Ductal carcinoma in situ and invasive breast cancer: diagnostic accuracy and prognosis

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Chapter 4

Long-term risk of subsequent ipsilateral lesions after a diagnosis of ductal carcinoma in situ

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ABSTRACT

Background
Radiotherapy (RT) following breast conserving surgery (BCS) for ductal carcinoma in situ (DCIS) reduces ipsilateral breast event rates in clinical trials. This study assessed the impact of DCIS treatment on 20-year risk of ipsilateral in situ (iDCIS) and invasive breast cancer (iIBC) in a population based cohort.

Methods
The cohort comprised all women diagnosed with DCIS in the Netherlands during 1989-2004 with follow-up until 2017. Cumulative incidence of iDCIS and iIBC following BCS and BCS+RT were assessed. Associations of DCIS treatment with iDCIS and iIBC risk were estimated in multivariable Cox models.

Results
The 20-year cumulative incidence of any ipsilateral breast event was 30.6% (95% confidence interval (CI);28.9-32.6%) after BCS compared to 18.2% (95%CI;16.3-20.3%) following BCS+RT.
Women treated with BCS compared to BCS+RT had higher risk to develop iDCIS and iIBC within five years after DCIS diagnosis (for iDCIS: $HR_{age<50}$ 3.2(95%CI;1.6-6.6); $HR_{age\geq50}$ 3.6(95%CI;2.6-4.8) and for iIBC: $HR_{age<50}$ 2.1(95%CI;1.4-3.2); $HR_{age\geq50}$ 4.3(95%CI;3.0-6.0)). After ten years, risk of iDCIS and iIBC after initial therapy no longer differed (for iDCIS: $HR_{age<50}$ 0.7(95%CI;0.3-1.5); $HR_{age\geq50}$ 0.7(95%CI;0.4-1.3) and for iIBC: $HR_{age<50}$ 0.6(95%CI;0.4-0.9); $HR_{age\geq50}$ 1.2(95%CI;0.9-1.6)).

Conclusion
Radiotherapy strongly reduces iDCIS and iIBC risk in the first decade after BCS for DCIS, but this benefit wanes thereafter.

Introduction

Since the introduction of population-based mammography breast cancer screening in the 1990s ductal carcinoma in situ (DCIS) comprises approximately 15% of all newly diagnosed neoplastic breast lesions[1,2]. DCIS is considered a non-obligate precursor of invasive breast cancer (IBC) and consists of neoplastic epithelial cells confined to the ductal system of the mammary gland. Because of its potential to become invasive, patients diagnosed with DCIS are usually treated as for invasive breast cancer with a mastectomy or with breast conserving surgery (BCS) often followed by radiotherapy to the whole breast (RT). DCIS itself, however, is not life-threatening and these treatment strategies by definition lead to overtreatment for those lesions that will never progress to IBC.

Radiotherapy as an adjunct to BCS as treatment for DCIS was evaluated in several clinical trials (NSABP B17, EORTC 10853, SweDCIS, UK/ANZ) and a meta-analysis demonstrated a 15% absolute ten-years risk reduction of both subsequent ipsilateral in situ (iDCIS) and invasive (iIBC) lesions for BCS+RT versus BCS only, without effect on breast cancer specific and overall survival[3–7]. However, how these trial data translate into reduction of ipsilateral breast events in large, population-based patient cohorts on the longer-term is unclear. We previously showed an absolute risk for iIBC of 15.4% for patients treated with BCS only compared to 8.8% for patients treated with BCS+RT at 15 years after diagnosis in a cohort with nationwide coverage[8]. Importantly, we also observed a trend towards a diminishing effect of radiotherapy after longer follow-up. In the same cohort, now with up to 28 years follow-up, we assess the very long-term risk of both iDCIS and iIBC after a diagnosis of primary DCIS and asses associations with initial DCIS treatment overall and in subgroups based on age and elapsed time since diagnosis.

Methods

Data collection

Our cohort comprises all women diagnosed with primary pure DCIS in the Netherlands between January 1st,1989 and December 31st, 2004[8]. Diagnoses of subsequent ipsilateral invasive breast (iIBC) lesions were derived from the Netherlands Cancer Registry (NCR) as well as through linkage of the NCR database with the nationwide registry of histology and cytopathology in the Netherlands (PALGA). Subsequent ipsilateral ductal carcinoma in situ (iDCIS) lesions are not registered within the NCR and therefore identification is solely based on pathology reports provided by the PALGA registry. iDCIS was defined as any ipsilateral ductal carcinoma in situ lesion including micro-invasive growth <1 mm at least 3 months after diagnosis of the index DCIS; iIBC was defined as any ipsilateral invasive breast lesion diagnosed at

