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REVIEW

Tumor characteristics as predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis

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Abstract While ductal carcinoma in situ (DCIS) is seldom life threatening, the management of DCIS remains a dilemma for patients and their physicians. Aggressive treatment reduces the risk of ipsilateral breast tumor recurrence (IBTR), but has never been proven to improve survival. There is interest in identifying the prognostic factors for determining low-risk DCIS patients, but a comprehensive review of high-quality evidence on tumor characteristics in predicting local recurrence has never been carried out. We examined the following tumor characteristics: biomarkers, comedonecrosis, focality, surgical margin, method of detection, tumor grade, and tumor size. For this systematic review we restricted the analyses to the results of subgroup analyses from randomized controlled trials (RCTs) and multivariate analyses from RCTs and observational studies. We identified 44 eligible articles. The pooled random-effects risk estimates for IBTR are comedonecrosis 1.71(95% CI, 1.36–2.16), focality 1.95(95% CI, 1.59–2.40), margin 2.25(95% CI, 1.77–2.86), method of detection 1.35(95% CI, 1.12–1.62), tumor grade 1.81(95% CI, 1.53–2.13), and tumor size 1.63(95% CI, 1.30–2.06). Limited evidence indicated that women whose DCIS is ER-negative, PR-negative, or HER2/neu receptor positive have an IBTR higher than those whose DCIS is ER-positive, PR-positive, and HER2/neu receptor negative. A variety of tumor characteristics are significant predictors for IBTR. These results are important for both clinicians and patients to interpret the risk of local recurrence and to decide on a course of treatment.

Keywords Ductal carcinoma in situ · Meta-analysis · Outcome research · Tumor characteristics · Predictors

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Introduction

The treatment for ductal carcinoma in situ (DCIS) ranges from mastectomy to breast-conserving surgery (BCS) with or without radiation and hormone therapy [1]. There is a trade-off between treatments. Aggressive treatment usually decreases the possibility of recurrence, but has difficult side effects, ranging from those caused by radiation and/or hormone therapy to the disfigurement caused by mastectomy. Given that DCIS is a heterogeneous disease, the one-size-fits-all approach to treatment seems inappropriate. As tumor characteristics are routinely evaluated by the pathologist, this information could provide valid predictors for recurrence and could optimize treatment decisions [2]. The association between these factors and patient outcomes has been reviewed before [3], but the research is somewhat outdated.

The Minnesota Evidence-based Practice Center conducted a systematic review to address the diagnosis and management of DCIS in preparation for a National Institutes of Health Consensus Conference [4, 5]. We conducted a comprehensive literature review of all published evidence in order to analyze the incidence of DCIS [6], treatment options [7], and the association between women, tumor characteristics, and clinical outcomes [8]. For this review, we focused on the association between tumor characteristics and the risk of local recurrence. We hypothesized that

tumor characteristics, including biomarkers, comedonecrosis, focality, margin, method of detection, tumor grade, and tumor size, are all associated with local recurrence in women treated for DCIS, after controlling for other contributing factors.

Methods

Literature review and quality assessment

We searched the PubMed database for studies of DCIS published in English from January 1970 to February 2009. The details of the search algorithm are described elsewhere [9]. Using the same algorithm, we have updated the literature search to include July 2010 in order to find the latest published and qualified studies. We included studies that investigated the association between eligible outcomes and patients characteristics, tumor characteristics, and/or treatment strategies. We selected randomized controlled trials (RCTs) and observational studies with more than 100 cases of DCIS. We did not exclude small studies which investigated biomarkers for DCIS due to the limited published research on biomedical markers. For the purpose of this review, we restricted studies to RCTs that provided subgroup data, or to any study applying multivariate analyses. When an RCT reported subgroup data and performed a multivariate analysis, the multivariate adjusted risk estimate was chosen. If we found more than one study from a particular institution, the results from the largest sample size, the latest published articles, or the most comprehensive models were used. We also included studies of any treatment for women with DCIS where the results were adjusted for at least one other confounding factor. From each eligible article, we recorded the risk estimates for the following tumor characteristics: biomarkers, comedonecrosis, focality, margin, method of detection, tumor grade, and tumor size. In order to be included, the study had to report ipsilateral breast tumor recurrence (IBTR; either invasive cancer or DCIS recurrence), ipsilateral DCIS recurrence, or ipsilateral invasive cancer recurrence. IBTR free intervals were not included in this study.

We assessed the level of evidence following the Agency for Healthcare Research and Quality guidelines for comparative effectiveness reviews, and the U.S. Preventive Task Force criteria [10, 11]. We analyzed associations, not cause, between tumor characteristics and IBTR. Our evaluation of the body of evidence defined high level of evidence when further research is very unlikely to change our confidence in the estimate of effect, moderate level of evidence if further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, and low level of evidence if further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Statistical analysis

We calculated the IBTR odds ratio (OR) for each tumor characteristic with a corresponding 95% confidence interval from the RCT subgroup data, stratified into treatment groups. Different arms from the same RCT, treated as unique separated studies, were included in the pooled analyses. We abstracted the multivariate adjusted relative risk (RR), hazard ratio (HR), or OR from the RCTs and observational studies. For simplicity, we will refer to them as the risk estimate for all three types of measures [12]. The logarithm of the risk estimate with its corresponding standard error provided the data points for the meta-analysis [13]. We used a random-effects model to compute the pooled risk estimates and assess the statistical heterogeneity [14]. We reported the overall results, as well as those stratified by the RCTs and observational studies. Meta-analyses were conducted using Stata statistical software, version 11 (StataCorp, College Station, Texas). We reported 95% confidence intervals (CIs). All statistical tests were two-sided.

Results

Eligible studies

We analyzed 44 eligible articles including five RCTs (eight articles) and 36 observational studies (Table 1) [15–58]. The subgroup data of three RCTs were analyzed because tumor characteristics of interest were not included in their multivariate analysis [16, 18, 21]. Seven observational studies that did not report the risk estimate or its corresponding 95% confidence interval were not included in the pooled analyses [52–58].

