TITLE PAGE

Title:

A prediction model for underestimation of invasive breast cancer after a biopsy diagnosis of ductal carcinoma in situ: based on 2 892 biopsies and 589 invasive cancers

Running Title:

Prediction of underestimation of breast cancer

Authors:

Claudia J.C. Meurs*[,1], Joost van Rosmalen[2], Marian B.E. Menke-Pluijmers[3], Albert P.M. ter Braak[4], Linda de Munck[5], Sabine Siesling[5], Pieter J. Westenend*[,6,7]

[1] CMAnalyzing, Gounodstraat 16, 6904 HC, Zevenaar, the Netherlands

[2] Department of Biostatistics, University Medical Center Rotterdam, Wytemaweg 80, 3015 CN Rotterdam, the Netherlands

[3] Department of Surgery, Albert Schweitzer Hospital, PO Box 444, 3300 AK Dordrecht, the Netherlands

[4] Department of Radiology, Albert Schweitzer Hospital, PO Box 444, 3300 AK Dordrecht, the Netherlands[5] Department of Research, Netherlands Comprehensive Cancer Organisation, PO Box 19079, 3501 DB Utrecht, the Netherlands

[6] Laboratory of Pathology Dordrecht, Karel Lotsyweg 145, 3318 AL Dordrecht, the Netherlands

[7] Regional screening organization South West the Netherlands, Maasstadweg 12, 3079 DZ Rotterdam, the Netherlands

Corresponding author:

dr P.J. Westenend

Laboratory of Pathology Dordrecht, Karel Lotsyweg 145, 3318 AL Dordrecht, the Netherlands

Telephone: +031 78 6542100

E-mail: pwestenend@paldordrecht.nl

ABSTRACT

Background:

Patients with a biopsy diagnosis of ductal carcinoma in situ (DCIS) might be diagnosed with invasive breast cancer at excision, a phenomenon known as underestimation. Patients with DCIS are treated based on the risk of underestimation or progression to invasive cancer. The aim of our study was to expand the knowledge on underestimation and to develop a prediction model.

Methods:

Population-based data were retrieved from the Dutch Pathology Registry and the Netherlands Cancer Registry for DCIS between January 2011 and June 2012.

Results:

Of 2 892 DCIS biopsies, 21% were underestimated invasive breast cancers. In multivariable analysis, risk factors were high grade DCIS (OR 1.43, 95%CI 1.05-1.95), a palpable tumour (OR 2.22, 95%CI 1.76-2.81), a BI-RADS score 5 (OR 2.36, 95%CI 1.80-3.09), and a suspected invasive component at biopsy (OR 3.84, 95% CI 2.69-5.46). The predicted risk for underestimation ranged from 9.5% to 80.2%, with a median of 14.7%. Of the 596 invasive cancers, 39% had unfavourable features.

Conclusions:

The risk for an underestimated diagnosis of invasive breast cancer after a diagnosis of DCIS at biopsy is considerable. With our prediction model, the individual risk of underestimation can be calculated based on routinely available pre-operatively known risk factors (https://www.evidencio.com/models/show/1074).

KEYWORDS

DCIS

ductal carcinoma in situ

breast cancer

underestimation

upstaging

risk factors

prediction model

unfavourable features

minimal-volume DCIS

BACKGROUND

Patients with ductal carcinoma in situ (DCIS) are treated based on the risk of underestimation or progression to invasive cancer. The standard treatment for patients with a biopsy diagnosis DCIS is wide local excision with radiation or mastectomy. Often a sentinel lymph node (SLN) biopsy is advised for axillary staging.[1,2] Both the standard treatment and the use of the SLN biopsy can constitute overtreatment. The standard treatment might be disproportionate for screen-detected DCIS patients that have a high chance that the DCIS would not even have been detected during their lifetime.[3] It has been estimated that between 14% and 53% of DCIS progress into invasive breast cancer.[4,5]

To address overtreatment, phase III trials investigate the safety of active surveillance of DCIS patients at low risk for developing or having invasive breast cancer.[6–11] Active surveillance is based on the result of the biopsy. By modelling of active surveillance of DCIS patients, the disease-specific cumulative mortality was related to underestimation.[12,13] Underestimation is the phenomenon that the invasive breast cancer is undetected at pre-operative biopsy and only becomes evident after pathological examination of the excision material. The use of the SLN biopsy can also constitute overtreatment. The SLN biopsy is done if an mastectomy is chosen and also for patients undergoing wide local excision who are at high risk of having an underestimated invasive breast cancer.[1,2] The reported risk of underestimation varies from 14% to 43% [14,15], and in a meta-analysis it was estimated to be 25.9% (95%CI: 22.5%-29.5%) [16]. These rates indicate that many patients will still have the diagnosis DCIS after examination of the excision material, so the SLN biopsy would not have been necessary.

Knowledge on the risk of underestimation is important in selecting high-risk or low-risk patients for treatment or active surveillance. The most frequently reported risk factors for underestimation are DCIS grade and factors found with radiological diagnostic work-up, such as the size of the lesion, mass on mammography or ultrasonography, and the BI-RADS score.[14–27] Furthermore, these studies reported that the risk of underestimation was associated with age, palpability, histologic suspicion of invasion, image guidance method, biopsy device and other factors. An overview of the found risk factors for underestimation is given in table 1. Based on

risk factors, several studies developed prediction models with the purpose to select patients for SLN biopsy [14,17,24,28–30].

Besides the underestimation rate, other factors are useful for making a treatment plan for a patient diagnosed at biopsy with DCIS. First of all, for some of these patients, no residual disease is found in the excision material; this is defined as minimal-volume DCIS. A rate of 9.3% was reported.[31] Second, of the underestimated invasive breast cancers the information on unfavourable features is of interest; the reported Her2Neu status is quite high [22,23] and the hormonal receptor statuses vary [21–23,25,26].

The diversity of identified risk factors for underestimation has resulted in differences between the clinical guidelines used in different countries. For example, according to the NICE guideline (United Kingdom) for the use of the SLN biopsy, risk factors for underestimation are a palpable mass or extensive micro-calcifications, while according to the Dutch guideline, these are age <55 years, intermediate or high grade DCIS, a mass on mammography and a suspected invasive component based on biopsy. For active surveillance, the main criterion for patient selection in Iow-risk DCIS trials are DCIS grade, and patients with mass or other relevant factors are excluded.