least 3 months after diagnosis of the index DCIS. Follow-up for both NCR and PALGA has been completed until January 1st, 2017. Initial treatment was categorized into three groups: breast conserving surgery alone (BCS only), BCS with additional whole breast radiotherapy (BCS+RT) or mastectomy (independent of subsequent RT). Chemotherapy and endocrine therapy was almost never administered to women with DCIS in the Netherlands during the time of the cohort accrual and patients who received chemotherapy or endocrine therapy for DCIS were excluded (n=123). For patients treated with a mastectomy the risk of iDCIS recurrences was not assessed. Intercurrent mastectomies were defined as mastectomies of the ipsilateral breast ≥3 months after primary DCIS diagnosis and applied for other reasons than our events of interest (iDCIS or iIBC) as identified from pathology reports provided by the PALGA registry. In this paper, subsequent ipsilateral lesions are referred to as 'recurrence' although we do not know whether these lesions are biologically related to the primary DCIS or represent independent secondary primaries.

Statistical analyses

Time at risk started at date of primary DCIS diagnosis and ended at date of the first event of interest (iDCIS or iIBC), date of death, emigration or January 1st, 2017, whichever came first. The cumulative incidence of iDCIS, iIBC and the combination of iDCIS and iIBC was estimated using the Aalen-Johanson estimator with death as the only competing risk and emigration as censoring event. If laterality of a subsequent iDCIS was unknown, this resulted in censoring at date of iDCIS (n=10). For the iIBC cumulative incidence analysis treatment was considered a time-varying variable. As a consequence if a patient initially treated with BCS or BCS+RT underwent an intercurrent mastectomy (i.e. for benign disease or for iDCIS), she contributed all person time from the date of mastectomy to the mastectomy group. In all other analyses an intercurrent mastectomy resulted in censoring.

Multivariable Cox proportional hazard analysis was used to examine the effects of treatment strategies on iDCIS and iIBC risk. Attained age was used as time-scale. The proportional hazard assumption was assessed using residual-based and graphical methods. Because the hazard ratios (HRs) for treatment were non-proportional with time since treatment, the models for iDCIS and iIBC risk were stratified by time since treatment, using intervals of 0-4, 5-9 and ≥10 years after diagnosis and an interaction term for treatment and time since treatment, using the above intervals, was added to the models[9]. Additionally, the HRs for treatment differed with age at diagnosis ($p_{interaction}$<0.001). Using the Aikake Information Criterion the iIBC model demonstrated the best fit when age at DCIS diagnosis was fitted as a dichotomous categorical variable (<50 years versus ≥50 years old) and an age-treatment interaction term was added to the model. For iDCIS, the best model fit was achieved by adjusting for age at DCIS diagnosis as a continuous variable. To keep the models for iDCIS and iIBC comparable, we, however, included

age as a dichotomous categorical variable (<50 years versus ≥50 years old), while also including an age-treatment interaction term, although for iDCIS this age-treatment interaction was non-significant ($p_{interaction}$=0.06).

The association of histological grade of the primary DCIS and iDCIS and iIBC risks was evaluated only among patients diagnosed in the period 1999-2004, as information on DCIS grade was incomplete before 1999. In the analysis of iDCIS risk among patients diagnosed in 1999-2004 the proportional hazards assumption was not violated and no interaction term for treatment and time since treatment was included and age neither modified the effect of treatment.
All analyses were performed in open source software R version 3.5.1 using the 'survival' and 'etm' packages[10].

Results

The study cohort comprised 10,045 women of whom 2,647 (26%) received BCS only, 2,604 (26%) received BCS+RT, and 4,794 (48%) underwent mastectomy as primary treatment. Additional patient characteristics are summarized in table 1. The median follow-up was 15.7 years (interquartile range: 9.2-22.3 years). During follow-up in total 774 (7.7%) iIBC and 497 (4.9%) iDCIS lesions were identified. The 10- and 20-year cumulative incidence of subsequent ipsilateral breast disease (iDCIS or iIBC) for women treated with BCS only was 24.6% (95% confidence interval (CI) 23.0-26.3) and 30.6% (95%CI 28.9-32.6), respectively, whereas for women treated with BCS+RT the cumulative incidence was 9.6% (95%CI 8.6-10.8) and 18.2% (95%CI 16.3-20.3) at 10 and 20 years, respectively (figure 1). The competing risk, death, varied for the different treatment strategies between 8.7% and 14.7% after 10 years and between 26.8% and 35.2% after 20 years since DCIS diagnosis (supplementary figure 1).