Biomarkers

Most research examining the association between biomarkers and the risk of subsequent recurrence was limited to post hoc analyses of case–control studies [32, 37, 40, 43, 46]. The biomarkers information was constructed retrospectively from the original paraffin-embedded tumors and was not available for making treatment decisions; the results were only used for prognosis. Two studies were not included in the pooled analyses because one did not report the risk estimate [37] and the other reported the risk estimate by certain combinations of biomarkers [46].

Table 1 Characteristics of eligible studies for the meta-analysis

Study	Publication year	Study duration	Source	Treatment	Risk estimate	Relevant tumor characteristics included in analyses
Randomized control trial						
Bijker [15]	2006	1986–1996	EORTC	BCS, BCSRT	HR	Grade, margin, method of detection
Bijker [16]	2001	1986–1996			OR[a]	Comedonecrosis
Fisher [17]	2001	1991–2000	NSABP B-24	BCSRT with/without tamoxifen	HR	Comedonecrosis, margin, method of detection
Fisher [18]	2007	1991–?			OR[a]	Focality, grade, tumor size
Fisher [19]	1999	1985–1998	NSABP B-17	BCS, BCSRT	RR	Comedonecrosis, focality, grade, margin, tumor size
Ringberg [20]	2007	1987–2001	SweDCIS Trial	BCS, BCSRT	HR	Comedonecrosis, grade, margin
Holmberg [21]	2008	1987–2005			OR[a]	Focality, method of detection, tumor size
Pinder [22]	2010	1990–1998	UKCCCR/ANZ	BCS, BCSRT with/without tamoxifen	HR	Grade, margin, tumor size
Observational study						
Wai [23]	2010	1985–1999	British Columbia Cancer Agency, Canada	BCS	HR	Comedonecrosis, grade, margin, tumor size
Ottesen [24]	2000	1982–1989	Danish nationwide prospective study	BCS	HR	Comedonecrosis, tumor size
Ben-David [25]	2007	1985–2002	University of Michigan	BCSRT	HR	Margin
Cutuli [26]	2001	1985–1992	Eight French cancer centers	M, BCS, BCSRT	HR	Method of detection, margin
Cox [27]	1997	1985–1996	University of South Florida	BCS, BCSRT	HR	Focality
Rudloff [28]	2010	1991–2006	Memorial Sloan-Kettering Cancer Center	BCS, BCSRT	HR	Comedonecrosis, grade, method of detection, margin
Chuwa [29]	2008	1994–2000	National Cancer Center in Singapore	M, BCS, BCSRT	RR	Margin
Meijnen [30]	2008	1986–2005	Cancer Institute of the Netherlands	M, BCS, BCSRT	HR	Grade, method of detection, margin
Boland [31]	2003	1979–1999	South Manchester	BCS, BCSRT	RR	Grade, margin
Barnes [32]	2005	1979–?		M, BCS, BCSRT	OR	Biomarkers
Altintas [33]	2009	NA	Antwerp University Hospital and Ghent University Hospital, Belgium	M, BCS, BCSRT	HR	Biomarkers*, grade, margin, tumor size
Schouten van der Velden [34]	2007	1989–2003	The Cancer Registry of the Comprehensive Cancer Center-East, The Netherlands	M, BCS, BCSRT	HR	Comedonecrosis, method of detection, margin
Omlin [35]	2006	1978–2004	The Rare Cancer Network	BCS, BCSRT	HR	Biomarkers, comedonecrosis, grade, margin, method of detection, tumor size
MacDonald [36]	2005	1972–2004	University of Southern California	BCS	RR	Comedonecrosis, grade, margin, tumor size
Cornfield [37]	2004	1982–2000	Thomas Jefferson University Hospital	BCS	OR	Comedonecrosis, tumor size
Stallard [38]	2001	1986–1997	University Department of Surgery and Pathology, Glasgow, UK	M, BCS, BCSRT	HR	Grade

Table 1 continued

Study	Publication year	Study duration	Source	Treatment	Risk estimate	Relevant tumor characteristics included in analyses
Sahoo [39]	2005	1986–2000	University of Chicago	BCSRT	HR	Comedonecrosis, grade, margin*, tumor size
de Roos [40]	2007	1996–2001	University of Groningen Medical Center and the Martini Hospital	M, BCS, BCSRT	HR	Biomarkers, grade, margin, tumor size
Rakovitch [41]	2007	1982–2000	University of Toronto	BCS, BCSRT	HR	Focality, grade, margin
Douglas-Jones [42]	2002	1989–1998	University of Wales, College of Medicine, South Glamorgan, UK	BCS	OR	Comedonecrosis, grade, margin
Provenzano [43]	2003	1988–1992	Victorian Cancer Registry	BCS, BCSRT	OR	Biomarkers
Habel [44]	1998	1980–1992	SEER: Western Washington	BCS, BCSRT	RR	Comedonecrosis, method of detection, tumor size
Kerlikowske [45]	2003	1983–1999	SEER: Northern California	BCS	OR	Grade, method of detection, margin
Kerlikowske [46]	2010	1983–2005			HR	Biomarkers, grade, method of detection, margin**
Warren [47]	2005	1991–2001	SEER	BCS, BCSRT	HR	Comedonecrosis, grade, margin, tumor size
Li [48]	2006	1988–2002			HR	Comedonecrosis, grade, tumor size**
Smith [49]	2006	1992–2002	SEER-Medicare	BCS, BCSRT	HR	Comedonecrosis, grade, tumor size**
Innos [50]	2008	1988–1999	California Cancer Registry	M, BCS, BCSRT	IRR, SIR	Comedonecrosis**
Warnberg [51]	2001	1960–1992	Swedish Cancer Registry	M, BCS, BCSRT	OR	Tumor size**
Solin [52]	2005	1973–1995	10 institutions in North America and Europe	BCSRT	HR	Margin*
Carlson [53]	2007	1991–2003	Emory University Hospital	SSM	OR	Comedonecrosis, grade, margin, tumor size*
de Mascarel [54]	2000	1971–1995	Regional Cancer Center, Bordeaux, France	BCS, BCSRT	RR	Grade, margin, tumor size*
Di Saverio [55]	2008	1976–2006	S. Orsola Malpighi University Hospital, Bologna, Italy	BCS, BCSRT	NA	Grade, margin, tumor size*
Miller [56]	2001	1979–1997	The Henrietta Banting Breast Center, Ontario, Canada	M, BCS, BCSRT	RR	Method of detection*
Vicini [57]	2000	1980–1993	William Beaumont Hospital, Royal Oak, Michigan	BCSRT	HR	Grade*
Vargas [58]	2005	1981–1999		BCS, BCSRT	HR	Margin*