The diversity in risk factors might be due to the study designs, since the investigated potential risk factors varied and many studies on underestimation were single institution studies with limited numbers of cases. Information at population level is lacking. In addition, there is hardly any data on minimal-volume DCIS nor on the presence of unfavourable features of the underestimated invasive breast cancer.

The aim of our study was to expand the knowledge on underestimation of invasive breast cancer for patients with a biopsy diagnosis DCIS in routine clinical practice in the Netherlands and to develop a prediction model based on population data. We also analysed the association of predicted risk with minimal-volume DCIS and with the occurrence of unfavourable features of the underestimated invasive breast cancer. The results could contribute to a treatment plan that is both patient-specific and helps in reducing overtreatment.

METHODS

Study design and population. This study used retrospective data that was nationwide.. Data were received from the Dutch Pathology Registry, which is managed by PALGA (the nationwide network and registry of histo- and cytopathology in the Netherlands) and were matched with data from the Netherlands Cancer Registry (NCR), which is hosted by the IKNL (the Netherlands Comprehensive Cancer Organisation). The Dutch Pathology Registry contains all the reports written by pathologists of material examined in all Dutch Pathology Laboratories.[32] The NCR contains information that is collected and coded by specially trained registration clerks from the hospitals' patient files of every patient with cancer, after notification from PALGA.[33]

Lesions were selected from PALGA, since this study is based on the biopsy diagnosis and the NCR registers the final diagnosis at excision. Histological breast biopsies were selected that were performed in the period January 1, 2011 until June 30, 2012. The diagnosis should be carcinoma in situ, with no invasive cancer in the same biopsy, no lymph node metastases found preoperative and also not melanoma in situ, Morbus Paget or Morbus Bowen. DCIS with micro-invasion was not included, nor were intracystic carcinoma, lobular carcinoma in situ (LCIS) and ductal hyperplasia lesions. Based on the PALGA conclusion (free text field) information on the diagnosis, DCIS grade, suspected invasive component, synchronous contralateral tumour and ipsilateral history were coded. The data were extended with those registered by the NCR; age, ipsilateral history, detection mode, palpability, BI-RADS score, pre-operative MRI, multidisciplinary team meeting, type of first resection, nodal status, and of the invasive cancers the morphology, grade, the receptors ER, PR, Her2Neu and tumour size. Lesions were excluded in case of incomplete registration, primarily no excision of the lesion, a biopsy diagnosis that was inconclusive as to whether the lesion was benign or DCIS, and in case of an ipsilateral history of DCIS or invasive breast cancer.

Data was categorized: the category detection mode consisted of screen-detected DCIS (DCIS detected within 12 months after a positive mammography at the population-based screening program) and otherwise detected DCIS (all other DCIS). DCIS grade was categorized into low, intermediate or high. If the tumour consisted of two different grades or if the grade was inconclusive, the highest DCIS grade was chosen. Suspected invasive component was coded

'yes' if it was mentioned as such in the conclusion of the pathology report and if it was not refuted with potential additional staining. For the BI-RADS score, no subgroup information for score 4 was available.[34] A synchronous contralateral lesion was defined as DCIS or invasive breast cancer in both breasts with a difference in incidence date of less than 3 months. Underestimation was defined as invasive cancer or micro-invasion found at excision after a biopsy diagnosis DCIS. Tumours were graded according to the Bloom-Richardson grade or another equivalent method. Tumour size and nodal status were used to categorize the TNM stage.[35] Underestimated invasive breast cancers were categorized based on unfavourable features. In the Dutch guideline[36], they were defined as features that, if present, would mean that systemic therapy would be recommended, because the absolute 10-year mortality risk was at least 15%. These features of the invasive cancers were:

- Her2Neu positive with size >5 mm
- age <35 years, except size ≤10 mm with grade I
- size >10 mm but ≤20 mm with grade II or III
- size >20 mm
- positive lymph nodes

Statistical analysis. The data were analysed to investigate associations and to develop a prediction model. First, the distribution of patient characteristics and potential risk factors was compared between patients with and without underestimated invasive breast cancer for the non-missing values, using the Mann-Whitney test or the Pearson chi-square test. The associations between potential risk factors were analysed with the Pearson chi-square test or the Fisher exact test. The risk for underestimation of invasive breast cancer was analysed with logistic regression analysis. The threshold for significance of risk factors was the two-sided p-value of 0.05. In this logistic regression, we only included characteristics that were known as independent variables prior to operation: age, detection mode, palpability, BI-RADS score, DCIS grade and suspected invasive component at biopsy. The decision to do a pre-operative MRI and the type of first resection were not included in the model, because no causal association with underestimation was expected. Next, to ensure that all relevant variables were

included in the prediction model, the independent variables were chosen via stepwise backward selection with a p-value threshold for elimination of $p<0.20$. In the prediction model, age was tested multiple times: continuously using both linear and quadratic terms and dichotomously with thresholds of 40, 45 and 55 years for comparison with previous publications.[1,6,21] Interaction was tested for combinations that were clinically the most plausible: suspected invasive component and DCIS grade, age <45 years (based on cut-off age in active surveillance) in combination with BI-RADS score, or palpability, or DCIS grade. To account for missing data, multiple imputation with fully conditional specification was used in the multivariable logistic analysis. Twenty imputed data sets were generated, and the results were pooled according to Rubin's rules. Based on the imputed data, a formula was defined to predict the risk. Finally, internal validation of the model was performed with bootstrap repetitions (200 times). The logistic regression model was evaluated with the area under the curve (AUC) of the receiver operating characteristic (ROC). Based on the predicted risks, patients were divided into five subgroups, and the association with minimal-volume DCIS and unfavourable features was analysed with the p-trend test for proportions. The analyses were done with STATA statistics/data analysis, version 13.1, StataCorp, Texas and in R, with the rms package for the evaluation of the predictive performance and the mice package for multiple imputation.

RESULTS

Of 3 281 lesions that were selected with a preoperative biopsy diagnosis DCIS, 64 (2.0%) were excluded because they were not registered in the NCR, and 15 (0.5%) because registration was incomplete. In addition, to answer the research question accurately, more were excluded: 60 (1.8%) that did primarily not undergo excision, 143 (4.4%) for which the biopsy diagnosis was inconclusive and 107 (3.3%) with an ipsilateral history of DCIS or invasive breast cancer, resulting in 2 892 DCIS diagnoses included in the study. Of these, 379 (13%) had missing data for one or more potential risk factor: 148 for palpability, 223 for BI-RADS score, 84 for DCIS grade and 81 for detection mode.