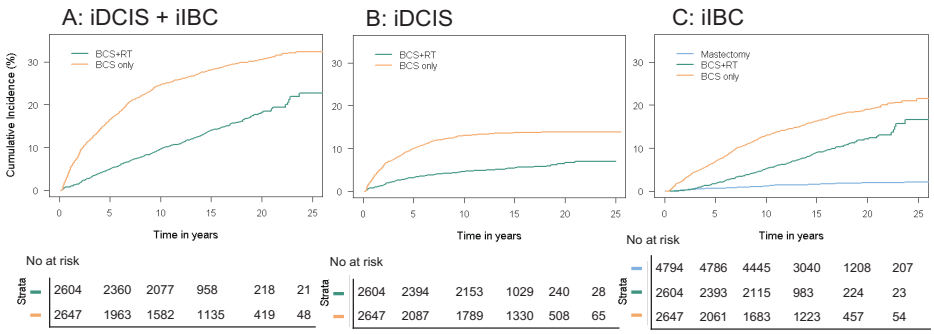

Figure 1. Cumulative incidence with death as competing risk by treatment strategy. A) in situ and invasive recurrences, B) iDCIS only, C) invasive recurrences only.

Table 1. Patient characteristics.

Initial DCIS treatment	BCS only N=2647	BCS+RT N=2604	Mastectomy N=4794	Total N=10045
Follow-up in years, median (IQR)	17.0 (9.7-24.4)	14.5 (9.9-19.1)	16.0 (9.0-22.9)	15.7 (9.2-22.3)
Age at DCIS diagnosis, years, median (IQR)	58.9 (43.0-74.8)	57.2 (43.2-71.2)	57.2 (40.6-73.8)	57.6 (41.9-73.3)
Age <50	474 (17.9%)	457 (17.5%)	1212 (25.3%)	2143 (21.3%)
Age ≥50	2173 (82.1%)	2147 (82.5%)	3582 (74.7%)	7902 (78.7%)
DCIS grade (1999-2004[a])				
Low (1)	302 (40.9%)	215 (13.7%)	190 (10.2%)	707 (16.9%)
Intermediate (2)	234 (31.7%)	578 (36.7%)	553 (29.7%)	1365 (32.7%)
High (3)	202 (27.4%)	780 (49.6%)	1121 (60.1%)	2103 (50.4%)
Unknown	240	285	342	867
Subsequent iIBC	445	240	89	774
Subsequent iDCIS	352	145	NA	497

[a]Data on grade is presented for patients diagnosed with primary DCIS from 1999-2004 (n=5042). iIBC denotes ipsilateral invasive breast cancer; iDCIS: ipsilateral ductal carcinoma in situ; BCS: breast conserving surgery; RT: radiotherapy; N: number; IQR: interquartile range; DCIS: ductal carcinoma in situ.

Subsequent iDCIS risk

Among patients treated with BCS only 352 iDCIS occurred compared to 145 iDCIS among patients treated with BCS+RT. Most iDCIS occurred within the first 10 years of follow-up with only 19 patients developing a late iDCIS (10 years or more after their initial DCIS diagnosis) after BCS only and 27 after BCS+RT (supplementary table 1). For women treated with BCS only, the 10- and 20-year cumulative incidence of iDCIS was 13.0% (95%CI 11.8-14.4) and 13.9% (95%CI 11.6-15.3), respectively, versus 4.6% (95%CI 3.9-5.5) and 6.7% (95%CI 5.5-8.1), respectively, for women treated with BCS+RT (figure 1, supplementary table 1).

Women <50 years treated with BCS only had a 3.2-times higher HR (95%CI 1.6-6.6) for iDCIS in the first five years after diagnosis compared to women treated with BCS+RT, while women ≥50 years treated with BCS only had a 3.6-times higher HR for iDCIS (95%CI 2.6-4.8) then women treated with BCS+RT (table 2). The relative risk to develop iDCIS among patients treated with BCS only compared to BCS+RT decreased in the interval 5-9 years after DCIS and risks no longer differed from 10 years after initial DCIS in both age groups (table 2). Women diagnosed between 1999 and 2004 had a slightly lower risk to develop iDCIS than women diagnosed between 1989 and 1998 (HR 0.9; 95%CI 0.7-1.0).
Among all women diagnosed with primary DCIS between 1999 and 2004, women with grade 1 DCIS had half the risk (HR 0.5; 95%CI 0.3-0.8) of iDCIS of women with grade 2 lesions (supplementary table 2). iDCIS risk did not differ for women with grade 3 lesions compared to those with grade 2 lesions.

Table 2. Multivariate Cox analysis to estimate the association of treatment with the risk of subsequent ipsilateral ductal carcinoma in situ (iDCIS) and ipsilateral invasive breast cancer (iIBC).