BCS Breast-conserving surgery only, *BCSRT* breast-conserving surgery plus radiotherapy, *IRR* incidence rate ratio, *HR* hazard ratio, *M* mastectomy, *OR* odds ratio, *RR* relative risk, *SSM* skin-sparing mastectomy

[a] Subgroup analysis

* The relative risk estimate or the 95% confidence interval was not reported or we could not reproduce their conclusions

** Outcomes are ipsilateral DCIS recurrences or ipsilateral invasive cancer recurrences

Estrogen receptor (ER) status

The risk estimates were consistently lower in women with ER-positive DCIS [35, 40, 43]. Three observational studies which included a total of 555 women with DCIS investigated the impact of ER status. The pooled data showed a 61% decreased risk of IBTR in patients with ER-positive DCIS (Table 2).

Table 2 Biomarkers and ipsilateral breast tumor recurrence, pooled results of case-series

Study	Publication year	Sample size	Relative measure of association	Estimate (95% CI)	% Weights from random-effects model
Estrogen receptor status (positive vs. negative)					
de Roos	2007	87	HR	0.56 (0.17, 1.67)	35.02
Omlin	2006	373	HR	0.71 (0.17, 2.96)	24.71
Provenzano	2003	95	OR	0.20 (0.10, 0.80)	40.27
Pooled estimate				0.39 (0.18, 0.86)	I-squared: 23.8% $P = 0.269$
Progesterone receptor status (positive vs. negative)					
de Roos	2007	87	HR	0.91 (0.33, 2.50)	41.3
Provenzano	2003	95	OR	0.40 (0.20, 0.90)	58.7
Pooled estimate				0.56 (0.25, 1.24)	I-squared: 38.9% $P = 0.201$
HER2/neu receptor status (positive vs. negative)					
de Roos	2007	87	HR	2.1 (0.7, 6.4)	56.41
Provenzano	2003	95	OR	5 (1.4, 17.5)	43.59
Pooled estimate				3.07 (1.32, 7.12)	I-squared: 2.5% $P = 0.311$

HR Hazard ratio, *OR* odds ratio

Progesterone receptor (PR) status

Across two observational studies, which included 182 women with DCIS, the risk of IBTR was consistently lower in women with PR-positive DCIS [40, 43]. The pooled data showed an insignificant 44% decreased risk of IBTR in patients with PR-positive DCIS (Table 2).

Human epidermal growth factor-2 oncoprotein (HER2/neu) status

Two observational studies showed that the risk estimates for IBTR were consistently higher in women with HER2/neu (also known as ERBB2) positive DCIS [40, 43]. The pooled data showed a significant increased risk of IBTR (ES = 3.1) in patients with HER2/neu positive DCIS (Table 2).

Other biomarkers

Evidence on association between other biomarkers and patient outcomes is limited. Two studies examined the association between IBTR and P53 [40, 43], but only one study showed that women with P53 positive DCIS have significantly higher IBTR [40]. Positive P21, or Ki67, and negative BCL-2 or Her4 are significant predictors of IBRT, according to the evidence of only one study [32, 43]. However, other markers such as cyclin D1, androgen receptor, cathepin D, and PS2 were found to be insignificant predictors [40, 43].

Comedonecrosis

The most commonly measured histopathologic architecture of DCIS is comedonecrosis. Architectural features of noncomedonecrosis DCIS include cribriform, solid, micropapillary, and papillary types. Comparisons between these noncomedonecrosis groups have been rarely reported and those that have are somewhat inconsistent. Many studies are available on the association between comedonecrosis and local recurrence. The results of four RCTs showed a consistent increased risk of IBTR in patients with comedonecrosis, ranging from 1.3 to 5.0 [16, 17, 19, 20]. The results from 11 observational studies showed that comedonecrosis increased IBTR, ranging from 0.7 to 9.3 [23, 24, 28, 34–37, 39, 42, 44, 47]. Meta-analyses of RCTs and observational studies, including 9,332 women with DCIS, showed a 79% increase of IBTR for RCTs and a 68% increase for observational studies for the risk of patients with comedonecrosis (Fig. 1). The summary risk estimate of comedonecrosis for IBTR in these studies was 1.71(95% CI 1.36–2.16).

The association between comedonecrosis and local DCIS recurrence was inconsistent in four studies [20, 47, 49, 50]. Six studies showed that DCIS patients with the presence of comedonecrosis had consistently higher risk of local invasive recurrence [20, 44, 47–50], two of which were significant [48, 50]. These studies had overlapping populations so we did not calculate the pooled estimate.

Focality

Three RCTs and two observational studies including 3,895 DCIS patients examined the association between focality

