One size does not fit all: towards personalised management of ductal carcinoma in situ

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Chapter 3

Association of DCIS size and margin status with risk of developing breast cancer post-treatment: multinational, pooled cohort study

Abstract

Objective: To examine the association between size and margin status of ductal carcinoma in situ (DCIS) and risk of developing ipsilateral invasive breast cancer and ipsilateral DCIS after treatment, and stage and subtype of ipsilateral invasive breast cancer.

Design: Multinational, pooled cohort study.

Setting: Four large international cohorts.

Participants: Patientleveldataon47695womenwithadiagnosis of pure, primary DCIS between 1999 and 2017 in the Netherlands, UK, and US who underwent surgery, either breast conserving or mastectomy, often followed by radiotherapy or endocrine treatment, or both. Main outcome measures: The main outcomes were 10-year cumulative incidence of ipsilateral invasive breast cancer and ipsilateral DCIS estimated in relation to DCIS size and margin status, and adjusted hazard ratios and 95% confidence intervals, estimated using multivariable Cox proportional hazards analyses with multiple imputed data

Results: The 10-year cumulative incidence of ipsilateral invasive breast cancer was 3.2%. In women who underwent breast conserving surgery with or without radiotherapy, only adjusted risks for ipsilateral DCIS were significantly increased for larger DCIS (20-49 mm) compared with DCIS <20 mm (hazard ratio 1.38, 95% confidence interval 1.11 to 1.72). Risks for both ipsilateral invasive breast cancer and ipsilateral DCIS were significantly higher with involved compared with clear margins (invasive breast cancer 1.40, 1.07 to 1.83; DCIS 1.39, 1.04 to 1.87). Use of adjuvant endocrine treatment was not significantly associated with a lower risk of ipsilateral invasive breast cancer compared to treatment with breast conserving surgery only (0.86, 0.62 to 1.21). In women who received breast conserving treatment with or without radiotherapy, higher DCIS grade was not significantly associated with ipsilateral invasive breast cancer, only with a higher risk of ipsilateral DCIS (grade 1:1.42,1.08to1.87; grade3:2.17,1.66to2.83). Greater age at diagnosis was associated with lower risk (per year) of ipsilateral DCIS (0.98, 0.97 to 0.99) but not ipsilateral invasive breast cancer(1.00,0.99to1.00). Women with large DCIS (≥50 mm) more often developed stage III and IV ipsilateral invasive breast cancer compared to women with DCIS <20 mm. No such association was found between involved margins and higher stage of ipsilateral invasive breast cancer. Associations between larger DCIS and hormone receptor negative and human epidermal growth factor receptor 2 positive ipsilateral invasive breast cancer and involved margins and hormone receptor negative ipsilateral invasive breast cancer were found.

Conclusions: The association of DCIS size and margin status with ipsilateral invasive breast cancer and ipsilateral DCIS was small. When these two factors were added to other known risk factors in multivariable models, clinicopathological risk factors alone were found to be limited in discriminating between low and high-risk DCIS.

Introduction

With the introduction of population based breast cancer screening[1] and the more recent introduction of digital mammography, [2, 3] the incidence of ductal carcinoma in situ (DCIS) has increased more than fivefold in western countries.[4-6] Currently, DCIS accounts for 20-25% of all newly detected breast cancers. [7] Although DCIS is a potential precursor of invasive breast cancer, it is estimated that as much as 80% of DCIS lesions will never progress to invasive disease. [8-11] As potentially progressive, high risk DCIS is difficult to distinguish from potentially non-progressive, low risk DCIS, almost all women with DCIS are treated by mastectomy or breast conserving surgery followed by radiotherapy or endocrine treatment, or both.[12] Yet no clear reduction of breast cancer mortality has been attributed to DCIS treatment. [13] Furthermore, the incidence of invasive breast cancer has not decreased, [4] suggesting a considerable reservoir of DCIS lesions exists that would never have progressed to invasive breast cancer. Consequently, concern is growing about the possible overtreatment of DCIS. [4, 8, 14 -16] The PRECISION (PREvent ductal Carcinoma In Situ Invasive Overtreatment Now) Cancer Grand Challenge Consortium aims to distinguish high risk from low risk DCIS to reduce the overtreatment of low risk DCIS. [14, 17]

Some clinicopathological features such as high grade lesions and young age are associated with increased risk of subsequent ipsilateral DCIS and ipsilateral invasive breast cancer. [18, 19] For other features, such as DCIS size and margin status, the association with risk of these two cancer types is less clear, and several relatively small studies (up to 2995 women with DCIS treated with breast conserving surgery only) have reported size to be associated with a higher risk. [20-23] In contrast, a UK study of 24 779 women treated with breast conserving surgery and mastectomy for DCIS reported no significant association between increasing DCIS size and ipsilateral invasive breast cancer. [19] Similarly, the literature has not reached consensus on the effect of margin status on risk of ipsilateral invasive breast cancer or ipsilateral DCIS. The UK study reported involved margins as an important risk factor for ipsilateral invasive breast cancer [19] as did other studies. [24, 25] Several smaller studies, however, did not find any associations between margin status and local recurrence,[22, 26, 27] or only did so in relation to ipsilateral DCIS.[28] Consequently, substantially larger studies with longer term follow-up are needed to validate the association between DCIS size and involved margins with risk of subsequent ipsilateral DCIS or ipsilateral invasive breast cancer. A better understanding of these and other related risk factors could provide insight as to which women may be candidates for de-escalation of treatment, allowing for more personalised management strategies and avoiding overtreatment of women with low-risk DCIS.

Using a large, multinational, pooled cohort we investigated whether DCIS size and margin status are associated with risk of developing ipsilateral invasive breast cancer and ipsilat-

eral DCIS. A secondary aim was to investigate whether DCIS size and margin status are associated with the subtype and stage of subsequent ipsilateral invasive breast cancer.

Methods

Study population

We analysed four cohorts of women with DCIS from the Netherlands, UK, and US as part of the PRECISION DCIS Consortium. Table 1 and the supplementary methods describe the cohorts. Data on participants' characteristics, DCIS status, treatment, and follow-up had been collected for each of the four cohorts. For this study, we recoded and harmonised original data following a set codebook. Inclusion criteria were women older than 18 years with pure, primary, unilateral DCIS who had undergone surgery (with or without adjuvant treatment) between 1999 and 2017. We excluded women with DCIS accompanying micro-invasive or invasive disease or Paget's disease, those who received chemotherapy or targeted therapy, those with missing information on treatment or follow-up, and those with follow-up shorter than six months or diagnosis with subsequent invasive breast cancer within six months after the primary DCIS diagnosis. As endocrine treatment is rarely prescribed for DCIS in the Netherlands, we excluded 148 women in the Dutch cohort who received endocrine treatment (supplementary figure S1).

Table 1. Patient and cohort characteristics

	Dutch cohort	*Sloane cohort*	*MDACC cohort*	*NCDB-Special study subset*	*Total cohort*
	n=18,986	*n=7,961*	*n=2,083*	*n=18,665*	*n=47,695*
Type of cohort	Population based, nationwide coverage, NL	Population based, nationwide coverage, UK	Single hospital, tertiary cancer centre, USA	Representative registry, nationwide coverage[a], USA	Multinational, mostly population based
Age at diagnosis DCIS *(Mean, SD) (years)*	58 (10.2)	60 (6.9)	55 (11.1)	60 (11.8)	59 (10.5)
Year of diagnosis *(range)*	1999-2015	2003-2012	1999-2017	2007-2015	1999-2017
Follow-up time *(Mean, SD) (years)*	8.2 (2.2)	5.3 (2.5)	7.2 (2.8)	5.8 (2.4)	6.7 (2.7)
Last update follow-up *(year)*	2020	2012	2020	2019	2012-2020
	n (%)	n (%)	n (%)	n (%)	n (%)
Grade					
Grade 1	2,844 (15)	778 (10)	160 (8)	3,095 (17)	6,877 (14)
Grade 2	5,949 (31)	2,250 (28)	860 (41)	6,589 (35)	15,648 (33)
Grade 3	8,938 (47)	4,926 (62)	1,058 (51)	7,482 (40)	22,404 (47)
Unknown grade	1,255 (7)	7 (0.1)	5 (0)	1,499 (8)	2,766 (6)
DCIS size					
<20mm	6,405 (34)	4,432 (56)	869 (42)	10,098 (54)	21,804 (46)
20-49mm	3,478 (18)	2,638 (33)	467 (22)	2,536 (14)	9,119 (19)
≥50mm	1,429 (8)	805 (10)	327 (16)	934 (5)	3,495 (7)
Unknown size	7,674 (40)	86 (1)	420 (20)	5,097 (27)	13,277 (28)
Treatment[b]					
BCS only	2,139 (11)	2,037 (26)	215 (10)	2,923 (16)	7,314 (15)
BCS+RT	9,646 (51)	2,678 (34)	418 (20)	4,454 (24)	17,196 (36)
BCS+ET	N.A[c]	333 (4)	70 (3)	1,254 (7)	1,657 (3)
BCS+RT+ET	N.A[c]	533 (7)	437 (21)	5,401 (30)	6,471 (14)
MST	7,201 (38)	2,380 (30)	943 (45)	4,533 (24)	15,057 (32)
Margin Status[d]					
Clear (≥2mm)	13,615 (72)	5,156 (65)	2,037 (98)	17,688 (95)	38,496 (81)
Involved (<2mm)	1,598 (8)	256 (3)	35 (2)	563 (3)	2,452 (5)
Unknown	3,773 (20)	2,549 (32)	11 (1)	414 (2)	6,747 (14)
Survival status					
Alive	17,497 (92)	7,701 (97)	1,979 (95)	17,533 (94)	44,710 (94)
Deceased	1,489 (8)	260 (3)	104 (5)	1,132 (6)	2,985 (6)

Abbreviations:

MDACC, MD Anderson Cancer center; NCDB, National Cancer Database; n, number; NL, the Netherlands; UK, United Kingdom; USA, United States of America; DCIS, ductal carcinoma in situ; n, number; BCS, breast conserving surgery; MST, mastectomy; RT, radiotherapy; ET, endocrine treatment (any type)

[a] Treatment-stratified random sample from NCDB special study, NCDB registers 70% of cancer patients in the USA.

[b] All treatment initiated within 6 months after primary diagnosis of DCIS.

[c] Endocrine treatment is not standard treatment in the Netherlands, therefore patients with endocrine treatment were excluded from the Dutch cohort.

[d] Margin status was defined at final surgery

Definitions

Contralateral and ipsilateral invasive breast cancer and ipsilateral DCIS were defined as an invasive breast cancer or DCIS diagnosed at least six months after the primary diagnosis of DCIS. Primary metastatic disease (n=32) without occurrence of contralateral breast cancer, and solitary axillary lesions (n=4) without an in-breast recurrence, were classified as ipsilateral invasive breast cancer. For 53 subsequent events, the laterality or invasive status of the event was unknown. For these women, follow-up was censored at time of the occurrence of the subsequent event. Use of endocrine treatment was defined as any such treatment initiated within six months after the primary diagnosis and, if known, a minimum duration of one year. Margin status was defined as the closest surgical margin width according to current treatment guidelines[29]; clear margins ≥2 mm and involved margins <2 mm margin width after final surgery (including re-resection). DCIS was divided into three size categories:<20mm,20-49mm, and ≥50mm. For multifocal disease, DCIS size was categorised on the basis of the largest diameter reported.

Stage of subsequent event was defined as 0 (DCIS) to IV according to the eighth edition of the anatomic TNM staging criteria. [30] For most subsequent ipsilateral invasive breast cancers, the number and location of positive lymph nodes was not available. As stages IIa-b and IIIa therefore could not be accurately distinguished, T0-2 N+ was defined as stage II. We categorised ipsilateral invasive breast cancers into four subtypes based on hormone receptor status (positive if oestrogen receptor positive or progesterone receptor positive; negative otherwise) and human epidermal growth factor receptor 2 (HER2) status: hormone receptor positive and HER2 negative, hormone receptor positive and HER2 positive, hormone receptor-negative and HER2-positive,and hormone receptor-negative and HER2-negative.

