treated with BCS between 1978 and 2010, with a median follow-up of 6.3 years, and observed similar declines in the risk of subsequent breast events with more recent years of DCIS diagnosis. They concluded that the decline in subsequent breast events after DCIS could only partially be explained by the increased proportion of screen-detected patients, more clear margins, and the increased use of RT[16]. In our study no information was available regarding resection margins, and since in the Netherlands patients do not receive adjuvant endocrine therapy, this was not a possible factor influencing risk of iIBC. Our study did not consider the non-invasive recurrences. Although they are clinically of less important, these lesions may have a severe impact on patient. Additionally, we investigated whether cumulative incidences in patients low-grade DCIS versus high-grade DCIS showed strong differences. However, these results showed only marginally and clinically non-significant differences (see figure 2 and 3).

This study has several strengths and limitations. A limitation of this study is the potential of confounding by indication, considering that women with less favorable characteristics more probably received more invasive treatment in terms of adjuvant radiotherapy which may have resulted in an underestimation of the difference in iIBC risk between BCS+RT and BCS alone. Furthermore, risk factors for developing iIBC such as primary lesion size and margin status could not be studied since information was not available. However, the magnitude of these risk factors associated with a subsequent iIBC after DCIS is still debated[23,24].

An important strength of this study is that the included population is reflective of the current management of DCIS since adjuvant RT was incorporated as standard care for DCIS, ensuring a homogeneous study population. Also, over the years, more detailed data have been registered by NCR and PALGA, enabling more complete datasets. For this study both the NCR- and PALGA-

data were scrutinized to identify primary DCIS patients, providing a true primary pure DCIS cohort. The nationwide NCR registers all primary DCIS patients in the Netherlands as of 2001 and includes both screen-detected and non-screen detected DCISs. Therefore, this dataset is unique with regard to its size and the robustness of the data due to the comprehensive registration of DCIS and IBC.

In conclusion, we report low absolute risks of iIBC after diagnosis of DCIS. These results are in line with more recently reported declining trends of a subsequent iIBC after DCIS. Possible explanations for this declining trend might be the more frequent use of adjuvant RT, an increased proportion of radical resection, and a higher proportion of screen-detected DCIS. The very low risk of an invasive recurrence observed in this study supports current efforts in active surveillance trials to determine whether it is safe to omit loco-regional treatment in patients with lower-grade (grade I/II) DCIS[25–27]. For high-grade DCIS the results of this study warrant a further exploration of omission of radiotherapy in selected patients.

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**Authors contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sena Alaeikhanehshir, Renee Schmitz and Maartje van Seijen. The first draft of the manuscript was written by Sena Alaeikhanehshir and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Data availability** The datasets generated and/or analyzed during the current study are not publicly available because consent was not obtained from study participants to make these data publicly available, but de-identified data are available from the corresponding author on reasonable request.

## Declarations

**Conflict of interest** The authors declare no conflict of interest

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** The study was approved by the review boards of the Netherlands Cancer Institute, Netherlands Cancer Registry and PALGA. The study used only unidentifiable patient information, and no informed consent was required.

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# CHAPTER 4

# Application of deep learning on mammographies to discriminate between low and high-risk DCIS for patient participation in active surveillance trials

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# ABSTRACT


### Background

Ductal Carcinoma In Situ (DCIS) can progress to invasive breast cancer, but most DCIS lesions never will. Therefore, four clinical trials (COMET, LORIS, LORETTA, AND LORD) test whether active surveillance for women with low-risk Ductal carcinoma In Situ is safe[1–4]. Low-risk is defined as grade I or II DCIS. Because DCIS grade is a major eligibility criteria in these trials, it would be very helpful to assess DCIS grade on mammography, informed by grade assessed on DCIS histopathology in pre-surgery biopsies, since surgery will not be performed on a significant number of patients participating in these trials.

### Objective

To assess the performance and clinical utility of a convolutional neural network (CNN) in discriminating high-risk (grade III) DCIS and/or Invasive Breast Cancer (IBC) from low-risk (grade I/II) DCIS based on mammographic features. We explored whether the CNN could be used as a decision support tool, from excluding high-risk patients for active surveillance.

### Methods

In this single centre retrospective study, 464 patients diagnosed with DCIS based on pre-surgery biopsy between 2000 and 2014 were included. The collection of mammography images was partitioned on a patient-level into two subsets, one for training containing 80% of cases (371 cases, 681 images) and 20% (93 cases, 173 images) for testing. A deep learning model based on the U-Net CNN was trained and validated on 681 two-dimensional mammograms. Classification performance was assessed with the Area Under the Curve (AUC) receiver operating characteristic and predictive values on the test set for predicting high risk DCIS-and high-risk DCIS and/ or IBC from low-risk DCIS.

### Results

When classifying DCIS as high-risk, the deep learning network achieved a Positive Predictive Value (PPV) of 0.40, Negative Predictive Value (NPV) of 0.91 and an AUC of 0.72 on the test dataset. For distinguishing high-risk and/or upstaged DCIS (occult invasive breast cancer) from low-risk DCIS a PPV of 0.80, a NPV of 0.84 and an AUC of 0.76 were achieved.

### Conclusion

For both scenarios (DCIS grade I/II vs III, DCIS grade I/II vs III and/or IBC) AUCs were high, 0.72 and 0.76, respectively, concluding that our convolutional neural network can discriminate low-grade from high-grade DCIS.


### Highlights

- Artificial intelligence could play a role in discriminating high- from low-risk DCIS
- The developed CNN could fairly discriminate high- from low-risk DCIS and/or IBC
- The NPV 0.84 may be clinically relevant for DCIS active surveillance trials

**Keywords**
DCIS, DCIS grade, Invasive breast cancer, Active surveillance, Artificial intelligence, Deep learning

**Key finding**

- An AUC of 0.72 was achieved on the test-set, with a PPV 40.3%, a NPV of 90.9%. In the upstaged scenario, thus low-risk DCIS versus high-risk DCIS and/or IBC, the AUC increased to 0.76 in the test set, with a PPV of 80.0% and NPV value of 83.9%.

**Importance**

- The CNN could be a supportive tool in combination with other clinicopathological factors, to personalize treatment in patients with DCIS.

# INTRODUCTION

At present, about 20% of all newly screen-detected 'breast cancers' are in fact Ductal Carcinoma In Situ (DCIS)[5,6]. DCIS is an intraductal proliferation of neoplastic cells with the absence of invasion into surrounding stromal breast tissue. Nonetheless, some DCIS lesions advance to invasive breast cancer (IBC) when left untreated[7–10]. Only a minority (~10%) of the DCIS lesions cause clinical symptoms (i.e. palpable mass, or bloody nipple discharge). The majority of DCIS is therefore detected on screening mammography, by the identification of associated calcifications (~90%)[11–14].



Since DCIS is considered to be a potential precursor of IBC, treatment of DCIS should prevent women from progression of DCIS to IBC. As a result, over the last decades, women with DCIS have been treated by breast-conserving surgery, often followed by radiotherapy, or even mastectomy, in some countries regularly supplemented with endocrine treatment. As the incidence of advanced stages of IBC has not decreased, however, the current therapeutic approach for screen-detected DCIS consists, at least partly, overtreatment[15,16].

Currently, four active surveillance trials (COMET, LORIS and LORD, LORETTA–trial)[1–4] are evaluating the safety of active surveillance for low-risk, defined as grade I or II DCIS and, for the LORD-trial, being estrogen receptor positive and HER2-negative as well. So, grade is an essential eligibility criterium for the active surveillance trial, as it is a strong predictor of prognosis[3,17,18], indicating the importance for appropriate differentiation in DCIS grade.

If these active surveillance trials indeed show that it is safe to leave low-risk DCIS in situ, it would be beneficial to determine the grade of DCIS based on mammography since histopathological diagnosis will be based on biopsy only in active surveillance patients. It may thus not properly document the heterogeneity within the lesion based on a limited tissue sample from the biopsy only, and may miss higher grade areas or invasive foci. However, radiologists have so far not been able to adequately predict occult invasive disease when DCIS presents as calcifications,

let alone determine the grade of eventual DCIS from the appearance of calcifications[19,20]. A recent study showed that radiologists were able to predict invasive disease when DCIS presents as calcifications better than chance, where accuracy increased particularly for smaller DCIS lesions (‹2 cm) and after exclusion of microinvasive disease[21]. However, this not consistent enough to rely on in daily clinical practice.

As there are clear indications that the shape and distribution of the calcifications are associated to the aggressiveness of the lesion[14,22,23] the inability of radiologists to distinguish between high- and low-risk DCIS may be due to the large inter-rater variability of both radiologists and pathologists[24–27]. For example, observers generally agree on the presence or absence of a mass or calcifications but disagree on calcification descriptors[24,28–32]. More importantly, calcification descriptors are associated with DCIS grade. However, large reader variability excists in reporting calcification descriptors, making it challanging for radiologists to report DCIS grade based on these calcification descriptors[19,20]. For instance, Roos et al. found that inear microcalcifications were significantly associated with high grade DCIS, while presence of fine granular calcifications was more often associated with lower grade[20].

Available Computer-Aided Detection (CADe) and Computer-Aided Diagnosis (CADx) algorithms were developed to support radiologists in assessment of mammograms. Several studies have been performed using CADe and CADx for calcification segmentation and detection on mammography[33–36], mainly to prevent overlook errors of radiologists. Other studies using CADe/CADx more specifically evaluated DCIS[37–39], focusing on segmentation of calcifications and prediction of occult invasive disease with DCIS[40].

Image analysis enhanced with artificial intelligence can be categorized into two approaches which transform imaging information into mineable data[41,42]. Both approaches have the same underlying concept of identifying and encoding simple patterns and many higher-order patterns of imaging features that are not visible with the naked eye. These features can be extracted from biomedical images (i.e. mammography) and be linked with clinical variables of interest (i.e. patient characteristics, clinical outcomes, tumor grade and tumor stage), enabling improved decision support[41,42]. Generally, CAD systems use handcrafted features coupled with imaging features extracted with machine learning, to identify a phenotypical fingerprint. On the contrary, a CNN, which is a deep learning method, based on a complex network, inspired by the human brain architecture, is able to learn high-level features automatically from obtained images such as mammographies[43,44]. Predicting tumor grade by utilizing a CNN on biomedical images have been studied earlier. For example, a study evaluated the diagnostic performance of a CNN for bladder cancer grading. The CNN was able to predict tumor grade based on tumor color, and achieved an accuracy of 94.1% to distinguish between low-grade and high-grade tumor using white light images[45]. In addition, another study predicting grade using a CNN, achieved accuracy of 90% in classifying meningioma grades based on MRI images[46].

In pursuit of reducing overtreatment of DCIS patients, the current study aims to identify a series of systematic differences in imaging characteristics by utilizing a CNN, and to investigate whether the CNN was able to separate high-risk from low-risk DCIS, and to improve the discrimination of DCIS with and without invasive components. To bridge the gap between daily clinical practice and risk of overtreatment of DCIS, a CNN might be a substantial support to clinicians. Therefore, we explored whether the CNN could be used as a decision support tool in order to facilitate active surveillance in patients with biopsy proven DCIS eligible for active surveillance trials.

# METHODS AND MATERIALS

## Patient selection

The current study population consists of women, aged 18 years or older, diagnosed with DCIS between 2000 and 2014 whose initial biopsy was performed at the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital or who were referred to the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital for a second opinion. Patients were eligible if pure DCIS was diagnosed on initial biopsy (vacuum 9G or core-needle biopsy 14G, the cases in this study have been collected over a long span of time and historical cases with 14G sampling have been included), and the pre-biopsy digital mammogram (Full-Field Digital Mammography, FFDM) was available, both screen and non-screen detected patients were included. Patients were excluded if lobular carcinoma in situ was reported, or when there was suspicion for, or evidence of, IBC on pre-surgery biopsy, or when there was a visible mass or architectural distortion on mammography. In this dataset all patients underwent definitive surgery. According to the Dutch guidelines patients with DCIS do not receive neoadjuvant hormone therapy or chemotherapy. Initially 606 DCIS patients were identified. A total of 142 patients were excluded for the following reasons: mammography not available (n=111), insufficient quality

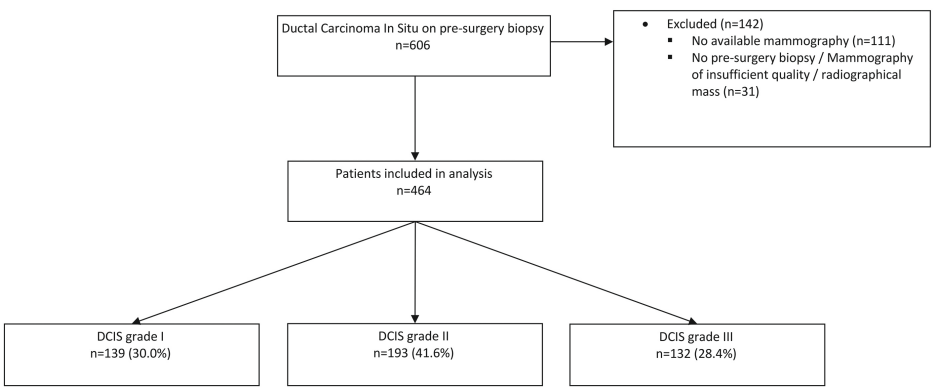


**Figure 1.** Flow-chart patient inclusion. DCIS, Ductal Carcinoma in Situ. Included patients were those diagnosed with DCIS between 2000 and 2014 whose initial biopsy was performed at the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital or who were referred to the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital for a second opinion.

of the obtained mammography and/or presence of radiological mass (n=31). Ultrasound is routinely used to identify disease suspicious for invasion / solid high-risk DCIS, considering that patients with a mass were excluded, no data regarding ultrasound was collected. After exclusion, 464 patients were eligible and included in this study, representing 854 unique images (392 Mediolateral-Oblique (MLO)and 386 CranioCaudal (CC) view, 76 other; i.e. true lateral views (ML and LM views), exaggerated craniocaudal views (XCCL), rolled lateral (RL), tangential (TAN) and lesion localization (LL) views). Magnification views were not included for analysis (figure 1).

## Data pre-processing and augmentation

Clinical information including patient age, localization, lesion size, and grade of primary DCIS lesion were extracted from the electronic patient record. Biopsies showing DCIS were selected through the Netherlands nationwide registry of histology and cytopathology records (PALGA)[47] and through the regional tumor registry at the Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital (NKI–AVL). These pre-surgical biopsies were either performed at NKI–AVL or were taken at another hospital and sent for routine second opinion to NKI–AVL. Information regarding localization, including approximate site, was used to manually annotate the calcified regions on the mammograms. In case of multiple groups of calcifications, the whole area was annotated. However, in case of multiple separate calcifications clusters, the cluster that was described in the radiology report as the biopsied area was annotated. In case of extensive calcifications the whole area was annotated. All calcified regions were manually annotated by two trained readers on the full image (SA: MD, MM: Technical Medicine researcher), supervised by a dedicated breast radiologist (RM) using 3D Slicer, version 4.10.2. Mammographies were split on a patient level and calcified regions were annotated once by one of the two trained readers, the two readers did consult each other if needed. Training and test sets were split randomly and stratified for grade. Study approval was granted by the IRB of our institute, 19.050/IRBd19016.

The histopathological report after surgical resection was considered the ground truth and accordingly patients were separated in pure low-risk DCIS (grade I/II) and grade III DCIS and/or invasive disease groups.

Before feeding images into the neural network, several augmentation operations were applied. Each image had one of the DICOM lookup tables provided by the vendor randomly applied and was subsequently linearly rescaled to the range [0, 1]. Subsequently, the images were cropped to a shape of 1024x1024 around the center of the lesion which was randomly perturbed by at most 150 pixels in both directions. Other data augmentations were a random horizontal flip (p=50%), a random gamma transform with gamma parameter between 0.95 and 1.05, and finally, Gaussian additive noise was applied with a magnitude which was at most 5% of the pixel intensity value.

## Network architecture

A novel fully convolutional neural network (fCNN) was designed to combine both segmentation of the lesion and image-level classification. The proposed network is based on the well-known U-Net architecture, first described by Ronneberger[48], which is an encoder-decoder architecture. In addition, we attached an extra convolutional branch at the bottleneck to perform classification into grade I/II or grade III DCIS /invasive breast cancer. The U-Net part of the complete network is of depth five, where each block in the encoder path consists out of a block containing convolutions, followed by a rectified linear unit (ReLU) and a max pooling operation for downsampling. During upsampling in the decoder pathway of the network, the max pooling operations were replaced by bilinear interpolation operations. The downsampling and upsampling pathways shared information using skip-connections by combining the low-level yet high-resolution features from the encoder pathway with the location information of the decoder pathway to compute global information and provide the network with the ability to compute high-resolution segmentation masks. The final segmentation output is generated resulting from a set of three final convolution operations see figure 2.

The classification branch of the network is constructed to classify the original input image as low-risk or high-risk DCIS. Connected at the final layer of the encoder, the classification branch consists of a single convolution followed by a double convolutional block and a final output convolutional layer. The classification of the input image is provided by a softmax function[49].



The final loss was the sum (equally balanced) of the segmentation and classification loss. The total loss consisted of the sum of the focal loss function for the image classification, and a top-k cross entropy to compute the loss of the segmentation branch. The difference between a normal cross-entropy loss and the top-k cross entropy loss is that only for the top-k worst classified pixels the loss is computed and backpropagated.

To train the network we used the Adam optimizer with a starting learning rate of 0.00025, where each 150 iterations, the learning rate was decreased by a factor of 0.5. We have selected the batch size to maximize the GPU memory usage and have adapted the learning rate accordingly' For our hardware this led to a batch size of 16.

The collection of mammography images was partitioned on a patient-level into two subsets, one for training containing 80% of cases (371 cases, 681 images) and the remaining 20% (93 cases, 173 images) for testing. The training subset was further divided into five folds, each fold containing a random selection of 80% of the patients for training and the other 20% for validation, see figure 3. The final prediction was the average of the combined MLO and CC view output probabilities of the same patient.

## Statistical analysis

To evaluate the performance of the network in segmenting and classifying the image, we used the dice similarity coefficient (DICE) and the area under the receiver operator characteristic

(AUROC)[50], respectively. Given an input image, the network produces a probability to which different discrimination thresholds were applied in order to predict class membership, reflected in the ROC curve. The clinical translation of the AUC values are as follows; a higher AUC value corresponds with a greater accuracy in predicting high-risk (grade III) DCIS. In the scenario where upstaging to invasive disease was evaluated by the CNN, a higher AUC value translated a greater accuracy in predicting high-risk (grade III) DCIS, and/or the presence of invasive disease. The final surgical specimen was the leading diagnosis as incorporated in the CNN model. In addition, positive predictive value (PPV) and negative predictive value (NPV) were calculated as secondary performance metrics to assess the performance of the classifier. Positive indicated DCIS that was upgraded to higher (III) grade DCIS and / or upstaged to invasive cancer at the time of surgery. Negative corresponded to pure DCIS without upstaging or upgrading to higher grade DCIS. It was assumed that from a likelihood of 0.5 for high-grade and/or invasive disease watchful waiting would be deemed too dangerous, hence NPV and PPV were calculated using this threshold. To this end we trained and tested the network to evaluate whether it was able to classify DCIS grade, in order to explore whether it is feasible that the network could be applied as an decision support tool next to classical histopathological assessment of DCIS grade. Training and testing of the network was performed on a NVIDIA Tesla T4 GPU (Nvidia Corporation, Santa Clara, California, United States). The deep learning network was implemented using Pytorch 1.5 and Python 3.7.

