Review

Cancer Epidemiology, Biomarkers & Prevention

Predictors of an Invasive Breast Cancer Recurrence after DCIS: A Systematic Review and Meta-analyses

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Abstract

We performed a systematic review with meta-analyses to summarize current knowledge on prognostic factors for invasive disease after a diagnosis of ductal carcinoma *in situ* (DCIS). Eligible studies assessed risk of invasive recurrence in women primarily diagnosed and treated for DCIS and included at least 10 ipsilateral-invasive breast cancer events and 1 year of follow-up. Quality in Prognosis Studies tool was used for risk of bias assessment. Meta-analyses were performed to estimate the average effect size of the prognostic factors. Of 1,781 articles reviewed, 40 articles met the inclusion criteria. Highest risk of bias was attributable to insufficient handling of confounders and poorly described study groups. Six prognostic factors were statistically significant in the meta-analyses: African-American race [pooled estimate (ES), 1.43; 95% confidence interval (CI), 1.15–1.79], premenopausal status (ES, 1.59; 95% CI, 1.20–2.11), detection by palpation (ES, 1.84; 95% CI, 1.47–2.29), involved margins (ES, 1.63; 95% CI, 1.14–2.32), high histologic grade (ES, 1.36; 95% CI, 1.04–1.77), and high p16 expression (ES, 1.51; 95% CI, 1.04–2.19). Six prognostic factors associated with invasive recurrence were identified, whereas many other factors need confirmation in well-designed studies on large patient numbers. Furthermore, we identified frequently occurring biases in studies on invasive recurrence after DCIS. Avoiding these common methodological pitfalls can improve future study designs.

Introduction

With the introduction of the population-based breast cancer screening program in the wealthy world, the incidence of ductal carcinoma *in situ* (DCIS) has increased almost 6-fold (1–6). Although some DCIS will develop into invasive breast cancer, the majority of DCIS, if left untreated, is not destined to progress and thus will never become life-threatening (7). This implies that many women are overtreated, as they are diagnosed with a disease that would not have caused symptoms or death (8). However, we are currently unable to predict which DCIS patients will subsequently develop invasive disease. As a result, almost all women diagnosed with DCIS are nowadays intensively treated with surgical treatment, adjuvant treatment, or both. Many women, who have a low risk to develop subsequent invasive disease, do not benefit from this treatment and thus suffer from overtreatment. Until breast cancer screening programs will include strategies to only detect hazardous disease, we will continue to be faced with large numbers of women diagnosed with low-risk DCIS annually worldwide.

Despite repeated calls for development of prognostic factors for predicting invasive recurrences following DCIS, progress in this field has been slow (9). Numerous prognostic factors have been reported, but none have shown to be of sufficient value for implementation into the clinic (10). This is due to a variety of reasons. For example, sufficiently large, unbiased patient cohorts are lacking to set up validation studies. Current guidelines dictate surgical excision of DCIS when such a lesion is detected. This makes that almost all DCIS is treated and the natural course of DCIS is poorly understood. On top of this, many previous prognostic factor studies have only limited power, given the low event rate in treated patients and the fact that it can take a decade before the presentation of an invasive recurrence. In all this, in-depth molecular analysis of DCIS is challenging due to the minimal quantity and often limited quality of the DNA and RNA extracted from DCIS. As a result, a multitude of factors are now lost in transition.

In this systematic review, we (1) give an overview of previously published studies on prognostic factors for subsequent invasive recurrence after DCIS, (2) assess these studies for potential bias using a standardized risk assessment tool, and (3) identify the factors with the strongest prognostic value that should be considered for validation. With these results, we want to make recommendations for future studies.

Materials and Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement to guide the conduct and reporting of this review (11).

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

M.K. Schmidt and J. Wesseling are the last authors of this article.

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Eligibility criteria and search strategy

Studies were identified through a systematic search in Pubmed until June 1, 2018, with no language restrictions using the search strategy that can be found in Supplementary Table S1; no limits were set. One reviewer (L.L. Visser) screened titles and abstracts of all articles and assessed their eligibility for the research topic: factors associated with the risk of subsequent ipsilateral-invasive breast cancer (iIBC) in women that were primarily diagnosed and treated for DCIS. Studies not reporting original data, letters to the editor, and commentaries were excluded from the review (non-research articles), as were non-English articles (Fig. 1). In addition, we selected for studies including at least 1 year of follow-up. Next, full-text articles were screened for inclusion by two reviewers (L.L. Visser and E.J. Groen) independently. Studies including less than ten subsequent invasive breast cancer events after DCIS treatment were excluded, as were studies that did not focus on subsequent invasive recurrences as primary end-point. Discrepancies were resolved by group discussion with team members.