Statistical analyses

We harmonized and pooled the patient level data of the four cohorts. Time at risk of developing ipsilateral DCIS or ipsilateral invasive breast cancer started six months after the date of the primary DCIS diagnosis and ended at date of diagnosis of the subsequent event (ipsilateral DCIS or ipsilateral invasive breast cancer), death, diagnosis of a competing risk (death by any cause, diagnosis of contralateral invasive breast cancer and of ipsilateral DCIS when studying ipsilateral invasive breast cancer, or of ipsilateral invasive breast cancer when studying ipsilateral DCIS), or end of follow-up. Follow-up duration was right censored at 10 years.

We used multiple imputation by chained equations to account for missing values for DCIS size (28%), margin status (14%), and grade (6%). [31, 32] The imputation model employed an

ordered logistic regression for DCIS size and grade and a nominal logistic regression for margin status.[33] The multiple imputation model included the variables age at diagnosis, year of diagnosis, cohort, and treatment type. The imputation process was repeated 40 times. We combined results using Rubin's rule.[34] Imputed results are shown as the primaryanalyses[31] (also see the supplementary material for analyses of the dataset including categories of missing information).

Cumulative incidences of ipsilateral invasive breast cancer and ipsilateral DCIS were estimated considering the competing risks and grouped by tumour size, margin status after final surgery, and treatment.

We used multivariable Cox proportional hazards models per treatment group in all pooled data and by cohort to estimate the association between DCIS size or margin status and the risk of subsequent ipsilateral invasive breast cancer or ipsilateral DCIS. Schoenfeld residuals and graphical methods were used to test the proportional hazards assumptions. Effect modification of the association between DCIS size or margin status and risk of ipsilateral invasive breast cancer or ipsilateral DCIS by other established risk factors of ipsilateral invasive breast cancer, such as age at diagnosis and DCIS grade, was examined. Data are reported as hazard ratios and 95% confidence intervals.

Selection of variables to be evaluated for potential confounding was based on existing literature (i.e., age at diagnosis, DCIS grade, treatment type, and year of diagnosis). These potentially relevant covariates were first evaluated individually then added to the model using forward selection. A covariate was considered a confounder when the difference between hazard ratios from the model with the covariate and the model without the covariate exceeded 10%. By this criterion, the only confounder identified was treatment type in the association between DCIS size and ipsilateral invasive breast cancer or ipsilateral DCIS. To ensure the results were comparable to those in the literature, however, variables included in the multivariable Cox regression analyses were DCIS size, margin status, age at diagnosis, DCIS grade, and treatment type. Furthermore, analyses were stratified by cohort. To assess whether the Dutch cohort, in which endocrine treatment was not prescribed, or hormone receptor negative DCIS influenced hazard ratios of ipsilateral invasive breast cancer and ipsilateral DCIS by treatment type, we performed two subgroup analyses: a cohort restricted to the UK and US based cohorts, and a cohort restricted to the UK and US based cohorts in women with oestrogen receptor positive DCIS.

For the full model, we calculated Harrell's C index to assess the potential clinical usefulness of all clinical variables, despite the model being over-fitted and the study not specifically

designed to develop a prediction model.
We estimated cumulative relative incidences to compare the incidence of stage and subtype of ipsilateral invasive breast cancer after DCIS compared with age and calendar year specific expected stages and subtypes of primary invasive breast cancer in the Dutch female population. Joint Cox proportional hazards models adjusted for treatment were used to estimate the association between DCIS size or margin status and risk of subtype specific or stage specific ipsilateral invasive breast cancer.[35] These analyses were carried out only in women with available information on stage or subtype of the ipsilateral invasive breast cancer.

All tests of statistical significance were two sided. A P value of <0.05 was considered statistically significant. All analyses were performed using STATA/SE15.0 (Stata Corp, College Station, TX) or open-source software R version 4.04.

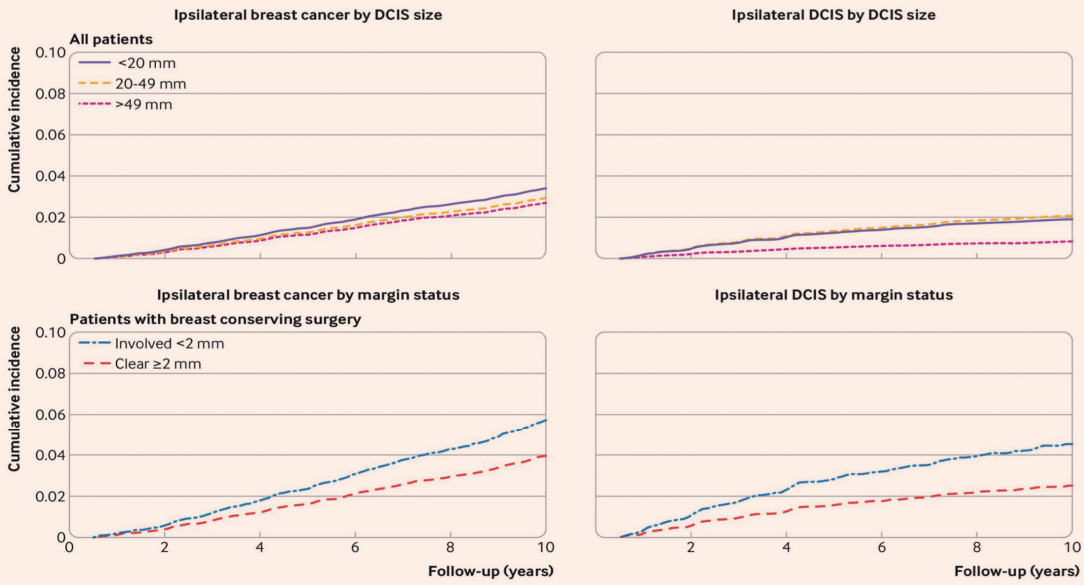
Patient and public involvement
The PRECISION patient advocates were involved in setting the research questions, interpreting the data, and writing up the results. All PRECISION patient advocates received the final draft of the manuscript and will be actively involved in the dissemination of the results to relevant patient communities.

Results
In total, 47 695 women were included in the analyses (supplementary figure S1). Table 1 presents the characteristics of the participants and lesions. Age at diagnosis ranged from 20 to 97 years (mean 59 years). Mean follow-up duration was 6.7 years. Fifteen per cent of participants received breast conserving surgery only, 36% breast conserving surgery with radiotherapy, 3% breast conserving surgery with endocrine treatment, and 14% breast conserving surgery with radiotherapy and endocrine treatment, and 32% underwent mastectomy. DCIS size was <20 mm in 46% of women, 20-49 mm in 19%, ≥50 mm in 7%, and missing in 28%. Margin status was clear (≥2 mm) in 81% of women, involved (<2 mm) in 5%, and missing in 14%. The 10-year cumulative incidence of ipsilateral invasive breast cancer and ipsilateral DCIS was 3.2% and 1.8%, respectively. The characteristics of participants with missing data were largely the same as those without missing data (supplementary table S1), although those with missing data more frequently received a diagnosis at a younger age and those with missing data on margin status more often had a mastectomy.

<u>DCIS size</u>
The 10-year cumulative incidence of ipsilateral invasive breast cancer according to DCIS size was 3.5% for <20 mm, 3% for 20-49 mm, and 2.7% for ≥50 mm. The corresponding

values for ipsilateral DCIS were 1.9%, 2.0%, and 0.9% (fig 1). Cumulative incidences differed by treatment group (see supplementary figure 2 for cumulative incidences by DCIS size category) and were highest in women receiving breast conserving surgery only, slightly reduced in women receiving breast conserving surgery with radiotherapy, and lowest in women undergoing mastectomy (supplementary figure S2).

Figure 1: Ten-year cumulative incidence of subsequent ipsilateral invasive breast cancer and ipsilateral DCIS



Competing risks were death by any cause, contralateral breast cancer, and, depending on analyses, ipsilateral DCIS or ipsilateral invasive breast cancer. Cumulative incidences in relation to DCIS size were calculated in the full, pooled cohort (n=47 695). Cumulative incidences on margin status were calculated in the full, pooled cohort, after exclusion of women who underwent mastectomy (n=37 721).

DCIS=ipsilateral ductal carcinoma in situ

In multivariable Cox regression analyses adjusted for age, DCIS grade and margin status, and treatment, the risk of ipsilateral invasive breast cancer was not significantly increased in women receiving breast conserving surgery with or without radiotherapy for larger DCIS compared with DCIS <20 mm: the hazard ratio for 20-49 mm was 1.13 (95% confidence interval 0.94 to 1.37) and for ≥50 mm was 0.91 (0.54 to 1.54) (table 2). In women who received breast conserving surgery and radiotherapy, DCIS 20-49 mm was associated with an increased risk for ipsilateral invasive breast cancer compared with <20 mm, although this was not statistically significant (1.24, 0.99 to 1.56). In women who received breast conserving surgery with or without radiotherapy, the risk of ipsilateral DCIS was higher in those with DCIS 20-49 mm (1.38, 1.11 to 1.72) compared with <20 mm (table 2). In women who underwent mastectomy, the risks for ipsilateral invasive breast cancer and ipsilateral DCIS were increased with larger DCIS size, although this was not statistically significant (table 3). Supplementary tables S2 and S3 show the results of analyses within each cohort. Risks for ipsilateral invasive breast cancer and ipsilateral DCIS by size category were largely similar in sensitivity analyses on the non-imputed data, including missing information as a separate category (supplementary tables S4-S11).

Table 2: Risk of subsequent ipsilateral DCIS or breast cancer in women who received breast conserving surgery, multivariable Cox proportional hazards analyses using multiple imputed data[a]

	Risk of iDCIS, BCS only *n=8,971 n(iDCIS)=251*		***Risk of iDCIS, BCS+RT*** *n=23,667 n(iDCIS)=375*		***Risk of iDCIS BCS+-/RT*** *n=32,638 n(iDCIS)=626*		***Risk of iIBC, BCS only*** *n=8,971 n(iIBC)=334*		***Risk of iIBC, BCS+RT*** *n=23,667 n(iIBC)=467*		***Risk of iIBC, BCS+/-RT*** *n=32,638 n(iIBC)=801*	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value
DCIS size												
<20mm	1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	1.45 (0.98-2.15)	0.06	1.36 (1.07-1.75)	0.01	1.38 (1.11-1.72)	0.004	0.98 (0.66-1.46)	0.92	1.24 (0.99-1.56)	0.07	1.13 (0.94-1.37)	0.21
≥50mm	1.14 (0.48-2.73)	0.76	1.30 (0.71-2.37)	0.39	1.23 (0.75-2.02)	0.42	0.50 (0.11-2.17)	0.35	1.15 (0.67-1.98)	0.62	0.91 (0.54-1.54)	0.72
Margin Status												
Clear ≥2mm	1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	1.40 (0.88-2.23)	0.16	1.33 (0.90-1.97)	0.15	1.39 (1.04-1.87)	0.03	1.35 (0.87-2.09)	0.18	1.41 (1.01-1.98)	0.05	1.40 (1.07-1.83)	0.02
Covariates												
Age at diagnosis[b]	1.00 (0.99-1.01)	0.63	0.97 (0.96-0.98)	<0.001	0.98 (0.97-0.99)	<0.001	1.01 (1.00-1.02)	0.03	0.99 (0.98-1.00)	0.004	1.00 (0.99-1.00)	0.39
DCIS grade												
Grade 1	1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	1.53 (1.05-2.22)	0.03	1.33 (0.87-2.04)	0.19	1.42 (1.08-1.87)	0.01	1.05 (0.79-1.40)	0.73	0.82 (0.61-1.10)	0.18	0.93 (0.76-1.13)	0.45
Grade 3	2.58 (1.81-3.67)	<0.001	1.91 (1.27-2.87)	0.002	2.17 (1.66-2.83)	<0.001	1.25 (0.93-1.67)	0.14	0.87 (0.65-1.15)	0.32	1.01 (0.83-1.24)	0.92
Treatment												
BCS only	1 (ref)		N.A.		1 (ref)		1 (ref)		N.A.		1 (ref)	
BCS+RT	N.A.		1 (ref)		0.37 (0.30-0.44)	<0.001	N.A.		1 (ref)		0.45 (0.38-0.54)	<0.001
BCS+ET	0.67 (0.40-1.11)	0.12	N.A.		0.50 (0.30-0.82)	0.006	1.08 (0.76-1.54)	0.67	N.A.		0.86 (0.62-1.21)	0.38
BCS+RT+ET	N.A.		0.69 (0.49-0.98)	0.04	0.36 (0.26-0.50)	<0.001	N.A.		0.79 (0.59-1.05)	0.10	0.49 (0.37-0.64)	<0.001

Abbreviations:

iDCIS, subsequent ipsilateral DCIS; BCS, breast conserving surgery; RT, radiotherapy; iIBC, subsequent ipsilateral invasive breast cancer; n, number; HR, hazard ratio; CI, confidence interval; mm, millimetre; RT, radiotherapy; ET, endocrine treatment; DCIS, ductal carcinoma in situ; ET, endocrine treatment.