Age at DCIS	Time since DCIS	Treatment	iDCIS	iIBC
years	years		HR (95%CI)	HR (95%CI)
<50	0-5	BCS+RT	Ref	Ref
		BCS only	3.2 (1.6-6.6)	2.1 (1.4-3.2)
		Mastectomy[a]	-	0.4 (0.2-0.6)
	5-10	BCS+RT	Ref	Ref
		BCS only	2.5 (1.1-5.3)	1.0 (0.7-1.5)
		Mastectomy[a]	-	0.1(0.1-0.3)
	≥10	BCS+RT	Ref	Ref
		BCS only	0.7 (0.3-1.5)	0.6 (0.4-0.9)
		Mastectomy[a]	-	0.1 (0.1-0.2)
≥50	0-5	BCS+RT	Ref	Ref
		BCS only	3.6 (2.6-4.8)	4.3 (3.0-6.0)
		Mastectomy[a]	-	0.3 (0.2-0.4)
	5-10	BCS+RT	Ref	Ref
		BCS only	2.7 (1.8-4.1)	2.1 (1.6-2.8)
		Mastectomy[a]	-	0.1 (0.1-0.2)
	≥10	BCS+RT	Ref	Ref
		BCS only	0.7 (0.4-1.3)	1.2 (0.9-1.6)
		Mastectomy[a]	-	0.1 (0.1-0.1)

[a]Information regarding mastectomy treatment was not available for iDCIS.
(Attained) age as primary time-scale, adjusted for period of initial DCIS diagnosis (1989-1998 vs 1999-2004) and age at DCIS diagnosis (<50 vs ≥50) including an age-treatment interaction term.
HR denotes hazard ratio; 95%CI: 95% confidence interval; Ref: Reference category; BCS: Breast conserving surgery; RT: radiotherapy; iDCIS: ipsilateral ductal carcinoma in situ; iIBC ipsilateral invasive breast cancer; DCIS: ductal carcinoma in situ.

Subsequent iIBC risk

Among patients treated with BCS only the 10- and 20-year cumulative incidence of iIBC was 13.9% (95%CI 11.7-14.3) and 19.1% (95%CI 17.5-20.8), respectively. The 10- and 20-year cumulative incidence was 5.2% (95%CI 4.4-6.2) and 12.1% (95%CI 10.5-14.0), respectively, in patients treated with BCS+RT and 1.1% (95%CI 0.9-1.5) and 1.9% (95%CI 1.6-2.4), respectively, in patients treated with mastectomy (figure 1, supplementary table 1). Women <50 years diagnosed with DCIS between 1999-2004 and treated with BCS+RT showed continuously lower absolute iIBC risks compared to those treated with BCS only (figure 2). In contrast, women <50 years diagnosed in the period 1989-1998 had approximately similar cumulative incidences after either BCS only or BCS+RT treatment from 10 years or more after DCIS diagnosis.