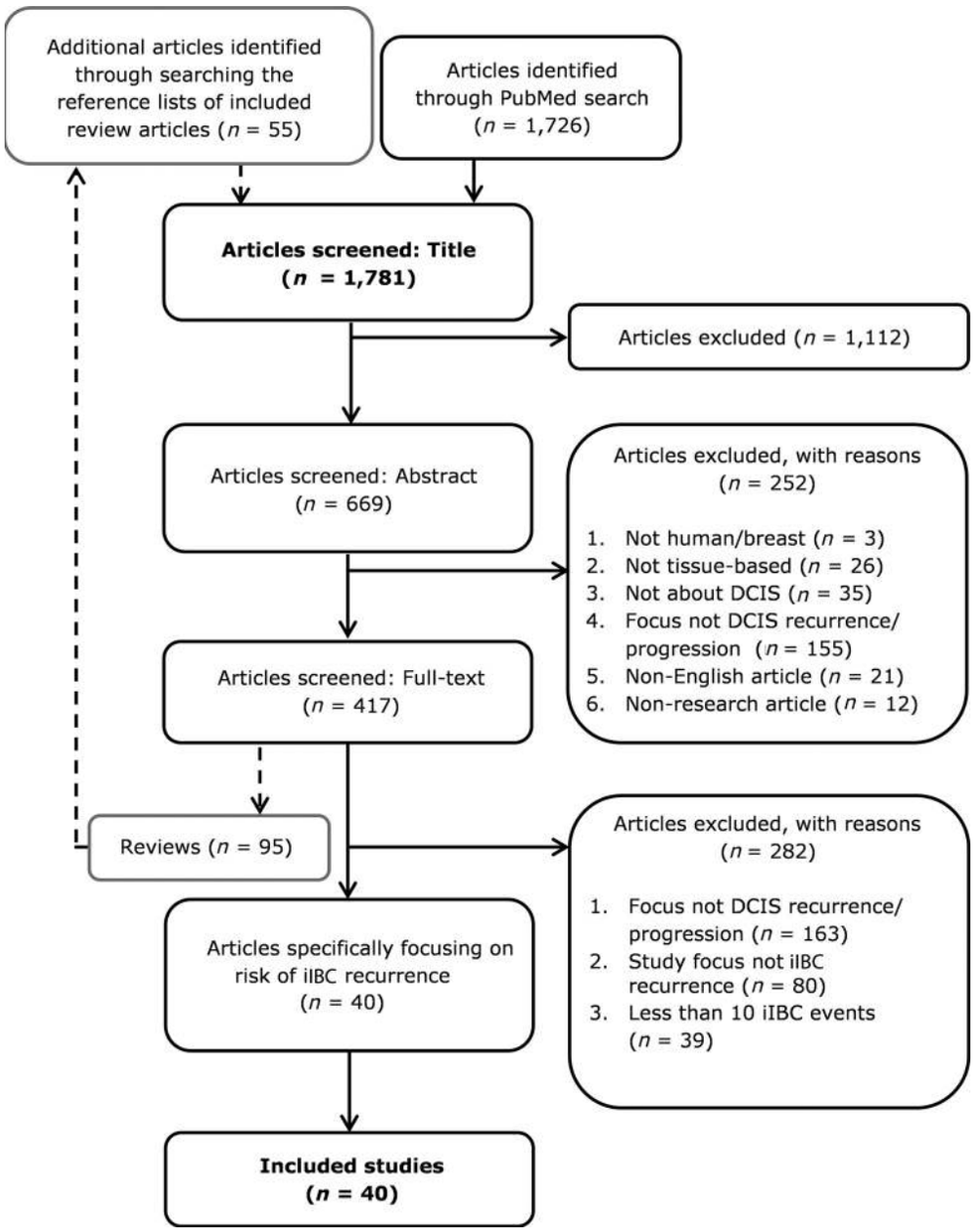


Figure 1.

Flow chart of the identification of eligible articles in the systematic literature review. Note that 1,781 articles were identified in the Pubmed database, of which 40 met our inclusion criteria. Reference lists of review articles were searched, and any reference with an ambiguous title was included for screening (arrows with dotted lines).

Reference lists of review articles were searched, and any reference with an ambiguous title was included for screening. When multiple studies using the same study population had been published, the study with the largest number of subjects and longest follow-up time was included. If studies used the same study population but reported different prognostic factors, each factor was included separately.

Following the definition of our search strategy, only tumor-related factors and age, race and/or ethnicity, detection method, or menopausal status were included in this systematic review. Incidentally, factors such as treatment, family history of breast cancer, body mass index, or lifestyle factors were described in the included studies, but these factors were not included in the analyses.

Data extraction and definitions

During the full-text screening phase, the following data were extracted: source of the study population, single- or multi-center study, study design, number of DCIS patients, number of iIBC events, period of recruitment, median follow-up time in years, received treatment for DCIS, the identified prognostic factors, the risk estimates—i.e., HR or OR with 95% confidence interval (CI), adjustments, and the statistical method used.

Quality assessment

Next, each study was evaluated independently by two reviewers (L.L. Visser and E.J. Groen) using the Quality in Prognosis Study (QUIPS) tool developed by Hayden and colleagues (12, 13). Details on the tool used for the assessment are shown in Supplementary Table S2. In brief, domains assessed for bias were study participation, study attrition, prognostic factor measurement, end-point definition, confounding measurement and handling, and statistical analysis and reporting. Each domain was assessed with the help of three to six prompting questions of which several were modified for the purpose of this study. The assessment for each study was completed by assigning a grade of low, moderate, or high risk of bias to each domain. Any discrepancy in grading was discussed, and if no consensus was reached, a third reviewer (M.K. Schmidt) was consulted. For consistence of assessment, we tested the QUIPS instrument between the two reviewers (L.L. Visser and E.J. Groen) before rating the included studies. The kappa for interobserver agreement was 0.9 (SE of 0.2). In addition, because we found DCIS treatment to be the most strongly confounding variable in previous studies, we explicitly specified this confounder in the QUIPS tool. We classified studies as "high quality (HQ) studies" if they were properly designed and well conducted: these studies were not allowed to have high risk of bias in any of the QUIPS domains and should account for the confounding effect of treatment. Prognostic factors identified in these HQ studies were considered as factors with the strongest predictive value.