[a] Variables DCIS grade, DCIS size and margin status were imputed with multivariate imputation by chained equations (MICE). The imputation model was a nominal logistic regression for margin status and an ordered logistic regression for DCIS size and DCIS grade. The model included the following variables: Age at diagnosis, year of diagnosis, cohort and treatment type. The imputation process was repeated 40 times. Rubin's rule was used to combine the results.

Multivariable Cox proportional hazard analyses, stratified by Cohort

[b] Continuous, HR per year

Table 3: Risk of subsequent ipsilateral DCIS or breast cancer in all patients, and women receiving mastectomy, multivariable Cox proportional hazards analyses, using multiple imputed dataa

	All patients iDCIS n= 47,695 n(iDCIS)=658		*Mastectomy iDCIS n=15,057 n(iDCIS)=32*		*All patients iIBC n= 47,695 n(iIBC)=981*		*Mastectomy iIBC n=15,057 n(iIBC)=180*	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
DCIS size								
<20mm	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	1.37 (1.11-1.70)	0.004	1.28 (0.47-3.45)	0.63	1.09 (0.91-1.30)	0.34	1.05 (0.67-1.62)	0.81
≥50mm	1.10 (0.69-1.76)	0.69	0.79 (0.24-2.63)	0.70	1.18 (0.88-1.59)	0.28	1.45 (0.95-2.20)	0.09
Margin Status								
Clear	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	1.30 (0.97-1.74)	0.08	N.A		1.13 (0.88-1.47)	0.34	0.51 (0.23-1.14)	0.10
Age[b]	0.98 (0.97-0.99)	<0.001	0.97 (0.94-1.01)	0.10	0.99 (0.99-1.00)	0.02	0.98 (0.96-0.99)	0.002
DCIS grade								
Grade 1	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	1.42 (1.09-1.86)	0.01	1.37 (0.30-6.38)	0.69	0.96 (0.79-1.17)	0.70	1.49 (0.76-2.94)	0.25
Grade 3	2.14 (1.65-2.79)	<0.001	1.74 (0.40-7.53)	0.46	1.04 (0.86-1.26)	0.68	1.52 (0.79-2.93)	0.21
Treatment								
BCS only	1 (ref)		N.A.		1 (ref)		N.A.	
BCS+RT	0.37 (0.31-0.45)	<0.001	N.A.		0.46 (0.39-0.55)	<0.001	N.A.	
BCS+ET	0.47 (0.29-0.78)	0.003	N.A.		0.80 (0.57-1.11)	0.18	N.A.	
BCS+RT+ET	0.34 (0.25-0.47)	<0.001	N.A.		0.43 (0.34-0.56)	<0.001	N.A.	
MST	0.04 (0.02-0.05)	<0.001	N.A		0.23 (0.18-0.28)	<0.001	N.A	

Abbreviations:

iDCIS, subsequent ipsilateral ductal carcinoma in situ; iIBC, subsequent ipsilateral invasive breast cancer; n, number; HR, hazard ratio; CI, confidence interval; mm, millimetre; BCS, breast conserving surgery; RT, radiotherapy ;ET, endocrine treatment; MST, mastectomy.

[a] Variables DCIS grade, DCIS size and margin status were imputed with multivariate imputation by chained equations (MICE). The imputation model was a nominal logistic regression for margin status and an ordered logistic regression for DCIS size and DCIS grade. The model included the following variables: Age at diagnosis, year of diagnosis, cohort and treatment type. The imputation process was repeated 40 times. Rubin's rule was used to combine the results.

Multivariable Cox proportional hazard analyses, stratified by Cohort

[b] Increase per year

Margin status

The 10 year cumulative incidence of ipsilateral invasive breast cancer was higher in participants with DCIS with involved margins (5.8%) compared with DCIS with clear margins (3.9%). The corresponding values for ipsilateral DCIS were 4.5% and 2.5% (fig 1).

In multivariable Cox regression analyses, adjusted risks for ipsilateral invasive breast cancer and ipsilateral DCIS were significantly higher for DCIS with involved margins compared with DCIS with clear margins in women who received breast conserving surgery with or without radiotherapy (ipsilateral invasive breast cancer 1.40, 1.07 to 1.83, and ipsilateral DCIS 1.39, 1.04 to 1.87) (table 2). In analyses that included women who underwent mastectomy, the risks for ipsilateral invasive breast cancer and ipsilateral DCIS did not increase significantly in women with involved margins (table 3). Supplementary tables S2 and S3 show the results of the analyses within each cohort. Risks for ipsilateral invasive breast cancer and ipsilateral DCIS by margin status were largely similar in sensitivity analyses on the non-imputed data, including missing information as a separate category (supplementary tables S4-S11).

Other risk factors

In stratified multivariable Cox regression analyses with multiple imputation data, higher grade of DCIS was not significantly associated with ipsilateral invasive breast cancer in any treatment group but was associated with a higher risk of ipsilateral DCIS in women who received breast conserving surgery with or without radiotherapy (grade 2: 1.42, 1.08 to 1.87; grade 3: 2.17, 1.66 to 2.83) (table2). Use of endocrine treatment in addition to breast conserving surgery was not significantly associated with a lower risk of ipsilateral invasive breast cancer compared to treatment with breast conserving surgery only (0.86, 0.62 to 1.21). Use of endocrine treatment in addition to breast conserving surgery, however, was associated with a lower risk of ipsilateral DCIS compared with breast conserving surgery only (0.50, 0.30 to 0.82) (table 2). In subgroup analyses excluding the Dutch cohort, the hazard ratio was 1.07 (0.76 to 1.53) for ipsilateral invasive breast cancer in women who received breast conserving surgery with endocrine treatment compared with women who received breast conserving surgery only (supplementary table S12). Subgroup analyses excluding both Dutch women and women with oestrogen receptor negative DCIS showed a risk for ipsilateral invasive breast cancer of 1.03 (0.69 to 1.52)
(supplementarytableS13). Harrell's C-index of the multiple imputed, multivariable Cox regression models including all participants were 0.64 for ipsilateral invasive breast cancer and 0.74 for ipsilateral DCIS.

Stage of ipsilateral invasive breast cancer

Cumulative relative incidences, estimating observed stage of ipsilateral invasive breast

cancer in the joint PRECISION cohort versus expected stages of invasive breast cancer in the Dutch population ranged between 0.99 and 1.01 for all stages (supplementary table S14), showing no difference in the stage of subsequent ipsilateral invasive breast cancer in women treated for DCIS compared with primary breast cancer in the Dutch female population. In multivariable joint Cox regression analyses, risks for stage III and IV ipsilateral invasive breast cancer were increased in women with DCIS ≥50 mm compared with <20 mm, (stage III: 3.93, 1.80 to 8.57; stage IV: 3.56, 1.84 to 6.91) (table 4). In contrast, no association was found between margin status and stage of ipsilateral invasive breast cancer.

Subtype of ipsilateral invasive breast cancer

Cumulative relative incidences for subtype of ipsilateral invasive breast cancer in the joint PRECISION cohort compared with subtypes of invasive breast cancer in the Dutch population ranged between 0.99 and 1.01 for all tumour subtypes (supplementary table S14), showing no difference in the subtype of subsequent ipsilateral invasive breast cancer in women treated for DCIS compared with primary breast cancer in the Dutch female population. In multivariable joint Cox regression analyses, the risk of hormone receptor negative and HER2 positive ipsilateral invasive breast cancer associated with DCIS >50 mm was significantly increased (2.64, 1.33 to 5.21) compared with <20mm (table 4). Similarly, the risks were increased for hormone receptor negative and HER2 positive ipsilateral invasive breast cancer (2.21, 1.06 to 4.62) and for hormone receptor negative and HER2 negative ipsilateral invasive breast cancer (1.91, 1.11 to 3.26) after DCIS with involved margins compared to DCIS with clear margins.

Table 4: Risk of stage and type of subsequent event, multivariable joint Cox proportional hazards analysesa, using multiple imputed data[b]

Stage	***Stage 0 iDCIS***		***Stage 1 iIBC***		***Stage 2 iIBC***		***Stage 3 iIBC***		***Stage 4 iIBC***	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Margin status[c]	n=626		n=385		n=165		n=29		n=38	
Clear (>2mm)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Involved (≤2mm)	1.64 (1.23-2.18)	<0.001	1.32 (0.90-1.94)	0.16	1.67 (1.04-2.71)	0.04	1.18 (0.24-5.72)	0.84	1.31 (0.44-3.85)	0.63
DCIS size[d]	n=658		n=439		n=208		n=50		n=68	
<20mm	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
20-49mm	1.43 (1.58-1.76)	<0.001	1.00 (0.78-1.30)	0.98	1.56 (1.14-2.13)	0.006	1.24 (0.57-2.73)	0.59	1.64 (0.92-2.92)	0.09
≥50mm	0.86 (0.55-1.35)	0.52	1.01 (0.65-1.58)	0.96	1.24 (0.68-2.24)	0.48	3.93 (1.80-8.57)	<0.001	3.56 (1.84-6.91)	<0.001

Subtype	***HR+ HER2+***		***HR+ HER2-***		***HR- HER2+***		***HR- HER2-***	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Margin status[c]	n=43		n=325		n=59		n=113	
Clear (>2mm)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Involved (≤2mm)	0.96 (0.31-2.95)	0.94	1.10 (0.73-1.65)	0.65	2.21 (1.06-4.62)	0.04	1.91 (1.11-3.26)	0.02
DCIS Size [d]	n=55		N=393		n=88		n=133	
<20mm	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
20-50mm	1.34 (0.74-2.42)	0.33	0.98 (0.76-1.26)	0.89	1.62 (0.96-2.73)	0.07	0.85 (0.54-1.35)	0.49
>50mm	0.87 (0.25-3.08)	0.83	0.82 (0.52-1.29)	0.39	2.64 (1.33-5.21)	0.005	0.96 (0.47-1.95)	0.91

Abbreviations:

iDCIS, ipsilateral ductal carcinoma in situ; iIBC, ipsilateral invasive breast cancer; HR, hazard ratio; CI, Confidence interval; n, number; mm, millimetre; HR+/-, hormone receptor positive/negative; HER2+/-, Human Epidermal growth factor Receptor positive/negative.

[a] Joint Cox regression analyses, in women for which stage/type of iIBC was available. Adjusted for treatment type, not stratified by Cohort.

[b] Variables DCIS grade, DCIS size and margin status were imputed with multivariate imputation by chained equations (MICE). The imputation model was a nominal logistic regression for margin status and an ordered logistic regression for DCIS size and DCIS grade. The model included the following variables: Age at diagnosis, year of diagnosis, cohort and treatment type. The imputation process was repeated 40 times. Rubin's rule was used to combine the results

[c] Patients receiving mastectomy were excluded from analyses

[d] Patients from all treatment groups were included in analyses

Discussion

In this large, multinational, pooled analysis we studied the association between DCIS size and margin status with risk of developing ipsilateral invasive breast cancer and ipsilateral DCIS and identified involved margins as a risk factor for both in women receiving breast conserving surgery with or without radiotherapy for DCIS. Larger DCIS was associated with higher risk of ipsilateral DCIS. Similarly, a slightly increased risk of ipsilateral invasive breast cancer was found in women with larger DCIS, although this finding was not statistically significant. The potential clinical value of these clinical variables was shown to be moderate at best (Harrell's C indices 0.64 for ipsilateral invasive breast cancer and 0.74 for ipsilateral DCIS). However, women with a large DCIS (≥50 mm) were more likely to develop stage III and IV ipsilateral invasive breast cancer compared to women with the smallest DCIS (<20 mm). No such association was found between involved margin status and higher stage of ipsilateral invasive breast cancer. Additional analyses on DCIS size or margin status and subtype of ipsilateral invasive breast cancer showed an association between larger DCIS and hormone receptor negative and HER2 positive ipsilateral invasive breast cancer and involved margin status, and hormone receptor negative ipsilateral invasive breast cancer.