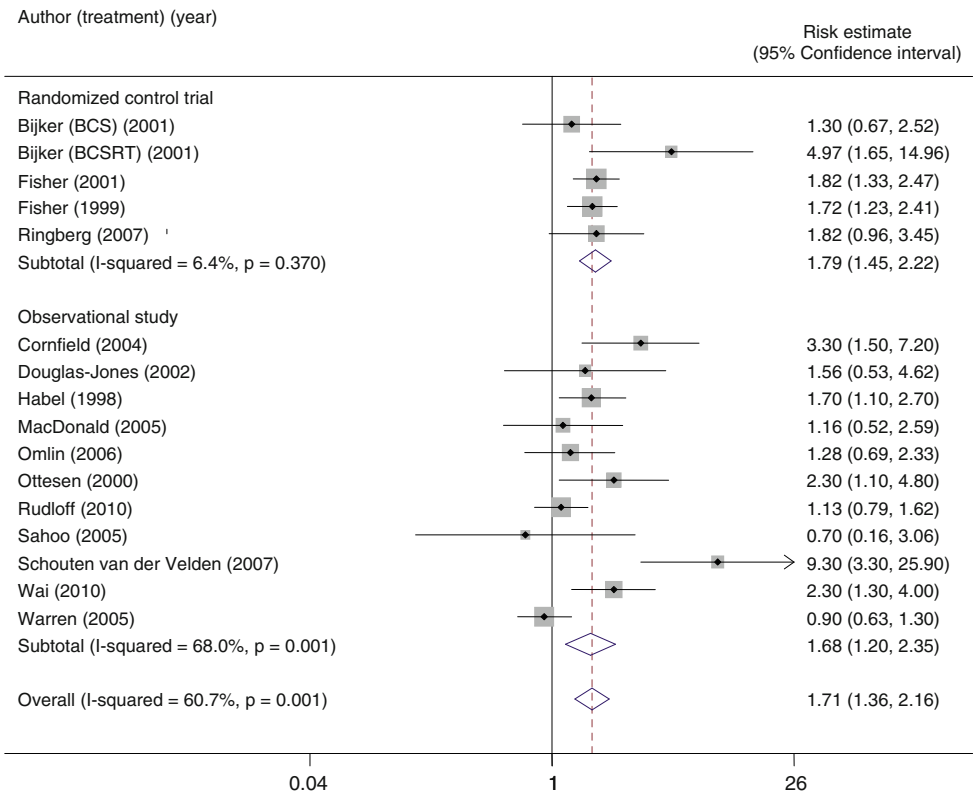

Fig. 1 Comedonecrosis and ipsilateral breast tumor recurrence. *BCS* Breast-conserving surgery, *BCSRT* breast-conserving surgery plus radiotherapy

and IBTR [18, 21, 27, 41]. Multifocal DCIS is consistently associated with higher risks of IBTR. Risk estimates range from 1.55 to 2.97 in RCTs and from 1.8 to 6.0 in observational studies. All but one finding was statistically significant. Meta-analyses stratified into RCTs or observational studies consistently show an increased risk in patients with multifocality (Fig. 2). The summary risk estimate for IBTR in these studies is 1.95(95% CI 1.59–2.40).

Margins

There was considerable variation across studies in terms of how margins were defined. Depending on the definition used, a positive margin was often classified as "involved" or "<1-mm", while a negative margin was classified as "free" or ">1-mm". Five RCTs and 22 observational studies examined the association between margin status and outcomes [15, 17, 19, 20, 22, 23, 25, 26, 28–31, 33–36, 40–42, 45–47, 52–55, 58]. Four RCTs showed that a positive margin was associated with increased IBTR [15, 17, 19, 22], two of which were statistically significant [15, 17]. The results from 17 observational studies were consistent with the findings of the RCTs. For women with positive surgical margins, the risk of IBTR increased from 19 to 880%. Thirteen of the seventeen results were statistically significant. Meta-analysis, including 12,086 women with DCIS, shows that compared with the free margin, the women with a positive margin had an increased risk of IBTR (Fig. 3). From RCTs, this is estimated at RR of 1.47(95% CI 1.12–1.94) and from observational studies, RR 2.84(95% CI 2.07–3.89). The summary risk estimate in these studies is 2.25(95% CI 1.77–2.85). Studies using log-transformed margin or margin as a continuous variable also supported the margin status as a significant factor for IBTR [36, 42].

The association between positive margin and local DCIS recurrence or local invasive recurrence differs from the Swedish Randomized trial (SweDCIS trial) and two studies using the Surveillance Epidemiology and End Results (SEER) data [20, 43, 45]. Two studies showed that compared to negative margins, close margins increase the risk of IBTR [25, 45]. A final study examined the value of a postoperative mammogram for assuring complete excision of the tumor. Compared to those without postoperative mammogram, Vargas et al. found that women with postoperative mammogram have lower IBTR (HR = 0.21 with *P*-value = 0.04) [58].

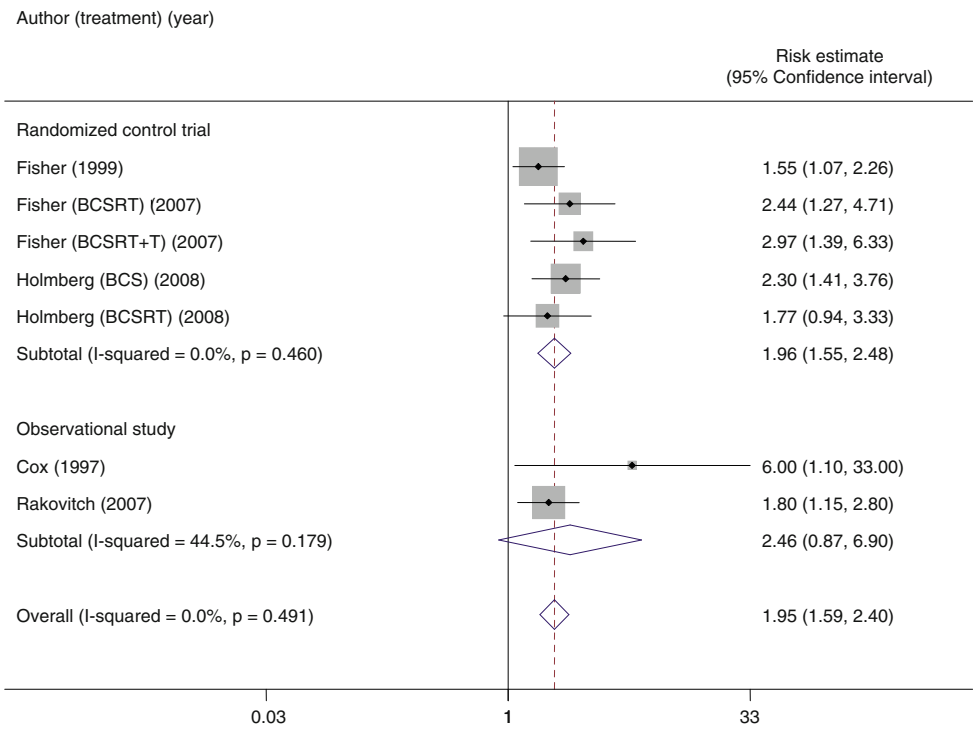

Fig. 2 Focality and ipsilateral breast tumor recurrence. *BCS* breast-conserving surgery, *BCSRT* breast-conserving surgery plus radiotherapy, *T* tamoxifen

