Predictors for local invasive recurrence of ductal carcinoma *in situ* of the breast: a meta-analysis

Xining Zhang, Hongji Dai, Ben Liu, Fengju Song and Kexin Chen

The introduction of mammographic screening has considerably increased the detection rate of ductal carcinoma *in situ* (DCIS), which has a high probability of recurrence. We carried out a meta-analysis to evaluate the predictive factors including biomarkers, tumor characteristics, and modes of detection on the risk of local invasive recurrence (LIR) following DCIS. Searches were performed in PubMed and EMBASE up to 8 July 2014. Risk estimates (hazard ratios, odds ratios, and relative risks) and their 95% confidence intervals (CIs) were extracted to calculate the strength of the associations between predictive factors and the risk of LIR after treatment of DCIS. STATA 12.0 was used to combine results in this meta-analysis. A total of 18 articles were included in the analysis. Pooled risk estimates and 95% CIs were 1.36 (1.04–1.69) for the positive margin, 1.38 (1.12–1.63) for the nonscreening detection method, 1.04 (0.84–1.24) for high nuclear grade 1, 1.32 (0.98–1.66) for intermediate nuclear grade 2, 1.18 (0.98–1.37) for comedonecrosis, 1.00 (0.92–1.08) for large tumor size, 1.34 (0.82–1.87) for multifocality, 0.74 (0.36–1.12) for estrogen receptor-positive tumors, 0.89 (0.47–1.31) for progesterone receptor-positive tumors, and 1.25 (0.7–1.81) for HER2/neu-positive tumors. Positive margin and non-screening-detected cancers were associated with a higher risk of LIR following DCIS. These predictive factors, after further validation, could be considered to tailor treatment for individual patients. *European Journal of Cancer Prevention* 25:19–28

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Department of Epidemiology and Biostatistics, Key Laboratory of Breast Cancer Prevention and Therapy, Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, National Clinical Research Center of Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, People's Republic of China

Correspondence to Kexin Chen, MD, PhD, Department of Epidemiology and Biostatistics, Key Laboratory of Breast Cancer Prevention and Therapy, Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, National Clinical Research Center of Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, People's Republic of China
Tel/fax: +86 222 337 2231; e-mail: chenkexin1963@yahoo.com

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Introduction

Ductal carcinoma *in situ* (DCIS) is not a single disease; it encompasses a heterogeneous group of lesions with different malignant tendencies. DCIS increased drastically after the introduction of screening mammography (Porter *et al.*, 2003; Chen *et al.*, 2013; Van Luijt *et al.*, 2013). Population-based studies indicated that the 10-year mortality rate for patients who received treatment for DCIS is less than 2% (Schwartz *et al.*, 2000). However, recurrence rates of DCIS vary after different treatments. Approximately half of the patients with local recurrence showed progression to new DCIS and the other half developed invasive carcinomas (Correa *et al.*, 2010). Patients with local invasive recurrence (LIR) have a higher risk of dying from breast cancer. Recent results from the Canadian National Breast Screening Study have indicated that about 20% of carcinoma *in situ* had progressed to invasive breast cancer (To *et al.*, 2014). It is necessary to discriminate the specific features of DCIS and identify possible predictive factors for LIR.

Considering the heterogeneity of DCIS, the best way to manage patients with DCIS is still under discussion. The usual treatment of DCIS is mastectomy. However, this could lead to overtreatment for patients with small lesions. Randomized clinical trials (RCTs) suggested that radiotherapy and breast-conserving surgery (BCS) may reduce the risk of local recurrence of DCIS (Fisher *et al.*, 1999; Emdin *et al.*, 2006; Holmberg *et al.*, 2008), but not all DCIS patients benefit from these treatments. It is useful to develop predictive factors to tailor treatment for individual patients. Some published literature has indicated that the risk factors for LIR and recurrence of DCIS may not be identical (Kerlikowske, 2003; Emdin *et al.*, 2006); thus, combining the DCIS recurrence and LIR into a single group may obscure the real risk factors for LIR. It was reported that younger age, premenopausal status, poor tumor characteristics, and some biomarkers were associated with a higher risk of local recurrence (Fisher *et al.*, 1999; Bijker *et al.*, 2001; Kerlikowske, 2003). However, to our knowledge, no meta-analysis has assessed predictive factors specifically for the risk of second local invasive breast cancer in DCIS patients. In this meta-analysis, we quantitatively measured the association between biomarkers, tumor characteristics, and modes of detection and the risk of LIR following DCIS.

Materials and methods

Search strategy and study selection

Two investigators separately estimated the methodological quality according to Preferred Reporting Items for

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Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009). Literature reviews were performed using the terms 'DCIS' or 'ductal carcinoma *in situ*' in combination with 'invasive breast cancer', 'local invasive recurrence', 'subsequent invasive breast cancer,' or 'ipsilateral invasive carcinoma' in two electronic databases (PubMed and EMBASE). The last literature search was updated on 8 July 2014. Only English articles were included. Each title and abstract of the remaining articles was reviewed to determine potential relevance to the review topic. The full text of each potentially relevant article was reviewed. We also manually searched references from the selected articles.

Inclusion and exclusion criteria

Studies were included if they fulfilled the following criteria: (i) case–control study, cohort study, or RCTs on the relationship between predictive factors and recurrence of DCIS; (ii) number of cases at least 100; (iii) patients with a clear diagnosis of DCIS; and (iv) the end-point of cases was defined as development of ipsilateral invasive breast cancer. Literature with the following conditions was excluded: (i) male patients with DCIS or breast cancer and (ii) risk estimates such as hazard ratios (HRs), odds ratio (OR), or relative risk (RR) and their 95% confidence intervals (CIs) not provided. In case of overlapping or duplicate data, the publications with the largest sample size or the latest articles were included.