Statistical analysis

To estimate the average effect size of the prognostic factors, meta-analyses were performed using the univariate effect sizes reported by the different studies; this was done for all factors reported by more than 1 HQ study. For the absolute effect size difference between studies, pooled estimates were calculated using weighting based on the number of included iIBC events per study [weight per study (%) = (n of DCIS patients with subsequent iIBC in that specific study/total number of DCIS patients with subsequent iIBC of all studies which were used to form the pooled estimate) $\times$ 100]. In a few articles, effect sizes were not reported or used categories were not comparable with the other studies assessing that specific prognostic factor; hence, these were excluded from the analysis. For the reported effect sizes, pooled estimates were visualized and summarized using a forest plot, and statistical heterogeneity was assessed using Random effect analysis (14).

A funnel plot was used to assess possible publication bias (15, 16). Because there were only a few estimates/studies for each of the factors, it was only possible to do this for all factors combined. χ^2 tests were performed to compare year of publication and risk of bias per QUIPS domain. For this, studies were divided at the median into publication years 1998–2011 and 2012–2018 and compared the risk of bias per domain. P values $\leq$ 0.05 (2-sided test) were considered statistically significant. All statistical analyses were done using Stata/SE (version 13.1, Statacorp).

Results

Until June 2018, 1,781 papers were identified in the Pubmed database, of which 40 met our inclusion criteria (Fig. 1; refs. 17–56). This low number of included studies was because only a few studies specifically focused on iIBC recurrence after DCIS. Many studies did not specify for the type of recurrence, *in situ* or invasive, and thus were excluded ($n = 80$).

Study and patient characteristics

Study and patient characteristics of the included studies can be found in Table 1. The sample size of the included studies ranged from 52 to 37,692 patients, and mean follow-up time ranged from 3.2 to 15.8 years. Seven studies included DCIS patients who also had an adjacent invasive component or microinvasion, and seven other studies explicitly excluded these patients. Furthermore, 14 studies included patients from all treatment modalities, breast-conserving surgery (BCS) alone, BCS + radiotherapy (RT)/hormonal therapy (HT), and mastectomy, whereas 16 other studies included only BCS-treated patients ($\pm$RT). Ten studies included patients who underwent one treatment modality: BCS+RT ($n = 1$) and BCS alone ($n = 9$).

For all studies, data were collected retrospectively, regarding patients diagnosed with DCIS between 1960 and 2010. For this, hospital registries, national registries, or data from clinical trials were used. Both cohort (80%) and case-control designs (20%) were used. Seventy percent were multi-center studies, and 30% involved only a single center.

Assessment of quality of prognosis studies (QUIPS)

We assessed six QUIPS domains: study participation, study attrition, end-point definition, prognostic factor measurement, confounding measurement and handling, and statistical analysis and reporting (Supplementary Table S2). A high or moderate risk of bias was identified in at least one domain in 39 of the 40 studies, with 22 studies having a high risk of bias in at least one domain (Table 2). The domains with the highest risk of bias were confounding measurement and handling and study participation, which had a high risk of bias in 16 and 8 of the 40 studies, respectively.

In total, 11 of the 40 studies (27.5%) used the study design to account for potential confounding through either matching,