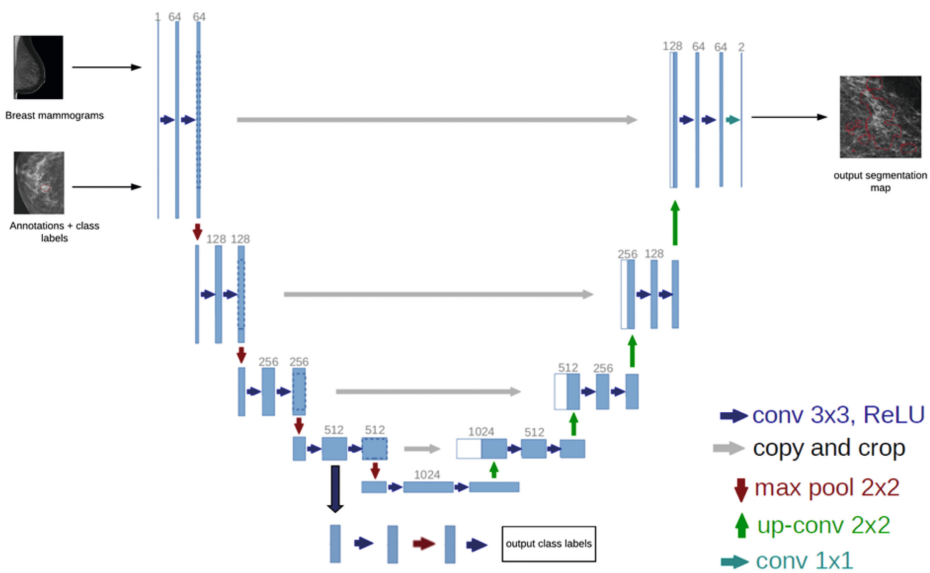


**Figure 2.** U-Net architecture with the segmentation and classification branches. Using mammography images as input, the segmentation branch is used to for segmentation of calcifications, whilst the classification branch is used to distinguish low-risk from high-risk DCIS.

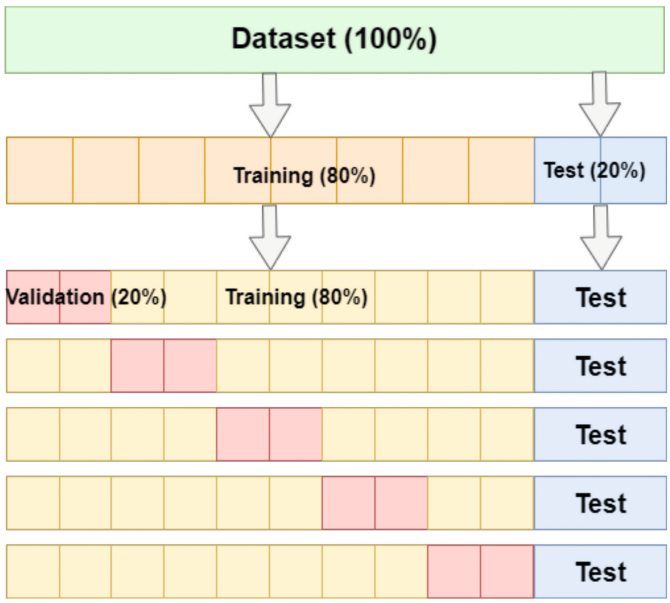


**Figure 3.** Overview of data partitioning.



# RESULTS

The median age of the included patients was 54 years (interquartile range 49-62) and approximately half (51.9%) of the patients were post-menopausal at diagnosis. Furthermore, over half (53.9%) of the DCIS lesions were detected during population screening. Mean lesion size was 29.8 mm, and approximately 70% of the patients had a low-risk DCIS lesion (grade I/II). Among those for whom information was available 225 (48.5%) patients were diagnosed using a 9G vacuum-assisted biopsy and 92 (19.8%) using a 14G core-needle biopsy, for 147 (31.7%) patients the method of biopsy that was used was unknown. A total of 47 (14.2%) patients were upgraded to an higher grade DCIS based on the final surgical excision specimen. Seventeen (36.2%) patients with grade I DCIS on biopsy were grade II DCIS on surgical resection specimen, two (4.3%) patients with grade I DCIS on biopsy had grade III DCIS on resection specimen and 28 (59.5%) patients had initially grade II DCIS on biopsy but grade III DCIS on final excised specimen. When sub classifying according to low and high-risk DCIS, 30 (63.8%) patients who had a primary diagnosis of low-risk (grade I/II) DCIS, were upgraded to high-risk DCIS upon examination of final surgical excision specimen. Additionally, 68 (14.7%) patients were upstaged, meaning that these patients harbored occult invasive disease, initially not diagnosed on pre-surgical biopsy, but determined on final surgical specimen. Of these 68 upstaged patients, 46 (67.6%) patients were initially diagnosed as low-risk (grade I/II) DCIS, whereas 22 (32.4%) patients who were upstaged, had an initial diagnosis of high-risk (grade III) DCIS. Table 1 shows patient and tumor characteristics.

**Table 1.** Patient and tumor characteristics (n =464).

| **Age at diagnosis** | **n (%)** |
|---|---|
| 20-49 | 146 (31.5) |
| 50-59 | 186 (40.1) |
| 50-69 | 96 (20.7 |
| 70+ | 36 (7.8) |
| Median (interquartile range) | 54 (49-62) |
| **Menopausal status** | |
| Pre-menopausal | 121 (26.1) |
| Peri-menopausal | 40 (8.6) |
| Post-menopausal | 241 (51.9) |
| Unknown | 62 (13.4) |
| **Method of detection** | |
| Screen-detected | 250 (53.9) |
| Symptomatic | 53 (11.4) |
| Unknown[a] | 161 (34.7) |
| **Lesion size (mammography, mm)** | |
| 0-19 | 158 (34.1) |
| 20-50 | 109 (23.5) |
| ≥50 | 79 (17.0) |
| unknown | 118 (25.4) |
| Mean (± standard deviation) | 29.8 (25.2) |
| **Grade (based on surgical specimen)** | |
| I | 139 (30.0) |
| II | 193 (41.6) |
| III | 132 (28.4) |
| **Upstage to IBC** | |
| Yes | 68 (14.7) |
| No | 396 (85.3) |

a) Including 110 diagnosed during follow-up for a previously treated breast lesion and 51 referred for routine second opinion.

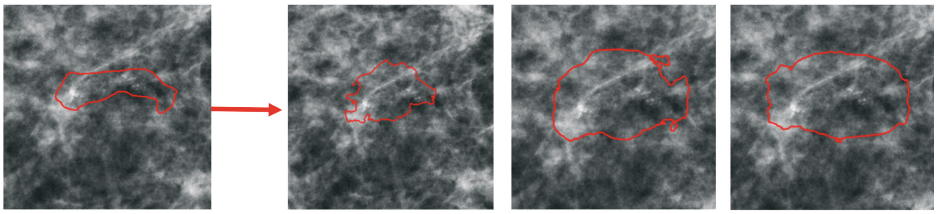


**Figure 4.** Improvement of calcification segmentation for different eppochs: Demonstratinghow the segmentation performance by the network improved during training, figure 3a gives an example of a ground-truth annotation that was used to train the network. A clear improvement in segmentation performance can be seen in figure 3b-3d, where in the beginning stages of training (figure 3b), the network did not include all calcifications. However, a more extensive and smoothly coverage of the calcifications can been seen as the data is further processed, figure 3c and 3d.

The 464 included patients yielded 854 mammograms which were used for our CNN algorithm. The network was trained using five folds for 500 epochs each. In the pure DCIS cases (thus excluding the upstaged cancers) where we aimed to discriminate low-risk DCIS from high risk, there were 93 cases in the test set. Overall, an AUC of 0.72 was achieved on the test-set, corresponding with a positive predictive value 40.3%, a negative predictive value of 90.9%. In the upstaged scenario, thus low-risk DCIS versus high-risk DCIS and/or IBC, the AUC increased to 0.76 in the test set. In this scenario a positive predictive value of 80.0% and a negative predictive value of 83.9% were determined. See figure 5 for ROC curve and AUC classification.



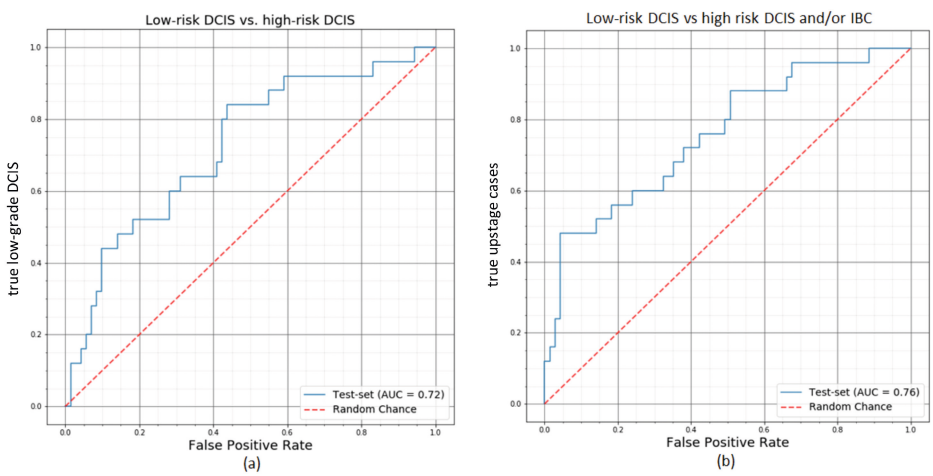


**Figure 5.** Test-set, ROC curve AUC.
(a) Classification of low-risk (grade I/II) vs high-risk (grade III) DCIS
(b) Classification of low-risk (grade I/II) vs high-risk (grade III) DCIS and/or IBC

# DISCUSSION

This study demonstrated that it is feasible to discriminate high- from low-risk DCIS, by applying a deep learning network on pre-surgical mammographies showing only calcifications. After external validation, the network could be applied as an extra decision support tool in patients opting for participation in the active surveillance trials. Thus, offering further refining of clinical decision making and treatment planning, together with the classical histopathological assessment of DCIS grade.

For network optimization, the network was first trained as a stand-alone U-Net architecture for the image segmentation task only. During optimization, the network parameters were tuned to maximize dice scores estimated on the validation set. With the best performing parameters, the classification branch was added to train the network for the classification task. This classification task achieved an AUC of 0.72 on the test-set, which excluded the upstaged cases. Positive predictive value was 40.3% and negative predictive value was 90.9%. In the clinically more realistic scenario where the upstaged cases were included the AUC was even higher, at 0.76, with a positive predictive value of 80.0% and a negative predictive value of 83.9% based on the used cut-off. Our results show that the network could discriminate high-grade from low-grade DCIS. More importantly the demonstrated NPVs are clinically relevant considering the relative low risk of including a high-risk DCIS patient for active surveillance.

Previous studies investigating mammographic image data to predict the presence of occult invasive breast disease next to the presence of DCIS demonstrated good performances[39,40,51,52]. In one study where deep features were extracted from digital mammograms using deep convolutional network, pre-trained on non-medical images, to predict the presence of occult invasive disease in patient with DCIS, an AUC of 0.70 (95% CI, 0.68-0.73) was achieved, which is comparable with the current study [51]. However, the main aim of the current study was to develop a CNN that is also able to differentiate low-risk (grade I/II) DCIS from high-risk (grade III) DCIS and invasive disease. The demonstrated negative predictive values of 90.9 and 83.9% are promising in guiding patients who are opting for active surveillance. The network could be applied as an extra safety measure before inclusion in active surveillance trials, where it can be utilized for definitive grading of DCIS. The most likely clinical scenario for our classifier is the scenario where upstaging is possible, as we would apply it on pre-surgical mammograms, where occult invasive disease could be present.

This study has several limitations and strengths. First, the main aim of this study has been the successful classification of calcifications on mammograms. Major inclusion criteria for the active surveillance trials is that the DCIS is detected by screening, in this cohort screen-detected status could be confirmed in only 54%. However, an additional 51 patients were referred to our hospital for a routine second opinion and while the majority of these patients likely also had screen-detected DCIS, we cannot exclude other means of detection. Thereby, the distribution of DCIS grade in the current study is different compared to an earlier study[53]

performed by our research group. Meaning that the current study is less reflective of a true screen-detected cohort of DCIS patients. Another limitation is that the manual calcification labeling was not performed by radiologists, but by trained researchers. Although intensively supervised by a dedicated breast radiologist, this might have affected the quality of labeling. Nevertheless, as the segmentation is merely meant as a proxy task for the classification, the impact of an non-perfect segmentation model is minor. In practice, a significant inter-rater variability is also seen when radiologists perform this task[24]. Also, we did not perform a risk-benefit analysis to demonstrate the performance of the CNN compared to traditional biopsies for DCIS grade assessment or upstage rate. However, to facilitate active surveillance for DCIS patients, we explored the feasibility of the CNN as an extra safety measurement in addition to the classical histopathological assessment of DCIS grade and upstage rate. Therefore, we believe that the clinical application of our CNN could only be applied after external validation and ideally with a risk-benefit analysis comparing the accuracy of the CNN with biopsies. A strength of this study is, that to our knowledge this is one of the largest datasets available to address the specific research question of identifying and classifying the grade of DCIS based on image features alone. However, this remains a relatively small data set with almost half the cases entered twice (CC and MLO). Furthermore, our CNN incorporated the segmentation and the classification in one neural network. Thereby we demonstrated high AUC of 0.72 for DCIS low-risk versus high-risk, and even a higher AUC of 0.76 for low-risk versus high risk DCIS and/or IBC.



## Conclusion

In conclusion our AUC for both models were high and we conclude that our CNN is a good discriminator of high- and low-grade DCIS. Furthermore, by adding the occult IBC to the CNN, we achieved even a higher AUC of 0.76, which is clinically relevant considering the shift in treatment strategy for low-risk DCIS. Following confirmation of the CNN in another independent dataset it could be a supportive tool in combination with other clinicopathological factors to offer personalized treatment in patients with DCIS.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| DCIS | ductal carcinoma in situ |
| CNN | convolutional neural network |
| IBC | invasive breast cancer |
| AUC | area under the curve |
| PPV | positive predictive value |
| NPV | negative predictive value |
| CADe | computer-aided detection |
| CADx | computer-aided diagnosis |
| FFDM | full-field digital mammography |
| MLO | mediolateral-oblique |
| CC | craniocaudal |
| ML | mediolateral |
| LM | lateralmedial |
| XXCL | exaggerated craniocaudal views |
| RL | rolled lateral |
| TAN | tangential |
| LL | lesion localization |
| PALGA | pathologisch-anatomisch landelijk geautomatiseerd archief |
| NKI–AVL | Netherlands Cancer Institute—Antoni van Leeuwenhoek |
| DICOM | digital imaging and communications in medicine |
| IRB | institutional review board |
| fCNN | fully convolutional neural network |
| ReLU | rectified linear unit |
| AUROC | area under the receiver operator characteristic |
| DSC | dice similarity coefficient |

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**Authors contribution**

SA participated in the design of the work, acquisition of the mammographies, writing the manuscript, labeling the ROI, interpretation of the results. MV contributed in the design of the work, writing, and labeling of the ROI, and performing the statistical analysis, and interpretation of the results. FvD contributed to the design of the work, interpretation of the results, and writing the manuscript. EL contributed to the design of the work, acquisition of the mammographies, interpretation of the results, and writing the manuscript. EG contributed to the acquisition of the mammographies and writing the manuscript. MvO participated in writing the manuscript. JL participated in writing the manuscript. SH participated in writing

the manuscript. JW participated in design of the work, interpretation of the results and writing the manuscript. RM participated the design of the manuscript, data acquisition, supervision in labeling the ROI, data interpretation and writing the manuscript. JT participated the design of the work, data acquisition, design of the CNN, performing the statistical analysis, data interpretation and writing the manuscript and supervising the first author.

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**Availability of data and materials**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
The study was approved by the Institutional Review Board of our center

**Consent for publication**
Not applicable

**Declaration of Competing Interest**
The author declare no competing interest

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# CHAPTER 5

# Loco-regional breast cancer recurrence in the EORTC 10041/BIG 03-04 MINDACT trial: analysis of risk factors including the 70-gene signature

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# ABSTRACT

**Purpose**

A number of studies are currently investigating de-escalation of radiation therapy in patients with a low-risk of in-breast relapses on the basis of clinicopathological factors and molecular tests. We evaluated whether 70-gene risk score is associated with risk of loco-regional recurrence (LRR), and estimated 8-year cumulative incidences for LRR in patients with early-stage breast cancer treated with breast conservation.

**Patients and Methods**

In this exploratory sub-study of EORTC 10041/BIG 03-04 MINDACT trial, we evaluated women with a known clinical and genomic 70-gene risk score test result and who had breast conserving surgery. The main endpoint was LRR at 8 years, estimated by cumulative incidences. Distant metastasis and death were considered competing risks.

**Results**

Among 6,693 enrolled patients, 5,470 (81.7%) underwent breast-conserving surgery, of whom 98% received radiotherapy. At 8 years follow-up, 189 patients experienced a loco-regional recurrence, resulting in an 8-year cumulative incidence of 3.2% (95% CI: 2.7-3.7). In patients with a low-risk 70-gene signature, 8-year loco-regional recurrence incidence was 2.7% (95% CI: 2.1-3.3). In univariable analysis, adjusted for chemotherapy, 5 out of 12 variables were associated with loco-regional recurrence, including the 70-gene signature. In multivariable modeling, adjuvant endocrine therapy and to a lesser extent tumor size and grade remained significantly associated with loco-regional recurrence.

**Conclusion**

This exploratory analysis of the MINDACT trial estimated an 8-year low loco-regional recurrence-rate of 3.2% after breast-conserving surgery. The 70-gene signature was not independently predictive of local-regional recurrence perhaps due to the low number of events observed, and can not currently be used in clinical decision making regarding locoregional recurrence. The overall low number of events does provide opportunity to design trials towards de-escalation of local therapy.

**Keywords**

Early-stage breast cancer, Loco-regional recurrence, 70-gene signature

**Key Objective**

Low-risk tumor biology may help to guide local treatment. We assessed local and regional recurrence outcomes in patients with early-stage breast cancer treated with breast conservation with a low-risk 70-gene signature in the prospective MINDACT trial.

**Knowledge Generated**

The overall cumulative incidence of local recurrences was 2.3% (95%CI: 1.9-2.8) and was the lowest in the clinical-low and genomic-low population with an incidence of 2.0% (95%CI: 1.4-2.6%) at 8 years. 70-gene signature was not independently predictive of local-regional recurrence perhaps due to the low number of events.

**Relevance**

The low local recurrence rates reported in our study support emerging efforts towards de-escalation of local therapy.

# INTRODUCTION

Over the last few decades, a substantial reduction is observed in the rate of loco-regional recurrence (LRR) in breast cancer as a result of the evolution of systemic therapies and optimized local treatment. Future improvements in breast cancer care should also address the large number of patients exposed to potential overtreatment for whom less intensive local treatment is achievable. Patients with early-stage breast cancer often receive adjuvant therapy such as endocrine treatment, chemotherapy and radiotherapy, to reduce the risk of recurrence and increase survival[1]. To assess the risk for recurrence and distant metastasis, clinicopathological factors such as tumor size, grade, number of involved lymph nodes, hormone receptor, HER2 receptor status, and patient characteristics (e.g. age, menopausal status) are considered[2–4]. Online tools such as Adjuvant Online[5], now discontinued, and PREDICT PLUS[6] incorporate these factors to estimate the risk of recurrence or breast-cancer related death and indicate the potential benefit of adjuvant systemic therapies.