Data extraction and quality assessment

From each included study, the following information was extracted in a standardized manner by two investigators: first author, publication year, study period, overall sample size, number of LIR, source of population, treatment, and risk estimates for the association between biomarkers, tumor characteristics or modes of detection, and risk of LIR. Biomarkers included estrogen receptor (ER) (positive vs. negative), progesterone receptor (PR) (positive vs. negative), and epidermal growth factor receptor-2 (HER2/neu) (positive vs. negative). Tumor characteristics extracted from each study included nuclear grade 1 (high vs. low) and nuclear grade 2 (intermediate vs. low), comedonecrosis (yes vs. no), margin (positive vs. negative), tumor size (large vs. small), and focality (multifocality/multicentric vs. unifocal). Modes of detection and the risk of LIR were compared using a non-screening-detected method and a screening-detected method. Immunochemical staining was used to evaluate the expression of ER, PR, and HER2/neu. Scores that ranged between 3 and 8 were defined as ER and PR positive, and HER2/neu positivity as HER2/neu scoring immunochemical 3+. Positive margin was often classified as '<1 mm' or 'involved'; negative margin was classified as '>1 mm' or 'free'. There was no standardized definition for the tumor size of DCIS; generally, we classified tumors less than 20 mm as small.

We used the US Preventive Service Task Force grading system (Harris *et al.*, 2001), the Newcastle Ottawa Scale (NOS) (Stang, 2010), and the Jadad score (Jadad *et al.*, 1996) to assess the quality of studies included. NOS was used to assess observational studies. The Jadad score was used to evaluate RCTs. The score of NOS ranged from 0 to 9, with 6 or more considered as higher quality studies. Jadad scores of 1–3 were considered as low quality and Jadad scores of 4–7 were considered as relatively high quality. Quality assessment of the studies included is shown in Supplementary Table 1. Discrepancies between two investigators were discussed and resolved by additional review.

Quantitative data synthesis

Meta-analysis was carried out using the STATA statistical software (version 12.0; StataCorp, College Station, Texas, USA). HRs, ORs, and RRs with their corresponding 95% CIs were used to calculate the associations between biomarkers, tumor characteristics, and modes of detection and the risk of LIR following DCIS. When the ORs were lower than 0.5 or higher than 2.5 or the incidence risk was over 10%, we converted the ORs into RRs, according to the method of Zhang and Yu (1998). The statistical significance of pooled HRs, ORs, or RRs was evaluated using the Z test. The Q test and the I^2 statistic were used to calculate the heterogeneity of the studies included (Kerlikowske, 2003). P value less than 0.05 indicated that there was heterogeneity among studies. The fixed model was used if there was no significant heterogeneity; otherwise, the random model was used. The Egger test and a funnel plot were used to examine potential publication bias. P value less than 0.05 from two-sided tests was defined as statistically significant (Kerlikowske *et al.*, 2010; Kong *et al.*, 2014). We reported the overall pooled results and those stratified by RCTs and observational studies.

Results

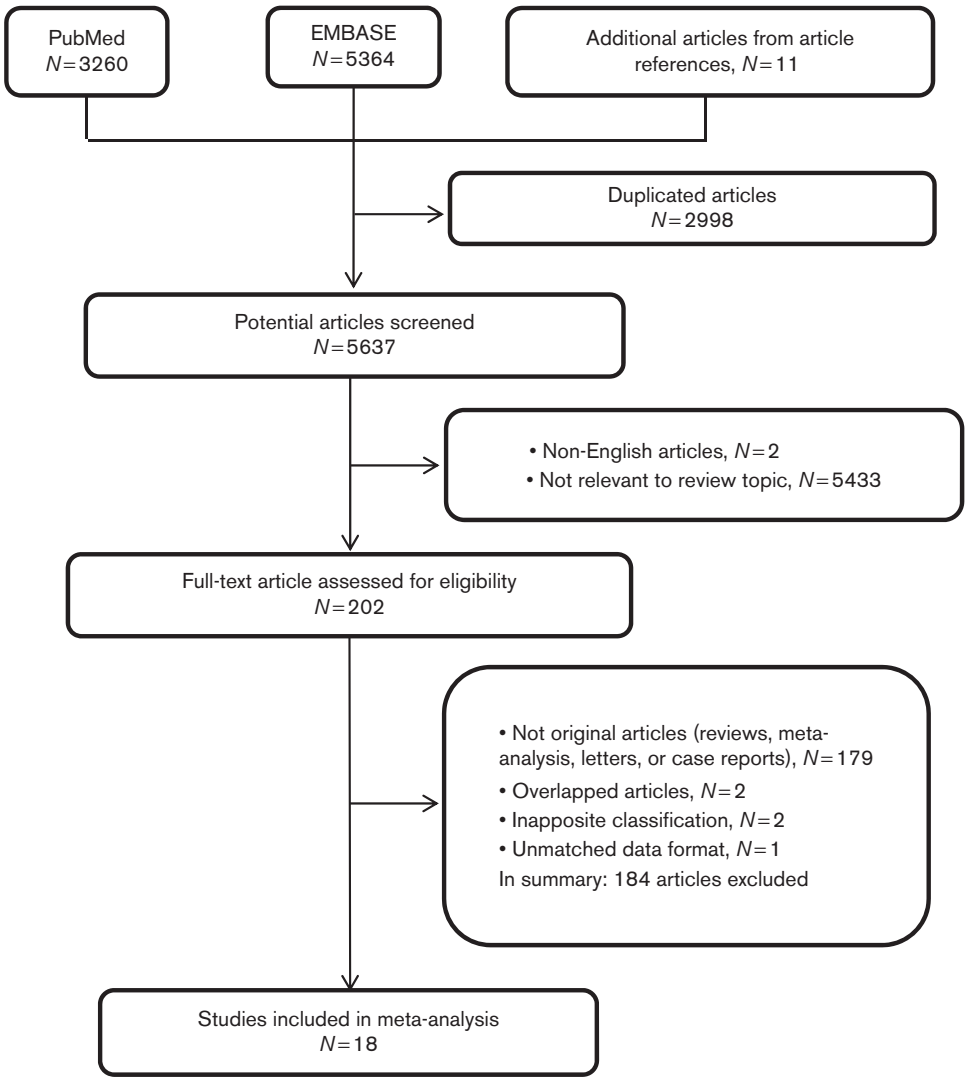
Result of the literature search and selection