Of the 2 892 DCIS diagnoses at biopsy, 596 (20.6%) were underestimated, as the diagnosis was invasive breast cancer at excision. Table 2 shows patient and biopsy characteristics and their relation with underestimation. Of biopsy DCIS, 66% was screen-detected, 22% was palpable, 13% had a BI-RADS score 3, 75% had a BI-RADS score 4, 12% had a BI-RADS score 5 and 5% had a suspected invasive component at biopsy. The DCIS grade distribution was 15% low, 39% intermediate and 46% high (p=0.001). Of the intermediates, 13% were low to intermediate or consisted of both low and intermediate grade DCIS, 21% were intermediate to high grade or consisted of both intermediate and high grade DCIS. The underestimation rate was 21% on average for all cases, 26% for non-screen-detected lesions, 36% for palpable lesions, 41% for BI-RADS score 5 and 23% for high grade DCIS (p-values between different categories were less than 0.001 for all variables). The risk factors with the greatest differences in underestimation rate for subgroups were palpability, with a 20% higher rate for palpable than for non-palpable lesions, BI-RADS score, with a 25% higher rate for BI-RADS score 5 than for score 3, and suspected invasive component, with a 31% higher rate for suspected invasive component than for none. Of 596 invasive breast cancers, 47 were T1mi and 207 were T1a. The underestimation rate when filtering out all lesions of 5 mm or smaller was 11.8% (n=342).

Table 3 shows the results of univariable and multivariable analysis of the risk for underestimation of pre-operatively known potential risk factors for invasive breast cancer. Age and detection mode were statistically significant in univariable analysis, but not in multivariable

analysis. Both were associated with palpability and BI-RADS score, and age was also associated with DCIS grade (shown in supplement 1, along with other associations). In multivariable analysis, grade, palpability, BI-RADS score and a suspected component were significant.

For each of the 2 892 DCIS, the risk of an underestimated invasive breast cancer was calculated based on the prediction model with the following formula:

Predicted risk=$\left(\frac{1}{1+e^{-Score}}\right)$*100%,

with score=-2.1131 + 0.1555*detection_mode_otherwise + 0.7985*palpable - 0.1464*BI-RADS_score_3 + 0.8589*BI-RADS_score_5 + 0.3111*intermediate_DCIS_grade + 0.3571*high_DCIS_grade + 1.3445*suspected_invasive_component

where for all risk factors: 1=if condition applies, 0=otherwise.

For example, the predicted risk is calculated as follows for a screen-detected DCIS which is non-palpable, has a BI-RADS score 4, an intermediate grade and no suspected invasive component:

Score=-2.1131 + 0.1555*0 +0.7985*0 - 0.1464*0 + 0.8589*0 + 0.3111*1 + 0.3571*0 + 1.3445*0 = -1.802, and Predicted risk=$\left(\frac{1}{1+e^{-(-1.802)}}\right)$*100%= 14.2%

The risk for an individual patient can be calculated in a user-friendly way with a calculation tool in evidencio, https://www.evidencio.com/models/show/1074.

The predicted risks ranged from 9.5% to 80.2%, the mean was 20.6% and the median was 14.7%. The predicted risk for underestimation was on average 27.4% for the biopsy DCIS that were underestimated invasive breast cancers, whereas it was on average 18.8% for the biopsy DCIS that also had the DCIS diagnosis at excision. The predicted risks for each combination of risk factors are shown in supplement 2. The matching of the predicted risks with the observed rate is shown in supplement 3.

The ability of the model to separate DCIS as diagnosis after excision from underestimated invasive breast cancer is shown in figure 1. To draw this figure, the DCIS were divided into low-risk or high-risk DCIS based on a cut-off point, and for each point the sensitivity and 1-specificty was calculated. In this study, the sensitivity means the rate of underestimated invasive breast cancer that was correctly predicted as high-risk, and 1-specificity means the rate of DCIS at

excision that was falsely predicted as high-risk. The AUC (c-index) of the ROC was 0.668 and the AUC, corrected for optimism by bootstrapping, was 0.661. The AUC for a model based only on lesions greater than 5 mm was 0.69.

Based on the predicted risks, the DCIS biopsies were divided into five subgroups; the characteristics of each subgroup are shown in table 4. From the subgroups with the lowest predicted risk to the subgroup with the highest predicted risk, the underestimation rate increased from 10.7% to 40.1%.

The associations between the predicted risks and minimal-volume DCIS were as follows: the rates of minimal-volume DCIS decreased from 18.0% to 1.6% from the subgroups with the lowest predicted risk to the subgroup with the highest predicted risk, $p<0.001$ (see table 4). On average, 6.8% of DCIS diagnoses at biopsy were minimal-volume DCIS, in which the DCIS was completely removed via biopsy (meaning 8.5% of the 2 296 lesions with the DCIS diagnosis at excision).

The associations between the predicted risks and unfavourable features were as follows: the percentage of invasive breast cancers with unfavourable features increased from 15.9% to 49.5% from the lowest to the highest predicted risk group, $p<0.001$ (see table 4). On average, 39% of the invasive breast cancers had unfavourable features. More details on the distribution of tumour characteristics of the 596 invasive breast cancers are shown in supplement 4. Of the invasive breast cancers, 27% were grade III, 26% were Her2Neu positive, 8% were triple negative, 77% were TNM stage 1A (size at maximum 2.0 cm and no metastasis), and the median size was 6 mm.

DISCUSSION

The aim of our study was to expand the knowledge on underestimation of invasive breast cancer at core needle biopsy in the routine clinical practice in the Netherlands and to develop a prediction model based on analysis of a retrospective population-based dataset of 2 892 DCIS diagnoses. We also analysed the association of predicted risk with minimal-volume DCIS and with the occurrence of unfavourable features of the underestimated invasive breast cancer.