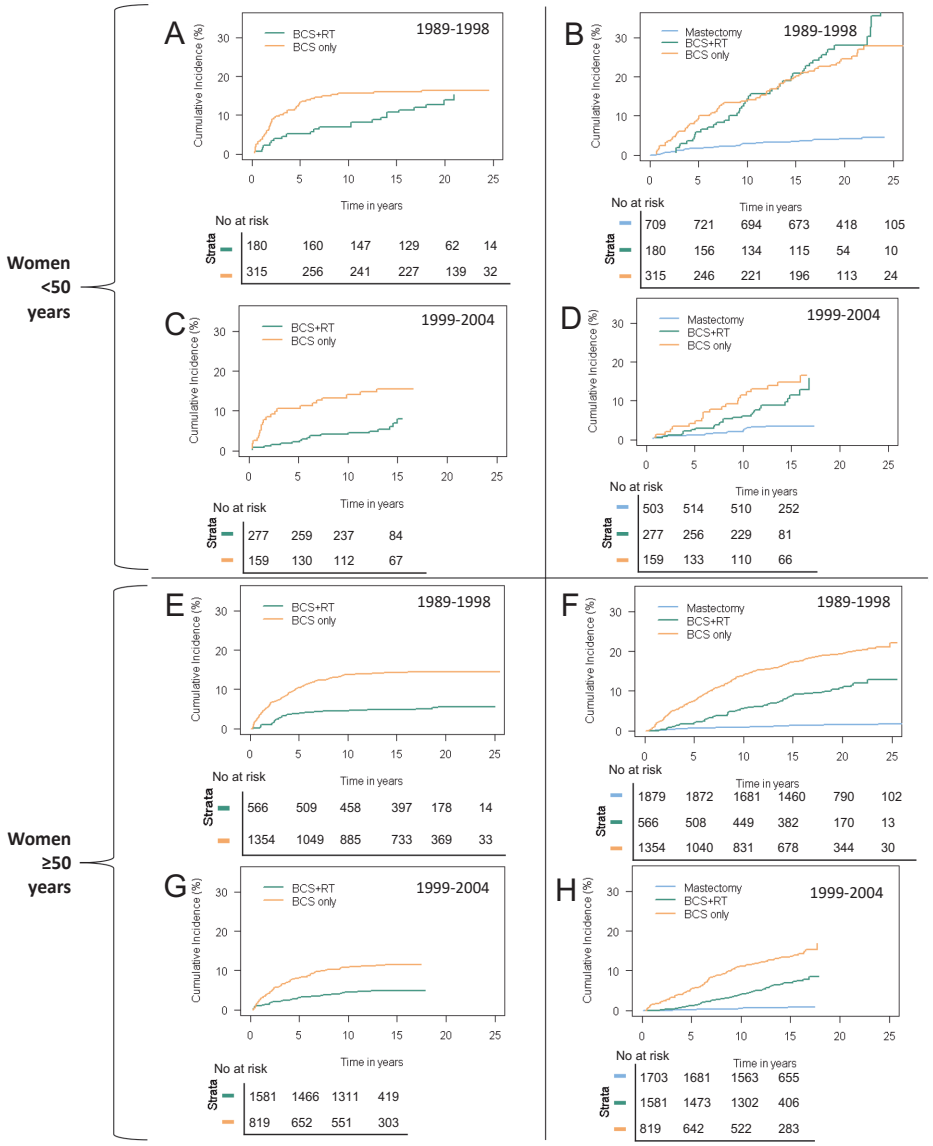

Figure 2. Cumulative incidence with death as competing risk in A) iDCIS risk of women < 50 years diagnosed between 1989-1998 for primary DCIS, B) iIBC risk of women < 50 years diagnosed between 1989-1998 for primary DCIS, C) iDCIS risk of diagnosed in women < 50 years diagnosed in 1999-2004 for primary DCIS and D) iIBC risk women < 50 years diagnosed between 1999-2004 for primary DCIS, E) iDCIS risk of women ≥50 years diagnosed between 1989-1998 F) iIBC risk of women ≥50 years diagnosed between 1989 -1998, G) iDCIS risk of women ≥50 years diagnosed between 1999-2004 iIBC risk of women ≥50 years diagnosed between 1999-2004.

In women <50 years at DCIS diagnosis, the HR for iIBC was 2.1-times (95%CI 1.4-3.2) higher in the first five years after diagnosis among those treated with BCS only compared to women treated with BCS+RT; the HR for iIBC was even 4.3-times (95%CI 3.0-6.0) higher for women ≥50 years treated with BCS only within the first five years after treatment compared to BCS+RT (table 2). The risk for developing an iIBC no longer differed from 5 years after DCIS diagnosis for women <50 years between those treated with BCS only or with BCS+RT (HR1.0; 95%CI 0.7-1.5). While for women ≥50 years this risk did not longer differed from 10 years after DCIS diagnosis (HR 1.2; 95%CI 0.9-1.6). Women treated with mastectomy had much lower risk to develop iIBC compared with women treated with BCS, irrespective of age at diagnosis or time since DCIS treatment (table 2). Women diagnosed with primary DCIS between 1999 and 2004 had a slightly lower risk to develop iIBC than women diagnosed between 1989 and 1999 (HR 0.8; 95%CI 0.6-0.9).
Inclusion of histological grade in the analysis did not affect the association of DCIS treatment with iIBC risk ($HR_{age\geq50}$ for BCS only versus BCS+RT in year 1-5: 4.8; 95%CI 2.7-8.5) for a model including grade and 4.8 (95%CI 2.7-8.6) for a model without grade, see supplementary table 3 for all estimates) and grade did not modify the association of initial treatment with iIBC risk ($p_{interaction}$=0.3).

Discussion

In this population-based study among 10,045 women treated for DCIS we showed, that patients treated with BCS only had an absolute risk of 14% to develop iDCIS and of 19% to develop iIBC at 20 years after treatment, while for BCS+RT treatment these risks were 7% and 12%, respectively. iDCIS predominantly occurred in the first 10 years after primary DCIS. Furthermore, from 5 years for younger and from 10 years for older women following the diagnosis of primary DCIS, the rate of iIBC recurrences did no longer differ between women treated with BCS only versus BCS+RT, indicating that the beneficial effect of RT is most prominent within the first years after DCIS diagnosis.

Although our study is based on a population-based cohort with complete follow-up provided by two registries, it has some limitations. Firstly, margin status and tumor size were not available for our patients while DCIS grade was only available for approximately half of the cohort. We had no information regarding the rationales underlying administering BCS only, BCS+RT or mastectomy. Additionally, patients in our cohort were diagnosed and treated sometimes decades ago and diagnosis and treatment strategies have evolved overtime.
Nonetheless, our data clearly show that late in situ recurrences, ≥10 years after DCIS diagnosis, rarely developed while incidence of iIBC continued to rise over time irrespective of initial treatment. This is concordant with the SweDCIS trial[11]

and with the Vermont cohort[12], which both reported few iDCIS occurrences after five years of follow-up.