The process of the literature search is shown in Fig. 1. We initially identified 8624 potential articles from the two databases and 11 additional articles from article references. After excluding duplicated articles ($N=2998$), non-English articles ($N=2$), and unrelated articles ($N=5435$), 202 full-text articles were assessed and reviewed. Furthermore, 184 articles were excluded because of nonoriginal articles ($N=179$), overlapped articles ($N=2$), inapposite classification ($N=2$), or unmatched data format ($N=1$). Finally, 18 articles (five RCTs and 13 observational studies) were used to evaluate the association between biomarkers, tumor characteristics, and modes of detection and the risk of LIR. Two reviewers researched a consensus on all the articles included.

Characteristics of the studies included

The baseline characteristics of the included studies are shown in Table 1. Except for one Asian study (Noh *et al.*,

Fig. 1



Flow diagram of the study selection procedure.

2013), the rest of the studies were from North America and Europe. The patients included in the studies were pathologically diagnosed with DCIS (alone or with microinvasion). The age range of DCIS patients in each study was from 20 to 80 years, with only one study designed for older (≥66 years) patients (Smith *et al.*, 2006). Diagnoses of DCIS were all confirmed by pathology. All DCIS patients had received clinical treatment, either BCS or breast-conserving surgery plus radiotherapy (BCSRT), with or without tamoxifen.

Biomarkers and the risk of local invasive recurrence following ductal carcinoma *in situ*

We investigated ER, PR, and HER2/neu status for the association between biomarkers and the risk of LIR. Across three observational studies (Habel *et al.*, 1998; Kerlikowske *et al.*, 2010; Han *et al.*, 2012) including 1556 women with DCIS, the risk of LIR was lower in women with ER-positive expression. Pooled HRs showed a nonsignificant decreased risk of LIR in women with ER-positive status (HR = 0.74; 95% CI 0.36–1.12) (Fig. 2a).

Three observational studies (Habel *et al.*, 1998; Kerlikowske *et al.*, 2010; Han *et al.*, 2012) including 1556 patients with DCIS investigated the impact of PR status. The results of pooled HR indicated a nonsignificantly decreased risk of LIR in patients with PR-positive status (HR = 0.89; 95% CI 0.47–1.31) (Fig. 2b).

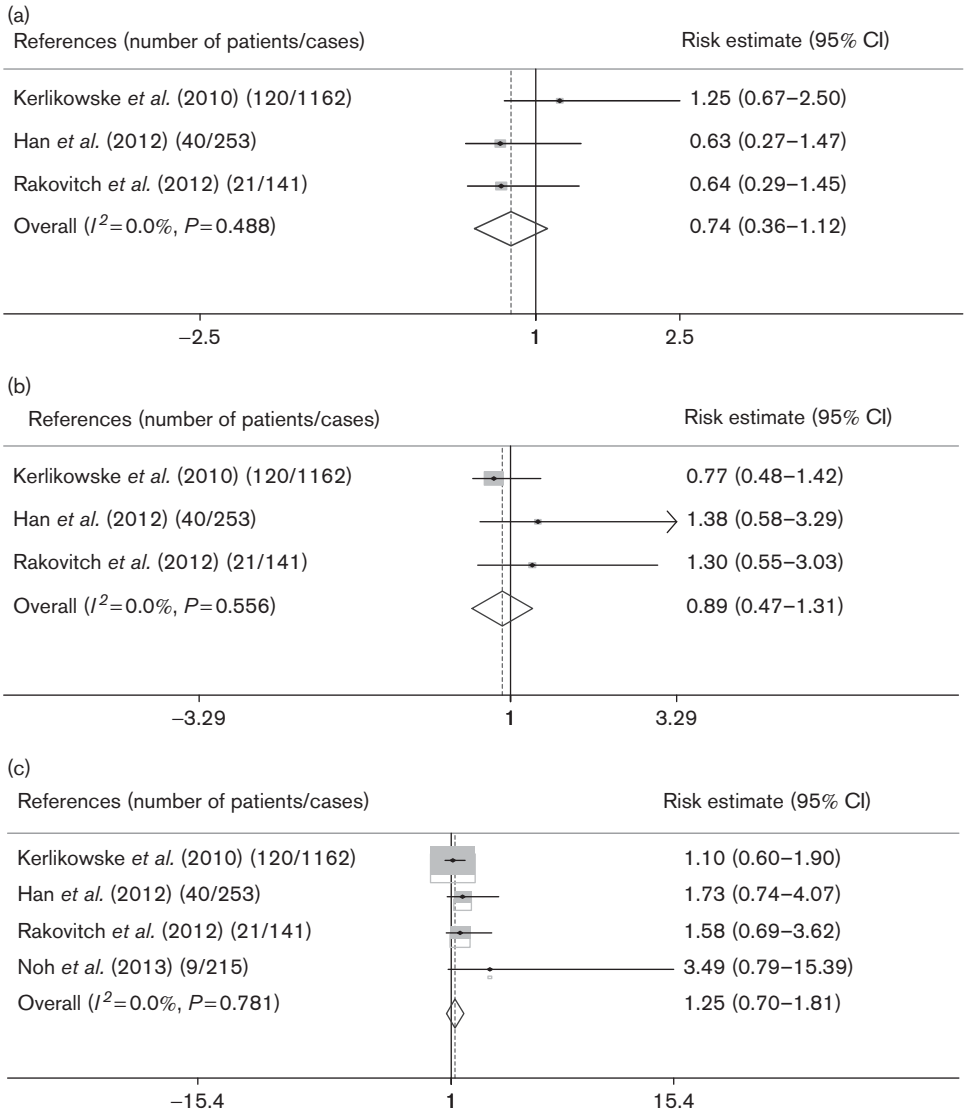
Four observational studies (Habel *et al.*, 1998; Kerlikowske *et al.*, 2010; Donker *et al.*, 2013; Noh *et al.*, 2013) with 1771 patients examined the influence of HER2/neu status. Results of pooled HRs showed a