The risk for underestimation of invasive breast cancer after a DCIS diagnosis was almost 21%. Pre-operatively known risk factors for an underestimated diagnosis of invasive breast cancer were a high DCIS grade, a palpable tumour, a BI-RADS score 5 and a histologically suspected invasive component. Detection mode was also included in the model although the association with underestimation was comparably weak. The predicted risk for underestimation ranged from 9.5% to 80.2%. Of the 596 underestimated invasive breast cancers, 39% had unfavourable features. Of the DCIS diagnoses at excisional pathology, 6.8% were minimal-volume DCIS.

The underestimation rate of 20.6% shows that excision of the DCIS is still not only important for preventing DCIS from progressing to invasive breast cancer but also for finding already existing invasive breast cancers. The rate found in our study was in-between the 25.9% of a meta-analysis published in 2011 and the recently reported 14.1% of a large single-institution study.[14,16] The underestimation rate is associated with the diagnostic work up whereby there is a tendency to decreasing underestimation rates in more recent time period. This study used data from 2011 and 2012. At that time vacuum assisted biopsy was not yet commonly used in the Netherlands, therefore we assume that the underestimation rate currently will be somewhat lower in the Netherlands. And in the period 2011-2012 hospitals often used screen-film mammography but the screening mammography was already digitized, therefore no major difference in underestimation rate The Netherlands currently is assumed because of this change in technique.

This population-based study showed several clinical, radiological and pathological features that are all routinely available before operation as risk factors for underestimation.

The risk factors we found are partly similar to those reported in literature. Differences could be due to sample size, as this study was much larger than other studies: studies in literature had 172 to 834 cases and up to 145 events, whereas we had 2892 cases and 589 events. Differences in study outcomes could also be caused by the combination of available data and the correlation between many data. For age, others found various risks for the youngest age category: no increase [25], increased but not significantly so [16] and univariable significant but not in multivariable analysis [14,21]. In our study, young age was also only univariably associated with underestimation. For DCIS grade, the risk of underestimation for intermediate grade was in-between the risk for low and high grade DCIS. This was also reported by some other studies [14,20,27], whereas others reported the risk for intermediate grade DCIS as comparable to that of the high grade risk [19,25]. In our study the DCIS grade was less discriminative than the other risk factors in the model, but on the other hand the underestimation rate of 15% for low DCIS grade was the lowest rate for a subgroup in the model and high grade was the largest subgroup with an increased risk. Palpability of the lesion has consistently been reported as a risk factor, which this study could confirm.[15,16,18,19,22–24,26,37] The BI-RADS score is an assessment categorization that should give an indication of the likelihood of cancer based on the interpretation of the radiologist. We showed that it is associated with the underestimation rate; the difference between BI-RADS score 4 and 5 was 23% in underestimation rate, which is much larger than the 7-8% found by others.[16,21] A larger difference was reported in a study with a high average underestimation rate due to a high rate of micro-invasion.[15] Still, the study of Kim is interesting because they found a somewhat higher underestimation rate for BI-RADS score 4c, compared to 4a and 4b. It is worth noting that the BI-RADS score has not yet been investigated very extensively. A suspected invasive component has also only been reported in a limited number of studies.[23,24]; all found a high risk for underestimation for biopsies with a suspected component.

The prediction model we developed with the identified risk factors must be used wisely. For selecting high-risk lesions it has to be noted that lesions with a high predicted risk still have a good chance of a final diagnosis of DCIS since the sensitivity of the model was low. The sensitivity or the AUC was higher in several other studies.[14,17,22,24,28] Each study with a

prediction model used different risk factors and therefore the models are not easily comparable. This has also been demonstrated in external validation of studies that applied published models to their cases; one study demonstrated a tendency towards lower or higher numbers of observed underestimates than expected [29], and another previous study demonstrated validation AUCs of 0.59 to 0.66, whereas the studies they validated reported validities of 0.70 to 0.85 [14]. The low AUC in this study could also be due to the absence of certain data that might have been important, such as the type of biopsy device and the size of the lesion on mammography. This is shown in table 1 were the references that were made bold are the results of the studies making a prediction model whereas the variable names that are given in bold are the variables that were analysed in this study.

Part of the DCIS were minimal-volume DCIS and thus removed in the biopsy itself. In this study minimal-volume DCIS was associated with the predicted underestimation risk. To our knowledge, this information has never been demonstrated before; one study demonstrated a similar rate of minimal-volume DCIS, but the association with underestimation was not investigated.[31] In our study, the minimal-volume DCIS was higher for the predicted low-risk group.

The invasive breast tumours that were found at excision were heterogeneous in prognostic and predictive features. Underestimated invasive tumours are often small: the median size was 6 mm, which is in line with or somewhat lower than the results of other studies.[17,25–27] On the other hand, 8% were TNM stage IIB or III, and 20% were triple negative or ER-PR-Her2Neu+. Where other studies analysed none or a few tumour characteristics, we had numerous tumour-related data of the 589 underestimates. Based on these data, we calculated the rate of cancers with unfavourable features, which was 39%. For these patients, systemic therapy was indicated. In our study, the rate of unfavourable features was higher for the predicted high-risk DCIS group.

Due to its retrospective nature, this study has certain limitations. A limitation in interpreting the results is that the pre-operative decisions and techniques were not standardized, and therefore the preferences of the treating physicians and the patients will have influenced the underestimation results. For instance, for a high grade DCIS with histological

suspicion of invasiveness, the biopsy can be repeated (and invasive breast cancer might be found pre-operatively) or initial treatment can be started (with an increased risk of underestimation). Also, for DCIS grade, other studies might have used different grading systems. Another limitation is that results of observational studies are difficult to compare because of differences in diagnostic work-up, differences in major selection criteria, such as the presence of micro-invasion, differences in investigated risk factors and associations between the investigated risk factors. Our dataset did not provide information on the number of biopsies nor on the biopsy device, and hence the amount of tumour taken at biopsy was not known. Some other factors were not available either, such as the presence of comedo-necrosis, the breast density, the visibility of the lesion on ultrasound, the presence of mammographic mass or the size of the lesion seen on the mammogram.

The model in this study is based on a large dataset that is based on nation-wide Dutch data, and it demonstrated the association of risk for underestimation with minimal-volume DCIS and unfavourable features of invasive cancer, which makes the results valuable. The prediction model could be improved by adding additional data; the most interesting targets of investigation for future research are the biopsy type and mammography-related data: BI-RADS score 4 subcategories, the underlying reasons for a BI-RADS score (such as mass), size of the lesion, and presence of residual mammographic abnormalities after biopsy. Furthermore, the prediction model should be validated externally.