Several clinical trials address overtreatment in different areas of breast cancer diagnostics and therapeutics and explore opportunities to de-escalate treatment. Prognostic gene assays, including the 70-gene signature (MammaPrint®, Agendia, Amsterdam, The Netherlands) and the 21-gene recurrence score (OncotypeDX®, Exact Sciences, Madison, WI, USA), were developed to determine in which early-stage breast cancer patients adjuvant chemotherapy may be omitted without compromising survival[7,8]. These prognostic signatures were tested in prospective trials, MINDACT, TailorX and RxPonder respectively, and confirmed their ability to predict the risk of 5 and 10-year distant breast cancer recurrence[9–14]. The MINDACT trial has demonstrated the ability to identify patients with high risk clinicopathological risk factors and a 70-gene genomic low-risk profile in whom chemotherapy could be safely omitted, as these patients had a 5-year distant disease-free survival of 95.1% (95%CI: 93.1-96.6) without chemotherapy at 8.7 years trial median follow-up[10]. The 70-gene signature thus enables de-escalation of chemotherapy therapy in appropriately selected early-stage breast cancer patients.

Previous studies have reported an association between local and distant disease recurrence[15–17]. Furthermore, a retrospective study evaluating 1053 patients demonstrated that patients with

a low-risk 70-gene signature score had a significantly lower risk of LRR compared to patients with a high-risk 70-gene signature score[18].

The primary objective of the current study was to assess the value of 70-gene signature as a prognostic factor for LRR as first relapse after breast-conserving surgery (BCS) for early-stage breast cancer patients included in the MINDACT trial. The secondary objective was to estimate the 8-year cumulative incidence of LRR in these patients. To this end, we conducted an exploratory analysis using the large prospective database of the MINDACT trial and selected those patients who were treated with BCS. Finally, we aimed at identifying consistent and reliable prognostic factors for LRR. These factors could be used in selecting patients for de-escalation of locoregional treatment in prospective studies.

# METHODS

## Patient selection

The population in this study includes all patients from the EORTC 10041/BIG 03-04 MINDACT trial who received breast conserving surgery[9,10]. Briefly, from 2007 through 2011, 6693 women with early-stage breast cancer, with complete surgical excision of the primary tumor (tumor-free margins were required) and a determined genomic risk (using the 70-gene signature), and clinical risk (using a modified version of Adjuvant! Online; i.e., Supplemental Table S1,[10]) were enrolled in MINDACT. Patients were between 18 and 70 years of age and had histologically confirmed early-stage breast cancer (stage T1 or T2 and operable T3) with 0-3 tumor positive lymph node(s). The majority of patients (71%) were treated with sentinel lymph node biopsy as an indicator of the modern series of patients included. After surgery, patients with concordant clinical and genomic high risk were to receive adjuvant chemotherapy, and endocrine therapy if hormone receptor positive. Patients with concordant low-risk cancers were to receive endocrine therapy, or no systemic treatment. Patients with discordant risk (i.e. either genomic high- and clinical low-risk, or genomic low- and clinical high-risk) were randomized to use their clinical or genomic risk to guide treatment. Beyond surgery, loco-regional treatments, including radiation therapy, followed local guidelines. After MINDACT enrollment some patients had a change in genomic risk or clinical risk, and for this study the corrected risk status was applied[10]. The median follow-up time of all patients was 8.7 years, as calculated using the reverse Kaplan-Meier method. For further details see supplementary Figure 1. Ethics committees at participating centers approved the protocol and all participating patients provided written informed consent.

## Statistical Analyses

This research has been performed in the subset of patients who were treated with breast conserving surgery (BCS).

Time to loco-regional recurrence (time to LRR) was calculated as the time until the first event (local or regional relapse whichever comes first). Secondary, we estimated incidences of

local recurrences (LR) (in breast recurrence) and regional recurrences (RR) (lymph nodes recurrences, without in breast recurrence) separately. Time to LR was calculated as the time until the first in-breast event, and time to regional recurrence (RR) as the time until the first regional event. Contralateral breast cancer and secondary cancers were not considered as LRR/LR/RR. Patients who experienced distant metastasis prior to local or regional relapse or death were analyzed as having a competing risk at the time of distant metastasis or death. For the RR endpoint, local recurrences were considered as a competing risk as well as regional recurrences for the LR endpoint, respectively. Patients who were alive without an event of LRR, LR, or RR nor competing risk of distant metastasis were censored at the date of the last disease assessment.

Risk of LRR, LR, RR were estimated based on the 8-year estimated cumulative incidence and its 95% confidence interval using the cumulative incidence function method accounting for competing risks. Prognostic factors of LRR were analyzed using Fine and Gray method accounting for competing risks in the subset of patients who received radiotherapy and who had no missing data on any covariate (5245 patients (98.0%) had no missing data on any covariates considered for the uni and multivariable model). The covariates of age at diagnosis, tumor size (log-transformation), genomic risk (70-gene signature), lymph node status, tumor grade, histological type, receptor status (ER, PgR, HER2), and adjuvant therapies (chemotherapy, endocrine therapy, trastuzumab) were included in the multivariable analysis to identify prognostic factors for LRR after BCS, see supplementary table 1. In this analysis we chose to include the individual components of the clinical score, ER, HER2, grade, nodal status and tumor size, rather than the resulting clinical risk in a binary form (low/high), as these clinical variables are also individually known as important prognostic factors in breast cancer. We evaluated the 70-gene signature as two categories, genomic high and genomic low, and in addition in three categories; ultralow-, low-not-ultralow-, and high-risk. Tumors were classified into 70-gene signature risk categories, on the basis of an index score ranging from –1 to 1; an index score equal to or ‹ 0 is classified as high risk and an index score › 0 is classified as low risk. For this study, a third category with an index score of › 0.355 classified as ultralow risk was explored regarding LRR[19,20]. By design, evaluation of prognostic factors were confounded by chemotherapy administration because key prognostic factors were used to decide on chemotherapy administration. Therefore, chemotherapy was included in all models in an attempt to adjust for its effect. Margin status was not assessed since in the MINDACT study, free margin status was required for inclusion, with the notable exception of deep (i.e. at pectoral muscle fascia) positive margins which were allowed if all other margins were negative and radiotherapy was administered. Multicollinearity between covariates was explored with utility of a widely accepted method of Variance Inflation Factors (VIF)[21]. Based on a VIF threshold of 10, breast cancer receptor subtypes were removed from consideration, and then all remaining VIF values were below 10. From a full multivariable Fine and Gray model including all covariates, a backward selection procedure was applied to retain only those covariates significant at the 5% level in the final multivariable model. Several sensitivity analyses were performed to assess the robustness of the main model.

For secondary objectives, 8-year cumulative incidence of LRR was estimated by clinical and genomic risk groups categories: c-low/g-low (cL/gL), c-low/g-high (cL/gH), c-high/g-low (cH/gL), c-high/g-high (cH/gH). Also, the analyses were done on different subgroups based on age (≤50 / › 50 years old), pathological tumor size (≤1cm/›1-2 cm/›2-3 cm/›3 cm), pathological nodal status (LN0, 1 positive LN, ›1 positive LN), histological type (ductal / lobular / mixed (ductolobular) / other), breast cancer subtype based on local lab pathology results (ER+ and/or PgR+, HER2- / ER+ and/or PgR+, HER2+/ ER-, PgR-, HER2+/ Triple negative). All statistical analyses were performed using SAS version 9.4. A statistical analysis plan was developed prior to conducting the analysis.

# RESULTS

## Patient and tumor characteristics

Among the initial 6,693 enrolled MINDACT patients, 5,470 (81.7%) had received breast conserving surgery and were included in the current study. Patient, tumor and treatment characteristics are listed in table 1. The majority (69%) of patients were over 50 years of age. In 4,172 patients (76.3%) tumor size was less than 2 cm, 4,406 (80.5%) patients had lymph node negative disease, and 4,453 (81.4%) had hormone receptor positive / HER2 negative disease. Most lesions (95.9%) were unifocal. Resection margins were clear in all patients but five (0.1%). Nearly, all patients (n=5,353) received adjuvant radiotherapy (97.8%). Furthermore, 2,174 (39.7%) patients received adjuvant chemotherapy, 4,232 (77.4%) patients received endocrine treatment, and a minority of 312 (5.7%) patients received trastuzumab, 509 (9.3%) patients received no adjuvant systemic treatment (neither chemotherapy nor endocrine therapy nor trastuzumab). By clinical risk assessment, 2,931 (53.6%) patients had a low clinical risk, and 2,538 (46.4%) had a high clinical risk. Low 70-gene signature genomic risk was shown in 3,578 (65.4%) patients (of whom 848 (15.5%) had an ultralow 70-gene signature risk) and 1,891 (34.6%) had a high 70-gene signature genomic risk.

## Risk for recurrence in breast and regional lymph nodes

At a median of 8.7 years follow-up, 189 out of 5,470 patients experienced a LRR, consisting of local recurrence in 115 patients, regional recurrence in 51 patients and concomitant local and regional recurrence in 23 patients. Distant metastasis or death without LRR was reported in 403 patients and 18 patients were diagnosed with distant metastasis before LRR, see table 2. An 8-year cumulative incidence of 3.2% (95% CI: 2.7-3.7) for LRR was observed among all patients, see table 3. For LR (in breast relapse only), the 8-year cumulative incidence was 2.3% (95% CI: 1.9-2.9), and 1.2% (95%CI: 1.0-1.6) for the regional recurrences, further details see supplementary tables 2 and 3.

When analyzed by combined clinical and genomic risk, 8-year incidence of LRR was highest in patients with clinical and genomic high-risk, at 4.4% (95% CI: 3.4-5.6) (table 3). The lowest 8-year incidence of 2.5% (95% CI: 1.9-3.3) was seen in patients with a clinical and genomic

low-risk. In patients with discordant risks, the incidence was 2.9% (95% CI: 2.0-4.1) in the clinical high-risk / genomic low-risk group, and 3.6% (95% CI: 2.1-5.6) in the clinical low-risk / genomic high-risk patients.

Among 5353 patients who received adjuvant radiotherapy, 5245 (98.0%) had no missing data on any covariates and were included in the uni- and multivariable models. 70-gene signature, grade, ER/PR status, and adjuvant endocrine treatment were significantly associated with risk of LRR in univariable analyses, see table 4. A high 70-gene signature risk score was associated with increased risk of LRR (HR 1.77 (95% CI: 1.23-2.55)) with an incidence of 4.2% (95% CI: 3.3-5.2) at 8 years, in the 70-gene signature low-risk group, 8-year LRR incidence was 2.7% (95% CI: 2.1-3.3), similarly, clinical low-risk 8-year LRR incidence was 2.7% (95% CI: 2.1-3.4) (table 3). Of note, genomic testing identifies 647 (10.9%) more patients as low-risk.

Tumor grade was also significantly associated with poorer local control in the univariable analysis, as poorly differentiated tumors had a two-fold increased risk for LRR as compared to well-differentiated tumors (HR 2.01 (95% CI: 1.25, 3.24)). A positive estrogen receptor status was associated with a two-third risk reduction (HR 0.41 (95% CI: 0.28-0.60)). A positive progesterone receptor reduced the risk for LRR to a lesser extent (HR 0.63 (95% CI: 0.46-0.86)) (table 4).

For patients aged 50 years or younger, the 8-year incidence of LRR was 4.0% (95% CI: 3.1-5.1), and for patients older than 50 years an 8-year incidence of 2.8% (95% CI: 2.3-3.4) was found (table 3), this difference was not significant in univariable analysis. Larger tumor size was associated with a higher 8-year incidence of LRR, 4.3% (95% CI: 2.0-7.9) for tumors larger than 3 cm, and the lowest incidence was seen for tumors ≤1 cm (2.8% (95% CI: 1.8-4.2)), albeit the association was non-significant in univariable analysis (HR 1.40 (95% CI: 0.94-2.07)).



Complete patient and tumor characteristics by outcome, and an overview of cumulative incidences by all included covariates are described in supplementary tables 4 and 5.

In the final multivariable model, tumor size (HR 1.58 (95%CI: 1.06-2.35)), and grade (HR 1.89 (95%CI: 1.14-3.13), grade 3 vs. grade 1) were significantly associated with LRR, together with adjuvant endocrine therapy (HR 0.42 (95%CI: 0.30-0.59), and adjuvant chemotherapy (HR 0.60 (0.41-0.89)) (Table 4). In a sensitivity analysis not including endocrine therapy and adjuvant trastuzumab as covariates but all other variables as previously described, ER status was the only variable remaining significant in the final model.

Additionally, we explored the impact on the hazard ratios and the 8-year cumulative incidences for the 70-gene signature by evaluating the risk score in three categories; ultralow-, low-not-ultralow-, and high-risk. The 8-year cumulative incidence for LRR in the ultralow-risk group was 2.3% (95% CI: 1.4-3.6). In the low-not-ultralow-risk group the incidence was 2.8% (95% CI: 2.2-3.5), and 4.2% (95% CI: 3.3-5.2) in the genomic high-risk group. When considering the 70- gene signature in three categories, a significant association (HR 1.82 (95%CI: 1.08-3.07)

P=0.010) for the 70-gene signature has been observed in univariable modeling but no longer in the full multivariable model (HR 1.38 (95%CI: 0.74-2.58) P=0.370).

# DISCUSSION

In this exploratory analysis derived from the prospective MINDACT trial population with over 5000 patients who had breast conserving therapy, a low overall 8-year cumulative incidence for local and regional recurrence of 3.2% was observed, of whom genomic low-risk 70-gene signature had a LRR incidence of 2.7%, and ultra-low 70-gene signature group even a lower incidence of 2.3%. Currently used known clinical factors (T1,N0, ER+) are also able to identify LRR low-risk, a similar 8-year cumulative incidence of 2.7%. However, genomic testing identifies 647 (10.9%) more patients as LRR low-risk. The 70-gene risk score, in an univariable analysis, was significantly associated with LRR. However, in multivariable analysis adjuvant endocrine therapy, adjuvant chemotherapy, grade and tumor size remained significant, whereas the genomic risk score was no longer significantly associated with the risk of LRR. Our observation is similar to the findings of two earlier studies performed by *Mamounas et al.,* on the NSABP B-14 / NSABP B-20 and the NSABP B-28 trial, albeit the 21-gene signature retained significance in the multivariable model for LRR [22,23]. However, in this analysis, the 21-gene signature was used as continuous variable and the hazard ratio was calculated using patients with an increment of 50 units difference in recurrence score (i.e., only including the lowest and highest recurrence score groups). This is different from how the 70-gene signature was evaluated in our multivariable model where we used the clinical test result, low-risk versus high-risk as applied in the clinic, which influences the modeling in particular at the low incidence rates of LRR as seen in our patients. A study investigating the association of the 21-gene signature and its prognostic value for LRR in a smaller population however showed no association[24]. Furthermore, Fitzal et al published a similar retrospective study on archival tissue blocks available from 1204 of the 3901 accrued patients in the ABCSG-8 trial, were the PAM 50 46-gene assay showed to be an independent prognostic factor for local recurrence[25]. However, regional recurrences were not assessed. For this analysis authors used a new PAM 50 Risk Of Recurrence (ROR) cut-off of 57, different from that used for predicting distant disease[25] (i.e., the cut-off was adjusted). These were all retrospective studies, as was the study by *Drukker et al.* which found an independent association of the 70-gene signature results with local recurrence risk[18].

Young age, hormone receptor status, lymph node status, tumor size, grade but also genetic factors are known risk factors for loco-regional recurrence[26–30]. We observed in this study concordance of clinical and genomic risks in over two-thirds of patients which may have resulted in the fact that the effect size of the 70-gene signature on LRR was mitigated by patient and tumor characteristics. However, in clinically high-risk patients with a discordant low-risk result of the 70-gene signature, the LRR incidence was 2.9% versus 4.4% in the concordant clinical and 70-gene signature high-risk patients. Additionally, in the concordant clinical and 70-gene signature low-risk patients LRR rate reduces to 2.5%. When further explored in clinical

trials designed to investigate locoregional management of patients treated with BCS, these prognostic gene signatures could be integrated with clinical parameters to evaluate their contribution to LRR prediction.

When interpreting these results, one should appreciate that the 70-gene signature was developed to compare gene expression by RNA microarray and identify tumors with a higher or lower chance of developing distant metastasis, not LRR[7]. It could well be that the process of regrowth of cancer within the stroma of the breast may differ from the process of hematogenous spread of breast cancer cells to distant organs[31]. This difference in underlying biology, together with the high genomic/clinical concordance and the effect of tumor size and grade in ER+ cancers on prognosis could explain why the 70-gene signature was not significantly associated with LRR in multivariable analysis.

Our study has several strengths and limitations. The prospective data collection in the MINDACT trial from many different participating European sites safeguards high quality data and a heterogeneous representative group of European patients. Gene signature assessment was performed prospectively and centrally in all patients. To our knowledge, this is the largest breast cancer cohort where LRR was assessed using gene expression data. As data were available for all patients and prospectively collected, bias due to retrospective analysis on archival material of a selection of patients is not present in this study. A limitation of this study is that the original MINDACT trial was not designed for this specific research question and in addition, since almost all patients (97.8%) received radiation therapy after breast conserving surgery, we could not study the role of omitting radiotherapy. In addition, information on boost irradiation, more often given to younger patients was not available, which may explain why age was not a prognostic factor in our analysis. A substantial proportion of the included population also received endocrine therapy (77.4%) and/or chemotherapy (39.7%) which influences the rate of relapse and distant metastasis[10,32], however, analyses were adjusted for the chemotherapy effect. Other variables that may influence local recurrence like the presence of ductal carcinoma in situ, lymphovascular invasion, or type of axillary surgery were not included here and may have influenced the rate of LRR. The overall incidence of LRR was low with 3.2% (95%CI: 2.7-3.7) at 8 years. This low LRR rate makes all uni- and multivariable modeling less robust, where small differences in event rates per category, or definition of categorization, may impact the estimates in univariable and multivariable analyses.



When considering only local recurrences, the 8-year cumulative incidence was 2.3% (95%CI: 1.9-2.8), and was 2.0% (95%CI: 1.4-2.6) restricted to the clinical-low and genomic-low population.

The 70-gene signature was not independently prognostic of local- regional recurrence perhaps due to the low number of events observed, and can not currently be used in clinical decision making regarding locoregional recurrence. The overall low number of events does provides opportunity to design trials towards de-escalation of local therapy.

This finding supports exploring options to de-escalate local treatment. Potential candidates for radiation de-escalation might be older patients with smaller and lower grade tumors and low risk genomic tests. A number of studies are currently investigating this de-escalation approach, including omitting radiation therapy in patients with a low-risk of in breast relapses on the basis of clinicopathological factors and multigene arrays[33–38].

The low loco-regional recurrence and local recurrence rates reported in our study supports the emerging efforts towards de-escalation of local therapy.