Table 1 Baseline characteristics of the studies included

References	Study period	Overall sample size	Number of LIR	Source of population	Type of treatment	Risk estimate	Predictors	Covariate and stratification factors
Kong *et al.* (2014)	1994–2003	1607	148	Ontario Cancer Registry (OCR)	BCSRT	HR	Nuclear grade, margin, focality	Age, multifocality, margin status, nuclear grade, boost
Noh *et al.* (2013)	1995–2007	215	9	Samsung Medical Center	BCSRT	HR	Nuclear grade, tumor size, focality, HER2/neu	Age, size, multifocality, nuclear grade, HER2/neu overexpression
Donker *et al.* (2013)	1986–2005	1010	123	EORTC	BCS, BCSRT	HR	Nuclear grade, margin, mode of detection	Age, method of detection, histologic type, architecture, margins, treatment
Collins *et al.* (2013)	1990–2001	2995	100	KPNC, KPSC, HPHC	BCS + tamoxifen, BCSRT	RR	Margin, mode of detection	Race, age, menopausal status, detection method, size, margin
Rakovitch *et al.* (2012)	1982–2000	141	21	Women's College Hospital Research Institute	BCS, BCSRT	HR	Nuclear grade, tumor size, focality, ER, PR, HER2/neu	High nuclear grade, multifocality, tumor size, margin size, architectural subtype, age at diagnosis
Han *et al.* (2012)	1987–2000	253	40	Sunnybrook Health Sciences Centre	BCS, BCSRT	HR	ER, PR, HER2/neu	HER2/neu, age, radiation
Wapnir *et al.* (2011)	1985–2007 1991–2007	2622	263	NSABP B-17 NSABP B-24	LRT LO LRT + TAM, LRT + placebo	HR	Comedonecrosis, tumor size, mode of detection	Age at diagnosis, tumor size, mode of detection, comedonecrosis, treatment group, tumor margin status
Falk *et al.* (2011)	1993–2007	3163	96	Norwegian Breast Cancer Screening Programme (NBCSP)	BC, BCSRT	HR	Nuclear grade, tumor size, mode of detection	Age at diagnosis, period of diagnosis, detection method, tumor size, grade, treatment
Pinder *et al.* (2010)	1990–1998	1224	154	UKCCR/ANZ	BCS, BCSRT with/without tamoxifen	HR	Nuclear grade, tumor size, margin	New grading system, XRT received, tumor size, excision, inflammation
Kerlikowske *et al.* (2010)	1983–2005	1162	120	SEER Northern California	BCS	HR	Nuclear grade, ER, PR HER2/neu, mode of detection	Age at diagnosis, nuclear grade, p16/COX-2/Ki67
Ringberg *et al.* (2007)	1987–2001	1046	155	SweDCIS trials	BCS, BCSRT	HR	Nuclear grade, margin	Age, tumor size, histopathological margins
Smith *et al.* (2006)	1992–2002	3409	107	SEER	BCS, BCSRT	HR	Nuclear grade, tumor size, comedonecrosis	Age, race, comorbidity score, tumor size, comedo, grade
Li *et al.* (2006)	1988–2002	37692	1504	SEER	BCS, RT, BCSRT	HR	Nuclear grade, comedonecrosis, tumor size	Age, year, registry, surgery/radiation
Bijker *et al.* (2006)	1986–1996	863	59	EORTC	BCS, BCSRT	HR	Nuclear grade	Treatment
Warren *et al.* (2005)	1991–2001	1103	62	SEER	BCS, BCSRT	OR	Nuclear grade, margin, tumor size	Tumor size, margin, necrosis, tumor grade, age, race, marital status, tamoxifen given
Kerlikowske (2003)	1983–1999	1036	71	SEER Northern California	BCS	OR	Margin	Age, detection, margin, nuclear grade, tumor size
Warnberg *et al.* (2001)	1960–1992	4661	118	Swedish Cancer Registry	BCS, BCSRT	HR	Tumor size	Age, size, treatment
Habel *et al.* (1998)	1980–1992	709	35	SEER, Washington	BCS, BCSRT	HR	Comedonecrosis, tumor size, mode of detection	Histology, tumor size, radiation therapy, detection

BCS, breast-conserving surgery only; BCSRT, breast-conserving surgery plus radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer; ER, estrogen receptor; HER2/neu, epidermal growth factor receptor-2; HPHC, Harvard Pilgrim Health Care; HR, hazard ratio; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; LIR, local invasive recurrence; LO, lumpectomy only; SweDCIS, Swedish randomized DCIS trial; LRT, lumpectomy followed by radiation therapy; LRT + TAM, LRT plus 5 years of tamoxifen; NBCSP, Norwegian Breast Cancer Screening Programme; NSABP B-17 and NSABP B-24, two National Surgical Adjuvant Breast Project (NSABP) randomized trials for DCIS; OR, odds ratio; PR, progesterone receptor; RR, relative risk; RT, radiation only; SEER, Surveillance, Epidemiology, and End Results program; UKCCCR/ANZ DCIS trial, UK Coordinating Committee on Cancer Research Ductal Carcinoma *in situ* Working Party; XRT, radiotherapy.