Conclusion. Our results demonstrated that the risk for an underestimated diagnosis of invasive breast cancer after a diagnosis of DCIS at biopsy is considerable. Of these invasive breast cancers, two-fifth have unfavourable features. With our prediction model, the individual risk of underestimation can be calculated based on routinely available pre-operatively known risk factors

ADDITIONAL INFORMATION

Ethics approval:

The study was approved by the scientific committee of PALGA (14.025 LZV1073) and the Privacy Review Board of IKNL (K14.021).

Availability of data:

The dataset generated for this current study are not publicly available due additional research questions to be answered but is available from the corresponding author on reasonable request. The prediction model is available for external validation via Evidencio (model 1074).

Conflict of interest:

The authors declare no conflict of interest.

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Authorship:

Study conception: CM / PW, study design: CM / JR / MM / PW, data coding: CM / PW, data analyses: CM / JR, data interpretation: CM / JR / MM / AB / LM / SS / PW, drafting article: CM, revision article: JR / MM / AB / LM / SS / PW.

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SUPPLEMENTARY INFORMATION

Supplementary information is available at the British Journal of Cancer's website. Supplement 1 (PDF) shows the associations in occurrence of the potential risk factors. Supplement 2 (PDF) lists the predicted risks for each combination of risk factors that was present in our dataset. Supplement 3 (PDF) shows the calibration plot of one of the imputed datasets. Supplement 4 (PDF) shows the tumour characteristics of underestimated invasive breast cancers.

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Figure 1: Performance of the model in relation to the chosen cut-off point of the predicted risks.

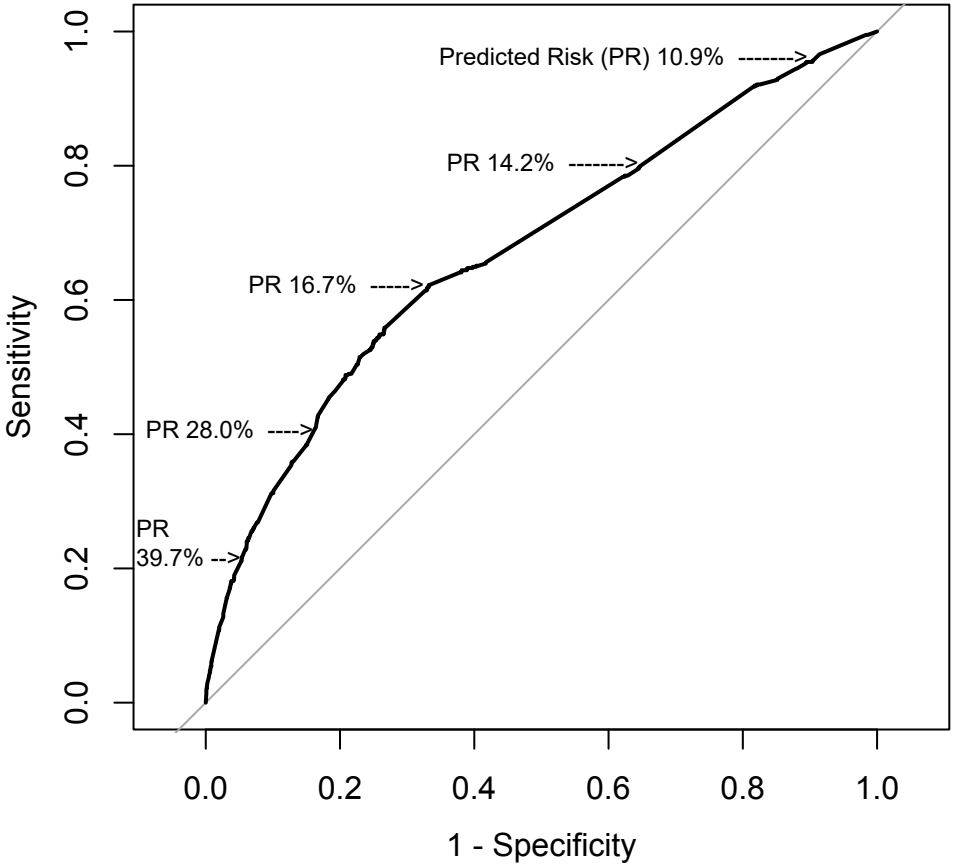

Predicted Risk (PR) 10.9%
PR 14.2%
PR 16.7%
PR 28.0%
PR
39.7%
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Table 1: Results of previous studies on risk factors for underestimation			
	Significance of potential risk factors, as described in literature[#, $]		
Variable[&, §]	**No**	**Yes, univariable[*]**	**Yes, multivariable[^]**
Age	15, 16, 18, **22, 24**, 25	**14**, 21	
Detection mode[~]		**14,** 16	
Palpable	**22**	16	15, 18, 23/**28**, **24**, 25, 26
Clinical size of mass		18	
BI-RADS[~]	21, 23	**14,** 15, 16	
Maximum size on imaging		16	**22**
Maximum size on mammography[~]		18, 21, 26	**14,** 20, **24**, 25
Maximum size on ultrasonography[~]		23	15, **30**
Maximum size on MRI		26	**30**
Mass on imaging			**14**
Mass on mammography		16, 26	18
Mass on ultrasonography	**30**	26	23/**28**
Visibility on ultrasonography	16		**24**
Type of mammgraphic abnormality[~]	**14**, 21, **24**	15	25
Calcifications on mammography	23, 26		**30**
Calcifications on ultrasonography			23/**28**
Suspicous findings on ultrasonography or MRI			**30**
Multicentric		**14**	
Breast density		**14**	
Residual disease on mammogram after biopsy			21
Calcification % removed by CNB		**14**	
Biopsy guidance technique[~]		**14**, 16, **24**, 26	
Biopsy type CNB, VAB	**24**	**16**, 25	15, **22**, 23/**28**
Biopsy needle gauge		14	
Number of cores obtained[~]	**14**, 21	15, 25, 26	
DCIS grade	26	16, 23, **24**, 25	**14**, 15, 20
Nuclear grade	26, **30**		**22**
Suspicious of invasion on biopsy			23/**28**, **24**
Comedo-necrosis	16, 18, 23, 26	**14**, **22**, 25	**30**
Intraductal structure			25
Cibriform	14		**22**
Sclerosing adenosis			**30**
Hormone receptor ER/PR			**22**
Progesterone receptor		**30**	
HER2	**22**		**30**
&: Variables in bold are variables that were analysed in this study			
§: Variables that were analysed but were not statistically significant in any study were: mass on MRI (30), mass on ultrasonography or MRI (30), abnormality on mammography; mass, asymetry or distortion (23), calcifications on imaging (22), suspicous findings on ultrasonography (30), suspicous findings on MRI (30), solid (14, 22) pappillary (14, 22), micropapillary (14, 22), necrosis (22), estrogen receptor (14,30), period from breast biopsy to surgery (25), Van Nuys grouping (23), family history (21), menopausal status (21), type of first resection (18)			
~: The categories of these variables were not uniformly defined between studies			
#: Listed are 12 studies with at least 100 cases of underestimation			
$: References in bold are of the 5 studies that developed a prediction model			
*: Reference 16 presents results of random-effect logistic regression models in a meta-analysis			
^: The multivariable significant variables of reference 23 were used in a prediction model, as described in reference 28			