**Table 1.** Patient, tumor and treatment characteristics of patients who received breast conserving surgery.

| | **Breast conserving surgery (n=5470)** |
|---|---|
| **Age** | |
| ≤50 years | 1697 (31.0) |
| ›50 years | 3773 (69.0) |
| **Pathological tumor size (main lesion)** | |
| ‹= 1 cm | 822 (15.0) |
| ›1-2cm | 3350 (61.2) |
| ›2-3 cm | 1095 (20.0) |
| ›3 cm | 203 (3.7) |
| Missing | 0 (0.0) |
| **Lymph node status (ITC considered as N0)** | |
| pN0 | 4406 (80.5) |
| 1 positive LN | 726 (13.3) |
| ›1 positive LN | 338 (6.2) |
| Missing | 0 (0.0) |
| **Immunohistochemical subtype** | |
| ER+ and/or PgR+, HER2- | 4453 (81.4) |
| ER+ and/or PgR+, HER2+ | 371 (6.8) |
| ER-, PgR-, HER2+ | 99 (1.8) |
| ER-, PgR-, HER2- | 538 (9.8) |
| Missing | 9 (0.2) |

*[continued on next page]*

**Table 1.** *[continued]*

| | Breast conserving surgery (n=5470) |
|---|---|
| **Tumor histology** | |
| ductal | 4628 (84.6) |
| lobular | 510 (9.3) |
| Other + mixed | 326 (6.0) |
| Missing | 6 (0.1) |
| **Histological grade** | |
| well differentiated | 1248 (22.8) |
| moderately differentiated | 2693 (49.2) |
| poorly differentiated or undifferentiated | 2693 (49.2) |
| Missing | 16 (0.3) |
| **Clear surgical margins** | |
| No | 5 (0.1) |
| Yes | 5465 (99.9) |
| **Multifocality** | |
| No | 5244 (95.9) |
| Yes | 210 (3.8) |
| Missing | 16 (0.3) |
| **Clinical Risk** | |
| Low risk | 2931 (53.6) |
| High risk | 2538 (46.4) |
| Missing[a] | 1 (0.0) |
| **Genomic risk** | |
| Low risk | 3578 (65.4) |
| High risk | 1891 (34.6) |
| Missing[a] | 1 (0.0) |
| **Risk** | |
| cL/gL | 2437 (44.6) |
| cL/gH | 495 (9.0) |
| cH/gL | 1142 (20.9) |
| cH/gH | 1396 (25.5) |

*[continued on next page]*

**Table 1.** *[continued]*

| | Breast conserving surgery (n=5470) |
|---|---|
| **Radiotherapy received** | |
| No[b] | 47 (0.9) |
| Yes | 5353 (97.8) |
| Missing | 70 (1.3) |
| **Adjuvant chemo received** | |
| No | 3269 (59.8) |
| Yes | 2174 (39.7) |
| Missing | 27 (0.5) |
| If Yes, Chemo type | |
| anthracycline (R-C) | 505 (23.2) |
| docetaxel + capecitabine (R-C) | 499 (23.0) |
| **non-randomized ACT** | 1170 (53.8) |
| **Adjuvant endocrine therapy received** | |
| No | 1142 (20.9) |
| Yes | 4233 (77.4) |
| Missing | 95 (1.7) |
| **Adjuvant trastuzumab received** | |
| No | 5067 (92.6) |
| Yes | 312 (5.7) |
| Missing | 91 (1.7) |

ITC: isolated tumor cells; pNmi: was considered as positive lymph node, ER: estrogen receptor expression; PgR: progesterone receptor expression; chemo: chemotherapy; R-C: patients were randomized between anthracylin-based and docetaxel-capecitabine regimen; ACT: adjuvant chemotherapy32 ()
a One patient has an unknown genomic risk because the wrong sample was analyzed at enrollment. This case will be classified as in the main analysis as cL/gL
b Patients not receiving radiotherapy are not included in the analysis of prognostic factors

**Table 2.** Type of recurrence and competing events.

| Type of loco-regional recurrence | Events (N) |
|---|---|
| **Loco-regional** | **189** (3.4%) |
| Local | 115 (2.1%) |
| Regional | 51 (0.9%) |
| Concomitant local and regional recurrence | 23 (0.4%) |
| **Competing risks** | **421** (7.7%) |
| Death or distant metastasis without prior locoregional recurrence | 403 (7.4%) |
| Distant metastasis occurred before locoregional recurrence | 18 (0.3%) |

**Table 3.** Estimated 8-year cumulative incidence of loco-regional recurrence.

| | N | Number of Events | Cumulative Incidence | 95% Confidence Interval |
|---|---|---|---|---|
| **Overall BCS population** | 5470 | 189 | 3.2% | (2.7-3.7) |
| **Genomic risk** | | | | |
| Low risk | 3578 | 105 | 2.7% | (2.1-3.3) |
| High risk | 1891 | 84 | 4.2% | (3.3-5.2) |
| **Clinical risk** | | | | |
| Low risk | 2931 | 90 | 2.7% | (2.1-3.4) |
| High risk | 2538 | 99 | 3.7% | (3.0-4.5) |
| **Clinical and genomic risk** | | | | |
| cL/gL | 2437 | 71 | 2.5% | (1.9-3.3) |
| cL/gH | 495 | 19 | 3.6% | (2.1-5.6) |
| cH/gL | 1142 | 34 | 2.9% | (2.0-4.1) |
| cH/gH | 1396 | 65 | 4.4% | (3.4-5.6) |
| **Age** | | | | |
| <= 50 years | 1697 | 68 | 4.0% | (3.1-5.1) |
| >50 years | 3773 | 121 | 2.8% | (2.3-3.4) |
| **Tumor size** | | | | |
| <=1 cm | 822 | 24 | 2.8% | (1.8-4.2) |
| >1-2cm | 3350 | 112 | 3.0% | (2.4-3.7) |
| >2-3 cm | 1095 | 44 | 3.8% | (2.7-5.1) |
| >3 cm | 203 | 9 | 4.3% | (2.0-7.9) |

**Table 4.** Univariable and multivariable analysis.

| | Descriptive analysis (N=5245)[a] | | | Univariable Fine and Gray model[b] | | Full multivariable Fine and Gray model | | Final multivariable Fine and Gray model (after backward selection) | |
|---|---|---|---|---|---|---|---|---|---|
| Covariate | No event/ No competing risk (N=4664) | Event (N=178) | Competing risk (N=403) | HR (95%CI) | p-value | HR (95%CI) | p-value | HR (95%CI) | p-value |
| **Adjuvant endocrine therapy** | | | | | | | | | |
| No | 923 (84.4) | 65 (5.9) | 106 (9.7) | **1.00** | **<.0001** | **1.00** | **<0.001** | **1.00** | **<0.0001** |
| Yes | 3741 (90.1) | 113 (2.7) | 297 (7.2) | **0.44 (0.33-0.59)** | | **0.40 (0.24-0.64)** | | **0.42 (0.30-0.59)** | |
| **Adjuvant chemotherapy** | | | | | | | | | |
| No | 2813 (89.9) | 104 (3.3) | 212 (6.8) | 1.00 | 0.760 | **1.00** | **0.004** | **1.00** | **0.011** |
| Yes | 1851 (87.5) | 74 (3.5) | 191 (9.0) | 1.05 (0.78-1.41) | | **0.50 (0.32-0.81)** | | **0.60 (0.41-0.89)** | |
| **Tumor size (cm)[c]** | | | | | | | | | |
| Median | 1.5 | 1.7 | 1.8 | 1.40 (0.94-2.07) | 0.095 | **1.57 (1.05- 2.33)** | **0.028** | **1.58 (1.06- 2.35)** | **0.023** |
| Q1-Q3 | 1.2 - 2.0 | 1.3 - 2.1 | 1.4 - 2.3 | | | | | | |
| **Tumor grade[d]** | | | | | | | | | |
| 1 | 1093 (91.2) | 34 (2.8) | 72 (6.0) | **1.00** | **0.003** | 1.00 | 0.122 | **1.00** | **0.044** |
| 2 | 2328 (89.8) | 77 (3.0) | 188 (7.3) | **1.12 (0.74-1.69)** | | 1.32 (0.85-2.05) | | **1.32 (0.86-2.02)** | |
| 3 | 1243 (85.5) | 67 (4.6) | 143 (9.8) | **2.01 (1.25-3.24)** | | 1.82 (1.03-3.22) | | **1.89 (1.14-3.13)** | |
| **Genomic risk** | | | | | | | | | |
| Low risk | 3111 (90.7) | 102 (3.0) | 216 (6.3) | **1.00** | **0.002** | 1.00 | 0.162 | | |
| High risk | 1553 (85.5) | 76 (4.2) | 187 (10.3) | **1.77 (1.23-2.55)** | | 1.41 (0.87-2.28) | | | |

*[continued on next page]*

**Table 4.** *[continued]*

| | Descriptive analysis (N=5245)[a] | | | Univariable Fine and Gray model[b] | | Full multivariable Fine and Gray model | | Final multivariable Fine and Gray model (after backward selection) | |
|---|---|---|---|---|---|---|---|---|---|
| Covariate | No event/ No competing risk (N=4664) | Event (N=178) | Competing risk (N=403) | HR (95%CI) | p-value | HR (95%CI) | p-value | HR (95%CI) | p-value |
| **Age at diagnosis** | | | | | | | | | |
| <= 50 years | 1447 (89.4) | 63 (3.9) | 109 (6.7) | 1.00 | 0.202 | 1.00 | 0.305 | | |
| > 50 years | 3217 (88.7) | 115 (3.2) | 294 (8.1) | 0.81 (0.59-1.12) | | 0.84 (0.61-1.17)] | | | |
| **Adjuvant trastuzumab** | | | | | | | | | |
| No | 4382 (88.8) | 170 (3.4) | 384 (7.8) | 1.00 | 0.300 | 1.00 | 0.537 | | |
| Yes | 282 (91.3) | 8 (2.6) | 19 (6.1) | 0.68 (0.32-1.42) | | 0.69 (0.22-2.21) | | | |
| **Nodal status** | | | | | | | | | |
| LN0 | 3778 (89.5) | 145 (3.4) | 299 (7.1) | 1.00 | 0.850 | 1.00 | 0.487 | | |
| 1 positive LN | 618 (88.2) | 21 (3.0) | 62 (8.8) | 0.95 (0.59-1.51) | | 1.17 (0.73-1.89) | | | |
| >1 positive LN | 268 (83.2) | 12 (3.7) | 42 (13.0) | 1.16 (0.64-2.11) | | 1.41 (0.76-2.61) | | | |
| **PgR status**[d] | | | | | | | | | |
| negative | 1035 (85.3) | 56 (4.6) | 122 (10.1) | **1.00** | **0.004** | 1.00 | 0.686 | | |
| positive | 3629 (90.0) | 122 (3.0) | 281 (7.0) | **0.63 (0.46, 0.86)** | | 1.11(0.67-1.86) | | | |

*[continued on next page]*

**Table 4.** *[continued]*

| | Descriptive analysis (N=5245)[a] | | | Univariable Fine and Gray model[b] | | Full multivariable Fine and Gray model | | Final multivariable Fine and Gray model (after backward selection) | |
|---|---|---|---|---|---|---|---|---|---|
| **Covariate** | **No event/ No competing risk (N=4664)** | **Event (N=178)** | **Competing risk (N=403)** | **HR (95%CI)** | **p-value** | **HR (95%CI)** | **p-value** | **HR (95%CI)** | **p-value** |
| **Histological type**[d] | | | | | | | | | |
| ductal | 3938 (88.6) | 157 (3.5) | 350 (7.9) | 1.00 | 0.440 | 1.00 | 0.673 | | |
| lobular | 448 (90.9) | 13 (2.6) | 32 (6.5) | 0.74 (0.42-1.29) | | 0.85 (0.48-1.50) | | | |
| Other | 278 (90.6) | 8 (2.6) | 21 (6.8) | 0.76 (0.37-1.54) | | 0.77 (0.38-1.57) | | | |
| **ER status**[d] | | | | | | | | | |
| negative | 550 (84.1) | 40 (6.1) | 64 (9.8) | **1.00** | **<.0001** | 1.00 | 0.822 | | |
| positive | 4114 (89.6) | 138 (3.0) | 339 (7.4) | **0.41 (0.28-0. 60)** | | 1.09 (0.53, 2.24) | | | |
| **HER2 status**[d] | | | | | | | | | |
| negative | 4262 (88.8) | 165 (3.4) | 374 (7.8) | 1.00 | 0.440 | 1.00 | 0.907 | | |
| positive | 402 (90.5) | 13 (2.9) | 29 (6.5) | 0.80 (0.44-1.42) | | 0.95 (0.38-2.37) | | | |

a: Analysis population: Patients who underwent breast conserving surgery and received radiotherapy, and had no missing data on covariates (n = 5245)a: Row percentages are shown
b: Univariable analysis adjusted for adjuvant chemotherapy
c: Tumor size considered using its log-transformation in Fine and Gray models
d: Based on local assessments

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Travel, Accommodations, *Expenses*: Pfizer, AstraZeneca, Roche

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Therapeutics, G1 Therapeutics, Menarini, Seattle Genetics, Camel-IDS, Immunomedics, Oncolytics, Radius Health
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The other authors declare no disclosures or conflict of interest.

**Trial registration**

ClinicalTrials.gov, NCT00433589, and the European Clinical Trials database, EudraCT2005–002625–31

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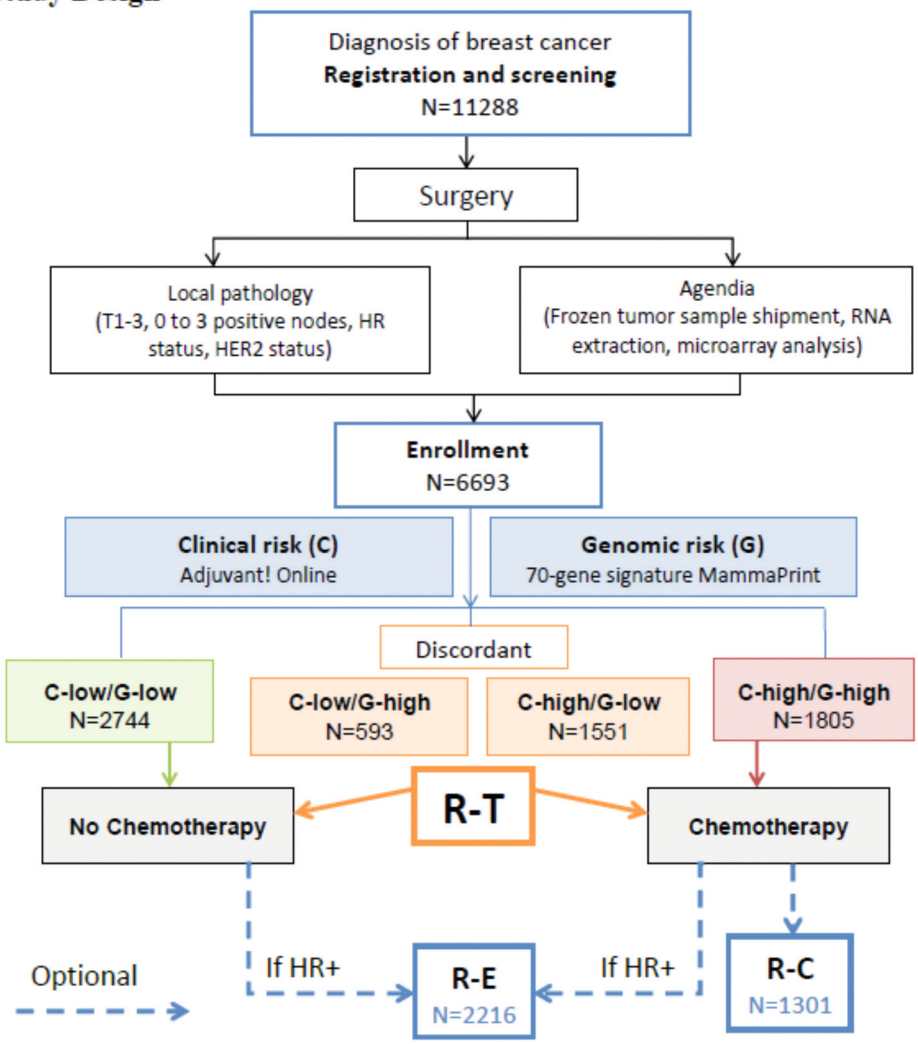
# SUPPLEMENTARY FILES

**Study Design**




Note that patient numbers for the risk groups correspond to the numbers in the corrected risk groups.

**Figure 1.** (MINDACT study design) Files

**Supplementary Table 1.** Included covariates for multivariate analysis.

| Covariate | Initial considerations |
|---|---|
| Age at diagnosis (years) | reference: ≤50 years/ age › 50 |
| Tumor size (cm) | Log-transformation |
| Genomic risk | Reference: low / high |
| Nodal status | Reference: N0 / 1 positive LN / ›1 Positive LN |
| Histological type | reference: ductal / lobular / other + mixed ductolobular |
| Tumor grade | reference: well differentiated/ moderately differentiated/ poorly differentiated or undifferentiated |
| ER status | reference: negative, positive |
| PgR status | reference: negative, positive |
| HER2 status | reference: negative, positive |
| BC subtype | reference: Luminal HER2- / Luminal HER2+ / HER2+ (non-luminal) / Triple negative) |
| Adjuvant chemotherapy | reference: no / yes |
| Adjuvant trastuzumab | reference: no / yes |

**Supplementary table 2.** Estimated 8-year cumulative incidence of local recurrence.

| | N | Number of Events | Cumulative Incidence | 95% Confidence Interval |
|---|---|---|---|---|
| **Overall BCS population** | 5470 | 138 | 2.3 | (1.9-2.8) |
| **Genomic risk** | | | | |
| Low risk | 3578 | 78 | 2.0% | (1.5-2.5) |
| High risk | 1891 | 60 | 3.0% | (2.3-3.9) |
| **Clinical risk** | | | | |
| Low risk | 2931 | 65 | 2.0% | (1.5-2.6) |
| High risk | 2538 | 73 | 2.7% | (2.1-3.4) |
| **Clinical and genomic risk** | | | | |
| cL/gL | 2437 | 54 | 2.0% | (1.4-2.6) |
| cL/gH | 495 | 11 | 2.3% | (1.2-4.0) |
| cH/gL | 1142 | 24 | 1.9% | (1.2-2.9) |
| cH/gH | 1396 | 49 | 3.3% | (2.4-4.4) |

**Supplementary table 3.** Estimated 8-year cumulative incidence of regional recurrence.

| | N | Number of Events | Cumulative Incidence | 95% Confidence Interval |
|---|---|---|---|---|
| **Overall BCS population** | 5470 | 74 | 1.2% | (1.0-1.6) |
| **Genomic risk** | | | | |
| Low risk | 3578 | 38 | 1.0% | (0.7-1.4) |
| High risk | 1891 | 36 | 1.8% | (1.2-2.5) |
| **Clinical risk** | | | | |
| Low risk | 2931 | 32 | 0.9% | (0.6-1.3) |
| High risk | 2538 | 42 | 1.6% | (1.2-2.2) |
| **Clinical and genomic risk** | | | | |
| cL/gL | 2437 | 23 | 0.8% | (0.5-1.2) |
| cL/gH | 495 | 9 | 1.6% | (0.7-3.1) |
| cH/gL | 1142 | 15 | 1.4% | (0.8-2.2) |
| cH/gH | 1396 | 27 | 1.8% | (1.2-2.7) |

**Supplementary Table 4.** Patient & Tumor characteristics by outcome – Breast-conserving surgery.

| | Loco-regional recurrence (competing risk) | | | |
|---|---|---|---|---|
| | **No event/No competingrisk (N=4860)** | **Event (N=189)** | **Competing risk (N=421)** | **Total (N=5470)** |
| **Age** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| ‹= 50 years | 1518 (31.2) | 68 (36.0) | 111 (26.4) | 3773 (69.0) |
| › 50 years | 3342 (68.8) | 121 (64.0) | 310 (73.6) | |
| **Age** | | | | |
| ‹= 40 years | 258 (5.3) | 13 (6.9) | 22 (5.2) | 293 (5.4) |
| ›40-50 years | 1260 (25.9) | 55 (29.1) | 89 (21.1) | 1404 (25.7) |
| ›50-70 years | 3305 (68.0) | 119 (63.0) | 300 (71.3) | 3724 (68.1) |
| › 70 years | 37 (0.8) | 2 (1.1) | 10 (2.4) | 49 (0.9) |
| Median | 55.4 | 53.8 | 57.1 | 55.5 |
| Range | 23.4 - 71.0 | 28.4 - 70.9 | 32.8 - 70.8 | 23.4 - 71.0 |
| Q1-Q3 | 48.2 - 62.4 | 45.2 - 61.0 | 49.2 - 63.7 | 48.1 - 62.4 |
| Mean (SD) | 54.9 (9.0) | 53.2 (9.6) | 56.0 (9.1) | 55.0 (9.0) |
| **Pathological tumor size (cm)** | | | | |
| ‹= 1 cm | 755 (15.5) | 24 (12.7) | 43 (10.2) | 822 (15.0) |
| ›1-2cm | 3006 (61.9) | 112 (59.3) | 232 (55.1) | 3350 (61.2) |
| ›2-3 cm | 931 (19.2) | 44 (23.3) | 120 (28.5) | 1095 (20.0) |
| ›3 cm | 168 (3.5) | 9 (4.8) | 26 (6.2) | 203 (3.7) |
| Median | 1.5 | 1.7 | 1.8 | 1.5 |
| Range | 0.2 - 12.0 | 0.4 - 5.5 | 0.3 - 5.0 | 0.2 - 12.0 |
| Q1-Q3 | 1.2 - 2.0 | 1.3 - 2.1 | 1.4 - 2.3 | 1.2 - 2.0 |
| Mean (SD) | 1.7 (0.7) | 1.8 (0.8) | 1.9 (0.7) | 1.7 (0.7) |