Table 1. Study and patient characteristics of included articles

Reference	First author, year		Source population	RCT or Obs	Single- or multi-center	Study design	Number, DCIS patients	Number, iIBC events	Period	Mean follow-up (years)	Adjacent invasion included?	Treatment
17	Rakovitch, 2018	HQ	ECOG E5194, Ontario DCIS Cohort	RCT[a], Obs	Multi	Cohort	773	65	1994–2003	9.4	N/a	BCS alone
18	Visser, 2018	HQ	Netherlands Cancer Registry	Obs	Multi	Case–control	674	200	1989–2004	12.0	No	BCS alone
19	Pruneri, 2017		European Institute of Oncology	Obs	Single	Cohort	1,488	136	1997–2008	8.2	N/a	All modalities
20	Molinaro, 2016	HQ	SEER Northern California	Obs	Multi	Case–control	1,492	167	1983–1996	12.6	No	BCS alone
21	Borgquist, 2015		Uppland, Västmanland (Sweden)	Obs	Multi	Cohort	324	46	1986–2004	15.3	N/a	All modalities
22	Williams, 2015		DCIS I, IBIS II, IRESSA trial, ERISAC, lapatinib DCIS	RCT	Multi	Cohort	314	22	1990–2010	5.0	Yes	All modalities
23	Curigliano, 2015	HQ	European Institute of Oncology	Obs	Single	Cohort	1,667	201	1996–2008	7.6	N/a	All modalities
24	Cheung, 2014	HQ	West Midlands Cancer Registry	Obs	Multi	Cohort	3,930	297	1988–2008	N/a	N/a	All modalities
25	Generali, 2014		John Radcliffe Hospital, Royal Brisbane and Women's Hospital	Obs	Multi	Cohort	174	25	N/a	12.1	N/a	All modalities
26	Kong, 2014	HQ	Ontario Cancer Registry	Obs	Multi	Cohort	1,607	148	1994–2003	10	No	BCS+RT
27	v Bockstal, 2013		Ghent University Hospital	Obs	Single	Cohort	64	12	1991–2003	9.3	Yes	All modalities
28	Solin, 2013		ECOG E5194	RCT[a]	Multi	Cohort	327	20	1997–2002	8.8	N/a	BCS ± HT
29	Donker, 2013		EORTC	RCT	Multi	Cohort	1,010	123	1986–1996	15.8	No	BCS ± RT
30	Collins, 2013	HQ	KPNC, KPSC, HPHC	Obs	Multi	Case–control	619	225	1990–2001	4.8	N/a	BCS ± RT
31	Holmberg, 2013	HQ	SweDCIS	RCT	Multi	Case–control	1,046	N/a	N/a	N/a	Yes	BCS ± RT
32	Knudsen, 2012		Thomas Jefferson University Hospital	Obs	Single	Cohort	236	27	1978–2008	9.0	No	BCS alone
33	Alvarado, 2012		University of Texas MD Anderson Cancer Center	Obs	Single	Cohort	2,037	16	1996–2009	5.2	N/a	All modalities
34	Rakovitch, 2012	HQ	Sunnybrook Health Sciences Centre	Obs	Single	Cohort	213	21	1982–2000	7.7	N/a	BCS ± RT
35	Han, 2012	HQ	Sunnybrook Health Sciences Centre	Obs	Single	Cohort	180	22	1987–2000	7.8	Yes	BCS ± RT
36	Witkiewicz, 2011		Thomas Jefferson University Hospital	Obs	Single	Cohort[b]	126	16	N/a	N/a	N/a	BCS alone
37	Wapnir, 2011		NSABP B-17, NSABP B-24	RCT	Multi	Cohort	2,612	263	1985–1994	14.7	N/a	BCS±RT ±HT
38	Falk, 2011		Norwegian Breast Cancer Screening Programme	Obs	Multi	Cohort	3,046	96	1993–2007	5.2	No	All modalities
39	Tunon-de-Lara, 2010		Institut Bergonie	Obs	Single	Cohort	812	47	1971–2001	9.8	No	All modalities
40	Zhou, 2010		Uppland, Västmanland (Sweden)	Obs	Multi	Cohort	392	34	1986–2004	10.2	N/a	All modalities
41	Pinder, 2010		UKCCR/ANZ	RCT	Multi	Cohort	1,224	55	1990–1998	N/a	Yes	BCS ± RT ± HT
42	Kerlikowske, 2010	HQ	SEER Northern California	Obs	Multi	Case–control	329	72	1983–1994	8.2	No	BCS alone
43	Witkiewicz, 2009		Thomas Jefferson University Hospital	Obs	Single	Cohort[b]	78	11	N/a	12.2	N/a	BCS alone
44	Nofech-Mozes, 2008		Sunnybrook Health Sciences Centre	Obs	Single	Cohort	133	21	1982–2000	8.9	Yes	BCS alone
45	Rakovitch, 2007		Sunnybrook Health Sciences Centre	Obs	Single	Cohort	615	36	1982–2000	5.9	Yes	BCS ± RT
46	Ringberg, 2007	HQ	SweDCIS	RCT	Multi	Case–control	1,046	155	1987–1999	5.2	N/a	BCS ± RT
47	Hwang, 2007	HQ	Breast Cancer Surveillance Consortium	Obs	Multi	Cohort	3,274	83	1993–2005	3.2	No	All modalities
48	Smith, 2006	HQ	SEER	Obs	Multi	Cohort	3,409	107	1992–1999	5.0	N/a	BCS ± RT
49	Li, 2006	HQ	SEER	Obs	Multi	Cohort	37,692	1,504	1988–2002	N/a	N/a	BCS ± RT
50	Bijker, 2006		EORTC	RCT	Multi	Cohort	1,010	108	1986–1996	10.5	No	BCS ± RT
51	Warren, 2005		SEER	Obs	Multi	Cohort	1,103	62	1991–1992	7.5	No	BCS ± RT
52	Kerlikowske, 2003	HQ	SEER Northern California	Obs	Multi	Cohort	1,036	71	1983–1994	6.5	No	BCS alone
53	Teo, 2003		Merseyside (UK)	Obs	Multi	Case—control	52	12	1989–1999	5.3	No	All modalities
54	Bijker, 2001	HQ	EORTC	RCT	Multi	Cohort	863	66	1986–1996	5.4	No	BCS ± RT
55	Wärnberg, 2001		Swedish Cancer Registry	Obs	Multi	Case–control	570	70	1960–1996	10	No	All modalities
56	Habel, 1998		SEER Washington	Obs	Multi	Cohort	709	55	1980–1992	5.2	N/a	BCS ± RT