Table 2: Distribution of underestimation rate							
		All	Underestimated invasive breast cancer				
			No		Yes		
		N	N	%	N	%	p-value
Total		2892	2296	79.4%	596	20.6%	
Age in years	mean (range)	58.7 (24-91)	58.9 (30-88)		57.8 (24-91)		0.033
Age categories							< 0.001
< 45 years		207	142	69%	65	31%	
≥ 45 years		2685	2154	80%	531	20%	
Detection mode							< 0.001
Screen-detected		1850	1521	82%	329	18%	
Otherwise		961	714	74%	247	26%	
Missing		81	61	75%	20	25%	
Palpable							< 0.001
No		2147	1794	84%	353	16%	
Yes		597	380	64%	217	36%	
Missing		148	122	82%	26	18%	
BI-RADS score							< 0.001
3		365	306	84%	59	16%	
4		1996	1638	82%	358	18%	
5		308	183	59%	125	41%	
Missing		223	169	76%	54	24%	
DCIS histological grade at biopsy							0.001
Low		422	360	85%	62	15%	
Intermediate		1083	866	80%	217	20%	
High		1303	1006	77%	297	23%	
Missing		84	64	76%	20	24%	
Suspected invasive component at biopsy							< 0.001
No		2743	2222	81%	521	19%	
Yes		149	74	50%	75	50%	
Synchronous contralateral breast tumour							0.181
No		2796	2225	80%	571	20%	
Yes		96	71	74%	25	26%	
Preoperative MRI							< 0.001
No (or unknown)		2188	1773	81%	415	19%	
Yes		704	523	74%	181	26%	
Preoperative multidisciplinary team meeting							0.364
No (or unknown)		301	245	81%	56	19%	
Yes		2591	2051	79%	540	21%	
1st resection							< 0.001
Wide Local Excision		1822	1510	83%	312	17%	
Mastectomy		1070	786	73%	284	27%	

Table 3. Risk factors for underestimation

Preoperative patient and lesion characteristics[#]	Logistic regression analysis for underestimation of invasive breast cancer					
	Univariable			Multivariable [$]		
	OR	95% CI	p-value	OR	95% CI	p-value
Age						not in the model[&]
< 45 years	1.86	1.34 - 2.53	<0.001			
≥ 45 years	1					
Detection mode						
Screen-detected	1			1		
Otherwise	1.60	1.33 - 1.93	<0.001	1.16	0.94 - 1.45	0.164
Palpable						
No	1			1		
Yes	2.90	2.37 - 3.55	<0.001	2.22	1.76 - 2.81	<0.001
BI-RADS score			<0.001			<0.001
3	0.88	0.65 - 1.19	0.487	0.86	0.64 - 1.17	0.348
4	1			1		
5	3.13	2.43 - 4.03	<0.001	2.36	1.80 - 3.09	<0.001
DCIS histological grade at biopsy			0.001			0.078
Low	1			1		
Intermediate	1.45	1.06 - 1.98	0.017	1.36	0.99 - 1.87	0.054
High	1.71	1.27 - 2.31	<0.001	1.43	1.05 - 1.95	0.025
Suspected invasive component biopsy						
No	1			1		
Yes	4.32	3.09 - 6.04	<0.001	3.84	2.69 - 5.46	<0.001

[$] Based on the imputed dataset

[&] Age: continuous: p=0.552, quadratic relationship (adding a quadratic term): p=0.257, dichotomous with threshold 40 years: p=0.923, dichotomous with threshold 45 years: p=0.421, dichotomous with threshold 55 years: p=0.644.

[#] For all interaction variables p>0.05: grade and suspect: p=0.469, age<45 and palpable p=0.168, age<45 and BI-RADS: p=0.996 and age<45 and DCIS grade: p=0.108

Table 4. Risk groups according to percentile of the predicted risk[$]											
	<20 percentile		**20-<40 percentile**		**40 - <60 percentile**		**60 - <80 percentile**		**≥80 percentile**		**p-value**
Number of lesions	472		526		643		632		619		
Mean predicted risk (range)	11.6 (9.5 - 14.1) %		14.2 (14.2 - 14.7) %		14.8 (14.7 - 16.1) %		21.9 (16.2 -28.0) %		39.1 (28.0 - 80.2) %		
Rate of underestimated invasive breast cancers (n)	10.4%	(49)	15.2%	(80)	13.2 %	(85)	21.8%	(138)	39.4 %	(244)	
Rate of invasive breast cancers with unfavourable features (n/total)	1.7%	(8/472)	4.0 %	(21/526)	4.7 %	(30/643)	9.0 %	(57/632)	19.1 %	(118/619)	p<0.001
Rate of minimal-volume DCIS, DCIS completely removed via biopsy (n/total)	18.4%	(87/472)	7.6 %	(40/526)	4.2%	(27/643)	4.9 %	(31/632)	1.8 %	(11/619)	p<0.001

[$] For each DCIS, a predicted risk was calculated with the prediction model. Based on these risks, the DCIS were divided into five subgroups, with the percentile <20% comprising the 20% of DCIS with the lowest predicted risk, percentile ≥ 80% comprising the 20% of DCIS with the highest risk, etc.

Supplement 1: Associations between risk factors

Of 2892 DCIS included in the study, 2513 had no missing data for one or more potential risk factor.