Strengths and limitations of this study

Our study used large previously assembled cohorts to assess risk factors for the development of subsequent ipsilateral invasive breast cancer and ipsilateral DCIS after a primary diagnosis of DCIS. The use of multinational, patient level, registry data implies that results are widely applicable. We reported on associations between DCIS margin status and stage and subtype of subsequent ipsilateral invasive breast cancer, whereas to date, only one case series comprising 32 patients with ipsilateral invasive breast cancer or ipsilateral

DCIS after treatment for DCIS has reported on stage of ipsilateral invasive breast cancer, in which only stage I and II ipsilateral invasive breast cancers were observed.[36] Even in the current large cohort, the numbers of events in these subcategories were small; interpretation of these results should therefore be undertaken with care.

This study also has some limitations. Firstly, the Netherlands Cancer Registry only recently registered data on margin status and DCIS size in the Dutch cohort. For earlier years, however, these data were manually extracted from 12 000 pathology reports provided by the Dutch Nationwide Pathology Databank: Palga, [37] by two trained researchers (RSJMS and CC) independently, in a standardised manner specifically for this study. Any disagreements were resolved through consensus or by consulting a pathologist (JW). Secondly, as this study mainly used registry data that differed across cohorts, we could only use broad categories of DCIS size and margin status. We found heterogeneity in the categorisation of DCIS size in existing literature, making comparison between studies difficult. To introduce an objective categorisation, we determined size categories in line with the TNM criteria for invasive breast cancer. [30] Thirdly, several values were missing in the data, with as much as 28% missing information on DCIS size. It was not possible to retrospectively collect this information. The characteristics of patients with missing data, compared to patients without missing data, showed that these patients were more often from the Dutch cohort and received a diagnosis in earlier years (supplementary table S1). Much of the missing information on margin status in the UK (Sloane) cohort was in those treated with mastectomy, as it was not required to report margin status in women who had undergone mastectomy. Including those with missing data in an unknown category (although an imperfect approach compared with multiple imputation) did not alter the outcomes of this study using multiple imputation (supplementary tables S3-S10), suggesting that the missing data did not have an important influence on the study outcomes. Fourthly, baseline hazards might differ between the cohorts and countries. The results were not, however, altered when applying stratification by cohort (applied in the Cox regression models), again suggesting this did not influence the outcomes of this study. Results were largely similar among cohorts (supplementary tables S2 and S3), although the hazard ratio for margin status was not available for the US (MD Anderson Cancer Center) cohort owing to a lack of power, with only 47 occurrences of ipsilateral invasive breast cancer and 34 of ipsilateral DCIS. Furthermore, as these were registry data, some variables that potentially could be relevant were not available, such as detailed information on nodal status of the ipsilateral invasive breast cancer, comorbidities, menopausal status, hormone replacement therapy, and screening status. [38] In future, such data will become available through new prospective DCIS registry cohorts or ongoing DCIS trials: Comparison of Operative versus Monitoring and Endocrine Therapy, [39] Low Risk DCIS Trial (LORIS [40] and LORD)[41] trials. Lastly, although this cohort was large, the

10 year incidence of ipsilateral invasive breast cancer (n=981) and ipsilateral DCIS (n=658) were relatively low. Although this finding emphasises the benign nature of DCIS, it did lead to small number events in subgroup analyses, especially in patients who underwent mastectomy for DCIS. Therefore, these results should be interpreted with caution.

Comparison with other studies

Our results on DCIS size are consistent with a multi-institutional nested case-control study including 939 patients with DCIS that found an association between larger DCIS and an increased risk of ipsilateral DCIS but not ipsilateral invasive breast cancer.[23] However, a 15 year update of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 (breast conserving surgery with or without radiotherapy) and B-24 (breast conserving surgery with or without endocrine treatment) randomised controlled trials among 2622 women with DCIS reported no such association.[26] These trials also studied the effect of margin status and concluded there was an association between involved margins and higher risk of ipsilateral invasive breast cancer and ipsilateral DCIS. Similarly, a retrospective study of 2996 women with DCIS and treated with breast conserving surgery with or without radiotherapy or endocrine treatment reported a trend (P for trend=0.087) in the association between increasing margin width and lower risk of recurrence (defined as any ipsilateral or metastatic breast event), although only in women who did not receive radiotherapy.[42] In the current study, the increased risks of ipsilateral invasive breast cancer and ipsilateral DCIS in patients with involved margins who underwent breast conserving surgery was independent of adjuvant treatment, which was also observed in the Swedish Ductal Carcinoma in Situ (SweDCIS) randomised controlled trial cohort, comprising 1046 patients.[43] Comparison between studies is difficult, however, owing to heterogeneity in the categorisation of DCIS size and in the definition of clear versus involved margins.

The results of our study highlight the low-risk nature of DCIS. Overall, 10-year cumulative incidence for ipsilateral invasive breast cancer was 3.2%. For reference, the 10-year risk of breast cancer in women aged 60 in the US general population is 3.5%.[44, 45] Additionally, it has been reported that about 20% of all ipsilateral invasive breast cancers diagnosed after treatment for DCIS are not related to the primary DCIS,[46, 47] implying that these breast cancer diagnoses are not a recurrent lesion but rather a second primary lesion. This would also explain why clinicopathological factors of DCIS are less useful in predicting subsequent ipsilateral invasive breast cancer but more useful in predicting ipsilateral DCIS.

In our analyses, the use of endocrine treatment in addition to breast conserving surgery with or without radiotherapy was not significantly associated with a lower risk of ipsilateral invasive breast cancer compared to treatment with breast conserving surgery only. The

benefits of endocrine treatment were also not observed in subgroup analyses that included only women with oestrogen receptor positive DCIS (supplementary table S13). Previous randomised trials of DCIS showed varying results on the potential benefit of endocrine treatment. A significantly lower risk of ipsilateral invasive breast cancer in patients who received breast conserving surgery with radiotherapy and endocrine treatment or placebo was reported in the NSABP B-24 trial.[26, 48] In the UK, Australia, and New Zealand DCIS randomised controlled trial, however, only a lower risk of ipsilateral DCIS, and not of ipsilateral invasive breast cancer, was reported in patients who received endocrine treatment compared with those who did not[49]—this was also seen in our study.

Conclusions

This pooled, multinational study provided an opportunity to review current clinical practice using real world data and enabled comprehensive, exploratory analyses of stage and type of ipsilateral invasive breast cancer after treatment for DCIS. The higher risk of stage III and IV breast cancer in women with a large DCIS (≥50 mm) found in our analyses, provides new insights into the characteristics of potentially harmful DCIS that may be expanded on and validated in future studies. Notably, even in this large cohort, numbers of events were limited, highlighting the low risk of subsequent breast cancer events after treatment for DCIS. Additionally, although the risks of ipsilateral invasive breast cancer and ipsilateral DCIS associated with DCIS size and margin status were increased, they were low. When these two factors were added to other perceived risk factors, the prognostic value of the combined factors was modest at best, highlighting the need for a shift in focus towards novel prognostic markers.

Additional information

Contributors: JW, EHL, and MKS contributed equally to this paper and are the guarantors of this manuscript. RSJMS, JW, EHL, MKS, AWBD, TL, DC, MDR, ES, ESH, and AT contributed to the study conceptualisation. RSJMS, JW, EHL, MKS, AWBD, MS, MDR, ES, ESH, and AT contributed to the study design and methodology. PB, KC, YR, CC, JT, YL, DB, BM, TH, ST, and JKL contributed to data collection and curation. PB contributed to project management and administration. RSJMS, AWBD, MS, and CC contributed to data analysis. RSJMS, AWBD, JW, EHL, and MKS participated in data interpretation and manuscript preparation. AWBD, JW, EHL, and MKS participated in supervision. All authors read and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from Cancer Research UK and by KWF Kankerbestrijding and Patient-Centered Outcomes Research Institute; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

The National Cancer Database (NCDB), under the guidance of the Commission on Cancer (CoC) leadership and committees, disseminates aggregate and individual data for CoC accredited programmes. NCDB special study data are primarily intended for internal use within CoC accredited cancer programmes. These data have permissible and non-permissible use and are therefore only able to be shared outside of the CoC accredited programme once an appropriate data sharing agreement has been established. For more information, please contact shelley.hwang@duke.edu. Data from the MDCC (MD Anderson Cancer Center) cohort can be made available upon request.

The corresponding author (MKS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
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Ethical approval: The data collection for the Dutch cohort was reviewed and approved by the Netherlands Cancer Registry and Palga review boards (data study Nos NCR: K12.281, K17.321; data study Nos Palga: lzv990, lzv2017-173). The dataset generated and analysed during the current study as the "MDACC cohort" was reviewed and collated as part of PA16-0612. A separate protocol, PA17-1020, governed the movement of data and specimens between PRECISION institutions. NCDB special study data were determined exempt by the Duke University Medical Centre institutional review board (Pro00081281).The Sloane study has been permitted to process personally identifiable data without consent under Regulation 5 of Statutory Instrument 2002 No 1438: The Health Service (Control of Patient Information) (15/CAG/0207) in line with the following clause: "quality assuring screening services to ensure they are effective and safe, and that any incidents are investigated and managed appropriately." This statutory exemption to common law permits the processing of personally identifiable data, as part of the core remit of population screening. The Sloane Project was able to send clinical data to the Netherlands Cancer Institute under the ethics committee approval research ethics committee reference: 18/WM/0400, protocol

No C38317/A24043, IRAS Project ID: 247823, and data sharing agreement between Public Health England/NHS England Reference ODR1819_019. Data protection and curation was done in compliance with current ethical and data protection regulations.

Data sharing: The datasets generated and analysed during the current study as the "Dutch cohort" are not publicly available, as the study used external data from the Netherlands Cancer Registry. The datasets will be made available from the Netherlands Cancer Registry upon reasonable request (data request study Nos K12.2871 and K17.321). To apply for data access, please visit https://www.iknl.nl/en/ncr/apply-for-data. Sloane Project data that forms part of the PRECISION Project cannot be accessed directly from the PRECISION team. However, the Sloane Project group welcomes applications from the UK, European Economic Area, and international organisations to collaborate and release data. Any data are subject to a common governance framework, which will ensure correct adherence to confidentiality provisions, legal permission, and ethical approvals. The dataset generated and analysed during the current study as the "MDACC cohort" are not publicly available. Any requests for access of this data should be directed to Afutreal@mdanderson.org.

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Supplementary files

Supplementary methods

Cohort details

The first cohort is a nationwide population-based cohort from the Netherlands Cancer Registry (NCR) with clinicopathological data on primary diagnosis of DCIS, treatment and outcome that are routinely collected by trained registration officers. Additionally, linkage of NCR with the Dutch Municipal Personal Records Database provided survival data and linkage with the nationwide network and registry of histo- and cytopathology in the Netherlands PALGA: Dutch Pathology Registry provided all related pathology reports1-3.

The second cohort is the Sloane cohort, a population-based, prospective screening cohort from the United Kingdom of women diagnosed with non-invasive neoplasms through the National Health Service (NHS) Breast Cancer Screening Programme in the UK, for which radiological, clinicopathological features, patterns of care, and outcome data were collected4,5,5. In addition, further outcome and mortality data were collected through linkage to datasets held by the National Disease Registration Service, NHS England6.

The third cohort is a single-centre cohort from the tertiary MD Anderson Cancer Center (MDACC).

The fourth cohort, the National Cancer Database Special Study (NCDB-SS) on DCIS, consists of a treatment-stratified random sample of DCIS patients from 1,330 Commission on Cancer-accredited facilities across the United States (US)7. In addition to routinely collected data fields as recorded in the NCDB, the NCDB-SS abstracted in-depth baseline and longitudinal treatment, cancer outcomes and survival data for up to 10 years after diagnosis.