*[continued on next page]*

**Supplementary Table 4.** *[continued]*

| | Loco-regional recurrence (competing risk) | | | |
|---|---|---|---|---|
| | **No event/No competingrisk (N=4860)** | **Event (N=189)** | **Competing risk (N=421)** | **Total (N=5470)** |
| **Lymph node status** | | | | |
| LN0 | 3938 (81.0) | 154 (81.5) | 314 (74.6) | 4406 (80.5) |
| 1 positive LN | 639 (13.1) | 23 (12.2) | 64 (15.2) | 726 (13.3) |
| >1 positive LN | 283 (5.8) | 12 (6.3) | 43 (10.2) | 338 (6.2) |
| **Tumor histology**[a] | | | | |
| ductal | 4096 (84.3) | 168 (88.9) | 364 (86.5) | 4628 (84.6) |
| lobular | 462 (9.5) | 13 (6.9) | 35 (8.3) | 510 (9.3) |
| other + mixed | 296 (6.1) | 8 (4.2) | 22 (5.2) | 326 (6.0) |
| Missing | 6 (0.1) | 0 (0.0) | 0 (0.0) | 6 (0.1) |
| **Histological grade**[a] | | | | |
| well differentiated | 1138 (23.4) | 36 (19.0) | 74 (17.6) | 1248 (22.8) |
| moderately differentiated | 2419 (49.8) | 79 (41.8) | 195 (46.3) | 2693 (49.2) |
| poorly differentiated or undifferentiated | 1288 (26.5) | 74 (39.2) | 151 (35.9) | 2693 (49.2) |
| Missing | 15 (0.3) | 0 (0.0) | 1 (0.2) | 16 (0.3) |
| **Clinico-pathological subtype** [a] | | | | |
| Luminal HER2- | 3983 (82.0) | 137 (72.5) | 333 (79.1) | 4453 (81.4) |
| Luminal HER2+ | 340 (7.0) | 8 (4.2) | 23 (5.5) | 371 (6.8) |
| HER2+ | 83 (1.7) | 8 (4.2) | 8 (1.9) | 99 (1.8) |
| Triple negative | 446 (9.2) | 35 (18.5) | 57 (13.5) | 538 (9.8) |
| Missing | 8 (0.2) | 1 (0.5) | 0 (0.0) | 9 (0.2) |
| [a]*: Based on local assessments* | | | | |
| **Clinical risk** | | | | |
| Low risk | 2671 (55.0) | 90 (47.6) | 170 (40.4) | 2931 (53.6) |
| High risk | 2188 (45.0) | 99 (52.4) | 251 (59.6) | 2538 (46.4) |
| Missing [a] | 1 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| **Genomic risk** | | | | |
| Low risk | 3249 (66.9) | 105 (55.6) | 224 (53.2) | 3578 (65.4) |
| High risk | 1610 (33.1) | 84 (44.4) | 197 (46.8) | 1891 (34.6) |
| Missing [a] | 1 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| **Risk and treatment allocation** | | | | |
| cL/gL | 2239 (46.1) | 71 (37.6) | 127 (30.2) | 2437 (44.6) |
| cL/gH allocated treatment: ACT | 222 (4.6) | 8 (4.2) | 20 (4.8) | 250 (4.6) |
| cL/gH allocated treatment: no ACT | 211 (4.3) | 11 (5.8) | 23 (5.5) | 245 (4.5) |
| cH/gL allocated treatment: ACT | 532 (10.9) | 13 (6.9) | 43 (10.2) | 588 (10.7) |
| cH/gL allocated treatment: no ACT | 479 (9.9) | 21 (11.1) | 54 (12.8) | 554 (10.1) |
| cH/gH | 1177 (24.2) | 65 (34.4)) | 154 (36.6) | 1396 (25.5) |

*One patient has an unknown genomic risk because the wrong sample was analyzed at enrollment. This case will be classified as in the main analysis as cL/gL*
*pNmi: was considered as positive lymph node*

*[continued on next page]*

**Supplementary Table 4.** *[continued]*

| | Loco-regional recurrence (competing risk) | | | |
|---|---|---|---|---|
| | **No event/No competingrisk (N=4860)** | **Event (N=189)** | **Competing risk (N=421)** | **Total (N=5470)** |
| **Radiotherapy received** | | | | |
| No[a] | 28 (0.6) | 8 (4.2) | 11 (2.6) | 47 (0.9) |
| Yes | 4762 (98.0) | 181 (95.8) | 410 (97.4) | 5353 (97.9) |
| Missing | 70 (1.4) | 0 (0.0) | 0 (0.0) | 70 (1.3) |
| **Adjuvant chemo received** | | | | |
| No | 2936 (60.4) | 109 (57.7) | 224 (53.2) | 3269 (59.8) |
| Yes | 1897 (39.0) | 80 (42.3) | 197 (46.8) | 2174 (39.7) |
| Missing | 27 (0.6) | 0 (0.0) | 0 (0.0) | 27 (0.5) |
| If Yes, Chemo type planned/ received | | | | |
| anthracycline (R-C) | 431 (22.7) | 19 (23.8) | 55 (27.9) | 505 (23.2) |
| docetaxel + capecitabine (R-C) | 444 (23.4) | 11 (13.8) | 44 (22.3) | 499 (23.0) |
| non-randomized ACT | 1022 (53.9) | 50 (62.5) | 98 (49.7) | 1170 (53.8) |
| **Adjuvant trastuzumab/HER2 status** | | | | |
| HER2- | 4429 (91.1) | 172 (91.0) | 390 (92.6) | 4991 (91.2) |
| HER2+ / Trastuzumab: No | 127 (2.6) | 7 (3.7) | 12 (2.9) | 146 (2.7) |
| HER2+ / Trastuzumab: Yes | 284 (5.8) | 9 (4.8) | 19 (4.5) | 312 (5.7) |
| Missing | 20 (0.4) | 1 (0.5) | 0 (0.0) | 21 (0.4) |

*a: Patients not receiving radiotherapy are not included in the analysis of prognostic factors*
*b: Based on local assessments*
*c: Includes 4 patients treated with endocrine treatment despite ER/PgR negative status*



**Supplementary table 5.** Estimated 8-year cumulative incidences of loco-regional recurrences.

| | **N** | **Number of Events** | **Cumulative Incidence** | **95% Confidence Interval** |
|---|---|---|---|---|
| **Overall BCS population** | 5470 | 189 | 3.2% | (2.7-3.7) |
| **Genomic risk** | | | | |
| Low risk | 3578 | 105 | 2.7% | (2.1-3.3) |
| High risk | 1891 | 84 | 4.2% | (3.3-5.2) |
| **Clinical risk** | | | | |
| Low risk | 2931 | 90 | 2.7% | (2.1-3.4) |
| High risk | 2538 | 99 | 3.7% | (3.0-4.5) |
| **Clinical and genomic risk** | | | | |
| cL/gL | 2437 | 71 | 2.5% | (1.9-3.3) |
| cL/gH | 495 | 19 | 3.6% | (2.1-5.6) |
| cH/gL | 1142 | 34 | 2.9% | (2.0-4.1) |
| cH/gH | 1396 | 65 | 4.4% | (3.4-5.6) |

*[continued on next page]*

**Supplementary Table 5.** *[continued]*

| | N | Number of Events | Cumulative Incidence | 95% Confidence Interval |
|---|---|---|---|---|
| **Age** | | | | |
| ‹= 50 years | 1697 | 68 | 4.0% | (3.1-5.1) |
| ›50 years | 3773 | 121 | 2.8% | (2.3-3.4) |
| **Tumor size** | | | | |
| ‹=1 cm | 822 | 24 | 2.8% | (1.8-4.2) |
| ›1-2cm | 3350 | 112 | 3.0% | (2.4-3.7) |
| ›2-3 cm | 1095 | 44 | 3.8% | (2.7-5.1) |
| ›3 cm | 203 | 9 | 4.3% | (2.0-7.9) |
| **Lymph node status** | | | | |
| LN0 | 4406 | 154 | 3.1% | (2.6-3.7) |
| 1 positive LN | 726 | 23 | 3.2% | (2.0-4.7) |
| ›1 positive LN | 338 | 12 | 3.5% | (1.9-6.0) |
| **Histological type** | | | | |
| Ductal | 4628 | 168 | 3.4% | (2.9-4.0) |
| Lobular | 510 | 13 | 1.8% | (0.8-3.4) |
| Mixed | 159 | 2 | 0.7% | (0.1-3.6) |
| Other | 167 | 6 | 3.4% | (1.3-7.2) |
| **Subtype (local lab)** | | | | |
| Luminal / HER | 4453 | 137 | 2.7% | (2.2-3.3) |
| Luminal / HER+ | 371 | 8 | 2.4% | (1.1-4.5) |
| HER+ (non-luminal) | 99 | 8 | 7.4% | (3.2-13.8) |
| Triple negative | 538 | 35 | 6.5% | (4.6-8.9) |
| **Adjuvant radiotherapy** | | | | |
| No | 47 | 8 | 20.0% | (8.5-35.0) |
| Yes | 5353 | 181 | 3.1% | (2.6-3.6) |

# CHAPTER 6

## Summarizing discussion and future perspectives

In this thesis, several aspects of the de-escalation of the treatment of Ductal Carcinoma In Situ (DCIS) treatment and Invasive Breast Cancer (IBC) were explored. For DCIS we determined the risk of a subsequent ipsilateral Invasive Breast Cancer (iIBC) after a primary diagnosis of DCIS by studying a recent Dutch nation-wide DCIS cohort and we aimed to offer insight in the potential modifiable risk factors as a target for risk reduction. Finally, we evaluated the role of Artificial Intelligence in assessment of pre-surgical mammographies of DCIS patients. For IBC we investigated whether the MammaPrint gene assay could predict the risk of a loco-regional recurrence in patients with early-stage breast cancer to determine if it would be safe to omit radiotherapy in a sub-group of patients with early stage breast cancer. In this final chapter our findings are summarized and clinical context and future perspectives are discussed.

# SUMMARY OF MAIN FINDINGS

## Ductal Carcinoma In Situ: de-escalation of invasive treatment

The majority of 'low-risk' (grade I/II) Ductal Carcinoma In Situ (DCIS) may not progress to invasive breast cancer during a women's lifetime[1,2]. Therefore, the safety of active surveillance versus standard surgical treatment for DCIS is prospectively being evaluated in clinical trials embedded in the PREvent ductal Carcinoma In Situ Invasive Now (PRECISION)-initiative[3]. If proven safe, a significant group of women with low-risk DCIS may forego surgery and radiotherapy in the future. Identification of modifiable and non-modifiable risk factors associated with prognosis after a primary DCIS would also enhance our care of women with low-risk DCIS. In **Chapter 2** we therefore aimed to identify potential targets for risk reduction. There are a limited number of recent studies published on the impact of modifiable and non-modifiable risk factors on subsequent events after DCIS showing moderate evidence for an association of a family history of breast cancer, premenopausal status, high BMI, and high breast density with a subsequent breast cancer or further DCIS. We concluded that the available evidence is insufficient to identify potential targets for risk reduction strategies, reflecting the relatively small numbers and the lack of long-term follow-up in DCIS, a low-event condition. **Chapter three** studied the effects of contemporary treatment of DCIS on the risk of developing an Ipsilateral Invasive Breast Cancer (iIBC) in a Dutch population-based cohort of women diagnosed with primary DCIS between 2005-2015 with follow-up until February 2020. Compared to an earlier Dutch population-based cohort study of primary DCIS (diagnosis years 1989-2004)[4], we demonstrated a reduced risk of approximately 50% for subsequent iIBC for patients treated with breast conserving surgery only and patients treated with breast conserving surgery with radiotherapy. Van Seijen *et al.* reported 10-year cumulative incidences of 5.2% after BCS+RT, 13.9% after BCS alone and 1.1% after MST with a median follow-up of 15.7 years after diagnosis.. Our current study with a median follow-up of 8.2 years reports iIBC incidences of 3.1% after BCS+RT, 7.1% after BCS after 1.6% after MST, with a median time to iIBC of 4.8 years. The 50% risk reduction for a subsequent iIBC was not seen in the mastectomy treated group. Nevertheless, a significantly higher relative risk of a subsequent iIBC was seen in patients treated with breast conserving surgery compared to breast conserving surgery with radiotherapy during the first 10 years after treatment. Demonstrating the protective effect of radiotherapy for iIBC after BCS, as was seen

by our two previous studies performed by Elshof et al[4] and van Seijen. Despite the declining risk of a subsequent iIBC after the first five years, it remained significantly higher for patients treated with breast conserving surgery than for those treated with breast conserving surgery + radiotherapy. The very low absolute risks of iIBC after diagnosis of DCIS reported in this thesis are relevant considering that the current study more accurately reflects the daily practice in managing DCIS. Possible explanations for this decline might be the increased administration of adjuvant RT over time, the higher proportion of screen-detected DCIS and smaller lesion sizes due to the implementation of digital mammography, and an increased proportion of radical resection due to better pre-surgical assessment. These very low absolute numbers justify current efforts to de-escalate invasive treatment of DCIS patients, specifically patients with low-risk DCIS, i.e. with grade I/II hormone receptor positive/ HER2 negative DCIS, as currently done in the LORD, COMET and Loretta trials[5–7].

Non-invasive identification of these low risk DCIS patients would be the next step towards decreasing patient discomfort and health care costs. In **Chapter four** we assessed the performance and clinical utility of a convolutional neural network applied on mammography images in discriminating low-risk (grade I/II) from high-risk (grade III) DCIS and/or IBC in order to support active surveillance in patients with biopsy proven DCIS. Available Computer aided detection (CADe) and computer-aided diagnosis (CADx) algorithms have been developed to support radiologists in mammogram assessment. Several studies have been performed using CADe and CADx for calcification segmentation and detection on mammography[8–11], mainly to prevent overlook errors of radiologists. Other studies using CADe/CADx more specifically evaluated DCIS[12–16], focusing on segmentation of calcifications and prediction of occult invasive disease with DCIS[16]. In the current study 464 patients diagnosed with DCIS between 2000 and 2014 were included. A deep learning model based on the U-Net convolutional network architecture was trained and validated on 681 two-dimensional mammograms. Classification performance was assessed with the Area Under the Curve (AUC) receiver operating characteristic and predictive values on the test set for predicting high-grade DCIS and high-grade DCIS and/or IBC from low-grade DCIS. For both scenarios AUCs were relatively high, 0.72 and 0.76, respectively, and we concluded that our convolutional neural network is a good classifier for low- versus high-grade DCIS. After independent validation, our classifier could be applied as a supportive tool to select the right treatment for patients with DCIS. Patients with low-grade DCIS could safely opt for active surveillance, patients with high-grade DCIS could go for conventional treatment.

## Early-stage Breast cancer: de-escalation of radiotherapy

**In Chapter five we explore** the potential role of the MammaPrint 70-gene signature gene assay in predicting the risk of Loco-Regional Recurrence (LRR). A number of studies are currently investigating a de-escalation approach in which radiotherapy is omitted in patients with a low risk of in-breast relapses on the basis of clinicopathological factors and multigene arrays[17–21]. We aimed to evaluate whether the 70-gene risk score is associated with the risk of LRR, and to estimate 8-year cumulative incidences for LRR in patients with early-stage breast cancer treated with breast conservation in the MINDACT-trial. This exploratory analysis

demonstrated an 8-year overall low LRR-rate of 3.2% after breast conserving surgery. The risk of LRR decreases with endocrine therapy, as expected, as well as smaller tumor size, and favorable clinicopathological and genomic features. More importantly, the overall cumulative incidence of Local Recurrences only was just 2.3% (95%CI: 1.9-2.8) and was the lowest in the clinical-low and genomic-low population with an incidence of 2.0% (95%CI: 1.4-2.6%) at 8 years. This finding supports exploring options to de-escalate local treatment. Potential candidates for radiation de-escalation are older patients with smaller and lower grade tumors and low risk genomic tests.

# FUTURE PERSPECTIVES

## Active surveillance in low-risk (grade I/II) DCIS

In order to address overtreatment of DCIS, different 'checkpoints' during diagnostics and potential treatment should be considered. At each level the risk of DCIS progression to invasive disease and its concomitant comorbidity and mortality should be taken into account and integrated as a whole to decide whether or not further testing or invasive treatment is indicated or not. The international and multidisciplinary PRECISION[3] initiative will contribute to reliably differentiate harmless DCIS from potential hazardous DCIS. The majority (~75%) of patients with DCIS present with calcification on mammography, detected during breast cancer screening[22]. In **chapter four** we developed a convolutional neural network that is able to differentiate low-risk (grade I/II) DCIS from high-risk (grade III) DCIS and/or invasive disease based on mammography calcifications. Using this technique at the imaging-level, after biopsy proven pure DCIS, we already have an extra 'checkpoint'. The network could be applied as extra safety measure before inclusion for active surveillance, where it can be utilized for definitive grading of DCIS. However, even before biopsy proven DCIS, detailed artificial intelligence based analysis of calcifications may reveal relevant prognostic information (i.e. regarding harboring benign or malignant disease)[23–25].

The next 'checkpoint' in the diagnostic and therapeutic approach to DCIS, would be after mammography indicates the necessity to perform a diagnostic breast biopsy. At this level, again artificial intelligence could play a supportive role next to the classical assessment of the histopathology of the breast biopsy by a pathologist. Computational algorithms are able to differentiate with high accuracy between DCIS and IBC, as ROC-AUC up to 0.960 and 0.977 for DCIS and IDC were achieved[26]. In addition, at this level, where DCIS is biopsy proven, ideally, molecular markers which are associated with the risk of DCIS progression to IBC should be included. Kerlikowske et al. demonstrated that the combination of Ki-67 with COX2 and p16 expression could predict development of recurrence[27]. More recently, this set of markers has been expanded to include HER2, PR, Ki-67, COX2, p16/INK4A, FOXA1 and SIAH2 and is available as a commercial assay (DCISionRT from PreludeDx) to identify the benefit of radiotherapy[28,29]. However, the true value of these biomarkers for clinical decision making is still unclear as most biomarkers are identified in small biased series, and clinical validity has

not been proven[30] In **chapter two** moderate evidence for an association of a family history of breast cancer, premenopausal status, high BMI, and high breast density with a subsequent breast cancer or further DCIS was shown. Nevertheless, the current active surveillance trials are incorporating questionnaires which address lifestyle factors and might provide further insights in modifiable and non-modifiable risk factors for invasive progression of DCIS. The factors demonstrated in chapter two, together with the factors which may be revealed in the near future from the integrated active surveillance trial questionnaires could be integrated together with radiological, clinicopathological and molecular factors associated with risk of progression DCIS to IBC in order to discriminate between hazardous and indolent DCIS.

