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

Keywords: breast cancer, ductal carcinoma in situ, local invasive recurrence, meta-analysis, tumor characteristic

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; Bijket 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
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. unilocular). Modes of detection and the risk of LIR were compared using a non-screening-detected method and a screening-detected method. Immunohistochemical staining was used to evaluate the expression of ER, PR, and HER2/neu. Scores that ranged between 3 and 8 were defined as ER (positive vs. negative), and PR positive, and HER2/neu positivity as HER2/neu scoring immunohistochemical 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 I² 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), inappropriate 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.,
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             | 2622                | 263           | NSABP B-17                 | LRT LO            | 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                                           | Age at diagnosis, nuclear grade, p16/COX2/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             | 37592               | 1504          | SEER                      | BCS, RT, BCSRT    | HR            | Nuclear grade, comedonecrosis, tumor size                                 | Age, year, registry, surgery/radiation |
| Bjer 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; KPC, 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.
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; Rakovich 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 0.55–1.30) (Fig. 2c). 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 = 1.25; 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 non-significant (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 1.04–1.70; 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.,
Forest plots for tumor characteristics (nuclear grade, comedonecrosis, margin, tumor size, and focality) and the risk of local 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.
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., 2001).

### 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] | I² (%) | Observational studies [risk estimate (95% CI)/number of studies] | I² (%) | Combined studies [risk estimate (95% CI)/number of studies] | I² (%) |
|-----------------|-----------------|-----------------------------------------------|--------|---------------------------------------------------------------|--------|---------------------------------------------------------------|--------|
| 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) | 45 440 | 0.9 (0.62–1.19)/2 | 0.0 | 1.41 (1.15–1.69)/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 (0.66–1.12)/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 $P < 0.05$. 

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

Acknowledgements
This work was partially supported by the National Natural Science Foundation of China (grants 81473039, 81071627, 81202275, 81302293, and 51302487) and the program for the Tianjin City High School Science & Technology Fund Planning Project (grant 20090137).

Conflicts of interest
There are no conflicts of interest.

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