Fig. 2



Forest plots for biomarkers (ER, PR, and HER2/neu) and the risk of invasive recurrence (LIR). (a) Forest plots for ER (positive/negative) and the risk of LIR. (b) Forest plot for PR (positive/negative) and the risk of LIR. (c) Forest plot for HER2/neu (positive/negative) and the risk of LIR. CI, confidence interval; ER, estrogen receptor; HER2/neu, epidermal growth factor receptor-2; PR, progesterone receptor.

nonsignificantly increased risk of LIR in patients with HER2/neu-positive status (HR = 1.25; 95% CI 0.70–1.81) (Fig. 2c).

Tumor characteristics and risk of local invasive recurrence following ductal carcinoma *in situ*

We examined nuclear grade, comedonecrosis, margins, tumor size, and focality for the association between tumor characteristics and the risk of LIR.

Twelve studies (Warren *et al.*, 2005; Bijker *et al.*, 2006; Li *et al.*, 2006; Smith *et al.*, 2006; Ringberg *et al.*, 2007; Kerlikowske *et al.*, 2010; Pinder *et al.*, 2010; Falk *et al.*, 2011; Rakovitch *et al.*, 2012; Donker *et al.*, 2013; Noh *et al.*, 2013; Kong *et al.*, 2014) including four RCTs investigated the association between nuclear grade and LIR. High nuclear grade nonsignificantly increased the risk of DCIS patients having LIR from the pooled result of the RCTs (HR = 1.33; 95% CI 0.86–1.79). However, according to results from observational studies, the high nuclear grade nonsignificantly decreased the risk of DCIS patients having LIR (HR = 0.97; 95% CI 0.75–1.19). The overall pooled risk estimate suggested a nonsignificantly increased risk in patients with high nuclear grade (HR = 1.04; 95% CI 0.84–1.24) (Fig. 3a). DCIS patients with intermediate nuclear grade have a nonsignificantly increased risk of LIR according to the pooled result (HR = 1.27; 95% CI 0.82–1.72). Results

from RCTs (HR = 1.38; 95% CI 0.86–1.89) and observational studies (HR = 1.32; 95% CI 0.98–1.66) were consistent (Fig. 3b).

Five studies on comedonecrosis were included in this meta-analysis. Three observational studies (Habel *et al.*, 1998; Li *et al.*, 2006; Smith *et al.*, 2006) showed that women with DCIS and comedonecrosis have a significantly increased risk of LIR (HR = 1.41; 95% CI 1.15–1.68). The pooled risk estimate from two RCTs (Wapnir *et al.*, 2011; Donker *et al.*, 2013) was nonsignificant (HR = 0.90; 95% CI 0.62–1.19). The overall risk estimate of comedonecrosis for LIR was (HR = 1.18; 95% CI 0.98–1.37) (Fig. 3c).

Seven studies on margins including three RCTs, two case–control studies, and two cohort studies (Kerlikowske, 2003; Warren *et al.*, 2005; Ringberg *et al.*, 2007; Pinder *et al.*, 2010; Collins *et al.*, 2013; Donker *et al.*, 2013; Kong *et al.*, 2014) were included in the analysis. Pooled results of four observational studies showed that positive margin was associated with an increased risk of LIR (HR = 1.62; 95% CI 1.14–2.10). The pooled risk estimate from RCTs was (HR = 1.15; 95% CI 0.72–1.59). The overall results indicated that the DCIS women with positive margin had a 37% increased risk of LIR; the summary risk was (HR = 1.36; 95% CI 1.04–1.69; $P = 0.127$) (Fig. 3d). We further carried out a subgroup analysis by the type of observational study; the pooled risk estimate was HR = 1.76 (95% CI 0.52–3.00) from case–control studies and HR = 1.59 (95% CI 1.07–2.11) from cohort studies. Results of the Q test and I^2 values indicated that there were no significant heterogeneities in the observational studies, but significant heterogeneities in the RCT studies. The overall results indicated that there were no significant heterogeneities.

Ten articles included in our analysis investigated the association between tumor size and the risk of LIR (Habel *et al.*, 1998; Warnberg *et al.*, 2001; Warren *et al.*, 2005; Li *et al.*, 2006; Smith *et al.*, 2006; Pinder *et al.*, 2010; Falk *et al.*, 2011; Wapnir *et al.*, 2011; Noh *et al.*, 2013). Two of these studies were RCTs and the others were observational studies including two case–control studies and six cohort studies. The results from ten studies were inconsistent. Pooled results were nonsignificant from eight observational studies (HR = 1.00; 95% CI 0.92–1.08), two RCTs (HR = 0.97; 95% CI 0.66–1.27), or combined studies (HR = 1.00; 95% CI 0.92–1.08) (Fig. 3e). The pooled risk estimate was HR = 1.33 (95% CI 0.35–2.31) from case–control studies and HR = 1.00 (95% CI 0.92–1.08) from cohort studies.

Three observational studies including 1963 DCIS patients investigated the association between focality and the risk of LIR (Habel *et al.*, 1998; Noh *et al.*, 2013; Kong *et al.*, 2014). The risk estimates of the three studies varied from 1.3 to 5.1. The pooled risk estimate was 1.34 (95% CI 0.82–1.87) (Fig. 3f).