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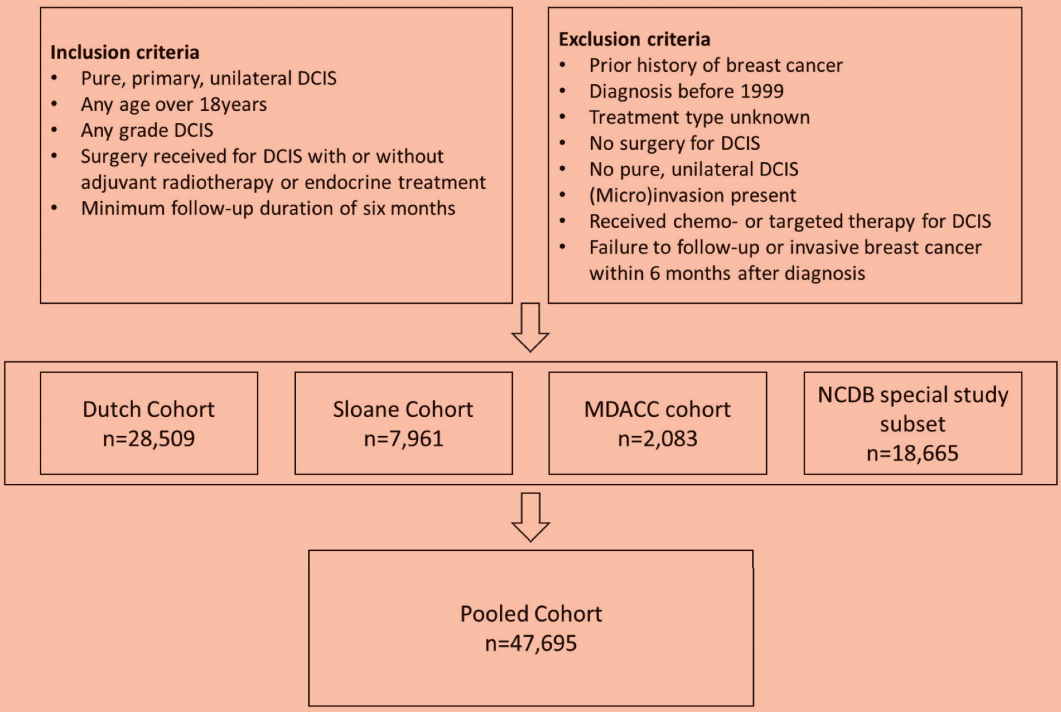
Supplementary tables and figures

Figure S1 Flowchart

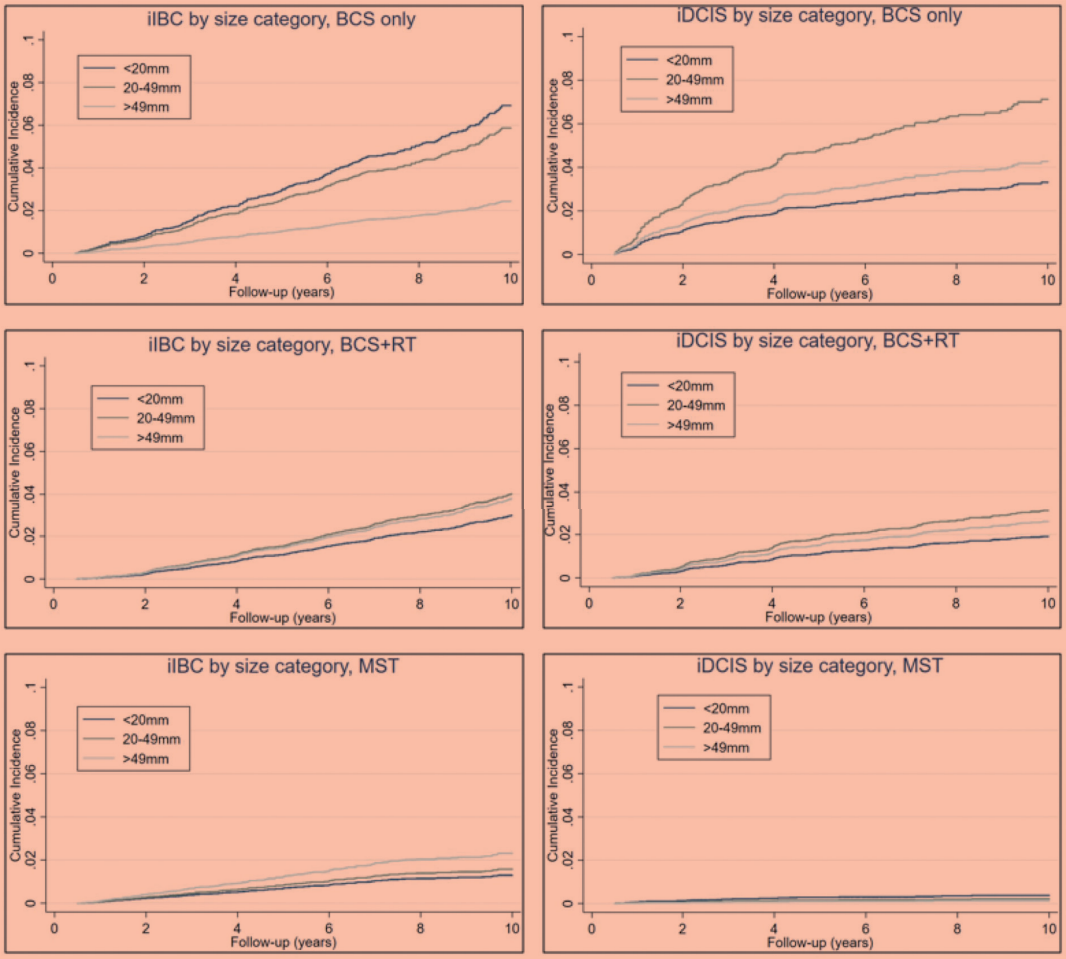


Abbreviations:

DCIS, Ductal carcinoma in situ; MDACC, MD Anderson Cancer Center; NCDB, National Cancer Database.

Figure S2 Ten-year cumulative incidence of subsequent ipsilateral invasive breast cancer and subsequent ipsilateral DCIS by size category, per treatment type.

size category, per treatment type.



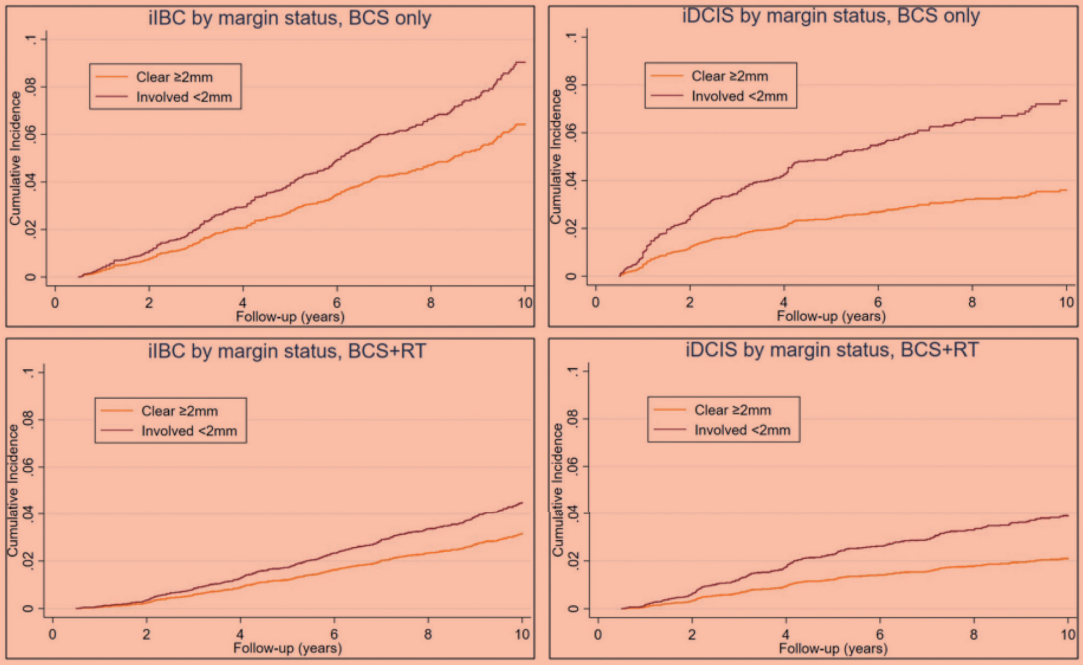
Abbreviations:

iIBC, subsequent ipsilateral invasive breast cancer; iDCIS, subsequent ipsilateral ductal carcinoma in situ; BCS, breast conserving surgery; RT, radiotherapy; MST, mastectomy; mm, millimetre

Cumulative incidences with competing risk analyses, with cut off at ten years. Competing risks: death by any cause, contralateral breast cancer and, depending on the analyses, ipsilateral DCIS or ipsilateral invasive breast cancer.

Number of patients per treatment group: BCS only, n=8,971; BCS+RT, n=23,667; MST, n=15,057

Figure S3 Ten-year cumulative incidence of subsequent ipsilateral invasive breast cancer and subsequent ipsilateral DCIS by margin status, per treatment type



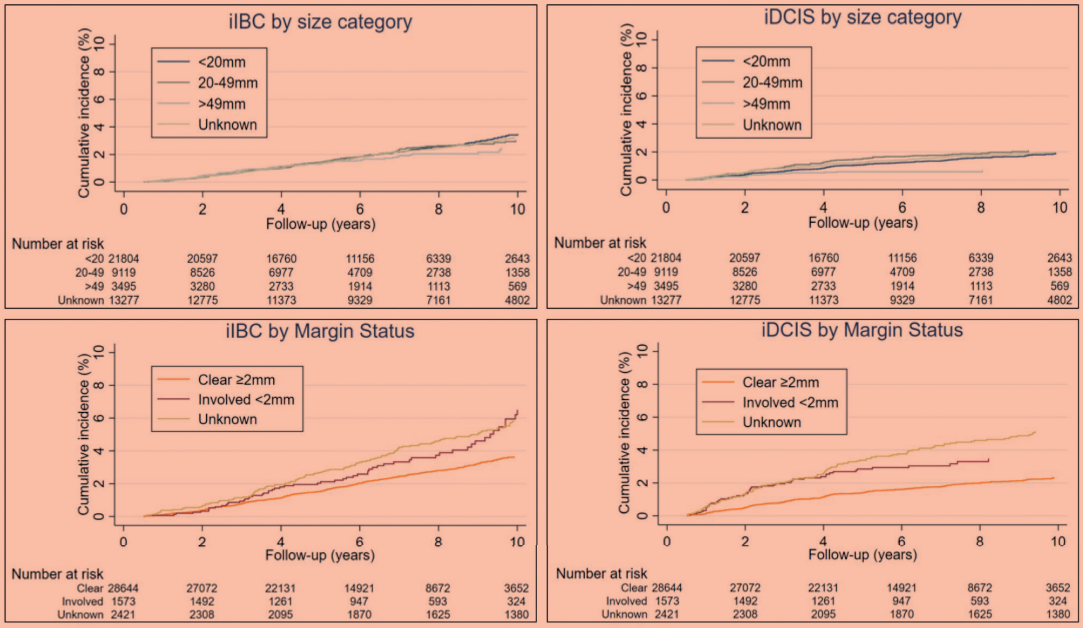
Abbreviations:

iIBC, subsequent ipsilateral invasive breast cancer; iDCIS, subsequent ipsilateral ductal carcinoma in situ; BCS, breast conserving surgery; RT, radiotherapy; mm, millimetre.

Cumulative incidences with competing risk analyses, with cut off at ten years. Competing risks: death by any cause, contralateral breast cancer and, depending on the analyses, ipsilateral DCIS or ipsilateral invasive breast cancer.

Number of patients per treatment group: BCS only, n=8,971; BCS+RT, n=23,667; MST, n=15,057

Figure S4 Ten-year cumulative incidence of subsequent ipsilateral invasive breast cancer and subsequent ipsilateral DCIS by size category and margin status in not-imputed data, including unknown category.



Abbreviations:

iIBC, subsequent ipsilateral invasive breast cancer; iDCIS, subsequent ipsilateral ductal carcinoma in situ; mm, millimetre.

Cumulative incidences with competing risk analyses, with cut off at ten years. Competing risks: death by any cause, contralateral breast cancer and, depending on the analyses, ipsilateral DCIS or ipsilateral invasive breast cancer. Cumulative incidences by size category were calculated in the full, pooled cohort n=47,853. Cumulative incidences by margin status only in women receiving breast conserving surgery with or without adjuvant treatment n=32,638.