An explanation for this plateau in risk of subsequent iDCIS lesions after 10 years might be that recurrent DCIS lesions were less detected after 10 years either due to the fact that patients were discharged from routine surveillance or were no longer within the age range invited for the population breast cancer screening program. Alternatively, the lack of in situ recurrences after 10 years may reflect the biology of these DCIS lesions, which would suggest that almost all subsequent iDCIS lesions originate from residual primary DCIS. This is supported by the high frequency of clonal relatedness of iDCIS to primary DCIS, reported to be 82% by Waldman et al.[13] while Shaw et al[14] even reported complete clonal relatedness of iDCIS to primary DCIS. Within our consortium, PREvent ductal Carcinoma In Situ Invasive Overtreatment Now (PRECISION)-initiative[15], we are conducting genomic studies to determine the clonal relatedness of in situ recurrences to the primary DCIS in order to better understand the relationship between the initial DCIS diagnosis and subsequent breast events.

Radiotherapy importantly reduces the risk of iDCIS and iIBC, particularly in the first 10 years after initial DCIS diagnosis. This is in line with prior meta-analysis which showed that radiotherapy reduced the absolute 10-years risk by 15% (28.1% any recurrence in BCS only group versus 12.9% in BCS+RT group[4)] and with several cohort studies which all showed that radiotherapy reduced breast events after radiotherapy in addition to BCS[12,16–18]. However, our analysis also showed that 10 years or more after DCIS diagnosis, the incidence of new iIBC is approximately similar in the BCS only and BCS+RT group (figure 1 and supplementary table 1). This is consistent with results of Rakovitch et al.[19] who showed lower risks of second breast events with increasing follow-up time after DCIS diagnosis. Since extensive clonal diversity is generated by mutations gradually evolving overtime[20], it becomes more likely that newly developed tumors represent an independent second primary tumor more than 10 years after initial DCIS. However, to our knowledge the association of follow-up time with clonal relatedness between primary DCIS and subsequent lesions has not yet been assessed. In addition, we cannot exclude the possibility that RT may induce (secondary) invasive breast tumors which may become apparent long after exposure to RT. Actually a meta-analysis by Akdeniz et al. did demonstrate a slightly increased risk of contralateral breast cancer after RT mainly in breast cancer patients treated<45 years of age[21].

Women <50 years diagnosed with primary DCIS between 1989 and 1998 had similar absolute late iIBC risk irrespective of treatment with BCS only or BCS+RT (figure 2). The SweDCIS trial neither showed a long-term beneficial effect of RT following BCS on iIBC risk in young women (<52 years)[11]. In our models we split age

at 50 years, because the Dutch nationwide breast cancer screening starts at the age of 50 and thus a diagnosis of primary DCIS in women <50 is rarely based on breast screening. These women may present with a different type of DCIS including more frequent symptomatic presentation (i.e. a lump) and/or be diagnosed in the light of familial genetic susceptibility syndromes, which may be accompanied by an increased risk of iIBC. In addition, some studies[19,22] showed that younger patients in general have higher risk of invasive recurrences compared to older patients. However, Ryser et al[23] did not found that iIBC risks were different between women aged <50 and ≥50 years, although this study was not powered to examine age differences. Therefore, we would caution against the interpretation that younger women benefit less from radiotherapy.

This large population-based DCIS cohort provides insight in the long-term risks of ipsilateral breast recurrences in women treated for DCIS. As DCIS is a not life-threatening disease, our ultimate goal should be to de-escalate treatment. There are efforts ongoing to determine whether molecular profiles of DCIS, such as Oncotype DX DCIS score[24] or DCISionRT signature[25] could support selection of women in whom radiotherapy could be safely omitted. Furthermore, three ongoing clinical trials (LORIS[26], LORD[27] and COMET[28] trials) currently randomize between active surveillance and conventional treatment to omit therapy for women with low risk DCIS. Understanding the dynamics of long-term residual breast cancer risk following treatment of DCIS contributes to the understanding of this disease and finally to reducing overtreatment.

Additional information

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Ethics approval and consent to participate

The Central Committee on Research involving Human Subjects determined that this study did not require approval from an ethics committee. The privacy review board of the NCR approved the study.

Data availability

The data generated and analysed during this study will be available from the corresponding author upon reasonable request.

Conflicts of interest

All the authors declare no conflict of interests.