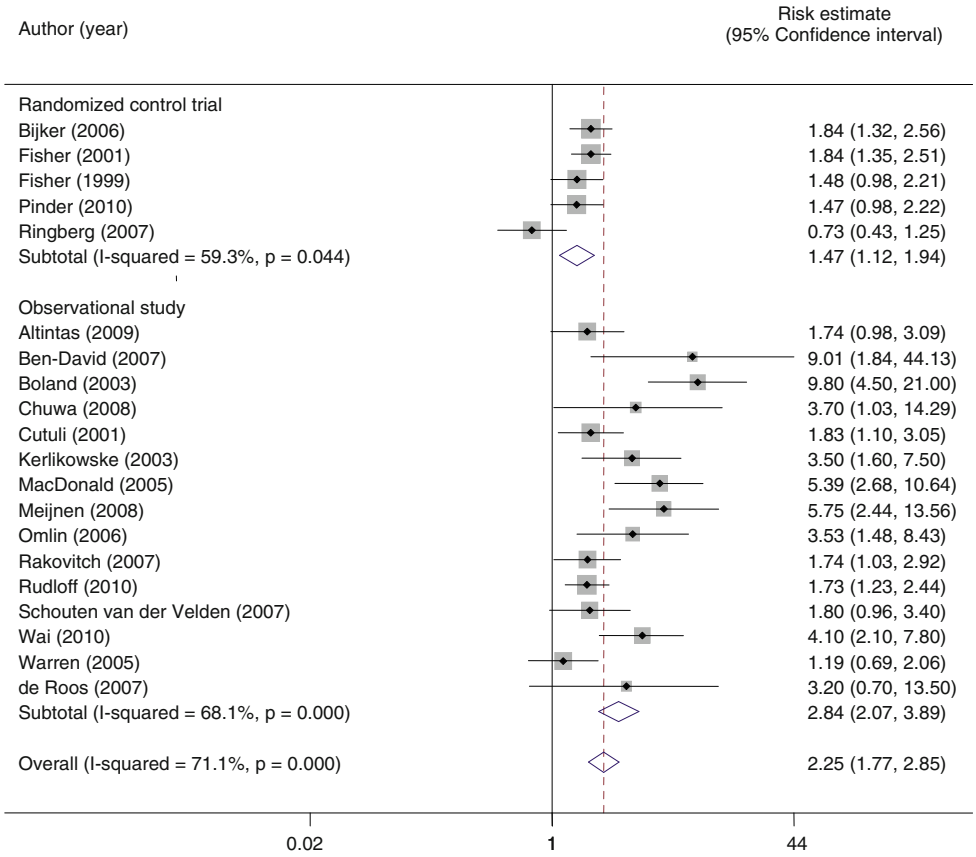

Fig. 3 Margin status (positive vs. free) and ipsilateral breast tumor recurrence

Method of detection

Three RCTs and nine observational studies examined the association between method of detection and outcome [15, 17, 21, 26, 28, 30, 34, 35, 44–46, 56]. We excluded one observational study because its relative risk estimate was not reported [56]. Women without palpable mass or nipple discharge tended to have decreased IBTR [15, 17, 21, 26, 28, 34, 45]. Two RCTs pooled across treatments showed the risk of IBTR to be 1.55 and 1.9, both being statistically significant [15, 17]. The analysis from the SweDCIS Trial's subgroup data showed a similar finding, although the result for the radiotherapy group was insignificant. Five out of seven observational studies showed that risks for IBTR increased in symptomatic women, of which one result was statistically significant. A meta-analysis of 9,442 DCIS patients shows that compared with those diagnosed by mammogram only, symptomatic women have an increased risk of IBTR, with an RR of 1.68(95% CI 1.38–2.04) from RCTs and an RR of 1.16(95% CI 0.91–1.48) from observational studies (Fig. 4). Summary risk estimate in these studies is 1.35(95% CI 1.12–1.62). Two SEER-based studies investigated the association between the method of detection and the risk of local invasive recurrence, but their directions were different [44, 45]. Kerlikowske et al. reported that the HR of detection by palpation versus mammography after adjusting biomarkers was 2.7(95% CI 1.4–5.5) [46].

Tumor Grades

Although labeled somewhat inconsistently, tumors that are assigned a higher pathological or nuclear grade have a consistently higher probability of IBTR than those assigned a low grade. Twenty-one studies including five RCTs examined the association between tumor grades and outcomes [15, 18–20, 22, 23, 28, 30–33, 35, 36, 38–42, 45–49, 53–55, 57]. We excluded five studies for our pooling meta-analysis because the risk point estimate and/or the 95% CI were not reported in three of these studies, and the other two studies used a different comparison method (per unit grade change) [38, 42, 53–55, 57]. Four RCTs pooled across treatments showed the risk estimates to be 1.36 and 2.77, but only two of them were significant [15, 19, 20, 22]. Analysis from the NSABP B-24 subgroup data found a similar effect, although only the result from the tamoxifen group was significant [18]. Twelve observational studies showed a consistently higher risk of IBTR in women with a high grade of DCIS [23, 28, 30, 31, 33, 35, 36, 39–41, 45, 47]. The risk estimates ranged from 1.11 to 4.17, and six of them were significant. The meta-analysis, which included 10,526 women with DCIS showed a 63% and 99% increase in risk for patients with a higher grade of DCIS, based on RCTs or observational studies (Fig. 5) [15, 18–20, 22, 23, 28, 30, 31, 33, 35, 36, 39–41, 45, 47]. The summary risk estimate in these studies was 1.81(95% CI 1.53–2.13).