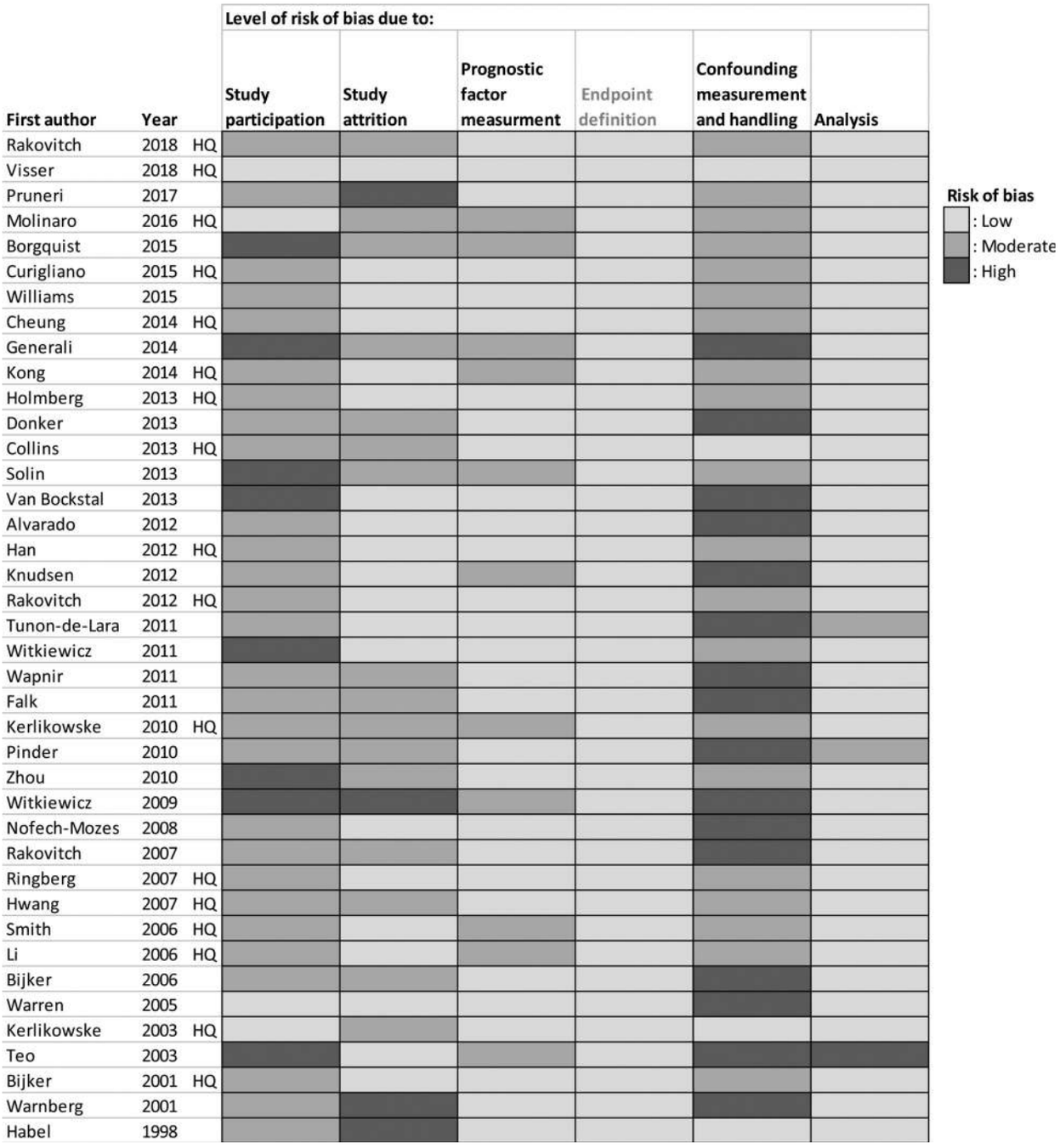
NOTE: "All modalities" consistent of BCS alone, BCS+RT/HT, and mastectomy.

Abbreviations: HPHC, Harvard Pilgrim Health Care; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; N/a, data not available; Obs, observational study; RCT, randomized clinical trial.

[a]Nonrandomized clinical trial.

[b]Selection of cohort used in analysis.

Table 2. Risk of bias per QUIPS domain for each individual study



NOTE: Endpoint definition was accounted for in study inclusion criteria.

stratification, or initial assembly of comparable groups. Eighteen of the 40 studies (45.0%) accounted for confounding effect in the analysis stage. The remaining 11 studies (27.5%) did not perform adjustments for confounding. The reasons for the high-risk-of-bias ratings in the study participation domain were incomplete description of inclusion and exclusion criteria and/or poorly described baseline characteristics of the study group. Cox proportional hazard analysis was performed in all studies but two. One of these two studies was assessed as having a high risk of bias in the statistical analysis domain, because the analysis used was not appropriate for the design of the study.

None of the studies had a high risk of bias in the domains endpoint definition and prognostic factor measurement.

Finally, we assessed the effect of time period of publication on risk of bias. We divided the studies at the median into publication years 1998–2011 and 2012–2018 and compared the risk of bias per domain. There was no significant difference in any of the study domains.

Exploring publication bias

Supplementary Fig. S1 shows the funnel plot that was used to assess publication bias by including all prognostic factors together in one plot. The funnel plot shows that both significant and nonsignificant factors related to outcome were published. As such, we conclude that there was no evidence for publication bias.

Identification of the HQ studies and their reported prognostic factors

We filtered for the studies without a high risk of bias in any of the QUIPS domains and selected only those studies that accounted for the confounding effect of treatment (HQ studies). Only 17 studies met these criteria (Tables 1 and 2). All together, these 17 HQ studies assessed 26 different factors and identified 10 different potential prognostic factors, which were assessed in Y HQ studies and reported to have statistically significant association with subsequent invasive breast cancer in X of these studies (X/Y): high histologic grade (1/7), young age at DCIS diagnosis (4/6), solid DCIS architecture (2/6), detection by palpation (2/4), premenopausal status (2/2), African-American race (1/2), presence of calcification (1/2), high p16 expression (1/2), high COX-2 expression (1/2), and presence of periductal fibrosis (1/1; Table 3; Supplementary Table S3). None of the studies assessed all prognostic factors. Notably, studies examining the same prognostic factor often showed inconsistent results (Supplementary Table S3).