Authors' contribution

Conception and design: MvS, EL, LE, JW, MS
Statistical support: DG, MR, MS
Data collection: MvS, LF, LM, LE, MS
Data analysis and interpretation: MvS, EL, DG, FvD, LM, AT, LE, MR, SH, ES, MS, PE, JW, MS
Manuscript writing: all authors
Final approval of manuscript: all authors

Consent for publication

Not applicable

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Supplementary files

Supplementary table 1. Absolute numbers of events and cumulative incidence, both split in periods of five years and split for initial DCIS treatment.

Type of Event	**iDCIS**				**iIBC**					
Treatment	**BCS only**		**BCS+RT**		**BCS only**		**BCS+RT**		**Mastectomy**	
	Events (n)	Cum inc % (95%CI)	Events (n)	Cum inc % (95%CI)	Events (n)	Cum inc % (95%CI)	Events (n)	Cum inc % (95%CI)	Events (n)	Cum inc % (95%CI)
0-4 year	258	10.0 (8.9-11.3)	84	3.3 (2.6-4.0)	173	6.9 (5.9-7.9)	46	1.8 (1.4-2.4)	33	0.7 (0.5-1.0)
0-9 year	333	13.0 (11.8-14.4)	118	4.6 (3.9-5.5)	315	13.9 (11.7-14.3)	131	5.2 (4.4-6.2)	55	1.1 (0.9-1.5)
0-14 year	349	13.7 (12.4-15.1)	137	5.5 (4.7-6.5)	390	16.3 (14.9-17.9)	207	9.0 (7.9-10.3)	79	1.6 (1.3-2.0)
0-19 year	352	13.9 (12.6-15.3)	144	6.7 (5.5-8.1)	432	19.1 (17.5-20.8)	231	12.1 (10.5-14.0)	87	1.9 (1.6-2.4)
0-24 year	352	13.9 (12.6-15.3)	145	7.0 (5.7-8.6)	444	21.6 (19.3-24.0)	239	16.6 (13.4-20.6)	89	2.2 (1.7-2.8)
0 - 4 year	258	10.0 (8.9-11.3)	84	3.3 (2.6-4.0)	173	6.9 (5.9-7.9)	46	1.8 (1.4-2.4)	33	0.7 (0.5-0.9)
5 - 9 year	75	3.6 (2.9-4.5)	34	1.4 (1.0-2.0)	142	7.0 (6.0-8.2)	85	3.6 (2.9-4.4)	22	0.5 (0.3-0.7)
10 - 14 year	16	0.9 (0.6-1.5)	19	1.1 (0.7-1.7)	75	4.7 (3.7-5.8)	76	4.4 (3.5-5.5)	24	0.6 (0.4-0.9)
15 - 19 year	3	0.3 (0.1-1.0)	7	1.5 (0.7-3.2)	42	4.4 (3.3-6.0)	24	4.2 (2.8-6.4)	8	0.4 (0.2-0.7)
20 - 24 year	0	NA	1	NA	12	5.1 (2.6-9.9)	8	7.4 (3.6-15.0)	2	0.4 (0.09-1.6)

iIBC denotes ipsilateral invasive breast cancer; iDCIS: ipsilateral ductal carcinoma in situ; BCS: breast conserving surgery; RT: radiotherapy; n: number; Cum inc: cumulative incidence; 95%CI: 95% confidence interval.

Supplementary table 2. Multivariable Cox analysis for iDCIS for patient diagnosed from 1999 – 2004.

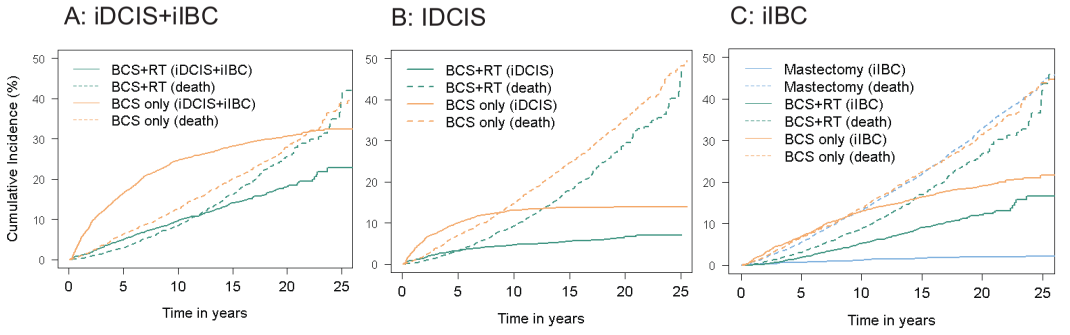
		iDCIS
		HR (95%CI)
Treatment	BCS+RT	Ref
	BCS only	3.2 (2.3-4.4)
Age	<50	0.6 (0.3-1.0)
	≥50	Ref
Grade*	Low (1)	0.5 (0.3-0.8)
	Intermediate (2)	Ref
	High (3)	1.2 (0.9-1.8)

*Patients with unknown grade were excluded (n=525).
**Age as primary time-scale and adjusted for age at DCIS diagnosis (<50 vs ≥50).
HR denotes hazard ratio; iDCIS: ipsilateral ductal carcinoma in situ; 95%CI 95% confidence interval; Ref: reference; BCS: breast conserving surgery; RT: radiotherapy.