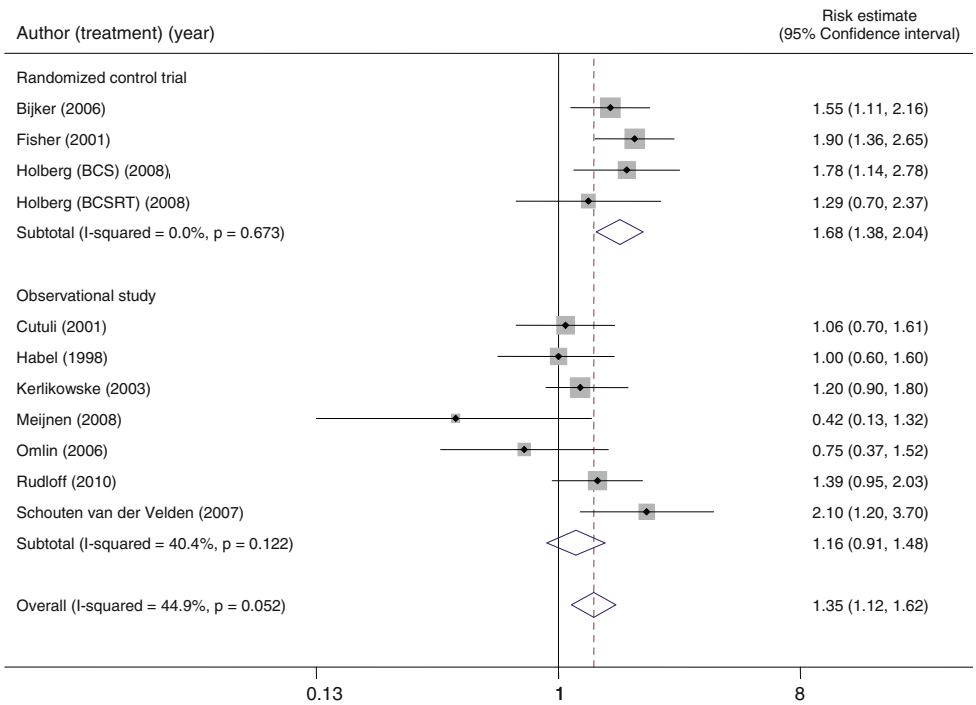

Fig. 4 Method of detection (symptomatic diagnosis vs. mammographic diagnosis) and ipsilateral breast tumor recurrence. *BCS* breast-conserving surgery, *BCSRT* breast-conserving surgery plus radiotherapy

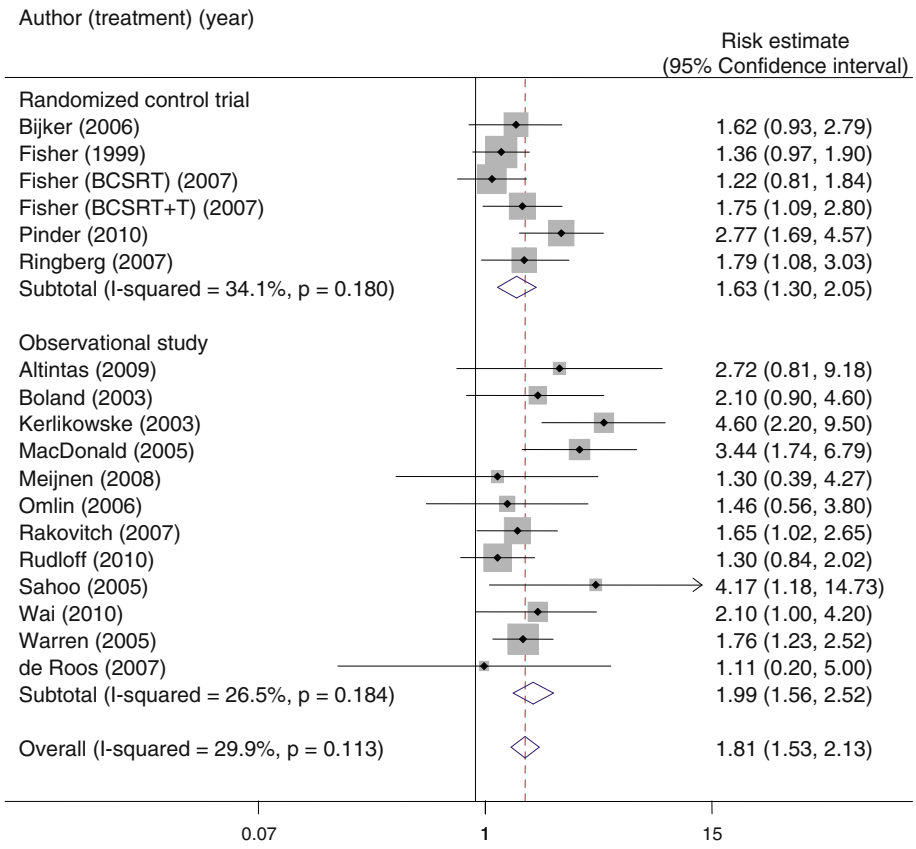

Fig. 5 Tumor grade (high vs. low) and ipsilateral breast tumor recurrence. *BCSRT* breast-conserving surgery plus radiotherapy, *T* tamoxifen

The SweDCIS trial and three observational studies showed consistently higher risks of local DCIS recurrence (RR 2.0–6.2) [20, 45, 47, 49], and five studies demonstrated higher risks of local invasive recurrence (RR 1.03–4.5) in high grade patients [20, 45, 47–49]. However, when using similar data but adjusting the biomarkers, Kerlikowske et al. found that the impact of tumor grade on local invasive recurrence or local DCIS recurrence decreased [44]. We did not pool the data analyses as most of the data came from the SEER dataset. The relationship between intermediate and low grade is similar to that between high and low grade. The summary risk estimate for IBTR based on eight studies including two RCTs is 1.79(95% CI 1.40–2.28) [15, 22, 30, 31, 35, 40, 41, 45].

Tumor size

There is no standardized definition for measuring the size of a DCIS tumor; yet, estimates generally classify tumors less than 20 mm as small. Four RCTs and 16 observational studies examined the association between tumor size and outcomes [18, 19, 21–24, 33, 35–37, 39, 40, 44, 47–49, 51, 53–55]. Two observational studies, using tumor size as a continuous variable or log-transformed tumor sizes, found an increased risk of local recurrence in patients with a large tumor size [36, 49]. Comparing the IBTR between large and small tumor sizes, 13 studies including four RCTs, showed an increased risk of IBTR in patients with large tumors [18, 19, 21–24, 33, 35, 37, 39, 40, 44, 47]. Four RCTs estimated that the risk ranged from 1.2 to 2.67 [18, 19, 21, 22], and nine observational studies showed that the relative estimates of risk ranged from 0.7 to 5.3. Meta-analyses including 7,097 women with DCIS showed a 62% to 68% increase in risk for patients with large tumors (Fig. 6). The summary risk estimate in these studies was 1.63(95% CI 1.30–2.06). Risks of local DCIS recurrence [45, 47] or local invasive recurrence [44, 47, 48, 51] also increased, but none was statistically significant. The comparison of IBTR between middle and small tumor sizes was less consistent.