Table 3. List of factors that were assessed in the HQ studies

	Number of HQ studies:	
Factor	Assessed factor	Statistical significant finding
Age at DCIS diagnosis	6	4
Calcification	2	1
Calgranulin status	1	0
COX-2 status	2	1
Cyclin D1 status	1	0
DCIS architecture	6	2
Detection method	4	2
ER status	3	0
Focality	1	0
Grade, histologic	7	1
HER2 status	3	0
Ki67 status	2	0
Lesion size	7	0
Margin status	4	0
Menopausal status	2	2
Necrosis	4	0
p16 status	2	1
p21 status	1	0
p53 status	3	0
Periductal fibrosis	1	1
Periductal lymphocytes	1	0
PR status	3	0
Psoriasin status	1	0
Race and/or ethnicity	2	1
Subtypes, intrinsic	2	0
Year of DCIS diagnosis	1	0

Meta-analyses

Meta-analyses were performed to estimate the average effect size of the prognostic factors; this was done for all factors reported by more than 1 HQ study, regardless of their statistically significance (Fig. 2; Supplementary Fig. S2). Most of the factors seemed to point to a higher relative risk of subsequent iIBC for DCIS patients, although effects were generally small. Six prognostic factors had a statistically significant pooled estimate: African-American race [pooled estimate (ES), 1.43; 95% CI, 1.15–1.79], premenopausal status (ES, 1.59; 95% CI, 1.20–2.11), detection by palpation (ES, 1.84; 95% CI, 1.47–2.29), involved margins (ES, 1.63; 95% CI, 1.14–2.32), high histologic grade (poorly differentiated; ES, 1.36; 95% CI, 1.04–1.77), and high p16 expression (ES, 1.51; 95% CI, 1.04–2.19). For these six prognostic factors, the heterogeneity test demonstrated consistency of the estimates reported in the included studies. Although histologic grade showed a trend toward heterogeneity ($P = 0.09$), none of the studies reported all these six prognostic factors. Meta-analyses could not be performed for the factors age at diagnosis, DCIS architecture, lesion size, and year of DCIS diagnosis because the categories used in the studies were not comparable.

Discussion

The purpose of this review was 2-fold. First, we aimed to identify prognostic factors with statistically significant association with subsequent iIBC that deserve validation. We identified 17 HQ studies, assessing 26 factors, of which 6 prognostic factors were statistically significantly associated with subsequent iIBC risk in the meta-analyses: African-American race, premenopausal status, detection by palpation, involved margins, high histologic grade (poorly differentiated), and high p16 expression. Second, we aimed to give insight into bias that was frequently introduced in previously published prognostic factor studies for subsequent iIBC after preceding DCIS. Highest risk of bias in the studies was attributable to insufficient measurement and handling of confounders and poorly described study groups.

The association between the six unfavorable prognostic factors and subsequent iIBC risk can be biologically explained. When DCIS has involved margins, this indicates that residual tumor cells are left behind at the resection site. These cells can subsequently grow out and form a recurrence, which could be invasive disease. Premenopausal status and African-American race are known independent predictors of a worse breast cancer outcome (57, 58). Furthermore, literature has shown that DCIS detected by palpation would be more aggressive than screening-detected DCIS, as these DCIS lesions are more often ER negative and HER2 positive (59). The same holds true for DCIS lesions of high histologic grade (60). Lastly, p16 mediates cell-cycle arrest through the p16/Rb signaling pathway. Disruption of the p16/Rb signaling pathway is an oncogenic event and results in sustained cellular proliferation, which can lead to DCIS progression to iIBC (61).

Whether or not to use histologic grade as a prognostic marker for invasive recurrence after DCIS is a matter of debate. In our meta-analysis, histologic grade showed a trend toward heterogeneity, which is likely caused by differences in histologic classification methods (41, 62–64). Moreover, all methods suffer from reproducibility problems causing high interobserver variability (65, 66).