Supplementary table 3. Multivariable Cox analysis for iIBC for patient diagnosed from 1999 – 2004 with and without including grade.

Age at DCIS	**Time since DCIS**	**Treatment**	**Model without grade**	**Model including grade**
years	years		HR (95%CI)	HR (95%CI)
<50	0-5	BCS+RT	Ref	Ref
		BCS only	2.7 (1.2-6.1)	2.8 (1.2-6.4)
		Mastectomy	0.5 (0.2-1.4)	0.5 (0.2-1.4)
	5-10	BCS+RT	Ref	Ref
		BCS only	1.8 (0.9-3.5)	1.8 (0.9-3.7)
		Mastectomy	0.2 (0.1-0.6)	0.2 (0.1-0.6)
	≥10	BCS+RT	Ref	Ref
		BCS only	0.8 (0.4-1.7)	0.8 (0.4-1.8)
		Mastectomy	0.2 (0.1-0.5)	0.2 (0.1-0.6)
≥50	0-5	BCS+RT	Ref	Ref
		BCS only	4.2 (2.4-7.4)	4.2 (2.4-7.6)
		Mastectomy	0.2 (0.1-0.4)	0.2 (0.1-0.4)
	5-10	BCS+RT	Ref	Ref
		BCS only	2.7 (1.8-4.2)	2.7 (1.8-4.3)
		Mastectomy	0.1 (0.0-0.2)	0.1 (0.0-0.2)
	≥10	BCS+RT	Ref	Ref
		BCS only	1.3 (0.7-2.1)	1.3 (0.8-2.2)
		Mastectomy	0.1 (0.0-0.2)	0.1 (0.0-0.2)
Grade*		Low (1)	-	0.9 (0.6-1.2)
		Intermediate (2)	-	Ref
		High (3)	-	0.9 (0.7-1.2)

*Patients with unknown grade were excluded (n=867)
** Age as primary time-scale, including a time-treatment interaction term and an age-treatment interaction term ($p_{interaction}$=0.002), adjusted for age at DCIS diagnosis (<50 vs ≥50)
HR denotes hazard ratio; iDCIS: ipsilateral ductal carcinoma in situ; 95%CI: 95% confidence interval; Ref: reference; BCS: breast conserving surgery; RT: radiotherapy; DCIS ductal carcinoma in situ



	iDCIS+iIBC		iDCIS		iIBC		
Treatment	**BCS only**	**BCS+RT**	**BCS only**	**BCS+RT**	**BCS only**	**BCS+RT**	**Mastectomy**
	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
Cumulative incidence of event of interest							
0-9 year	24.6 (23.0-26.3)	9.6 (8.6-10.8)	13.0 (11.8-14.4)	4.6 (3.9-5.5)	13.9 (11.7-14.3)	5.2 (4.4-6.2)	1.1 (0.9-1.5)
0-19 year	30.6 (28.9-32.6)	18.2 (16.3-20.3)	13.9 (12.6-15.3)	6.7 (5.5-8.1)	19.1 (17.5-20.8)	12.1 (10.5-14.0)	1.9 (1.6-2.4)
*Cumulative incidence of competing risk (death)**							
0-9 year	12.6 (11.4-13.9)	8.4 (7.4-9.6)	14.7 (13.4-16.1)	9.2 (8.1-10.4)	13.7 (13.4-16.1)	8.7 (8.2-10.4)	13.2 (12.3-14.2)
0-19 year	27.9 (26.0-29.9)	25.7 (23.3-28.4)	35.2 (33.2-37.4)	29.2 (26.6-32.1)	31.4 (29.3-33.6)	26.8 (26.7-32.0)	32.7 (31.3-34.3)

Supplementary figure 1. Cumulative incidence of A) in situ and invasive recurrences, B) in situ recurrences only, C) invasive recurrences only including the competing risk (death) at 10 and 20 years following DCIS diagnosis.
*Death in absence of iDCIS and/or iIBC.
iIBC denotes ipsilateral invasive breast cancer; iDCIS: ipsilateral ductal carcinoma in situ; BCS: breast conserving surgery; RT: radiotherapy; 95%CI: 95% confidence interval.