Modes of detection and risk of invasive local recurrence following ductal carcinoma *in situ*

Two RCTs (Wapnir *et al.*, 2011; Donker *et al.*, 2013) and four observational studies (Habel *et al.*, 1998; Kerlikowske *et al.*, 2010; Falk *et al.*, 2011; Collins *et al.*, 2013) investigated the association between the detection method and the outcome of DCIS. Six studies including 10 866 patients with DCIS showed a higher risk in patients with a non-screening-detected method (symptom/palpation/clinical) than a screening-detected method (mammogram) (HR = 1.38; 95% CI 1.12–1.63). Results from observational studies (HR = 1.36; 95% CI 0.95–1.74) were consistent with those from RCTs (HR = 1.40; 95% CI 1.06–1.75) (Fig. 4). Results of the Q test and I^2 values indicated that there were no significant heterogeneities in RCT studies, whereas there were significant heterogeneities in the observational studies. The overall results indicated that there were no significant heterogeneities among the studies included.

Pooled risk estimates of the association between biomarkers, tumor characteristics, or modes of detection, and risk of LIR by the study design are summarized in Table 2.

Publication bias

We generated funnel plots for each analysis. For ER, tumor characteristics, and modes of detection, there were no obvious asymmetries for the distributions of HRs from the studies included with their corresponding 95% CI. For PR and HER2, there were obvious asymmetries. The possible reason for this could be the small number of cases and the risk estimates selected from univariate analysis. The results of the Egger test showed that there was no significant publication bias for studies on ER, tumor characteristics, and modes of detection. For PR and HER2, the studies included showed significant publication bias (shown in Supplementary Figs 1–7).

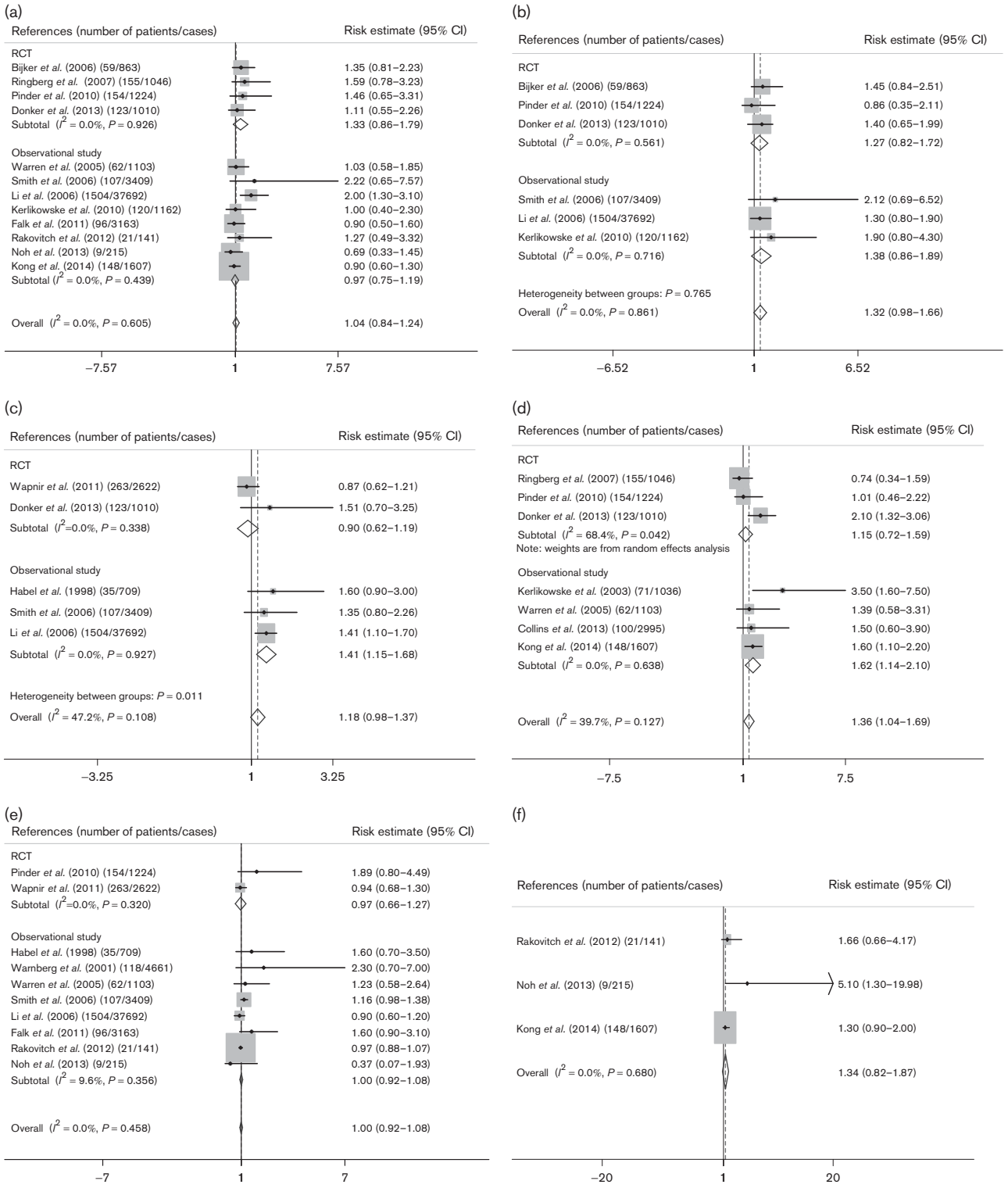
Discussion

In this meta-analysis, we assessed the association between tumor characteristics, biomarkers, and modes of detection with LIR after treatment of DCIS. When LIR and DCIS recurrence were separated, we found that positive margin and non-screening-detected cancers were associated with a higher risk of LIR in women with DCIS.