At the final 'checkpoint' after diagnosis of DCIS, consultation by a physician about the next step regarding treatment is essential. A consensus in the medical community is lacking on how to effectively communicate to patients about DCIS and the associated risks of developing invasive cancer[31]. In **chapter three** we demonstrated reduced risks for a subsequent iIBC for patients treated with breast conserving surgery only and patients treated with breast conserving surgery with radiotherapy **c**ompared to an earlier Dutch population-based cohort study of primary DCIS (diagnosis years 1989- 2004). It has also been demonstrated that the number of missed invasive breast cancers based on pre-surgical biopsies is lower than previously assumed, and that most missed cancers have an excellent prognosis and delayed detection during follow-up will most likely not compromise survival[32]. These lower numbers and good prognosis justify current efforts to de-escalate invasive treatment of DCIS patients and more importantly, they can help physicians to explain the DCIS-associated risks of developing invasive cancer after diagnosis of DCIS and contribute to shared-decision making to profoundly weigh the advantages and disadvantages of treating or not treating patients with DCIS. Interestingly, most of the patients invited to participate in the LORD-trial, choose active surveillance, implying that the perception of DCIS and its potential risk to progress to invasive disease is changing in the medical and patient community.



## Multigene assays for local control after Early-Stage Breast Cancer

In **chapter five** we showed that in univariate analysis, adjusted for chemotherapy, 5 out of 12 variables were associated with LRR, including the 70-gene signature. A low overall 8-year cumulative incidence for local and regional recurrence of 3.2% was observed. A low-risk 70-gene signature was associated with a lower LRR incidence of 2.7%, and in the ultra-low 70-gene signature group even a lower incidence of 2.3% was seen. But in the multivariate analysis, this association was no longer significant. Our observation is similar to the findings of two earlier studies performed by Mamounas et al., on the NSABP B-14 / NSABP B-20 and the NSABP B-28 trial, albeit the 21-gene signature retained significance in the multivariate model for LRR[33,34]. The same roadmap in diagnostic and therapeutic work-up as mentioned above regarding DCIS could be more or less applied for early-stage breast cancer. Briefly, AI methods could be further explored to see whether mammographic features could predict which patients would benefit from adjuvant radiotherapy. The same applies to AI methods for histopathological slides, where features could be extracted which are associated with LRR.

Together with classical clinicopathological factors, features extracted from mammography and features extracted from histopathological slides combined with the results from the 70-gene signature score could lead to a tailored approach for patients with early-stage breast cancer to individualize risk estimates for LRR and explore options to see whether radiotherapy could be omitted. Furthermore, our demonstrated low absolute risks for LRR in patients treated with breast conserving surgery could be used during consultation with patients to better understand the risk of LRR in case of omitting radiotherapy. When interpreting these results, one should appreciate that the 70-gene signature was developed to compare gene expression by RNA microarray and identify tumors with a higher or lower chance of developing distant metastasis, not LRR[35]. Nonetheless the overall cumulative incidence of local recurrences was 2.3% (95%CI: 1.9-2.8) and was the lowest in the clinical-low and genomic-low population with an incidence of only 2.0% (95%CI: 1.4-2.6%) at 8 years. These very low absolute numbers considering local recurrence support exploring options to de-escalate local treatment. Potential candidates for radiation de-escalation might be older patients with smaller and lower grade tumors and low risk genomic tests. We believe that selection of patients for locoregional management using gene signatures designed to assess genes associated with distant metastases, should be integrated with clinical parameters.

# CONCLUSION

This thesis showed that discriminating potential hazardous DCIS from harmless DCIS with the current available knowledge is challenging. However, artificial intelligence on the level of imaging and histopathology is promising and should be further explored. Also, potential biomarkers considering DCIS progression to IBC is intensively being studied within the PRECISION-initiative. These ongoing studies are promising and might reveal the 'holy grail' regarding the development of invasive disease after DCIS diagnosis. We further demonstrated that identifying potential targets for risk reduction is currently difficult considering that there is limited literature available, and that DCIS is a low-event rate disease which asks for large, well powered studies with a sufficient number of informative events. Nonetheless, the ongoing trials are documenting lifestyle factors of the included patients and may reveal potential targets for risk reduction in the near future. We also investigated the risk of subsequent iIBC after a diagnosis of DCIS and showed the risk after being treated by surgery is very low in the present-day management of DCIS. More importantly, we demonstrated a declining trend in the risk of subsequent iIBC after DCIS diagnosis, in accordance with other studies. These numbers are of clinical significance when informing patients about the risk of invasive disease after DCIS diagnosis. Similar to DCIS, treatment of early breast cancer might be de-escalated in patients with a very low risk of recurrence We found that the 70-gene signature was not independently associated with the risk of LRR. However, we reported very low absolute numbers for the risk of LRR, which further underscore the necessity individualize treatment for breast cancer patients and supports ongoing efforts of studies who investigate patients with a low-risk of in breast relapses on the basis of clinicopathological factors and multigene to de-escalate local therapy.

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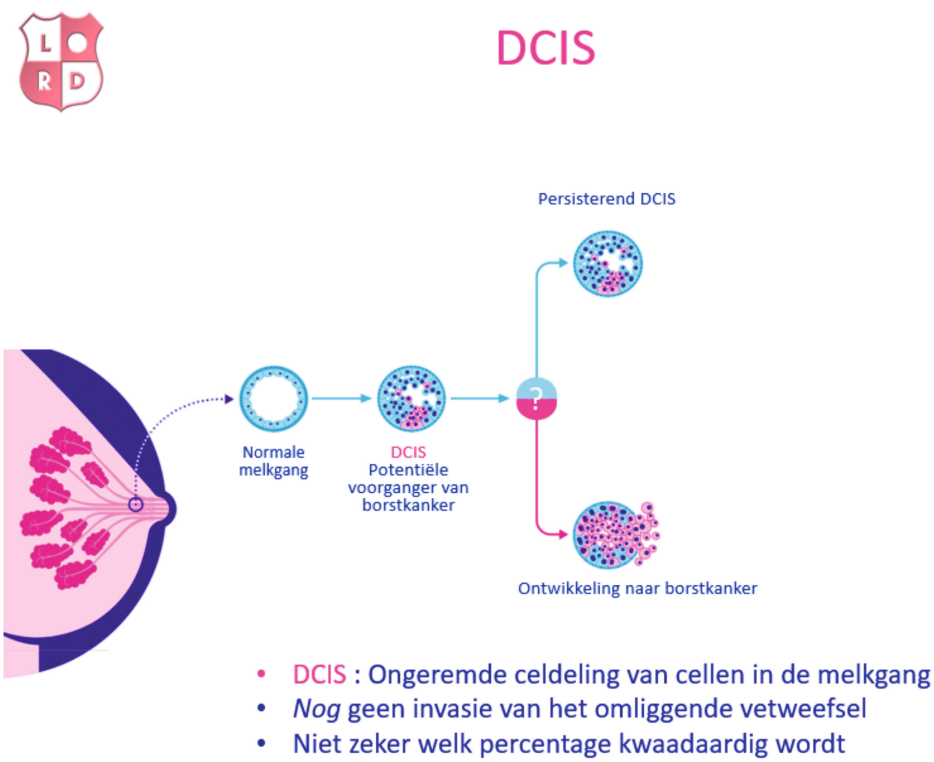
# APPENDICES

# NEDERLANDSE SAMENVATTING

## De-escalatie van de behandeling van Ductaal Carcinoma In Situ en vroegstadium borstkanker

### Ductaal Carcinoma in Situ en borstkanker

Borstkanker is doodsoorzaak nummer één onder vrouwen wereldwijd. Tevens is het de meest voorkomende kankersoort bij vrouwen. In Nederland krijgen ongeveer 18.000 vrouwen jaarlijks de kwaadaardige ('maligne') diagnose 'borstkanker'. In ongeveer 20% betreft het Ductaal Carcinoma In Situ tumoren (DCIS). Bij DCIS blijven de kwaadaardige cellen tot de melkgangetjes beperkt (figuur 1). Daarom wordt DCIS steeds vaker niet als borstkanker beschouwd, maar hooguit als een voorstadium. Ongeveer 80% van de diagnoses 'borstkanker' betreft zonder twijfel daadwerkelijk borstkanker. Dit omdat de kwaadaardige cellen het borstweefsel zijn binnengedrongen. Men spreekt dan van 'invasie'. Uiteindelijk kunnen die cellen uitzaaien naar de nabijgelegen lymfklieren in bijvoorbeeld de oksel en uiteindelijk ook naar elders in het lichaam, zoals de longen en het bot. Dat uitzaaien is voor DCIS niet aan de orde, omdat DCIS beperkt blijft tot de melkgangetjes.




**Figuur 1.**

## Bevolkingsonderzoek naar borstkanker

Ook al wordt DCIS beschouwd als een voorloper van invasieve borstkanker, zal de meerderheid van DCIS-afwijkingen nooit uitgroeien tot borstkanker en is dus niet gevaarlijk. Helaas is nog niet duidelijk welke DCIS-afwijkingen zullen uitgroeien tot borstkanker en welke DCIS-afwijkingen niet.

Ongeveer drie decennia geleden zijn een aantal westerse landen waaronder de Verenigde Staten, het Verenigd Koninkrijk en Nederland begonnen met het screenen van hun vrouwelijke inwoners op borstkanker. Als gevolg hiervan hebben wij in Nederland tegenwoordig het bevolkingsonderzoek naar borstkanker. Het bevolkingsonderzoek borstkanker is een onderzoek dat bij vrouwen tussen de 50 en 75 jaar elke 2 jaar wordt gedaan. Op deze manier willen artsen op tijd borstkanker herkennen, zodat dit zo snel mogelijk behandeld kan worden. Vanaf het 50e levensjaar krijgen vrouwen een uitnodiging om een röntgenfoto van de borsten te laten maken. Binnen 10 dagen na de foto is de uitslag bekend.

Wanneer de uitslag niet afwijkend is, is er geen verder onderzoek nodig. Wanneer er een afwijking is geconstateerd, is dit reden voor verder onderzoek. In Nederland was er al vroeg belangstelling voor het screenen van vrouwen op borstkanker. In 1974 en 1975 startten in Utrecht en in Nijmegen twee proefbevolkingsonderzoeken met een verschillend ontwerp. Daaruit bleek dat een screeningsinterval van vier jaar te lang was om borstkanker in een wezenlijk vroeger stadium op te kunnen sporen. Naar aanleiding van de uitkomsten van de proefbevolkingsonderzoeken begon men in Nederland serieus een landelijk bevolkingsonderzoek borstkanker te overwegen. Een proef in 1987 met een verplaatsbare screeningsunit was succesvol voor wat betreft de opkomst (deelname) en liet zien dat ook mobiele screening mogelijk was. Het landelijk bevolkingsonderzoek borstkanker is in Nederland gestart in 1990. Tot 1998 werd de doelgroep 50-70 jaar gescreend. In 1998 is de leeftijdgrens opgeschoven naar 75 jaar. Het resultaat was dat eind jaren 90 een volledig, functioneel en landelijk screeningprogramma voor borstkanker bestond. Eén van de grootste veranderingen sindsdien is de invoering van de digitale mammografie i.p.v. de analoge mammografie in 2009/2010.

Het idee achter het bevolkingsonderzoek naar borstkanker is dat borstkanker eerder ontdekt kan worden, waardoor de kans groter is dat de behandeling succesvol is. Ook is vaak een minder ingrijpende behandeling nodig. Het bevolkingsonderzoek heeft ervoor gezorgd dat er een betere algemene overleving is na een diagnose van borstkanker. De grote keerzijde van bevolkingsonderzoek is overdiagnostiek. Hierbij wordt een aandoening gediagnosticeerd die niet geleid zou hebben tot klachten of overlijden als er geen screening zou zijn verricht. Bij overdiagnostiek ontstaat de neiging om datgene wat gevonden wordt ook te behandelen, terwijl dat geen voordeel oplevert. Men spreekt dan van overbehandeling. Bij overbehandeling loopt men het risico op bijwerkingen en in zeldzame gevallen overlijden als gevolg van de bijwerking van de behandeling. In dit geval heeft men dus de onnodige risico's van bijwerkingen van de behandelingen, terwijl er geen evident voordeel is. Deze overdiagnostiek geeft ook onnodige onrust bij vrouwen aangezien je eerder weet dat je een afwijking hebt zonder dat je dat enig

voordeel oplevert. Ondanks deelname aan het bevolkingsonderzoek wordt toch nog 1 op de 3 gevallen van borstkanker gemist. Daarnaast bestaat het fenomeen ‘de interval borstkanker’. Hierbij presenteert een borstkanker zich tussen twee screeningsmomenten in.
Deze tumoren zijn vaak agressiever en al uitgezaaid naar de lymfeklieren.

**DCIS**

Sinds in 1989 in Nederland het bevolkingsonderzoek op borstkanker is geïntroduceerd, is het aantal nieuwe diagnoses van DCIS per jaar (incidentie) tenminste verzesvoudigd tot ruim 2300 nieuwe gevallen per jaar. In meer dan 80% van de gevallen wordt DCIS dan ook gevonden bij het bevolkingsonderzoek dat aan vrouwen elke 2 jaar wordt aangeboden tussen hun 50e en 75e levensjaar. Dit omdat DCIS doorgaans niet met symptomen gepaard gaat, maar gedetecteerd wordt op basis van met DCIS geassocieerde calcificaties (verkalkingen) welke bij mammografie (röntgenfoto van de borst) vaak goed te zien zijn. Bij de minderheid van de vrouwen met DCIS is wel sprake van symptomen. Het betreft dan veelal een palpabele (voelbare) afwijking, bloederige tepeluitvloed of een combinatie van beide.

De vrouwelijk borst is opgebouwd uit vet en een vertakkend systeem van klieren en melkgangetjes (figuur 1). In de klieren wordt melk geproduceerd dat door de melkgangetjes naar de tepel wordt voortgestuwd. DCIS ontstaat in deze melkgangen, wanneer daar ongecontroleerde celdeling plaatsvindt welke zich beperkt tot het melkgangetje.

De diagnose DCIS wordt uiteindelijk gesteld door een patholoog (ziektekundige). De belangrijkste taak van de patholoog is het (vooral microscopisch) onderzoeken van weefselmonsters van patiënten, om de aard van een afwijking vast te stellen. Bij het weefselonderzoek door de patholoog wordt in het geval van DCIS gekeken in welke mate de DCIS-cellen nog lijken op de normale cellen die zich in de melkgangetjes bevinden. Hierbij wordt een gradering systeem gebruikt welke drie graderingen kent laaggradig ( i.e. graad I), matig gedifferentieerd (i.e. graad II) en slecht gedifferentieerd/hooggradig ( i.e. graad III). In het geval van graad I DCIS, lijken de DCIS-cellen nog sterk op de normale cellen in de melkkliergangetjes. Bij graad II is er matige gelijkenis en bij graad III slechte gelijkenis. In dit proefschrift bestaat er enige nuance in het gradering systeem van DCIS, namelijk de indeling op laag-risico versus hoog-risico. Hierbij wordt graad I DCIS beschouwd als een laag-risico afwijking en een graad III DCIS als een hoog risico. DCIS graad II wordt alleen als laag risico beschouwd als de DCIS afwijking aan een aantal andere criteria voldoet bij het pathologisch onderzoek. Er moeten namelijk ook bepaalde eiwitten aanwezig en afwezig zijn in de DCIS-afwijking waar hormonen en/of groeifactoren aan kunnen binden. Het gaat hierbij om de hormonen oestrogeen, progestageen en de groeifactor HER2.

Wanneer een graad II DCIS gevoelig is voor oestrogeen en niet gevoelig is voor de groeifactor HER2, zal de DCIS graad II afwijking als een laag-risico afwijking gezien worden. *Borstkanker*

Borstkanker is een vorm van kanker die uitgaat van de melkklieren en melkgangetjes in de borst. Het is de meest voorkomende soort kanker bij vrouwen. Wereldwijd krijgen jaarlijks

ongeveer één miljoen vrouwen de diagnose borstkanker. Onder vrouwen tussen 30 en 59 jaar is het de meest voorkomende doodsoorzaak.

Invasieve borstkanker is niet één ziekte, maar bestaat uit verschillende soorten (subtypes). De meest gangbare indeling is op basis van de aanwezigheid van bepaalde eiwitten in de tumor waar hormonen en/of groeifactoren aan kunnen binden. Daarnaast wordt beoordeeld of een invasieve borstkanker bestaat uit cellen en structuren die nog enigszins lijken op normale borstkankercellen, 'goed gedifferentieerd (graad I)', sterk afwijkend, 'slecht gedifferentieerd (graad III) of iets er tussenin, i.e. 'matig gedifferentieerd (graad II)' zijn. Vervolgens is de grootte van de tumor belangrijk en of er lymfklieren in de nabijheid van de borst al dan niet al aangedaan zijn door een uitzaaiing van de borstkanker.

De behandeling van invasieve borstkanker hangt af van het stadium van de ziekte en het subtype ervan. Hierbij wordt gekeken of er al uitzaaiingen zijn naar de regionale lymfeklieren, of uitzaaiingen naar de organen en naar voor welke hormonen en groeifactoren de tumor gevoelig is. Als er sprake is van borstkanker in een vroeg stadium, dan is de borstkanker nog niet uitgezaaid naar andere organen en is de tumor relatief klein. Daarbij kan er bij zo'n borstkanker in een vroeg stadium wel sprake zijn van een beperkt aantal uitzaaiingen in de nabijgelegen lymfeklieren, maar dus niet naar de organen.

## Bevolkingsonderzoek naar borstkanker met als gevolg overdiagnostiek en overbehandeling van DCIS

Om de uitgroei van DCIS tot borstkanker te voorkomen, worden vrijwel alle vrouwen met DCIS behandeld door middel van een borstsparende operatie, veelal gevolgd door radiotherapie. Wanneer de DCIS-afwijking te groot is voor zo'n sparende behandeling wordt de gehele borst verwijderd, een zogenoemde borstamputatie. De operatieve verwijdering van een DCIS-afwijking zou moeten leiden tot een afname van de incidentie van verder gevorderde stadia van borstkanker, omdat een potentiële voorloper wordt verwijderd. Opvallend genoeg is deze afname niet evident. Dit suggereert dat er sprake is van overdiagnostiek en overbehandeling van in elk geval een deel van de vrouwen met DCIS. Omdat bijna alle vrouwen met DCIS worden behandeld, is het niet goed mogelijk om uitspraken te doen over het daadwerkelijke risico of een bepaalde DCIS-afwijking ooit borstkanker zal worden. Summiere informatie komt uit een enkele kleine studie waarbij DCIS, na diagnose op basis van een biopsie, niet werd behandeld. Daaruit blijkt dat tussen de 50 en 85% van alle DCIS-afwijkingen zich niet ontwikkelden tot borstkanker. Bovendien weten we uit onderzoek bij vrouwen die zijn overleden aan iets anders dan borstkanker, dat er in deze groep bij 4 op de 10 vrouwen DCIS voorkomt. Zij hadden dus geen symptomen of klachten van deze DCIS afwijking en zijn komen te overlijden aan iets anders dan deze DCIS afwijking. Het is bekend dat vrouwen behandeld voor DCIS nauwelijks een verhoogde kans op sterfte aan borstkanker hebben. Dit blijkt onder andere uit een grote observationele studie waarbij ruim 100.000 vrouwen werden geïncludeerd. Ondanks de excellente prognose ervaren vrouwen met DCIS niet zelden evenveel angst en ongerustheid als vrouwen met daadwerkelijk borstkanker. Het zou daarom enorm helpen om onderscheid

te kunnen maken tussen DCIS-afwijkingen die gepaard gaan met een extreem laag risico op ontwikkeling tot borstkanker en DCIS afwijkingen die wel een substantieel verhoogd risico hierop hebben. Het is waarschijnlijk dat veel vrouwen met een zeer laag risico DCIS geen behandeling behoeven. Als we beter kunnen vaststellen welke DCIS inderdaad een zeer laag risico hebben op het uitgroeien tot borstkanker, dan kan dit vele vrouwen de last van een intensieve maar onnodige behandeling besparen.