Summary of tumor characteristics

Table 3 summarizes the risk of IBTR based on tumor characteristic and study design. Most risk estimates from

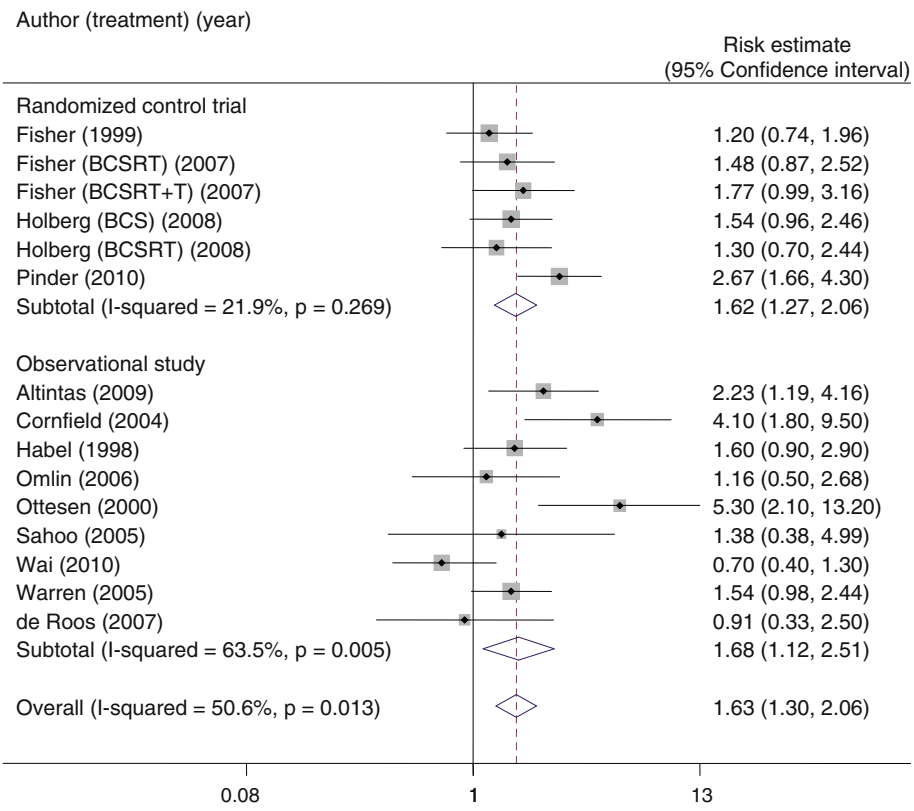

Fig. 6 Tumor size (large vs. small) and ipsilateral breast tumor recurrence. *BCS* breast-conserving surgery, *BCSRT* breast-conserving surgery plus radiotherapy, *T* tamoxifen

Table 3 Summary of ipsilateral breast tumor recurrence according to tumor characteristics and study design

Tumor characteristics	RCT/Number of studies	Observational studies/ No. of studies	Overall	Level of evidence
ER (positive vs. negative)	–	**0.39 (0.18, 0.86)/3***	–	Low
PR (positive vs. negative)	–	0.56 (0.25, 1.24)/2*	–	Low
HER2/neu (positive vs. negative)	–	**3.07 (1.32, 7.12)/2***	–	Low
Comedonecrosis (yes vs. no)	**1.79 (1.45, 2.22)/5***	**1.68 (1.20, 2.35)/11**	**1.71 (1.36, 2.16)**	High
Focality (yes vs. no)	**1.96 (1.55, 2.48)/5***	2.46 (0.87, 6.9)/2*	**1.95 (1.59, 2.40)***	Moderate
Margin (positive vs. negative)	**1.47 (1.12, 1.94)/5**	**2.84 (2.07, 3.89)/15**	**2.25 (1.77, 2.85)**	High
Method of detection (symptomatic vs. no)	**1.68 (1.38, 2.04)/4***	1.16 (0.91, 1.48)/7*	**1.35 (1.12, 1.62)***	Moderate
Grade (high vs. low)	**1.63 (1.30, 2.05)/6***	**1.99 (1.56, 2.52)/12***	**1.81 (1.53, 2.13)***	High
(intermediate vs. low)	**1.78 (1.26, 2.51)/2***	**1.79 (1.27, 2.53)/6***	**1.79 (1.40, 2.28)***	
Tumor size (large vs. small)	**1.62 (1.27, 2.06)/4***	**1.68 (1.12, 2.51)/9**	**1.63 (1.30, 2.06)**	High

Bold numbers are significant association at 95% confidence level

* Non-significant heterogeneity

observational studies are higher than those from RCTs; yet, RCTs demonstrated larger magnitude of the association between method of detection or comedonecrosis with IBTR.

Discussion

Five RCTs focusing on DCIS patients examined the effect among different treatments. The analysis of tumor

characteristics on outcomes, investigated using multivariate or subgroup analyses, turned out to be the best evidence. In contrast, unadjusted results from observational studies were vulnerable to selection bias. For example, patients with severe tumor characteristics tended to receive more aggressive treatment, such as additional radiotherapy or mastectomy. Therefore, crude risk estimates without any adjustment may be misleading. In order to analyze the available evidence, we restricted our analysis to multivariate or subgroup analyses from RCTs and multivariate analyses from observational studies in order to minimize bias. We acknowledge that multivariate analysis is not immune to selection bias and that there is inconsistent adjustment for both treatment and tumor characteristics across the studies. Our analyses, however, will be more accurate than that based on crude rates without any adjustment. Since it is impossible to randomize tumor characteristics, we believe that our approach is appropriate for synthesizing the current evidence.