Boyages *et al.* (1999) carried out the first meta-analysis and found that comedonecrosis, margin, nuclear grade, and tumor size were considerable predictors of local recurrence for DCIS. A decade later, Wang *et al.* (2011) further suggested that multifocality and nonscreening detection were associated with a higher risk of ipsilateral breast tumor recurrence.

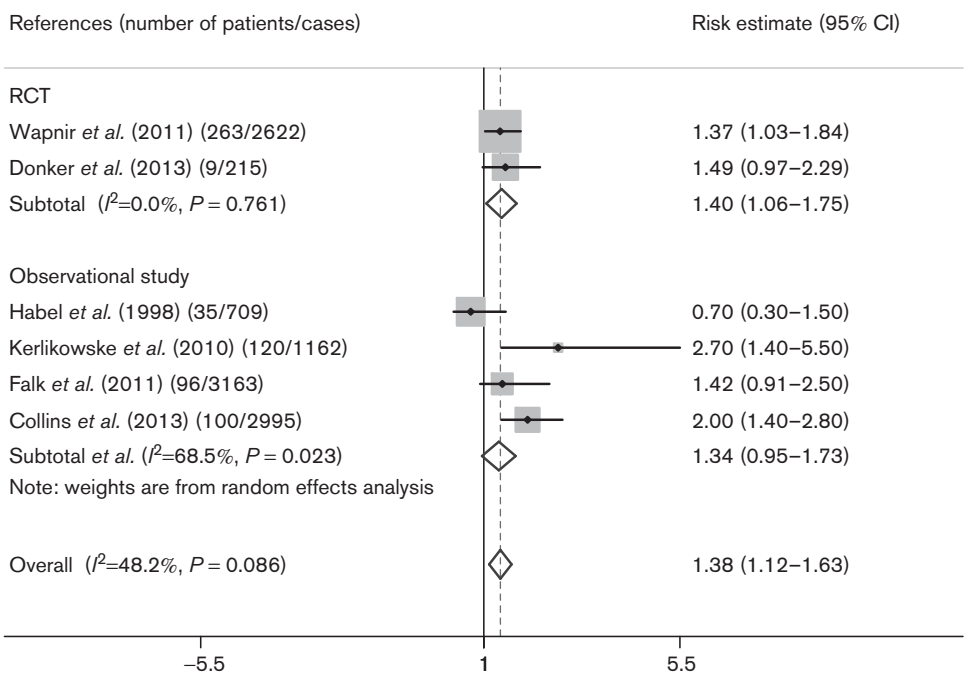
Several studies showed that marginal status was an important predictor for local recurrence of DCIS (Silverstein *et al.*, 1999; Douglas-Jones *et al.*, 2002). Positive surgical margins were associated with an increased risk of DCIS recurrence and LIR (Fisher *et al.*,

Fig. 3



Forest plots for tumor characteristics (nuclear grade, comedonecrosis, margin, tumor size, and focality) and the risk of invasive recurrence (LIR). (a) Forest plot for nuclear grade (high/low) and the risk of LIR. (b) Forest plot for nuclear grade (intermediate/low) and the risk of LIR. (c) Forest plot for comedonecrosis (yes/no) and the risk of LIR. (d) Forest plot for margin (positive/negative) and the risk of LIR. (e) Forest plot for tumor size (large/small) and the risk of LIR. (f) Forest plot for focality (yes/no) and the risk of LIR. CI, confidence interval; RCT, randomized clinical trial.

Fig. 4



Forest plot for modes of detection (symptomatic/no) and the risk of invasive recurrence (LIR). CI, confidence interval; RCT, randomized clinical trial.

Table 2 Risk estimates of associations between biomarkers, tumor characteristics, or modes of detection and the risk of local invasive recurrence

Characteristics	Number of cases	RCT [risk estimate (95% CI)/number of studies]	I^2 (%)	Observational studies [risk estimate (95% CI)/number of studies]	I^2 (%)	Combined studies [risk estimate (95% CI)/number of studies]	I^2 (%)
Biomarkers							
ER (positive vs. negative)	1556	–	–	0.74 (0.36–1.12)/3	0.0	0.74 (0.36–1.12)/3	0.0
PR (positive vs. negative)	1556	–	–	0.89 (0.47–1.31)/3	0.0	0.89 (0.47–1.31)/3	0.0
HER2/neu (positive vs. negative)	1771	–	–	1.25 (0.70–1.81)/4	0.0	1.25 (0.70–1.81)/4	0.0
Tumor characteristics							
Nuclear grade							
High/low	52 635	1.33 (0.86–1.79)/4	0.0	0.97 (0.75–1.19)/8	0.0	1.04 (0.84–1.24)/12	0.0
Intermediate/low	45 360	1.27 (0.82–1.72)/3	0.0	1.38 (0.86–1.89)/3	0.0	1.32 (0.98–1.66)/6	0.0
Comedonecrosis (yes vs. no)	45 442	0.9 (0.62–1.19)/2	0.0	**1.41 (1.15–1.68)**/3	0.0	1.18 (0.98–1.37)/5	47.2
Margins (positive vs. negative)	10 021	1.15 (0.72–1.59)/3	68.4	**1.62 (1.14–2.10)**/4	0.0	**1.36 (1.04–1.69)**/7	39.7
Tumor size (large vs. small)	54 939	0.97 (0.66–1.27)/2	0.0	1.00 (0.92–1.08)/8	9.6	1.00 (0.92–1.08)/10	0.0
Focality (multifocality/ multicentric vs. unifocal)	1963	–	–	1.34 (0.82–1.87)/3	0.0	1.34 (0.82–1.87)/3	0.0
Mode of detection (nonscreening detection vs. screening detection)	10 866	**1.40 (1.06–1.75)**/2	0.0	1.36 (0.95–1.74)/4	68.5	**1.38 (1.12–1.63)**/6	48.2

CI, confidence interval; ER, estrogen receptor; HER2/neu, epidermal growth factor receptor-2; PR, progesterone receptor; RCT, randomized clinical trial.
Bold indicates P <0.05.