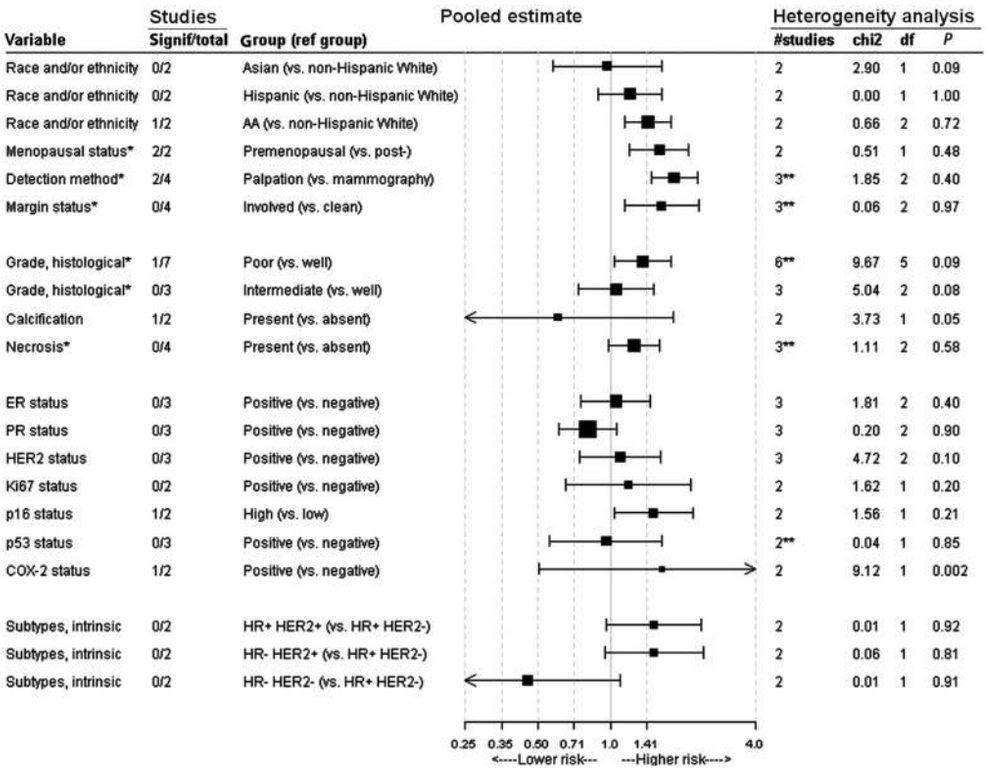


Figure 2.

Pooled estimates and heterogeneity analysis of prognostic factors reported in more than one HQ study. Pooled estimates were calculated using weighting based on the number of included iIBC events per study [weight per study (%) = (n of DCIS patients with subsequent iIBC in that specific study/total number of DCIS patients with subsequent iIBC of all studies which are used to form the pooled estimate) × 100]. Heterogeneity was assessed using random effect (DerSimonian and Laird) analyses. The column "studies signif/total" represents the number of HQ studies that reported a statistical significant association for the prognostic factor and subsequent iIBC risk and the total number of HQ studies that assessed the prognostic factor. *, factors used in routine clinical practice for DCIS; **, number of studies included in the analysis: A few studies did not report effect sizes or used categories that were not comparable with the other studies assessing that specific prognostic factor; hence, these studies were excluded from the analysis. AA, African American.

Zhang and colleagues carried out the first meta-analysis specifically focusing on ipsilateral *invasive* recurrence after DCIS (67). In line with our study, they found that positive margins and non–screening-detected lesions were associated with a higher risk of iIBC after DCIS. However, they included only 18 studies. Although Zhang and colleagues performed bias assessment of the included articles, using a different method than we did, they did not report on the results from the bias assessment, making it likely that also studies with a high risk of bias were included in their meta-analyses. In addition to the study by Zhang and colleagues, two other meta-analyses have been published, although focusing on ipsilateral tumor recurrence (both *in situ* and invasive) preceding DCIS. Boyages and colleagues found that the presence of necrosis, involved margin, high histologic grade, and large tumor size were predictive of ipsilateral recurrence for DCIS (68). In addition to these factors, Wang and colleagues reported that multifocality and symptomatic DCIS were also associated with high risk of ipsilateral breast recurrence (69). In our study, multifocality was not assessed, and meta-analyses of necrosis, histologic grade, and tumor size yielded nonstatistically significant results. However, previous literature has indicated that risk factors for subsequent invasive disease and recurrence of DCIS may not be identical; thus, combining *in situ* recurrence and invasive recurrence into a single group may obscure the real risk factors for invasive disease after DCIS (52). This could explain the inconsistent meta-analysis results of our study and the studies mentioned above and highlights the need to specify for the type of recurrence when performing a prognostic factor study for DCIS.

Next to the prognostic factors we found to be statistically significant in the meta-analyses, many other factors were identified in the included studies. This variability could firstly be explained by underreporting of the prognostic factors, because none of the studies assessed all prognostic factors. Secondly, the presence of unadjusted confounding could also play a role in this, because this makes that any risk estimate could be misleading. The most important confounder in the studies was DCIS treatment: This variable was risk factors for subsequent iIBC among DCIS patients while at the same time associated with the prognostic factors of interest (70). Confounding can be accounted for at the design stage of the study (e.g., by matching or randomization) and/or at the analysis stage, given the confounders have been measured properly. Twenty-nine included studies properly adjusted for confounding effect. Remarkably, 11 studies did not include any adjustments at all.

All patients included in prognostic factor studies for DCIS are treated. As most studies did not include genomic characterization,

we could not confirm whether the invasive recurrences studied were indeed all clonally related to the primary DCIS lesion. As they might also be second primary tumors, the prognostic factors identified could also be risk factors for any second invasive breast event after DCIS. In addition, some DCIS cases developed early recurrences (within 4 months), questioning if these were not missed invasive cancers. As we know that the rate of missed invasive disease at DCIS diagnosis is 11% to 25%, it is unlikely that this will be a major percentage of the recurrences reported (71–74).