More than a decade ago, Boyages et al. provided a systematic literature review on the predictors of local recurrence after treatment of DCIS [6]. They analyzed local recurrence by stratifying treatment and tumor factors. Although few studies were available at that time, their results suggested that comedonecrosis, grade, margin, and tumor size, in addition to the treatment received, were important predictors for local recurrence, but no estimate of the effect size was provided. This study not only updates the analysis and estimates the effect size based on currently available high-quality evidence, but also includes more tumor factors that are significant predictors of local recurrence. For example, in the previous review tumor grade was evaluated from seven studies including about 1,000 women with DCIS, while our analysis about tumor grade is based on 12 studies including more than 10,000 patients. We also evaluated the effects of several important characteristics such as biomarkers, focality, and method of detection. Our findings suggest that women whose features of DCIS include comedonecrosis, positive margin, higher tumor grade, large tumor size or multifocality, or who are diagnosed due to a palpable mass or nipple discharge are associated with a higher risk of IBTR. Our results also indicate that although some features are statistically insignificant, patients whose DCIS is ER-negative, PR-negative, or HER2/neu receptor positive have a higher IBTR than those who do not present these features. The risk estimates ranged from 1.35 for method of detection to 3.07 for positive HER2/neu receptor status. Our risk estimates provide important information for both physicians and patients when discussing risk of local recurrence and choice of treatment.

Our analysis has several implications for future research. First of all, biomarker expression as a predictor of local recurrence is promising, especially the large effective size for HER2/neu and ER status. However, it should be noted that our results with respect to biomarkers are derived from limited and relatively small studies. In addition, the role of other biomarkers is not well documented, but future studies should confirm which markers will be predictors of outcomes. Second, in conventional pathological evaluations, the effect size of the resection margin is the largest. Our results highlight the importance of margin status as a predictor of IBTR, which agrees with previous findings [42, 59, 60]. However, two recent surveys showed that there is still a lack of consensus among surgeons on what defines a good margin [61, 62]. Although a minimum 2-mm free margin has been proposed [63], further studies are warranted to understand how much negative margin is sufficient for patients with DCIS.

It is worth discussing the relationship between biomarkers and systematic treatment. The current treatment options for DCIS include mastectomy, BCS with radiotherapy, or BCS alone in selected patients. The addition of tamoxifen to BCS seems helpful as two RCTs showed that tamoxifen use reduced the risk of subsequent breast cancers, though this result was only statistically significant in one study [17, 64]. A subsequent analysis showed that the benefits of tamoxifen might be confined to those patients with ER-positive DCIS [65]. This finding suggested ER expression is an important predictor of response to tamoxifen in DCIS patients. National Comprehensive Cancer Network practice guidelines suggested that the workup of DCIS includes determination of ER status [66]. However, since a small clinically significant benefit of tamoxifen for women with ER-negative DCIS could not be ruled out, the Update Committee of the American Society of Clinical Oncology concluded that current data are insufficient to support using the ER status of DCIS for making decisions about tamoxifen treatment [67]. Currently, ER and PR statuses are included, though not required, in the protocol proposed by the College of American Pathologists (CAP) for reporting DCIS [68]. Several ongoing studies evaluating the effects of aromatase inhibition therapy or selective estrogen receptor modulators will demonstrate the value of these markers for predicting response to hormone therapy [7].

Although HER2/neu status should be assessed for all invasive breast cancer [69], DCIS is rarely tested for HER2/neu positivity. For example, the CAP's protocol does not include HER2 test [68]. Furthermore, it is not specified whether HER2 should be tested by immunohistochemistry or fluorescence in situ hybridization [69]. Nonetheless, the promise of treating HER2/neu positive tumors with trastuzumab or lapatinib is being studied in ongoing trials [7]. Their results will shed light on whether there is value in routine testing of HER2 status for DCIS.

Clinical decision making might be facilitated if the results we report are integrated into staging systems or prediction models. For example, Rudloff et al. developed a nomogram for predicting the risk of local recurrence for DCIS [28]. Tumor factors in that model include margin, grade, necrosis, and method of detection. Adding the significant factors, such as tumor size and focality from our analysis, to their prediction model might improve the predictive accuracy of their model. For many factors, the effect sizes derived from observational studies tend to be larger than that from RCTs. A notable exception is the effect of method of detection and comedonecrosis. Plausible explanations include publication bias of observational studies and also the interaction between tumor characteristics and treatment. For example, compared to noncomedonecrosis, EORCT 10853 found that there was a 397% increase in risk (significant) of recurrence for comedonecrosis patients receiving breast-conserving surgery (BCS) plus radiotherapy, but only a 30% increase in risk (insignificant) of recurrence for those receiving BCS only. This finding indicated that the impact of comedonecrosis might differ among different treatment groups, and that further studies are warranted.

Our study has some limitations. The synthesis of evidence of the association between tumor characteristics and patient outcomes was hampered by the different definitions of predictor categories, especially margin status, tumor grade, and tumor size, as well as architecture and other pathological features. The protocol proposed by the CAP for reporting DCIS will improve the clinical management of patients with this disease [68]. We combined the data from different study designs. Randomized trials assigned women to different treatments but not to tumor characteristics. The randomization process is irrelevant in either RCTs or observational studies when they investigated the association between tumor characteristics and outcomes. We believe that both approaches can address the common question of whether tumor characteristics influence the outcome of DCIS, as suggested in the previous literature [13]. In order to enhance comparable groups, we treated three different risk estimates (RR, HR, and OR) as being the same. We acknowledge that ORs cannot approximate RRs when the incidence risk is more than 10% or when the ORs are higher than 2.5 or less than 0.5 [70]. However, there are trade-offs, because we must exclude the data when the information necessary for this conversion is unavailable. For example, case–controlled studies that investigate biomarkers must be excluded since the incidence of recurrence in the positive biomarker group is unknown. We, therefore, converted ORs to RRs using the method of Zhang and Yu [70]. The results are similar except for those regarding biomarkers (data not shown). Finally, we admit that there may be potential publication bias, though we used several strategies to reduce bias, including reference lists of systematic reviews, contacts with experts for additional references they might provide, and agreement on eligibility status by several investigators.

In conclusion, this meta-analysis demonstrates that a variety of tumor characteristics are significant predictors for IBTR. The findings of this study are important for both clinicians and patients in order to interpret the risk of local recurrence and to decide on a course of treatment.

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