Table S1 Patient characteristics of patients with missing data on DCIS size, margin status or DCIS grade

	Patients with missing data on DCIS size n=13,277	Patients with missing data on margin status n=6,747	Patients with missing data on DCIS grade n=2,766	Patients with any missing data n=17,678	Patients without missing data n=30,017
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age at diagnosis	59 (10.9)	59 (9,9)	60 (11.6)	59 (10.5)	59 (10.5)
Year of diagnosis	2008 (4.6)	2005 (3.8)	2008 (5.0)	2008 (4.4)	2010 (3.7)
Follow-up time	7.8 (2.6)	7.7 (2.9)	7.4 (2.7)	7.4 (2.7)	6.3 (2.6)
	n (%)	n (%)	n (%)	n (%)	n (%)
Cohort					
Dutch cohort	7,674 (58)	3,773 (56)	1,255 (45)	8,615 (49)	10,371 (35)
Sloane Cohort	86 (1)	2,549 (38)	7 (0)	2,568 (15)	5,393 (18)
MDACC Cohort	420 (3)	11 (0)	5 (0)	431 (2)	1,652 (6)
NCDB special study[a]	5,097 (38)	414 (6)	1,499 (54)	6,064 (34)	12,601 (42)
Treatment type[b,c]					
BCS only	2,278 (17)	776 (12)	647 (23)	2,692 (15)	4,622 (15)
BCS+RT	4,628 (35)	1,484 (22)	801 (29)	5,326 (30)	11,870 (40)
BCS+ET	442 (3)	46 (1)	101 (4)	521 (3)	1,136 (4)
BCS+RT+ET	1,495 (11)	115 (2)	409 (15)	1,784 (10)	4,687 (16)
MST	4,434 (33)	4,326 (64)	808 (29)	7355 (42)	7,702 (26)
Survival status					
Alive	12,212 (92)	6,259 (93)	2,493 (90)	16,373 (93)	28,337 (94)
Deceased	1,065 (8)	488 (7)	273 (10)	1,305 (7)	1,680 (6)

Abbreviations:

DCIS, ductal carcinoma in situ; n, number; SD, standard deviation; MDACC, MD Anderson Cancer center; NCDB, National Cancer Database; BCS, breast conserving surgery; RT, radiotherapy; ET, endocrine treatment; MST, mastectomy;

aTreatment-stratified random sample from NCDB special study, NCDB registers 70% of cancer patients in the USA.

bAll treatment initiated within 6 months after primary diagnosis of DCIS.

cEndocrine treatment is not standard treatment in the Netherlands, therefore patients with endocrine treatment were excluded from the Dutch cohort

Table S2 Risk of subsequent ipsilateral invasive breast cancer in all patients per cohort; Cox regression analyses using multiple imputed data[a]

	Dutch cohort n=18,986 n(iIBC)=488		Sloane n=7.961 n(iIBC)=226		MDACC[b] n=2.083 n(iIBC)=47		NCDB special study[c] n=18,665 n(iIBC)=220	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
DCIS size								
<20mm	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	1.25 (0.96-1.62)	0.10	0.92 (0.65-1.29)	0.61	0.78 (0.33-1.86)	0.58	1.15 (0.79-1.67)	0.48
≥50mm	1.35 (0.87-2.09)	0.18	1.08 (0.56-2.06)	0.83	1.62 (0.65-4.04)	0.30	0.98 (0.51-1.88)	0.95
Margin Status								
Clear (≥2mm)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved (<2mm)	1.25 (0.93-1.68)	0.14	1.03 (0.53-2.01)	0.93	N.A	N.A.	0.70 (0.29-1.69)	0.42
Age	0.98 (0.93-0.99)	<0.001	1.01 (0.99-1.02)	0.63	0.96 (0.94-0.99)	0.007	1.01 (1.00-1.02)	0.06
DCIS grade								
Grade 1	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	1.04 (0.79-1.37)	0.79	1.04 (0.68-1.61)	0.85	1.44 (0.42-4.88)	0.56	0.92 (0.63-1.32)	0.64
Grade 3	1.15 (0.88-1.50)	0.31	1.28 (0.83-1.97)	0.26	1.36 (0.40-4.68)	0.62	0.86 (0.59-1.25)	0.42
Treatment								
BCS only	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+RT	0.33 (0.27-0.41)	<0.001	0.45 (0.32-0.63)	<0.001	1.18 (0.46-3.04)	0.73	1.11 (0.71-1.73)	0.65
BCS+ET[d]	N.A.		0.70 (0.40-1.20)	0.19	0.40 (0.05-3.32)	0.39	1.88 (1.11-3.18)	0.019
BCS+RT+ET[d]	N.A.		0.27 (0.14-0.53)	<0.001	0.62 (0.22-1.73)	0.36	1.07 (0.69-1.66)	0.76
MST	0.13 (0.09-0.17)	<0.001	0.23 (0.15-0.38)	<0.001	0.28 (0.10-0.82)	0.02	0.92 (0.57-1.49)	0.74

Abbreviations:

MDACC, MD Anderson Cancer center; NCDB, National Cancer Database; iIBC, subsequent ipsilateral invasive breast cancer; n, number; HR, hazard ratio; mm, millimetre; BCS, breast conserving surgery; RT, radiotherapy; RT, radiotherapy; ET, endocrine treatment; DCIS, ductal carcinoma in situ; ET, endocrine treatment.

[a] Variables DCIS grade, DCIS size and margin status were imputed with multivariate imputation by chained equations (MICE). The imputation model was a nominal logistic regression for margin status and an ordered logistic regression for DCIS size and DCIS grade. The model included the following variables: Age at diagnosis, year

[b] For the MDACC cohort, margin status was omitted from this table, as this cohort, on its own, does not include sufficient events for these analyses.

diagnosis, cohort and treatment type. The imputation process was repeated 40 times. Rubin's rule was used to combine the results.

[c] Treatment-stratified random sample from NCDB special study, NCDB registers 70% of cancer patients in the USA.

[d] As endocrine treatment is not part of standard treatment in the Netherlands,, in the Dutch cohort, women who received endocrine treatment (n=148) were excluded from analyses

Table S3 Risk of subsequent ipsilateral DCIS in all patients per cohort; Cox regression analyses using multiple imputed data[a]

	Dutch cohort n=18,986 n(iDCIS)=354		Soane n=7.961 n(iDCIS)=159		MDACC[a] n=2.083 n(iDCIS)=34		NCDB special study[c] n=18,665 n(iDCIS)=111	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
DCIS size								
<20mm	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	1.22 (0.88-1.68)	0.24	1.56 (1.10-2.23)	0.01	2.44 (1.16-5.13)	0.02	1.52 (0.91-2.52)	0.11
≥50mm	0.83 (0.37-1.85)	0.65	2.55 (1.08-6.04)	0.03	1.86 (0.48-7.16)	0.37	1.41 (0.60-3.32)	0.43
Margin Status								
Clear (≥2mm)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved (<2mm)	1.39 (0.98-1.68)	0.06	1.23 (0.65-2.34)	0.53	N.A.	N.A.	0.79 (0.25-2.50)	0.69
Age	0.98 (0.97-0.99)	<0.001	1.00 (0.98-1.02)	0.91	0.94 (0.90-0.97)	<0.001	0.99 (0.97-1.01)	0.17
DCIS grade								
Grade 1	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	1.70 (1.17-2.45)	0.005	1.73 (0.86-3.49)	0.13	1.21 (0.34-4.22)	0.76	0.96 (0.55-1.67)	0.89
Grade 3	2.64 (1.85-3.75)	<0.001	3.86 (1.98-7.55)	<0.001	0.84 (0.23-3.07)	0.79	1.03 (0.60-1.78)	0.92
Treatment								
BCS only	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+RT	0.26 (0.21-0.33)	<0.001	0.37 (0.26-0.54)	<0.001	0.55 (0.24-1.27)	0.16	1.09 (0.62-1.92)	0.77
BCS+ET[d]	N.A.	N.A.	0.66 (0.34-1.28)	0.22	0.24 (0.03-1.91)	0.18	0.73 (0.29-1.84)	0.51
BCS+RT+ET[d]	N.A.	N.A.	0.24 (0.12-0.49)	<0.001	0.20 (0.07-0.57)	0.002	0.92 (0.53-1.60)	0.76
MST	0.02 (0.01-0.04)	<0.001	0.01 (0.00-0.04)	<0.001	0.03 (0.01-1.14)	<0.001	0.32 (1.15-0.67)	0.003

Abbreviations:

MDACC, MD Anderson Cancer center; NCDB, National Cancer Database; iIBC, subsequent ipsilateral invasive breast cancer; n, number; HR, hazard ratio; mm, millimetre; BCS, breast conserving surgery; RT, radiotherapy; RT, radiotherapy; ET, endocrine treatment; DCIS, ductal carcinoma in situ; ET, endocrine treatment.

[a] Variables DCIS grade, DCIS size and margin status were imputed with multivariate imputation by chained equations (MICE). The imputation model was a nominal logistic regression for margin status and an ordered logistic regression for DCIS size and DCIS grade. The model included the following variables: Age at diagnosis, year

[b] For the MDACC cohort, margin status was omitted from this table, as this cohort, on its own, does not include sufficient events for these analyses.

diagnosis, cohort and treatment type. The imputation process was repeated 40 times. Rubin's rule was used to combine the results.

[c] Treatment-stratified random sample from NCDB special study, NCDB registers 70% of cancer patients in the USA.

[d] As endocrine treatment is not part of standard treatment in the Netherlands,, in the Dutch cohort, women who received endocrine treatment (n=148) were excluded from analyses

Table S4 Risk of subsequent ipsilateral invasive breast cancer in patients treated with breast conserving surgery without radiotherapy; Cox regression analyses with and without stratification and without multiple imputation

	BCS only n=8,971								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	176	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	28	0.95 (0.64-1.41)	0.80	1.03 (0.69-1.54)	0.87	0.90 (0.60-1.35)	0.61	0.97 (0.65-1.46)	0.89
≥50mm	1	0.13 (0.02-0.94)	0.04	0.21 (0.03-1.51)	0.12	0.13 (0.02-0.89)	0.04	0.20 (0.03-1.45)	0.11
Unknown	129	1.10 (0.88-1.39)	0.40	1.33 (.00-1.76)	0.05	0.90 (0.70-1.16)	0.41	1.19 (0.89-1.61)	0.25
Margin Status									
Clear	241	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	22	1.52 (0.98-2.35)	0.06	1.42 (0.92-2.21)	0.12	1.54 (0.99-2.39)	0.06	1.44 (0.92-2.25)	0.11
Unknown	71	2.08 (1.59-2.72)	<0.001	1.65 (1.23-2.22)	0.001	2.10 (1.56-2.83)	<0.001	1.51 (1.10-2.06)	0.01
Age		1.00 (0.99-1.01)	0.52	1.01 (1.00-1.02)	0.02	1.00 (0.99-1.01)	0.45	1.01 (1.00-1.02)	0.03
DCIS grade									
Grade 1	97	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	108	0.99 (0.75-1.30)	0.93	1.08 (0.81-1.43)	0.60	1.04 (0.79-1.37)	0.80	1.06 (0.80-1.40)	0.69
Grade 3	97	1.20 (0.90-1.59)	0.21	1.29 (0.97-1.72)	0.08	1.24 (0.93-1.64)	0.14	1.27 (0.95-1.70)	0.10
Unknown	32	1.05 (0.70-1.57)	0.81	1.20 (0.80-1.80)	0.38	0.95 (0.63-1.42)	0.78	1.07 (0.71-1.61)	0.75
Treatment									
BCS only	293	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+ET	41	0.67 (0.48-0.93)	0.02	1.07 (0.75-1.52)	0.72	0.74 (0.53-1.03)	0.07	1.08 (0.76-1.54)	0.66

Abbreviations:

BCS, breast conserving surgery; n, number; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; RT, radiotherapy; ET, endocrine treatment

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S5 Risk of subsequent ipsilateral DCIS; Cox regression analyses in patients treated with breast conserving surgery without radiotherapy; without multiple imputation