High risk of bias attributed to selective study participation was mostly because the source of patient (clinical and histopathologic) information was often not mentioned or not properly described. The same holds true for details on inclusion and exclusion criteria. Incomplete description of these criteria can bias the estimates in an uncertain direction. In addition, baseline characteristics were often not adequately described and should at least comprise the factors that are reported during routine diagnosis and treatment, such as age at diagnosis, histologic grade, clinical presentation, received treatment for DCIS, lesion size, and margin status. Furthermore, some studies included DCIS patients with an adjacent invasive component or microinvasion. Prognostic factor studies for DCIS are aiming to find predictors of subsequent invasive diseases. Yet, DCIS lesion with a (micro)invasive component is already invasive disease. Including these lesions in the analysis is not appropriate, because this may obscure the risk factors for subsequent iIBC after DCIS. Thus, DCIS with an adjacent invasive component or microinvasion should be excluded from such a study. The same holds true for the inclusion of patients treated by mastectomy. Because the recurrence risk after mastectomy is negligible, inclusion of these patients into a study assessing risk of invasive recurrence after DCIS is likely to be less adequate. Of note, two HQ studies, Cheung and colleagues and Curigliano and colleagues, included a substantial proportion of patients treated with mastectomy. Despite this, these studies were still considered as HQ studies following our predefined criteria. Exclusion of these two studies from the meta-analyses did not substantially alter the results (data not shown).

Although study attrition did not introduce a high risk of bias, it was a recurrent problem. Next to the proportion of the initial patient group available for analysis at the end of the study, it is also important to report the reasons why certain patients were not included in the analysis. If the reason for exclusion was related to the study's end-point (missingness not at random), this can substantially affect risk estimates, either toward unity or away from it. Only a few studies included in this review explored differences between drop-outs and non–drop-outs. This could contribute to the wide variations in prognostic factors identified and nonreproducibility of prognostic factors between studies. Most of the factors identified were associated with small effect sizes, and the clinical relevance of these factors therefore is questionable.

Many studies included in this systematic review are retrospective studies that used hospital registries or national registries as a data source, and working with these data is a challenge. Registry-based studies often depend on the size, quality, completeness of relevant variables, and features of the registry on which the study is based (75). Furthermore, there are worries about data quality related to end-point measures in registries, and end-point information such as migration abroad or death from other causes is not always included (76, 77). This is a general concern regarding registry-based studies which can only be solved by improving source data. The remainder of the studies used clinical trial data as data source. Clinical trials have the advantage in finding prognostic factors as patient groups are often randomized and thus the analysis does not suffer from confounding. Yet, as clinical trials may focus on highly selected patient groups (e.g., specific age range, lesion size range, etc.), generalizability of trial results might be limited.

This systematic review has several strengths. First, to our knowledge, we are the first to perform bias assessment on prognostic factor studies for DCIS. Second, using the QUIPS tool, we were able to provide insight into the most frequently occurring biases in prognostic factor studies in a standardized way. This enabled us to subsequently identify the studies including the least bias, in order to identify factors with the strongest predictive value regarding subsequent iIBC risk after DCIS.

Our study also has some limitations. First, use of the QUIPS tool still involved subjective judgment in assigning a score for each of the six domains, although we minimized this by assessing the included studies in a consistent manner using specific criteria for each domain and by assigning two independent assessors. The interobserver kappa value showed an excellent consistency between the two assessors. Second, because the prognostic factors examined differed widely among the studies, the prognostic evidence of the factors obviously only relied on a few publications available: but all studies included in the analysis were HQ studies. Third, studies that we classified as HQ were not allowed to have high risk of bias in any of the QUIPS domains. However, studies with high risk of bias in at least one QUIPS domain might be as good (or bad) as studies with moderate risk of bias in three domains.

In conclusion, measurement and evaluation of prognostic factors have the potential to improve the clinical management of women diagnosed with DCIS. Nonetheless, studies assessing these factors should be of sufficient rigor to reach a high level of specificity and sensitivity. We highly recommend the six prognostic factors for independent validation, although with a critical note added to the use of histologic grade as a prognostic factor. Next to this, we encourage researchers to remain searching for other factors. Also, we could not assess all reported prognostic factors in our meta-analyses, as some were only assessed by a single study. Thus, the potential of these factors remains unproven, but could be confirmed in future studies. In addition, we showed that not accounting for the confounding effect of DCIS treatment is the main cause of study bias, indicating that is of utmost importance to correct for this. Furthermore, we encourage researchers to describe their used patient groups in high detail. Lastly, in the analysis stage, the type of recurrence should be specified: *in situ* or invasive. This, because invasive recurrences increase a patient's risk of dying from breast cancer and thus should be an (additional) important end-point of interest in prognostic factor studies of DCIS. These insights and the use of for example the STROBE guidelines (78) can help researchers improve their study designs and avoid common methodological pitfalls.

This systematic review underlines the high need of well-designed studies with large patient numbers that undergo independent validation (79). Currently, initiatives have been established to make this happen and translate promising

prognostic factors to clinical practice. One of these initiatives is the PRECISION (PREvent ductal Carcinoma In Situ Invasive Overtreatment Now) initiative, funded by Cancer Research UK and the Dutch Cancer Society (https://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/grand-challenge-award/funded-teams-wesseling; ref. 80). In addition, noninferiority trials, like LORD, LORIS, and COMET, have been initiated and will be important in prospective validation of prognostic factors (81–83). We hope our review will ultimately contribute to the identification of reliable and clinically meaningful prognostic factors for DCIS in the near future. This may help us to distinguish indolent from potentially hazardous DCIS, thereby putting an end to the current overtreatment dilemma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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