For these the associations between risk factors are shown in the table. The percentages in the table are row percentages.

For overview purposes not all values of a category are shown in the columns; the percentages of the values ≥ 45 years, detection mode otherwise, non-palpable and no suspected invasive component can be deducted from the other values. For example, there were 175 patients that were < 45 years, the DCIS of 60% was palpable and of 40% non-palpable.

Age and detection mode were both associated with palpability and BI-RADS score, and age was also associated with DCIS grade.

	Number	%	p-value	%	p-value	%	p-value	%	%	%	p-value	%	%	%	p-value	%	p-value
		Age		Detection mode		Palpable		BI-RADS score				DCIS grade at biopsy				Suspected invasive component	
		<45 years		Screen-detected		Yes		3	4	5		Low	Inter-mediate	High		Yes	
Age			x		<0.001		<0.001				<0.001				0.012		0.857[$]
< 45 years	175	x		0%		60%		23%	58%	18%		10%	33%	57%		5%	
>=45 years	2338	x		72%		18%		13%	76%	11%		15%	39%	46%		5%	
Detection mode			<0.001[$]		x		<0.001				<0.001				0.939		0.327
Screening	1689	0%		x		10%		11%	80%	10%		15%	39%	46%		5%	
Otherwise	824	21%		x		43%		20%	64%	15%		15%	38%	47%		6%	
Palpable			<0.001		<0.001		x				<0.001				0.760		<0.001
No	1990	4%		76%		x		14%	78%	8%		15%	39%	46%		4%	
Yes	523	20%		33%		x		14%	60%	26%		14%	38%	48%		8%	
BI-RADS score			<0.001		<0.001		<0.001				x				<0.001		0.079
3	349	12%		52%		20%		x	x	x		24%	42%	34%		4%	
4	1874	5%		72%		17%		x	x	x		14%	38%	48%		5%	
5	290	11%		56%		47%		x	x	x		9%	35%	56%		8%	
DCIS grade at biopsy			0.012		0.939		0.760				<0.001				x		<0.001[$]
Low	371	5%		67%		20%		22%	71%	7%		x	x	x		2%	
Intermediate	971	6%		68%		20%		15%	74%	11%		x	x	x		3%	
High	1171	9%		67%		21%		10%	76%	14%		x	x	x		7%	
Suspected invasive component			0.857[$]		0.327		<0.001				0.079				<0.001[$]		x
No	2388	7%		67%		20%		14%	75%	11%		15%	39%	45%		x	
Yes	125	7%		63%		34%		11%	71%	18%		5%	26%	70%		x	

[$]: Fisher's exact test. Other associations were tested with the Pearson chi-square test.

Supplement 2: Predicted risk for each combination of risk factors

Of 2892 DCIS included in the study, 2513 had no missing data for one or more potential risk factor.

For these, the combination of risk factors is shown in the table along with the size of the group, the predicted risk and the percentile group. Highlighted in colour are the combinations with the highest number of DCIS;

number of DCIS: 50 - <100 number of DCIS: ≥ 100

Based on the predicted risk, the DCIS were grouped in one of the five percentile groups. The group <20% comprises the 20% of DCIS with the lowest predicted risk, percentile ≥ 80% comprises the 20% of DCIS with the highest risk, etc. The predicted risks on average per percentile groups were 11.6%, 14.2%, 14.8%, 21.9% and 39.1%.

In the percentile group with the lowest risk, all DCIS were non-palpable and had no suspected invasive component at biopsy. DCIS with a suspected invasive component were all in the highest percentile group.

Percentile group	Predicted risk (%)	Number of DCIS	Detection mode	Palpable (before biopsy)	BI-RADS score	DCIS grade at biopsy	Suspected invasive component at biopsy
<20	9.45	35	screen-detected	no	3	low	no
	10.78	173	screen-detected	no	4	low	no
	10.87	30	otherwise	no	3	low	no
	12.37	38	otherwise	no	4	low	no
	12.47	73	screen-detected	no	3	intermediate	no
	12.98	61	screen-detected	no	3	high	no
20 - <40	14.16	461	screen-detected	no	4	intermediate	no
	14.27	42	otherwise	no	3	intermediate	no
40 - <60	14.73	537	screen-detected	no	4	high	no
	14.84	27	otherwise	no	3	high	no
60 - <80	16.16	114	otherwise	no	4	intermediate	no
	16.79	170	otherwise	no	4	high	no
	18.83	2	screen-detected	yes	3	low	no
	21.17	21	screen-detected	yes	4	low	no
	21.32	15	otherwise	yes	3	low	no
	22.20	11	screen-detected	no	5	low	no
	23.88	26	otherwise	yes	4	low	no
	24.05	2	screen-detected	yes	3	intermediate	no
	24.90	4	screen-detected	yes	3	high	no
	25.00	6	otherwise	no	5	low	no
	26.82	36	screen-detected	yes	4	intermediate	no
	27.00	27	otherwise	yes	3	intermediate	no
	27.74	51	screen-detected	yes	4	high	no
	27.92	17	otherwise	yes	3	high	no
>80	28.03	42	screen-detected	no	5	intermediate	no
	28.97	57	screen-detected	no	5	high	no
	29.98	85	otherwise	yes	4	intermediate	no
	30.96	73	otherwise	yes	4	high	no
	31.27	16	otherwise	no	5	intermediate	no
	31.68	3	screen-detected	no	4	low	yes
	31.88	1	screen-detected	no	3	low	yes
	32.27	14	otherwise	no	5	high	no
	35.35	2	screen-detected	no	3	intermediate	yes
	36.40	4	screen-detected	no	3	high	yes