	BCS only n=8,971								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	106	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	36	2.07 (1.41-3.02)	<0.001	2.25 (1.54-3.30)	<0.001	1.78 (1.21-2.62)	0.003	1.94 (1.32-2.86)	0.001
≥50mm	5	1.13 (0.46-2.77)	0.79	2.01 (0.82-4.99)	0.13	0.92 (0.37-2.27)	0.86	1.59 (0.64-3.97)	0.32
Unknown	107	2.07 (1.41-3.02)	<0.001	1.92 (1.37-2.69)	<0.001	1.27 (0.94-1.72)	0.12	1.61 (1.11-2.32)	0.11
Margin Status									
Clear	168	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	19	1.97 (1.23-3.17)	0.005	1.78 (1.11-2.88)	0.02	1.59 (0.99-2.57)	0.06	1.41 (0.86-2.30)	0.17
Unknown	64	3.15 (2.35-4.20)	<0.001	2.07 (1.50-2.85)	<0.001	2.68 (1.93-3.73)	<0.001	1.71 (1.20-2.42)	0.003
Age		0.99 (0.98-1.00)	0.04	1.00 (0.99-1.01)	0.83	0.99 (0.98-1.00)	0.08	1.00 (0.98-1.01)	0.56
DCIS grade									
Grade 1	46	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	74	1.37 (0.95-1.98)	0.10	1.68 (1.15-2.44)	0.01	1.53 (1.05-2.21)	0.03	1.66 (1.14-2.43)	0.008
Grade 3	101	2.57 (1.81-3.64)	<0.001	3.17 (2.22-4.53)	<0.001	2.61 (1.83-3.71)	<0.001	2.95 (2.06-4.22)	<0.001
Unknown	30	2.20 (1.39-3.49)	<0.001	2.46 (1.55-3.92)	<0.001	1.83 (1.15-2.91)	0.01	2.18 (1.36-3.48)	0.001
Treatment									
BCS+RT	234	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+RT+ET	17	0.33 (0.20-0.54)	<0.001	0.65 (0.39-1.09)	0.11	0.39 (0.24-0.64)	<0.001	0.67 (0.40-1.12)	0.13

Abbreviations:

BCS, breast conserving surgery; n, number; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; RT, radiotherapy; ET, endocrine treatment

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S6 Risk of subsequent ipsilateral invasive breast cancer in patients treated with breast conserving surgery and radiotherapy and/or endocrine treatment; Cox regression analyses with and without stratification and without multiple imputation

	BCS+RT n=23,667								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	213	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	101	1.50 (1.18-1.90)	0.001	1.34 (1.06-1.71)	0.02	1.44 (1.14-1.83)	0.003	1.33 (1.05-1.70)	0.02
≥50mm	12	1.27 (0.71-2.27)	0.42	1.27 (0.71-2.28)	0.41	1.25 (0.70-2.24)	0.45	1.25 (0.70-2.24)	0.46
Unknown	141	1.08 (0.87-1.34)	0.49	1.14 (0.91-1.42)	0.26	1.02 (0.81-1.28)	0.86	1.11 (0.88-1.41)	0.38
Margin Status									
Clear	382	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	36	1.56 (1.10-2.19)	0.01	1.51 (1.07-2.14)	0.02	1.46 (1.04-2.06)	0.03	1.49 (1.05-2.10)	0.03
Unknown	49	1.14 (0.85-1.54)	0.39	1.10 (0.80-1.49)	0.56	1.12 (0.81-1.56)	0.48	1.07 (0.77-1.49)	0.68
Age		0.99 (0.98-1.00)	0.005	0.99 (0.98-1.00)	0.005	0.99 (0.98-1.00)	0.003	0.99 (0.98-1.00)	0.004
DCIS grade									
Grade 1	64	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	145	0.86 (0.64-1.16)	0.33	0.83 (0.62-1.11)	0.21	0.85 (0.63-1.14)	0.27	0.82 (0.61-1.10)	0.19
Grade 3	232	1.02 (0.77-1.34)	0.91	0.90 (0.68-1.19)	0.46	0.95 (0.72-1.26)	0.72	0.87 (0.63-1.15)	0.33
Unknown	26	0.92 (0.58-1.45)	0.72	0.98 (0.62-1.55)	0.94	0.91 (0.58-1.44)	0.69	0.96 (0.61-1.52)	0.85
Treatment									
BCS+RT	382	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+RT+ET	85	0.71 (0.56-0.90)	0.004	0.80 (0.60-1.07)	0.13	0.73 (0.57-0.92)	0.009	0.79 (0.59-1.05)	0.11

Abbreviations:

BCS, breast conserving surgery; RT, radiotherapy; n, number; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; ET, endocrine treatment

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S7 Risk of subsequent ipsilateral DCIS in patients treated with breast conserving surgery and radiotherapy and/or endocrine treatment; Cox regression analyses; without multiple imputation

	BCS+RT n=23,667								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	165	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	99	1.87 (1.46-2.40)	<0.001	1.59 (1.24-2.05)	<0.001	1.65 (1.28-2.12)	<0.001	1.50 (1.17-1.94)	0.002
≥50mm	11	1.48 (0.81-2.73)	0.21	1.52 (0.83-2.81)	0.18	1.41 (0.77-2.61)	0.27	1.44 (0.78-2.66)	0.24
Unknown	100	1.07 (0.83-1.37)	0.60	1.09 (0.84-1.41)	0.53	0.91 (0.69-1.19)	0.49	0.97 (0.74-1.29)	0.85
Margin Status									
Clear	300	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	28	1.60 (1.08-2.35)	0.02	1.46 (0.99-2.16)	0.06	1.41 (0.96-2.08)	0.08	1.38 (0.93-2.03)	0.11
Unknown	47	1.60 (1.18-2.18)	0.003	1.40 (1.02-1.93)	0.04	1.69 (1.20-3.38)	0.003	1.53 (1.08-2.16)	0.02
Age		0.97 (0.96-0.99)	<0.001	0.97 (0.96-0.98)	<0.001	0.97 (0.96-0.98)	<0.001	0.97 (0.96-0.98)	<0.001
DCIS grade									
Grade 1	27	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	102	1.42 (0.93-2.18)	0.10	1.35 (0.89-2.06)	0.17	1.39 (0.91-2.12)	0.13	1.34 (0.88-2.05)	0.18
Grade 3	230	2.35 (1.57-3.49)	<0.001	2.03 (1.36-3.04)	0.001	2.12 (1.42-3.16)	<0.001	1.95 (1.30-2.92)	0.001
Unknown	16	1.38 (0.74-2.56)	0.31	1.51 (0.81-2.80)	0.19	1.33 (0.72-2.48)	0.37	1.42 (0.76-2.65)	0.27
Treatment									
BCS+RT	322	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+RT+ET	53	0.49 (0.37-0.65)	<0.001	0.68 (0.49-0.97)	0.03	0.53 (0.39-0.71)	<0.001	0.69 (0.49-0.98)	0.04

Abbreviations:

BCS, breast conserving surgery; RT, radiotherapy; n, number; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; ET, endocrine treatment

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S8 Risk of subsequent ipsilateral breast cancer in women receiving mastectomy; Cox regression analyses; without multiple imputation

	Mastectomy n=15,057								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	40	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	45	1.12 (0.73-1.71)	0.61	1.10 (0.71-1.70)	0.68	1.11 (0.72-1.71)	0.63	1.08 (0.69-1.67)	0.75
≥50mm	45	1.66 (1.09-2.55)	0.02	1.66 (1.08-2.57)	0.02	1.57 (1.02-2.41)	0.04	1.54 (0.99-2.39)	0.05
Unknown	50	0.91 (0.60-1.39)	0.68	1.01 (0.66-1.56)	0.96	0.89 (0.58-1.38)	0.61	1.08 (0.68-1.70)	0.75
Margin Status									
Clear	121	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	4	0.30 (0.11-0.81)	0.02	0.30 (0.11-0.81)	0.02	0.29 (0.11-0.79)	0.02	0.29 (0.11-0.79)	0.02
Unknown	55	1.01 (0.73-1.38)	0.97	0.71 (0.45-1.12)	0.14	1.11 (0.79-1.54)	0.56	0.76 (0.46-1.26)	0.28
Age		0.98 (0.97-0.99)	0.002	0.98 (0.96-0.99)	0.001	0.98 (0.97-0.99)	0.003	0.98 (0.96-0.99)	0.002
DCIS grade									
Grade 1	10	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	52	1.61 (0.82-3.17)	0.17	1.60 (0.81-3.15)	0.17	1.53 (0.77-3.01)	0.22	1.55 (0.79-3.05)	0.21
Grade 3	110	1.72 (0.90-3.28)	0.10	1.66 (0.87-3.17)	0.13	1.58 (0.82-3.03)	0.17	1.58 (0.82-3.02)	0.17
Unknown	8	1.20 (0.48-3.05)	0.70	1.28 (0.50-3.24)	0.61	1.30 (0.51-3.29)	0.59	1.39 (0.55-3.53)	0.49

Abbreviations:

n, number; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre.

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S9 Risk of subsequent ipsilateral DCIS in women receiving mastectomy; Cox regression analyses; without multiple imputation

	Mastectomy n=15,057								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	8	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	10	1.26 (0.50-3.19)	0.63	1.56 (0.60-4.03)	0.37	1.41 (0.55-3.59)	0.47	1.47 (0.56-3.82)	0.43
≥50mm	4	0.75 (0.22-2.47)	0.63	0.89 (0.26-3.03)	0.86	0.74 (0.22-2.46)	0.62	0.78 (0.23-2.65)	0.69
Unknown	10	1.00 (0.39-2.54)	0.99	1.09 (0.42-2.86)	0.86	1.36 (0.53-3.48)	0.53	1.41 (0.54-3.73)	0.49
Margin Status									
Clear	28	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	0	N.A.		N.A.		N.A.		N.A.	
Unknown	4	0.32 (0.11-0.92)	0.04	0.34 (0.08-1.39)	0.13	0.32 (0.11-0.93)	0.04	0.33 (0.08-1.42)	0.14
Age		0.97 (0.94-1.00)	0.07	0.98 (0.95-1.01)	0.11	0.98 (0.94-1.01)	0.1	0.97 (0.94-1.01)	0.11
DCIS grade									
Grade 1	2	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	9	1.38 (0.30-6.38)	0.68	1.39 (0.30-6.43)	0.68	1.38 (0.30-6.40)	0.68	1.38 (0.30-6.42)	0.68
Grade 3	21	1.62 (0.38-6.91)	0.51	1.76 (0.41-7.55)	0.45	1.73 (0.40-7.44)	0.46	1.74 (0.40-7.51)	0.46
Unknown	0	N.A.		N.A.		N.A.		N.A.	

Abbreviations:

n, number; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre.

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S10 Risk of subsequent ipsilateral invasive breast cancer including all women; Cox regression analyses; without multiple imputation

	All patients n=47,659								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	429	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	174	0.97 (0.81-1.15)	0.69	0.87 (0.73-1.04)	0.12	1.21 (1.01-1.46)	0.04	1.17 (0.97-1.40)	0.10
≥50mm	58	0.81 (0.62-1.07)	0.14	0.77 (0.58-1.01)	0.06	1.29 (0.97-1.72)	0.08	1.33 (1.00-1.79)	0.05
Unknown	320	0.97 (0.83-1.12)	0.63	1.10 (0.94-1.29)	0.23	0.95 (0.82-1.12)	0.55	1.12 (0.95-1.33)	0.18
Margin Status									
Clear	744	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	62	1.10 (0.85-1.42)	0.48	1.04 (0.80-1.36)	0.75	1.16 (0.89-1.50)	0.27	1.31 (0.87-1.47)	0.36
Unknown	175	1.12 (0.94-1.32)	0.20	0.88 (0.74-1.04)	0.13	1.42 (1.18-1.70)	<0.001	1.16 (0.96-1.40)	0.13
Age		1.00 (0.99-1.00)	0.34	1.00 (0.99-1.00)	0.27	0.99 (0.99-1.00)	0.005	0.99 (0.99-1.00)	0.01
DCIS grade									
Grade 1	171	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	305	0.80 (0.66-0.96)	0.02	0.78 (0.65-0.94)	0.009	1.00 (0.82-1.21)	0.98	0.98 (0.81-1.18)	0.80
Grade 3	439	0.80 (0.67-0.96)	0.01	0.72 (0.61-0.87)	<0.001	1.11 (0.92-1.34)	0.26	1.06 (0.88-1.28)	0.55
Unknown	66	0.87 (0.65-1.15)	0.33	0.97 (0.73-1.29)	0.85	0.98 (0.74-1.30)	0.88	1.08 (0.81-1.45)	0.58
Treatment									
BCS only	293	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+RT	382	0.47 (0.40-0.55)	<0.001	0.47 (0.40-0.55)	<0.001	0.45 (0.38-0.53)	<0.001	0.47 (0.40-0.55)	<0.001
BCS+ET	41	0.67 (0.48-0.93)	0.02	0.79 (0.57-1.10)	0.17	0.70 (0.50-0.97)	0.03	0.81 (058-1.13)	0.20
BCS+RT+ET	85	0.33 (0.26-0.42)	<0.001	0.45 (0.35-0.58)	<0.001	0.33 (0.26-0.42)	<0.001	0.44 (0.34-0.57)	<0.001
MST	180	0.25 (0.21-0.30)	<0.001	0.25 (0.21-0.30)	<0.001	0.20 (0.17-0.25)	<0.001	0.22 (0.18-0.27)	<0.001