Als borstkanker ontstaat uit DCIS, dan heeft de invasieve tumor qua differentiatiegraad zeer grote overeenkomsten met de graad van DCIS. Dit betekent dat laaggradig DCIS, mocht het leiden tot borstkanker, vaak resulteert in een laaggradige en dus laag risico borstkanker. Een laaggradige borstkanker groeit langzaam, is veelal gevoelig voor hormonale remming en zal zeer waarschijnlijk op tijd gedetecteerd worden indien regelmatig mammografie verricht wordt.

## Laag risico DCIS

Om ontwikkeling tot borstkanker te voorkomen, worden vrijwel alle vrouwen met DCIS behandeld door middel van een amputatie of een borstsparende operatie, in geval van sparende chirurgie gevolgd door radiotherapie. Helaas kunnen we met de huidige kennis geen onderscheid maken tussen DCIS-afwijkingen die waarschijnlijk tot borstkanker leiden en DCIS-afwijkingen waarbij geen borstkanker ontstaat. Dit heeft ertoe geleid dat een groep van internationale wetenschappers en artsen in samenwerking met patiëntvertegenwoordigers het 'PREvent ductal Carcinoma In Situ Invasive Now' (PRECISION)-initiatief hebben opgezet. Het doel van PRECISION is om DCIS-afwijkingen die tot borstkanker leiden te onderscheiden van onschuldige DCIS-afwijkingen, zodat kan worden vastgesteld welke patiënt met DCIS een behandeling nodig heeft en bij welke patiënt een jaarlijkse controle middels mammografie voldoende is. PRECISION bestaat uit een team biologen, artsen en patiëntvertegenwoordigers waarbij vanuit verschillende invalshoeken DCIS wordt onderzocht (figuur 2). Zo worden bijvoorbeeld zogenaamde muismodellen gemaakt waarbij DCIS-cellen in de melkgang bij muizen worden gespoten. Deze muizen met DCIS bieden de mogelijkheid om DCIS-afwijkingen in een levend organisme te onderzoeken. Daarnaast wordt er ook onderzoek gedaan met DCIS-weefsel verkregen na een operatieve ingreep. Hierbij wordt gekeken of bepaalde weefseleigenschappen in de DCIS ons iets kunnen vertellen over het risico dat de DCIS-afwijking uit zal groeien tot borstkanker of juist niet. Een belangrijk onderdeel van PRECISION zijn de zogenoemde klinische studies. Momenteel lopen er drie grote DCIS-trials die samenwerken in PRECISION (COMET, LORETTA, en LORD-trial). Hier wordt onderzocht of regelmatige controle zonder operatieve behandeling (zogenaamde 'active surveillance') veilig is. De ene groep patiënten met DCIS krijgt de standaardbehandeling (borstsparende operatie + radiotherapie, dan wel borstamputatie) terwijl de andere groep niet geopereerd wordt ('active surveillance' groep). Alleen vrouwen met een laag-risico DCIS, dat wil zeggen graad I of II DCIS welke positief is voor de oestrogeenreceptor en negatief voor de HER2-receptor, mogen deelnemen aan deze klinische trials. Uiteindelijk wordt in deze studies bepaald wat het percentage is van vrouwen dat na 10 jaar follow-up geen borstkanker heeft gekregen. Zo kan er geëvalueerd worden of jaarlijkse screening veilig is voor vrouwen met laag-risico DCIS en dus niet 'slechter' is qua overleving dan opereren.

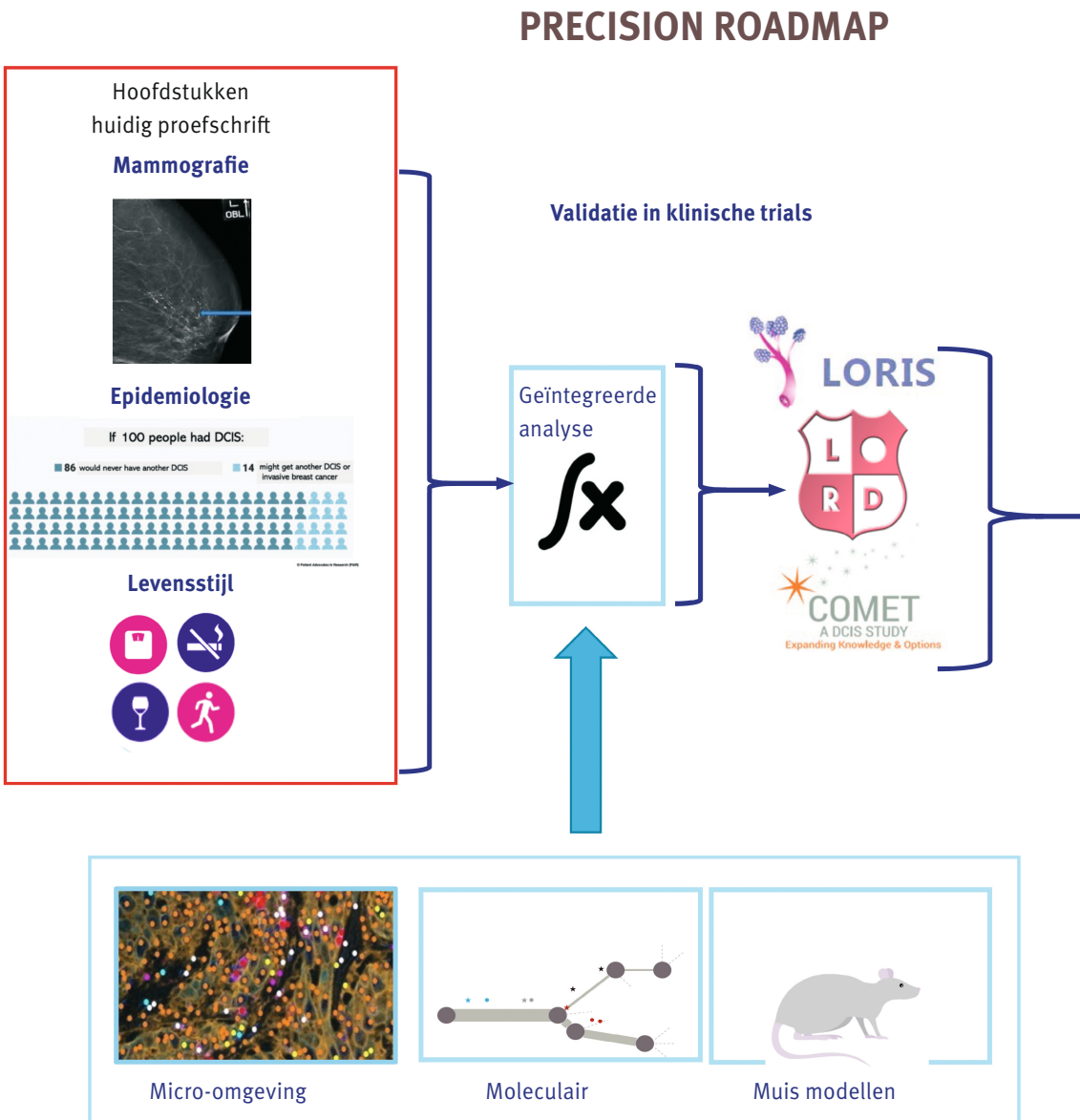
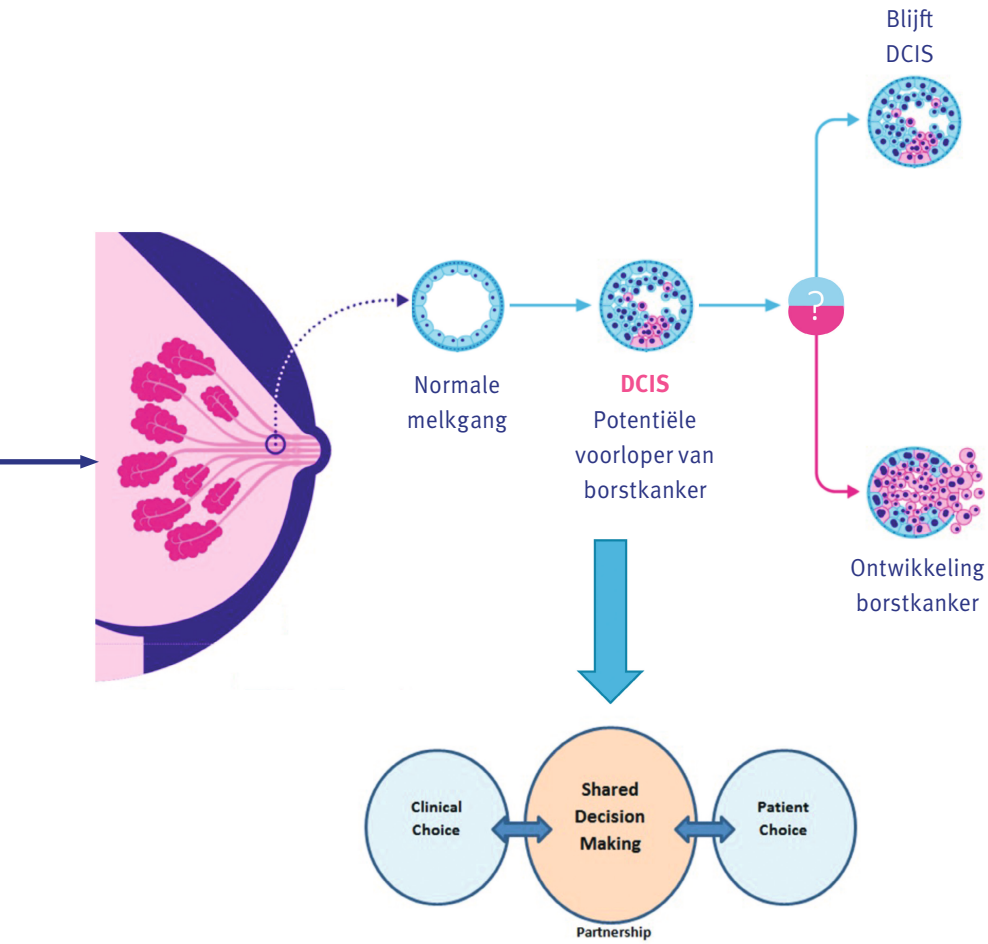



**Figure 1.** Precision roadmap, current thesis investigates mammography features, epidemiological data and lifestyle factor for DCIS.


Blijft
DCIS
Normale
melkgang
DCIS
Potentiële
voorloper van
borstkanker
?
Ontwikkeling
borstkanker


Clinical
Choice
Shared
Decision
Making
Patient
Choice
Partnership

## Borstkanker in een vroeg stadium

De behandeling van invasieve borstkanker, onafhankelijk of het nu door bevolkingsonderzoek is gevonden of niet, hangt af van het stadium van de ziekte en het subtype. Hierbij wordt gekeken of er al uitzaaiingen zijn naar de regionale lymfeklieren en/of uitzaaiingen naar de organen en welke hormonen en groeifactoren er tot uiting komen op de borstkanker. Soms is alleen locoregionale behandeling (chirurgie gevolgd door radiotherapie) voldoende, echter als de ziekte al meer uitgebreid is, is soms een systemische therapie (medicamenteus i.e. chemotherapie en/of hormoontherapie) nodig. Dat wil zeggen dat een patiënt een chemokuur en/of hormoonkuur *vóór* (neo-adjuvante behandeling) en/of *na* (adjuvante behandeling) de operatieve ingreep nodig heeft. Over de jaren heen is er veel progressie geboekt in de behandeling van borstkanker op het gebied van chirurgie, bestraling en de systemische therapieën. Door deze sterke verbetering in de behandeling van borstkanker zien we na de behandeling van borstkanker minder uitzaaiingen en locoregionale recidieven (terugkeer van de ziekte in de borst en/of in de nabijgelegen lymfeklieren zoals de oksel). Het moge duidelijk zijn dat niet elke vorm van borstkanker het volledig arsenaal aan therapie behoeft om een recidief te voorkomen. Veel patiënten zouden nog steeds een uitstekende overleving hebben zonder de toepassing van systemische therapieën. Er wordt veel onderzoek gedaan naar de de-escalatie van de behandelingen van borstkanker, zowel bij DCIS als ook bij borstkanker in een vroeg stadium. Bij de-escalatie is sprake van minder belastende behandelingen of het achterwege laten van één of meer behandelingen, met als doel een vergelijkbare (of eventueel iets lagere) kans op genezing met minder late bijwerkingen. De behandeling van borstkanker in een vroeg stadium bestaat uit een operatie gevolgd door bestraling van de borst en de oksel waarbij soms ook een adjuvante behandeling noodzakelijk is. Adjuvante behandeling kan hormoontherapie, chemotherapie of immunotherapie zijn. Deze adjuvante behandelingen worden gegeven om het risico op een recidief (terugkeer van de ziekte) en uitzaaiingen te verkleinen en zo de kans op overleving te vergroten. Om de noodzaak van een adjuvante behandeling vast te stellen wordt er gekeken naar o.a. de grootte van de tumor, hoe snel de cellen delen, of er lymfeklier uitzaaiingen zijn, de expressie van eiwitten/groeifactoren op de tumor, maar ook naar de patiënt eigenschappen (i.e. leeftijd, menopausale status). Er zijn online 'tools' beschikbaar die naar deze verschillende factoren kijken en bepalen of een patiënt baat zal hebben bij adjuvante chemotherapie. In het afgelopen decennium zijn daarnaast een aantal genetische testen beschikbaar gekomen zoals de Oncotype en MammaPrint. Deze testen kijken of er bepaalde genen in de borstkanker actief zijn, en doen op basis van dit 'genexpressieprofiel' een uitspraak of een patiënt wel of niet baat zal hebben bij adjuvante chemotherapie. Bij de MammaPrint test wordt een set van 70 genen onderzocht bij patiënten die op basis van de klassieke factoren zoals onder andere leeftijd, inclusief of een vrouw al wel of niet in de menopauze is, en tumorkenmerken een hoog risico hebben op het krijgen van uitzaaiingen naar de organen. Met behulp van het resultaat van de Mammaprint kan beter ingeschat worden of deze patiënten baat hebben bij adjuvante chemotherapie d.w.z. of chemotherapie *de kans op uitzaaiingen in andere organen* voldoende vermindert. Met andere woorden, de MammaPrint test is dus in staat om de systemische behandeling van borstkanker in een vroeg stadium te de-escaleren.

Er zijn een aantal studies die onderzoek hebben gedaan met deze genetische testen zoals de MammaPrint om te kijken of de test ook kan voorspellen of patiënten baat hebben bij bestraling na een borstsparende operatie om de *kans op terugkeer van ziekte alleen in de borst* te verkleinen.

## UITEENZETTING PROEFSCHRIFT

In dit proefschrift worden er een aantal handvatten geboden om de behandeling van DCIS en vroeg-stadium borstkanker te kunnen verfijnen.

In **hoofdstuk 2** wordt onderzocht hoe levensstijl invloed heeft op het krijgen van invasieve borstkanker na een eerste diagnose van DCIS (primair DCIS). Dit hoofdstuk heeft als doel om de hiaten in kennis met betrekking tot DCIS te dichten en in kaart te brengen hoe je het risico op het krijgen van een invasief recidief kan verlagen door gedragsverandering (i.e. meer bewegen, stoppen roken, etc.).

**Hoofdstuk 3** beschrijft de resultaten van een grote groep ('cohort') van vrouwen in Nederland bij wie in de eerste plaats alleen DCIS was gediagnosticeerd. Deze informatie werd verkregen via het Integraal Kankercentrum Nederland (IKNL) en Pathologisch Anatomisch Landelijk Geautomatiseerd Archief (PALGA). Hierbij hebben wij gekeken naar het risico op het krijgen van een invasieve borstkanker na een eerste diagnose van DCIS in dezelfde borst als waar de DCIS aanvankelijk ontstaan was. Daarbij hebben we ook gepoogd risicofactoren te identificeren voor het krijgen van zo'n borstkanker.

In **Hoofdstuk 4** hebben we gekeken of kunstmatige intelligentie kan worden toegepast op röntgenfoto's van de borst. Hierbij was het doel om te kijken of met behulp van kunstmatige intelligentie de DCIS-gradering kan worden voorspeld op basis van het mammogram zonder weefselonderzoek. Tevens werd onderzocht of hiermee DCIS kan worden onderscheiden van invasieve borstkanker.

In **hoofdstuk 5** wordt gekeken of de Mammaprint gebruikt kan worden om patiënten te selecteren die geen baat zullen hebben van adjuvante radiotherapie.

Tot slot worden in **hoofdstuk 6** de bevindingen uit dit proefschrift samengevat en gekeken naar de klinische toepasbaarheid waarbij mogelijke vervolgstappen worden weergegeven.

# SAMENVATTING VAN DE HOOFDBEVINDINGEN

## De-escalatie van de behandeling van DCIS

Het overgrote deel van de patiënten met laag-risico DCIS (graad I of graad II DCIS dat positief is voor ER en negatief voor HER2), zal waarschijnlijk nooit een invasieve borstkanker ontwikkelen. Dit inzicht heeft ertoe geleid dat er momenteel klinische trials worden uitgevoerd om te kijken of het veilig is om de DCIS-afwijking niet te opereren maar jaarlijks te evalueren middels een mammografie. Als deze trials laten zien dat het veilig is om patiënten met laag-risico DCIS niet meer te behandelen, zal er een significant deel van deze patiënten in de toekomst niet meer geopereerd en bestraald worden. Identificatie van levensstijl factoren en andere risicofactoren die invloed hebben op eventuele progressie van DCIS, is daarin cruciaal. Met name de levensstijlfactoren welke door veranderd gedrag (i.e. stoppen met roken, afvallen) het risico op het krijgen van een invasieve borstkanker na een eerste diagnose van DCIS positief kunnen beïnvloeden zijn essentieel.

In **Hoofdstuk 2** hebben we door middel van een literatuurstudie in kaart gebracht wat hier over bekend is. We hebben laten zien dat er met name specifiek voor dit onderwerp een beperkt aantal studies zijn verricht. Er is beperkt bewijs dat een belaste familievoorgeschiedenis voor borstkanker (borstkanker bij moeder/zus/tantes etc.) een verhoogd risico geeft op het krijgen van borstkanker of een recidief van DCIS na een eerste diagnose van DCIS. Daarnaast hadden vrouwen die premenopauzaal zijn, een verhoogd BMI hebben en vrouwen die veel borstklierweefsel hebben, een verhoogd risico op het krijgen van borstkanker of een recidief van de DCIS-afwijking. De conclusie van dit onderzoek was dat met de huidige kennis er onvoldoende bewijs is om levensstijl veranderingen aan te bevelen die het risico op het krijgen van een invasieve borstkanker of een recidief DCIS verlagen. Dit kwam met name door het beperkte aantal beschikbare studies en het feit dat deze studies relatief kleine aantallen patiënten hadden geïncludeerd met een korte follow-up (tijd dat patiënten gevolgd worden tijdens een onderzoek). De lange follow-up is essentieel aangezien DCIS een aandoening is die lange tijd nodig heeft om progressie te vertonen naar invasieve borstkanker.

**Hoofdstuk 3** heeft onderzocht wat het effect is van de hedendaagse standaardbehandeling (chirurgie al dan niet gevolgd door bestraling) voor DCIS op het krijgen van een invasieve borstkanker na behandeling. Hierbij hebben we de absolute risico's en de relatieve risico op de progressie van DCIS berekend en onderzocht. Cumulatieve incidentie: is een frequentiemaat die in de epidemiologie wordt gebruikt als maatstaf om te kijken hoe vaak een ziekte optreedt in een bepaalde periode. Relatieve risico's ook wel de hazard ratio genoemd: geeft aan hoeveel meer of minder risico een groep personen gemiddeld over de follow-up periode loopt ten opzichte van een andere groep. Bijvoorbeeld een hazard ratio van 1,2, betekent dat je 20% meer kans hebt op de aandoening en een hazard ratio van 0.8 betekent 20% minder risico op de aandoening. We onderzochten in hoeverre de risico's afhingen van het type behandeling dat de vrouwen initieel gehad hadden. Dit onderzoek werd verricht in een Nederlands cohort van vrouwen met een eerste diagnose van DCIS tussen 2005 tot en met 2015. De follow-up

van deze patiënten was compleet tot februari 2020. Ons onderzoek liet een risicoreductie zien van ongeveer 50% t.o.v. een eerder vergelijkbare studie op het krijgen van een invasieve borstkanker bij patiënten die waren geopereerd middels borstsparende chirurgie en bij patiënten met borstsparende chirurgie + radiotherapie. Deze circa 50% risicoreductie was in vergelijking met een eerder onderzoek naar patiënten met primaire DCIS, die gediagnosticeerd waren in de periode van 1989 tot en 2004.