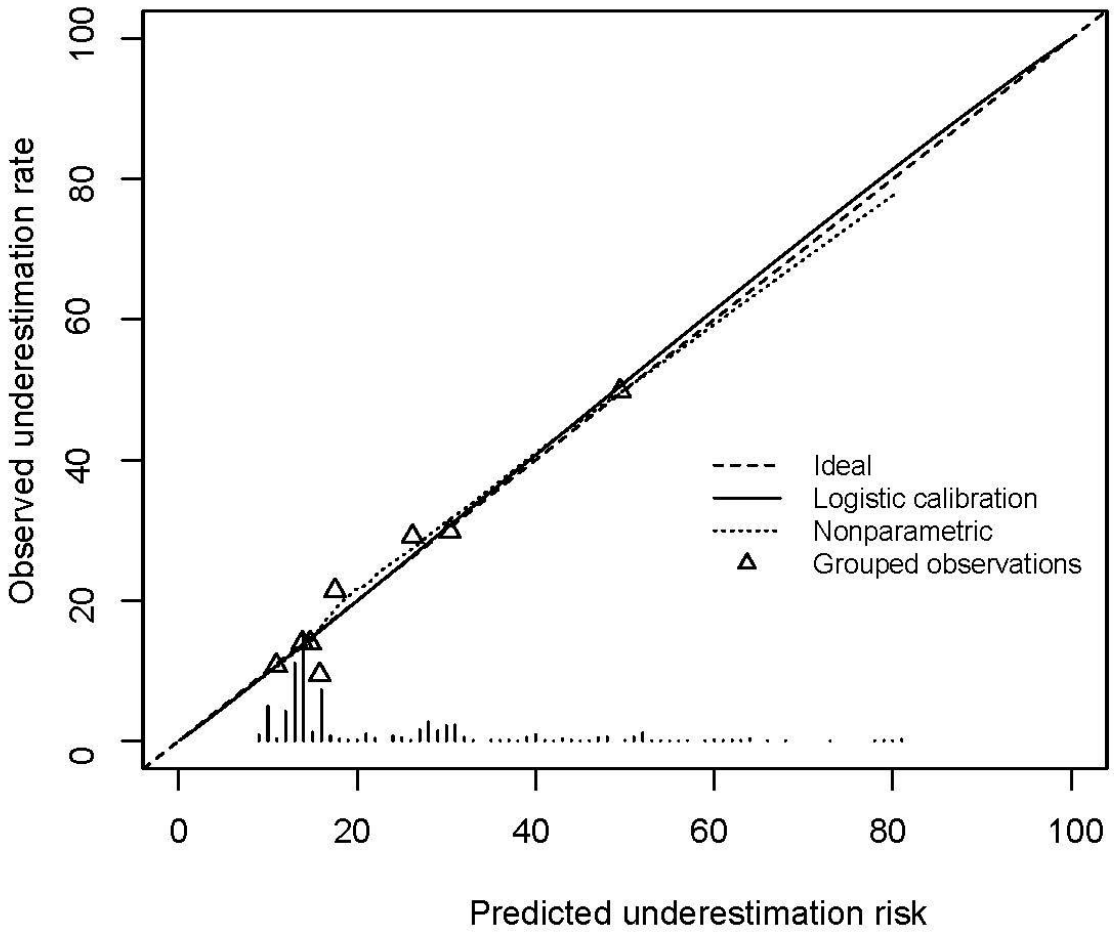
Percentile group	Predicted risk (%)	Number of DCIS	Detection mode	Palpable (before biopsy)	BI-RADS score	DCIS grade at biopsy	Suspected invasive component at biopsy
	38.76	18	screen-detected	no	4	intermediate	yes
	38.80	2	screen-detected	yes	5	high	no
	38.97	1	otherwise	no	3	intermediate	yes
	39.85	35	screen-detected	no	4	high	yes
	40.07	3	otherwise	no	3	high	yes
	42.51	2	otherwise	no	4	intermediate	yes
	42.55	6	otherwise	yes	5	low	no
	43.63	7	otherwise	no	4	high	yes
	46.39	18	screen-detected	yes	5	intermediate	no
	47.54	24	screen-detected	yes	5	high	no
	50.27	23	otherwise	yes	5	intermediate	no
	51.42	49	otherwise	yes	5	high	no
	54.62	2	otherwise	yes	4	low	yes
	55.99	1	screen-detected	yes	3	high	yes
	58.44	2	screen-detected	yes	4	intermediate	yes
	58.66	1	otherwise	yes	3	intermediate	yes
	59.55	6	screen-detected	yes	4	high	yes
	59.77	1	otherwise	yes	3	high	yes
	59.90	2	screen-detected	no	5	intermediate	yes
	61.00	3	screen-detected	no	5	high	yes
	62.16	2	otherwise	yes	4	intermediate	yes
	63.24	12	otherwise	yes	4	high	yes
	64.63	2	otherwise	no	5	high	yes
	77.66	3	screen-detected	yes	5	high	yes
	79.50	2	otherwise	yes	5	intermediate	yes
	80.24	10	otherwise	yes	5	high	yes

Supplement 3: Calibration plot of the prediction model

Of 2892 DCIS included in the study, 379 (13%) had missing data for one or more potential risk factors. These missing data were accounted for via multiple imputations (20 times). For one of these imputed datasets the calibration plot was drawn.

The predicted risk for an underestimated invasive breast cancer versus the observed rate is plotted in the figure below. The distance between the grouped observations and the 45 degree line is a measure of the error of the prediction model. The statistics for the plot for this imputed dataset are: c-statistic (ROC) of 0.666, R^2 of 0.110, Intercept of -0.019, slope of 0.985.

The histogram of the x-axis reflects the frequency of a predicted risk. 9.0% of DCIS have a risk of <12.0%, 54.6% of DCIS have a predicted risk of <15.0% and 26.0% have a risk of >25.0%.



Supplement 4: Predicted risk for each combination of risk factors

Of 2892 DCIS diagnoses at biopsy, 596 were underestimated invasive breast cancers.

Below are the tumour characteristics, based on the excisional specimens of these 596 cancers.

			N	%
Morphology			596	
Lobular			14	2%
Ductal			531	89%
Mixed Ductal and Lobular			29	5%
Other			22	4%
Grade of the invasive tumour			534	
I			165	31%
II			225	42%
III			144	27%
ER receptor			542	
Negative			106	20%
Positive			436	80%
PR receptor			542	
Negative			206	38%
Positive			336	62%
Her2Neu			524	
Negative			386	74%
Positive			138	26%
Receptor combinations			520	
ER -	PR -	Her2Neu -	39	8%
ER +		Her2Neu -	343	66%
ER -	PR -	Her2Neu +	61	12%
ER +		Her2Neu +	75	14%
ER -	PR +		2	<1%
Tumour size (in mm)			570	
mean - median (range)			9.5 - 6 (0 - 90)	
TNM stage			596	
I A			460	77%
I B			16	3%
II A			73	12%
II B			22	4%
III A			16	3%
III B			0	0%
III C			9	1%
IV			0	0%