Abbreviations:

n, number; HR, Hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; BCS, breast conserving surgery; RT, radiotherapy; ET, endocrine treatment; MST, mastectomy

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S11 Risk of subsequent ipsilateral DCIS including all women; Cox regression analyses; without multiple imputation

	All patients n=47,659								
		Univariate		Univariate; Stratified by cohort		Multivariable		Multivariable; Stratified by cohort	
	n events	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size									
<20mm	276	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
20-49mm	145	1.26 (1.03-1.54)	0.03	1.07 (0.88-1.31)	0.51	1.68 (1.37-2.06)	<0.001	1.60 (1.30-1.97)	<0.001
≥50mm	20	0.44 (0.28-0.70)	<0.001	0.39 (0.25-0.61)	<0.001	1.10 (0.69-1.74)	0.70	1.23 (0.77-1.96)	0.39
Unknown	217	1.12 (0.93-1.33)	0.23	0.19 (0.98-1.44)	0.08	1.09 (0.90-1.33)	0.39	1.21 (0.98-1.49)	0.08
Margin Status									
Clear	496	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Involved	47	1.34 (0.99-1.81)	0.06	1.16 (0.86-1.57)	0.33	1.37 (1.01-1.85)	0.04	1.29 (0.95-1.74)	0.10
Unknown	115	1.20 (0.98-1.47)	0.09	0.85 (0.70-1.05)	0.13	1.84 (1.47-2.32)	<0.001	1.48 (1.17-1.88)	0.001
Age		0.99 (0.98-1.00)	0.007	0.99 (0.98-11.00)	0.009	0.98 (0.97-0.99)	<0.001	0.98 (0.98-0.99)	<0.001
DCIS grade									
Grade 1	75	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Grade 2	185	1.10 (0.84-1.44)	0.49	1.07 (0.82-1.40)	0.63	1.50 (1.15-1.97)	0.003	1.54 (1.17-2.02)	0.002
Grade 3	352	1.46 (1.14-1.87)	0.003	1.30 (1.01-1.67)	0.04	2.35 (1.81-3.05)	<0.001	2.37 (1.82-3.09)	<0.001
Unknown	46	1.44 (1.00-2.08)	0.05	1.63 (1.13-2.35)	0.01	1.64 (1.13-2.37)	0.009	1.88 (1.30-2.73)	0.001
Treatment									
BCS only	234	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
BCS+RT	322	0.52 (0.44-0.61)	<0.001	0.48 (0.40-0.57)	<0.001	0.42 (0.35-0.50)	<0.001	0.38 (0.32-0.46)	<0.001
BCS+ET	17	0.33 (0.20-0.54)	<0.001	0.47 (0.29-0.78)	0.003	0.36 (0.22-0.59)	<0.001	0.49 (0.30-0.81)	0.005
BCS+RT+ET	53	0.25 (0.19-0.34)	<0.001	0.42 (0.30-0.58)	<0.001	0.23 (0.17-0.31)	<0.001	0.35 (0.25-0.48)	<0.001
MST	32	0.06 (0.04-0.08)	<0.001	0.05 (0.04-0.08)	<0.001	0.04 (0.02-0.05)	<0.001	0.03 (0.02-0.05)	<0.001

Abbreviations:

n, number; HR, Hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; BCS, breast conserving surgery; RT, radiotherapy; ET, endocrine treatment; MST, mastectomy

Univariate and multivariable cox regression analyses without imputed data; not stratified and stratified by cohort.

Table S12 Risk of subsequent ipsilateral invasive breast cancer; subgroup analysis, excluding Dutch patients, multivariable Cox regression analysis

	BCS only n=6,832 n(iIBC)=182		**BCS+RT** n=14,021 n(iIBC)=221		**BCS+/-RT** n=20,853 n(iIBC)=403	
	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size						
<20mm	1 (ref)		1 (ref)		1 (ref)	
20-49mm	0.93 (0.57-1.50)	0.76	1.20 (0.87-1.67)	0.27	1.04 (0.79-1.36)	0.79
≥50mm	N.A.		1.19 (0.59-2.41)	0.63	0.80 (0.40-1.58)	0.52
Margin Status						
Clear	1 (ref)		1 (ref)		1 (ref)	
Involved	0.54 (0.20-1.46)	0.23	1.27 (0.67-2.41)	0.46	0.90 (0.52-1.53)	0.69
Age	1.01 (0.99-1.02)	0.38	0.99 (0.98-1.01)	0.31	1.00 (0.99-1.01)	0.79
DCIS grade						
Grade 1	1 (ref)		1 (ref)		1 (ref)	
Grade 2	0.96 (0.66-1.42)	0.85	0.81 (0.53-1.26)	0.35	0.93 (0.70-1.24)	0.61
Grade 3	1.30 (0.88-1.92)	0.18	0.71 (0.46-1.09)	0.12	0.94 (0.70-1.26)	0.68
Treatment						
BCS only	1 (ref)		N.A.		1 (ref)	
BCS+RT	N.A.		1 (ref)		0.66 (0.52-0.85)	0.001
BCS+ET	1.07 (0.76-1.53)	0.68	0.78 (0.59-1.04)	0.09	1.00 (0.71-1.42)	0.99
BCS+RT+ET	N.A.		N.A.		0.59 (0.44-0.79)	<0.001

Abbreviations:

BCS, breast conserving surgery; RT, radiotherapy; n, number; iIBC, subsequent ipsilateral invasive breast cancer; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; ET, endocrine treatment

Univariate and multivariable Cox regression analyses using multiple imputed data; stratified by cohort.

Sensitivity analyses excluding the Dutch cohort in order to further study effect of endocrine treatment.

Table S13 Risk of subsequent ipsilateral invasive breast cancer, subgroup analysis; excluding Dutch patients and ER- DCIS, multivariable Cox regression analysis

	BCS only n=4,636 n(iIBC)=111		**BCS+RT** n=10,197 n(iIBC)=135		**BCS+/-RT** n=14,833 n(iIBC)=246	
	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
DCIS size						
<20mm	1 (ref)		1 (ref)		1 (ref)	
20-49mm	1.05 (0.59-1.90)	0.86	1.24 (0.79-1.93)	0.35	1.08 (0.76-1.53)	0.67
≥50mm	N.A.		1.45 (0.64-3.31)	0.38	0.92 (0.42-2.06)	0.85
Margin Status						
Clear	1 (ref)		1 (ref)		1 (ref)	
Involved	0.23 (0.03-1.67)	0.15	0.70 (0.22-2.20)	0.54	0.46 (0.17-1.24)	0.13
Age	1.00 (0.98-1.02)	0.97	1.00 (0.98-1.01)	0.64	1.00 (0.98-1.01)	0.57
DCIS grade						
Grade 1	1 (ref)		1 (ref)		1 (ref)	
Grade 2	0.95 (0.58-1.56)	0.83	0.67 (0.42-1.08)	0.1	0.83 (0.59-1.16)	0.27
Grade 3	1.47 (0.88-2.44)	0.14	0.53 (0.38-1.02)	0.06	0.89 (0.62-1.27)	0.52
Treatment						
BCS only	1 (ref)		N.A.		1 (ref)	
BCS+RT	N.A.		1 (ref)		0.63 (0.45-0.89)	0.009
BCS+ET	1.03 (0.69-1.52)	0.90	N.A.		1.02 (0.69-1.51)	0.93
BCS+RT+ET	N.A.		0.73 (0.51-1.02)	0.07	0.51 (0.36-0.73)	<0.001

Abbreviations:

ER, oestrogen receptor; BCS, breast conserving surgery; RT, radiotherapy; n, number; iIBC, subsequent ipsilateral invasive breast cancer; HR, hazard ratio; DCIS, Ductal carcinoma in situ; mm, millimetre; ET, endocrine treatment

Univariate and multivariable Cox regression analyses using multiply imputed data; stratified by cohort.

Sensitivity analyses excluding the Dutch cohort and including only women with ER-positive DCIS in order to further study effect of endocrine treatment.

Table S14 Observed incidence of stage and subtype of IBC compared with the Dutch general population, Cumulative relative incidence.

	Full cohort[a]		Dutch cohort[b]	
	CRI (95%CI)	10-year OCI[c] (%)	CRI (95%CI)	10-year OCI[c]
IBC Stage				
Stage 1	1.01 (1.00-1.01)	1.53	1.00 (1.00-1.01)	1.72
Stage 2	1.01 (1.00-1.01)	0.71	1.01 (1.00-1.01)	0.65
Stage 3	1.00 (1.00-1.00)	0.16	1.00 (1.00-1.00)	0.25
Stage 4	1.00 (1.00-1.00)	0.21	1.00 (1.00-1.00)	0.22
Unknown Stage	0.99 (0.99-1.00)	0.79	1.00 (1.00-1.00)	0.52
IBC Subtype				
HR+ HER2+	1.00 (1.00-1.00)	0.46	1.00 (1.00-1.00)	0.41
HR+ HER2-	1.02 (1.02-1.02)	0.21	1.02 (1.02-1.02)	0.33
HR- HER2+	1.00 (1.00-1.00)	1.30	1.00 (1.00-1.00)	1.27
HR- HER2-	1.00 (1.00-1.00)	0.20	1.00 (1.00-1.00)	0.20
Unknown Subtype	0.99 (0.99-1.00)	0.82	1.00 (0.99-1.00)	0.69

Abbreviations:

IBC, Invasive Breast Cancer; CRI, Cumulative relative incidence; CI, Confidence interval; HR+/-, Hormone Receptor; HER2+/-, Human Epidermal growth factor Receptor 2.

[c] Cumulative relative incidence: Observed incidence in the Joint PRECISION cohort divided by the expected incidence in the Dutch general population

[b] Standardized incidence ratio's: Observed incidence in the Dutch cohort divided by the expected incidence in the Dutch general population

[c] 10-year observed cumulative incidences in both the full cohort and the Dutch cohort, in percentages

Table S15 Risk of stage and type of subsequent event; multivariable joint Cox regression analysesa

Stage	Stage 0 iDCIS		Stage 1 iIBC		Stage 2 iIBC		Stage 3 iIBC		Stage 4 iIBC	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Margin status[c]	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Clear (≥2mm)	1.63 (1.22-2.20)	0.001	1.29 (088-1.90)	0.20	1.87 (1.16-3.04)	0.01	0.69 (0.09-5.12)	0.71	1.24 (0.38-4.05)	0.72
Involved (<2mm)										
DCIS size[d]										
<20mm	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
20-49mm	1.65 (1.35-2.02)	<0.001	1.00 (0.76-1.31)	0.99	1.97 (1.41-2.77)	<0.001	1.11 (0.44-2.83)	0.83	1.49 (0.81-2.74)	0.20
≥50mm	0.84 (0.52-1.35)	0.47	0.98 (0.60-1.59)	0.92	1.47 (0.79-2.79)	0.23	5.51 (2.34-12.97)	<0.001	4.10 (2.07-8.14)	<0.001

Subtype	HR+ HER2+		HR+ HER2-		HR- HER2+		HR- HER2-	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Margin status[c]	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Clear (>2mm)	0.84 (0.21-3.37)	0.81	0.99 (0.60-1.64)	0.97	3.35 (1.58-7.14)	0.002	2.15 (1.15-4.01)	0.02
Involved (≤2mm)								
DCIS Size[d]								
<20mm	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
20-50mm	1.30 (0.64-2.64)	0.49	1.07 (0.80-1.44)	0.65	2.00 (1.10-3.64)	0.02	0.87 (0.51-1.50)	0.62
>50mm	0.74 (0.17-3.14)	0.68	0.89 (0.53-1.48)	0.65	3.84 (1.89-7.79)	<0.001	0.96 (0.41-2.24)	0.92

Abbreviations:

iDCIS, ipsilateral ductal carcinoma in situ; iIBC, ipsilateral invasive breast cancer; HR, hazard ratio; CI, Confidence interval; mm, millimetre; HR+/-; hormone receptor positive/negative; HER2+/-; Human Epidermal growth factor Receptor positive/negative.

[a]Joint Cox regression analyses; adjusted for treatment type; not stratified by cohort. Complete case analyses

[c] Patients receiving mastectomy were excluded from analyses

[d] Patients from all treatment groups were included in analyses