De eerdere studie die verricht werd door Elshof *et al*., had een mediane follow-up tijd van 10.7 jaar en rapporteerde cumulatieve incidenties van 8.8% bij patiënten na borstsparende chirurgie + radiotherapie, 15.4% na sparende chirurgie alleen en 1.9% voor patiënten die een borstamputatie kregen. De huidige studie in dit proefschrift had een mediane follow-up duur van 8.2 jaar en hierin werden incidenties gevonden van 3.1% voor patiënten die geopereerd waren middels borstsparende chirurgie + radiotherapie, 7.3% voor de patiënten geopereerd met alleen borstsparende chirurgie en 1.6% voor patiënten die een borstamputatie hadden gekregen. De circa 50% risicoreductie op het krijgen van een invasieve borstkanker na de behandeling van primaire diagnose DCIS werd niet gezien in de groep patiënten die waren behandeld door middel van een borstamputatie. Een andere belangrijke bevinding van de huidige studie is dat bestraling na een operatieve ingreep nog steeds ongeveer 50% verlaging geeft van het risico op invasieve borstkanker. Dit beschermende effect van bestraling na de behandeling van een primaire DCIS afwijking is ook aangetoond door de eerdere studie verricht door Elshof *et al*. Deze getoonde lage absolute risico's zijn klinisch relevant, ze geven namelijk goed het effect van de huidige behandeling van DCIS weer. Het eerdere onderzoek van Elshof *et al*., betrof een periode waarin er nog niet standaard radiotherapie werd toegepast na een borstsparende ingreep.

Bovendien was dit de implementatie fase van het bevolkingsonderzoek, met andere woorden in deze tijdsjaren werd nog niet iedereen die daarvoor in aanmerking kwam gescreend voor borstkanker. Mogelijke verklaringen voor deze dalende trend in absolute risico's voor het krijgen van een invasieve borstkanker na een primaire diagnose van DCIS zijn: toename van het aantal patiënten dat bestraald wordt, relatief meer patiënten met DCIS die gevonden zijn in het bevolkingsonderzoek, relatief meer kleinere DCIS afwijkingen die werden vastgesteld na introductie van de digitale mammografie, en het completer weghalen van de DCIS afwijkingen door een betere pre-operatieve beoordeling van patiënten met DCIS. Deze lage absolute risico's op het krijgen van een invasieve borstkanker na een diagnose zijn zeer belangrijk, zij rechtvaardigen namelijk de huidige inspanningen om de invasieve behandeling van DCIS patiënten te de-escaleren.

In **Hoofdstuk 4** hebben we gekeken naar de klinische toepasbaarheid van een kunstmatig intelligentie model om laag-risico DCIS (graad I of II DCIS, positief voor ER en negatief voor HER2) te kunnen identificeren en of het model in staat was om een invasieve borstkanker naast de DCIS-afwijking te identificeren. Hierbij hebben we ruim 600 mammografieën aangeboden aan het model en het laten leren om de DCIS met een eventuele invasieve borstkanker o.b.v.

calcificaties op de mammografie te identificeren. Daarna hebben wij het netwerk ook laten trainen om het onderscheid in classificatie van de graad van de DCIS te maken. De graad van de DCIS is een van de hoofdcriteria voor patiënten in de klinische trials aangezien alleen patiënten met een graad I of II DCIS kunnen deelnemen.

Ons uiteindelijke doel is om dit kunstmatige intelligentie model als ondersteunend middel toe te kunnen passen in de klinische praktijk zodat men nog zekerder kan zijn of het daadwerkelijk een laag-risico DCIS betreft. Dit onderzoek werd verricht op een dataset met 464 patiënten en de bijbehorende 681 mammografieën. De diagnose DCIS was gesteld tussen de jaren 2000 en 2014. Hierbij vonden we dat het model goed in staat was om het onderscheid te maken in patiënten met graad I of II versus graad III DCIS met een eventuele invasieve borstkanker naast de DCIS-afwijking. In het scenario waarbij alleen de opdracht aan het model werd gegeven om naar de gradering van DCIS te kijken (dus geen focus op een eventuele nabijgelegen invasieve borstkanker) werd een Area Under the Curve (AUC) van 0.72 behaald. De AUC geeft aan hoe goed en betrouwbaar een test is: 1 is een perfecte test, die alle zieken kan identificeren zonder dat er foutief niet-zieken toch als ziek worden getest ('fout-positief') en 0,5 is een waardeloze test, omdat die evenveel terecht-positieven als fout-positieven detecteert. Wanneer de opdracht werd gegeven om naast de classificatie ook te kijken naar een eventuele nabijgelegen invasieve borstkanker, werden scores van AUC 0.76 gehaald. Hieruit concludeerden wij dat ons kunstmatige intelligentie netwerk een goede voorspeller is voor de graad van DCIS en een goede 'verklikker' voor de aanwezigheid van een eventuele nabijgelegen invasieve borstkanker. Het model zou klinisch als ondersteuning voor de radioloog en patholoog kunnen worden toegepast nadat het model in een onafhankelijke dataset is gevalideerd om zo met nog meer zekerheid te kunnen zeggen of men daadwerkelijk te maken heeft met een laag-risico DCIS-afwijking en daardoor met meer zekerheid en veiligheid deel kan nemen aan de klinische trials.

## De-escalatie van de behandeling van vroegstadium borstkanker

In **hoofdstuk 5** werd de potentiële rol van de MammaPrint onderzocht om te kijken of de test een voorspellende waarde had met betrekking tot het krijgen van een locoregionaal recidief (recidief in de borst en/of in de nabijgelegen lymfeklieren) na borstsparende behandeling van een patiënt met borstkanker in een vroeg stadium. Momenteel zijn er een aantal studies die onderzoeken of het veilig is om radiotherapie weg te laten. In ons huidige onderzoek hebben we gekeken naar de associatie van de MammaPrint met het krijgen van invasief borstkanker in dezelfde borst. Ook hebben we gekeken naar hoe vaak vrouwen na 8 jaar weer borstkanker krijgen in dezelfde borst of in de omgeving (zoals bijvoorbeeld de lymfklieren in de oksel), de zogenaamde 'locoregionale recidief' (LRR), na de behandeling van de eerste borstkanker als die nog in een vroeg stadium is. In de gehele groep vonden wij een laag-risico voor het krijgen van LRR van 3.2% in patiënten die middels een borstsparende ingreep waren behandeld. Daarnaast hebben wij ook de incidentie bepaald van een lokaal recidief (recidief alleen in de borst). Hierbij werd een incidentie van slechts 2.3% gevonden bij 8 jaar follow-up. Dit risico werd nog lager als de MammaPrint aangaf dat het een laag risico tumor was, namelijk 2.0% bij 8 jaar follow-up. Helaas was de MammaPrint zelf geen onafhankelijke voorspeller voor

het krijgen van een LRR na een borstsparende behandeling van borstkanker in een vroeg stadium. Desondanks ondersteunen deze lage absolute risico's op het krijgen van een LRR de klinische trials die aan het onderzoeken zijn of radiotherapie in een specifieke groep patiënten achterwege gelaten kan worden. In onze optiek zijn potentiële kandidaten patiënten ouder dan 50 jaar, met een relatief kleine tumor die laaggradig is, dus langzaam groeit, en waarbij de MammaPrint een laag risico aangeeft.

## De blik naar voren en de klinische toepasbaarheid

**Active surveillance bij patiënten met laag-risico (graad I/II ER+ HER2-) DCIS**

Om de overbehandeling van DCIS tegen te gaan moet gedurende het diagnostisch proces en de potentiële behandeling van DCIS-patiënten op verschillende 'niveaus' overwogen worden om verdere diagnostiek te verrichten en een eventuele behandeling te starten. Op elk niveau van de diagnostiek en/of de behandeling moet worden bedacht wat het risico is van de DCIS-afwijking om uit te groeien tot borstkanker. Het PRECISION-initiatief zal op termijn hier uitkomst in bieden door het onderscheid te maken tussen gevaarlijke DCIS-afwijkingen en de onschuldige DCIS. Het merendeel (~80%) van de DCIS-patiënten presenteert zich met calcificaties die gedetecteerd worden tijdens bevolkingsonderzoek middels een mammografie.

In **hoofdstuk 4** hebben we een op kunstmatige intelligentie gebaseerd model ontwikkeld, dat in staat is om laag-risico DCIS te detecteren en te classificeren. Dit model zou dus op het niveau van diagnostiek middels een mammografie een rol kunnen gaan spelen. In de huidige praktijk wordt de diagnose DCIS gesteld o.b.v. een biopt. Het uiteindelijke doel van ons model is het biopt in elk geval deels te kunnen vervangen door het kunstmatige intelligentie model, immers kleven er ook risico's aan het verrichten van een biopt (i.e. infectie, bloeding, pijn). Het doel van hoofdstuk 4 in dit proefschrift was dat het model dient als ondersteuning in het rondkrijgen van de diagnose DCIS met de bijbehorende differentiatiegraad, zodat patiënten met meer veiligheid en zekerheid kunnen deelnemen aan de klinische trials. De volgende stap in het diagnostisch traject zou de toepasbaarheid van kunstmatige intelligente op verkregen borstbiopten zijn. Nadat er borstweefsel is verkregen via een biopt, wordt er een zogenaamde coupe (objectglaasje waarop gekeken kan worden hoe de DCIS-afwijking eruit ziet onder de microscoop) van gemaakt die door de patholoog wordt beoordeeld. Hierbij wordt gekeken of er sprake is van borstkanker, DCIS of een goedaardige afwijking. De beoordeling door de patholoog is de huidige gouden standaard. Het is echter bekend dat er variatie bestaat tussen pathologen in het graderen van DCIS. Kunstmatige intelligentie zou meer consistentie kunnen creëren in de gradering van DCIS op basis van hoe de DCIS-afwijking er onder de microscoop uitziet. Er bestaan momenteel kunstmatige intelligentie modellen die met hoge zekerheid al kunnen zeggen of er sprake is van een kwaadaardige tumor of DCIS. Op het moment dat de diagnose DCIS ondersteund door kunstmatige intelligentie modellen vrijwel zeker is, zou men kunnen kijken naar risicofactoren geassocieerd met het ontstaan van borstkanker uit de DCIS-afwijking. Er is al veel onderzoek verricht naar potentiële risicofactoren voor het krijgen van borstkanker na de diagnose DCIS.

Helaas is de klinische toepasbaarheid van deze eigenschappen om hoog-risico van laag-risico DCIS te kunnen onderscheiden allesbehalve zeker, omdat resultaten in de beschikbare wetenschappelijke literatuur vaak gebaseerd zijn op analyses van kleine aantallen patiënten waarvan de representativiteit met betrekking tot alle vrouwen met DCIS sterk ter discussie staat. Bovendien zijn deze resultaten vrijwel nooit bevestigd in andere groepen patiënten ('gevalideerd').

In **hoofdstuk 2** hebben we getoond dat er gering bewijs is voor het krijgen van borstkanker na een eerste diagnose van DCIS wanneer een patiënt een belaste familievoorgeschiedenis heeft voor borstkanker (borstkanker bij moeder, zus(sen), tantes, enzovoort). Daarnaast hadden vrouwen die premenopauzaal zijn, een verhoogd BMI hebben en vrouwen die compact borstklierweefsel hebben een verhoogd risico op het krijgen van borstkanker of een recidief van de DCIS-afwijking. De conclusie van dit literatuuronderzoek was, dat met de huidige kennis er onvoldoende bewijs is om levensstijl veranderingen aan te bevelen. De huidige klinische trials sturen vragenlijsten naar de deelnemende patiënten waarin levensstijlfactoren worden uitgevraagd op een systematische wijze. De resultaten hiervan kunnen dan op hun beurt weer worden toegepast in de klinische praktijk om risico-reducerend gedrag bij patiënten gericht te bevorderen.

De in **hoofdstuk 3** getoonde lage absolute risico's op het krijgen van een invasieve borsttumor na de behandeling van DCIS kunnen hier een bijdrage in leveren. De kansen zijn erg klein dat je een invasieve tumor krijgt na DCIS. Bovendien is het zo, dat de kans op het missen van een invasieve tumor, wanneer de diagnose DCIS wordt gesteld op basis van een biopt, lager is dan voorheen aangetoond. Zo werd door Groen *et al*., gevonden dat het veelal kleine tumoren zijn die geen nadelig effect hebben op de overleving van deze patiënten. Deze lage risico's en goede prognoses zijn van belang bij de communicatie over DCIS van artsen naar patiënten toe. Zij kunnen bijdragen aan het proces om samen met de patiënt tot een besluit te komen om een DCIS-afwijking wel of niet te gaan behandelen. Een ander interessant gegeven is, dat momenteel de meerderheid van de vrouwen die wordt gevraagd om deel te nemen aan de LORD-trial, zelf kiest om niet behandeld te worden voor hun DCIS-afwijking.

De hierboven beschreven toepassingen moet men in de toekomst bundelen teneinde individuele benadering toe te passen bij een patiënt met DCIS. Behoeft een patiënt een behandeling of is het veilig om de afwijking jaarlijks te gaan volgen middels röntgenfoto's van de borst?

## Genetische testen voor de de-escalatie van radiotherapie bij borstkanker in een vroeg stadium

In **hoofdstuk 5** lieten we zien dat vijf factoren, waaronder de MammaPrint uitslag, geassocieerd waren met het krijgen van een locoregionale recidief (LRR). Daarnaast zagen we in de gehele groep vrouwen behandeld middels een borstsparende operatie een lage 8-jaars incidentie van 3.2% voor het krijgen van LRR. Hierbij zagen we ook dat wanneer de MammaPrint een laag risico tumor aangaf de incidentie slechts 2.7% was en in de ultra-laag risicogroep nog maar

2.3%. Helaas was deze associatie niet meer significant in een multivariabele analyse en was de MammaPrint dus geen onafhankelijke voorspeller voor het krijgen van LRR.

De bevindingen in hoofdstuk 5 zijn vergelijkbaar met andere studies die zijn gedaan, echter met het gebruik van Oncotype als genetische test. Daarentegen zagen zij wel een onafhankelijke associatie van de Oncotype test met het krijgen van LRR.

Bij het de-escaleren van radiotherapie bij de behandeling van een vroeg stadium borstkanker kunnen dezelfde strategieën toegepast worden zoals hierboven beschreven voor de benadering van DCIS. Kunstmatige intelligentie zou kunnen worden toegepast op mammografieën van patiënten met in een vroeg stadium borstkanker om te kijken of daaruit karakteristieken gefilterd kunnen worden die een voorspellende waarde hebben op het krijgen van LRR. Hetzelfde geldt voor de verkregen pathologische coupes. Deze verkregen karakteristieken kunnen samen naast de klassieke risicofactoren in combinatie met de MammaPrint testuitslag worden toegepast om een persoonlijke behandeling aan te kunnen bieden bij patiënten met borstkanker in een vroeg stadium. Daarbij kunnen onze gevonden lage risico's op het krijgen van een LRR in spreekkamer worden toegepast om de daadwerkelijke risico's goed uit te kunnen leggen aan patiënten met borstkanker wanneer overwogen wordt om bestraling achterwege te laten.

## CONCLUSIE

Uit dit proefschrift blijkt dat met de huidige kennis van DCIS het nu nog erg lastig is om DCIS met een hoog risico op uitgroei tot borstkanker te kunnen onderscheiden van DCIS waarbij dit risico heel laag is. Kunstmatige intelligentie op het niveau van de röntgenfoto van de borst en op het niveau van hoe de DCIS-afwijking eruitziet onder de microscoop is hierin veelbelovend. Om dit onderscheid te kunnen maken worden momenteel in meerdere werkgroepen van het PRECISION-initiatief getest op betrouwbaarheid. Verder hebben wij laten zien dat er momenteel te weinig informatie is over de bijdrage van gedragsveranderingen aan risico-reductie op progressie van DCIS naar borstkanker. De vragenlijsten in de klinische trials zullen dit in de toekomst inzichtelijk gaan maken en daarin ook handvatten kunnen gaan bieden voor artsen en patiënten. Daarnaast hebben we aangetoond dat het risico op het krijgen van invasieve borstkanker erg klein is na de behandeling van een vrouw met DCIS.

Wat betreft de toegevoegde waarde van chemotherapie voor borstkanker in een vroeg stadium, bleek dat de MammaPrint niet geschikt is om het risico op een locoregionale recidief in te schatten, waarschijnlijk ook omdat de kans daarop sowieso heel laag is. Dit laat onverlet dat deze test waarschijnlijk wel nut kan hebben in de beslissing of er al dan niet aanvullende chemotherapie gegeven moet worden bij een deel van de vrouwen met oestrogeenreceptor-positieve, HER2-negatieve borstkanker met ongunstige klinische kenmerken.

# LIST OF PUBLICATIONS

## Publications, part of this thesis

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# ABOUT THE AUTHOR

Sena Alaeikhanehshir was born in Teheran, Iran, on August the 20th, 1988. In 2008, he graduated from high school and the same year he started studying medicine at the University of Amsterdam – Academical Medical Center, Amsterdam. For his bachelor degree he enrolled in a scientific internship, in which he investigated the relationship of developing an aneurysm of the posterior circumflex humeral artery (one of the branches of the axillary artery) in elite volleyball athletes due to their overhead strike of the ball. This project was under the supervision of dr. Paul Kuijer, dr. Daan van de Pol (at the time PhD-student) and prof. dr. Mario Maas, and was a combined project involving the department of occupational health, radiology, and vascular surgery. This work led to several publications (not in this thesis), and was extended to another scientific internship for the writing of his master thesis. During this period Sena discovered his affiliation with science and decided to pursue a PhD after graduating from medical school.

In 2017 he attended his final medical internship at the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital, at the department of surgical oncology. Here, he met dr. Frederieke van Duijnhoven, prof. dr. Jelle Wesseling and dr. Esther Lips. After the pleasant introduction with prof. dr. Jelle Wesseling and dr. Esther lips, Sena started his PhD trajectory in the group of prof. dr. Jelle Wesseling in July 2017. During the first year of his PhD, Sena focused on increasing patient accrual for the LORD-trial together with Carine Sondermeijer (clinical project manager) and later also joined by Renée Schmitz (MD PhD-student group Wesseling). After several adaptions were made to the LORD-trial, the LORD-trial is now a successful patient preference trial with over 1200 included patients. Following the successful start of the LORD trial, he continued his research efforts into diagnosis and treatment of DCIS, the results of which are described in this thesis. The project investigating the prognostic value of MammaPrint in locoregional recurrences was performed in close collaboration with prof. dr. Emiel Rutgers and prof. dr. Laura van ‘t Veer.

While finishing his last articles, Sena started working in the surgery department in the Maasstad Hospital in Rotterdam, and as per March 2023 he is a resident in training to become a general practitioner. He also holds a position as a medical advisor at Hybion and 10Kate laboratories.

Sena lives together with Marie-Claire Engelen in Amsterdam. The household currently exists of two cats, called Puss and Boots. In 2021 their family was expanded by adopting a four year old French bulldog named Harry.

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