2001). Our analysis found that the positive margin was associated with a higher risk of LIR. We also carried out a subgroup analysis according to the type of observational study; the results from cohort studies may be more reliable than case–control studies, which is consistent with the overall study. The positive margin status indicated that there were residual tumor cells in the tumor bed; a relatively hypoxic environment may have been formed because of the scar after an operation, which led to hypoxia of the tumor cells and influenced the effect of the radiotherapy. The patients with a positive margin have a large tumor burden and a poor prognosis. Data from clinics showed that even in patients with a positive margin who received a larger dose of radiotherapy, the rate of local recurrence was still obviously increased (Park *et al.*, 2000). DCIS detected by a nonscreening method had an increased risk of LIR, which is consistent with previous studies (Kerlikowske, 2003, 2010; Zhou *et al.*,

2013). A possible interpretation is that DCIS found by a non-screening detection method would be more aggressive than DCIS found by a screening detection method, or nonscreening DCIS may have a greater stromal response (Silverstein *et al.*, 2001; Kerlikowske *et al.*, 2010). Symptomatic detection women are more likely to have pathologically aggressive disease than screening-detected women, who are usually ER negative, HER2/neu positive, or lymph node positive (Barnes *et al.*, 2014).

Comedonecrosis is a common histopathologic feature of DCIS. It is considered a unique factor of DCIS and associated with an increased risk of recurrence (Warnberg *et al.*, 2001; Li *et al.*, 2006). Our result suggested a slightly increased risk (19%) for LIR after DCIS with comedonecrosis, but this was insignificant.

High nuclear grade was reported to be associated with a higher probability of DCIS local recurrence than intermediate or low grade (Kerlikowske, 2003). Kong *et al.* (2014) found that only high nuclear grade was significantly associated with a higher risk of DCIS recurrence; however, high nuclear grade nonsignificantly decreased the risk of invasive outcome (HR = 0.9; 95% CI 0.6–1.3). Our meta-analysis found that nuclear grade may not be an independent predictor of LIR.

Large tumor size could be associated with local recurrence because of its poor characteristics (Zhou *et al.*, 2013). The study carried out by Falk *et al.* (2011) showed that only the unreported tumor size significantly increased the risk of ipsilateral invasive carcinoma compared with those with small tumors (< 20 mm); the possible reason for this might be that the group with unreported tumor size included a number of large tumors with multifocal pathology (Donker *et al.*, 2013). In this study, we failed to find this association between tumor size and LIR.

Several studies have assessed the prognostic significance of biomarkers such as ER, PR, and HER2/neu as predictors in DCIS patients; the results were inconsistent because of small sample sizes or short periods of follow-up (Ringberg *et al.*, 2001; Provenzano *et al.*, 2003). Findings from NSABP protocol B-24 showed that the use of tamoxifen could significantly reduce the risk of local recurrence in patients with DCIS whose ER status is positive (Allred *et al.*, 2002). We found that ER-positive or PR-positive tumors could nonsignificantly decrease the risk of LIR, and HER2/neu-positive tumors were associated with a higher risk of LIR, but this was not statistically significant.

The strengths of our analysis were that we used data from multivariate analyses to investigate the tumor characteristics to obtain the best evidence. The patients included in some studies may have received individualized treatment. The risk estimates we obtained were adjusted by treatment; the differences in treatments present in our study may not have affected the results. Observational studies, including case–control studies and cohort studies, and three case–control studies, were included in our analysis. We also carried out a subgroup analysis by considering the type of observational study to find the source of heterogeneity. To include more studies, risk estimates (RR, HR, OR) were treated as the same. According to the method of Zhang and Yu (1998), we converted the ORs into RRs when the ORs were lower than 0.5 or higher than 2.5 or the incidence risk was higher than 10%. According to the results of the Egger test and funnel plots, there was no significant publication bias among the studies included; on the basis of the evidence we included, the results were relatively convincing.

Several limitations should also be considered. First, the number of eligible studies in this meta-analysis was relatively small, and most studies were carried out in America and Europe. Different study types and patient selection criteria may be the possible explanations for the heterogeneity. Second, different definitions of tumor predictors, such as tumor size, nuclear grade, and detection of margin, hampered our synthesis of the association between tumor characteristics and invasive outcomes. Third, the expression levels of biomarkers are often correlated (Latta *et al.*, 2002); it is therefore difficult to assess multiple markers simultaneously in a multivariable model. The combined expression of HER2/neu and Ki67 as well as other combinations of biomarkers may help to define high-risk subgroups, whereas the information in the literature was not enough for assessment in our analysis.

In conclusion, our meta-analysis suggested several predictive factors for LIR after DCIS. The understanding of tumor characteristics that drive invasive recurrence may be useful for clinicians to choose a better treatment and minimize overtreatment of patients. Given the limitations of our analysis, further research should identify biomarkers that distinguish patients at risk of DCIS local recurrence from those at high risk of LIR; a larger sample size and more integral data will be needed for a more relevant analysis.

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Conflicts of interest

There are no conflicts of interest.

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